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Prevention and Treatment of Cancer-Related Infections, Version 2.2016

Clinical Practice Guidelines in Oncology

Lindsey Robert Baden, MD; Sankar Swaminathan, MD; Michael Angarone, DO; Gayle Blouin, PharmD, BCOP; Bernard C. Camins, MD; Corey Casper, MD, MPH; Brenda Cooper, MD; Erik R. Dubberke, MD; Ashley Morris Engemann, PharmD, BCOP; Alison G. Freifeld, MD; John N. Greene, MD; James I. Ito, MD; Daniel R. Kaul, MD; Mark E. Lustberg, MD, PhD; Jose G. Montoya, MD; Ken Rolston, MD; Gowri Satyanarayana, MD; Brahm Segal, MD; Susan K. Seo, MD; Shmuel Shoham, MD; Randy Taplitz, MD; Jeffrey Topal, MD; John W. Wilson, MD; Karin G. Hoffmann, RN, CCM; and Courtney Smith, PhD

Overview

There is an increased risk of infection in patients with cancer that results in higher morbidity and mortality. In certain instances, the cancer itself can predispose patients to severe or recurrent infections. Neutropenia has been recognized as a major risk fac-

Abstract

Infectious diseases are important causes of morbidity and mortality in patients with cancer. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prevention and Treatment of Cancer-Related Infections characterize the major pathogens to which patients with cancer are susceptible, with a focus on the prevention, diagnosis, and treatment of major common and opportunistic infections. This portion of the guidelines highlights the sections on antifungal and antiviral prophylaxis. Antifungal and antiviral prophylaxis recommendations have expanded over the past few years. New agents for the treatment of fungal infections and incorporation of therapeutic drug monitoring are presented. Antiviral prophylaxis for hepatitis B and management considerations for hepatitis C and HIV have been further developed.

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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

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. **The full NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections are not printed in this issue of *JNCCN* but can be accessed online at NCCN.org.**

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

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Prevention and Treatment of Cancer-Related Infections Panel members can be found on page 913. (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.

tor for the development of infections in patients with cancer receiving chemotherapy. Effective strategies to anticipate, prevent, and manage these infectious complications have led to improved outcomes.[1–12] Because of advances in antimicrobial therapy, it is less common for patients with acute leukemia or those undergoing hematopoietic cell transplantation (HCT) to die of infections during the neutropenic period.

Although neutropenia remains a key risk factor for infections, other immunocompromised states pose at least an equal risk. Patients who have undergone allogeneic HCT with neutrophil recovery and require intensive immunosuppressive therapy (IST) for graft-versus-host disease (GVHD) are an example of non-neutropenic patients at great risk for common bacterial, viral, and opportunistic infections.[13–16] The spectrum of infectious diseases in allogeneic HCT recipients with GVHD is distinct from neutropenia. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prevention and Treatment of Cancer-Related Infections discuss infections in neutropenic and immunocompromised non-neutropenic patients with cancer. In addition to corticosteroids and purine analogs, the increased use of monoclonal antibodies, proteasome inhibitors, and other emerging cancer therapeutics has generated an ever more complex assessment of the immunocompromised patient. The scope of this NCCN Guideline is to address infections that may be seen in all of these immunocompromised populations. This manuscript highlights only a portion of the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections. Please refer to NCCN.org for the complete guidelines.

Text cont. on page 891.

NCCN Prevention and Treatment of Cancer-Related Infections Panel Members

*Lindsey Robert Baden, MD/ChairΦ
Dana-Farber/Brigham and Women's Cancer Center
*Sankar Swaminathan, MD/Vice-ChairΦ
Huntsman Cancer Institute at the University of Utah
Michael Angarone, DOΦÞ
Robert H. Lurie Comprehensive Cancer Center of Northwestern University
*Gayle Blouin, PharmD, BCOPΣ
Massachusetts General Hospital Cancer Center
*Bernard C. Camins, MDΦ
University of Alabama at Birmingham Comprehensive Cancer Center
*Corey Casper, MD, MPHΦ
Fred Hutchinson Cancer Research Center/ Seattle Cancer Care Alliance
*Brenda Cooper, MD†
Case Comprehensive Cancer Center/ University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute
Erik R. Dubberke, MDΦÞ
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine
Ashley Morris Engemann, PharmD, BCOPΣ‡
Duke Cancer Institute
*Alison G. Freifeld, MDΦÞ
Fred & Pamela Buffett Cancer Center
John N. Greene, MDΦÞ
Moffitt Cancer Center
James I. Ito, MDΦÞ
City of Hope Comprehensive Cancer Center
Daniel R. Kaul, MDΦ
University of Michigan Comprehensive Cancer Center
*Mark E. Lustberg, MD, PhDΦ
The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute
Jose G. Montoya, MDΦ
Stanford Cancer Institute
Ken Rolston, MDΦÞ
The University of Texas MD Anderson Cancer Center
Gowri Satyanarayana, MDΦ
Vanderbilt-Ingram Cancer Center
*Brahm Segal, MDΦ
Roswell Park Cancer Institute
*Susan K. Seo, MDΦÞ
Memorial Sloan Kettering Cancer Center
*Shmuel Shoham, MDΦ
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
*Randy Taplitz, MDΦ
UC San Diego Moores Cancer Center
Jeffrey Topal, MDÞ
Yale Cancer Center/Smilow Cancer Hospital
*John W. Wilson, MDΦ
Mayo Clinic Cancer Center

NCCN Staff: Karin G. Hoffmann, RN, CCM, and Courtney Smith, PhD

KEY:

*Discussion Section Writing Committee

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

OVERALL INFECTION RISK IN PATIENTS WITH CANCER[a]	DISEASE/THERAPY EXAMPLES	FEVER & NEUTROPENIA RISK (See FEV-2*)	ANTIMICROBIAL PROPHYLAXIS [d,e,f,g,h,i]
Low	• Standard chemotherapy regimens for most solid tumors • Anticipated neutropenia less than 7 d	Incidence low	• Bacterial - None • Fungal - None • Viral - None unless prior HSV episode
Intermediate	• Autologous HCT • Lymphoma[c] • Multiple myeloma[c] • CLL[c] • Purine analog therapy (ie, fludarabine, clofarabine, nelarabine, cladribine) • Anticipated neutropenia 7–10 d	Incidence usually high, significant variability may exist	• Bacterial - Consider fluoroquinolone prophylaxis • Fungal - Consider prophylaxis during neutropenia and for anticipated mucositis (See INF-2); consider PCP prophylaxis (See INF-6*) • Viral - During neutropenia and longer depending on risk (See INF-3, INF-4, INF-5)
High[b]	• Allogeneic HCT including cord blood • Acute leukemia ▸ Induction ▸ Consolidation • Alemtuzumab therapy • GVHD treated with high-dose steroids (>20 mg daily) • Anticipated neutropenia greater than 10 d	Incidence usually high, significant variability may exist	• Bacterial - Consider fluoroquinolone prophylaxis • Fungal - Consider prophylaxis during neutropenia (See INF-2); consider PCP prophylaxis (See INF-6*) • Viral - During neutropenia and longer depending on risk (See INF-3, INF-4, INF-5)

KEY: CLL = chronic lymphocytic leukemia, GVHD = graft-versus-host disease, HCT = hematopoietic cell transplant, HSV = herpes simplex virus, PCP = *p*neumo*c*ystis *p*neumonia

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

[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 HCT recipients with GVHD.

[c]This is a heterogenous disease. Therefore, treatment modalities and the type of malignancy affect risk level.

[d]Pneumocystis prophylaxis (See INF-6*).

[e]See Antibacterial Agents (FEV-A*) for dosing, spectrum, and specific comments/cautions.

[f]See Antifungal Agents (FEV-B*) for dosing, spectrum, and specific comments/cautions.

[g]See Antiviral Agents (FEV-C*) for dosing, spectrum, and specific comments/cautions.

[h]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.

[i]For patients who are intolerant to fluoroquinolone, consider TMP/SMX.

OVERALL INFECTION RISK IN PATIENTS WITH CANCER[a]	DISEASE/THERAPY EXAMPLES	ANTIFUNGAL PROPHYLAXIS[f,l]	DURATION
INTERMEDIATE TO HIGH	ALL	Consider: • Fluconazole[m] or Micafungin • Amphotericin B products[n] (category 2B)	Until resolution of neutropenia
	MDS (neutropenic) AML (neutropenic)	Consider: • Posaconazole[m] (category 1) • Voriconazole[m], Fluconazole[m], Micafungin, or Amphotericin B products[n] (all category 2B)	
	Autologous HCT with mucositis[j]	Consider: • Fluconazole[m] or Micafungin (both category 1)	
	Autologous HCT without mucositis	Consider no prophylaxis (category 2B)	
	Allogeneic HCT (neutropenic) See Antipneumocystis Prophylaxis (INF-6*)	Consider: • Fluconazole[m] or Micafungin (both category 1) • Voriconazole[m], Posaconazole[m], or Amphotericin B product[n] (all category 2B)	Continue during neutropenia and for at least 75 d after transplant
	Significant GVHD[k] See Antipneumocystis Prophylaxis (INF-6*)	Consider: • Posaconazole[m] (category 1) • Voriconazole[m], Echinocandin, Amphotericin B products[n] (all category 2B)	Until resolution of significant GVHD

KEY: ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, MDS = myelodysplastic syndromes, GVHD = graft-versus-host disease, HCT = hematopoietic cell transplant, HSV = herpes simplex virus

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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 Antifungal Agents (FEV-B*) for dosing, spectrum, and specific comments/cautions.

[j]Mucositis is a risk factor for candidemia in patients with hematologic malignancies and hematopoietic cell transplant recipients not receiving antifungal prophylaxis.

[k]Consider antifungal prophylaxis in all patients with GVHD receiving immunosuppressive therapy (IST).

[l]There is substantial variability in practice among NCCN Member Institutions. Physicians need to take into account local susceptibility patterns.

[m]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 (eg, vincristine).

[n]A lipid formulation is generally preferred based on less toxicity.

PREVENTION OF HERPES SIMPLEX VIRUS (HSV) AND VARICELLA ZOSTER VIRUS (VZV) REACTIVATION OR DISEASE[o]

OVERALL INFECTION RISK IN PATIENTS WITH CANCER[a]	DISEASE/THERAPY EXAMPLES	VIRAL INFECTION or REACTIVATION	ANTIVIRAL PROPHYLAXIS	MINIMUM DURATION[g]
Low	• Standard chemotherapy regimens for solid tumors	HSV	None unless prior HSV episode	During active therapy including periods of neutropenia
Intermediate	• Autologous HCT • Lymphoma[c] • Multiple Myeloma[c] • CLL[c] • Purine analog therapy (eg, fludarabine)	HSV VZV	Acyclovir Famciclovir Valacyclovir	HSV prophylaxis • Consider during active therapy and possibly longer depending on degree of immunosuppression VZV prophylaxis • Consider for at least 6–12 months after autologous HCT
High	• Acute leukemia ▸ Induction ▸ Consolidation	HSV	Acyclovir Famciclovir Valacyclovir	HSV prophylaxis during active therapy including periods of neutropenia
	• Proteasome inhibitors	VZV	Acyclovir Famciclovir Valacyclovir	VZV prophylaxis during active therapy including periods of neutropenia
	• Alemtuzumab therapy • Allogeneic HCT • GVHD requiring steroid treatment	HSV VZV	Acyclovir Famciclovir Valacyclovir	HSV prophylaxis • Minimum of 2 mo after alemtuzumab and until CD4 ≥200 cells/mcL VZV prophylaxis • Prophylaxis should be considered for at least 1 y after allogeneic HCT

KEY: CLL = chronic lymphocytic leukemia, CMV = cytomegalovirus, GVHD = graft-versus-host disease, HBV = hepatitis B virus, HCT = hematopoietic cell transplant

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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.

[c]This is a heterogenous disease. Therefore, treatment modalities and the type of malignancy affect risk level.

[g]See Antiviral Agents (FEV-C*) for dosing, spectrum, and specific comments/cautions.

[o]For CMV antiviral prophylaxis, see INF-4. For HBV, HCV, and HIV antiviral prophylaxis, see INF-5.

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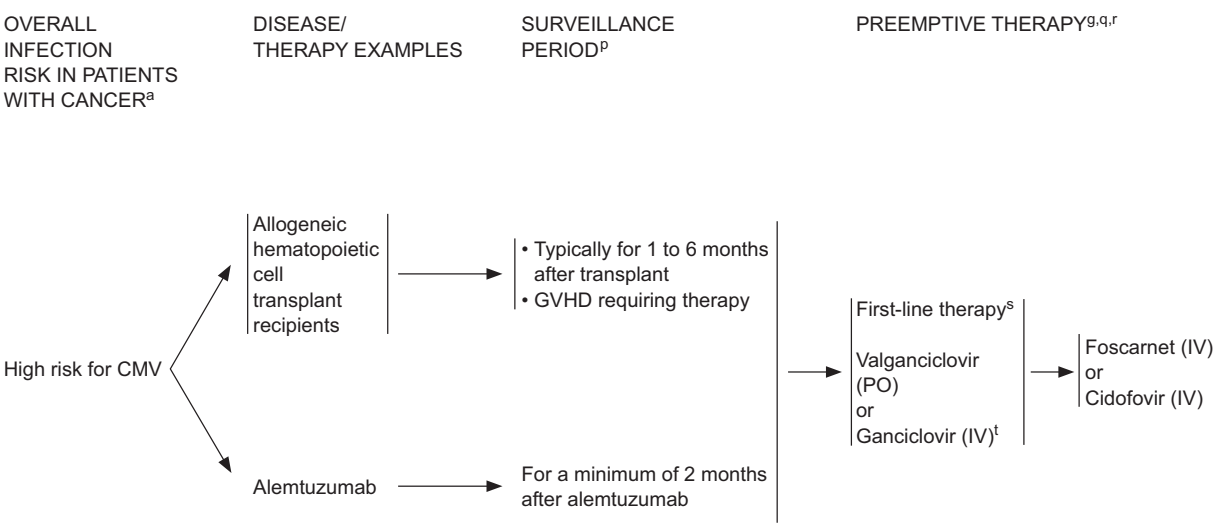
PREVENTION OF CYTOMEGALOVIRUS (CMV) REACTIVATION OR DISEASE



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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.

[g]See Antiviral Agents (FEV-C*) for dosing, spectrum, and specific comments/cautions.

[p]CMV surveillance consists of at least weekly monitoring by PCR.

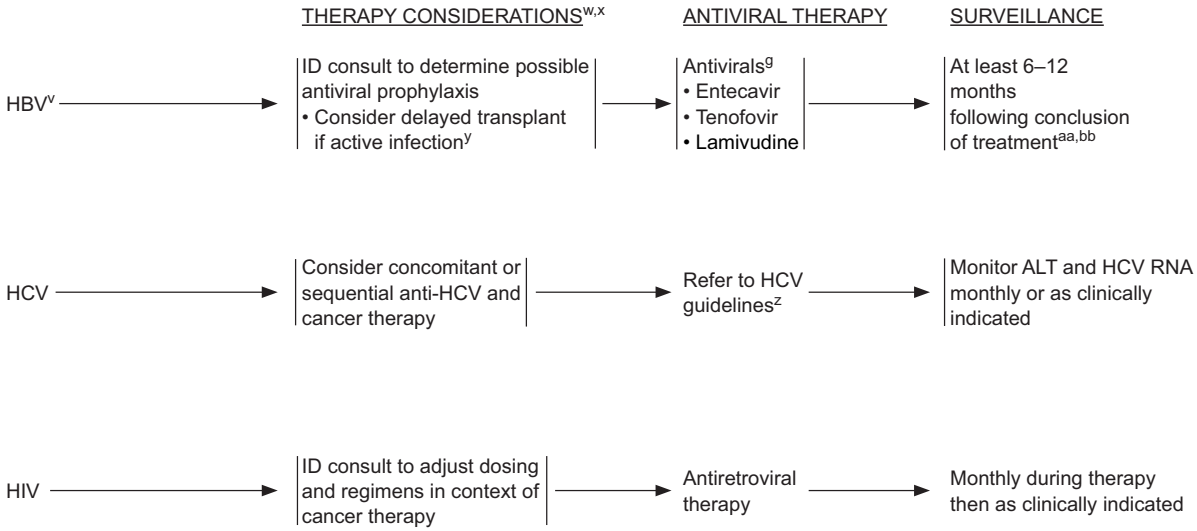
[q]Preemptive therapy is defined as administration of antiviral agents to asymptomatic patients at high risk for clinical infection based on laboratory markers of viremia. Duration of antiviral therapy generally is for at least 2 weeks and until CMV is no longer detected.

[r]Clinicians should measure for end-organ disease and tailor duration of preemptive therapy accordingly.

[s]Typically therapy is initiated with oral valganciclovir unless there are absorption or toxicity issues and would be continued at a minimum until a negative PCR. However, some centers prefer ganciclovir over valganciclovir.

[t]Foscarnet or cidofovir should be used for cases of ganciclovir-resistant CMV or when ganciclovir is not tolerated (eg, ganciclovir-induced myelosuppression).

PREVENTION OF HEPATITIS B VIRUS (HBV), HEPATITIS C VIRUS (HCV), AND HUMAN IMMUNODEFICIENCY VIRUS (HIV) REACTIVATION OR DISEASE[u]



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

[g]See Antiviral Agents (FEV-C*) for dosing, spectrum, and specific comments/cautions.

[u]Any patient who is expected to receive IST or chemotherapy should be screened for HBV, HCV, and HIV prior to treatment. Other patients at high risk of developing infection should also be screened. See Discussion for other high-risk groups.

[v]High risk of HBV is defined as patients with HBsAg+ serology or with prior resolved HBV infection (HBsAg-, HBsAb+, HBcAb+ serology) or with increasing HBV viral load planned for allogeneic HCT or anti-CD20, anti-CD52 monoclonal antibody therapy.

[w]Diagnostic monitoring and treatment for HBV, HCV, and HIV are an evolving field; consultation with an infectious disease expert or hepatologist should be sought in the management of all patients with reactivation or disease.

[x]Drug interactions may complicate therapies. Consultation is recommended.

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

[z]Therapy should be given by provider experienced in Hepatitis C. See American Association for the Study of Liver Diseases/Infectious Diseases Society of America HCV Guidelines.

[aa]If viral load is consistently undetectable, treatment is considered prophylactic. If viral load fails to drop or previously indetectable PCR becomes positive, consult hepatologist and discontinue anti-CD20 antibody therapy.

[bb]Duration of therapy may depend on various factors. The risk of reactivation continues after rituximab treatment is concluded and is increased if treatment is halted too early.

GENERAL RECOMMENDATIONS FOR VACCINATION IN PATIENTS WITH CANCER

- General comment: Live viral vaccines should NOT be administered during chemotherapy.
- Influenza vaccination[gg]: Patients with hematologic or solid tumor malignancies should receive inactivated influenza vaccine annually.
- Pneumococcal vaccination[gg]: The conjugate pneumococcal vaccine (PCV13) should be administered to newly diagnosed adults with cancer who are pneumococcal vaccine-naïve, followed by the polysaccharide pneumococcal vaccine (PPSV23) at least 8 weeks later. Subsequent doses of PPSV23 should follow current PPSV23 recommendations for adults at high risk. For patients who have previously received PPSV23, the PCV13 dose should be given at least 1 year after the last PPSV23 dose. For those who require additional doses of PPSV23, the first such dose should be given no sooner than 8 weeks after the PCV13 dose.
- Meningococcal vaccination[gg]: The addition of serogroup B meningococcal vaccination has been recommended for patients at increased risk for meningococcal disease. These at-risk patients include those with persistent complement component deficiencies or taking eculizumab or patients with anatomic or functional asplenia. Depending on the vaccine, it is available in a 2-dose or 3-dose series.
- Human Papillomavirus (HPV) vaccination[gg]: The recombinant 3-dose HPV vaccine should be offered to patients up to 26 years of age.

[gg]Vaccination should be deferred in patients who are unlikely to respond (eg, receipt of anti-B-cell antibodies within 6 months, induction and consolidation chemotherapy for acute leukemia).

RECOMMENDED VACCINATION SCHEDULE AFTER AUTOLOGOUS OR ALLOGENEIC HCT

Inactivated Vaccines[hh]	Recommended Timing After HCT	Number of Doses
DTaP (Daptacel = Diphtheria/Tetanus/Acellular Pertussis)	6–12 mo	3
Haemophilus influenzae type b (Hib)	6–12 mo	3
Pneumococcal vaccination • Conjugated 13-valent vaccine • Upon completion of PCV13 series, then Pneumococcal polysaccharide vaccine 23	6–12 mo ≥12 mo	3 1
Hepatitis A[ii] (Hep A)	6–12 mo	2
Hepatitis B[ii] (Hep B)	6–12 mo	3
Meningococcal conjugate vaccine[jj]	6–12 mo	1–2
Influenza (injectable)	4–6 mo	1, annually[mm]
Inactivated Polio vaccine	6–12 mo	3

Live Vaccines		
Measles/Mumps/Rubella (MMR)[kk]	≥24 mo (if no GVHD or ongoing immunosuppression and patient is seronegative for measles, mumps, and/or rubella)	1–2
Varicella vaccine[kk]	≥24 mo (if no GVHD or ongoing immunosuppression and patient is seronegative for varicella)	1
Zoster vaccine[kk,ll] (category 3)	May be considered at ≥24 mo (if no GVHD or ongoing immunosuppression)	1

[hh]Inactivated vaccines may be given together at the same time. Vaccination may be postponed for patients receiving >20 mg of prednisone.

[ii]Strongly consider if clinically indicated. May consider Hep A and B combined vaccine if immunization for both is needed.

[jj]Meningococcal B vaccine should be considered for high-risk patients such as patients with asplenia or complement deficiency or patients receiving eculizumab.

[kk]Give MMR and varciella/zoster vaccine together or 4 weeks apart.

[ll]Because of insufficient data on safety and efficacy of zoster vaccine among HCT recipients, physicians should assess the immune status of each recipient on a case-by-case basis and determine the risk for infection before using the vaccine.

[mm]Use of live virus vaccine is contraindicated.

Cont. from page 883.

Prevention of Infectious Diseases

Preventive measures against infections in patients with cancer include upfront prophylaxis or preemptive therapy using broad spectrum antimicrobial agents directed against the most common infecting pathogens (eg, bacterial, viral, and fungal) in patients who are at high risk (see INF-1; page 884). Vaccination and minimization of potential exposures to opportunistic pathogens, which may be harmful to patients who are immunocompromised due to cancer, are additional components of infectious diseases prevention.

Antifungal Prophylaxis

Antifungal prophylaxis should not be used routinely in all 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 HCT.[17] Selection of an antifungal agent is determined by the disease or therapy and includes azoles, amphotericin B products, and echinocandins (see INF-2; page 885).

Azoles: Azoles are among the most commonly used medications for the prevention and treatment of fungal infections. Early generation azoles such as ketoconazole and itraconazole are less commonly used because of toxicity, drug interactions, and limited spectrum of activity. First generation triazoles (ie, fluconazole) are widely used because of their low cost and minimal toxicity but are limited by increasing resistance among Candida species and lack of activity against most molds. Several second generation triazoles have been developed in recent years. These drugs extend the spectrum of activity of triazoles to include potent activity against many molds (importantly, activity differs within the class), but they can also have complicated drug interactions and distinct toxicities and remain extremely costly with extended use.

Fluconazole prophylaxis has been shown to effectively decrease fungal colonization, invasive infection, and fungal infection–related mortality in nontransplant patients with leukemia and in autologous HCT recipients in a placebo-controlled trial.[18] The benefit of fluconazole prophylaxis was greatest in autologous HCT recipients not receiving colony-stimulating growth factor support and in those with leukemia receiving mucotoxic regimens consisting of cytarabine plus anthracycline.[18] In neutropenic allogeneic HCT recipients, prophylactic fluconazole controlled yeast colonization and decreased the rate of mucosal candidiasis and invasive Candida infections.[19,20] A decrease in mortality was noted in one study in which most of the patients were allograft recipients.[20] Fluconazole conferred significant long-term improvement in survival, possibly by decreasing Candida antigen–induced gastrointestinal tract GVHD.[21] 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.[22,23]

Prophylaxis with voriconazole was compared with fluconazole in a large randomized double-blind study that included serum galactomannan surveillance in allogeneic HCT recipients (N=600).[24] Patients were randomized to receive the study drugs for 100 or 180 days in the higher-risk cohort of patients. 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%) was noted in the voriconazole arm, although the differences were not statistically significant. No differences in relapse-free and overall survival rates and incidence of severe adverse events were observed between treatment arms.[24]

Posaconazole is equally effective compared with fluconazole as primary therapy for oropharyngeal candidiasis;[25] however, it has not been evaluated as primary therapy for invasive fungal infections. In a multicenter randomized trial, prophylaxis with posaconazole in neutropenic patients with acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) receiving induction or reinduction chemotherapy, significantly reduced the rate of invasive fungal infections during the treatment period (2% vs 8%; $P<.001$) and during the 100 days after randomization (5% vs 11%; $P=.003$), reduced the incidence of invasive aspergillosis (1% vs 7%; $P<.001$), and was associated with a significant survival benefit ($P=.04$) versus the fluconazole/itraconazole arm.[26] Data from a prospective randomized study showed that posaconazole was as effective as prophylaxis in

allogeneic HCT recipients with severe GVHD and reported reduced incidence of invasive aspergillosis and overall invasive fungal infections compared with those receiving fluconazole.[27]

Isavuconazole was approved in March 2015 for the treatment of invasive aspergillosis and invasive mucormycosis.[28] It should be noted that isavuconazole is dosed as the prodrug isavuconazonium to achieve improved delivery. A phase III randomized trial comparing isavuconazole with voriconazole for the primary treatment of invasive aspergillosis and other filamentous fungi showed the noninferiority of isavuconazole compared with voriconazole (19% vs 20%; adjusted difference –1.0%; 95% CI, –7.8 to 5.7).[29] Treatment-emergent adverse events were similar between isavuconazole and voriconazole (96% vs 98%; *P*=.122) with gastrointestinal disorders and infections or infestations being the most common. Isavuconazole demonstrated a lower incidence of hepatobiliary disorders, eye disorders, and skin or subcutaneous tissue disorders. Drug-related adverse events were also lower for isavuconazole compared with voriconazole (42% vs 60%; *P*<.001). Data are emerging for the clinical activity of isavuconazole regarding invasive aspergillosis and mucormycosis.

Toxicities and Drug–Drug Interactions: Experience to date suggests that fluconazole and posaconazole are generally well-tolerated, and serious adverse events are rare (primarily liver toxicity). Toxicities for voriconazole include neurologic and ophthalmic adverse events that may be associated with renal toxicity because of the accumulation of the solvent vehicle sulphobutylether beta cyclodextrin sodium contained within the intravenous formulation. There are emerging data to suggest that longer-term use of voriconazole may be associated with severe photosensitivity and other adverse events including cutaneous malignancies, elevated serum fluoride levels, and periosteitis. Itraconazole may be associated with hepatic toxicity and gastrointestinal intolerance,[30] and 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 are associated with hyperbilirubinemia and nephrotoxicity during the early transplant period.[31] Fluconazole, itraconazole, posaconazole, and voriconazole may cause QTc prolongation. Conversely, isavuconazole has been associated with dose-dependent QTc shortening in healthy individuals.[28] In a clinical trial treating patients with invasive mold infections with isavuconazole, 7.5% (17/257) showed QTc shortening.[32]

Azole-associated drug–drug interactions are common clinical occurrences. Both the addition and withdrawal of azoles can result in either increased uptake of these other drugs or subtherapeutic exposure and potential transplant rejection or GVHD. Several studies show the interaction of azoles with hepatic enzymatic pathways. Administration of itraconazole with medications metabolized by the 3A4 isoenzyme can increase plasma concentrations causing QTc prolongation and ventricular tachyarrhythmias.[33,34] These findings reinforce a note of caution about itraconazole (and by extension, fluconazole, voriconazole, and posaconazole), with regard to potential serious drug–drug interactions through inhibition of the cytochrome P450 3A4 isoenzyme. Additionally, fluconazole and voriconazole have shown inhibition of CYP2C9 and CYP2C19 enzymes and high interpatient variability of genetic CYP2C19 polymorphisms that may also affect dosing.

The potential for QTc prolongation is a concern exacerbated by the combination of azoles and other drugs (eg, fluoroquinolones, macrolides, ondansetron) and with some chemotherapies (eg, nilotinib for chronic myelogenous leukemia, panobinostat for myeloma). Itraconazole and posaconazole are also known inhibitors of gastric P-glycoprotein, which can increase systemic levels of drugs affected by this transport system. The list of drug–drug interactions is expansive and continues to grow. Although azoles may be necessary for antifungal therapy, they should only be incorporated after consultation with an infectious diseases expert.

Therapeutic Drug Monitoring of Azoles: Therapeutic drug monitoring (TDM) for the pharmacokinetic evaluation of antifungal agents provides guidance for achieving adequate plasma drug concentration while reducing toxicity. This is an area of active research, though clinical use is limited by the need for optimization of methods and training of personnel regarding interpretation of results. As a result, these tests generally require sending samples to a reference laboratory thereby increasing wait time for results. The support of an infectious diseases consultant is recommended to address the multiple variables that may affect TDM.

TDM should be considered for patients receiving triazoles; there is no current evidence to support the use of TDM for the evaluation of polyenes or echinocandins. Fluconazole and isavuconazole are the 2 triazoles that do not require TDM. Fluconazole has linear pharmacokinetics that eliminates the need for TDM,[35–39] though patients in renal failure should receive a modified dose.[40] Studies intended to define a therapeutic range for isavuconazole have not been performed, thus TDM is not currently recommended for isavuconazole. TDM should be considered for posaconazole, itraconazole, and voriconazole. Variability of therapeutic drug levels may be affected by the route of drug administration, timing of monitoring, location of the infection, and intrinsic patient factors (ie, age, weight).

There are 3 formulations of posaconazole: oral suspension, delayed-release tablet, and intravenous solution. Pharmacokinetic studies with the oral suspension of posaconazole in healthy individuals showed that administration with or after a high-fat meal, or with any meal or nutritional supplement, greatly enhanced its absorption up to 400%.[41,42] The plasma concentration of posaconazole can be reduced by proton pump inhibitors due to the increase in gastric pH when given orally.[41] Subtherapeutic concentrations and breakthrough fungal infections have been reported.[43,44] As reported by Brüggemann et al,[45] a substantial list of drug interactions with azole antifungal drugs can result in subtherapeutic effects or toxicity. The recent approval of the tablet formulation of posaconazole has improved absorption and demonstrates a more predictable bioavailability.[42] Gastric pH does not affect plasma concentration of extended-release posaconazole,[46] nor does it have the same interaction with proton pump inhibitors or metoclopramide.[47] The intravenous formulation has also shown similar pharmacokinetics and safety compared with the extended-release tablet.[48] A target concentration of posaconazole for prophylactic TDM of greater than 0.7 mcg/mL is supported by individual studies[44,49,50] and by 2 phase III studies[26,27]; however, doses as low as 0.5 mcg/mL have been reported as effective.[44,50-54] TDM may not be necessary when the extended-release tablet or intravenous formulation is used in the prophylactic setting, because data indicate that a dose of 300 mg/d results in at least 0.5 mcg/mL in more than 95% of patients. Treatment of an established infection is recommended to have a trough concentration greater than 1 mcg/mL, with potentially higher doses based on the pathogen resistance.[55,56]

Studies of itraconazole demonstrate a significant rate of breakthrough infections when plasma drug concentrations are less than 1 mcg/mL[57,58]; however, increased mortality was observed at plasma drug concentrations greater than 0.5 mcg/mL.[59,60] Targeting a lower itraconazole plasma concentration for prophylaxis and a higher dose may be beneficial if an active infection is being. Studies suggest that trough concentrations of itraconazole between 1 and 2 mcg/mL have shown the best therapeutic responses for invasive infections,[61–64] although a trough concentration of greater than 0.5 mcg/mL may be sufficient for prophylaxis. Currently, an upper limit of 17 mcg/mL measured by bioassay has been suggested,[65] but studies for the upper limit have not been extensive. Itraconazole should be given either 1 hour before or 1 hour after meals based on the 43% increase in bioavailability in patients who fasted.[66]

Target voriconazole trough values between 0.5 and 2 mcg/mL have been proposed in clinical studies.[67–74] Although 0.5 mcg/mL is a suggested target for prophylaxis, a higher range of 1 to 2 mcg/mL may be necessary for active disease and for patients with disease that has a poor prognosis. Higher concentrations may also benefit immunocompromised patients by reducing breakthrough infection.[75,76] Trough concentrations of 4 mcg/ml or greater have correlated with toxicity in various studies.[67,71,74,77–81] Voriconazole bioavailability was lowered by approximately 22% when taken with food and by 34% when taken with a high-fat meal.[82,83] Therefore, voriconazole should be given either 1 hour before or 1 hour after meals.

Studies have shown a general consensus regarding a minimal level of plasma concentration necessary for the triazoles, though the lack of prospective studies has limited the adoption of formal monitoring standards. The British Society for Medical Mycology has published their guidelines for the use of TDM of antifungal agents based on available literature.[84] These guidelines provide recommendations similar to those proposed by Andes et al.[85] Consideration of TDM is recommended by the NCCN panel in conjunction with involvement of an infectious diseases expert.

Amphotericin B Formulations: Amphotericin B formulations are broad spectrum antifungal agents that have activity through disruption of the fungal cell

wall synthesis and subsequent development of pores in the membrane leading to cell death. The original formulation, amphotericin B deoxycholate, was associated with dose-limiting toxicities including infusion-related reactions and nephrotoxicity. Three lipid-associated formulations, amphotericin B lipid complex, liposomal amphotericin B (L-AmB), and amphotericin B colloidal dispersion, have since been developed to have a reduced toxicity.

Low-dose amphotericin B formulations have been studied in high-risk patients and have been shown to provide protection against invasive molds, although no survival benefit in randomized studies was seen when compared with fluconazole.[30,86,87] Based on the toxicity of amphotericin B products and the availability of safer and equally effective alternative agents, amphotericin B products are 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. Use of the lipid formulation is particularly important for patients at high risk for renal failure, such as those with preexisting renal disease, HCT recipients, and those who are concurrently receiving other nephrotoxic agents.[88,89]

Aerosolized delivery of amphotericin B products has been considered for several years, with the advantage of local delivery to the lungs while simultaneously avoiding systemic toxicity. A recent randomized placebo-controlled trial found that aerosolized L-AmB was useful for preventing invasive pulmonary aspergillosis in patients with prolonged neutropenia.[90] Limitations for the use of aerosolized amphotericin B for prophylaxis relate to the variability of this treatment because of different nebulizers and amphotericin B formulations, the lack of dosing optimization, and a dearth of direct comparative data with systemically administered mold-active azoles or echinocandins.[91]

Echinocandins: Echinocandins are a class of antifungal agents that disrupt the integrity of the fungal cell wall through noncompetitive inhibition of β-(1,3)-D-glucan synthase, a component specific to the cell wall of many fungi. Echinocandins have fungicidal activity against Candida species and are fungistatic towards Aspergillus species. Combination therapy with amphotericin B or triazoles has been proposed to improve activity against molds, however clinical evidence for this remains limited. Advantages of this family of antifungals are the relatively low toxicity profiles and limited drug–drug interactions. Though echinocandins demonstrate activity against Candida species that are resistant to other antifungal agents,[92] there is limited or no activity against dimorphic fungi. Three echinocandins are approved for use: caspofungin, micafungin, and anidulafungin. All 3 agents are approved for the treatment of esophageal candidiasis. Caspofungin and anidulafungin have additional indications for the treatment of candidemia and other infections caused by Candida species. Caspofungin is indicated for the treatment of candidal pleural space infections, empiric treatment of fungal infections in patients with neutropenia, and treatment of invasive aspergillosis in patients who are refractory to or intolerant of other antifungal agents. Micafungin has the additional indication for prophylaxis of candidal infections in patients receiving HCT.

Caspofungin was evaluated in a double-blind study including 128 patients with esophageal candidiasis.[93] Patients received either caspofungin or amphotericin B deoxycholate. Two doses of caspofungin were evaluated (50 mg or 70 mg intravenously, once daily), with a greater response observed in the patients on the higher dose (96% vs 85%). Both groups treated with caspofungin had a better response than patients receiving amphotericin B (78%). At 2-week follow-up, a greater percentage of patients remained negative for candidiasis with the caspofungin treatment (89% in the 70 mg group, 74% in the 50 mg group, and 63% in the amphotericin B group). Furthermore drug-related adverse events were lower with caspofungin (7%, 4%, and 24%, respectively). Several studies have evaluated the role of caspofungin in the treatment of invasive aspergillosis in patients refractory to or intolerant of other antifungals, supporting its recommendation in this capacity.[94,95]

Micafungin is an echinocandin approved for prophylaxis against Candida infections in patients undergoing HCT.[96] In a randomized double-blind trial of autologous and allogeneic HCT recipients, the success rate with micafungin was superior to 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 treatment period, and absence of proven or prob-

able infection during the 4-week posttreatment period).[97] The duration of this study 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 there was a trend for fewer episodes of invasive aspergillosis in allogeneic HCT recipients receiving micafungin. Survival and drug-related toxicity were similar between treatment arms.[97] Micafungin has shown activity in the treatment of aspergillosis in patients refractory to or intolerant of other antifungal agents.[98–100]

Anidulafungin has been shown to be an effective antifungal agent against Candida infection in several studies. A randomized double-blind study in 601 patients with esophageal candidiasis demonstrated noninferiority of intravenous anidulafungin to oral fluconazole (97.2% vs 98.8%, respectively) and lower rates of adverse effects (9.3% vs 12.0%) and recurring infections at 2-week follow-up (64.4% vs 89.5%).[101] In a smaller study of 19 patients with triazole-refractory mucosal candidiasis, anidulafungin treatment resolved infection in 18 patients.[102] A larger phase III trial similarly showed superiority of anidulafungin compared with fluconazole in the treatment of candidemia and invasive candidiasis (75.6% vs 60.2%).[103] Response at 2-week follow-up was 64.6% in the anidulafungin group compared with 49.2% in the fluconazole group.

NCCN Recommendations for Antifungal Prophylaxis: CYP3A4 inhibition by azoles can lead to toxicity when administered with several classes of drugs used in cancer therapy, including proteasome inhibitors, tyrosine kinase inhibitors, and vinca alkaloids. Thus, mold-active azoles should be stopped several days before the potential interacting drug is given. These azoles should also not be started until the other agent has been discontinued and sufficient time has elapsed for the drug to be eliminated. Because of variations in drug pharmacokinetics, firm recommendations regarding a minimum time from drug discontinuation to azole administration cannot be made. Consultation with pharmacology and infectious diseases experts is recommended.

The NCCN Guidelines Panel recommends posaconazole (category 1 recommendation) for antifungal prophylaxis in neutropenic patients with AML and MDS receiving induction or reinduction chemotherapy (see INF-2; page 885).[17] The role of antifungal prophylaxis in patients with acute leukemia receiving consolidation chemotherapy has not been adequately evaluated. Voriconazole, fluconazole, micafungin, or amphotericin B products are all category 2B recommendations in this disease setting. Antifungal prophylaxis should be continued until resolution of neutropenia.

In patients receiving autologous HCT with mucositis, antifungal prophylaxis with fluconazole or micafungin (both category 1) is recommended until resolution of neutropenia. No prophylaxis is recommended in autologous HCT recipients without mucositis.

The NCCN Guidelines Panel recognizes that strong evidence exists for the use of fluconazole or micafungin as prophylaxis in neutropenic allogeneic HCT recipients (category 1) (see INF-2; page 885).[17] However, it should be noted that fluconazole use can predispose patients to colonization and bloodstream infection by fluconazole-resistant Candida strains.[104,105] Posaconazole as prophylaxis has not been evaluated during the neutropenic period after conditioning in allogeneic HCT recipients, and thus the safety of this approach is unknown. Drug–drug interactions during conditioning for HCT, specifically with posaconazole or voriconazole, complicate treatment of fungal infections in these patients. Prophylaxis may need to be tailored after consultation with an infectious diseases expert. Posaconazole, voriconazole, and amphotericin B products are all considered category 2B recommendations. Antifungal prophylaxis should be considered until at least day 75 after allogeneic HCT (see INF-2; page 885).[17,21]

Although many centers reasonably use antifungal prophylaxis in non-neutropenic allogeneic HCT recipients with GVHD, this practice was only evaluated in a single properly designed study. In the prospective, randomized, double-blind study, posaconazole was compared with fluconazole as prophylaxis in allogeneic HCT recipients with severe GVHD requiring intensive IST.[27] Grade II to IV GVHD, chronic extensive GVHD, or intensive IST consisting of either high-dose corticosteroids, antithymocyte globulin, or a combination of 2 or more immunosuppressive agents or types of treatment were inclusion criteria. Prophylaxis with posaconazole resulted in reduced incidences of invasive aspergillosis, total invasive fungal infections while on treat-

ment, and deaths attributed to fungal infection.[27] Posaconazole is recommended (category 1) as prophylaxis in patients with GVHD receiving intensive IST, as defined by the inclusion criteria in this trial. Prophylactic posaconazole can be considered in all patients with GVHD receiving IST (category 1), although the benefit/risk ratio of mold-active prophylaxis in patients receiving less intensive IST has not been established. Voriconazole, echinocandins, and amphotericin B products are all category 2B recommendations.

Patients with chronic severe neutropenia (absolute neutrophil count <500 neutrophils/mcL) due to the underlying disease (eg, aplastic anemia) are at substantial risk for invasive aspergillosis.[106] 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).

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[107] or with invasive filamentous fungal infection[108] during subsequent cycles of chemotherapy or HCT. In those with invasive aspergillosis before HCT, antifungal therapy for more than a month and resolution of radiologic abnormalities correlate with a lower likelihood of posttransplant recurrence of infection.[109] Secondary prophylaxis with a mold-active agent is advised for the entire period of immunosuppression.

Antiviral Prophylaxis and Preemptive Antiviral Therapy

Herpes Simplex Virus: Herpes simplex virus (HSV) is an important pathogen in patients who develop neutropenia and mucositis. 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 HCT recipients and patients (without prophylaxis) with acute leukemia undergoing induction or reinduction therapy who are seropositive for HSV.[110–112] Among allogeneic HCT recipients, HSV disease is most likely to occur within the first month posttransplant, but may occur in later stages during intense immunosuppression.[113,114] Although disseminated HSV infection is uncommon, infection from viral reactivation is frequently associated with increased mucosal damage, resulting in increased pain, limited ability to maintain oral hydration and nutrition, and an increased risk of bacterial and fungal superinfections.

NCCN Recommendations for HSV Prophylaxis: Antiviral prophylaxis against HSV is advised during the period of neutropenia in HSV-seropositive patients who are receiving chemotherapy (induction or consolidation) for acute leukemia, and during neutropenia and possibly longer in allogeneic and autologous HCT recipients depending on the degree of immunosuppression (see INF-3, page 886). A longer period of prophylaxis should be considered in allogeneic HCT recipients with GVHD or with frequent HSV reactivations before transplantation.[16] Acyclovir, famciclovir, or valacyclovir are the initial agents of choice for HSV prophylaxis.[17,115] Foscarnet is typically reserved for patients with acyclovir-resistant HSV infection.[17,115] In patients receiving antiviral prophylaxis with ganciclovir or foscarnet for prevention of cytomegalovirus (CMV) reactivation, additional prophylaxis with acyclovir is not necessary given that these agents are active against HSV.[115]

HSV and herpes zoster infections are common in patients with chronic lymphocytic leukemia (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 and until CD4+ cell counts are 200 cells/mcL or more.[116,117]

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 HSV reactivation requiring treatment, the panel recommends HSV prophylaxis for that patient during all future episodes of neutropenia induced by cytotoxic therapy.

Varicella Zoster Virus: Impaired cellular immunity is the principal risk factor for varicella zoster virus (VZV) disease. In allogeneic HCT recipients with a history of VZV infection, approximately 30% have reactivation of VZV disease without antiviral prophylaxis.[118] In patients with a history of chicken pox, oral acyclovir administered from 1 to 2 months until

1 year after allogeneic HCT significantly decreased the incidence of VZV disease compared with placebo (5% vs 26%, respectively).[118] The frequency of VZV disease in the postprophylactic period was similar between 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 HCT. Patients who received anti-VZV prophylaxis with acyclovir or valacyclovir for 1 year post-HCT had significantly reduced 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.[119] Long-term (1 year postallogeneic HCT) 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.[120,121]

NCCN Recommendations for VZV Prophylaxis: The NCCN Guidelines Panel recommends prophylaxis against VZV for at least 1 year after allogeneic HCT in patients seropositive for VZV pretransplant (see INF-3, page 886), and recommends considering the extension of prophylaxis in patients who continue to receive systemic IST. Although higher doses are necessary, the same agents used as HSV prophylaxis are also active against VZV.

Among autologous HCT recipients, HSV reactivation is more likely to occur in the early neutropenic phase, whereas the risk of VZV reactivation extends through the first year.[122] Thus, VZV prophylaxis for at least 6 to 12 months posttransplant should be considered in autologous HCT recipients. Prophylaxis against VZV should be considered in other patients at intermediate risk for viral reactivation, including patients with hematologic malignancies with prolonged neutropenia or those receiving T-cell–depleting agents (eg, fludarabine, alemtuzumab). Bortezomib is associated with an increased risk of VZV reactivation during active therapy[123–126]; carfilzomib may also be associated with VZV reactivation.[127] Prophylaxis with acyclovir, valacyclovir, or famciclovir should be protective and can be considered in these settings.[127–129] As previously discussed, among patients with CLL receiving alemtuzumab treatment, antiviral prophylaxis is recommended until 2 months after completion of treatment and until the CD4+ cell counts reach 200 cells/mcL or more (see INF-3, page 886).[116,117]

Cytomegalovirus: CMV infections most frequently occur in patients with cancer who undergo allogeneic HCT or who receive alemtuzumab therapy. CMV is a common cause of opportunistic infections during the early postengraftment phase following allogeneic HCT, but can also occur in the late postengraftment phase (particularly for patients with GVHD during the latter phase).[113,114] 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 HCT recipients with CMV-seropositive status prior to transplant.[130] Among CMV-seropositive patients undergoing allogeneic HCT (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 approximately 10%–30% of seropositive recipients) even with routine surveillance and antiviral prophylaxis or preemptive therapy.[130–133]

In 2 randomized studies, prophylaxis with acyclovir was associated with increased survival in allogeneic HCT recipients, but the rates of CMV reactivation and disease were fairly high.[134,135] Oral valacyclovir (a valine esterified analogue of acyclovir with high oral bioavailability) was compared with acyclovir as prophylaxis in allogeneic HCT recipients in whom either the donor or recipient was CMV seropositive.[136] All patients received initial intravenous acyclovir until day 28 after transplantation or until discharge, and then either oral valacyclovir or acyclovir until week 18. 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 difference was observed in CMV disease, adverse events, or overall survival.[136] In another study, acyclovir and valacyclovir were demonstrated to be acceptable agents for CMV prophylaxis, but surveillance and preemptive therapy with ganciclovir or foscarnet were still necessary.[115] The poor sensitivity of CMV to acyclovir is likely due to the lack of a CMV-encoded thymidine kinase and lower activity of acyclovir against the CMV DNA polymerase. Routine use of acyclovir or vala-

cyclovir for primary prophylaxis of CMV infection is not recommended.

Valganciclovir and ganciclovir are the agents of choice for first-line preemptive therapy; foscarnet is more commonly used for patients who cannot tolerate ganciclovir or for second-line preemptive therapy.[115] Foscarnet and ganciclovir had similar efficacy as preemptive CMV therapies in allogeneic HCT recipients, but ganciclovir was associated with a higher rate of early discontinuation because of neutropenia or thrombocytopenia.[137] Although ganciclovir had a higher rate of early discontinuation, there remains a paucity of data to recommend foscarnet as first-line treatment for CMV. Additionally, breakthrough CMV infection and disease with foscarnet have been reported.[138–140]

Pharmacokinetic studies have demonstrated the feasibility and safety of using oral valganciclovir, a pro-drug of ganciclovir, in place of ganciclovir in patients who underwent allogeneic HCT.[141,142] 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 HCT recipients, including patients with grades I and II gastrointestinal GVHD.[141,143–145] Thus, valganciclovir is a highly acceptable oral option for preemptive therapy for CMV in the absence of substantial gastrointestinal GVHD. Reports of higher rates of CMV disease with oral valganciclovir compared with intravenous ganciclovir in patients with hepatic dysfunction restricted approval for solid tumor transplant patients by specifically excluding liver transplant patients.[146–148] It is postulated that hepatic dysfunction decreases cleavage of the valine ester, thereby limiting conversion to the active form.[147]

Cidofovir has been evaluated as both primary and secondary preemptive therapy in allogeneic HCT recipients.[149–152] In a retrospective study of allogeneic HCT recipients (N=82) treated for CMV disease (n=20), primary preemptive therapy (n=24), or secondary preemptive therapy (n=38), cidofovir demonstrated an observed response in 50% of patients treated for CMV disease (mainly CMV pneumonia) and 62% of those treated for primary preemptive therapy.[151] Moreover, secondary preemptive therapy with cidofovir resulted in a response rate of 66% in patients in whom treatment failed or relapse occurred (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.[151]

Late CMV disease, defined as occurring after day 100 of HCT, 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.[153] Results of T-cell reconstitution at 3 months after allogeneic HCT appear to be useful in risk stratification for late CMV disease. CD4+ T-cell counts less than 50 cells/mcL, total lymphocyte counts less than 100 cells/mcL, undetectable CMV-specific T-cell responses, and GVHD were all associated with late CMV disease or death in CMV-seropositive allogeneic HCT recipients.[154] In addition, a CD4+ cell count less than 100 cells/mcL, a CD8+ count less than 50 cells/mcL, and use of high-dose steroids (2 mg/kg/d or greater) were significantly predictive of delayed recovery of CMV-specific immunity at 3 months after allogeneic HCT; use of steroids impaired both CD4+ and CD8+ T-cell function in a dose-dependent manner.[155] In patients who did not receive high-dose steroids and received CMV prophylaxis with ganciclovir, subclinical CMV antigenemia appeared 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.

CMV reactivation is common among patients with lymphoproliferative malignancies (most commonly CLL) receiving alemtuzumab therapy, and occurs most frequently between 3 to 6 weeks after initiation of therapy when T-cell counts reach a nadir.[156–159] 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.[156–158,160] 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).[159]

NCCN Recommendations for CMV Prophylaxis: Based on the available data that predict the risk of CMV disease, the NCCN Prevention and Treatment

of Cancer-Related Infections Panel recommends routine CMV surveillance after allogeneic HCT, together with preemptive anti-CMV therapy with oral valganciclovir or intravenous ganciclovir. In cases of ganciclovir-resistant CMV or when ganciclovir is not tolerated (eg, ganciclovir-induced myelosuppression), intravenous foscarnet or intravenous cidofovir may be used (see INF-4, page 887). Surveillance should typically occur for 1 to 6 months posttransplant and during chronic GVHD requiring IST. Note that the CD4+ count will be reduced by systemic corticosteroids and by other lymphocyte-depleting agents. Most cases of late CMV disease occur within the first year of transplant and less than 5% occur after the second year.[153] Therefore, the value of CMV surveillance beyond 2 years after HCT is unknown but can be considered in patients with significant chronic GVHD. There is debate about how to treat patients after a negative test for CMV. There is not enough data to determine whether patients should be transitioned to surveillance or continue with chronic maintenance therapy, and if so, for how long. The benefits must be weighed against the potential toxicity associated with long-term antiviral use. Ganciclovir and valganciclovir are associated with bone marrow suppression that may increase the risk of common opportunistic infections. Foscarnet can cause nephrotoxicity and electrolyte abnormalities but is tolerated.[137,161,162] Cidofovir can be associated with substantial nephrotoxicity[151,152]; although less frequent, ocular toxicity has been reported.[163] Acyclovir and valacyclovir have excellent safety profiles but are only weakly active against CMV and are not recommended as prophylaxis or treatment of CMV infection.

The NCCN Panel recommends routine surveillance for CMV reactivation using polymerase chain reaction (PCR) and weekly monitoring during alemtuzumab therapy and at least 2 months after completion of treatment.[116,164] On confirmation of CMV viremia (defined as PCR-positivity for CMV in ≥2 consecutive samples obtained 1 week apart[116]), the panel recommends preemptive therapy with oral valganciclovir or intravenous ganciclovir for at least 2 weeks and until CMV is no longer detectable (see INF-4, page 887). Intravenous foscarnet or intravenous cidofovir should be used for cases of ganciclovir-resistant CMV or when ganciclovir is not tolerated (eg, ganciclovir-induced myelosuppression). Following a negative test of CMV, there are not enough data to determine whether patients should continue with chronic maintenance therapy, and if so, for how long, or move to surveillance.

For the prevention and treatment of CMV, adjunctive intravenous immunoglobulin (IVIG) can be administered; however, IVIG is generally not recommended for prophylactic use except in limited situations due to cost and the limited evidence of activity of this treatment. Although no optimal dosing regimen has been determined, IVIG is commonly administered every other day for 3 to 5 doses. CMV-specific IVIG has not been shown to be any more efficacious than standard IVIG.

Hepatitis B Virus: Individuals with risk factors for hepatitis B virus (HBV) infection include those with a personal or parental history of an intermediate to high prevalence of HBV infection in their birthplace (defined as a prevalence of hepatitis B surface antigen [HBsAg] positivity in >2% of the population); patients with household and sexual contact with HBsAg-positive persons; those with multiple sexual partners or history of sexually transmitted diseases; individuals who have been inmates of correctional facilities; patients with chronically elevated aspartate transaminase or alanine transaminase (ALT) levels; patients with a history of injection drug use; men who have sex with other men; and patients positive for hepatitis C virus (HCV) or HIV.

A positive HBsAg is associated with active infection or a window period before the development of protective immunity in a patient exposed to HBV. An individual who has been vaccinated for HBV typically has the following serology: negative HBsAg, positive hepatitis B surface antibody (HBsAb), and negative hepatitis B core antibody (HBcAb).[165] False-negative HBsAg results may occur in patients with chronic liver disease.[166] HBsAb positivity is generally equated with protective immunity, although reactivated HBV disease may occur in the setting of significant immunosuppression in HBcAb-positive individuals.[167] A patient with resolved hepatitis B infection will be HBcAb-positive but HBsAg-negative. As mentioned earlier, some patients with cancer are at increased risk for HBV reactivation due to profound immunosuppression stemming from cytotoxic regimens and/or the underlying malignancy (eg, leukemia, lymphoma).

Patients with malignancies who are HBsAg-positive and/or HBcAb-positive are at risk for HBV

reactivation with cytotoxic chemotherapy. Approximately 20% to 50% of patients with HBsAg positivity and 3% to 45% with HBcAb positivity develop HBV reactivation.[165,168–177] Complications of HBV reactivation can range from self-limited hepatitis to fulminant hepatic failure and death.[177–182] HBV reactivation can lead to early discontinuation or delayed initiation of treatment.[183,184] In patients with B-cell lymphoid malignancies treated with rituximab-containing regimens, HBV reactivation was observed in patients with HBcAb positivity (with or without HBsAb positivity), even among those who were HBsAg-negative before initiation of treatment.[170,175,177] In a recent meta-analysis and evaluation of the FDA safety reports, HBcAb positivity correlated with increased incidence of rituximab-associated HBV reactivation.[169] A retrospective study showed that allogeneic HCT recipients who were HBsAg-negative but HBcAb-positive had a high risk of seroconversion to HBsAg positivity and HBV reactivation (subsequently leading to hepatitis) following allogeneic HCT.[185] After allogeneic HCT, loss of HBV-specific immunity may occur (ie, loss of HBsAb and development of HBsAg and HBV PCR positivity). This has been observed in up to 40% of susceptible individuals in one report[186] and may be confused with hepatic GVHD.

There are several nucleos(t)ide analogs approved by the FDA for the prevention and treatment of HBV. Historically, data supporting the use of these analogues have been based on lamivudine, a reverse transcriptase inhibitor. Antiviral prophylaxis with lamivudine has been shown to reduce the risks for HBV reactivation in HBsAg-positive patients with hematologic malignancies treated with IST.[187–189] In a meta-analysis of clinical trials evaluating lamivudine prophylaxis in HBsAg-positive lymphoma patients treated with IST, prophylaxis resulted in a significant reduction 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.[189] In allogeneic HCT recipients considered at high risk for HBV reactivation (ie, HBsAg-positive recipient or donor, or HBsAg-negative/HBcAb-positive recipient), antiviral prophylaxis with lamivudine demonstrated effective control of HBV reactivation and reduced the risk for developing hepatitis.[174,190] However, despite its initial effectiveness, virologic breakthrough was high, with reports of resistance in 80% of patients after 5 years of therapy.[191] Thus lamivudine monotherapy has fallen out of favor. Recent studies suggest one of the newer agents (such as entecavir or tenofovir) may be preferable or combination therapy may have a possible role for patients with lamivudine-resistant HBV infections.[192,193]

Tenofovir has demonstrated superior antiviral efficacy compared with adefovir in a phase III randomized double-blind study in patients with chronic HBV infection, and is the preferred agent in this setting[194]; however, limited data are available regarding its use in patient populations with cancer. No detectable resistance to tenofovir was reported in patients with chronic hepatitis B after 6 years of treatment.[195] In another study, sequencing of the HBV polymerase/reverse transcriptase indicated sequence changes at polymorphic sites, although none resulted in drug resistance.[196] In total, there were only 16 cases of virologic breakthrough, of which 12 were associated with nonadherence to study medication. Resistance for tenofovir remained undetectable throughout a 5-year span.[196] By comparison, lamivudine resistance was calculated to be 24% in the first year, and this number steeply increased to 70% by year 5.[196]

Entecavir and telbivudine have shown improved antiviral activity compared with adefovir in randomized open-label studies in patients with chronic hepatitis B.[197,198] A few small case studies have evaluated entecavir in the prevention[199] or treatment of HBV in patients with cancer (reviewed by Liu et al[200]). Entecavir had a low drug resistance of 1.2% at 5-years[201] compared with adefovir, which had an intermediate resistance that increased from 0% in the first year to 29% by year 5.[194,202,203] Conversely, telbivudine had a higher resistance, reaching 17% in the second year.[204] In a phase III clinical trial, greater than 10% of patients who did not have genotypic resistance after 2 years and continued to receive telbivudine developed resistance after 4 years.[205]

In addition to drug resistance, the safety profile of the nucleos(t)ide analogues should affect drug selection. Nephrotoxicity has been seen with adefovir[206,207] and tenofovir,[208] whereas myopathy and neuropathy are more commonly associated with telbivudine.[209,210] No significant side effects have been reported with lamivudine or entecavir; however, it is recommended that all patients be monitored for lactic acidosis and severe hepatomegaly with steatosis.

NCCN Recommendations for HBV Prophylaxis

Risk-based screening is recommended by ASCO[211] and the American Association for the Study of Liver Disease (AASLD).[212] Although it is possible that risk-based screening may be more cost-effective than universal screening, there are currently no validated risk tools that could be easily implemented in clinical practice. Furthermore, less than 60% of patients with HBV infection may have obvious risk factors,[213] and only 10% to 35% of infected patients may be aware of their own HBV infection.[214,215] Therefore, any patient expected to receive IST or chemotherapy should be screened. Implementation of universal screening, as recommended by the Centers for Disease Control and Prevention (CDC), should be considered.[216]

In patients undergoing intensive IST, including HCT, both patient and donor should be screened for HBV, HCV, and HIV beforetreatment.[217,218] Evaluation of HBsAg, HBcAb, and HBsAb levels should be considered at baseline.[115,165,218] Vaccination against HBV should be strongly considered in HBV-naïve patients (ie, negative for HBsAg, HBsAb, and HBcAb) (see "Vaccination," page 903).[115,165] In HBV-naïve patients undergoing allogeneic HCT, 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 hematopoietic cell collection.

In HBsAg-positive or HBcAb-positive individuals, baseline quantitative PCR for HBV DNA should be obtained. In allogeneic HCT candidates with evidence of active HBV infection (chronic hepatitis based on biopsy or positive HBsAg or high levels of HBV DNA), transplant procedure should be delayed when possible, and antiviral therapy should be given for 3 to 6 months before conditioning (see INF-5, page 888).[115] In HCT 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). All allogeneic HCT recipients should continue surveillance until 6 to 12 months after transplant or during GVHD.

Similarly, the NCCN Guidelines for Non-Hodgkin's Lymphoma (NHL) recommend HBsAg and HBcAb testing for all patients with B-cell NHL planned for treatment with anti-CD20 monoclonal antibody–containing regimens (see NCCN Guidelines for NHL, available at NCCN.org).[219] The panel recommends that baseline quantitative PCR for HBV DNA be obtained to determine viral load in patients who test positive for HBsAg and/or HBcAb. For patients undergoing antitumor therapy, the NCCN NHL Panel suggests prophylactic antiviral therapy (for cases of HBsAg positivity; also preferred for HBsAg-negative/HBcAb-positive cases) or preemptive antivirals upon detection of increasing viral load (an option for HBsAg-negative/HBcAb-positive cases with concurrent high levels of HBsAb).[219] During antitumor therapy, HBV viral load should be monitored via PCR monthly, then every 3 months after treatment completion. Prophylaxis with antivirals should be continued (for up to 12 months after completion of antitumor therapy) if viral load remains undetectable.[219] The optimal choice of antiviral agents for prophylaxis (or preemptive approaches) will primarily be driven by institutional standards. Monitoring of viral load and transaminases should be considered for patients without active HBV infection who are not receiving prophylaxis.

In addition to patients at risk for HBV, the NCCN Prevention and Treatment of Cancer-Related Infections panel recommends that any patient expected to receive IST or chemotherapy should be screened before treatment. Preferred agents for HBV prophylaxis are entecavir, tenofovir, and lamivudine. Monitoring of viral load and transaminases should be considered for patients without active HBV infection who are not receiving prophylaxis.

Hepatitis C Virus: Studies for HCV reactivation in patients with cancer are not as expansive as studies for hepatitis B; however, an increase in mortality was reported in patients with cancer who had HCV infection compared with those who were HCV-negative.[220] A review by Yazici et al[221] summarized studies of HCV reactivation in patients receiving targeted therapies, and the data correlated an increase in HCV reactivation with these therapies.[221] Differences in outcomes between patients who are HCV-positive with cancer and those without cancer were reported to include higher occurrence of occult infection, higher risk of developing early cirrhosis, higher rate of fibrosis progression, development of viral reactivation, and poorer virologic outcomes (reviewed by Borchardt et al[222]). The guidelines from the joint Infectious Diseases Society of America

(IDSA) and American Association for the Study of Liver Diseases (AASLD) panels for the testing, managing, and treating of HCV recommend that treatment be considered for patients with chronic HCV with life expectancy of greater than 12 months.[223]

NCCN Recommendations for HCV Screening and Management: Patients who should be screened for HCV include all who are receiving chemotherapy or IST (see INF-5, page 888).The data are limited regarding the treatment of HCV in patients with cancer, but it is generally not recommended that HCV treatment and cancer therapy be given concurrently.[222] The IDSA/AASLD guidelines can provide additional guidance for antiviral therapy, but an infectious diseases consult is necessary to evaluate the use of concomitant or sequential anti-HCV and cancer therapy.[223] Monitoring of ALT levels and HCV viral load monthly, or as clinically indicated, should be initiated as part of surveillance. The NCCN Guidelines for NHL address the management of HCV infection in patients with HCV-associated lymphomas (to view the most recent version of these guidelines, visit NCCN.org).[219]

HIV: The CDC surveillance report estimates that 1.2 million persons aged 13 years and older are living with HIV in the United States. This includes the estimated 156,300 persons whose infection has not yet been diagnosed.[224] There is support for HIV testing in all patients receiving treatment for cancer.[225] Patients who are HIV-positive and have cancer are classified as having either AIDS-defining cancer (ADC) or non–AIDS-defining cancer (NADC). ADC includes Kaposi sarcoma, non-Hodgkin's lymphoma, and cervical cancer. There is a higher incidence of these cancers in HIV-positive patients than in HIV-negative patients.[226]

The incidence of NADC is increasing, likely due to the longer life expectancy of HIV-positive patients resulting from the advancement of treatment options.[227] HIV-positive patients with NADC were shown to have an overall worse cancer outcome when compared with HIV-negative patients with the same cancer.[228] However, improvement in outcome was seen when HIV-positive patients received highly active antiretroviral therapy (HAART).[229] Caution is warranted regarding the concomitant administration of select antiretroviral therapies (including the protease inhibitors and non-nucleoside reverse transcriptase inhibitors) and cancer therapy, because adverse events through cytochrome P450 3A4 have been documented.[230]

A recent publication from MD Anderson Cancer Center retrospectively evaluated the use of HIV screening in patients before initiation of systemic cancer therapy.[231] Of the 18,874 patients in this study, 3,514 tested positive for HIV at the initiation of systemic cancer therapy. Patient histories indicated a higher incidence in patients with sexually transmitted disease (37.7% vs 18.5%; $P<.001$) or a history of illegal drug use (46.2% vs 18.6%; $P<.001$). Patients screened for HIV included 12.1% with NADC and 9.4% with cervical cancer. Interestingly, a significantly higher percentage of patients with NHL (88.4%) were screened for HIV, which may be partially attributed to clinician education of the role of HIV in these patients.[231]

NCCN Recommendations for HIV Screening: In 2006, the CDC published recommendations for routine HIV testing in all patients (13–64 years of age) in the health care setting.[232] The testing is intended to be voluntary, and conducted only with consent from patients. Under these guidelines, patients are informed either verbally or in written format that HIV testing would 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.[232] The implementation of these guidelines is largely dependent on institutional practices and the prevalence of undiagnosed HIV infections in specific institutions. However, the NCCN panel strongly encourages concordance with the CDC recommendations.

In addition to the CDC recommendations, the NCCN panel emphasizes that all patients receiving chemotherapy or IST be screened for HIV (see INF-5, page 888).[225] Patients coinfected with hepatitis pose an additional complication. Select antiretroviral therapies, including the integrase-strand inhibitors and nucleoside/nucleotide reverse transcriptase inhibitors, have demonstrated fewer drug–drug interactions compared with the protease inhibitors and non-nucleoside reverse transcriptase inhibitors. However, consultation with an infectious diseases expert is necessary for the treatment of HIV in patients with cancer, because therapies continuously evolve. Patients should be monitored monthly during therapy and then as clinically indicated.

Screening for Respiratory Viruses: Rapid PCR panels should be considered for detection of respiratory viruses including respiratory syncytial virus (RSV),

influenza, parainfluenza virus, adenovirus, rhinovirus, and metapneumovirus in patients with cough and/or shortness of breath that might indicate a viral infection (for discussion on nonviral causes of respiratory infections, see "Site-Specific Evaluation and Therapy: Lung Infiltrates" in the complete NCCN Guidelines [FEV-8], available at www.nccn.org). Ribavirin and IVIG have been proposed as antiviral therapies[233–237]; however, data are not sufficient to provide recommendations.

RSV is a major cause of severe infection in immunocompromised patients, with mortality rates up to 80% in HCT recipients.[238,239] Progression of RSV to the lower respiratory tract occurs in up to half of patients receiving HCT or chemotherapy.[240–242] The virulent nature of RSV requires hospitalization for treatment. Treatment options are limited to ribavirin and adjunctive IVIG. There is a diversity of practice among the institutions for the treatment of RSV disease. Based on limited data[243,244] and strong panel disagreement regarding the use of ribavirin and, if used, the best method of delivery, ribavirin was designated a category 3 recommendation. Recommendations for inhaled versus oral ribavirin should be based on the individual institution.

Rapid screening tests are available for detection of influenza. Clinical benefit is highest when treatment is initiated within the first 48 hours of influenza symptoms, although benefits can still be seen when initiated after the 48-hour window.[245] During the influenza season, empiric antiviral therapy should be considered for patients within 48 hours after the development of symptoms that are suggestive of influenza (eg, high fever, coryza, myalgia, dry cough), especially during community outbreaks. Both the Infectious Diseases Society of America (2007) and CDC guidelines (2011) recommend antiviral treatment with the neuraminidase inhibitors oseltamivir or zanamivir, which are active against both influenza A and B viruses.[246,247] Both agents are approved by the FDA for the treatment of influenza within 48 hours of symptomatic onset; the indicated duration of treatment is 5 days.[248,249] However, longer courses of treatment (eg, 10 days) and until resolution of symptoms can be considered in immunocompromised patients, although this is controversial. Some centers have used higher doses of oseltamivir (eg, 150 mg twice daily) in these patients with mixed results. Pandemic influenza does not have a predictable seasonal pattern, and may spread in the community concurrently with a seasonal influenza strain. Antiviral susceptibility of influenza strains is variable and cannot be predicted based on previous influenza outbreaks. In cases of seasonal influenza and pandemic strains, practitioners must be familiar with susceptibility patterns and guidelines on appropriate antiviral treatment.[250] Some data are available on the activity of peramivir; however the activity has been uneven across studies.[251] Peramivir, available only as an intravenous injection, can be considered for patients who cannot absorb oral oseltamivir or tolerate oseltamivir or inhaled zanamivir.[252]

Vaccination

Vaccination in patients with cancer can reduce the morbidity and mortality associated with infection. In general, patients with hematologic malignancies have a greater risk for infection than those with solid tumors. HCT patients may lose immunity to pathogens posttransplant. Therefore, the vaccination recommendations for these patients are more expansive than those for the general population of patients with cancer. In any immunocompromised patient, live attenuated viral vaccines (LAIV) have the potential to cause disease; however, inactivated vaccines can be safely administered. Although 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.

Influenza Vaccine: Influenza infections cause significant morbidity and mortality in patients with cancer. Among bone marrow transplant recipients, influenza accounts for approximately 10% to 40% of all community-acquired viral respiratory infections.[253–255] An increase in both the incidence and duration of influenza infections has been observed in patients with cancer who are immunosuppressed compared with healthy controls.[256,257] During community outbreaks, influenza infections may represent a significant proportion of fever and neutropenia episodes.[258] Influenza infections in patients with cancer who are severely immunocompromised are often associated with hospitalizations, delays in potentially lifesaving chemotherapy, and occasionally death.[256–258] As a result, annual vaccination against influenza with the inactivated influenza virus is recommended for all indi-

viduals at increased risk due to immunosuppression.[259] The Advisory Committee on Immunization Practices (ACIP) for the CDC's guidelines includes health care professionals and household members or caregivers in their target group for annual immunization to prevent transmission of influenza to high-risk patients.[259]

The intranasal vaccine should be avoided in patients with immunosuppression, because an LAIV is still capable of replication, which could theoretically lead to infection in immunocompromised individuals.[259,260] Because no data are available assessing the risk for person-to-person transmission of the LAIV from vaccine recipients to immunosuppressed contacts, the CDC recommends that inactivated influenza vaccine should be used in household contacts, health care workers, and others who have close contact with severely immunocompromised patients (ie, those requiring a protected environment). Persons with close contact to patients with a lesser degree of immunosuppression (eg, those receiving chemotherapy or corticosteroids, HIV-positive patients) may receive the LAIV.[259,260]

Pneumococcal Vaccine: The pneumococcal conjugate vaccine can be given in newly diagnosed adults with hematologic or solid tumor malignancies following assessment of their immune status. The conjugate pneumococcal vaccine (PCV13) should be administered to newly diagnosed adults with cancer who are pneumococcal vaccine–naïve, followed by the polysaccharide pneumococcal vaccine (PPSV23) at least 8 weeks later. Subsequent doses of PPSV23 should follow current PPSV23 recommendations for adults at high risk.[261] For patients who have previously received PPSV23, the PCV13 dose should be given at least 1 year after the last PPSV23 dose. For those who require additional doses of PPSV23, the first such dose should be given no sooner than 8 weeks after the PCV13 dose.

Vaccination with the conjugated 13-valent vaccine 6 to 12 months after HCT followed by the polysaccharide pneumococcal vaccine at least 1 year after cessation of immunosuppression in HCT is recommended along with revaccination with the polysaccharide pneumococcal vaccine after 5 years.[262,263] Patients with asplenia should receive the pneumococcal vaccine. The pneumococcal vaccine should be administered at least 2 weeks before elective splenectomy.[264] Penicillin prophylaxis is advised in asplenic patients to prevent pneumococcal disease.[265,266]

Meningococcal Conjugate Vaccine: The meningococcal vaccine is recommended for patients with increased risk for meningococcal disease, including those with persistent complement component deficiency, taking eculizumab, and with anatomic or functional asplenia. The ACIP recommends that asplenic persons be immunized with the meningococcal vaccine.[267] The meningococcal vaccine should be administered at least 2 weeks before elective splenectomy.[264] The conjugated meningococcal vaccine (MCV4) is preferred in adults 55 years of age or younger, because it confers longer lasting immunity than the polysaccharide vaccine. Revaccination for the meningococcal vaccine with MCV4 after 5 years is recommended for functional asplenic patients who received MCV4 or MPSV4.[267] The meningococcal vaccine is also recommended 6 to 12 months after HCT.

Human Papillomavirus Vaccine: The human papillomavirus (HPV) vaccine is a recombinant 3-dose vaccine that can be given to patients up to 26 years of age. The lower age limit for this vaccine is 9 years of age. No evidence indicates that this vaccine is helpful in patients who are already HPV-positive at the time of vaccination.

Haemophilus Influenzae Type b Vaccine: Immunization of adults with the pediatric *Haemophilus influenzae* type b (Hib) vaccine is considered optional because of limited data on efficacy in older children and adults, although studies suggest good immunogenicity in immunocompromised patients. The Hib vaccine is recommended 6 to 12 months post-HCT. For patients with planned splenectomy, immunization is ideally performed at least 2 weeks in advance. If this is not feasible, immunization is advisable after splenectomy, because such patients are still capable of mounting a protective antibody response.

Varicella/Zoster Vaccines: The varicella/zoster vaccines are live vaccines and should be given no earlier than 24 months following HCT. The varicella vaccine may be administered to HCT recipients who are seronegative for varicella, and who do not have GVHD or ongoing immunosuppression. Because of limited data in using the varicella vaccine among HCT recipients, physicians should assess the immune status of each recipient on a case-by-case basis and determine the risk for infection before using the vaccine. For patients who are seropositive for varicella, the zoster vaccine may be advisable (category

3). Because of insufficient data for the safety and efficacy of the zoster vaccine among HCT recipients, physicians should assess the immune status of each recipient and assess the potential benefit before using the vaccine. Specific antivirals (eg, acyclovir, famciclovir, and valacyclovir) cannot be given within the 24 hours before vaccination nor during the 14 days after vaccination.

Vaccine Summary: Although efficacy data are lacking for the use of vaccines in patients with cancer, recommendations for their use are based on the principles of immunization and safety data (see INF-7, page 889 and INF-8, page 890). Persons receiving chemotherapy or radiation therapy for malignancies should not be given a LAIV for at least 3 months after cessation of therapy and until the patient is presumed to be immunocompetent.[264] Data are emerging that indicate a reduced response to vaccination in patients receiving IST. In patients receiving blinatumomab, suppressed immunoglobulin levels were measured, which persisted through the first year following the conclusion of treatment.[268] Similarly, anti-CD20 therapy has correlated with decreased serum immunoglobulins.[269–275] Live vaccines are contraindicated during treatment and for a period of at least 6 to 12 months in patients who are receiving IST (eg, blinatumomab, CAR T-cells, monoclonal antibodies). These patients may also have a blunted response to inactivated vaccines. Certain live viral vaccines can be safely administered to household members of severely immunocompromised patients (eg, measles, mumps, rubella vaccine), whereas others cannot (eg, smallpox 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 therapy or IST; however, this timing is often not feasible in patients with cancer. In general, vaccination should not be given on the same day as cytotoxic therapy, because cytotoxic therapy may reduce the proliferative lymphocytic responses required for protective immunity. In patients receiving chemotherapy, immunization between cytotoxic chemotherapy courses is likely to be associated with higher response rates than during chemotherapy administration.[276,277] Patients vaccinated less than 2 weeks before starting cytotoxic therapy or IST or while receiving these agents may have a limited response to vaccination. These patients should be revaccinated at least 3 months after therapy is discontinued and once immune competence has been restored.[264]

In summary, the NCCN panel recommends that patients with cancer receive the influenza, pneumococcal, meningococcal, and HPV vaccines. HCT recipients should also receive the inactivated vaccines for diphtheria/tetanus/acellular pertussis (DTaP), Hib, hepatitis A and B, and polio. The live vaccine for measles, mumps, rubella may be given if no GVHD or ongoing immunosuppression is seen 2 years after transplant in patients who are seronegative. The live varicella vaccine may also be given 2 years after transplant if the patient is seronegative. There remains disagreement among the panel about the zoster vaccine.

Summary

Substantial progress has been made in the prevention and treatment of infectious complications associated with neutropenia and IST in patients with cancer. Certain populations of patients are at increased risk for developing infectious complications during the course of their disease and cancer 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 status of immune function. It is therefore imperative that patients 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. It is important to note that upfront prophylaxis is not necessary in all patients with cancer; prophylactic measures should only be used in those at high risk for specific pathogens during the high-risk period in order to avoid the emergence of resistant pathogens. With more patients undergoing treatment with potent cytotoxic regimens (eg, in acute leukemia) and

receiving allogeneic HCT, opportunistic viral and fungal infections have become important causes of mortality in these patients. In addition, the increasing prevalence of antibiotic-resistant pathogens is a challenge. Infection control should not only rely on antiinfective prophylaxis but also continue to incorporate standard infection control measures (eg, careful hand-washing by health care professionals). When selecting antimicrobial agents for prophylaxis and/or preemptive therapy, consideration should be given to the local susceptibility and resistance patterns of pathogens.

In summary, prevention and treatment of infections in patients with cancer is a complex and continuously evolving field. This excerpt highlights prophylaxis for antifungal and antiviral infections, including discussion of TDM for azoles; expanded HBV, HCV, and HIV recommendations; and incorporation of vaccination strategies. However, the advances in treatment have only further emphasized the need for multidisciplinary care. These NCCN Guidelines provide an overview of the risk categorization and recommended strategies for prevention of infections in high-risk patient populations, and recommendations for empiric therapy, evaluation, follow-up, and monitoring in patients with signs and/or symptoms of infections. Individualized risk evaluation for infections, incorporation of preventive measures, and prompt identification and treatment of active infections are essential components of the overall spectrum of care in cancer management, and can contribute to optimizing treatment outcomes in patients with cancer.

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Individual Disclosures of the NCCN Cancer-Related Infections Panel				
Panel Member	**Clinical Research Support/Data Safety Monitoring Board**	**Scientific Advisory Boards, Consultant, or Expert Witness**	**Promotional Advisory Boards, Consultant, or Speakers Bureau**	**Date Completed**
Michael Angarone, DO	None	None	None	6/18/16
Lindsey Robert Baden, MD	Crucell; and NIH-funded research	None	None	7/3/15
Gayle Blouin, PharmD, BCOP	None	None	None	6/20/16
Bernard C. Camins, MD	None	None	None	7/2/16
Corey Casper, MD, MPH	Janssen Pharmaceutical Products, LP; and Roche Laboratories, Inc.	GlaxoSmithKline; and TempTime	None	6/16/16
Brenda Cooper, MD	None	None	None	8/30/15
Erik R. Dubberke, MD	Merck & Co., Inc.; Rebiotix; and sanofi pasteur	Merck & Co., Inc.; Rebiotix; and sanofi pasteur	None	10/23/15
Ashley Morris Engemann, PharmD, BCOP	None	Astellas	None	9/30/15
Alison G. Freifeld, MD	Astellas; and Merck & Co., Inc.	None	None	5/20/15
John N. Greene, MD	None	None	None	7/5/16
James I. Ito, MD	City of Hope	Astellas; Merck & Co., Inc.; and Vical	Astellas Merck & Co., Inc.	5/20/15
Daniel R. Kaul, MD	Chimerix; Gilead; NeuralStem; and ViroPharma	None	None	6/7/16
Mark E. Lustberg, MD, PhD	None	None	None	8/18/15
Jose G. Montoya, MD	K-PAX Pharmaceuticals	Cubist Pharmaceuticals	None	9/11/15
Ken Rolston, MD	Allergan; JMI Laboratories; and Merck & Co., Inc.	Allergan	None	7/4/16
Gowri Satyanarayana, MD	None	None	None	7/2/16
Brahm Segal, MD	Astellas; Merck & Co., Inc.; and Ventrus	Astellas; and Merck & Co., Inc.	None	5/21/15
Susan K. Seo, MD	None	None	None	6/27/16
Shmuel Shoham, MD	Ansun; Astellas; Chimerix; HHS/ASPR; Gilead; Merck & Co., Inc.; NIAID Influenza Research Collaboration Social & Scientific Systems, Inc.; Pfizer Inc.; scynexis; Viropharma; and World Health Information Science Consultants	Biota Pharmaceuticals; LEK Consulting; Medical legal consultation to law firms; Mycoses Study Group Education and Research Consortium; SunTrust Robinson Humphrey, Inc; and Theravance	None	3/30/16
Sankar Swaminathan, MD[a]	GLG	None	None	9/2/15
Randy Taplitz, MD	None	None	None	5/20/15
Jeffrey Topal, MD	None	None	None	7/4/16
John W. Wilson, MD	None	None	None	6/19/16

[a]The following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty conflict:
Sankar Swaminathan, MD: Bristol-Myers Squibb Company, Gilead, Merck & Co., Inc., and Pfizer Inc.
The NCCN Guidelines staff have no conflicts to disclose.