Prevention and Treatment of Cancer-Related Infections

Lindsey Robert Baden, William Bensinger, Michael Angarone, Corey Casper, Erik R. Dubberke, Alison G. Freifeld, Ramiro Garzon, John N. Greene, John P. Greer, James I. Ito, Judith E. Karp, Daniel R. Kaul, Earl King, Emily Mackler, Kieren A. Marr, Jose G. Montoya, Ashley Morris-Engemann, Peter G. Pappas, Ken Rolston, Brahm Segal, Susan K. Seo, Sankar Swaminathan, Maoko Naganuma and Dorothy A. Shead

Online article	http://www.jnccn.org/content/10/11/1412.full
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Prevention and Treatment of Cancer-Related Infections

Clinical Practice Guidelines in Oncology

Lindsey Robert Baden, MD; William Bensinger, MD;
Michael Angarone, DO; Corey Casper, MD, MPH;
Erik R. Dubberke, MD; Alison G. Freifeld, MD;
Ramiro Garzon, MD; John N. Greene, MD; John P. Greer, MD;
James I. Ito, MD; Judith E. Karp, MD; Daniel R. Kaul, MD;

Earl King, MD; Emily Mackler, PharmD; Kieren A. Marr, MD;
Jose G. Montoya, MD; Ashley Morris-Engemann, PharmD;
Peter G. Pappas, MD; Ken Rolston, MD; Brahm Segal, MD;
Susan K. Seo, MD; Sankar Swaminathan, MD;
Maoko Naganuma, MSc; and Dorothy A. Shead, MS

Overview

Infectious diseases are important causes of morbidity and mortality in patients with cancer. In certain instances, the malignancy itself can predispose patients to severe or recurrent infections. Neutropenia has been recognized for many decades as a major risk factor for the development of infections in patients undergoing chemotherapy. Effective strategies to anticipate, prevent, and manage infectious complications in neutropenic patients with cancer have led

Abstract

Patients with cancer are at increased risk for developing infectious complications during the course of their disease and treatment. The following sections of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prevention and Treatment of Cancer-Related Infections provide an overview of the risk factors for infectious complications, recommendations for infectious risk categorization, and strategies for prevention of infections in high-risk patient populations with cancer. Individualized risk evaluation for infections and incorporation of preventative measures are essential components of the overall spectrum of cancer care, and may contribute to optimizing treatment outcomes for patients. (*JNCCN* 2012;10:1412–1445)

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Please Note

Disclosures for the NCCN Prevention and Treatment of Cancer-Related Infections Panel

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Individual disclosures for the NCCN Prevention and Treatment of Cancer-Related Infections Panel members can be found on page 1445. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

to improved outcomes.[1–12] Because of advances in antimicrobial therapy, it is now uncommon for patients with acute leukemia or those undergoing stem cell transplantation to die of infections during the neutropenic period.

Although neutropenia remains a key risk factor for infections, other immunocompromised states pose at least equal risk. Allogeneic hematopoietic stem cell transplant (HSCT) recipients with neutrophil recovery who require intensive immunosuppressive therapy for graft-versus-host disease (GVHD) are an example of nonneutropenic patients at great risk for common bacterial, viral, and opportunistic infections.[13–16] The infectious diseases that can affect allogeneic HSCT recipients with GVHD are distinct from those that can affect patients with neutropenia.

These guidelines discuss infections in neutropenic and immunocompromised nonneutropenic patients with cancer. The scope also includes other highly immunocompromised patients with cancer (eg, those receiving high-dose corticosteroids, purine analogues, or monoclonal antibody therapy).

The major categories of immunologic deficits in persons with cancer and the major pathogens to which they are susceptible are characterized. Specific guidelines are provided on the prevention, diagnosis, and treatment of the major common and opportunistic infections that afflict patients with cancer. These guidelines should be applied in conjunction with careful individual patient evaluation and an understanding of host factors that predispose patients to specific infectious diseases and of antimicrobial susceptibility patterns.

NCCN Prevention and Treatment of Cancer-Related Infections Panel Members

*Lindsey Robert Baden, MD/Co-ChairΦ
  Dana-Farber/Brigham and Women's Cancer Center
*William Bensinger, MD/Co-Chair†
  Fred Hutchinson Cancer Research Center/
  Seattle Cancer Care Alliance
Michael Angarone, DO
  Robert H. Lurie Comprehensive Cancer Center of
  Northwestern University
Corey Casper, MD, MPHΦ
  Fred Hutchinson Cancer Research Center/
  Seattle Cancer Care Alliance
Erik R. Dubberke, MDΦ
  Siteman Cancer Center at Barnes-Jewish Hospital and
  Washington University School of Medicine
Alison G. Freifeld, MDΦÞ
  UNMC Eppley Cancer Center at
  The Nebraska Medical Center
Ramiro Garzon, MD
  The Ohio State University Comprehensive Cancer Center -
  James Cancer Hospital and Solove Research Institute
John N. Greene, MDΦÞ
  Moffitt Cancer Center
John P. Greer, MD‡
  Vanderbilt-Ingram Cancer Center
James I. Ito, MDΦ
  City of Hope Comprehensive Cancer Center
Judith E. Karp, MD‡Þ
  The Sidney Kimmel Comprehensive Cancer Center at
  Johns Hopkins

Daniel R. Kaul, MDΦ
  University of Michigan Comprehensive Cancer Center
Earl King, MDΞ
  Fox Chase Cancer Center
Emily Mackler, PharmDΣ
  University of Michigan Comprehensive Cancer Center
Kieren A. Marr, MDΦ
  The Sidney Kimmel Comprehensive Cancer Center at
  Johns Hopkins
Jose G. Montoya, MD
  Stanford Cancer Institute
Ashley Morris-Engemann, PharmDΣ
  Duke Comprehensive Cancer Center
Peter G. Pappas, MDΦ
  University of Alabama at Birmingham
  Comprehensive Cancer Center
Ken Rolston, MD
  The University of Texas MD Anderson Cancer Center
*Brahm Segal, MD
  Roswell Park Cancer Institute
Susan K. Seo, MDΦÞ
  Memorial Sloan-Kettering Cancer Center
Sankar Swaminathan, MD
  Huntsman Cancer Institute at the University of Utah
NCCN Staff: Maoko Naganuma, MSc, and Dorothy A. Shead, MS

KEY:

*Writing committee member

Specialties: ΦInfectious Diseases; ‡Hematology/Hematology
Oncology; ÞInternal Medicine; ΞPulmonary Medicine;
†Medical Oncology; ΣPharmacology

OVERALL INFECTION RISK IN CANCER PATIENTS[a]	DISEASE/THERAPY EXAMPLES	FEVER & NEUTROPENIA RISK CATEGORY (see facing page)	ANTIMICROBIAL PROPHYLAXIS[c,d,e,f,g,h]
Low	• Standard chemotherapy regimens for most solid tumors • Anticipated neutropenia less than 7 d	Low	• Bacterial - None • Fungal - None • Viral - None unless prior HSV episode
Intermediate	• Autologous HSCT • Lymphoma • Multiple myeloma • CLL • Purine analog therapy (eg, fludarabine, clofarabine, nelarabine, cladribine) • Anticipated neutropenia 7 to 10 d	Usually HIGH, but some experts suggest modifications depending on patient status Purine analogs, intermediate risk when used as single agents; when combined with intensive chemotherapy regimens, the risk converts to high	• Bacterial - Consider fluoroquinolone prophylaxis • Fungal - Consider fluconazole during neutropenia and for anticipated mucositis • Viral - During neutropenia and at least 30 d after HSCT

High[b]	• Allogeneic HSCT, including cord blood
	• Acute leukemia
	  ➤ Induction
	  ➤ Consolidation
	• Alemtuzumab therapy
	• GVHD treated with high-dose steroids
	• Anticipated neutropenia >10 d
		Usually HIGH, but significant variability exists related to duration of neutropenia, immunosuppressive agents, and status of underlying malignancy	• Bacterial - Consider fluoroquinolone prophylaxis
			• Fungal - See facing page
			• Viral - during neutropenia and at least 30 d after HSCT

Abbreviations: CLL, chronic lymphocytic leukemia; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplant; HSV, herpes simplex virus.

[a] Categories of risk are based on several factors, including underlying malignancy, whether disease is in remission, duration of neutropenia, prior exposure to chemotherapy, and intensity of immunosuppressive therapy.
[b] In high-risk patients, additional prophylaxis may be necessary; for example, consider penicillin and TMP/SMX for allogeneic HSCT recipients with GVHD.
[c] Pneumocystis prophylaxis (see page 1418).
[d] See Antibacterial Agents (FEV-A*) for dosing, spectrum, and specific comments/cautions.
[e] See Antifungal Agents (FEV-B*) for dosing, spectrum, and specific comments/cautions.
[f] See Antiviral Agents (FEV-C*) for dosing, spectrum, and specific comments/cautions.
[g] Although data support levofloxacin prophylaxis for low- and intermediate-risk patients, the panel discourages this practice in low-risk patients (because of concerns about antimicrobial resistance); however, it can be considered in intermediate-risk patients.
[h] For patients who are intolerant to fluoroquinolone, consider TMP/SMX.

*Available online, in these guidelines, at NCCN.org.

INF-1

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OVERALL INFECTION RISK IN CANCER PATIENTS[a]	DISEASE/THERAPY EXAMPLES	ANTIFUNGAL PROPHYLAXIS[e,k]	DURATION
Intermediate to High	ALL	Consider: • Fluconazole[l] • Amphotericin B products[m] (category 2B)	Until resolution of neutropenia
	MDS (neutropenic) AML (neutropenic)	Consider: • Posaconazole (category 1)[l] • Voriconazole (category 2B)[l] • Fluconazole (category 2B)[l] • Amphotericin B products[m] (category 2B)	
	Autologous HSCT with mucositis[i]	Consider: • Fluconazole (category 1)[l] • Micafungin (category1)	
	Autologous HSCT without mucositis	Consider no prophylaxis (category 2B)	
	Allogeneic HSCT (neutropenic) See Pneumocystis Prophylaxis (page 8)	Consider: • Fluconazole (category 1)[l] • Micafungin (category 1) • Itraconazole (category 2B)[l] • Voriconazole (category 2B)[l] • Posaconazole (category 2B)[l] • Amphotericin B product[m] (category 2B)	Continue during neutropenia and for at least 75 d after transplant
	Significant GVHD[j] See Pneumocystis Prophylaxis (page 8)	Consider: • Posaconazole (category 1)[l] • Voriconazole (category 2B)[l] • Echinocandin (category 2B) • Amphotericin B products[m] (category 2B)	Until resolution of significant GVHD

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplant; HSV, herpes simplex virus; MDS, myelodysplastic syndromes.

[j]Consider antifungal prophylaxis in all patients with GVHD receiving immunosuppressive therapy.
[k]There is substantial variability in practice among NCCN Member Institutions. Physicians need to take into account local susceptibility patterns.
[l]Itraconazole, voriconazole, and posaconazole are more potent inhibitors of hepatic cytochrome P450 3A4 isoenzymes than fluconazole, and may significantly decrease the clearance of several agents used to treat cancer.
[m]A lipid formulation is generally preferred based on less toxicity.

INF-2

OVERALL INFECTION RISK IN CANCER PATIENTS[a]	DISEASE/THERAPY EXAMPLES	VIRAL INFECTION or REACTIVATION	ANTIVIRAL PROPHYLAXIS	DURATION[f]
Low	• Standard chemotherapy regimens for solid tumors	HSV	None unless prior HSV episode	During neutropenia
Intermediate	• Autologous HSCT • Lymphoma • Multiple myeloma • CLL • Purine analog therapy (ie, fludarabine)	HSV VZV	Acyclovir Famciclovir Valacyclovir	During neutropenia and at least 30 d after HSCT (Consider VZV prophylaxis given for at least 1 year after HSCT)
High	• Acute leukemia ➤ Induction ➤ Consolidation	HSV	Acyclovir Famciclovir Valacyclovir	During neutropenia
	• Bortezomib therapy	VZV	Acyclovir Famciclovir Valacyclovir	During active therapy
	• Alemtuzumab therapy • Allogeneic HSCT	HSV VZV CMV HBV	Acyclovir Famciclovir or Valacyclovir as HSV prophylaxis (See page 1417) for CMV (See page 1418) for HBV	VZV prophylaxis • In allogeneic transplant recipients, acyclovir prophylaxis should be considered for at least 1 y after HSCT HSV prophylaxis • Minimum of 2 mo after alemtuzumab and until CD4 ≥200 cells/mcL • During neutropenia and at least 30 d after HSCT Preemptive therapy for CMV (see page 1417) Antiviral therapy for HBV (see page 1418)

Abbreviations: CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; HSCT, hematopoietic stem cell transplant; HSV, herpes simplex virus; VZV, varicella zoster virus.

[a]Categories of risk are based on several factors, including underlying malignancy, whether disease is in remission, duration of neutropenia, prior exposure to chemotherapy, and intensity of immunosuppressive therapy.
[f]See Antiviral Agents (FEV-C) for dosing, spectrum, and specific comments/cautions (available online, in these guidelines, at NCCN.org).

INF-3

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PREVENTION OF CYTOMEGALOVIRUS (CMV) REACTIVATION OR DISEASE

INFECTION RISK IN CANCER PATIENTS[a]	DISEASE/THERAPY EXAMPLES	SURVEILLANCE PERIOD[n]	PREEMPTIVE THERAPY[f,o]

High risk for CMV

Allogeneic stem cell transplant recipients → • 1 to 6 months after transplant • GVHD

Alemtuzumab → For a minimum of 2 mo after alemtuzumab

Cidofovir (IV) or Foscarnet (IV) or Ganciclovir (IV) or Valganciclovir (PO)

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[a] Categories of risk are based on several factors, including underlying malignancy, whether disease is in remission, duration of neutropenia, prior exposure to chemotherapy, and intensity of immunosuppressive therapy.

[f] See Antiviral Agents (FEV-C) for dosing, spectrum, and specific comments/cautions (available online, in these guidelines, at NCCN.org).

[n] CMV surveillance consists of at least weekly monitoring of CMV by PCR or antigen testing.

[o] Pre-emptive therapy is defined as administration of antiviral agents to asymptomatic patients at high risk for clinical infection based on laboratory markers of viremia (eg, increase in viral DNA load in serum or blood).

INF-4

PREVENTION OF HEPATITIS B VIRUS (HBV) REACTIVATION OR DISEASE

INFECTION RISK IN CANCER PATIENTS[a]

DISEASE/THERAPY EXAMPLES

ANTIVIRAL THERAPY[f,q]

SURVEILLANCE AND THERAPY PERIOD[n]

High risk for HBV[r]

- Allogeneic stem cell transplant candidate
  - Active HBV infection[p] → • Delay transplant • Treat with antivirals for 3-6 mo and then reevaluate
  - No active HBV infection → Consider antiviral prophylaxis if HBsAg+ (without HBeAg+), or HBcAb+

  → Adefovir or Entecavir or Lamivudine or Telbivudine or Tenofovir → Allogeneic stem cell transplant recipient → • At least 6-12 mo after transplant • GVHD

- Anti-CD20 monoclonal antibodies (rituximab, ofatumumab) and alemtuzumab → Adefovir or Entecavir or Lamivudine or Telbivudine or Tenofovir → At least 6-12 mo after last dose of antibody therapy
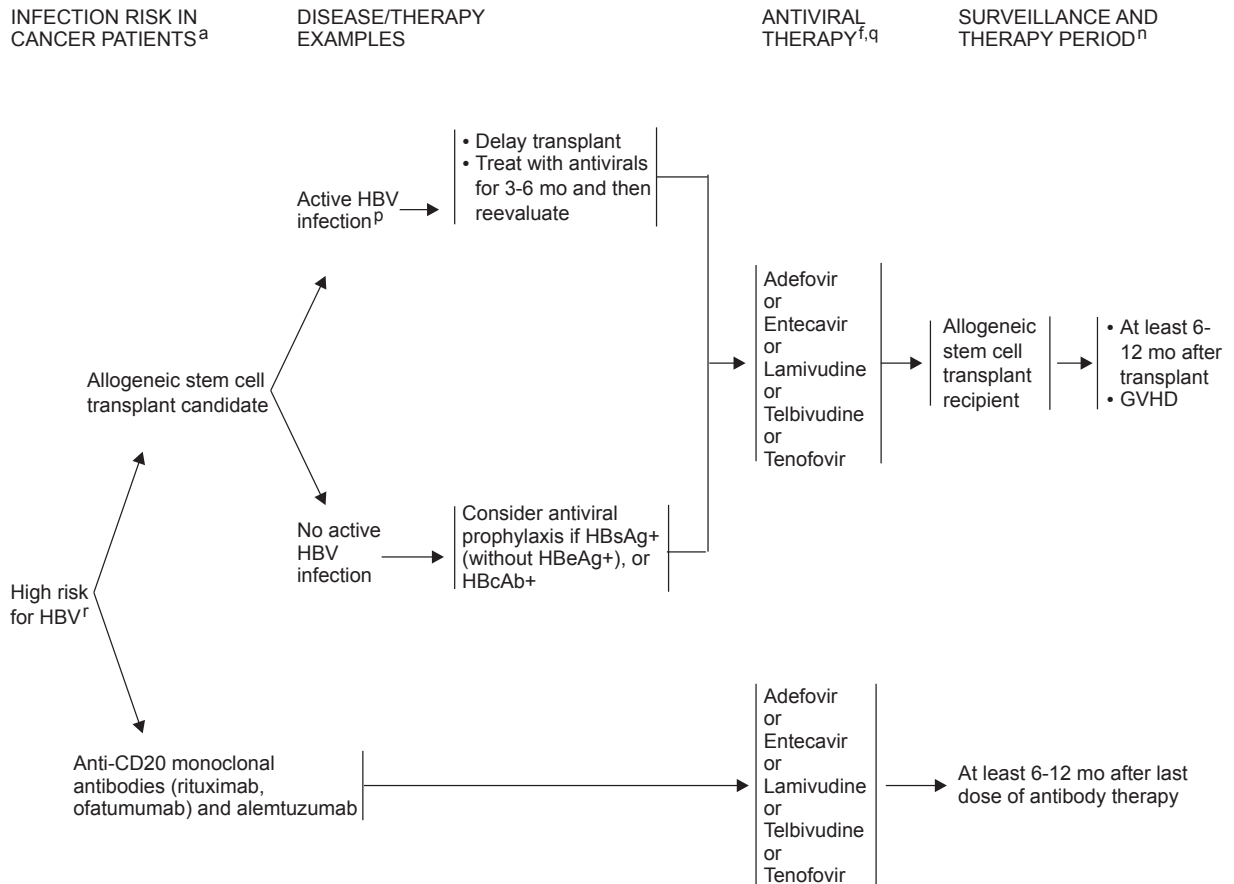
[f]See Antiviral Agents (FEV-C) for dosing, spectrum, and specific comments/cautions (available online, in these guidelines, at NCCN.org)

[p]Chronic hepatitis based on biopsy or active viral replication (ie, high levels of HBsAg+ and/or HBeAg+). Biopsy should be performed if clinical suspicion of disease. In case of cirrhosis reconsider decision for transplant.

[q]Order of listed agents is alphabetical and does not reflect preference.

[r]Defined as patients with HBsAg+ serology or with prior resolved HBV infection (HBsAg-, HBsAb+, HBcAb+ serology) planned for allogeneic HSCT or anti-CD20, antiCD52 monoclonal antibody therapy.

INF-5

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INFECTION RISK IN CANCER PATIENTS[a]

DISEASE/THERAPY EXAMPLES

DURATION OF PROPHYLAXIS

ANTIPNEUMOCYSTIS PROPHYLAXIS[d]

High risk for *Pneumocystis jirovecii (Pneumocystis carinii)*

- Allogeneic stem cell recipients (category 1) → For at least 6 mo and while receiving immunosuppressive therapy

- Acute lymphocytic leukemia (category 1) → Throughout antileukemic therapy

- Alemtuzumab → For a minimum of 2 mo after alemtuzumab and until CD4 count is >200 cells/mcL

TMP/SMX (preferred)[u] or Atovaquone[v], dapsone, aerosolized pentamidine, or if TMP/SMX intolerant[v]

Consider (category 2B):

- Recipients of purine analog therapy and other T-cell-depleting agents → Until CD4 count is >200 cells/mcL

- Recipients of prolonged corticosteroids[s] or receiving temozolomide + radiation therapy[t] →

- Autologous stem cell recipients → 3-6 mo after transplant

[a]Categories of risk are based on several factors, including underlying malignancy, whether disease is in remission, duration of neutropenia, prior exposure to chemotherapy, and intensity of immunosuppressive therapy.
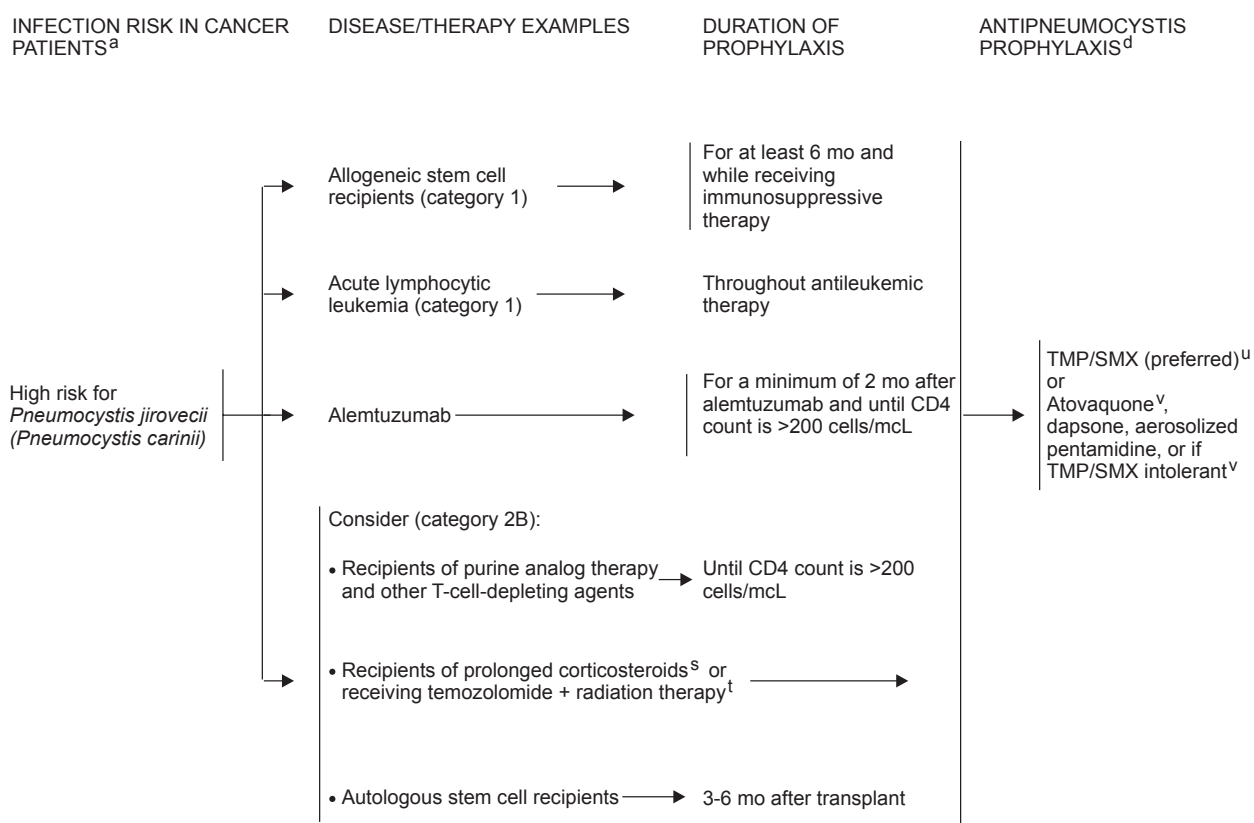[d]See Antibacterial Agents (FEV-A) for dosing, spectrum, and specific comments/cautions (available online, in these guidelines, at NCCN.org).
[s]Risk of *Pneumocystis jirovecci* pneumonia (PCP) is related to the daily dose and duration of corticosteroid therapy. Prophylaxis against PCP can be considered in patients receiving the prednisone equivalent of ≥20 mg/d for ≥4 weeks.
[t]PCP prophylaxis should be used when temozolomide is administered concomitantly with radiation therapy and should be continued until recovery from lymphocytopenia.
[u]In addition, this agent has some activity against other pathogens (eg, Nocardia, Toxoplasma, Listeria).
[v]Consider trimethoprim/sulfamethoxazole desensitization or dapsone, aerosolized pentamidine, or atovaquone when PCP prophylaxis is required, and patients are trimethoprim/sulfamethoxazole intolerant.

INF-6

These guidelines are divided into 4 sections comprising discussions on the following: risk factors for infection (major host factors that predispose patients to infectious diseases); management of neutropenic fever; management of site-specific infections (eg, pneumonia, abdominal infections, catheter-associated infections); and, importantly, prevention of infectious complications, including the use of antimicrobial prophylaxis and preemptive therapy.

This discussion addresses risk factors for infections in patients with cancer and strategies for infection prevention.

Host Factors That Predispose Patients to Infectious Complications

Immunodeficiencies Associated With Primary Malignancy

Certain malignancies are inherently associated with immune deficits. Patients with hematologic malignancies (chronic and acute leukemias, non-Hodgkin's lymphoma [NHL]) and myelodysplastic syndromes (MDS) may be leukopenic from infiltration of the marrow with malignant cells or a dysfunctional marrow. Patients with chronic lymphocytic leukemia (CLL) frequently have hypogammaglobulinemia leading to increased susceptibility to encapsulated bacteria, principally *Streptococcus pneumoniae*.[17] These patients may have recurrent sinopulmonary infections and septicemia. Patients with multiple myeloma are often functionally hypogammaglobulinemic; the total level of immunoglobulin production may be elevated, but the repertoire of antibody production is restricted. Savage et al[18] noted a biphasic pattern of infection among patients with multiple myeloma. Infections by *S pneumoniae* and *Haemophilus influenzae* occurred early in the disease course and in patients experiencing response to chemotherapy, whereas infections by *Staphylococcus aureus* and gram-negative pathogens occurred more commonly in advanced disease and during neutropenia.

Patients with advanced or refractory malignancy are at greater risk for infectious complications than those who experience response to therapy. Refractory hematologic malignancies can be associated with marrow failure from the underlying disease itself and from multiple lines of prior cytotoxic or immunosup-

pressive therapy. In patients with CLL, those who receive multiple chemotherapeutic regimens are at significantly increased risk for developing severe infections.[19] A retrospective study showed that nearly 90% of heavily pretreated patients (median, 3 prior regimens; range, 1–8) with fludarabine-refractory CLL experienced serious infectious complications requiring hospitalization.[20] Pathogens responsible for the infections were bacterial, viral (eg, herpes simplex virus [HSV], varicella zoster virus [VZV]), fungal, and opportunistic pathogens, including *Pneumocystis jirovecii*.[20]

Solid tumors may predispose patients to infection because of anatomic factors. Tumors that overgrow their blood supply become necrotic, thus forming a nidus for infection. Endobronchial tumors may cause recurrent postobstructive pneumonias. Abdominal tumors may obstruct the genitourinary or hepatobiliary tracts, predisposing patients to pyelonephritis and cholangitis, respectively. Direct invasion through the colonic mucosa is associated with local abscess formation and sepsis by enteric flora. Patients undergoing surgery for malignancies may be at high risk for infectious complications as a result of the type of surgery (eg, esophagectomy and hepatobiliary reconstruction are surgeries associated with a high risk for infection), extent of tumor burden, preoperative performance status, and previous surgery, chemotherapy, and radiation therapy. Patients with advanced malignancy are also commonly malnourished, which further increases the risk of infection.

Neutropenia

The absence of granulocytes; the disruption of the integumentary, mucosal, and mucociliary barriers; and the inherent microbial flora shifts that accompany severe illness and antimicrobial use predispose neutropenic patients to infection. The signs and symptoms of infection are often absent or muted in the absence of neutrophils, but fever remains an early, although nonspecific, sign.[7] Approximately 50% to 60% or more of the patients who become febrile have an established or occult infection.[21] Roughly 10% to 20% or more of patients with neutrophil counts less than 100/mcL will develop a bloodstream infection.[9] Primary sites of infection are the alimentary tract (ie, mouth, pharynx, esophagus, large and small bowel, and rectum), sinuses, lungs, and skin.

The pathogens responsible for initial infections early in the course of fever and neutropenia

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are primarily bacteria, whereas antibiotic-resistant bacteria, yeast, other fungi, and viruses are common causes of subsequent infections.[22,23] Coagulase-negative staphylococci, *S aureus*, viridans group streptococci, and enterococci are the major gram-positive pathogens. Coliforms (eg, *Escherichia coli*, *Klebsiella*, *Enterobacter* species) and *Pseudomonas aeruginosa* are the most common gram-negative infections complicating neutropenia.[22] HSV, respiratory syncytial virus (RSV), parainfluenza, and influenza A and B are also occasionally initial pathogens.[23] Infections from *Candida* species may occur later in the course of neutropenia, particularly as a consequence of gastrointestinal mucositis. *Aspergillus* species and other filamentous fungi are an important cause of morbidity and mortality in patients with severe and prolonged neutropenia.[22,24] Deaths resulting from infections identified at the onset of fever during neutropenia remain uncommon, and most infection-associated deaths result from subsequent infections during the course of neutropenia.

Studies from more than 4 decades ago have shown that as the neutrophil count decreases to less than 500/mcL (defined as *neutropenia*), the susceptibility to infection increases.[25] The frequency and severity of infection are inversely proportional to the neutrophil count; the risks of severe infection and bloodstream infection are greatest when the neutrophil count is less than 100/mcL. The rate of decline of the neutrophil count and the duration of neutropenia are also critical factors. These latter 2 aspects are a measure of bone marrow reserve and are highly correlated with severity of infection and clinical outcome.

Disruption of Mucosal Barriers

The mucosal linings of the gastrointestinal, sinopulmonary, and genitourinary tracts constitute the first line of host defense against a variety of pathogens. Chemotherapy and radiation therapy impair mucosal immunity at several different levels. When the physical protective barrier conferred by the epithelial lining is compromised, local flora may invade. Neutropenia and loss of the epithelial cell anatomic barrier may predispose patients to typhlitis (neutropenic enterocolitis). Chemotherapy-related gastrointestinal mucositis predisposes patients to bloodstream infections by viridans group streptococci,[26–29] gram-negative rods, and *Candida* species.[30,31]

Splenectomy and Functional Asplenia

In the spleen, rapid antigen presentation occurs, which leads to the production of opsonizing antibodies by B cells. The removal of nonopsonized bacteria protects against encapsulated bacteria to which the patient is not yet immune. Splenic irradiation results in functional asplenia, which predisposes patients to pneumococcal sepsis. Functional asplenia is also a late complication of severe GVHD.[32] Thus, in allogeneic HSCT recipients, fever in the late transplant period must be evaluated promptly (similar to patients with asplenia) because of the risk of overwhelming infection by encapsulated pathogens.

Asplenic patients are principally at risk for overwhelming sepsis by encapsulated bacteria. The most common pathogen is *S pneumoniae*, but other pathogens include *H influenzae* and *Neisseria meningitidis*. The Advisory Committee on Immunization Practices (ACIP) for the Centers for Disease Control and Prevention (CDC) recommends that asplenic persons be immunized with the pneumococcal polysaccharide and meningococcal vaccines.[33] The conjugated meningococcal vaccine (MCV4) is preferred in adults aged 55 years or younger because it confers longer-lasting immunity than the polysaccharide vaccine. Immunization of adults with the pediatric *H influenzae* type B (Hib) vaccine is considered optional because of lack of data on efficacy in older children and adults, although studies suggest good immunogenicity in immunocompromised patients. Immunization is ideally performed at least 2 weeks in advance of splenectomy. If this is not feasible, immunization is still advisable after splenectomy, because these patients are still capable of mounting a protective antibody response. One-time reimmunization with the pneumococcal vaccine is advised in asplenic persons 5 years after the initial vaccination. Revaccination with MCV4 after 5 years is recommended for functional asplenic patients who received MCV4 or MPSV4.[33] Prophylaxis with penicillin is advised in asplenic patients to prevent pneumococcal disease.

Corticosteroids and Other Lymphotoxic Agents

High-dose corticosteroids have profound effects on the distribution and function of neutrophils, monocytes, and lymphocytes. In patients with cancer, corticosteroids are seldom the only immunosuppressive agents being administered, and therefore the degree of impairment in host defense elicited by the corticosteroid regimen alone is difficult to delineate.

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The risk of infections is a function of the dose and duration of corticosteroids, coexisting immunodeficiencies (such as neutropenia and use of other immunosuppressive agents), and the status of the malignancy. Corticosteroids blunt fever and local signs of infection, such as peritonitis.

Lymphocyte-depleting agents increase the risk of common and opportunistic infectious diseases. Fludarabine is a fluorinated analogue of adenine that has been used in a variety of hematologic malignancies. Fludarabine is a lymphotoxic compound, primarily affecting CD4+ lymphocytes. In previously treated patients with CLL, fludarabine treatment (especially in combination with other immunosuppressive therapy) was associated with infections such as listeriosis, pneumocystosis (P jirovecii pneumonia [PCP]), mycobacterial infections, and opportunistic fungal and viral infections.[34] When used alone, purine analogs (eg, fludarabine, clofarabine) are associated with an increased risk for infection; when combined with other immunosuppressive or cytotoxic agents, purine analogs are associated with an even higher risk for infection.[35] The combination of fludarabine and corticosteroids is more immunosuppressive than either agent alone.[36] Fludarabine plus prednisone results in a uniform depression of CD4+ cells that may persist for several months after completion of therapy.[37] In one series, 14 of 264 patients (5%) with CLL developed either PCP or listeriosis, and 3 cases occurred more than 1 year after therapy in patients who were experiencing remission.[37]

Patients with hematologic malignancies and allogeneic HSCT recipients are increasingly being treated with novel monoclonal antibodies that cause a depletion of lymphocyte subsets. Alemtuzumab is a humanized monoclonal antibody that targets CD52, which is abundantly expressed on most normal and malignant B and T lymphocytes. This agent has been used most extensively in patients with CLL for whom fludarabine therapy has failed. Alemtuzumab has been associated with grade 3 or 4 neutropenia in approximately 40% of patients with previously untreated CLL and in 56% to 78% of patients with fludarabine-refractory disease.[38–41] Alemtuzumab is also associated with prolonged and severe lymphopenia in most patients. Four weeks after initiation of alemtuzumab, the median CD4+ count was 0/mcL, and 6 months after discontinuation, the count was 238/mcL in previously untreated patients.[38] The

CD8+ cell counts also changed in a similar manner. In previously treated patients receiving alemtuzumab, CD4+ and CD8+ counts may not recover to baseline levels until more than 1 year after completion of therapy.[38]

Infections pose a concern for morbidity and/or mortality in alemtuzumab recipients, particularly for patients with heavily pretreated fludarabine-refractory disease.[20,40,42] Bacterial, viral, fungal, mycobacterial, and P jirovecii infections have been reported with alemtuzumab.[40,42,43] Antiinfective prophylaxis against herpes viruses and PCP is recommended in patients receiving alemtuzumab treatment (see "Antiviral Prophylaxis and Preemptive Antiviral Therapy and Prophylaxis for P jirovecii," pages 1430 and 1436, respectively).[38] Patients treated with alemtuzumab have increased susceptibility to cytomegalovirus (CMV) reactivation and disease.[38–40,44–46] Therefore, routine surveillance for CMV reactivation using PCR or antigen-based methods is recommended in these patients (see "Antiviral Prophylaxis and Preemptive Antiviral Therapy: CMV," page 1431). However, the Infectious Diseases Working Party of the German Society of Hematology and Oncology does not recommend CMV surveillance in alemtuzumab recipients in the absence of large randomized controlled trials to substantiate this approach.[47] Other compounds known to cause lymphopenia, such as bortezomib, are associated with an increased risk of herpes zoster reactivation. For these patients, prophylaxis with acyclovir or valacyclovir is recommended.

Anti-CD20 monoclonal antibodies (eg, rituximab, ofatumumab) are widely used in the treatment of patients with B-cell lymphoid malignancies. The use of these monoclonal antibodies has been associated with increased risks for hepatitis B virus (HBV) reactivation, which can lead to fulminant hepatitis, liver failure, and/or death.[48–55] Antiviral prophylaxis is generally recommended for patients who test positive for HBV surface antigen (see "Antiviral Prophylaxis and Preemptive Antiviral Therapy: HBV," page 1433). In addition, the use of anti-CD20 monoclonal antibodies in patients with B-cell malignancies has been associated with rare instances of progressive multifocal leukoencephalopathy (PML).[48,49] PML is a demyelinating disease of the central nervous system (CNS) resulting from reactivation of the John Cunningham (JC) virus, and

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occurs in severely immunocompromised individuals. Although rare, PML is most often fatal. In reports of PML potentially associated with rituximab treatment in patients with B-cell malignancies, rituximab was typically given in combination with chemotherapy regimens or patients had received prior immunosuppressive regimens.[56–63] Moreover, patients who developed PML often presented with low CD4+ counts or an abnormal (low) CD4+/CD8+ ratio,[56,58,61,63] which indicates a critical role of T-cell immunity in suppressing reactivation of the JC virus.

HSCT

Autologous HSCT recipients generally have fewer infectious complications than allogeneic transplant recipients. Most infections in autologous HSCT recipients occur during neutropenia or within the first few months after transplantation before reconstitution of cellular immunity. However, CD34+ cell enrichment of autografts leads to a substantial reduction in T cells, natural killer cells, and monocytes compared with unmanipulated autografts, which delays immune reconstitution.[64] Recipients of CD34+ cell-enriched autografts seem to be at a similar risk level for CMV and other opportunistic infections as allogeneic HSCT recipients.[64] Severe or ulcerative mucositis, which develops as a result of myeloablative high-dose therapy administered before HSCT, is associated with the occurrence of bacteremia in autologous HSCT recipients.[65–67] Recently, a multicenter prospective study evaluated the potential role of granulocyte colony-stimulating factor (G-CSF) responsiveness in predicting the occurrence of infections in patients with hematologic malignancies undergoing high-dose therapy and autologous HSCT.[68] Responsiveness to G-CSF was determined by the administration of a single dose of G-CSF after completion of high-dose therapy (but before HSCT), and measuring the induced leukocyte peak 12 to 14 hours after the G-CSF dose. G-CSF responsiveness showed a significant inverse correlation with incidences of febrile neutropenia and infections (ie, higher responsiveness associated with lower infection rates), and was shown to be the only independent predictor of infections based on multivariate analysis.[68]

The spectrum of pathogens to which allogeneic HSCT recipients are most susceptible follows a timeline corresponding to the predominant immune defects. In the first month after HSCT (preengraftment period), neutropenia and breakdown of mucocutaneous barrier constitute the principal host defense defect, which predisposes patients to bacterial and fungal infections.[69,70] In addition, reactivation of HSV can often occur during this period. After myeloid engraftment, qualitative dysfunction of phagocytes persists because of corticosteroids and other immunosuppressive agents. The risk of infection by opportunistic viruses and filamentous fungi (molds) during this period is strongly associated with the severity of GVHD and the requirement for potent immunosuppressive regimens.

Defects in cell-mediated immunity are the primary factor that contributes to susceptibility to infections during the early postengraftment period, and can persist for several months even in recipients of uncomplicated allogeneic HSCT, predisposing them to common bacterial and viral infections and multiple opportunistic infections (eg, candidiasis, invasive mold infections, *P jirovecii*, *Cryptococcus neoformans*, dimorphic fungal infections [eg, histoplasmosis and coccidioidomycosis], HSV, CMV, herpes zoster, Epstein-Barr virus–associated lymphoproliferative disease, community respiratory viruses, legionellosis, listeriosis, nocardiosis, toxoplasmosis, mycobacterial diseases). In particular, the dominant pathogens during this early postengraftment period can include herpes viruses (especially CMV), *P jirovecii*, and invasive molds such as *Aspergillus*.[69,70] Although mature and cooperative T- and B-cell functions are usually reconstituted by 1 to 2 years after engraftment, chronic GVHD is associated with persistently depressed cell-mediated and humoral immunity.

Defective reconstitution of humoral immunity is a major factor contributing to increased infection susceptibility in the late postengraftment transplant period. Winston et al[71] noted a high frequency of pneumococcal infections between 7 and 36 months after transplantation, associated with serum opsonic deficiency for *S pneumoniae*. Kulkarni et al[72] reported that pneumococcal sepsis occurred a median of 10 months after transplant (range, 3–187 months) and was significantly more frequent in patients with chronic GVHD.

Guidelines from the CDC recommend that allogeneic HSCT recipients with severe hypogammaglobulinemia (IgG <400 mg/dL) and with recurrent infections receive intravenous immunoglobulin (IVIG) prophylaxis; IVIG is not recommended in other patient groups or in autologous HSCT recipi-

ents routinely.[16] The CDC published guidelines on vaccination of HSCT recipients and household members to prevent infections after transplantation.[16] Recent guidelines (published in 2009) on the prevention of infections in HSCT recipients (jointly sponsored by the CDC, Infectious Diseases Society of America [IDSA], American Society of Blood and Marrow Transplantation [ASBMT], and European Blood and Marrow Transplant Group [EMBT], among other organizations) reported similar recommendations on the use of IVIG, and also provides specific recommendations on the prevention of bacterial, viral, and fungal infections, and on administration of vaccines in this patient population.[70]

Allografts from HLA-matched unrelated donors, partially mismatched related donors, and cord blood are associated with a higher risk of GVHD. T-cell depletion delays immune reconstitution and, consequently, carries a greater risk of infectious complications, most notably by opportunistic viral[73] and fungal[74,75] pathogens. Cord blood transplant recipients may have a higher risk of infections than other allograft recipients during the early transplant period because of slower myeloid engraftment.

NCCN Recommendations for Categories of Infection Risk

These guidelines provide a summary of infection risk categories (low, intermediate, and high risk) in patients with cancer, which are based on factors such as the underlying malignancy, disease status (eg, active disease, disease in remission), duration of neutropenia, prior exposure to chemotherapy, and intensity of immunosuppressive therapies (see "Overall Infection Risk in Cancer Patients," pages 1414–1416). Patients with solid tumors receiving standard chemotherapy regimens and who have an anticipated duration of neutropenia shorter than 7 days are generally considered at low risk for infectious complications; thus, antimicrobial prophylaxis is not routinely recommended in these patients.[22] For patients with HSV-positive serology who are otherwise at low risk for infections, prophylaxis with antivirals can be considered.

Patients with an anticipated duration of neutropenia of 7 days or longer are considered to be at greater risk for developing infectious complications.[22] In these guidelines, patients with an anticipated duration of neutropenia of 7 to 10 days are considered to be at intermediate risk for infections; in addition,

patients with lymphoma, multiple myeloma, or CLL; autologous HSCT recipients; or patients receiving treatment with purine analog–containing regimens (most often for hematologic malignancies such as NHL or CLL) are also considered intermediate-risk (see "Overall Infection Risk in Cancer Patients," pages 1414–1416). Patients with NHL (particularly T-cell malignancy subtypes) or CLL treated with alemtuzumab-containing regimens are considered at high risk for infections (see discussion that follows for this patient population). For intermediate-risk patients, prophylaxis with antibacterials (eg, fluoroquinolones) should be considered. Antivirals should be given during periods of neutropenia and, for autologous HSCT recipients, until at least 30 days after transplant (however, antiviral prophylaxis for VZV should be considered for at least 1 year after HSCT). In addition, for intermediate-risk patients, antifungals should be considered during periods of neutropenia and for anticipated mucositis (with the latter pertaining to autologous HSCT).

Patients with an anticipated duration of neutropenia longer than 10 days, those undergoing intensive induction/consolidation therapy for acute leukemias (ie, acute lymphoblastic leukemia [ALL] or acute myeloid leukemia [AML]), those undergoing treatment with alemtuzumab-containing regimens, allogeneic HSCT recipients, and those with GVHD after allogeneic HSCT are considered at high risk for infectious complications. For these high-risk patients, prophylaxis with antibacterials (eg, fluoroquinolones) should be considered. These patients should receive antiviral prophylaxis during periods of neutropenia and, HSCT recipients should receive it until at least 30 days after transplant (however, antiviral prophylaxis for VZV should be considered for at least 1 year after HSCT). In addition, prophylaxis with antifungals can be considered for patients with ALL and neutropenic patients with AML/MDS.[22] For allogeneic HSCT recipients or those with significant GVHD undergoing immunosuppressive therapy, antifungal prophylaxis can also be considered during periods of neutropenia and until resolution of GVHD. For allogeneic HSCT recipients with GVHD, additional prophylactic measures such as administration of penicillin and trimethoprim-sulfamethoxazole (TMP/SMX) should also be considered. In addition, allogeneic HSCT recipients, patients with ALL, and patients treated with alemtuzumab are all at increased risk for infec-

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tion with *P jirovecii* (formerly *P carinii*). These patients should receive TMP/SMX for prevention of PCP (see "Prophylaxis for *P jirovecii*," page 1436).

Prevention of Infectious Diseases

Preventive measures against infections in patients with cancer generally involves upfront prophylaxis or preemptive therapy using broad-spectrum antimicrobial agents directed against the most common infecting pathogens (including bacterial, viral, and fungal) in high-risk patients.

Antibacterial Prophylaxis During Neutropenia

Patients with cancer and chemotherapy-induced neutropenia are at risk for severe bacterial infections. Fluoroquinolones are the most commonly used prophylactic antibacterial agents in adults with chemotherapy-induced neutropenia. In a meta-analysis that evaluated 18 trials (N=1408) in which fluoroquinolones were compared with either placebo or TMP/SMX, fluoroquinolone prophylaxis significantly reduced the incidence of gram-negative infections by approximately 80% compared with those without prophylaxis (relative risk, 0.21; 95% CI, 0.12–0.37), leading to an overall reduction in total infections.[76] The reduction in fever was small, and in blinded trials was not significant. Fluoroquinolone prophylaxis did not affect infection-related mortality rates in this meta-analysis. Moreover, the rate of gram-positive infections and fungal infections was not significantly affected by fluoroquinolone prophylaxis.[76] This is an important consideration given the occurrence of an increased rate of gram-positive infections in some trials of fluoroquinolone prophylaxis.[77] Viridans group streptococcal bacteremia breakthroughs have been associated with quinolone prophylaxis,[26,78,79] which poses a concern given the potential for substantial morbidity and mortality associated with this pathogen in neutropenic patients.

The potential benefit of antibacterial prophylaxis was evaluated in a single-center randomized study in patients undergoing high-dose therapy followed by autologous HSCT (N=157).[80] Patients were randomized to receive prophylaxis (with 500 mg oral ciprofloxacin twice daily and 1000 mg intravenous vancomycin once daily) or no prophylaxis; all patients received antifungal prophylaxis with fluconazole. Empirical therapy (comprising amikacin, ceftazidime, and full-dose vancomycin) was initiated when neutropenic fever developed. The use of antibacterial prophylaxis significantly reduced the incidences of neutropenic fever (56% vs 91%; *P*<.001) and bacteremia (6% vs. 35%; *P*=.005) compared with no prophylaxis, but at the expense of decreased responses to first-line empirical therapy (66% vs. 84%; *P*=.025).[80] Among the patients who received prophylaxis and developed neutropenic fever, 34% required second-line therapy that included a carbapenem, suggesting that these patients developed infections resistant to the prophylactic regimen. Duration of hospitalization and overall survival rates were similar between study arms. These results led the study investigators to conclude that routine antibacterial prophylaxis was not recommended in patients undergoing high-dose therapy and autologous HSCT.[80] Notably, however, the prophylactic regimen in this study included vancomycin (albeit at a lower dose), which is not supported by the panel for use as either antimicrobial prophylaxis or initial empirical therapy for fever and neutropenia. This view is in agreement with the published guidelines of the IDSA.[22]

Studies have provided additional insight into the benefits and limitations of prophylaxis among neutropenic patients with varying degrees of risk for serious infectious complications. Gafter-Gvili et al[81] conducted a meta-analysis of 95 randomized controlled trials comparing antibiotic prophylaxis with either placebo or no intervention or with another antibiotic in afebrile neutropenic patients. Antibiotic prophylaxis significantly decreased the risk for all-cause death compared with placebo or no treatment (relative risk, 0.67; 95% CI, 0.55–0.81); significant risk reductions were also observed for infection-related mortality, fever, clinically and microbiologically documented infections, gram-positive and gram-negative infections, and bacteremia. Similar results were obtained when the analysis was restricted to prophylaxis with fluoroquinolones. Fluoroquinolone prophylaxis significantly reduced the risk for all-cause mortality (relative risk, 0.52; 95% CI, 0.35–0.77) and all of the secondary measures indicated earlier.[81] Most of the trials involved hospitalized patients with hematologic malignancies, and data were inadequate to assess the relationship between duration and degree of neutropenia and relative risk of mortality. No significant increase was observed in fluoroquinolone-resistant bacterial infections, although the length of observation may have been too short to detect the emergence of resistant bacteria.[81]

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A subsequent systematic review and meta-analysis conducted by the same group of investigators evaluated the risks associated with colonization and infections by fluoroquinolone-resistance bacteria.[82] Most of the studies (48 of 55 trials) included patients with hematologic malignancies or HSCT recipients. Results of the analysis (based on 56 trials, N=7878; data on colonization by resistant bacteria based on 27 trials) showed that quinolone prophylaxis was associated with an increase (although not statistically significant) in colonization with quinolone-resistant organisms compared with placebo or no intervention (relative risk, 1.68; 95% CI, 0.71–4.00). However, no differences were observed in the incidence of infections caused by quinolone-resistant organisms (relative risk, 1.04; 95% CI, 0.73–1.50), regardless of whether these were resistant gram-negative or gram-positive bacteria.[82]

Moreover, in an analysis of trials comparing quinolones with TMP/SMX (11 trials), prophylaxis with quinolones was associated with fewer incidences of colonization and infections by resistant bacteria (those resistant to the prophylactic agents) compared with the use of TMP/SMX.[82] This analysis suggests that prophylaxis with quinolones does not appear to increase the rate of infections by resistant organisms. In a recent systematic review and meta-analysis (based on 109 trials, N=13,579) of trials comparing antibacterial prophylaxis with placebo or no intervention or with another agent in afebrile neutropenic patients, the use of antibacterial prophylaxis was found to significantly reduce the risk of all-cause mortality (risk ratio, 0.66; 95% CI, 0.55–0.79) and infection-related deaths (risk ratio, 0.61; 95% CI, 0.48–0.77) compared with placebo or no intervention.[83] The use of prophylaxis also significantly reduced the incidence of fever and clinically or microbiologically documented infections.

Although no significant differences in all-cause or infections-related mortality were seen between prophylactic quinolones or TMP/SMX, the use of quinolones was associated with fewer adverse events leading to discontinuation of drug and less resistance to the drugs used.[83] The panel recognizes the substantial limitations associated with meta-analyses. However, the panel believes that the risks and benefits of antibacterial prophylaxis in patients with hematologic malignancies and in the HSCT setting remain complex and undecided given the potential detriments related to adverse effects and/or the potential development of resistance.

Two large randomized, placebo-controlled studies showed the benefit of levofloxacin prophylaxis in neutropenic patients at different levels of risk for infectious complications.[84,85] Levofloxacin has similar activity against gram-negative pathogens compared with ciprofloxacin and ofloxacin; however, levofloxacin has improved activity against certain gram-positive pathogens, including streptococci. Bucaneve et al[84] evaluated levofloxacin prophylaxis in adult patients with cancer in whom chemotherapy-induced neutropenia (<1000 neutrophils/mcL) was expected to occur for more than 7 days. This protocol intentionally excluded patients anticipated to have a short duration of neutropenia who would generally be candidates for outpatient management of neutropenic fever. Levofloxacin recipients had a lower rate of microbiologically documented infections, bacteremias, and single-agent gram-negative bacteremias than did placebo recipients.[84] The effects of prophylaxis were also similar between patients with acute leukemia and those with solid tumors or lymphoma. Mortality and tolerability were similar in these groups.[84]

Cullen et al[85] evaluated levofloxacin prophylaxis after chemotherapy for solid tumors and lymphomas in patients anticipated to have brief durations of neutropenia and typically categorized as low risk. The primary outcome was the incidence of clinically documented febrile episodes (temperature >38°C) attributed to infection. Secondary outcomes included the incidence of all probable infections, severe infections, and hospitalization. A total of 1565 patients underwent randomization, 87% with solid tumors and 13% with lymphoma. During the entire chemotherapy course, approximately 11% of levofloxacin recipients had at least 1 febrile episode compared with 15% of placebo recipients (P=.01).[85] Hospitalization was required for the treatment of infection (suspected and documented) in approximately 16% of patients in the levofloxacin group and 22% of patients in the placebo group (P=.004). The incidences of severe infections, infection-related mortality, and overall mortality were similar in both groups.[85]

Thus, the main advantage of levofloxacin prophylaxis in intermediate- and higher-risk patients with chemotherapy-induced neutropenia was a reduction in clinically significant bacterial infections,

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including gram-negative rod bacteremia.[84] In contrast, the main advantage of prophylaxis in lower-risk neutropenic patients was a small but statistically significant reduction in fever and hospitalization for neutropenic fever.[85] Neither study conducted a systematic long-term evaluation of antimicrobial resistance. The panel considers that reduction in the incidence of significant infections is a more clinically meaningful end point than reduction in the incidence of neutropenic fever. Using the primary end point of prevention of neutropenic fever in the study by Cullen et al,[85] 1000 hypothetical low-risk patients would have to receive prophylaxis during each cycle of chemotherapy-induced neutropenia to benefit only 44 patients.

An important consideration for low-risk patients with short durations of neutropenia is whether fluoroquinolone prophylaxis is of greater benefit than the option of outpatient fluoroquinolone treatment for fever and neutropenia, should it occur. Both the panel and IDSA[22] recommend oral fluoroquinolone-based regimens as outpatient empiric therapy for neutropenic fever in adults who meet criteria for low risk of complications. Use of fluoroquinolone prophylaxis may preclude their later use as empiric therapy for neutropenic fever in the same patient. The modest difference in rates of hospitalization for suspected infection in patients treated with levofloxacin compared with placebo recipients (16% vs. 22%, respectively) in the study by Cullen et al[85] may be offset by the exclusion of outpatient oral empiric therapy in patients receiving fluoroquinolone prophylaxis. To target antibacterial use, Cullen et al[86] recently suggested more limited prophylaxis using levofloxacin only in cycle 1 of myelosuppressive cancer chemotherapy and on subsequent cycles after a fever in cycle 1.

The decision whether to use antibacterial prophylaxis and the selection of the specific agent requires a balance between expected benefit and risk. The concept of risk applies to immediate adverse effects of the drug (eg, rash, gastrointestinal intolerance), the potential for selection for resistant pathogens that can harm the individual receiving prophylaxis, and the risk of resistant organisms to a specific population of patients (eg, those being treated at a cancer center). The link between fluoroquinolone use and severe *C difficile* and methicillin-resistant *S aureus* infections provides an ad-

ditional cautionary note regarding excess use of fluoroquinolones.[87–90]

The panel advises that fluoroquinolone prophylaxis (levofloxacin is preferred) be considered in patients with expected duration of neutropenia (absolute neutrophil count [ANC] <1000/mcL) for more than 7 days. This is in agreement with the recommendations of the recent IDSA guidelines for the use of antimicrobial agents in neutropenic patients with cancer.[22] Among patients with neutropenia who are at lower risk of infectious complications (a category that includes most patients with solid tumor malignancies), the main benefit of antibacterial prophylaxis relates to a reduction in fever rather than in documented infections. In patients with neutropenia expected to last less than 7 days who are not receiving immunosuppressive regimens (eg, systemic corticosteroids), the panel suggests no antibiotic prophylaxis.[22]

Prophylaxis for Pneumococcal Infection

Prophylaxis against pneumococcal infection is advised in allogeneic HSCT recipients.

Patients undergoing allogeneic HSCT are at increased risk for pneumococcal sepsis from functional asplenia and impaired B-cell immunity. Pneumococcal sepsis is most common in the late transplant period, between 3 months to years after HSCT.[72,91] Immunosuppressive therapy for GVHD delays reconstitution of B-cell immunity and significantly increases the risk of posttransplant pneumococcal sepsis.[72,92]

The panel advises that penicillin prophylaxis be initiated at 3 months after HSCT and be continued until at least 1 year after transplant. Patients should receive prophylaxis regardless of prior administration of pneumococcal vaccines.[93] Prophylaxis should be continued in patients with chronic GVHD until immunosuppressive therapy has been discontinued. Posttransplant pneumococcal infection is generally community-acquired, and the frequency of resistance to antibiotics reflects regional antibiotic susceptibility patterns. In some areas, as many as 35% of pneumococcal isolates have intermediate- or high-level resistance to penicillin,[94] and cross-resistance to other classes of antibiotics is common. Breakthrough pneumococcal sepsis in HSCT recipients receiving penicillin prophylaxis is well described.[95] Thus, in areas with a significant frequency of penicillin-resistant pneumococcal isolates, alternative agents

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should be considered based on local susceptibility patterns. Daily TMP/SMX used as prophylaxis for PCP is likely to be protective against pneumococcal disease. Vaccination with the polysaccharide pneumococcal vaccine is also strongly recommended at 1 year after cessation of immunosuppression in HSCT recipients, with revaccination after 5 years.[93,96]

Antifungal Prophylaxis

Antifungal prophylaxis should not be used routinely in patients with neutropenia. The rationale for antifungal prophylaxis is to prevent fungal infections in a targeted group of high-risk patients, especially those with longer durations of neutropenia or with GVHD after allogeneic HSCT.[22] In neutropenic allogeneic HSCT recipients, 2 double-blind placebo-controlled trials have shown that prophylactic fluconazole controlled yeast colonization and also decreased the rate of mucosal candidiasis and invasive *Candida* infections.[97,98] A decrease in mortality was noted in one study in which most of the patients were allograft recipients.[98] Fluconazole conferred significant long-term improvement in survival, possibly through decreasing *Candida* antigen-induced gastrointestinal tract GVHD.[99]

Fluconazole prophylaxis decreased fungal colonization, invasive infection, and fungal infection–related mortality in nontransplant patients with leukemia and in autologous HSCT recipients in a placebo-controlled trial.[100] However, only 30% of the patients received growth factors, and the median duration of neutropenia was 14 to 16 days. The benefit of fluconazole prophylaxis was greatest in autologous transplant recipients not receiving colony-stimulating growth factor support and in patients with leukemia receiving mucotoxic regimens consisting of cytarabine plus anthracycline.[100] Therefore, no antifungal prophylaxis can be considered (category 2B) in autologous HSCT recipients who receive growth factor support and who do not have significant mucositis (see "Overall Infection Risk in Cancer Patients: Antifungal Prophylaxis," page 1415). Other studies of nontransplant patients with acute leukemia showed no significant benefit of fluconazole in preventing invasive fungal infections, reducing mortality, or reducing the requirement for amphotericin B.[101,102]

The panel recognizes that strong evidence exists for the use of fluconazole as prophylaxis in neutropenic allogeneic HSCT recipients (category 1).[22] However, fluconazole use can predispose to colonization and bloodstream infection by fluconazole-resistant *Candida* strains.[75,103]

Low-dose amphotericin B product and itraconazole have also been studied in high-risk patients and been shown to provide protection against invasive molds, although they have provided no survival benefit compared with fluconazole in randomized studies.[104–106] Itraconazole, however, may be associated with hepatic toxicity and gastrointestinal intolerance.[105] Itraconazole is contraindicated in patients with a decreased cardiac ejection fraction or a history of congestive heart failure based on its negative inotropic properties. It can also increase cyclophosphamide metabolites, which in turn are associated with hyperbilirubinemia and nephrotoxicity during the early transplant period.[107] This finding reinforces a note of caution about itraconazole (and by extension, voriconazole and posaconazole), a potent inhibitor of the cytochrome P450 3A4 isoenzyme, with regard to potential serious drug–drug interactions. Based on the toxicity of amphotericin B products and the availability of safer and equally effective alternative agents, amphotericin B products were considered a category 2B recommendation for prophylaxis. If an amphotericin B product is used, a lipid formulation is generally preferred because of less infusional and renal toxicity compared with conventional amphotericin B. This recommendation is made more strongly for patients at high risk for renal failure, such as those with preexisting renal disease, HSCT recipients, and those receiving coadministration of other nephrotoxic agents.[108,109]

Aerosolized delivery of amphotericin products has been considered for several years, and has the advantage of local delivery to lungs while avoiding systemic toxicity. A recent randomized, placebo-controlled trial found that aerosolized liposomal amphotericin B was useful for preventing invasive pulmonary aspergillosis in patients with prolonged neutropenia.[110] Limitations to aerosolized amphotericin B as prophylaxis include different nebulizers and amphotericin B formulations, lack of optimization of dosing, and lack of direct comparative data with systemically administered mold-active azoles or echinocandins.[111]

The echinocandin micafungin is approved[112] for prophylaxis against *Candida* infections in patients undergoing HSCT (category 1). In a randomized, double-blind trial in autologous and allogeneic

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HSCT recipients, the success rate with micafungin was superior to that with fluconazole (80% vs. 73.5%; absolute difference +6.5%; 95% CI, 0.9%–12%; P=.03) based on prespecified criteria for treatment success (absence of suspected, proven, or probable invasive fungal infections during the treatment period and absence of proven or probable infection during the 4-week period after treatment).[113] The duration of study drug encompassed the neutropenic period but not the period after neutrophil recovery when GVHD would be expected to occur. The frequency of breakthrough candidemia was similar in both arms, but a trend was seen toward fewer episodes of invasive aspergillosis in allogeneic HSCT recipients receiving micafungin. Survival and drug-related toxicity were similar between treatment arms.[113]

Prophylaxis with voriconazole was compared with fluconazole in a large, randomized, double-blind study that included serum galactomannan surveillance in allogeneic HSCT recipients (N=600).[114] No difference was noted in the primary end point (invasive fungal infection-free survival rate at 180 days) between the fluconazole and voriconazole prophylaxis arms (75% vs. 78%, respectively), but a trend for reduced incidence of *Aspergillus* infections (17% vs. 9%), reduced incidence of invasive fungal infections (11% vs. 7%), and less-frequent use of empiric antifungal treatment (30% vs. 24%) were noted in the voriconazole arm, although the differences were not statistically significant. No differences were noted between treatment arms regarding relapse-free and overall survival rates and incidence of severe adverse events.[114] Emerging data suggest that long-term use of voriconazole may be associated with severe photosensitivity and other adverse events. [115–117] Although these reports are anecdotal cases, further evaluation is warranted to determine the long-term side effects associated with voriconazole use.

Posaconazole is available as an oral formulation and should be taken with a full meal or liquid nutritional supplements to ensure adequate absorption. Pharmacokinetic studies with posaconazole in healthy individuals showed that giving this drug with or after a high-fat meal, or with any meal or nutritional supplement, greatly enhanced its absorption.[118] Posaconazole is as effective as fluconazole as primary therapy for oropharyngeal candidiasis,[119] but has not been evaluated as primary therapy for invasive fungal infections. In a multicenter randomized trial that evaluated prophylaxis with posaconazole compared with fluconazole or itraconazole in neutropenic patients with AML or MDS receiving induction or reinduction chemotherapy, posaconazole was associated with significantly reduced invasive fungal infections during the treatment period (primary end point: 2% vs. 8%; P<.001) and during the 100 days after randomization (5% vs. 11%; P=.003).[120] In addition, posaconazole prophylaxis reduced the incidence of invasive aspergillosis (1% vs. 7%; P<.001) and was associated with a significant survival benefit at 100 days after randomization (P=.04) compared with the fluconazole/itraconazole arm.[120]

The panel recommends posaconazole (category 1) for antifungal prophylaxis in neutropenic patients with AML and MDS receiving induction or reinduction chemotherapy (see "Overall Infection Risk in Cancer Patients: Antifungal Prophylaxis," page 1415).[22] The role of antifungal prophylaxis in patients with acute leukemia receiving consolidation chemotherapy has not been adequately evaluated. Posaconazole as prophylaxis has not been evaluated during the neutropenic period after conditioning in allogeneic HSCT recipients, and thus the safety of this approach is unknown. As indicated earlier, ingestion of a meal (ideally high-fat) or liquid nutritional supplement with each posaconazole dose is essential for achieving adequate posaconazole serum levels[121]; patients who are unable to tolerate this oral intake should not receive this drug for prophylaxis.

The panel advises that prophylaxis with posaconazole, itraconazole, and voriconazole be avoided in patients receiving vinca alkaloid–based regimens (such as vincristine in ALL) because of the potential of these azoles to inhibit the cytochrome P450 3A4 isoenzyme, reducing clearance of vinca alkaloids. Severe vinca alkaloid–induced neurotoxicity has occurred from coadministration with itraconazole[122]; data on pairing vinca alkaloids with posaconazole and voriconazole are lacking. Although the package inserts of voriconazole and posaconazole advise caution if coadministered with vinca alkaloids and consideration of dose-reducing the vinca alkaloid, no data are provided on the level of dose reduction required.[121,123] Prophylaxis with fluconazole (which is a less potent inhibitor of cytochrome P450 3A4 than the mold-active azoles), an echinocandin, or an amphotericin B formulation should be considered in these patients as a safer alternative to the mold-active azoles.

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Patients with chronic severe neutropenia (ANC <500/mcL) from the underlying disease (such as aplastic anemia) are at substantial risk for invasive aspergillosis.[124] Although this population has not been evaluated in clinical trials of antifungal prophylaxis, some panel members advise the use of a prophylactic mold-active agent (eg, posaconazole or voriconazole) in these patients.

In patients with acute leukemia or MDS and in autologous HSCT recipients, antifungal prophylaxis is administered until neutrophil recovery. Antifungal prophylaxis should be considered until at least day 75 after allogeneic HSCT (see "Overall Infection Risk in Cancer Patients: Antifungal Prophylaxis," page 1415).[22,99] Although many centers reasonably use antifungal prophylaxis in nonneutropenic allogeneic HSCT recipients with GVHD, this practice was evaluated only recently in a properly designed study that focused specifically on this patient group. Posaconazole was compared with fluconazole as prophylaxis in allogeneic HSCT recipients with severe GVHD requiring intensive immunosuppressive therapy in a prospective, randomized, double-blind study.[125] The inclusion criteria included either grade II to IV GVHD, chronic extensive GVHD, or receiving intensive immunosuppressive therapy consisting of either high-dose corticosteroids, antithymocyte globulin, or a combination of 2 or more immunosuppressive agents or types of treatment. Prophylaxis with posaconazole resulted in reduced incidences of invasive aspergillosis, total invasive fungal infections while on treatment, and deaths attributed to fungal infection.[125] Posaconazole is recommended (category 1) as prophylaxis in patients with GVHD receiving intensive immunosuppressive therapy, as defined by the inclusion criteria in this trial. Prophylactic posaconazole can be considered in all patients with GVHD receiving immunosuppressive therapy, although the benefit/risk ratio of mold-active prophylaxis in patients receiving less-intensive immunosuppressive regimens has not been established.

Secondary antifungal prophylaxis is defined as administration of antifungal therapy in a patient with a prior fungal infection to prevent recrudescence. The panel recommends secondary prophylaxis with an appropriate antifungal agent in patients with prior chronic disseminated candidiasis[126] or with invasive filamentous fungal infection[127] during subsequent cycles of chemotherapy or HSCT. In patients with invasive aspergillosis before HSCT, antifungal therapy for more than a month and resolution of radiologic abnormalities correlate with a lower likelihood of posttransplant recurrence of infection.[128] Secondary prophylaxis with a mold-active agent is advised for the entire period of immunosuppression. Secondary prophylaxis is generally administered for the duration of immunosuppression.

Antiviral Prophylaxis and Preemptive Antiviral Therapy

HSV: HSV is an important pathogen in patients who develop neutropenia and mucositis. These HSV infections primarily result from reactivation of latent virus. The presence of latent HSV can be determined by pretreatment HSV serology. Reactivation and infection with HSV occur in 60% to 80% of HSCT recipients and in patients (without prophylaxis) with acute leukemia undergoing induction or reinduction therapy who are seropositive for HSV.[129–131] Among allogeneic HSCT recipients, HSV disease is most likely to occur within the first month posttransplant, but may occur in later stages during intense immunosuppression.[69,70] Although disseminated HSV infection is uncommon, infection from viral reactivation is frequently associated with increased mucosal damage, resulting in increased pain, limitation of the patient's ability to maintain oral hydration and nutrition, and an increased risk of bacterial and fungal superinfections.

Antiviral prophylaxis (acyclovir, valacyclovir, or famciclovir) against HSV is advised during the period of neutropenia in HSV-seropositive patients receiving chemotherapy (induction or consolidation) for acute leukemia, and during neutropenia and at least 30 days after HSCT for both allogeneic and autologous transplant recipients (see "Overall Infection Risk in Cancer Patients: Antiviral Prophylaxis," page 1416). A longer period of prophylaxis should be considered in allogeneic HSCT recipients with GVHD or with frequent HSV reactivations before transplantation.[16] Acyclovir or valacyclovir is the initial agent of choice for HSV prophylaxis.[22,132] Foscarnet is typically reserved for patients with acyclovir-resistant HSV infection.[22,132] In patients who are receiving antiviral prophylaxis with ganciclovir or foscarnet to prevent CMV reactivation, additional prophylaxis with acyclovir is not necessary given that these agents are active against HSV.[132]

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HSV and herpes zoster infections are common in patients with CLL treated with the CD52 monoclonal antibody alemtuzumab. For these patients, antiviral prophylaxis is advised until at least 2 months after completion of alemtuzumab therapy or until CD4+ cell counts are 200/mcL or greater, whichever occurs later.[38,133]

Prophylaxis against HSV should be considered in other patients at intermediate risk for HSV reactivation, including those with hematologic malignancies with prolonged neutropenia or those receiving high-dose corticosteroids or T-cell–depleting agents (eg, fludarabine). Once a patient has had an HSV reactivation requiring treatment, the panel recommends HSV prophylaxis for that patient during all future episodes of neutropenia induced by cytotoxic therapy.

VZV: Impaired cellular immunity is the principal risk factor for VZV disease. In allogeneic HSCT recipients with a history of VZV infection without antiviral prophylaxis, approximately 30% have VZV disease after reactivation.[134] In patients with a history of chicken pox, oral acyclovir administered from 1 to 2 months until 1 year after allogeneic HSCT significantly decreased the incidence of VZV disease compared with placebo (5% vs. 26%, respectively).[134] The frequency of VZV disease in the post-prophylactic period was similar in the groups and predominantly occurred in patients who required systemic immunosuppression. This prolonged course of acyclovir prophylaxis is likely to also prevent HSV reactivations. Subsequent studies have consistently demonstrated the benefit of long-term antiviral prophylaxis against VZV disease in recipients of allogeneic HSCT. Patients who received anti-VZV prophylaxis with acyclovir or valacyclovir for 1 year after HSCT had a significantly reduced incidence of VZV disease compared with those who did not receive long-term prophylaxis (9% vs. 25%; P<.001); no evidence of rebound VZV disease was observed.[135] Long-term (1 year after allogeneic HSCT) prophylaxis with lower doses of acyclovir or valacyclovir was associated with a 19% to 35% cumulative incidence of VZV reactivation, but successfully prevented the occurrence of severe VZV disease comprising visceral involvement or serious complications.[136,137] The panel recommends acyclovir prophylaxis against VZV for at least 1 year after allogeneic HSCT in patients seropositive for VZV pretransplant, and recommends considering extending prophylaxis in patients who continue to receive systemic immunosuppressive therapy. Agents used as HSV prophylaxis are also active against VZV.

Among autologous HSCT recipients, the highest risk period for HSV reactivation is during neutropenia after conditioning, whereas the risk of VZV reactivation encompasses the first year.[138] Thus, VZV prophylaxis for at least 1 year posttransplant should also be considered in autologous HSCT recipients. Prophylaxis against VZV should also be considered in other patients at intermediate risk for viral reactivation, including those with hematologic malignancies with prolonged neutropenia or those receiving T-cell–depleting agents (eg, fludarabine, alemtuzumab). Bortezomib, a proteasome inhibitor, is associated with an increased risk of VZV reactivation during active therapy.[139–142] Prophylaxis with acyclovir, valacyclovir, or famciclovir should be protective and can be considered in these settings.[143,144] Among patients with CLL receiving alemtuzumab treatment, antiviral prophylaxis is recommended until 2 months after completion of treatment or until the CD4+ cell counts reach 200/mcL or greater, whichever occurs later.[38,133]

CMV: CMV is a common cause of opportunistic infections in patients undergoing allogeneic HSCT, mainly during the early postengraftment phase, but also occurring in the late postengraftment phase (particularly for patients with GVHD during the latter phase).[69,70] Infection can result from viral reactivation (in immunocompromised CMV-seropositive patients) or primary infection (in CMV-seronegative patients). The risk for CMV reactivation and disease is highest among HSCT recipients with CMV-seropositive status before transplant.[145] Among CMV-seropositive patients undergoing allogeneic HSCT (with graft sources from peripheral blood, bone marrow, or umbilical cord blood), the incidence of CMV reactivation ranged from 50% to 60% (with CMV disease in 10%–30% of seropositive recipients), even with routine surveillance and antiviral prophylaxis or preemptive therapy.[145–148] Testing HSCT candidates and donors for CMV serology is advised before transplant.

In allogeneic HSCT recipients at risk for CMV reactivation, the following preventative approaches have been evaluated[149]: 1) prophylaxis: antiviral agents are administered to all allogeneic HSCT recipients if either the donor or recipient is

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CMV-seropositive; and 2) preemptive therapy: antiviral agents are initiated after asymptomatic CMV reactivation is detected during active surveillance (ie, detection of CMV pp65 antigen or viral DNA in peripheral blood). Antiviral agents potently active against CMV have substantial toxicity with long-term use. Ganciclovir is associated with bone marrow suppression, which may increase the risk of common and opportunistic infections. Foscarnet can cause nephrotoxicity but is generally well tolerated.[150,151] Cidofovir (generally used as a second-line anti-CMV agent) can be associated with substantial nephrotoxicity.[152,153] Acyclovir and valacyclovir have an excellent safety profile but are only weakly active against CMV.

In 2 randomized studies, prophylaxis with acyclovir was associated with increased survival in allogeneic HSCT recipients, but the rates of CMV reactivation and disease were fairly high.[154,155] Ljungman et al[156] compared oral valacyclovir (a valine-esterified analog of acyclovir with high oral bioavailability) with acyclovir as prophylaxis in allogeneic HSCT recipients in whom either the donor or recipient was CMV-seropositive. All patients received initial intravenous acyclovir until day 28 after transplantation or until discharge, and then either oral valacyclovir or acyclovir until week 18 after transplantation. Valacyclovir was more effective than acyclovir in preventing CMV infection (28% vs. 40%; hazard ratio, 0.59; 95% CI, 0.46–0.76; $P<.0001$); no differences were observed in CMV disease, adverse events, or overall survival.[156] Thus, acyclovir and valacyclovir are acceptable agents for CMV prophylaxis, but surveillance and preemptive therapy with ganciclovir or foscarnet are still necessary.[132]

Highly sensitive methods for early diagnosis of CMV reactivation include detection of the CMV pp65 antigen in peripheral blood leukocytes and of CMV DNA using PCR.[157–159] Triggers for preemptive antiviral therapy are either a single positive CMV antigenemia or 2 consecutive positive PCR results. Ganciclovir is frequently the preferred agent for first-line preemptive therapy; foscarnet is more commonly used for patients who cannot tolerate ganciclovir or as second-line preemptive therapy.[132] Foscarnet and ganciclovir had similar efficacy as preemptive CMV therapies in allogeneic HSCT recipients, but ganciclovir was associated with significantly higher rates of early discontinuation because of either neu-

tropenia or thrombocytopenia.[151] Pharmacokinetic studies have shown the feasibility and safety of using oral valganciclovir, a prodrug of ganciclovir, in place of ganciclovir in patients who underwent allogeneic HSCT.[160,161] Oral valganciclovir used as preemptive anti-CMV therapy was shown to have acceptable oral bioavailability and was safe and effective in controlling CMV infection in allogeneic HSCT recipients, including in patients with grades I and II gastrointestinal GVHD.[160,162-164] Thus, valganciclovir is a highly acceptable oral option for preemptive therapy for CMV in the absence of substantial gastrointestinal GVHD.

Cidofovir has been evaluated as both primary and secondary preemptive therapy in allogeneic HSCT recipients.[152,153,165,166] In a retrospective study in allogeneic HSCT recipients (N=82) that evaluated cidofovir for treatment of CMV disease (n=20), primary preemptive therapy (n=24), or secondary preemptive therapy (n=38), response was observed in 50% of patients treated for CMV disease (mainly CMV pneumonia) and 62% treated for primary preemptive therapy.[152] Moreover, secondary preemptive therapy with cidofovir resulted in response in 66% of patients who had experienced either failure or relapse (defined as continued presence or recurrence of pp65 antigenemia or viral DNA after at least 1 week of antivirals) after initial preemptive therapy with ganciclovir, foscarnet, or the combination of these agents.[152] Maribavir is another oral anti-CMV agent under investigation in the setting of allogeneic HSCT. An earlier phase II randomized study showed that maribavir was effective as prophylaxis against CMV infection and CMV disease compared with placebo in allogeneic HSCT recipients. Moreover, in contrast to agents such as ganciclovir, maribavir was not associated with significant neutropenia or thrombocytopenia.[167] However, a recent double-blind, randomized, controlled phase III trial evaluating maribavir versus placebo in allogeneic HSCT recipients failed to show an advantage with maribavir in reducing the incidence of CMV disease.[168]

Late CMV disease, defined as occurring after day 100 of HSCT, remains a persistent problem in the era of CMV prophylaxis and preemptive therapy. In one series, 92% of patients with late CMV pneumonia had chronic GVHD or had received T-cell–depleted transplants.[169] Results of T-cell reconstitution at 3 months after allogeneic HSCT seem to be useful in

risk stratification for late CMV disease. At 3 months after HSCT, CD4 T-cell counts less than 50/mcL, total lymphocyte counts less than 100/mcL, undetectable CMV-specific Tcell responses, and GVHD were associated with late CMV disease or death in CMV-seropositive allogeneic HSCT recipients.[170] In addition, a CD4+ cell count less than 100/mcL, CD8+ count less than 50/mcL, and use of high-dose steroids (≥2 mg/kg/d) were significantly predictive of delayed recovery of CMV-specific immunity at 3 months after allogeneic HSCT; use of steroids impaired both CD4+ and CD8+ T-cell function in a dose-dependent manner.[171] In patients who did not receive high-dose steroids and received CMV prophylaxis with ganciclovir, subclinical CMV antigenemia seemed to stimulate functional recovery of both CD4+ and CD8+ cells. This finding may have implications for investigating potential CMV vaccine strategies in this clinical setting. Tetramer technology allows quantification of CMV antigen–specific CD4+ and CD8+ cells as a marker for reconstitution of CMV-specific cellular immunity; it may more precisely stratify the risk for CMV disease and need for CMV surveillance.[172] Although tetramer staining allows for monitoring of quantitative recovery of T cells, it does not assess the functional activity of T cells, which may be impaired; thus, the presence of a large proportion of CMV-specific T cells with impaired function may hinder recovery of CMV immunity.[171,173]

Based on the available data that predict risk of CMV disease, the panel recommends routine CMV surveillance for at least 6 months after allogeneic HSCT, together with preemptive anti-CMV therapy with intravenous ganciclovir, intravenous foscarnet, oral valganciclovir, or intravenous cidofovir (see "Prevention of Cytomegalovirus Reactivation or Disease: Allogeneic Stem Cell Transplant Recipients," page 1417). Additional surveillance should be strongly considered during chronic GVHD requiring immunosuppressive therapy and until the CD4+ count is 100/mcL or more. Note that the CD4+ count will be reduced by systemic corticosteroids and other lymphocyte-depleting agents. Most cases of late CMV disease occur within the first year of transplant and fewer than 5% occur after the second year.[169] Therefore, the value of CMV surveillance beyond 2 years after HSCT is unknown but can be considered in patients with significant chronic GVHD.

CMV reactivation is common among patients with lymphoproliferative malignancies (most commonly, CLL) receiving alemtuzumab therapy, and occurs most frequently between 3 and 6 weeks after initiation of therapy when T-cell counts reach a nadir.[40,44–46] Several studies of alemtuzumab in patients with CLL have demonstrated the effectiveness of using routine CMV monitoring coupled with preemptive anti-CMV therapy with ganciclovir in preventing overt CMV disease.[40,44,45,174] More recently, a small randomized study in patients with lymphoproliferative disease treated with alemtuzumab-containing regimens (N=40) showed that upfront CMV prophylaxis with oral valganciclovir significantly reduced the incidence of CMV reactivation compared with oral valacyclovir (0% vs. 35%; P=.004).[46] The panel recommends routine surveillance for CMV reactivation using PCR or antigen-based methods and monitoring weekly during alemtuzumab therapy and at least 2 months after completion of treatment.[38,175] On confirmation of CMV antigenemia (defined as PCR-positivity for CMV in ≥2 consecutive samples obtained 1 week apart[38]), the panel recommends preemptive therapy with intravenous ganciclovir, intravenous foscarnet, oral valganciclovir, or intravenous cidofovir for at least 2 weeks and until CMV is no longer detectable (see "Prevention of Cytomegalovirus Reactivation or Disease: Alemtuzumab," page 1417).

HBV: Reactivation of latent HBV may occur in the setting of significant immunosuppression (eg, immunosuppressive anti-tumor therapy, HSCT). HBV carriers with lymphoid malignancies, especially those treated with anthracycline-based regimens, have a high risk of HBV reactivation.[176] Moreover, as previously discussed, patients with B-cell lymphoid malignancies treated with anti-CD20 monoclonal antibodies (eg, rituximab, ofatumumab) may have increased risks for HBV reactivation and HBV disease, including rare instances of fulminant hepatitis or death.[48,49] Rare cases of liver failure and death associated with HBV reactivation have occurred in patients receiving rituximab-containing regimens.[49,50,177–179]

Fulminant hepatitis and mortality may occur after HBV reactivation in immunocompromised patients. Thus, it is prudent in these settings to assess for prior HBV infection, especially in individuals who have spent significant time in HBV-endemic areas or have risk factors for blood-borne exposure.

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Positive hepatitis B surface antigen (HBsAg) test results are associated with active infection (or a window before the development of protective immunity in a patient exposed to HBV). Some patients with cancer are at increased risk for HBV reactivation because of profound immunosuppression stemming from cytotoxic regimens and/or the underlying malignancy (eg, leukemia, lymphoma). In HBsAg-positive patients with cancer undergoing cytotoxic chemotherapy, approximately 20% developed hepatitis from HBV reactivation.[180] An individual who has been vaccinated for HBV typically has the following pattern serologically: negative HBsAg, positive hepatitis B surface antibody (HBsAb), and negative hepatitis B core antibody (HBcAb) serology status.[181] False-negative HBsAg results may occur in chronic liver disease.[182] HBsAb positivity is generally equated with protective immunity, although reactivated HBV disease may occur in the setting of significant immunosuppression in HBcAb-positive individuals.[183]

In patients with B-cell lymphoid malignancies treated with rituximab-containing regimens, HBV reactivation was observed in those with HBcAb positivity (with or without HBsAb positivity), even among those who were HBsAg-negative before initiation of treatment.[53,54] In a recent meta-analysis and evaluation of FDA safety reports concerning HBV reactivation in patients with lymphoproliferative disorders, HBcAb positivity was correlated with increased incidence of rituximab-associated HBV reactivation.[184] In addition, a recent retrospective study showed that allogeneic HSCT recipients who were HBsAg-negative but HBcAb-positive had high risk of seroconversion to HBsAg positivity and HBV reactivation (subsequently leading to hepatitis) after allogeneic HSCT.[185] After allogeneic HSCT, loss of HBV-specific immunity may occur (ie, loss of HBsAb and development of HBsAg and HBV PCR positivity); this was observed in up to 40% of susceptible individuals in one report,[186] and may be confused with hepatic GVHD.

In patients undergoing intensive immunosuppressive therapy, including HSCT, evaluation of HBsAg, HBcAb, and HBsAb should be considered at baseline.[132,181,187] Evaluation of HBV and hepatitis C virus infection should be routine in both HSCT recipients and donors.[187,188] Vaccination against HBV should be strongly considered in HBV-naïve patients

(ie, serology negative for HBsAg, HBsAb, and HBcAb).[132,181] In HBV-naïve patients undergoing allogeneic HSCT, grafts from HBsAg-positive or HBV DNA–positive donors should be avoided wherever possible. Donors who have not been exposed to HBV should be considered for HBV vaccination before stem cell collection. In HBsAg-positive or HBcAb-positive individuals, baseline quantitative PCR for HBV DNA should be obtained. In allogeneic HSCT candidates with evidence of active HBV infection (chronic hepatitis based on biopsy or positive HBV DNA load or high levels of HBsAg), transplant procedures should be delayed where possible, and antiviral therapy should be given for 3 to 6 months before conditioning (see "Prevention of Hepatitis B Virus Reactivation or Disease," page 1418).[132] These patients should continue to undergo surveillance (for monitoring of HBV DNA) and receive antiviral prophylaxis throughout the transplant procedure, and at least 6 to 12 months after transplant or during periods of GVHD.

In HSCT candidates who are HBsAg-positive or HBcAb-positive but without evidence of active HBV replication, antiviral prophylaxis should be considered (starting shortly before the transplant procedure) and continued until 6 to 12 months after transplant or during GVHD (see "Prevention of Hepatitis B Virus Reactivation or Disease," page 1418). In allogeneic HSCT recipients considered at high risk for HBV reactivation (ie, HBsAg-positive recipient or donor, or HBsAg-negative/HBcAb-positive recipient), antiviral prophylaxis with lamivudine has been shown to effectively control HBV reactivation and reduce the risk for developing hepatitis.[189,190] Routine surveillance for HBV DNA and antiviral prophylaxis (or preemptive therapy on detection of high levels of HBsAg or positive HBV DNA load) are recommended in HBsAg-positive or HBcAb-positive patients with hematologic malignancies undergoing immunosuppressive therapy with monoclonal antibodies. Surveillance and possibly antiviral prophylaxis (or preemptive therapy) should be continued for at least 6 to 12 months after the last dose of therapy (see "Prevention of Hepatitis B Virus Reactivation or Disease," on page 1418).[181]

Antiviral prophylaxis with lamivudine has also been shown to reduce the risks for HBV reactivation in HBsAg-positive patients with hematologic malignancies treated with immunosuppressive cyto-

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toxic agents.[176,191,192] In a meta-analysis of clinical trials evaluating the benefit of lamivudine prophylaxis in HBsAg-positive patients with lymphoma treated with immunosuppressive regimens, prophylaxis resulted in significant reductions in HBV reactivation (risk ratio, 0.21; 95% CI, 0.13–0.35) and a trend for reduced HBV-related deaths (risk ratio, 0.68; 95% CI, 0.19–2.49) compared with no prophylaxis.[192] The optimal antiviral strategy in the clinical settings discussed earlier remains unclear. Prophylaxis with lamivudine has been evaluated in both the settings of HSCT and therapy with immunosuppressive agents. Adefovir has been evaluated in combination with lamivudine in patients with lamivudine-resistant HBV infections.[193,194] Tenofovir has shown superior antiviral efficacy compared with adefovir in phase III randomized double-blind studies in patients with chronic HBV infection, and is the preferred agent in this setting[195]; however, limited data are available regarding its use in patient populations with cancer. Entecavir and telbivudine have also been evaluated in randomized open-label studies with adefovir as the comparator arm in patients with chronic hepatitis B, and both agents have shown improved antiviral activity compared with adefovir.[196,197]

Vaccination: The current version of these guidelines does not specifically address vaccination strategies for patients with cancer. Guidelines on the prevention of infections in HSCT recipients (jointly sponsored by the CDC, IDSA, ASBMT, EMBT, among other organization) were published in 2009, which include recommendations for vaccination in the HSCT setting.[198] In addition, the Advisory Committee on Immunization Practices (ACIP) recently updated their recommendations on immunization for adults, including in immunocompromised patients.[96] The following discussion briefly describes the general principles of vaccination in patients with cancer, with a focus on influenza.

Live attenuated viral vaccines have the potential to cause disease in immunocompromised patients. Vaccines that are not live attenuated organisms can be safely administered to this patient population. However, the immunogenicity of the vaccines may be reduced in immunocompromised patients. The potential for protection conferred by antigen-derived vaccines, even if incomplete, is better than no protection if the vaccine is withheld. Persons receiving chemotherapy or radiation thera-py for malignancies should not receive live attenuated vaccines for at least 3 months after therapy has been stopped and until the patient is presumed to be immunocompetent.[199] Certain live viral vaccines can be safely administered to household members of severely immunocompromised patients (eg, measles, mumps, rubella [MMR]), whereas others cannot (eg, small pox vaccine) because of the potential risk of transmission. The package insert for the vaccine should be reviewed before administration.

Ideally, patients should be vaccinated at least 2 weeks before receiving cytotoxic or immunosuppressive therapy; however, this timing is often not feasible in patients with cancer. Administering vaccines on the same day as cytotoxic therapy is not advised, because proliferative lymphocytic responses are required for protective immunity. Immunization between cytotoxic chemotherapy courses is likely to be associated with higher response rates than during chemotherapy administration.[200,201] Patients should be considered unprotected if they were vaccinated fewer than 2 weeks before starting cytotoxic or immunosuppressive therapy or while receiving these agents. These patients should be revaccinated at least 3 months after therapy is discontinued if immune competence has been restored.[199] Pneumococcal, meningococcal, and Hib vaccines should be administered at least 2 weeks before elective splenectomy.[199]

Influenza infections cause significant morbidity and mortality in patients with cancer. Among bone marrow transplant recipients, influenza accounts for 10% to 40% of all community-acquired viral respiratory infections.[202–204] An increased incidence and duration of influenza infections have also been observed in immunosuppressed patients with cancer compared with healthy controls.[205,206] During community outbreaks, influenza infections may represent a significant proportion of episodes of febrile neutropenia.[207] Influenza infections in severely immunocompromised patients with cancer are often associated with hospitalizations, delays in potentially life-saving chemotherapy, and, occasionally, death.[205–207] As a result, annual vaccination against influenza with the inactivated influenza virus is currently recommended for all individuals at increased risk from immunosuppression.[208] The guidelines also include health care professionals and household members or caregivers in their target group for annual immunization because they can transmit influenza to high-risk patients.[208]

The intranasal vaccine (FluMist) should be avoided in patients with immunosuppression, because it contains live attenuated influenza viruses still capable of replication, which could theoretically lead to infection in immunocompromised individuals.[208,209] The CDC recommends that persons with known or suspected immunodeficiency diseases or those receiving immunosuppressive therapies should not be immunized with the live influenza vaccine.[208,209] In addition, because no data are available assessing the risk for person-to-person transmission of FluMist from vaccine recipients to immunosuppressed contacts, the CDC also recommends that inactivated influenza vaccine should be used in household contacts, health care workers, and others who have close contact with immunocompromised patients.[208,209]

HIV Screening in Hospital Settings: In 2006, the CDC published recommendations for routine HIV testing in all patients (13–64 years of age) in the health care setting.[210] The testing is intended to be voluntary, and conducted only with consent from patients. According to these guidelines, patients are informed either verbally or in written format that HIV testing will be conducted unless the patient declines testing (opt-out screening). The CDC recommends that patients at high risk for HIV infection be screened at least annually.[210] The implementation of these guidelines would largely depend on institutional practices and the prevalence of undiagnosed HIV infections in specific institutions.

Prophylaxis for *P jirovecii*

TMP/SMX prophylaxis for *P jirovecii* is highly effective in preventing PCP.[211–214] Studies have documented the efficacy of this prophylactic therapy in patients with ALL and in HSCT recipients. In a systematic review and meta-analysis of 12 randomized studies (N=1245; primarily in patients with acute leukemias or in HSCT recipients), prophylaxis with TMP/SMX resulted in a significant 91% reduction in PCP occurrence compared with placebo, no treatment, or treatment with non-PCP antibiotics (relative risk, 0.09; 95% CI, 0.02–0.32); in addition, TMP/SMX prophylaxis significantly reduced PCP-related mortality (relative risk, 0.17; 95% CI, 0.03–0.94).[211] TMP/SMX also has the potential advantage of activity against other infectious complications (eg, common bacterial infections, listeriosis, nocardiosis, toxoplasmosis) that may afflict patients

with severe T-cell depletion or impairment.[215] TMP/SMX is considered the preferred treatment for PCP prophylaxis (see "Infection Risk in Cancer Patients: High Risk for *Pneumocystis jirovecii*," page 1419). In cases of intolerance, TMP/SMX desensitization should be considered. Daily dapsone and aerosolized pentamidine are thought to be effective alternatives to TMP/SMX, although some data suggest that these agents may be inferior when used prophylactically in allogeneic HSCT recipients.[216–219] Atovaquone seems to be equivalent to dapsone in patients with HIV who cannot tolerate TMP/SMX.[220] In pediatric patients with acute leukemias who were intolerant of TMP/SMX, atovaquone was reported to be an effective strategy for PCP prophylaxis.[221] Thus, atovaquone is another alternative for patients with cancer who require prophylaxis and who are intolerant of TMP/SMX.

Prophylaxis against PCP should be used in allogeneic HSCT recipients (category 1), patients receiving treatment with alemtuzumab,[38] and those with ALL (category 1). Prophylaxis against PCP is also advised in patients receiving concomitant temozolomide and radiotherapy, and should be continued until recovery from lymphocytopenia (see "Infection Risk in Cancer Patients: High Risk for *Pneumocystis jirovecii*," page 1416).[222] Some panel members advise prophylaxis against PCP (category 2B) for patients receiving purine analog therapy (eg, fludarabine, cladribine [2-CdA]) and other T-cell depleting agents, autologous HSCT recipients, and patients with neoplastic diseases receiving intensive corticosteroid treatment (eg, the equivalent of ≥20 mg of prednisone daily for ≥4 weeks).[223–226]

Protected Environments

Although well-designed clinical trials have not validated the use of high-efficiency particulate air (HEPA) filtration, the CDC recommends that allogeneic HSCT recipients be placed in rooms with HEPA filters.[16] Using HEPA filtration for nontransplant patients with prolonged neutropenia is also reasonable. The principal benefit of HEPA filtration is likely to be related to prevention of mold infections. In a retrospective analysis, HEPA filters were protective in highly immunocompromised patients with hematologic malignancies in the setting of an outbreak of aspergillosis.[227] The value of laminar air flow in preventing infections is unclear and not generally recommended.

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Summary

Certain populations of patients with cancer are at increased risk for developing infectious complications during the course of their disease and treatment. Infectious complications remain an important cause of morbidity and mortality in patients undergoing antitumor therapy. The extent of infectious risk is highly dependent on an individual patient's underlying malignancy, degree of neutropenia, past history of infections and exposure to pathogens, treatment with myelosuppressive regimens, and overall immune function status. Patients should therefore be evaluated individually for risk of infection to minimize the occurrence of infection-related complications.

Preventive measures for infection management in patients with cancer include routine surveillance to monitor for early laboratory indications of infection (especially in the context of viral reactivations) and the appropriate use of prophylaxis and/or preemptive therapy with antimicrobial agents in high-risk patient groups. Not all patients with cancer require upfront antimicrobial prophylaxis; prophylactic measures should only be used in patients at increased risk for specific pathogens during the high-risk period to avoid the emergence of resistant pathogens. When selecting antimicrobial agents for prophylaxis and/or preemptive therapy, the local susceptibility and resistance patterns of pathogens should be considered.

These sections of the guidelines provide an overview of the factors associated with risks for infection in patients with cancer, risk categorization, and recommendations for prevention of infections in high-risk patient populations. Individualized risk evaluation for infections and incorporation of preventive measures are essential components of the overall spectrum of cancer care, and can contribute to optimizing treatment outcomes in patients with cancer. The complete version of these guidelines is available online at NCCN.org.

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Individual Disclosures for the NCCN Guidelines Panel for Prevention and Treatment of Cancer-Related Infections					
Panel Member	Clinical Research Support	Advisory Boards, Speakers Bureau, Expert Witness, or Consultant	Patent, Equity, or Royalty	Other	Date Completed
Michael Angarone, DO	None	None	None	None	8/14/12
Lindsey Robert Baden, MD	NIH funded research	None	None	None	7/10/11
William Bensinger, MD	AstraZeneca Pharmaceuticals LP; Bristol-Myers Squibb Company; Celgene Corporation; Genentech, Inc.; Genzyme Corporation; Millennium Pharmaceuticals, Inc.; Novartis Pharmaceuticals Corporation; and Onyx Pharmaceuticals, Inc.	Celgene Corporation; Genzyme Corporation; Millennium Pharmaceuticals, Inc.; and Onyx Pharmaceuticals, Inc.	None	None	4/9/12
Corey Casper, MD, MPH	None	None	None	None	4/10/12
Erik R. Dubberke, MD	Merck & Co., Inc.; and ViroPharma Incorporated	Merck & Co., Inc.; Optimer Pharmaceuticals, Inc.; and sanofi-aventis U.S.	None	None	9/26/11
Alison G. Freifeld, MD	Merck & Co., Inc.; Astellas US LLC; and Vical Incorporated	None	None	None	12/7/11
Ramiro Garzon, MD	None	None	None	None	8/18/12
John N. Greene, MD	None	None	None	None	9/20/12
John P. Greer, MD	None	None	None	None	10/8/12
James I. Ito, MD	Astellas US LLC; and Roche Laboratories, Inc.	Merck & Co., Inc.; Astellas US LLC; Cubist Pharmaceuticals Inc.; Optimer Pharmaceuticals, Inc.; Sigma Tau; and Pfizer Inc.	None	None	9/28/11
Judith E. Karp, MD	None	None	None	None	11/8/11
Daniel R. Kaul, MD	Chimerix, Inc.	None	None	None	8/19/12
Earl King, MD	None	None	None	None	12/3/09
Emily R. Mackler, PharmD	None	None	None	None	10/17/12
Kieren A. Marr, MD	Merck & Co., Inc.; Astellas US LLC; and Pfizer Inc.	Merck & Co., Inc.	None	None	7/18/11
Jose G. Montoya, MD	None	Forest Pharmaceuticals, Inc.; and Gilead Sciences, Inc.	None	None	10/6/11
Ashley Morris-Engemann, PharmD	None	None	None	None	3/5/12
Peter G. Pappas, MD	Merck & Co., Inc.; and Pfizer Inc.	Astellas US LLC	None	None	4/20/10
Ken Rolston, MD	Merck & Co., Inc.	None	None	None	9/23/11
Brahm Segal, MD	Astellas US LLC	Merck & Co., Inc.	None	None	11/9/11
Susan K. Seo, MD	None	None	None	None	10/8/12
Sankar Swaminathan, MD	None	None	Bristol-Myers Squibb Company; Johnson & Johnson; Optimer Pharmaceuticals; and Pfizer Inc.	None	10/13/12

The NCCN guidelines staff have no conflicts to disclose.