National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Prevention and Treatment of Cancer-Related Infections

Version 1.2016

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2016
Prevention and Treatment of Cancer-Related Infections

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Prevention and Treatment of Cancer-Related Infections

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

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus.

Updates in Version 1.2016 of the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections from Version 2.2015 include:

INF-1

- **Overall Infection Risk In Patients With Cancer (Intermediate and High)**
  - **Under Antimicrobial Prophylaxis, statement added: *"Consider PCP prophylaxis"***
- **Footnote "g" revised: "See Antiviral Agents (FEV-C) for dosing, spectrum, and specific comments/cautions. ~~The antivirals are not equal in terms of efficacy, side effects, and resistance~~."**

(Also for INF-3, INF-4, and INF-5)

INF-2

- **Antifungal Prophylaxis**
  - **For ALL,"*Micafungin*" was added.**
  - **For MDS (neutropenic), AML (neutropenic), and Significant GVHD, "Micafungin (category 2B)" was added.**
  - **For Allogeneic HCT (neutropenic), Itraconazole (category 2B) was removed.**
  - **Footnote "k" revised: "Consider antifungal prophylaxis in all patients with GVHD receiving *immunosuppressive therapy (IST)*"**
  - **Footnote "m" revised: "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)*."**

INF-3

- **Overall Infection Risk In Patients With Cancer (Intermediate)**
  - **Minimum Duration revised:**
    - **"Consider during active therapy and *possibly longer depending on degree of immunosuppression* ~~at least 30 d after HSCT~~"**
    - **"Consider for at least ~~1 y~~ 6–12 months after autologous ~~HSCT~~ *HCT* ~~after allogencic *HCT* and at least 6–12 months~~"**

INF-3 continued

- **Disease/Therapy Examples: Alemtuzumab therapy/Allogeneic HCT/GVHD requiring steroid treatment**
  - **Minimum Duration revised:**
    - **"Minimum of 2 mo after alemtuzumab and until CD4 ≥200 cells/mcL ~~During active therapy including periods of neutropenia and at least 30 d after HSCT~~"**
    - **"~~Acyclovir~~ Prophylaxis should be considered for at least 1 y after allogeneic HSCT ~~Preemptive therapy for CMV (See INF-4) Antiviral therapy for HBV (See INF-5~~)"**
- **Footnote "o" added: *"For CMV antiviral prophylaxis, see INF-4. For HBV, HCV and HIV antiviral prophylaxis see INF-5."***

INF-4

- **Surveillance Period (High risk for CMV)**
  - **Allogeneic *hematopoietic* ~~stem~~ cell transplant recipients statement revised:**
    - ***"Typically for* 1 *to 6* month~~s~~ after transplant"**
    - **"GVHD requiring therapy*"***
  - **Footnote "p" revised: "CMV surveillance consists of at least weekly monitoring by PCR ~~or antigen testing~~."**
  - **Footnote "t" revised: "Foscarnet or cidofovir should be used for cases of ganciclovir-resistant CMV or when ganciclovir is not tolerated (eg, ganciclovir-induced ~~neutropenia~~ *myelosuppression*)."**

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INF-5

- Prevention Of Hepatitis B Virus (HBV), *Hepatitis C Virus (HCV), and Human Immunodeficiency Virus (HIV)* Reactivation Or Disease
  - High-Risk Examples for HBV, HCV, and HIV were removed.
  - Therapy Considerations
    - ◊ HCV was revised: "~~ID consult to evaluate~~ *Consider* concomitant or sequential anti-HCV and cancer therapy"
    - ◊ HIV was revised: "ID consult to adjust dosing and regimens ~~for concurrent treatment~~ *in context of cancer therapy"*
    - ◊ Footnote "x" was added: "*Drug interactions may complicate therapies. Consultation is recommended."*
  - Antiviral Therapy
    - ◊ HBV: Adefovir and Telbivudine were removed.
    - ◊ Footnote was removed: "Integrase-strand transfer inhibitor treatments or non-nucleoside reverse transcriptase inhibitors may have fewer drug-drug interactions with cancer treatments compared to protease inhibitors."
  - Surveillance
    - ◊ HCV bullets were revised: "Monitor ALT ~~levels every 1–2 weeks~~, and HCV RNA monthly *or as clinically indicated* ~~during therapy, and Monitor HCV RNA monthly thereafter for 6–12 months~~"

INF-6

- Antipneumocyctis Prophylaxis
  - High risk for pneumocystis jirovecii statement was revised: "TMP/SMX *(Preferred)* (category 1) or Atovaquone, dapsone, pentamidine (aerosolized or IV) if TMP/SMX intolerant"
  - Footnote "ee" was revised: "~~In addition, this agent has some activity against other pathogens (eg, Nocardia,Toxoplasma, Listeria~~). *Trimethoprim/sulfamethoxazole (TMP/SMX) has additional benefit of activity against other pathogens, including Nocardia, Toxoplasma, and Listeria."*

INF-6 continued

- Footnote "ff" was revised: "The list of agents is alphabetical and does not reflect preference. Consider TMP/SMX ~~trimethoprim/sulfamethoxazole~~ desensitization or atovaquone, dapsone, or pentamidine (aerosolized or IV); or when PCP prophylaxis is required; and patients who are ~~trimethoprim/sulfamethoxazole~~ *TMP/SMX* intolerant. *For patients receiving dapsone, consider assessing G6PD levels.*"

INF-7

- *"General* Recommendations For Vaccination In Patients With Cancer" page was extensively revised.

INF-8

- "Recommended Vaccination Schedule *After Autologous Or Allogeneic HCT"* title was revised.
- Inactivated Vaccines
  - "*Inactivated Polio vaccine*" was added.
  - Number of Doses of Meningococcal conjugate vaccine was revised: "1–2"
  - Footnote "jj" was added: *"Meningococcal B vaccine should be considered for high-risk patients such as patients with asplenia or complement deficiency or patients receiving eculizumab."*
- Live Vaccines
  - *Zoster vaccine corrected to "varicella vaccine"*
  - *"Zoster vaccine (category 3)"* was added
- Recommended Timing After HCT
  - Zoster Vaccine *(category 3)* added: *"May be considered at ≥24 mo (if no GVHD or ongoing immunosuppression)"*
  - Footnote "ll" was added: *"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."*

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FEV-5

- Initial Empiric Therapy For Fever And Neutropenia
  - Footnote was removed: "May interfere with galactomannan measurement."

FEV-7

- Additions to Initial Empiric Regimen
  - Abdominal pain and Diarrhea
    - ◊ Statement revised: "Oral vancomycin *(preferred)*"
    - ◊ Footnote "t" for C. difficile was added: *"The safety of probiotics or Fecal Microbiota Transplantation (FMT) in this setting has not been shown."*

FEV-8

- Evaluation
  - 5th sub-bullet revised: "Consider BAL, *including galactomannan,* particularly if no response to initial therapy or if diffuse infiltrates present"
- Additions to Initial Empiric Regimen
  - 2nd sub-bullet revised: "Antiviral therapy during *peak* influenza ~~outbreaks~~ *season in local area"*
  - Bullet added: *"Re-evaluate for ability to de-escalate"*
  - Bullet removed: "Adjunctive therapies may be considered in certain patient populations"
  - Footnote removed: "See Adjunctive Therapies (FEV-E)."

FEV-9

- Footnote removed: "See Adjunctive Therapies (FEV-E)."
- Footnote removed: "See Appropriate Use of Vancomycin and Other Agents for Gram-Positive Resistant Infections (FEV-F)"

FEV-11

- Suggested Minimum Duration of Therapy For Documented Infection
  - 3rd sub-bullet revised: "S. aureus: *typically requires 4* ~~at least 2~~ weeks after first negative blood culture; treatment may need to be prolonged in cases of endovascular involvement; *encourage ID consult "*
  - 5th sub-bullet revised: "~~Consider~~ Catheter removal *favored* for bloodstream infections with Candida, S. aureus, Pseudomonas aeruginosa, Corynebacterium jeikeium, Acinetobacter, Bacillus organisms, atypical mycobacteria, yeasts, molds, vancomycin-resistant enterococci, and Stenotrophomonas maltophilia"

FEV-A (1 of 4)

- Comments/Precautions
  - Vancomycin, bullet added: *"Loading dose may be considered"*
  - Daptomycin, bullet removed: "Myositis is a potential toxicity"

FEV-A (2 of 4)

- Dose
  - Footnote "b" for dosing revised: "Requires dose adjustment in patients with renal insufficiency. *Dosing variations exist.*"
- Comments/Precautions
  - Cefepime, bullet added: *"Neurotoxicity may occur"*

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FEV-A (3 of 4)

- Antibacterial Agents: Other
  - Amoxicillin/clavulanate moved from "Dose" to "Other Antibacterial Agents"
  - Ciprofloxacin
    - Spectrum, 3rd bullet revised: "*Ciprofloxacin alone has no activity against anaerobes*"
  - Levofloxacin and Moxifloxacin
    - Spectrum, 4th bullet revised: "Moxifloxacin has limited activity *against Pseudomonas*"
  - *"Metronidazole"* added
    - Dose: *"500 mg infused every 6 h or 500 mg PO every 6–8 h"*
    - Spectrum: *"Good activity against anaerobic organisms"*

FEV-B (1 of 4)

- Antifungal Agents: Azoles
  - "Isavuconazole" added
    - Dose: *"372 mg every 8 h x 6 doses IV/PO; then 372 mg every day IV/PO"*
    - Spectrum: *"Data are emerging for clinical activity for patients with invasive aspergillosis and mucormycosis"*
    - Comments/Cautions: *"Can be considered in patients intolerant or refractory to first-line anti-mold therapy"*
  - Posaconazole
    - Dose: *"200 mg TID oral solution"* was added.
    - Comments/Cautions:
      - 3rd bullet revised: "~~Older~~ *Liquid* formulation should be administered with a full meal or liquid nutritional supplement or an acidic carbonated beverage."
      - 5th bullet revised: "Proton pump inhibitors decrease posaconazole plasma concentration *with oral solution*"

FEV-B (1 of 4) continued

  - Voriconazole
    - 3rd bullet revised: "~~Fluoride levels should be checked to prevent toxicity and in response to bone/muscle pain~~ *Fluorosis may occur with prolonged use and is associated with bone/muscle pain*"

FEV-B (2 of 4)

- Liposomal amphotericin B (L-AMB), dosing was revised: "~~≥3~~ *3–5* mg/kg/d IV"
- Footnote "g" was added: *"Slowing the rate of infusion is an additional way to manage amphotericin infusion reactions."*

FEV-B (3 of 4)

- Antifungal Agents
  - Anidulafungin
    - Comments/Cautions
      - 1st bullet revised: "~~Primary~~ *Empiric* therapy for candidemia and invasive candidiasis (category 1), *pending susceptibility data*"
      - 2nd bullet revised: "~~Superior~~ Efficacy *established* compared to fluconazole as primary therapy for candidemia and invasive candidiasis"
  - Caspofungin
    - Dose, 2nd bullet revised: "Some investigators use 70 mg IV daily as therapy for aspergillosis *in salvage cases*"
  - Micafungin
    - Dose, 2nd bullet revised: "150 mg/d IV used at some centers for *Aspergillus sp.* infection *in salvage cases*"
  - Footnote "h" was revised: "A number of centers use combination voriconazole and an echinocandin for invasive aspergillosis based on ~~in vitro, animal, and limited~~ clinical data. *Evidence for combination therapy remains limited.*"

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FEV-B (4 of 4)

- Reference "6" was added: *"Marr KA, Schlamm HT, Herbrecht R, Rottinghaus ST, Bow EJ, Cornely OA, et al. Combination antifungal therapy for invasive aspergillosis: a randomized trial. Ann Intern Med 2015;162:81-89."*

FEV-C (1 of 4)

- Antiviral Agents
  - 2nd heading modified: *"COMMON* INDICATION*"* Also for FEV-C (page 3 of 4)
  - Ganciclovir
    - ◊ Bullet removed: "Prophylaxis for CMV: 5–6 mg/kg IV every day for 5 days/week from engraftment until day 100 after HSCT"
  - Valganciclovir
    - ◊ 2nd bullet revised: "Preemptive therapy for CMV: *Induction with* 900 mg PO BID for *at least* 2 weeks *and until negative test;* consider additional 900 mg PO daily for at least 7 days after a negative test *for maintenance*"
    - ◊ Footnote "d" revised: "In general, the strategy of CMV surveillance testing by ~~antigenemia or~~ PCR followed by preemptive anti-CMV therapy for a positive result is favored over universal long-term prophylaxis in allogeneic HCT patients."

FEV-C (2 of 4)

- Antiviral Agents
  - Oseltamivir
    - ◊ 2nd sentence revised: "Treatment: 75 mg BID ~~(higher dose 150 mg BID can be considered)~~"
    - ◊ Footnote "e" for Cidofovir added: *"A dose of 1 mg/kg administered three times a week is common for less severe adenovirus infections."*
    - ◊ Footnote "f" for Oseltamivir and Zanamivir added: *"Consider peramivir for patients who cannot have oral oseltamivir or inhaled zanamivir."*

FEV-C (3 of 4)

- Antiviral Agents
  - Ribavirin
    - ◊ *"category 3"* was added
    - ◊ Treatment revised: "Consider for treatment of RSV disease: ~~(~~6 gm administered by continuous inhalation via SPAG-2 nebulizer every 12–18 h daily ~~for 7 days~~ or 2 g over 2 h TID~~)~~; or *600–800 mg PO BID*; may be paired with IVIG (400–500 mg/kg every other day)"
    - ◊ Reference 12 was added: *"Marcelin JR, Wilson JW, Razonable RR.Oral ribavirin therapy for respiratory syncytial virus infections in moderately to severely immunocompromised patients. Transpl Infect Dis 2014;16: 242-250."*
  - Adefovir removed from the table.
  - Telbivudine removed from the table.

FEV-E

- Adjunctive Therapies page was removed.

FEV-F

- Appropriate Use Of Vancomycin and Other Agents for Gram-Positive Resistent Infections page was removed.

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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

[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.

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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], or Micafungin (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

[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.

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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

[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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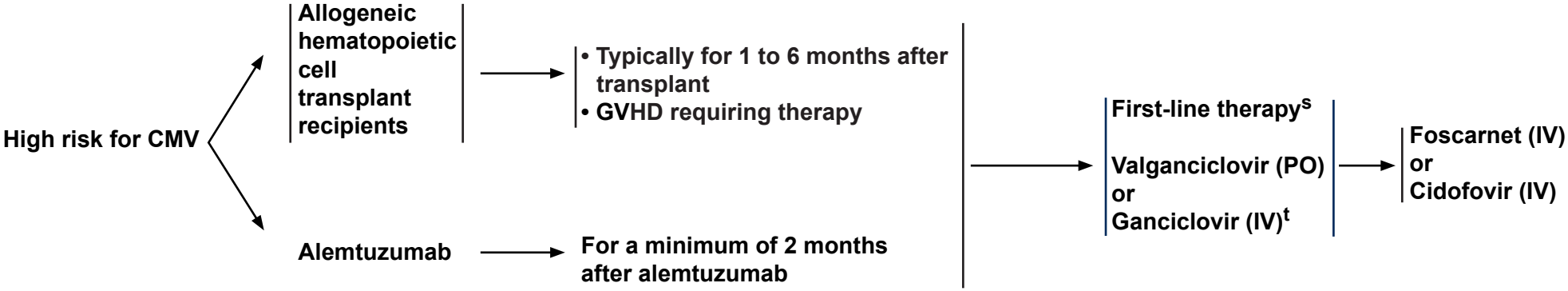
PREVENTION OF CYTOMEGALOVIRUS (CMV) REACTIVATION OR DISEASE



[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).

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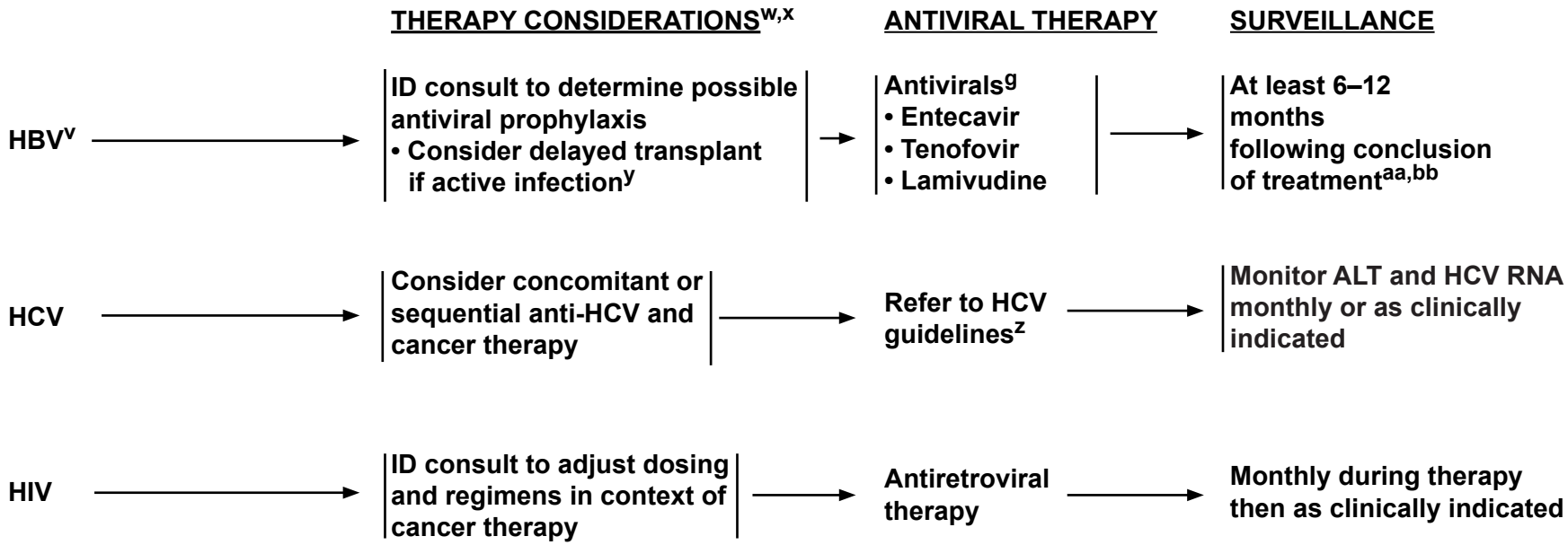
PREVENTION OF HEPATITIS B VIRUS (HBV), HEPATITIS C VIRUS (HCV), AND HUMAN IMMUNODEFICIENCY VIRUS (HIV) REACTIVATION OR DISEASE[u]



[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.

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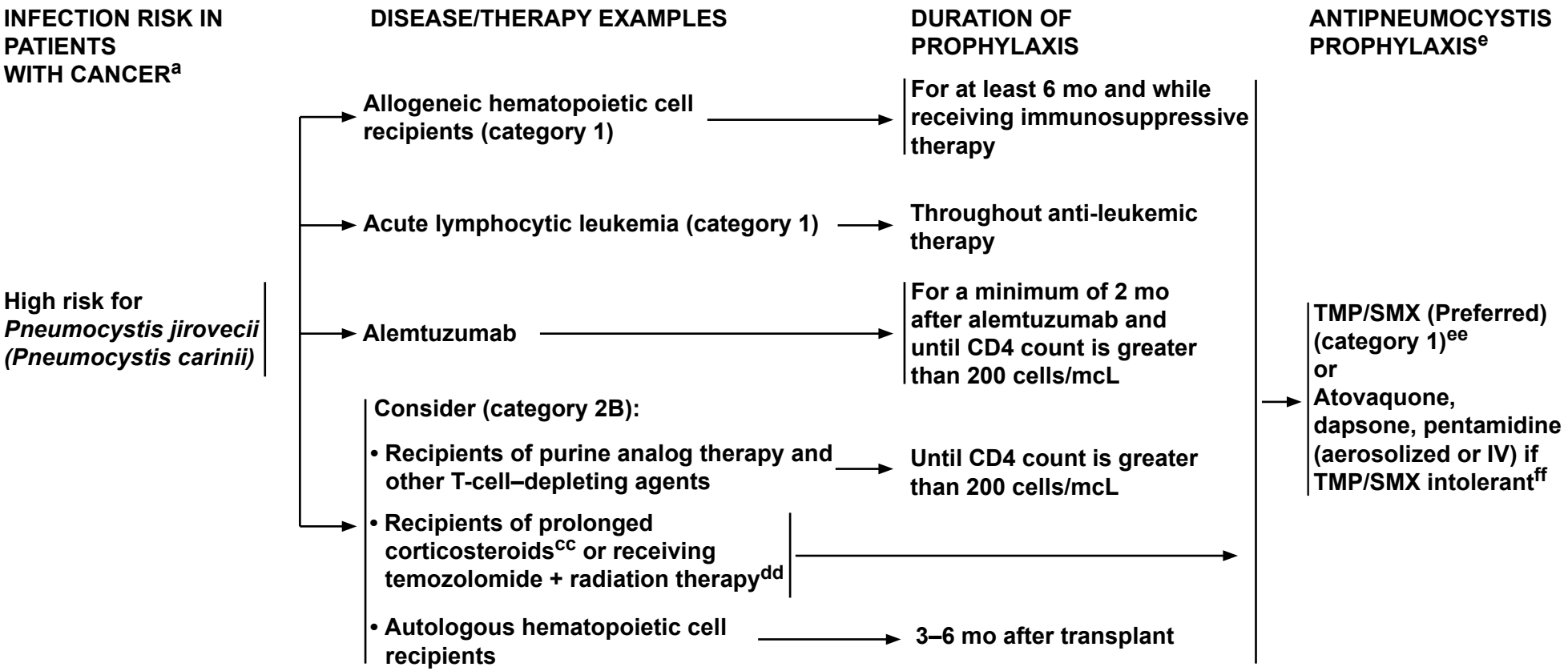

[a]Categories of risk are based on several factors, including underlying malignancy, whether disease is in remission, duration of neutropenia, prior exposure to chemotherapy, and intensity of immunosuppressive therapy.
[e]See Antibacterial Agents (FEV-A) for dosing, spectrum, and specific comments/cautions.
[cc]Risk of pneumocystis pneumonia (PCP) is related to the daily dose and duration of corticosteroid therapy. Prophylaxis against PCP can be considered in patients receiving the prednisone equivalent of 20 mg or more daily for 4 or more weeks.
[dd]PCP prophylaxis should be used when temozolomide is administered concomitantly with radiation therapy and should be continued until recovery from lymphocytopenia.
[ee]Trimethoprim/sulfamethoxazole (TMP/SMX) has additional benefit of activity against other pathogens including Nocardia, Toxoplasma, and Listeria.
[ff]The list of agents is alphabetical and does not reflect preference. Consider TMP/SMX desensitization or atovaquone, dapsone, or pentamidine (aerosolized or IV) when PCP prophylaxis is required in patients who are TMP/SMX intolerant. For patients receiving dapsone, consider assessing G6PD levels.

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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).

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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 varicella/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.

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CLINICAL PRESENTATION

Fever:
- **Single temperature equivalent to ≥38.3°C orally**

or
- **Equivalent to ≥38.0°C orally over 1-h period**

Neutropenia:
- **<500 neutrophils/mcL**

or

<1,000 neutrophils/mcL and a predicted decline to ≤500/mcL over the next 48 h

→

INITIAL EVALUATION OF FEVER AND NEUTROPENIA

Site-specific H&P including:
- **Intravascular access device**
- **Skin**
- **Lungs and sinus**
- **Alimentary canal**
- **Perivaginal/perirectal**
- **Urologic**
- **Neurologic**

Supplementary historical information:
- **Major comorbid illness**
- **Time since last chemotherapy administration**
- **History of prior documented infections**
- **Recent antibiotic therapy/prophylaxis**
- **Medications**
- **Exposures:**
  - **Others at home with similar symptoms**
  - **Pets**
  - **Travel**
  - **Tuberculosis exposure**
  - **Recent blood product administration**
  - **Marijuana use**

Laboratory/radiology assessment:
- **CBC including differential, platelets, BUN, electrolytes, creatinine, and LFTs**
- **Consider chest x-ray, urinalysis, pulse oximetry**
- **Chest x-ray for all patients with respiratory symptoms**

→

MICROBIAL EVALUATION

- **Blood culture x 2 sets (one set consists of 2 bottles). Options include:**
  - **One peripheral + one catheter (preferred)[a]**

  or
  - **Both peripheral**

  or
  - **Both catheter (if unable to obtain a peripheral blood)**
- **Urine culture (if symptoms, urinary catheter, abnormal urinalysis)**
- **Site-specific culture:**
  - **Diarrhea (*Clostridium difficile* assay, enteric pathogen screen)**
  - **Skin (aspirate/biopsy of skin lesions)**
  - **Vascular access cutaneous site with inflammation (consider routine/fungal/mycobacterial)**
- **Viral diagnostics:**
  - **PCR- and DFA-based tests**
  - **Vesicular/ulcerated lesions on skin or mucosa**
  - **Throat or nasopharynx for respiratory virus symptoms, especially during outbreaks**

→ **See Initial Risk Assessment (FEV-2)**

[a]Preferred for distinguishing catheter-related infections from secondary sources.

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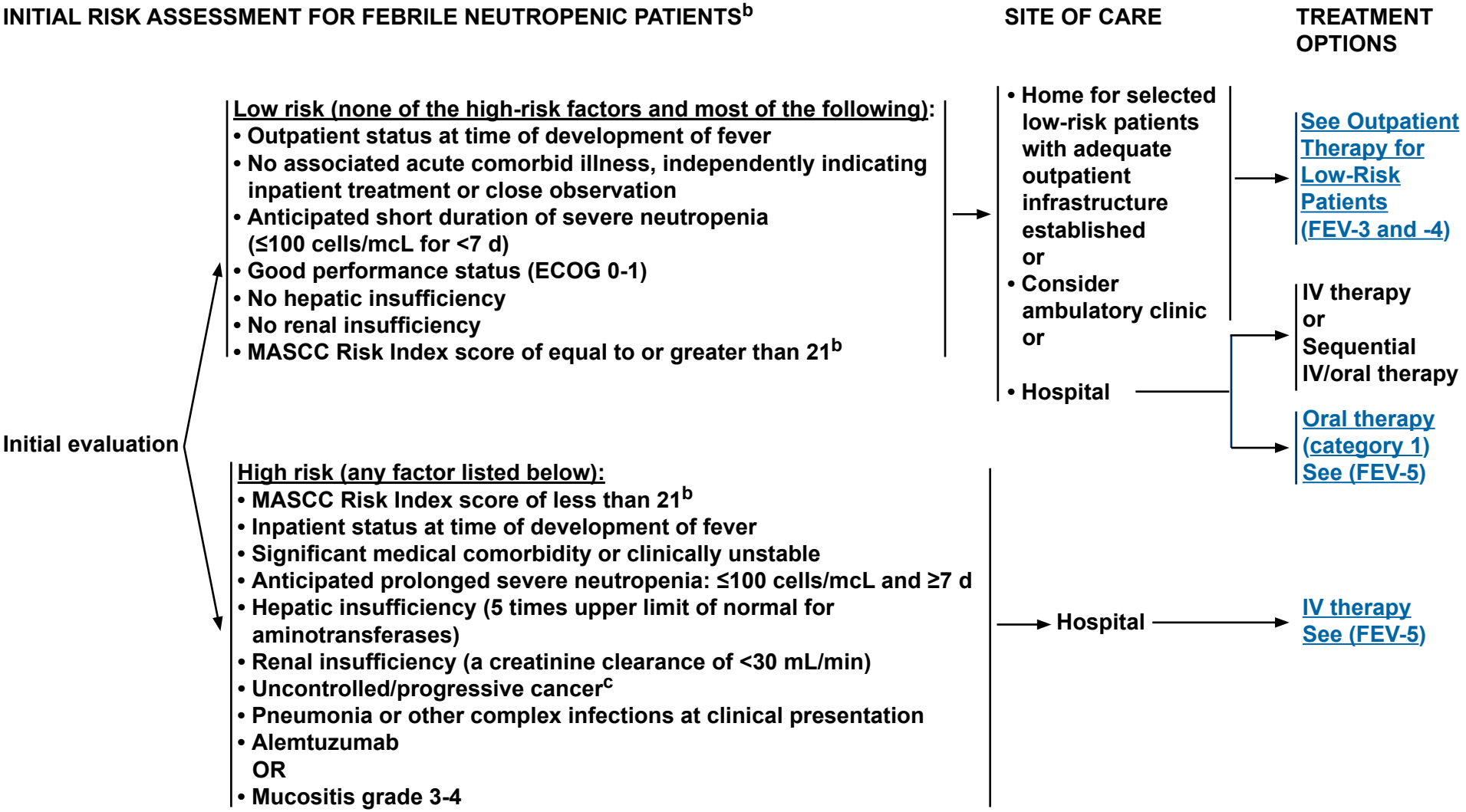

[b]Risk categorization refers to risk of serious complications, including mortality, in patients with neutropenic fever. See Risk Assessment Resources (FEV-D).
[c]Uncontrolled/progressive cancer is defined as any patients with leukemia not in complete remission, or patients without leukemia with evidence of disease progression after more than 2 courses of chemotherapy.

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OUTPATIENT THERAPY FOR LOW-RISK PATIENTS

INDICATION	ASSESSMENT	MANAGEMENT
Patient determined to be in low-risk category on presentation with fever and neutropenia[b]	• Careful examination • Review lab results: no critical values • Review social criteria for home therapy ▸ Patient consents to home care ▸ 24-h home caregiver available ▸ Home telephone ▸ Access to emergency facilities ▸ Adequate home environment ▸ Distance within approximately one hour of a medical center or treating physician's office • Assess for oral antibiotic therapy ▸ No nausea and vomiting ▸ Able to tolerate oral medications ▸ Not on prior fluoroquinolone prophylaxis	Observation period (2–12 h) (category 2B) in order to: • Confirm low-risk status and ensure stability of patient • Observe and administer first dose of antibiotics and monitor for reaction • Organize discharge plans to home and follow-up • Patient education • Telephone follow-up within 12–24 h

→ See Treatment and Follow-up (FEV-4)

[b]Risk categorization refers to risk of serious complications, including mortality, in patients with neutropenic fever. See Risk Assessment Resources (FEV-D).

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OUTPATIENT THERAPY FOR LOW-RISK PATIENTS

TREATMENT OPTIONS

- Intravenous (IV) antibiotics at home
- Daily long-acting IV agent ± oral therapy
  - Home or office
- Oral therapy only[d]:
  - Ciprofloxacin[e] plus amoxicillin/clavulanate[f] (category 1)
  - Levofloxacin
  - Moxifloxacin[e,g] (category 1)

→

FOLLOW-UP

- Patient should be monitored daily
- Daily assessment (clinic or home visit) for the first 72 h to assess response, toxicity, and compliance; if responding, then telephone follow-up daily thereafter.
- Specific reasons to return to clinic:
  - Any positive culture
  - New signs/symptoms reported by the patient
  - Persistent or recurrent fever at days 3–5
  - Inability to continue prescribed antibiotic regimen (ie, oral intolerance)
  - Office visit for infusion of IV antibiotics

[d]Criteria for oral antibiotics: no nausea or vomiting, patient able to tolerate oral medications, and patient not on prior fluoroquinolone prophylaxis.
[e]The fluoroquinolone chosen should be based on reliable Gram-negative bacillary activity, local antibacterial susceptibilities, and the use of quinolone prophylaxis of fever and neutropenia.
[f]Use clindamycin for penicillin-allergic patients.
[g]Not active against Pseudomonas. Recommended for low-risk patients who may not require Pseudomonas coverage.

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INITIAL EMPIRIC THERAPY FOR FEVER AND NEUTROPENIA[h,i]

Initial antibiotic therapy should be based on:
- Infection risk assessment (See FEV-2)
- Broad-spectrum coverage including antipseudomonal activity
- Potential infecting organisms include multidrug-resistant organisms (MDROs)
- Colonization with or prior infection with methicillin-resistant *Staphylococcus aureus* (MRSA)
- Site of infection
- Local antibiotic susceptibility patterns
- Organ dysfunction/drug allergy
- Previous antibiotic therapy
- Bactericidal

Uncomplicated
- IV antibiotic monotherapy (choose one):
  - Cefepime[j] (category 1)
  - Imipenem/cilastatin (category 1)
  - Meropenem (category 1)
  - Piperacillin/tazobactam (category 1)
  - Ceftazidime[k] (category 2B)
- Oral antibiotic combination therapy for low-risk patients:
  - Ciprofloxacin + amoxicillin/clavulanate (category 1)
  - Moxifloxacin[e,g] (category 1)
  - Oral antibiotic regimen recommended should not be used if quinolone prophylaxis was used

Complicated[l,m]
- IV antibiotic monotherapy (preferred)
- IV combination therapy could be considered especially in cases of resistance

Site-Specific Evaluation and Therapy:

Mouth, Esophagus and Sinus/Nasal (FEV-6)

Abdominal Pain, Perirectal Pain, Diarrhea, Urinary Tract Symptoms (FEV-7)

Lung Infiltrates (FEV-8)

Cellulitis, Vascular Access Devices, Vesicular Lesions, Disseminated Papules or Other Lesions, Central Nervous System Symptoms (FEV-9)

OR

Follow-up (FEV-10)

[e]The fluoroquinolone chosen should be based on reliable Gram-negative bacillary activity, local antibacterial susceptibilities, and the use of quinolone prophylaxis of fever and neutropenia.
[g]Not active against Pseudomonas. Recommended for low-risk patients who may not require Pseudomonas coverage.
[h]Consider local antibiotic susceptibility patterns when choosing empirical therapy. At hospitals where infections by antibiotic-resistant bacteria (eg, MRSA or drug-resistant gram-negative rods) are commonly observed, policies on initial empirical therapy of neutropenic fever may need to be tailored accordingly.
[i]See Antibacterial Agents (FEV-A) for dosing, spectrum, and specific comments/cautions.
[j]Meta-analysis reported increased mortality associated with cefepime in randomized trials of neutropenic fever. Based on the results of the FDA's meta-analyses, the FDA has determined that cefepime remains an appropriate therapy for its approved indications.
[k]Weak Gram-positive coverage and increased breakthrough infections limit utility.
[l]Choice of antibiotic may depend on local antibiotic susceptibility patterns and individual patient syndromes.
[m]In patients treated with escalated dosing, reassess after 48–72 hours and consider de-escalation.

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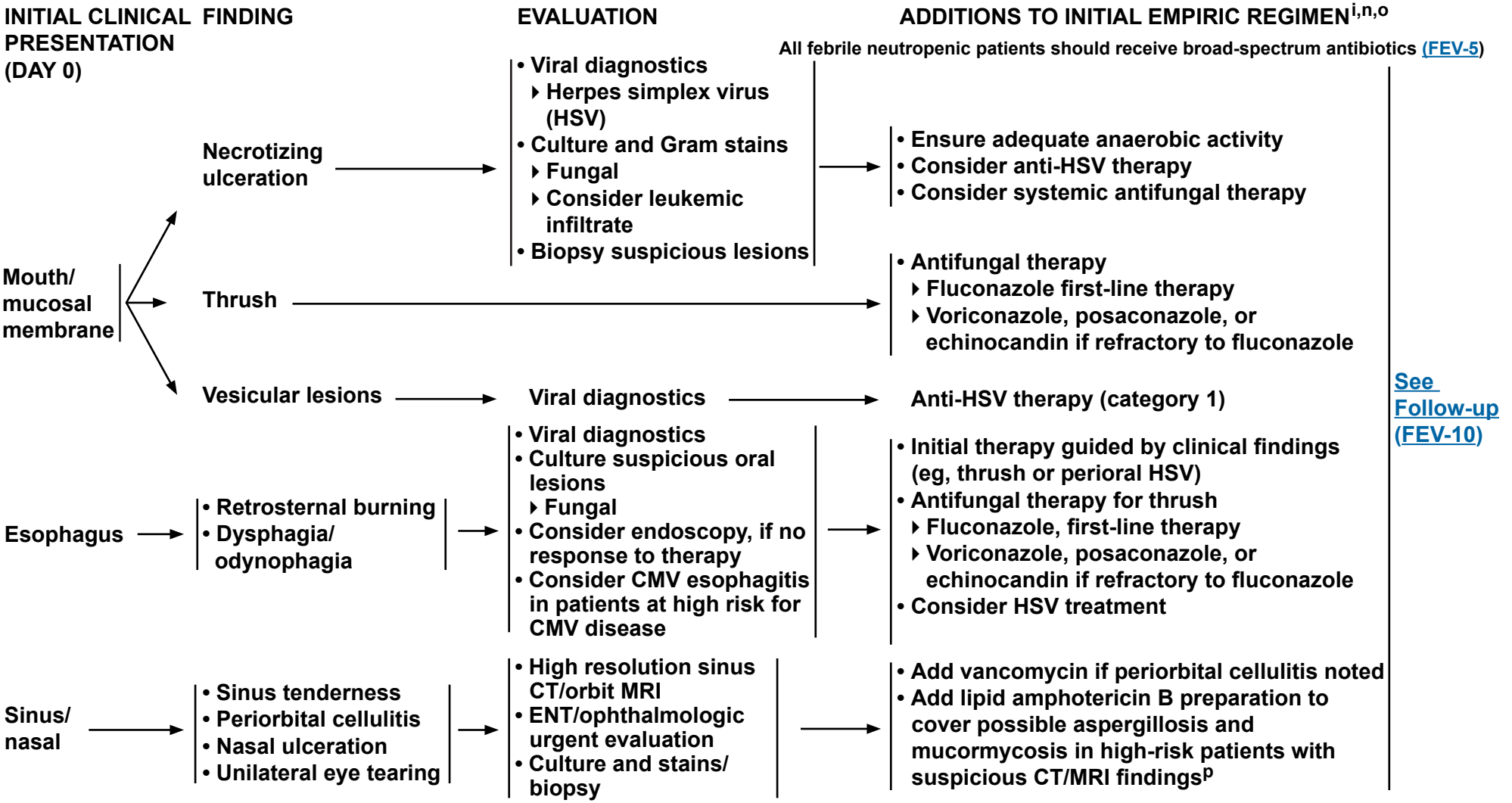

[i] See Antibacterial Agents (FEV-A) for dosing, spectrum, and specific comments/cautions.
[n] See Antifungal Agents (FEV-B) for dosing, spectrum, and specific comments/cautions.
[o] See Antiviral Agents (FEV-C) for dosing, spectrum, and specific comments/cautions. The antivirals are not equal in terms of efficacy, side effects, and resistance.
[p] Posaconazole or isavuconazole can be considered for patients who have invasive, refractory infections or who have intolerance to amphotericin B formulations. Posaconazole is not approved by the FDA as either primary or invasive refractory therapy for invasive fungal infections.

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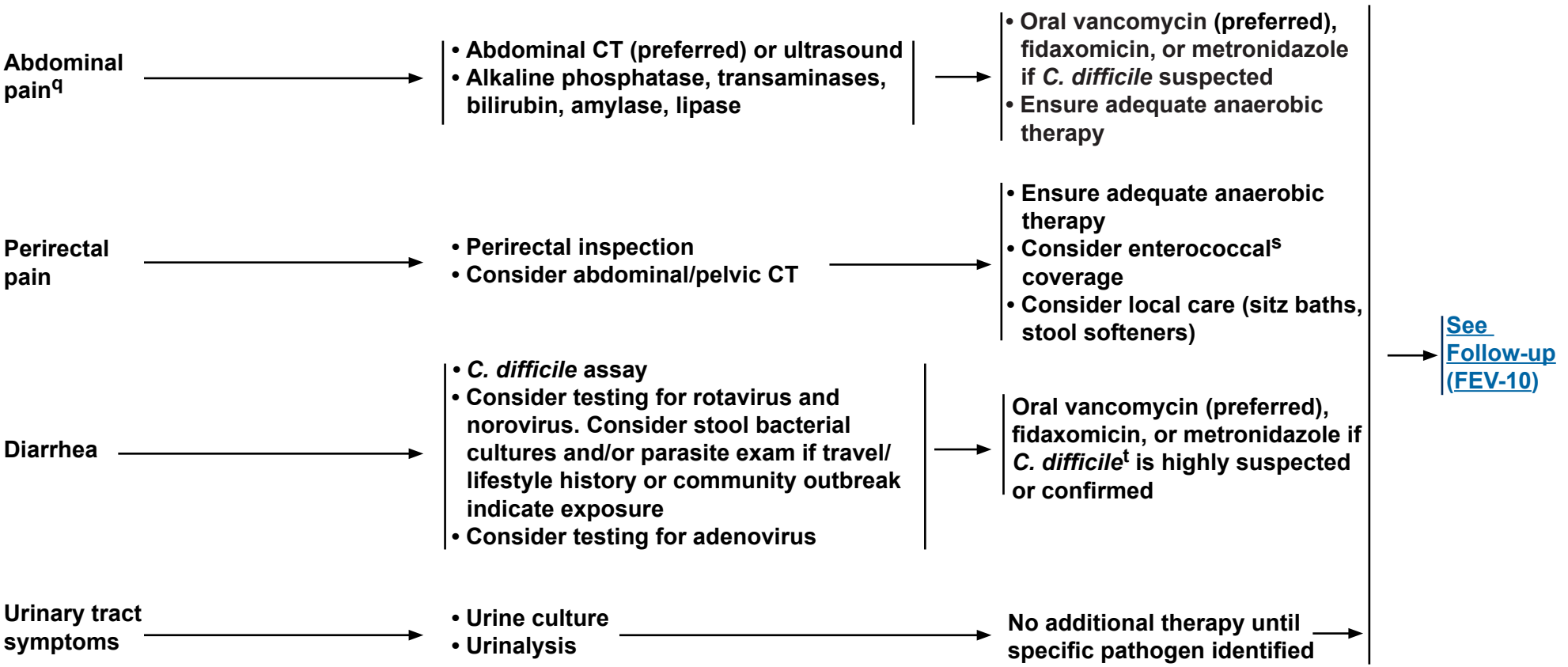

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[o] See Antiviral Agents (FEV-C) for dosing, spectrum, and specific comments/cautions. The antivirals are not equal in terms of efficacy, side effects, and resistance.
[q] Surgical and other subspecialty (eg, gastroenterology, interventional radiology) consultations should be considered for these situations as clinically indicated.
[r] Lab studies include CMV antigens/PCR and abdominal/pelvic CT.
[s] Enterococcal colonization must be differentiated from infection. Vancomycin use must be minimized because of the risk of vancomycin resistance.
[t] The safety of probiotics or Fecal Microbiota Transplantation (FMT) in this setting has not been shown.

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INITIAL CLINICAL PRESENTATION (DAY 0)

EVALUATION[u,v]

ADDITIONS TO INITIAL EMPIRIC REGIMEN[i,n,o]

All febrile neutropenic patients should receive broad-spectrum antibiotics (FEV-5)

Lung infiltrates →

- **Blood and sputum cultures**
- **Consider depending on risk:**
  - **Nasal wash for respiratory viruses, rapid tests[w]**
  - **Legionella urine Ag test**
  - **Serum galactomannan or β-glucan test in patients at risk for mold infections (in intermediate to high-risk patients; see (INF-1))**
  - **CT of chest to better define infiltrates**
  - **Consider BAL, including galactomannan, particularly if no response to initial therapy or if diffuse infiltrates present**
  - **Consider diagnostic lung biopsy**

→

- **Azithromycin or fluoroquinolone added to cover atypical bacteria**
- **Consider adding:**
  - **Mold-active antifungal agent (in intermediate to high-risk patients; see (INF-1))**
  - **Antiviral therapy during peak influenza season in local area[x]**
  - **TMP/SMX if *Pneumocystis jirovecii* is possible etiology**
  - **Vancomycin or linezolid if MRSA suspected**
- **Re-evaluate for ability to de-escalate**

→ **See Follow-up (FEV-10)**

[i] See Antibacterial Agents (FEV-A) for dosing, spectrum, and specific comments/cautions.
[n] See Antifungal Agents (FEV-B) for dosing, spectrum, and specific comments/cautions.
[o] See Antiviral Agents (FEV-C) for dosing, spectrum, and specific comments/cautions. The antivirals are not equal in terms of efficacy, side effects, and resistance.
[u] Other diagnoses to consider include pulmonary edema, hemorrhage, and drug toxicities.
[v] Assess for health care-acquired pneumonia and/or resistant pathogens.
[w] Rapid immunofluorescent viral antigen tests may be negative for H1N1 (swine flu).
[x] Antiviral susceptibility of influenza strains is variable and cannot be predicted based on prior influenza outbreaks. In cases of seasonal influenza and pandemic strains (eg, H1N1), it is necessary to be familiar with susceptibility patterns and guidelines on appropriate antiviral treatment.

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INITIAL CLINICAL PRESENTATION (DAY 0) | **EVALUATION** | **ADDITIONS TO INITIAL EMPIRIC REGIMEN[i,n,o]**

All febrile neutropenic patients should receive broad-spectrum antibiotics (FEV-5)

Cellulitis/skin and soft tissue infections → **Consider aspirate or biopsy for culture** → **Add gram-positive active agents**

Vascular access devices (VAD)

- **Entry or site inflammation** → • Swab entry site drainage (if present) for culture • Blood culture from each port of VAD → **Vancomycin initially or add it if site not responding after 48 h of empiric therapy**
- **Tunnel infection/ port pocket infection, septic phlebitis** → **Blood culture from each port of VAD** → • Remove catheter and culture surgical wound • Add vancomycin[y]

Vesicular lesions → **Aspiration or scraping for VZV or HSV PCR, or direct fluorescent antibody (DFA), herpes virus cultures if PCR unavailable** → **Consider acyclovir, famciclovir, or valacyclovir**

Disseminated papules or other lesions → **Aspiration or biopsy for bacterial, fungal, mycobacterial cultures and histopathology, consider evaluation for VZV** → • Consider vancomycin • Consider mold-active antifungal therapy in high-risk patients

Central nervous system symptoms → • CT and/or MRI • Lumbar puncture (if possible) • Neurology consult →

- Initial empiric therapy pending infectious disease (ID) consult
- Suspected meningitis should include an antipseudomonal beta-lactam agent that readily enters CSF (eg, cefepime, ceftazidime, meropenem) plus vancomycin, plus ampicillin (to cover listeriosis). If meropenem is used, addition of ampicillin is unnecessary
- For encephalitis, add high-dose acyclovir with hydration and monitor renal function

See Follow-up (FEV-10)

[i] See Antibacterial Agents (FEV-A) for dosing, spectrum, and specific comments/cautions.
[n] See Antifungal Agents (FEV-B) for dosing, spectrum, and specific comments/cautions.
[o] See Antiviral Agents (FEV-C) for dosing, spectrum, and specific comments/cautions. The antivirals are not equal in terms of efficacy, side effects, and resistance.

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PRINCIPLES OF DAILY FOLLOW-UP

- Daily site-specific H&P
- Daily review of laboratory tests and cultures: document clearance of bacteremia, fungemia with repeat blood cultures
- Evaluate for response to therapy (in 3–5 d) and drug toxicity:
  - Fever trends
  - Signs and symptoms of infection
- Evaluation of drug toxicity including end-organ toxicity (LFTs and renal function tests at least 2x/wk)

Responding/clinically stable
- Decreasing fever trend
- Signs and symptoms of infection are stable or improving
- Patient is hemodynamically stable

→ No change in initial empiric regimen. If initially started appropriately on agent for gram-positive resistant infection, continue course of therapy. Initial antibiotic regimen should be continued at least until neutrophil count is ≥500 cells/mcL and increasing

Persistently febrile/otherwise hemodynamically stable

→ No change in initial empiric regimen. If initially started appropriately on agent for gram-positive resistant infection, continue course of therapy. Initial antibiotic regimen should be continued at least until neutrophil count is ≥500 cells/mcL and increasing

Non-responding/clinically unstable
- Persistently or intermittently febrile
- Signs and symptoms of infection are not improving
- Patient may be hemodynamically unstable
- Persistent positive blood cultures

→
- Broaden coverage to include anaerobes, resistant Gram-negative rods, and resistant Gram-positive organisms, as clinically indicated
- Consider reevaluation with CT scans
- Consider adding G-CSF or GM-CSF (category 2B)
- Ensure coverage for *Candida*
- ID consult

FOLLOW-UP THERAPY

Documented infection → See Duration (FEV-11)

Neutrophils ≥500 cells/mcL → Discontinue therapy

Fever resolved, unknown origin

Neutrophils <500 cells/mcL[y] → Continue current regimen until neutropenia resolves[z]

- Consider antifungal therapy with activity against molds for fever continuing ≥4 days of empiric antibiotic therapy[aa,bb]
- Duration of therapy depends on clinical course, neutropenia recovery, toxicity, and opinions of ID consultants

[y] In the case of prolonged neutropenia (>14 days), consider judicious assessment of empiric therapy.
[z] In patients who defervesced, it may be appropriate in some cases to de-escalate to fluoroquinolone.
[aa] The timing to add empirical antifungal therapy varies with the risk of invasive mold infection but generally ranges between 4–7 days of neutropenic fever. In patients at high-risk for mold infection (neutropenia >10 days, allogeneic hematopoietic cell transplant recipients, high-dose corticosteroids), the panel recommends adding empirical antifungal therapy after the fourth day unless patient is receiving prophylaxis directed against molds.
[bb] Antifungal treatment regimens are highly variable and may include preemptive or empiric antifungal therapy or anti-mold azoles.

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FOLLOW-UP THERAPY FOR RESPONDING DISEASE

Documented infection →

- Initial antibiotic regimen should generally be continued until neutrophil count is ≥500 cells/mcL and increasing
- Duration of antimicrobial therapy may be individualized based upon:
  - Neutrophil recovery
  - Rapidity of defervescence
  - Specific site of infection
  - Infecting pathogen
  - Patient's underlying illness

→

SUGGESTED MINIMUM DURATION OF THERAPY FOR DOCUMENTED INFECTION[i,n,o]

These are general guidelines and may need to be revised for individual patients.

- Skin/soft tissue: 7–14 d
- Bloodstream infection (uncomplicated)
  - Gram-negative: 10–14 d
  - Gram-positive: 7–14 d
  - *S. aureus*: typically requires 4 weeks after first negative blood culture; treatment may need to be prolonged in cases of endovascular involvement; encourage ID consult
  - Yeast: ≥2 wks after first negative blood culture
  - Catheter removal favored for bloodstream infections with *Candida, S. aureus, Pseudomonas aeruginosa, Corynebacterium jeikeium, Acinetobacter, Bacillus* organisms, atypical mycobacteria, yeasts, molds, vancomycin-resistant enterococci, and *Stenotrophomonas maltophilia*
- Bacterial sinusitis: 7–14 d
- Catheter removal for septic phlebitis, tunnel infection, or port pocket infection
- Bacterial pneumonia: 7–14 d
- Fungal (mold and yeast):
  - *Candida*: minimum of 2 wks after first negative blood culture
  - Mold (eg, *Aspergillus*): minimum of 12 wks
- Viral:
  - HSV/VZV: 7–10 d (category 1); acyclovir, valacyclovir, or famciclovir (uncomplicated, localized disease to the skin)
  - Influenza: Oseltamivir is approved by the FDA for 5 d based on data from ambulatory otherwise healthy individuals with intact immune systems; longer courses (eg, at least 10 d) and until resolution of symptoms should be considered in the highly immunocompromised[cc]

[i] See Antibacterial Agents (FEV-A) for dosing, spectrum, and specific comments/cautions.
[n] See Antifungal Agents (FEV-B) for dosing, spectrum, and specific comments/cautions.
[o] See Antiviral Agents (FEV-C) for dosing, spectrum, and specific comments/cautions. The antivirals are not equal in terms of efficacy, side effects, and resistance.
[cc] Some centers use a higher dose (eg,150 mg).

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ANTIBACTERIAL AGENTS: EMPIRIC GRAM-POSITIVE ACTIVITY

Gram-positive Agents[a]	DOSE	SPECTRUM[c]	COMMENTS/PRECAUTIONS
Vancomycin	15 mg/kg IV every 12 h[b] For *C. difficile*: 125 mg PO every 6 h	Gram-positive organisms, with exception of VRE and a number of rare Gram-positive organisms	IV Formulation • Should not be considered as routine therapy for neutropenia and fever unless certain risk factors present (See FEV-D) • Dosing individualized with monitoring of levels • Loading dose may be considered
Daptomycin	6 mg/kg/d IV[b]	• Gram-positive organisms • Has in vitro activity against VRE but is not FDA-approved for this indication	• Weekly CPK to monitor for rhabdomyolysis • Not indicated for pneumonia due to inactivation by pulmonary surfactant • Consider an ID consult if using daptomycin above 6 mg/kg
Linezolid	600 mg PO/IV every 12 h	Gram-positive organisms, including VRE	• Hematologic toxicity (typically with prolonged cases, >2 wks) may occur, thrombocytopenia most common (0.3%–10%) • Serotonin syndrome is rare, use cautiously with SSRIs[1] • Not routinely used in fever and neutropenia, although may impair neutrophil and platelet recovery for extended use • Treatment option for VRE and MRSA • Peripheral/optic neuropathy with long-term use

[a]These drugs are not recommended as monotherapy for fever in the setting of neutropenia and should only be added for documented infection with resistant Gram-positive organisms or if certain risk factors are present. (See FEV-D)
[b]Requires dose adjustment in patients with renal insufficiency. Dosing variations exist.
[c]Once culture data are available, directed therapy may be initiated following an ID consult as appropriate for gram-positive pathogens.

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ANTIBACTERIAL AGENTS: ANTI-PSEUDOMONAL[d]

ANTI-PSEUDOMONAL AGENTS[e]	DOSE[b]	SPECTRUM	COMMENTS/PRECAUTIONS
Cefepime	2 g IV every 8 h	• Broad-spectrum activity against most Gram-positive and Gram-negative organisms • Not active against most anaerobes and *Enterococcus spp*	• Use for suspected/proven CNS infection with susceptible organism • Increased frequency of resistance among Gram-negative rod isolates at some centers • Empiric therapy for neutropenic fever (category 1) • Neurotoxicity may occur
Ceftazidime	2 g IV every 8 h	• Relatively poor Gram-positive activity • Breakthrough streptococcal infections reported • Not active against most anaerobes and *Enterococcus spp.*	• Use for suspected/proven CNS infection with susceptible organism • Increased frequency of resistance among Gram-negative rod isolates at some centers • Empiric therapy for neutropenia fever (category 2B; due to resistance among certain Gram-negative rods)
Imipenem/cilastatin sodium	500 mg IV every 6 h	• Broad-spectrum activity against most Gram-positive, Gram-negative, and anaerobic organisms • Preferred against extended spectrum beta-lactamase (ESBL) and serious *Enterobacter* infections • Carbapenem-resistant Gram-negative rod infections are an increasing problem at a number of centers	• Use for suspected intra-abdominal source • Meropenem is preferred over imipenem for suspected/proven CNS infection • Carbapenems may lower seizure threshold in patients with CNS malignancies or infection or with renal insufficiency • Effective in nosocomial pneumonia and intra-abdominal infections • Empiric therapy for neutropenic fever (category 1) • Data are limited, but we would expect that Doripenem, as an anti-pseudomonal beta-lactam like Meropenem, would be efficacious
Meropenem	1 g IV every 8 h (2 g IV every 8 h for meningitis)		
Doripenem	500 mg IV every 8 h		
Piperacillin/tazobactam	4.5 g IV every 6 h Some institutions use extended infusion: 3.375 g IV every 8 h	• Broad-spectrum activity against most Gram-positive, Gram-negative, and anaerobic organisms	• Use for suspected intra-abdominal source • Not recommended for meningitis • May result in false-positive galactomannan[2] • Empiric therapy for neutropenic fever (category 1)

[b]Requires dose adjustment in patients with renal insufficiency. Dosing variations exist.
[d]Emerging data may support continuous infusion use for higher potency against resistant cases.
[e]None of these agents are active against MRSA or VRE.

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ANTIBACTERIAL AGENTS: OTHER

OTHER ANTIBACTERIAL AGENTS	DOSE	SPECTRUM	COMMENTS/CAUTIONS
Aminoglycosides • Amikacin • Gentamicin • Tobramycin	Consider single loading dose in critically ill patients with individualized monitoring of levels[b]	Activity primarily against Gram-negative organisms	Often used as empiric therapy in seriously ill or hemodynamically unstable patients
Ciprofloxacin[f] in combination with Amoxicillin/ clavulanate	500–750 mg PO every 12 hours or 400 mg IV every 8–12 h[b] 875 mg PO every 12 h[g]	• Good activity against Gram-negative and atypical (eg, *Legionella spp.*) organisms • Less active than "respiratory" fluoroquinolones against Gram-positive organisms • Ciprofloxacin alone has no activity against anaerobes	• Avoid for empiric therapy if patient recently treated with fluoroquinolone prophylaxis • Increasing Gram-negative resistance in many centers • Oral antibiotic combination therapy in low-risk patients
Levofloxacin	500–750 mg oral or IV daily[b]	• Good activity against Gram-negative and atypical (eg, *Legionella spp.*) organisms • Improved Gram-positive activity compared to ciprofloxacin • Levofloxacin no activity against anaerobes • Moxifloxacin has limited activity against Pseudomonas	• Prophylaxis may increase bacterial resistance and superinfection[5] • Limited studies as empirical therapy in patients with fever and neutropenia • Prophylaxis in neutropenic patients[3,4]
Moxifloxacin	400 mg oral or IV daily		
Metronidazole	500 mg infused every 6 h or 500 mg PO every 6–8 h	Good activity against anaerobic organisms	
Trimethoprim/ sulfamethoxazole (TMP/SMX)	Prophylaxis: Single or double strength daily or Double strength 3 times per wk[b] Therapy: 15 mg/kg daily in divided doses	Activity against *P. jiroveccii*	• Highly effective as prophylaxis against *P. jirovecii* in high-risk patients (See INF-6) • Monitor for myelosuppression, hepatotoxicity, and hyperkalemia

[b]Requires dose adjustment in patients with renal insufficiency.
[f]Consider adding a second agent in cases of severe infection based on local susceptibility pattern.
[g]Although study data list 500 mg every 8 h, common practice uses amoxicillin/clavulanate 875 every 12 h.

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ANTIFUNGAL AGENTS: AZOLES

AZOLES[a]	DOSE	SPECTRUM	COMMENTS/CAUTIONS
Fluconazole	In adults with normal renal function: 400 mg IV/PO daily	• Active against *Candida* • Active against coccidioidomycosis and *C. neoformans*	• *Candida glabrata* is associated with variable resistance in vitro and *Candida krusei* is always resistant • Inactive against molds (eg, *Aspergillus* sp., Zygomycetes)
Isavuconazole	372 mg every 8 h x 6 doses IV/PO; then 372 mg every day IV/PO	Data are emerging for clinical activity for patients with invasive aspergillosis and mucormycosis	• Can be considered in patients intolerant or refractory to first-line anti-mold therapy
Itraconazole[b]	Oral 400 mg daily (aim for trough of >0.25 mcg/mL after 7 d of therapy)	• Active against *Candida*, *Aspergillus* sp., and some of the rarer molds • Active against dimorphic fungi and *C. neoformans*	• Itraconazole has negative inotropic properties and is contraindicated in patients with significant cardiac systolic dysfunction
Posaconazole[b]	• Prophylaxis: ▸ Oral tablet 300 mg BID on day 1 and then 300 mg PO every day[c] ▸ IV 300 mg every 12 h on day1 and then 300 mg IV every day after ▸ 200 mg TID oral solution	• Effective as prophylaxis in neutropenic patients with myelodysplastic syndrome and acute myelogenous leukemia[4], and in HCT recipients with significant GVHD[5] • Active against *Candida, Aspergillus* sp., some Zygomycetes sp., and some of the rarer molds • Active against dimorphic fungi and *C. neoformans*	• Evaluated as treatment of refractory infection (but not FDA-approved) in several invasive fungal diseases • Data on posaconazole as primary therapy for invasive fungal infections are limited • Liquid formulation should be administered with a full meal or liquid nutritional supplement or an acidic carbonated beverage. New formulation is better absorbed, though it should be taken with food. • For patients who cannot eat a full meal or tolerate an oral nutritional supplement alternative antifungal therapy should be considered • Proton pump inhibitors decrease posaconazole plasma concentration with oral solution
Voriconazole[b]	• IV 6 mg/kg every 12 h x 2 doses, then 4 mg/kg every 12 h; oral 200 mg PO BID (for invasive aspergillosis);[1] • IV 6 mg/kg every 12 h x 2, then 3 mg/kg every 12 h for non-neutropenic patients with candidemia[2]	• Active against *Candida, Aspergillus* sp., and some of the rarer molds • Active against dimorphic fungi and *C. neoformans* • Standard of care as primary therapy for invasive aspergillosis (category 1)[1,3] • Effective in candidemia in non-neutropenic patients[2]	• Poor activity against Zygomycetes • Long-term complications resulting from metabolic irregularities may include increased risk for squamous cell carcinoma and hyperphosphatemia • Fluorosis may occur with prolonged use and is associated with bone/muscle pain • Evidence for combination therapy remains limited[6] • IV formulation should be used with caution in patients with significant pre-existing renal dysfunction

[a]Azoles inhibit fungal cell membrane synthesis and inhibit cytochrome P450 isoenzymes that may lead to impaired clearance of other drugs metabolized by this pathway. Fluconazole is a less potent inhibitor of cytochrome P450 isoenzymes than the mold-active azoles. Drug-drug interactions are common and need to be closely monitored (consult package inserts for details). Reversible liver enzyme abnormalities are observed. QT prolongation and interactions have been reported.
[b]Therapeutic drug monitoring (TDM) is an ongoing area of research; TDM should be considered in consultation with ID specialists. (See Discussion).
[c]Liquid formulation may be used as needed.

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ANTIFUNGAL AGENTS: EMPIRIC AMPHOTERICIN B FORMULATIONS[d]

AMPHOTERICIN B FORMULATIONS[e]	DOSE	SPECTRUM	COMMENTS/CAUTIONS[g]
Amphotericin B deoxycholate (AmB-D)	Varies by indication, generally 0.5–1.5 mg/kg/d	Broad spectrum of antifungal activity including *Candida* *Aspergillus* sp., (excluding *Aspergillus terreus*) Zygomycetes, rarer molds, *Cryptococcus neoformans*, and dimorphic fungi	• Substantial infusional and renal toxicity including electrolyte wasting • Saline loading may reduce nephrotoxicity • Infusional toxicity may be managed with anti-pyretics, an anti-histamine, and meperidine (for rigors)
Amphotericin B lipid complex (ABLC)	5 mg/kg/d IV for invasive mold infections		Reduced infusional and renal toxicity compared to AmB-D
Liposomal amphotericin B (L-AMB)	3–5 mg/kg/d IV[7,f]		Reduced infusional and renal toxicity compared to AmB-D

[d]Can be considered for prophylaxis with ID consult for appropriate dosing recommendations.
[e]Broad spectrum of antifungal activity. Significant infusional and renal toxicity, less so with lipid formulations.
[f]The vast majority of subjects in this trial had invasive aspergillosis; optimal dosing of L-AMB for other mold infections (such as mucormycosis with 3 mg/kg/d IV) was as effective but less toxic than 10 mg/kg/d as initial therapy for invasive mold infections.
[g]Slowing the rate of infusion is an additional way to manage amphotericin infusion reactions.

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ANTIFUNGAL AGENTS: ECHINOCANDINS

ECHINOCANDINS[6,h]	DOSE	SPECTRUM	COMMENTS/CAUTIONS
Anidulafungin	200 mg IV x 1 dose, then 100 mg/d IV	Active against Candida and *Aspergillus sp*. Not reliable or effective against other fungal pathogens.	• Empiric therapy for candidemia and invasive candidiasis (category 1), pending susceptibility data • Efficacy established compared to fluconazole as primary therapy for candidemia and invasive candidiasis[12] • Excellent safety profile
Caspofungin	• 70 mg IV x 1 dose, then 50 mg IV daily; (35 mg IV daily for patients with moderate liver disease) • Some investigators use 70 mg IV daily as therapy for aspergillosis in salvage cases		• Primary therapy for candidemia and invasive candidiasis (category 1)[8] • Treatment for invasive, refractory aspergillosis. Similar efficacy compared to AmB-D as primary therapy for candidemia and invasive candidiasis but significantly less toxic[8] • 45% success rate as therapy for invasive, refractory aspergillosis[9] • Similar efficacy, but less toxic compared with L-AMB as empirical therapy for persistent neutropenic fever[8] • Excellent safety profile
Micafungin	• 100 mg/d IV for candidemia and 50–100 mg/d IV as prophylaxis • 150 mg/d IV used at some centers for *Aspergillus sp.* infection in salvage cases		• Primary therapy for candidemia and invasive candidiasis (category 1) • Similar efficacy compared to caspofungin[10] and compared to L-AMB[11] as primary therapy for candidemia and invasive candidiasis • Excellent safety profile

[h]A number of centers use combination voriconazole and an echinocandin for invasive aspergillosis based on clinical data. Evidence for combination therapy remains limited.

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ANTIFUNGAL AGENTS – REFERENCES (page 4 of 4)

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ANTIVIRAL AGENTS[a]

AGENT	COMMON INDICATION	SPECTRUM	COMMENTS/CAUTIONS
Acyclovir	• Prophylaxis[b]: HSV (400–800 mg PO BID); VZV in allogeneic HCT recipients (800 mg PO BID)[1]; CMV in allogeneic HCT recipients (800 mg PO QID)[2,c] for patients unable to tolerate oral therapy, 250 mg/m^2 IV every 12 h • Post-VZV exposure prophylaxis: 800 mg PO 5 times daily • Treatment: significant mucocutaneous HSV (5 mg/kg IV every 8 h for 7–10 days); single dermatomal VZV (800 mg PO 5 times daily or 10 mg/kg IV every 8 h for 7–10 days); disseminated HSV or VZV including viral encephalitis (10 mg/kg IV every 8 h)[3]	HSV, VZV	• Hydration to avoid crystal nephropathy with high dose • Dosing based upon ideal body weight
Famciclovir	Prophylaxis: HSV or VZV (250 mg PO BID) Treatment: HSV (250 mg PO TID) or VZV (500 mg PO TID)[5,6]	HSV, VZV	No data for oncologic related prophylaxis
Ganciclovir	• Preemptive therapy for CMV: 5 mg/kg every 12 h for 2 weeks; if CMV remains detectable, further ID evaluation may be required • Treatment: CMV disease (5 mg/kg every 12 h for 2 weeks followed by 5–6 mg/kg daily for at least an additional 2–4 weeks and resolution of all symptoms). Consider adding IVIG for CMV pneumonia. Formulations and dosages of IVIG vary in different series"	CMV, HSV, VZV, HHV-6	May cause bone marrow suppression
Valacyclovir	• Prophylaxis[b]: HSV or VZV (500 mg PO BID or TID) CMV in allogeneic HCT recipients (2 gm PO QID)[c,4] • Treatment: HSV or VZV (Valacyclovir 1 gm PO TID)[3]	HSV, VZV	
Valganciclovir	• Prophylaxis: CMV (900 mg daily)[d] • Preemptive therapy for CMV: Induction with 900 mg PO BID for at least 2 weeks and until negative test; consider additional 900 mg PO daily for at least 7 days after a negative test for maintenance	CMV HSV, VZV, HHV-6	May cause bone marrow suppression

[a]Requires dose adjustment in patients with renal insufficiency.
[b]Antiviral prophylaxis should be targeted to specific high-risk patients (see INF-3). In non-transplant high-risk patients, prophylaxis should be administered to patients seropositive for HSV or VZV (or with a history of chicken pox). In HCT recipients, prophylaxis is only indicated if either the donor or recipient is seropositive for the virus in question. The indicated doses for antiviral agents are for adults with normal renal function; consult package insert for dose modification in pediatric patients and in patients with renal impairment. Prophylactic antiviral doses may be higher than those routinely used in immunocompetent persons (for example, for recurrent cold sores); there is substantial variability in the prophylactic doses of acyclovir used in different clinical trials in patients with hematologic malignancies and in HCT recipients.
[c]High-dose acyclovir and valacyclovir have been used as prophylaxis for CMV. Because these agents have weak activity against CMV, a strategy of CMV surveillance and preemptive therapy with ganciclovir, valganciclovir, or foscarnet is required among patients at high risk for CMV disease.
[d]In general, the strategy of CMV surveillance testing by PCR followed by preemptive anti-CMV therapy for a positive result is favored over universal long-term prophylaxis in allogeneic HCT patients.

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ANTIVIRAL AGENTS[a]

AGENT	COMMON INDICATION	SPECTRUM	COMMENTS/CAUTIONS
Cidofovir[e]	**Treatment: Cidofovir 5 mg/kg IV every wk for 2 wks, followed by cidofovir 5 mg/kg every 2 wks with probenecid 2 gm PO 3 h before the dose, followed by 1 gm PO 2 h after the dose and 1 gm PO 8 h after the dose and IV hydration**	**CMV, HZV, VZV, adenovirus**	**Ocular toxicity, bone marrow toxicity, hydration, and probenecid required to reduce nephrotoxicity** **Third-line for CMV**
Foscarnet	**Prophylaxis for CMV: 60 mg/kg IV every 8–12 h for 7 d, followed by 90–120 mg/kg IV daily until day 100 after HCT[d,7,8]** **Preemptive therapy for CMV: Induction for 2 wks, either 60 mg/kg IV every 8 h or 90 mg/kg IV every 12 h.** **Therapy: Acyclovir-resistant HSV (40 mg/kg every 8 h for 7–10 days); CMV disease (90 mg/kg every 12 h for 2 wks followed by 120 mg/kg daily for at least an additional 2–4 wks and resolution of all symptoms). Add IVIG for CMV pneumonia.**	**HSV, VZV, CMV, HHV-6**	**Drug of choice for acyclovir-resistant HSV and VZV and ganciclovir-resistant CMV; nephrotoxic; monitor electrolytes**
Oseltamivir[f]	**Prophylaxis: 75 mg PO daily[g,9]** **Treatment: 75 mg BID**	**Influenza A & B**	**May cause nausea (improved when taken with food)**
Zanamivir[f]	**Prophylaxis: 2 oral inhalations (5 mg/inhalation) daily** **Treatment: 2 oral inhalations (5 mg/inhalation) BID**	**Influenza A & B**	**Duration influenced by nature of exposure (ongoing vs. time limited); may cause bronchospasm**

[a]Requires dose adjustment in patients with renal insufficiency.
[d]In general, the strategy of CMV surveillance testing by PCR followed by preemptive anti-CMV therapy for a positive result is favored over universal long-term prophylaxis in allogeneic HCT patients.
[e]A dose of 1 mg/kg administered three times a week is common for less severe adenovirus infections.
[f]Consider peramivir for patients who cannot have oral oseltamivir or inhaled zanamivir.
[g]Prophylaxis among highly immunocompromised persons during community and nosocomial outbreaks of influenza A should be considered.

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ANTIVIRAL AGENTS

AGENT	COMMON INDICATION	SPECTRUM	COMMENTS/CAUTIONS
Intravenous immuno-globulin (IVIG)	Doses of IVIG vary among different studies and different viral illnesses. A dose of 400–500 mg/kg administered daily for 5 days is common for parvovirus B19-associated disease.[10] For CMV pneumonia and RSV disease, adjunctive IVIG (400 mg/kg) every other day for 3–5 doses is commonly administered; the optimal dosing schedule is undefined.	RSV, Parvovirus B19, CMV	• Pathogen-specific immunoglobulin or monoclonal antibodies may be considered • CMV-specific IVIG is not more efficacious than standard IVIG
Ribavirin (category 3)	Consider for treatment of RSV disease[h]: 6 gm administered by continuous inhalation via SPAG-2 nebulizer every 12–18 h daily or 2 g over 2 h TID; or 600–800 mg PO BID; may be paired with IVIG (400–500 mg/kg every other day)[11,12]	RSV	• Experience in immunocompromised adults with RSV disease is limited, but should be considered given potential morbidity and mortality associated with RSV infection • Ribavirin is teratogenic; precautions are required during administration (see package insert)
Entecavir	0.5 mg PO every day (nucleoside-treatment-naïve with compensated liver disease); or 1 mg PO every day (lamivudine-refractory or known lamivudine resistance mutations or decompensated liver disease)	HBV	• Potential for HBV resistance: ▸ Lamivudine: high (especially as monotherapy) ▸ Tenofovir: none reported to date ▸ Entecavir: low • Dose adjustment recommended for renal impairment • Lactic acidosis and severe hepatomegaly with steatosis reported with nucleoside analogues • Tenofovir potential for nephrotoxicity; monitor for renal function Entecavir and tenofovir monotherapy are generally preferred. Choice of agent is heavily influenced by the overall condition of the patient, renal insuffiency, and the type of chemotherapy planned. Combination therapy is not generally recommended unless viral load is significantly elevated.
Lamivudine	100 mg PO every day		
Tenofovir DF	300 mg PO every day		

[h]Inhaled ribavirin is only FDA approved for hospitalized infants and young children with severe lower respiratory tract RSV disease.

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RISK ASSESSMENT RESOURCES

USING THE MASCC RISK-INDEX SCORE

- Using the visual analogue score, estimate the patient's burden of illness at the time of initial clinical evaluation. No signs or symptoms or mild signs or symptoms are scored as 5 points; moderate signs or symptoms are scored as 3 points. These are mutually exclusive. No points are scored for severe signs or symptoms or moribund.
- Based on the patient's age, past medical history, present clinical features, and site of care (input/output when febrile episode occurred), score the other factors in the model and total the sum.

BURDEN OF ILLNESS

How sick is the patient at presentation?

No signs or symptoms	Mild signs or symptoms	Moderate signs or symptoms	Severe signs or symptoms	Moribund

Estimate the burden of illness considering all comorbid conditions

MASCC RISK-INDEX SCORE/MODEL[1]

Characteristic	Weight
• Burden of illness	
▸ No or mild symptoms	5
▸ Moderate symptoms	3
• No hypotension	5
• No COPD	4
• Solid tumor or hematologic malignancy with no previous fungal infection	4
• No dehydration	3
• Outpatient status	3
• Age <60 years	2

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Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 08/11/14

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.

Table of Contents

Overview

Infectious diseases are important causes of morbidity and mortality in patients with cancer. In certain instances, the malignancy itself can predispose patients to severe or recurrent infections. Neutropenia has been recognized for many decades as a major risk factor for the development of infections in patients with cancer undergoing chemotherapy. Effective strategies to anticipate, prevent, and manage infectious complications in neutropenic patients with cancer have led to improved outcomes.[1-12] Due to advances in antimicrobial therapy, it is now uncommon for patients with acute leukemia or patients undergoing stem cell transplantation to die from infections during the neutropenic period.

Although neutropenia remains a key risk factor for infections, other immunocompromised states pose at least equal risk. Allogeneic hematopoietic stem cell transplant (HSCT) recipients with neutrophil recovery who require intensive immunosuppressive therapy for graft-versus-host disease (GVHD) are an example of non-neutropenic patients at great risk for common bacterial, viral, and opportunistic infections.[13-16] The spectrum of infectious diseases in allogeneic HSCT 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. Our scope also includes other highly immunocompromised patients with cancer (eg, patients receiving high-dose corticosteroids, purine analogues, monoclonal antibody therapy).

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

The NCCN Guidelines on Prevention and Treatment of Cancer-Related Infections are largely divided into four sections comprising discussions on the following: risk factors for infection (major host factors that predispose patients to infectious diseases), prevention of infectious complications (including the use of antimicrobial prophylaxis and pre-emptive therapy), management of neutropenic fever, and management of site-specific infections (eg, pneumonia, abdominal infections, catheter-associated infections).

Host Factors That Predispose Patients to Infectious Complications

Immunodeficiencies Associated With Primary Malignancy

Certain malignancies are inherently associated with immune deficits. Patients with hematologic malignancies (eg, chronic and acute leukemias, non-Hodgkin's lymphoma [NHL], myelodysplastic syndrome [MDS]) may be leukopenic due to infiltration of the marrow with malignant cells or due to a dysfunctional marrow. Patients with chronic lymphocytic leukemia (CLL) frequently have hypogammaglobulinemia leading to increased susceptibility to encapsulated bacteria, principally *Streptococcus pneumoniae*.[17] Such patients may have recurrent sinopulmonary infections and septicemia. Patients with multiple myeloma are often functionally hypogammaglobulinemic; the total level of immunoglobulin production may be elevated, but the repertoire of antibody production is restricted. Savage et al[18] noted a biphasic pattern of infection among patients with multiple myeloma. Infections by *S*

pneumoniae and *Haemophilus influenzae* occurred early in the disease and in patients responding to chemotherapy, whereas infections by *Staphylococcus aureus* and gram-negative pathogens occurred more commonly in advanced disease and during neutropenia.

Patients with advanced or refractory malignancy have a greater risk of infectious complications than those who respond to therapy. Refractory hematologic malignancies can be associated with marrow failure caused by the underlying disease or from the multiple lines of prior cytotoxic or immunosuppressive therapy. In patients with CLL, those who receive multiple chemotherapeutic regimens are at a significantly increased risk for developing severe infections.[19] A retrospective study showed that nearly 90% of heavily pretreated patients (median 3 prior regimens; range, 1-8) with fludarabine-refractory CLL experienced serious infectious complications requiring hospitalization.[20] Pathogens responsible for the infections were bacterial, viral, fungal, and opportunistic pathogens, including *Pneumocystis jirovecii* (formerly called *Pneumocystis carinii)*.[20]

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

Neutropenia

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

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

of fever during neutropenia remain uncommon, and most infection-associated deaths result from subsequent infections during the course of neutropenia.

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

Disruption of Mucosal Barriers

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

Splenectomy and Functional Asplenia

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

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

Corticosteroids and Other Lymphotoxic Agents

High-dose corticosteroids (>20 mg prednisone daily) have profound effects on the distribution and function of neutrophils, monocytes, and lymphocytes. In patients with cancer, corticosteroids are seldom the only immunosuppressive agents administered, and it is therefore difficult to delineate the degree of impairment in host defense elicited by the corticosteroid regimen alone. The risk of infections is a function of the dose and duration of corticosteroids, co-existing immunodeficiencies (such as neutropenia and use of other immunosuppressive agents), and the status of the malignancy. Corticosteroids blunt fever and local signs of infection, such as peritonitis.

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

An increasing number of patients with hematologic malignancies and allogeneic HSCT recipients are being treated with novel monoclonal antibodies that cause a depletion of lymphocyte subsets. Alemtuzumab is a humanized monoclonal antibody that targets CD52, which is abundantly expressed on most normal and malignant B- and T-lymphocytes. This agent has been used most extensively in patients with CLL who have failed fludarabine therapy. Alemtuzumab has been associated with grade 3 or 4 neutropenia in about 40% of patients with previously untreated CLL and in 56%-78% of patients with fludarabine-refractory disease.[38-41] Alemtuzumab is also associated with prolonged and severe lymphopenia in most patients. Four weeks after initiation of alemtuzumab, the median CD4+ count was 0 cells/mcL and 6 months after discontinuation, the count was 238 cells/mcL in previously untreated patients.[38] The CD8+ cell counts also changed in a similar manner. In previously treated patients receiving alemtuzumab, CD4+ and CD8+ counts may not recover to baseline levels until more than 1 year after completion of therapy.[38] Infections pose a concern for morbidity and/or mortality in alemtuzumab recipients, particularly for patients with heavily pretreated, fludarabine-refractory disease.[20,40,42] Bacterial, viral, fungal, mycobacterial, and *P jirovecii* infections have been reported with alemtuzumab.[40,42,43] Anti-infective prophylaxis against herpes viruses and PCP is recommended in patients receiving alemtuzumab treatment (see *Antiviral Prophylaxis and Preemptive Antiviral Therapy and Prophylaxis for Pneumocystis jirovecii* in this Discussion).[38] Several studies have shown that patients treated with alemtuzumab have increased susceptibility to cytomegalovirus (CMV) reactivation and disease;[38-40,44-46] however, in the absence of a large randomized controlled trial, the Infectious Diseases Working Party of

the German Society for Hematology and Oncology does not currently recommend CMV surveillance in alemtuzumab recipients.[47] Conversely, both the Working Group of the UK CLL Forum on behalf of the British Committee for Standards in Haematology and the International Workshop on Chronic Lymphocytic Leukemia on behalf of the National Cancer Institute recommend routine monitoring for CMV in patients with CLL that have therapies associated with the potential for CMV reactivation (eg, alemtuzumab or HSCT).[48,49] The NCCN Panel recommends that surveillance for CMV reactivation is conducted routinely using polymerase chain reaction (PCR) or antigen-based methods in alemtuzumab recipients (see *Antiviral Prophylaxis and Preemptive Antiviral Therapy: Cytomegalovirus* in this Discussion). Other compounds known to cause lymphopenia (eg, proteasome inhibitors) are associated with an increased risk of herpes zoster reactivation; therefore, prophylaxis with acyclovir or valacyclovir is recommended.

Anti-CD20 monoclonal antibodies (eg, rituximab, ofatumumab) are widely used in the treatment of patients with B-cell lymphoid malignancies.[50,51] The use of these monoclonal antibodies has been associated with increased risks for hepatitis B virus (HBV) reactivation, which can lead to fulminant hepatitis, liver failure, and/or death.[51-58] Antiviral prophylaxis is generally recommended for patients who test positive for HBV surface antigen (see *Antiviral Prophylaxis and Preemptive Antiviral Therapy: Hepatitis B virus* in this Discussion). In addition, the use of anti-CD20 monoclonal antibodies in patients with B-cell malignancies has been associated with rare instances of progressive multifocal leukoencephalopathy (PML).[51,52] PML is a demyelinating disease of the CNS resulting from reactivation of the John Cunningham (JC) virus, and occurs in severely immunocompromised individuals. Though rare, PML is most often fatal. In reports of PML potentially associated with rituximab treatment in patients with B-cell malignancies, rituximab was typically given in combination with chemotherapy regimens or patients had received prior immunosuppressive regimens.[59-66] Moreover, patients who developed PML often presented with low CD4+ counts or abnormal (low) CD4+/CD8+ ratio,[59,61,64,66] which points to a critical role of T-cell immunity in suppressing reactivation of the JC virus.

Hematopoietic Stem Cell Transplantation

Autologous HSCT recipients generally have fewer infectious complications than allogeneic transplant recipients. Most infections in autologous HSCT recipients occur during neutropenia or within the first few months after transplantation before reconstitution of cellular immunity. However, compared to unmanipulated autografts, CD34+ cell enrichment of autografts leads to a substantial reduction in T cells, natural killer cells, and monocytes which delays immune reconstitution.[67] Recipients of CD34+ cell-enriched autografts appear to have a similar level of risk as allogeneic HSCT recipients for contracting CMV and other opportunistic infections.[67] Severe or ulcerative mucositis, which develops as a result of myeloablative high-dose therapy administered prior to HSCT, is associated with the occurrence of bacteremia in autologous HSCT recipients.[68-70] Recently, a multicenter prospective study evaluated the potential role of G-CSF responsiveness in predicting the occurrence of infections in patients with hematologic malignancies undergoing high-dose therapy and autologous HSCT.[71] Responsiveness to G-CSF was determined by the administration of a single dose of G-CSF after completion of high-dose therapy (but prior to HSCT), and measuring the induced leukocyte peak occurring 12-14 hours after the G-CSF dose. G-CSF responsiveness showed a significant inverse correlation with incidences of febrile neutropenia and infections (ie, higher responsiveness associated with

lower infection rates), and was shown to be the only independent predictor of infections based on multivariate analysis.[71]

The spectrum of pathogens to which allogeneic HSCT recipients are most susceptible follows a time line corresponding to the predominant immune defects. In the first month after HSCT (pre-engraftment period), neutropenia and breakdown of the mucocutaneous barrier comprise the principal host defense defect, which predisposes patients to bacterial and fungal infections.[72,73] In addition, reactivation of HSV can often occur during this period. After myeloid engraftment, qualitative dysfunction of phagocytes persists due to corticosteroid and other immunosuppressive agents. The risk of infection by opportunistic viruses and filamentous fungi (molds) during this period is strongly associated with the severity of GVHD and with the requirement for potent immunosuppressive regimens.

Susceptibility to infections during the early post-engraftment period is primarily due to defects in cell-mediated immunity that can persist for several months even in uncomplicated allogeneic HSCT recipients, predisposing them to common bacterial and viral infections and to multiple opportunistic infections (eg, molds, viruses, atypical bacteria). In particular, the dominant pathogens during this early post-engraftment period can include herpes viruses (especially CMV), *P jirovecii*, and invasive molds such as *Aspergillus*.[72,73]

Whereas mature and cooperative T- and B-cell functions are usually reconstituted by 1 to 2 years following engraftment, chronic GVHD is associated with persistently depressed cell-mediated and humoral immunity. Defective reconstitution of humoral immunity is a major factor contributing to increased infection susceptibility in the late post-engraftment transplant period. Winston et al[74] noted a high frequency of pneumococcal infections between 7 and 36 months after transplantation, associated with serum opsonic deficiency for *S pneumoniae*. Kulkarni et al[75] reported that pneumococcal sepsis occurred a median of 10 months after transplant (range, 3–187 months) and was significantly more frequent in patients with chronic GVHD.

Guidelines from the CDC recommend that allogeneic HSCT recipients with severe hypogammaglobulinemia (IgG<400 mg/dL) and with recurrent infections receive intravenous immunoglobulin (IVIG) prophylaxis; IVIG is not recommended in other patient groups or in autologous HSCT recipients routinely.[16] The CDC has published guidelines on vaccination of HSCT recipients and household members to prevent infections following transplantation.[16] The 2009 guidelines on the prevention of infections in HSCT recipients (jointly sponsored by the CDC, IDSA, ASBMT, EMBT, among other organizations) reported similar recommendations on the use of IVIG, and also provides specific recommendations on the prevention of bacterial, viral, and fungal infections, and on the administration of vaccines in this patient population.[73]

Allografts from human leukocyte antigen (HLA)–matched unrelated donors, partially mismatched related donors, and cord blood are associated with a higher risk of GVHD. T-cell depletion delays immune reconstitution and, consequently, carries a greater risk of infectious complications, most notably by opportunistic viral[76] and fungal[77,78] pathogens. Cord blood transplant recipients may have a higher risk of infections than other allograft recipients during the early transplant period because of slower myeloid engraftment.

NCCN Recommendations for Categories of Infection Risk

The NCCN Guidelines provide a summary of infection risk categories (low, intermediate, and high risk) in patients with cancer, which are based on factors such as the underlying malignancy, disease status

(eg, active disease or disease in remission), duration of neutropenia, prior exposure to chemotherapy, and intensity of immunosuppressive therapies (see Overall Infection Risk in Cancer Patients on pages INF-1 to INF-3). Patients with solid tumors receiving standard chemotherapy regimens and who have an anticipated duration of neutropenia shorter than 7 days are generally considered at low risk for infectious complications; thus, antimicrobial prophylaxis is not routinely recommended in these patients.[22] For patients with HSV-positive serology who are otherwise at low risk for infections, prophylaxis with antivirals can be considered.

Patients with an anticipated duration of neutropenia of 7 days or longer are considered to be at greater risk for developing infectious complications.[22] In the NCCN Guidelines, patients with an anticipated duration of neutropenia of 7 to 10 days are considered to be at intermediate risk for infections (see *Overall Infection Risk in Cancer Patients* on page INF-1). In addition, patients with lymphoma, multiple myeloma, or CLL, autologous HSCT recipients, or those receiving treatment with purine analog-containing regimens (most often for hematologic malignancies such as NHL or CLL) are also considered intermediate risk. Patients with NHL (in particular, for T-cell malignancy subtypes) or CLL treated with alemtuzumab-containing regimens are considered at high risk for infections. For the intermediate-risk patients, prophylaxis with antibacterials (eg, fluoroquinolones) should be considered. Antivirals should be given during periods of neutropenia, and for autologous HSCT recipients, until at least 30 days following transplant (however, consider antiviral prophylaxis for varicella zoster virus [VZV] for at least 1 year after HSCT). Antifungals should be considered during periods of neutropenia and for anticipated mucositis (with the latter pertaining to autologous HSCT) for intermediate-risk patients.

Patients with anticipated duration of neutropenia longer than 10 days, those undergoing intensive induction/consolidation therapy for acute leukemias (ie, acute lymphoblastic leukemia [ALL] or acute myeloid leukemia [AML]), patients undergoing treatment with alemtuzumab-containing regimens, allogeneic HSCT recipients, and those with GVHD following allogeneic HSCT are considered at high risk for infectious complications. For these high-risk patients, prophylaxis with antibacterials (eg, fluoroquinolones) should be considered. These patients should receive antiviral prophylaxis during periods of neutropenia, and for at least 30 days after transplant for HSCT recipients (however, consider antiviral prophylaxis for VZV for at least 1 year after HSCT). In addition, prophylaxis with antifungals can be considered for patients with ALL and for neutropenic patients with AML/MDS.[22] For allogeneic HSCT recipients or those with significant GVHD receiving immunosuppressive therapy, antifungal prophylaxis can also be considered during periods of neutropenia and until resolution of GVHD (see *Overall Infection Risk in Cancer Patients* on pages INF-1 to INF-3). For allogeneic HSCT recipients with GVHD, additional prophylactic measures such as administration of penicillin and trimethoprim-sulfamethoxazole (TMP/SMX) should also be considered. Allogeneic HSCT recipients, patients with ALL, and patients treated with alemtuzumab are all at increased risk for infection with *P jirovecii*. These patients should receive TMP/SMX for prevention of PCP (see *Prophylaxis for Pneumocystis jirovecii* in this Discussion).

Prevention of Infectious Diseases

Preventive measures against infections in patients with cancer generally involve upfront prophylaxis or pre-emptive therapy using broad spectrum antimicrobial agents directed against the most common

infecting pathogens (including bacterial, viral, and fungal) in high-risk patients.

Antibacterial Prophylaxis During Neutropenia

Patients with cancer and chemotherapy-induced neutropenia are at risk for severe bacterial infections. Fluoroquinolones are the most commonly used prophylactic antibacterial agents in adults with chemotherapy-induced neutropenia. In a meta-analysis that evaluated 18 trials (N=1408) in which fluoroquinolones were compared to either placebo or TMP/SMX, fluoroquinolone prophylaxis significantly reduced the incidence of gram-negative infections by about 80% compared with trials without prophylaxis (relative risk [RR], 0.21; 95% CI, 0.12–0.37), leading to an overall reduction in total infections.[79] The reduction in fever was small, and in blinded trials, was not significant. Fluoroquinolone prophylaxis did not affect infection-related mortality rates in this meta-analysis. Moreover, the rate of gram-positive infections and fungal infections was not significantly affected by fluoroquinolone prophylaxis.[79] This is an important consideration given the occurrence of an increased rate of gram-positive infections in some trials of fluoroquinolone prophylaxis.[80] Viridans group streptococcal bacteremia breakthroughs have been associated with quinolone prophylaxis,[26,81,82] which poses a concern given the potential for substantial morbidity and mortality associated with this pathogen in neutropenic patients.

The potential benefit of antibacterial prophylaxis was evaluated in a single-center randomized study in patients undergoing high-dose therapy followed by autologous HSCT (N=157).[83] Patients were randomized to receive prophylaxis (with 500 mg oral ciprofloxacin twice daily and 1000 mg intravenous (IV) vancomycin once daily) or no prophylaxis; all patients received antifungal prophylaxis with fluconazole. Empirical therapy (comprising amikacin, ceftazidime and full-dose vancomycin) was initiated when neutropenic fever developed. The use of antibacterial prophylaxis significantly reduced the incidences of neutropenic fever (56% vs. 91%; $P < .001$) and bacteremia (6% vs. 35%; $P = .005$) compared with no prophylaxis, but at the expense of decreased responses to first-line empirical therapy (66% vs. 84%; $P = .025$).[83] Among the patients who received prophylaxis and developed neutropenic fever, 34% required second-line therapy that included a carbapenem, suggesting that these patients developed infections resistant to the prophylactic regimen. Duration of hospitalization and overall survival rates were similar between study arms. These results led the study investigators to conclude that routine antibacterial prophylaxis was not recommended in patients undergoing high-dose therapy and autologous HSCT.[83] It should be noted, however, that the prophylactic regimen in this study included vancomycin (albeit at a lower dose), which is not supported by the panel for use as either antimicrobial prophylaxis or initial empirical therapy for fever and neutropenia. This view is in agreement with the published guidelines of the IDSA.[22]

Studies have provided additional insight into the benefits and limitations of prophylaxis among neutropenic patients with varying degrees of risk for serious infectious complications. Gafter-Gvili et al[84] conducted a meta-analysis of 95 randomized controlled trials comparing antibiotic prophylaxis with placebo, no intervention or prevention with another antibiotic in afebrile neutropenic patients.[84] Antibiotic prophylaxis significantly decreased the risk for all-cause death when compared with placebo or no treatment (RR, 0.67; 95% CI, 0.55–0.81); significant risk reductions were also observed for infection-related mortality, fever, clinically and microbiologically documented infections, gram-positive and gram-negative infections, and bacteremia. Similar results were

obtained when the analysis was restricted to prophylaxis with fluoroquinolones. Fluoroquinolone prophylaxis significantly reduced the risk for all-cause mortality (RR, 0.52; 95% CI, 0.35–0.77), as well as for all secondary measures indicated above.[84] Most of the trials involved hospitalized patients with hematologic malignancies, and data were inadequate to assess the relationship between duration and degree of neutropenia and relative risk of mortality. No significant increase was observed in fluoroquinolone-resistant bacterial infections, although the length of observation may have been too short to detect the emergence of resistant bacteria.[84] A subsequent systematic review and meta-analysis conducted by the same group of investigators evaluated the risks associated with colonization and infections by fluoroquinolone-resistant bacteria.[85] Most of the studies (48 of 56 trials) included patients with hematologic malignancies or HSCT recipients. Results of the analysis (based on 56 trials, N=7878; data on colonization by resistant bacteria based on 27 trials) showed that quinolone prophylaxis was associated with an increase (although not statistically significant) in colonization with quinolone-resistant organisms compared with placebo or no intervention (RR,1.68; 95% CI, 0.71–4.00). However, no differences were observed in the incidence of infections caused by quinolone-resistant organisms (RR, 1.04; 95% CI, 0.73–1.50), regardless of whether these were resistant gram-negative or gram-positive bacteria.[85] Moreover, in an analysis of trials comparing quinolones with TMP/SMX (11 trials), prophylaxis with quinolones was associated with fewer incidents of colonization and infections by resistant bacteria (those resistant to the prophylactic agents) compared with the use of TMP-SMX.[85] This analysis suggests that prophylaxis with quinolones does not appear to increase the rate of infections by resistant organisms. In a recent systematic review and meta-analysis (based on 109 trials, N=13,579) of trials comparing antibacterial prophylaxis with placebo, no intervention or prevention with another agent in afebrile neutropenic patients, the use of antibacterial prophylaxis was found to significantly reduce the risk of all-cause mortality (risk ratio, 0.66; 95% CI, 0.55–0.79) as well as infection-related deaths (risk ratio, 0.61; 95% CI, 0.48–0.77) compared with placebo or no intervention.[86] The use of prophylaxis also significantly reduced the incidence of fever and clinically or microbiologically documented infections. Although no significant differences in all-cause or infection-related mortality were seen between prophylactic quinolones or TMP/SMX, the use of quinolones was associated with fewer adverse events that resulted in discontinuation of the drug and decreased drug resistance.[86] The NCCN Guidelines Panel recognizes the substantial limitations associated with meta-analyses. Due to the complexity of treating infections, the panel believes that the risks and benefits of antibacterial prophylaxis in patients with hematologic malignancies and in the HSCT must take into account the potential detriments related to adverse effects and/or the potential development of resistance; therefore, judicious use of antibacterial prophylaxis is recommended over universal prophylaxis of all patients.

Two large randomized, placebo-controlled studies showed the benefit of levofloxacin prophylaxis in neutropenic patients at different levels of risk for infectious complications.[87,88] Levofloxacin has similar activity against gram-negative pathogens compared to ciprofloxacin and ofloxacin; however, levofloxacin has improved activity against certain gram-positive pathogens, including streptococci. Bucaneve et al[87] evaluated levofloxacin prophylaxis in adult patients with cancer in whom chemotherapy-induced neutropenia (less than 1000 neutrophils/mcL) was expected to occur for more than 7 days. This protocol intentionally excluded patients anticipated to have a short duration of neutropenia who would generally be candidates for outpatient management of neutropenic fever. Levofloxacin recipients had a lower rate of

microbiologically documented infections, bacteremias, and single-agent gram-negative bacteremias than did placebo recipients.[87] The effects of prophylaxis were also similar between patients with acute leukemia and those with solid tumors or lymphoma. Mortality and tolerability were similar between the 2 groups.[87]

Cullen et al[88] evaluated levofloxacin prophylaxis after chemotherapy for patients with solid tumors and lymphomas that were anticipated to have brief durations of neutropenia categorizing these patients as low risk. The primary outcome was the incidence of clinically documented febrile episodes (temperature more than 38°C) attributed to infection. Secondary outcomes included the incidence of all probable infections, severe infections, and hospitalization. A total of 1565 patients, 87% with solid tumors and 13% with lymphoma, were randomized to receive either levofloxacin or the placebo.. During the entire chemotherapy course, 10.8% of levofloxacin recipients had at least one febrile episode compared with 15.2% of placebo recipients (P = .01).[88] Hospitalization was required for the treatment of infection (suspected and documented) in 15.7% of patients in the levofloxacin group and 21.6% of patients in the placebo group (P = .004). The incidence of severe infections, infection-related mortality, and overall mortality were similar between both groups.[88]

Thus, the main advantage of levofloxacin prophylaxis in intermediate and higher risk patients with chemotherapy-induced neutropenia was a reduction in clinically significant bacterial infections, including gram-negative rod bacteremia.[87] In contrast, the main advantage of prophylaxis in lower risk neutropenic patients was a small, but statistically significant, reduction in fever and hospitalization for neutropenic fever.[88] Neither study conducted a systematic long-term evaluation of antimicrobial resistance. The NCCN Guidelines Panel considers that reduction in the incidence of significant infections is a more clinically meaningful endpoint than reduction in the incidence of neutropenic fever. Using prevention of neutropenic fever as the primary endpoint in this study by Cullen et al,[88] 1000 hypothetical low-risk patients would have to receive prophylaxis during each cycle of chemotherapy-induced neutropenia to benefit only 44 patients.

An important consideration for low-risk patients with short durations of neutropenia is whether fluoroquinolone prophylaxis is of greater benefit than outpatient fluoroquinolone treatment for fever and neutropenia, should it occur. Both the NCCN Guidelines Panel and IDSA[22] recommend oral fluoroquinolone-based regimens as outpatient empiric therapy for neutropenic fever in adults who meet criteria for a low risk of complications. Fluoroquinolone prophylaxis may preclude its subsequent use as empiric therapy for neutropenic fever in the same patient. The modest difference in rates of hospitalization for suspected infection in levofloxacin compared to placebo recipients (15.7% vs. 21.6%, respectively) may be offset by exclusion of outpatient oral empiric therapy in patients receiving fluoroquinolone prophylaxis. To limit antibacterial use, Cullen et al[89] have suggested prophylaxis with levofloxacin on cycle 1 of myelosuppressive cancer chemotherapy and only in subsequent cycles if a febrile episode occurs.[89]

The decision whether to use antibacterial prophylaxis and the selection of the specific agent requires a balance between expected benefit and risk. The concept of risk applies to immediate adverse effects of the drug (eg, rash, GI intolerance), the potential for selection for resistant pathogens that can harm the individual receiving prophylaxis, and the risk of resistant organisms to a specific population of patients (eg, those being treated at a cancer center). The link between fluoroquinolone use and severe *Clostridium difficile* as well as MRSA infections provides an additional cautionary note regarding excess use of fluoroquinolones.[90-93]

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

Prophylaxis for Pneumococcal Infection

Prophylaxis against pneumococcal infection is advised in allogeneic HSCT recipients. Patients undergoing allogeneic HSCT are at an increased risk for pneumococcal sepsis due to functional asplenia and impaired B-cell immunity. Pneumococcal sepsis is most common in the late transplant period, between 3 months to years after HSCT.[75,94] Immunosuppressive therapy for GVHD delays reconstitution of B-cell immunity and significantly increases the risk of post-transplant pneumococcal sepsis.[75,95]

The NCCN Guidelines Panel advises that penicillin prophylaxis be initiated at 3 months after HSCT and be continued until at least 1 year following transplant. Patients should receive prophylaxis regardless of prior administration of pneumococcal vaccines.[96] Prophylaxis should be continued in patients with chronic GVHD until immunosuppressive therapy has been discontinued. Post-transplant pneumococcal infection is generally community-acquired, and the frequency of resistance to antibiotics reflects regional susceptibility patterns. In some regions as many as 35% of pneumococcal isolates have intermediate- or high-level resistance to penicillin,[97] and cross-resistance to other classes of antibiotics is common. Breakthrough pneumococcal sepsis in HSCT recipients receiving penicillin prophylaxis is well described.[98] Thus, in areas with a significantly higher frequency of penicillin-resistant pneumococcal isolates, alternative agents should be considered based on local susceptibility patterns. Daily TMP/SMX used as prophylaxis for PCP is likely to be protective against pneumococcal disease. Vaccination with the polysaccharide pneumococcal vaccine is also strongly recommended at 1 year after cessation of immunosuppression in HSCT patients with revaccination after 5 years.[96,99]

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 HSCT.[22]

Azoles

In neutropenic allogeneic HSCT recipients, 2 double-blind, placebo-controlled trials have shown that prophylactic fluconazole controlled yeast colonization and also decreased the rate of mucosal candidiasis and invasive Candida infections.[100,101] A decrease in mortality was noted in one study in which most of the patients were allograft recipients.[101] Fluconazole conferred significant long-term improvement in survival, possibly by decreasing Candida antigen-induced GI tract GVHD.[102]

Fluconazole prophylaxis decreased fungal colonization, invasive infection, and fungal infection-related mortality in nontransplant patients with leukemia and in autologous HSCT recipients in a placebo-controlled trial.[103] However, only 30% of the patients received growth factors, and the median duration of neutropenia was 14 to 16 days. The

benefit of fluconazole prophylaxis was greatest in autologous transplant recipients not receiving colony-stimulating growth factor support and in patients with leukemia receiving mucotoxic regimens consisting of cytarabine plus anthracycline.[103] Therefore, no antifungal prophylaxis can be considered (category 2B) in autologous HSCT recipients who receive growth factor support and who do not have significant mucositis (see *Overall Infection Risk in Cancer Patients* on page INF-2). 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.[104,105]

Prophylaxis with voriconazole was compared with fluconazole in a large randomized double-blind study that included serum galactomannan surveillance in allogeneic HSCT recipients (N=600).[106] No difference was noted in the primary endpoint (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, nor incidence of severe adverse events were noted between treatment arms.[106] There are emerging data to suggest that the long-term use of voriconazole may be associated with severe photosensitivity and other adverse events.[107-109] Although these reports are anecdotal cases, further evaluation is warranted to determine the long-term side effects associated with voriconazole use.

Posaconazole is equally effective compared to fluconazole as primary therapy for oropharyngeal candidiasis,[110] but has not been evaluated as primary therapy for invasive fungal infections. In a multicenter randomized trial that evaluated prophylaxis with posaconazole compared with fluconazole or itraconazole in neutropenic patients with AML or MDS receiving induction or re-induction chemotherapy, posaconazole was associated with a significantly reduced rate of invasive fungal infections during the treatment period (primary end point: 2% vs. 8%; $P < 0.001$) and during the 100 days following randomization (5% vs. 11%; $P = .003$).[111] In addition, posaconazole prophylaxis reduced the incidence of invasive aspergillosis (1% vs. 7%; $P < 0.001$) and was associated with a significant survival benefit 100 days following randomization ($P = .04$) compared with the fluconazole/itraconazole arm.[111]

The NCCN Guidelines Panel recognizes that strong evidence exists for the use of fluconazole as prophylaxis in neutropenic allogeneic HSCT recipients (category 1) (see *Overall Infection Risk in Cancer Patients* on page INF-2).[22] However, it should be noted that fluconazole use can predispose patients to colonization and bloodstream infection by fluconazole-resistant *Candida* strains.[78,112]

The NCCN Guidelines Panel advises that prophylaxis with posaconazole, itraconazole, and voriconazole be avoided in patients receiving vinca alkaloid-based regimens (such as vincristine in ALL) because of the potential of these azoles to inhibit the cytochrome P450 3A4 isoenzyme, reducing clearance of vinca alkaloids. Severe vinca alkaloid-induced neurotoxicity has occurred when co-administered with itraconazole;[113] data on pairing vinca alkaloids with posaconazole and voriconazole are lacking. Although the package inserts of voriconazole and posaconazole advise both caution if co-administered with vinca alkaloids and consideration of vinca alkaloid dose reduction, there are no data provided on the level of dose reduction required.[114,115] Prophylaxis with fluconazole (which is a less potent inhibitor of cytochrome P450 3A4 than the mold-active azoles), an echinocandin, or

an amphotericin B formulation should be considered in these patients as a safer alternative to the mold-active azoles.

The NCCN Guidelines Panel recommends posaconazole (category 1) for antifungal prophylaxis in neutropenic patients with AML and MDS receiving induction or re-induction chemotherapy (see *Overall Infection Risk in Cancer Patients* on page INF-2).[22] The role of antifungal prophylaxis in patients with acute leukemia receiving consolidation chemotherapy has not been adequately evaluated. Posaconazole as prophylaxis has not been evaluated during the neutropenic period following conditioning in allogeneic HSCT recipients, and thus the safety of this approach is unknown. Ingestion of a meal (ideally high-fat) or liquid nutritional supplement or an acidic carbonated beverage with each posaconazole dose is essential for achieving adequate posaconazole serum levels;[115] patients who are unable to tolerate such oral intake should not receive this drug for prophylaxis.

In patients with acute leukemia or MDS and in autologous HSCT recipients, antifungal prophylaxis is administered until neutrophil recovery. Antifungal prophylaxis should be considered until at least day 75 after allogeneic HSCT (see *Overall Infection Risk in Cancer Patients* on page INF-2).[22,102] Although many centers reasonably use antifungal prophylaxis in non-neutropenic allogeneic HSCT recipients with GVHD, this practice was only evaluated in a singular, properly designed study that focused specifically on this patient group. In a prospective, randomized, double-blind study, posaconazole was compared with fluconazole as prophylaxis in allogeneic HSCT recipients with severe GVHD requiring intensive immunosuppressive therapy.[116] Grade II to IV GVHD, chronic extensive GVHD, or intensive immunosuppressive therapy 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 treatment, and deaths attributed to fungal infection.[116] Posaconazole is recommended (category 1) as prophylaxis in patients with GVHD receiving intensive immunosuppressive therapy, as defined by the inclusion criteria in this trial. Prophylactic posaconazole can be considered in all patients with GVHD receiving immunosuppressive therapy, although the benefit/risk ratio of mold-active prophylaxis in patients receiving less intensive immunosuppressive regimens has not been established.

Patients with chronic severe neutropenia (ANC<500 neutrophils/mcL) due to the underlying disease (such as aplastic anemia) are at substantial risk for invasive aspergillosis.[117] Although this population has not been evaluated in clinical trials of antifungal prophylaxis, some panel members advise the use of a prophylactic mold-active agent (eg, posaconazole or voriconazole) in such patients.

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[118] or with invasive filamentous fungal infection[119] during subsequent cycles of chemotherapy or HSCT. In patients with invasive aspergillosis before HSCT, antifungal therapy for more than a month and resolution of radiologic abnormalities correlate with a lower likelihood of post-transplant recurrence of infection.[120] Secondary prophylaxis with a mold-active agent is advised for the entire period of immunosuppression. Secondary prophylaxis is generally administered for the duration of immunosuppression.

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 and while the growing trend is to incorporate TDM into clinical treatment, there remains a level of optimization for methods and interpretation of results; therefore, the support of an infectious disease consultant is recommended to address the multiple variables that may affect TDM.

TDM is generally recommended for the patients receiving triazoles; there is no current evidence to support the use of TDM for the evaluation of polyenes or echinocandins. Variability of TDM may be attributed to the administration of the drug, timing of monitoring, location of the infection and intrinsic patient factors (ie, age, weight). One significant factor for the triazoles is the effect of gastric pH or food. This is evident by the increased bioavailability of itraconazole by 43% in patients that fasted.[121] Similarly, voriconazole bioavailability was lowered by about 22% when taken with food and by 34% when given with a high-fat meal.[114,122] Therefore, both itraconazole and voriconazole should be given either 1 hour before or 1 hour after meals. Pharmacokinetic studies with posaconazole in healthy individuals showed that giving this drug with or after a high-fat meal, or with any meal or nutritional supplement greatly enhanced its absorption up to 400% with the high-fat meal.[123] As previously discussed, posaconazole should be taken with a full meal, a liquid nutritional supplement or an acidic carbonated beverage (if a full meal cannot be taken) to ensure adequate absorption.[115] Additionally, the plasma concentration of posaconazole can be reduced by proton pump inhibitors due to the increase in gastric pH.[123] As reviewed by Brüggemann et al,[124] a substantial list of drug interactions with azole antifungal drugs can result in subtherapeutic effects or toxicity, making TDM an integral component of patient care.

Fluconazole is the only triazole that does not generally require TDM as it has linear pharmacokinetics[125-129] though patients in renal failure should receive a modified dose.[130] Itraconazole, voriconazole and posaconazole are all recommended for TDM. Studies of itraconazole demonstrate a significant rate of breakthrough infections when dosed below 1 mcg/ml;[131,132] however, increased mortality was observed at doses greater than 0.5 mcg/ml.[133,134] Therefore, it may be useful to target itraconazole plasma concentration at a lower level for prophylaxis while requiring a higher dose if an active infection is being treated. Trough concentrations of itraconazole between 1 and 2 mcg/ml have shown the best therapeutic responses for invasive infections,[135-138] while 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[139] but studies for upper limit have not been prolific. Itraconazole may be associated with hepatic toxicity and GI intolerance[140] 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 in turn are associated with hyperbilirubinemia and nephrotoxicity during the early transplant period.[141] This finding reinforces a note of caution about itraconazole (and by extension, voriconazole and posaconazole), a potent inhibitor of the cytochrome P450 3A4 isoenzyme, with regard to potential serious drug-drug interactions.

Dose adjustments of voraconazole have resulted in better clinical responses while reducing toxicity.[142] Target voriconazole trough values between 0.5 and 2 mcg/ml have been published based on clinical studies.[142-149] While 0.5 mcg/ml is a suggested target for prophylaxis, a

higher range of 1 to 2 mcg/ml should be sought for active disease and for patients with disease that has a poor prognosis. Higher concentrations may also benefit immunocompromised patients as breakthrough infection is more likely in this population.[150,151] Trough concentrations greater than or equal to 4 mcg/ml have correlated with toxicity in various studies[142,146,149,152-156] suggesting that voriconazole should not exceed 6 mcg/ml in the blood at trough and even lower levels may should be considered in the context of individual cases.

The target concentration of posaconazole for prophylactic TDM of greater than 0.7 mcg/ml is supported by individual studies[157-159] as well as two Phase III studies;[111,116] however, doses as low as 0.5 mcg/ml have also been reported as effective.[157,159-163] Treatment of an established infection is recommended to have a trough concentration greater than 1 mcg/ml. Higher doses may be necessary based on the pathogen resistance.[164,165] Similarly to fluconazole, posaconazole is well-tolerated and has not yet been associated with toxicity.

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 recently published their guidelines for the use of TDM of antifungal agents based on available literature.[166] These guidelines provide similar recommendations as those proposed in an earlier review by Andes et al.[167] However, until more data is available, the NCCN Guidelines Panel does not provide any recommendations on the specific use of TDM.

Amphotericin B

Low-dose amphotericin B product has been studied in high-risk patients and has been shown to provide protection against invasive molds, although no survival benefit in randomized studies was seen when compared with fluconazole.[140,168,169] 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 to conventional amphotericin B. Use of the lipid formulation is particularly important for patients at high risk for renal failure, such as patients with pre-existing renal disease, HSCT recipients and patients that are concurrently receiving other nephrotoxic agents.[170,171]

Aerosolized delivery of amphotericin products has been considered for several years, and has the advantage of local delivery to the lungs while simultaneously avoiding systemic toxicity. A recent randomized, placebo-controlled trial found that aerosolized liposomal amphotericin B was useful for preventing invasive pulmonary aspergillosis in patients with prolonged neutropenia.[172] Limitations to the use of aerosolized amphotericin B for prophylaxis relate to the variability of this treatment due to 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.[173]

Micafungin

The echinocandin micafungin is approved for prophylaxis against *Candida* infections in patients undergoing HSCT (category 1).[174] In a randomized, double-blind trial of autologous and allogeneic HSCT 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 pre-specified criteria for treatment success (absence of suspected, proven or probable invasive fungal infections during treatment period and absence of proven or probable infection during the 4-week period after treatment).[175] The duration of this study

encompassed the neutropenic period, but not the period after neutrophil recovery where GVHD would be expected to occur. The frequency of breakthrough candidemia was similar in both arms, but there was a trend to fewer episodes of invasive aspergillosis in allogeneic HSCT recipients receiving micafungin. Survival and drug-related toxicity were similar between treatment arms.[175]

Antiviral Prophylaxis and Preemptive Antiviral Therapy

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 HSCT recipients and patients (without prophylaxis) with acute leukemia undergoing induction or re-induction therapy who are seropositive for HSV.[176-178] Among allogeneic HSCT recipients, HSV disease is most likely to occur within the first month post-transplant, but may occur in later stages during intense immunosuppression.[72,73] 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.

Antiviral prophylaxis (acyclovir, valacyclovir, or famciclovir) against HSV is advised during the period of neutropenia in patients with HSV-seropositive disease receiving chemotherapy (induction or consolidation) for acute leukemia, and during neutropenia and at least 30 days after HSCT for both allogeneic and autologous transplant recipients (see *Overall Infection Risk in Cancer Patients* on page INF-3). A longer period of prophylaxis should be considered in allogeneic HSCT recipients with GVHD or with frequent HSV reactivations before transplantation.[16] Acyclovir or valacyclovir is the initial agent of choice for HSV prophylaxis.[22,179] Foscarnet is typically reserved for patients with acyclovir-resistant HSV infection.[22,179] In patients who are receiving antiviral prophylaxis with ganciclovir or foscarnet for prevention of CMV reactivation, additional prophylaxis with acyclovir is not necessary given that these agents are active against HSV.[179]

HSV and herpes zoster infections are common in patients with CLL treated with the CD52 monoclonal antibody alemtuzumab. For these patients, antiviral prophylaxis is advised until at least 2 months after completion of alemtuzumab therapy or until CD4+ cell counts are 200 cells/mcL or more, whichever occurs later.[38,180]

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 VZV disease. In allogeneic HSCT recipients with a history of VZV infection without antiviral prophylaxis, about 30% have VZV disease after reactivation.[181] In patients with a history of chicken pox, oral acyclovir administered from 1 to 2 months until 1 year after allogeneic HSCT significantly decreased the incidence of VZV disease compared to placebo (5% vs. 26%, respectively).[181] The frequency of VZV disease in the post-prophylactic period was similar between the 2 groups and predominantly occurred in patients who required systemic immunosuppression. This prolonged course of acyclovir prophylaxis is likely to also prevent HSV reactivations. Subsequent studies have

consistently demonstrated the benefit of long-term antiviral prophylaxis against VZV disease in recipients of allogeneic HSCT. Patients who received anti-VZV prophylaxis with acyclovir or valacyclovir for 1 year post-HSCT 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.[182] Long-term (1 year post-allogeneic HSCT) prophylaxis with lower doses of acyclovir or valacyclovir was associated with a 19% to 35% cumulative incidence of VZV reactivation, but successfully prevented the occurrence of severe VZV disease comprising visceral involvement or serious complications.[183,184] The NCCN Guidelines Panel recommends acyclovir prophylaxis against VZV for at least 1 year after allogeneic HSCT in patients seropositive for VZV pretransplant (see *Overall Infection Risk in Cancer Patients* on page INF-3), and recommends considering the extension of prophylaxis in patients who continue to receive systemic immunosuppressive therapy. Agents used as HSV prophylaxis are also active against VZV.

Among autologous HSCT recipients, the highest risk period for HSV reactivation is during neutropenia following conditioning, whereas the risk of VZV reactivation encompasses the first year.[185] Thus, VZV prophylaxis for at least 1 year post-transplant should also be considered in autologous HSCT recipients. Prophylaxis against VZV should also be considered in other patients at intermediate risk for viral reactivation, including those with hematologic malignancies with prolonged neutropenia or those receiving T-cell depleting agents (eg, fludarabine, alemtuzumab). Bortezomib, a proteasome inhibitor, is associated with an increased risk of VZV reactivation during active therapy.[186-189] Carfilzomib, another proteasome inhibitor that was recently approved (in 2012) for the treatment of multiple myeloma, may also be associated with risks of VZV reactivation.[190] Prophylaxis with acyclovir, valacyclovir, or famciclovir should be protective and can be considered in these settings.[190-192] As previously discussed, among patients with CLL receiving alemtuzumab treatment, antiviral prophylaxis is recommended until 2 months after completion of treatment or until the CD4+ cell counts reach 200 cells/mcL or more, whichever occurs later (see *Overall Infection Risk in Cancer Patients* on page INF-3).[38,180]

Cytomegalovirus

CMV infections most frequently occur in patients with cancer that undergo HSCT or who receive alemtuzumab therapy. CMV is a common cause of opportunistic infections in patients undergoing allogeneic HSCT, mainly during the early post-engraftment phase, but also occurring in the late post-engraftment phase (particularly for patients with GVHD during the latter phase).[72,73] Infection can result from viral reactivation (in immunocompromised CMV-seropositive patients) or primary infection (in CMV-seronegative patients). The risk for CMV reactivation and disease is highest among HSCT recipients with CMV-seropositive status prior to transplant.[193] Among CMV-seropositive patients undergoing allogeneic HSCT (with graft sources from peripheral blood, bone marrow, or umbilical cord blood), the incidence of CMV reactivation ranged from 50 to 60% (with CMV disease in about 10–30% of seropositive recipients) even with routine surveillance and antiviral prophylaxis or pre-emptive therapy.[193-196] It is advised that HSCT candidates and donors be tested for CMV serology prior to the transplant.

In allogeneic HSCT recipients at risk for CMV reactivation, the following preventive approaches have been evaluated:[197] 1) prophylaxis – antiviral agents are administered to all allogeneic HSCT recipients if either the donor or recipient is CMV seropositive; and 2) pre-emptive therapy – initiation of antiviral agents after detection of asymptomatic CMV reactivation by active surveillance (ie, detection of CMV pp65

antigen or viral DNA in peripheral blood). Antiviral agents potently active against CMV have substantial toxicity with long-term use. Ganciclovir is associated with bone marrow suppression that may increase the risk of common opportunistic infections. Foscarnet can cause nephrotoxicity but is generally well tolerated.[198,199] Cidofovir (generally used as a third-line anti-CMV agent) can be associated with substantial nephrotoxicity.[200,201] Acyclovir and valacyclovir have an excellent safety profile but are only weakly active against CMV.

In two randomized studies, prophylaxis with acyclovir was associated with increased survival in allogeneic HSCT recipients, but the rates of CMV reactivation and disease were fairly high.[202,203] Ljungman et al[204] compared oral valacyclovir (a valine esterified analogue of acyclovir with high oral bioavailability) with acyclovir as prophylaxis in allogeneic HSCT recipients in whom either the donor or recipient was CMV seropositive. All patients received initial IV acyclovir until day 28 after transplantation or until discharge, and then either oral valacyclovir or acyclovir until week 18 after transplantation. Valacyclovir was more effective than acyclovir in preventing CMV infection (28% vs. 40%; hazard ratio [HR], 0.59; 95% CI, 0.46–0.76; $P < .0001$); no difference was observed in CMV disease, adverse events, or overall survival.[204] Thus, acyclovir and valacyclovir are acceptable agents for CMV prophylaxis, but surveillance and pre-emptive therapy with ganciclovir or foscarnet are still necessary.[179]

Highly sensitive methods for early diagnosis of CMV reactivation include detection of the CMV pp65 antigen from peripheral blood leukocytes and of CMV DNA by PCR.[205-207] Triggers for pre-emptive antiviral therapy are either a single positive CMV antigenemia or 2 consecutive positive PCR results. Ganciclovir is frequently the agent of choice for first-line pre-emptive therapy; foscarnet is more commonly used for patients who cannot tolerate ganciclovir or for second-line pre-emptive therapy.[179] Foscarnet and ganciclovir had similar efficacy as pre-emptive CMV therapies in allogeneic HSCT recipients, but ganciclovir was associated with a significantly higher rate of early discontinuation because of either neutropenia or thrombocytopenia.[199] 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 HSCT.[208,209] Oral valganciclovir used as pre-emptive anti-CMV therapy was shown to have acceptable oral bioavailability and was safe and effective in controlling CMV infection in allogeneic HSCT recipients, including patients with grades I and II GI GVHD.[208,210-212] Thus, valganciclovir is a highly acceptable oral option for pre-emptive therapy for CMV in the absence of substantial GI GVHD. Cidofovir has been evaluated as both primary and secondary pre-emptive therapy in allogeneic HSCT recipients.[200,201,213,214] In a retrospective study that evaluated cidofovir in allogeneic HSCT recipients (N=82) for the treatment of CMV disease (n=20), primary pre-emptive therapy (n=24), or secondary pre-emptive therapy (n=38), response to cidofovir was observed in 50% of patients treated for CMV disease (mainly CMV pneumonia) and 62% for primary pre-emptive therapy.[200] Moreover, secondary pre-emptive therapy with cidofovir resulted in response rate of 66% in patients where treatment failed or relapse occurred (defined as continued presence or recurrence of pp65 antigenemia or viral DNA after at least 1 week of antivirals) following initial pre-emptive therapy with ganciclovir, foscarnet, or the combination of these agents.[200] Maribavir is another oral anti-CMV agent under investigation in the setting of allogeneic HSCT. An earlier phase II randomized study showed that maribavir was effective as prophylaxis against CMV infection and CMV disease compared with placebo in allogeneic HSCT recipients; moreover, in contrast to agents such as ganciclovir, maribavir was not associated with significant neutropenia or thrombocytopenia.[215] However, a recent phase III

double-blind, randomized controlled trial evaluating maribavir versus placebo in allogeneic HSCT recipients failed to demonstrate an advantage with maribavir in reducing the incidence of CMV disease.[216]

Late CMV disease, defined as occurring after day 100 of HSCT, remains a persistent problem in the era of CMV prophylaxis and pre-emptive therapy. In one series, 92% of patients with late CMV pneumonia had chronic GVHD or had received T cell–depleted transplants.[217] Results of T-cell reconstitution at 3 months after allogeneic HSCT appear to be useful in risk stratification for late CMV disease. At 3 months after HSCT, 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 HSCT recipients.[218] 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/day or greater) were significantly predictive of delayed recovery of CMV-specific immunity at 3 months after allogeneic HSCT; use of steroids impaired both CD4+ and CD8+ T-cell function in a dose-dependent manner.[219] Interestingly, 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. Tetramer technology allows quantification of CMV antigen-specific CD4+ and CD8+ cells as a marker for reconstitution of CMV-specific cellular immunity; it may more precisely stratify the risk for CMV disease and need for CMV surveillance.[220] Although tetramer staining allows for monitoring of quantitative recovery of T cells, it should be noted that it does not assess the functional activity of T cells, which may be impaired; thus, the presence of a large proportion of CMV-specific T cells with impaired function may hinder recovery of CMV immunity.[219,221]

Based on the available data that predict the risk of CMV disease, the NCCN Guidelines Panel recommends routine CMV surveillance for at least 6 months after allogeneic HSCT, together with pre-emptive anti-CMV therapy with IV ganciclovir or oral valganciclovir, IV foscarnet, or IV cidofovir (see *Prevention of Cytomegalovirus Reactivation or Disease* on page INF-4). Additional surveillance should be strongly considered during chronic GVHD requiring immunosuppressive therapy and until the CD4+ count is 100 cells/mcL or more. Note that the CD4+ count will be reduced by systemic corticosteroids and by other lymphocyte-depleting agents. The majority of cases of late CMV disease occur within the first year of transplant and less than 5% occur after the second year.[217] Therefore, the value of CMV surveillance beyond 2 years after HSCT is unknown but can be considered in patients with significant chronic GVHD. There is still debate about how to treat patients after a negative test of 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.

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.[40,44-46] Several studies of alemtuzumab in patients with CLL have demonstrated the effectiveness of using routine CMV monitoring coupled with pre-emptive anti-CMV therapy with ganciclovir in preventing overt CMV disease.[40,44,45,222] More recently, a small randomized study in patients with lymphoproliferative disease treated with alemtuzumab-containing regimens (N=40) showed that upfront CMV prophylaxis with oral valganciclovir significantly reduced the incidence of CMV reactivation compared with oral

valacyclovir (0% vs. 35%; *P* = .004).[46] The NCCN Guidelines Panel recommends routine surveillance for CMV reactivation using PCR or antigen-based methods and monitoring weekly during alemtuzumab therapy and at least 2 months after completion of treatment.[38,223] Upon confirmation of CMV antigenemia (defined as PCR-positivity for CMV in ≥ 2 consecutive samples obtained 1 week apart[38]), the panel recommends pre-emptive therapy with IV ganciclovir or oral valganciclovir, IV foscarnet, or IV cidofovir for at least 2 weeks and until CMV is no longer detectable (see *Prevention of Cytomegalovirus Reactivation or Disease* on page INF-4). Following a negative test of CMV, there is 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 IVIG can be administered. 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

Reactivation of latent HBV may occur in the setting of significant immunosuppression (eg, immunosuppressive anti-tumor therapy, HSCT). HBV carriers with lymphoid malignancies, especially those treated with anthracycline-based regimens, have a high risk of HBV reactivation.[224] Moreover, as previously discussed, patients with B-cell lymphoid malignancies treated with anti-CD20 monoclonal antibodies (eg, rituximab, ofatumumab) may have increased risks for HBV reactivation and HBV disease, including rare instances of fulminant hepatitis or death.[51,52] Rare cases of liver failure and death associated with HBV reactivation have occurred in patients receiving rituximab-containing regimens.[51,53,225-227] Other chemotherapeutic agents that have been associated with hepatitis B reactivation include alkylating agents, anthracyclines, antimetabolites, antitumor antibiotics, corticosteroids, platinum-containing drugs, taxanes, vinca alkaloids, tyrosine kinase inhibitors and immune modulators (reviewed by Kawsar et al[228] and Torres et al[229]). Fulminant hepatitis and mortality may occur following HBV reactivation in immunocompromised patients. Thus, it is prudent in these settings to assess patients for prior HBV infection, especially in individuals who have spent significant time in HBV endemic areas or have risk factors for blood-borne exposure. Patients that are also co-infected with HIV are an especially complicated population. As evidenced by the growing list of risk factors including both patient specific characteristics as well as treatment-related factors, it is critical that oncologists consult an infectious disease expert.

The risk factors for HBV infection include personal or parental history of an intermediate to high prevalence of HBV infection in their birthplace (defined as a prevalence of HBsAg positivity in greater than 2% of the population), household and sexual contacts of HBsAg+ persons, individuals with multiple sexual partners or history of sexually transmitted diseases, inmates of correctional facilities, patients with chronically elevated AST or ALT levels, patients with a history of injection drug use, men who have sex with other men, and patients with HCV or HIV infection. In patients with cancer that are anticipated to receive systemic chemotherapy but have obvious risk factors for HBV infection, HBV screening at the beginning of therapy is recommended.[230,231]

This risk-based screening is aligned with recommendations from American Society of Clinical Oncology[232] and from the American Association for the Study of Liver Disease.[230] Although it is possible that risk-based screening may be more cost-effective than universal screening, there are currently no validated risk tools which could be

easily implement into clinical practice. Furthermore, less than 60% of patients with HBV infection may have obvious risk factors,[233] and only 10 to 35% of infected patients may be aware of their own HBV infection.[234,235]

Thus, all patients should be assessed for risk factors of HBV infection, and those with risk factors should definitely be screened with HBsAg and anti-HBc tests. If risk-based screening cannot be implemented, then consideration should be made for universal screening as is recommended by the Centers for Disease Control and Prevention.[231] Future population-based studies are needed to determine best screening strategies for patients with cancer who are anticipating systemic chemotherapy.

A positive hepatitis B surface antigen (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).[236] False-negative HBsAg results may occur in patients with chronic liver disease.[237] HBsAb positivity is generally equated with protective immunity, although reactivated HBV disease may occur in the setting of significant immunosuppression in HBcAb-positive individuals.[238] A patient with resolved hepatitis B infection will be HBcAb positive but HBsAg negative. As mentioned above, 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.[56,236,239-247] 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 prior to initiation of treatment.[56,241,247] In a recent meta-analysis and evaluation of the U.S. Food and Drugs Administration (FDA) safety reports concerning HBV reactivation in patients with lymphoproliferative disorders, it was reported that HBcAb positivity was correlated with increased incidence of rituximab-associated HBV reactivation.[240] In addition, a retrospective study showed that allogeneic HSCT 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 HSCT.[248] After allogeneic HSCT, 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,[249] and may be confused with hepatic GVHD.

In patients undergoing intensive immunosuppressive therapy, including HSCT, evaluation of HBV surface antigen (HBsAg), core antibody (HBcAb), and surface antibody (HBsAb) should be considered at baseline.[179,236,250] Evaluation of HBV and hepatitis C virus (HCV) infection should be routine in both HSCT recipients and donors.[250,251] Vaccination against HBV should be strongly considered in HBV-naïve patients (ie, negative for HBsAg, HBsAb, and HBcAb).[179,236] In HBV-naïve patients undergoing allogeneic HSCT, grafts from HBsAg-positive or HBV DNA-positive donors should be avoided wherever possible. Donors who have not been exposed to HBV should be considered for HBV vaccination before stem cell collection.

In HBsAg-positive or HBcAb-positive individuals, baseline quantitative PCR for HBV DNA should be obtained. In allogeneic HSCT candidates

with evidence of active HBV infection (chronic hepatitis based on biopsy or positive HBV DNA load or high levels of HBsAg), transplant procedure should be delayed where possible, and antiviral therapy should be given for 3-6 months prior to conditioning.[179] These patients should continue surveillance (for monitoring of HBV DNA) and receive antiviral prophylaxis throughout the transplant procedure, and at least 6-12 months after transplant or during periods of GVHD (see *Prevention of Hepatitis B Virus Reactivation or Disease* on page INF-5). In HSCT candidates who are HBsAg-positive or HBcAb-positive but without evidence of active HBV replication, antiviral prophylaxis should be considered (starting shortly before the transplant procedure) and continued until 6 to 12 months after transplant or during GVHD. In allogeneic HSCT recipients considered at high risk for HBV reactivation (ie, HBsAg-positive recipient or donor, or HBsAg-negative/HBcAb-positive recipient), antiviral prophylaxis with lamivudine has been shown to effectively control HBV reactivation and reduce the risk for developing hepatitis.[245,252]

Routine surveillance for HBV DNA and antiviral prophylaxis (or pre-emptive therapy upon detection of high levels of HBsAg or positive HBV DNA load) are recommended in HBsAg-positive or HBcAb-positive patients with hematologic malignancies undergoing immunosuppressive therapy with monoclonal antibodies. Surveillance and antiviral prophylaxis (or pre-emptive therapy) should be continued for at least 6 to 12 months following the last dose of therapy (see *Prevention of Hepatitis B Virus Reactivation or Disease* on page INF-5).[236] Similarly, the NCCN Guidelines for NHL recommend HBsAg and HBcAb testing for all patients with B-cell NHL planned for treatment with anti-CD20 monoclonal antibody-containing regimens.[253] 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. Furthermore, for patients undergoing anti-tumor therapy, the NHL panel suggests prophylactic antiviral therapy (for cases of HBsAg positivity; also preferred for HBsAg negative/HBcAb positive cases) or pre-emptive antivirals upon detection of increasing viral load (an option for HBsAg negative/HBcAb positive cases with concurrent high levels of HBsAb).[253] During anti-tumor 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 anti-tumor therapy) if viral load remains undetectable.[253] The optimal choice of antiviral agents for prophylaxis (or pre-emptive approaches) will primarily be driven by institutional standards. Additionally, the NCCN Guidelines for NHL addresses the management of HCV infection in patients with HCV-positive lymphomas (see *NCCN Guidelines for NHL)*.[253] Monitoring of viral load and transaminases should be considered for patients without active HBV infection that are not receiving prophylaxis.

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 has 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 immunosuppressive cytotoxic agents.[224,254,255] In a meta-analysis of clinical trials evaluating the benefit of lamivudine prophylaxis in HBsAg-positive lymphoma patients treated with immunosuppressive regimens, prophylaxis resulted in a significant reduction in HBV reactivation (risk ratio, 0.21; 95% CI, 0.13–0.35) and in a trend for reduced HBV-related deaths (risk ratio, 0.68; 95% CI, 0.19–2.49) compared with no prophylaxis.[255] However, despite its initial effectiveness, virologic breakthrough is high, with some studies indicating 80% of patients

showing resistance after 5 years of therapy.[256] Even after the second year, almost half of all patients will be resistant.[256] Lamivudine monotherapy has fallen out of favor; however, more recent studies demonstrating the effectiveness of lamivudine in combination with adefovir in patients with lamivudine-resistant HBV infections may suggest its value in combination therapy.[257,258]

More recently, tenofovir has demonstrated superior antiviral efficacy compared with adefovir in phase III randomized double-blind studies in patients with chronic HBV infection, and is the preferred agent in this setting;[259] however, limited data are available regarding its use in patient populations with cancer. In a recent publication, no detectable resistance to tenofovir was reported in patients with chronic hepatitis B after 6 years of treatment.[260] This study evaluated 347 hepatitis B e-antigen negative and 238 hepatitis B e-antigen positive patients in two phase III studies. While sequencing of the HBV polymerase/reverse transcriptase indicated sequence changes at polymorphic sites, none resulted in drug resistance. In total, there were only 16 cases of virologic breakthrough, of which 12 were associated with nonadherence to study medication. In the first year, lamivudine resistance was calculated as 24% and this number steeply climbs to 70% by year 5. Conversely, resistance for tenofovir is undetectable throughout a 5 year span.[261]

Entecavir and telbivudine have also been evaluated in randomized open-label studies with adefovir as the comparator arm in patients with chronic hepatitis B, and both agents have shown improved antiviral activity compared with adefovir.[262,263] Only a few small cases studies have evaluated entecavir in the prevention[264] or treatment of HBV in patients with cancer (reviewed by Liu et al[265]). Entecavir has a low drug resistance of 1.2%[266] at 5-years compared to adefovir which has an intermediate resistance that increases from 0% in the first year to 29% by year 5.[259,267,268] Conversely, telbivudine has a higher resistance, reaching 17% in the second year.[269] Furthermore, greater than 10% of patients in a phase III clinical trial who did not have genotypic resistance after 2 years and continued to receive telbivudine, developed resistance after 4 years[270]

In addition to drug resistance, the safety profile of the nucleos(t)ide analogues should also affect drug selection. Nephrotoxicity has been seen with adefovir[271,272] and tenofovir[273] while myopathy and neuropathy is more commonly associated with telbivudine.[274,275] 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.

Vaccination

The current version of the NCCN Guidelines does not specifically address vaccination strategies for patients with cancer. Guidelines on the prevention of infections in HSCT recipients (jointly sponsored by the CDC, IDSA, ASBMT, EMBT, among other organization) have been published (2009), which include recommendations for vaccination in the HSCT setting.[276] In addition, the ACIP updated their recommendations on immunization for adults, including immunocompromised patients.[99] Most recently, the IDSA published clinical practice guidelines for the vaccination of the immunocompromised host.[277] Here we briefly discuss the general principles of vaccination in patients with cancer, with a focus on influenza.

Live attenuated viral vaccines have the potential to cause disease in immunocompromised patients. However, vaccines that are not live attenuated organisms can be safely administered to this patient population. 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. Persons receiving chemotherapy or radiation therapy for malignancies should not receive live attenuated vaccines for at least 3 months after cessation of therapy and until the patient is presumed to be immunocompetent.[278] Certain live viral vaccines can be safely administered to household members of severely immunocompromised patients (eg, measles, mumps, rubella [MMR]), whereas others cannot (eg, small pox vaccine) because of the potential risk of transmission. The package insert for the vaccine should be reviewed prior to administration.

Ideally, patients should be vaccinated at least 2 weeks before receiving cytotoxic or immunosuppressive therapy; however, this timing is often not feasible in patients with cancer. Administering vaccines on the same day as cytotoxic therapy is not advised, because proliferative lymphocytic responses are required for protective immunity. Immunization between cytotoxic chemotherapy courses is likely to be associated with higher response rates than during chemotherapy administration.[279,280] Patients should be considered unprotected if they were vaccinated less than 2 weeks before starting cytotoxic or immunosuppressive therapy or while receiving these agents. These patients should be revaccinated at least 3 months after therapy is discontinued once immune competence has been restored.[278] Pneumococcal, meningococcal, and Hib vaccines should be administered at least 2 weeks before elective splenectomy.[278]

Influenza infections cause significant morbidity and mortality in cancer patients. Among bone marrow transplant recipients, influenza accounts for about 10 to 40% of all community-acquired viral respiratory infections.[281-283] An increased incidence and duration of influenza infections have also been observed in patients with cancer that are immunosuppressed compared to healthy controls.[284,285] During community outbreaks, influenza infections may represent a significant proportion of episodes of febrile neutropenia.[286] Influenza infections in patients with cancer that are severely immunocompromised are often associated with hospitalizations, delays in potentially life-saving chemotherapy, and occasionally, death.[284-286] As a result, annual vaccination against influenza with the inactivated influenza virus is currently recommended for all individuals at increased risk due to immunosuppression.[287] The guidelines also include health care professionals and household members or caregivers in their target group for annual immunization to prevent transmission of influenza to high-risk patients.[287]

The intranasal vaccine (FluMist) should be avoided in patients with immunosuppression, because FluMist contains live attenuated influenza viruses still capable of replication, which could theoretically lead to infection in immunocompromised individuals.[287,288] The CDC recommends that persons with known or suspected immunodeficiency diseases or those who are receiving immunosuppressive therapies should not be immunized with the live influenza vaccine.[287,288] In addition, because no data are available assessing the risk for person-to-person transmission of FluMist from vaccine recipients to immunosuppressed contacts, the CDC also recommends that inactivated influenza vaccine should be used in household contacts, health-care workers, and others who have close contact with immunocompromised patients.[287,288]

HIV Screening in Hospital Settings

In 2006, the CDC published recommendations for routine HIV testing in all patients (13 to 64 years of age) in the healthcare setting.[289] 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.[289] The implementation of these guidelines are largely dependent upon institutional practices and the prevalence of undiagnosed HIV infections in specific institutions.

Prophylaxis for *Pneumocystis jirovecii*

TMP/SMX prophylaxis for *P jirovecii* is highly effective in preventing PCP.[290-293] Studies have documented the efficacy of this prophylactic therapy in patients with ALL and in HSCT recipients. In a systematic review and meta-analysis of 12 randomized studies (N=1245; primarily in patients with acute leukemias or in HSCT recipients), prophylaxis with TMP/SMX resulted in a significant reduction in PCP occurrence by 91% compared with placebo, no treatment, or treatment with non-PCP antibiotics (RR, 0.09; 95% CI, 0.02–0.32). In addition, TMP/SMX prophylaxis significantly reduced PCP-related mortality (RR, 0.17; 95% CI, 0.03–0.94).[290] TMP/SMX also has the potential advantage of activity against other infectious complications (such as common bacterial infections, listeriosis, nocardiosis, and toxoplasmosis) that may afflict patients with severe T-cell depletion or impairment.[294] TMP/SMX is considered the treatment of choice for PCP prophylaxis (category 1; see *Antipneumocystis Prophylaxis* on page INF-6). In cases of intolerance, TMP/SMX desensitization should be considered. Daily dapsone and aerosolized pentamidine are thought to be effective alternatives to TMP/SMX, although some data suggest that these agents may be inferior when used prophylactically in allogeneic HSCT recipients.[295-298] Atovaquone appears to be equivalent to dapsone in HIV patients who cannot tolerate TMP/SMX.[299] In pediatric patients with acute leukemias who were intolerant of TMP/SMX, atovaquone was reported to be an effective strategy for PCP prophylaxis.[300] Thus, atovaquone is another alternative for patients with cancer who require prophylaxis and who are intolerant to TMP/SMX.

Prophylaxis against PCP should be used in allogeneic HSCT recipients, patients receiving treatment with alemtuzumab [38], and patients with ALL (category 1) (see *Antipneumocystis Prophylaxis* on page INF-6). Prophylaxis against PCP is also advised in patients receiving concomitant temozolomide and radiotherapy and should be continued until recovery from lymphocytopenia .[301] Some panel members advise prophylaxis against PCP for the following patients (category 2B): 1) patients receiving purine analog therapy (eg, fludarabine, cladribine [2-CdA]) and other T-cell depleting agents; 2) autologous HSCT recipients; and 3) patients with neoplastic diseases receiving intensive corticosteroid treatment (eg, the equivalent of 20 mg or more of prednisone daily for 4 weeks or more).[302-305]

Protected Environments

Although well-designed clinical trials have not validated the use of high-efficiency particulate air (HEPA) filtration, the CDC recommends that allogeneic HSCT recipients be placed in rooms with HEPA filters.[16] It is also reasonable to use HEPA filtration in nontransplant patients with prolonged neutropenia. The principal benefit of HEPA filtration is likely to be related to the prevention of mold infections. In a retrospective analysis, HEPA filters were protective in highly immunocompromised patients with hematologic malignancies in the setting of an outbreak of aspergillosis.[306] The value of laminar air flow in preventing infections is unclear and is not generally recommended.

Management of Neutropenic Patients With Fever

The definitions of fever and neutropenia in the NCCN Guidelines are consistent with those developed by the Infectious Diseases Society of

America (IDSA) and the FDA for evaluating antimicrobial therapy for fever and neutropenia.[4] *Fever* is defined as a single oral temperature 38.3°C (or equivalent) or higher or 38.0°C or higher over 1 hour in the absence of an obvious cause. Axillary or rectal temperature measurements should be avoided.[22] Although uncommon, a patient with neutropenia and signs or symptoms of infection (eg, abdominal pain, severe mucositis, perirectal pain) without fever should be considered to have an active infection. The concomitant administration of corticosteroids may blunt fever response and any localizing signs of infection. The NCCN Guidelines define *neutropenia* as either 1) an absolute neutrophil count (ANC) less than 500 neutrophils/mcL, or 2) an ANC less than 1000 neutrophils/mcL and a predicted decline to 500 neutrophils/mcL or less over the next 48 hours.

Initial Evaluation

The initial evaluation should focus on determining the potential sites and causative organisms of infection and on assessing the patient's risk of developing an infection-related complication. A site-specific history and physical examination should be performed promptly, cultures should be obtained, and empiric antibiotics started soon after the time of presentation (see *Initial Evaluation of Fever and Neutropenia* on page FEV-1). The common sites of infection for patients with fever and neutropenia (such as the alimentary tract, skin, lungs, sinus, ears, perivaginal/perirectal, urological, neurological and intravascular access device sites) should be thoroughly assessed. Other important factors in patient history to consider include major comorbid illness, medications, time since last chemotherapy administration, recent antibiotic therapy, and exposure to infections from household members (see *Initial Evaluation of Fever and Neutropenia* on page FEV-1).

Initial laboratory/radiology evaluation should include a complete blood count with differential analysis and blood chemistry tests to assess liver function (eg, total bilirubin, albumin, ALT, AST) and renal function (eg, blood urea nitrogen, creatinine, electrolytes). Oxygen saturation and urinalysis should be considered, depending on symptoms. Chest radiographs should be done for all patients with respiratory signs or symptoms; however, radiographic findings may be absent in neutropenic patients with pulmonary infection.[307]

Cultures

Culture specimens should be collected during or immediately after completing the examination. Two blood samples should be cultured. When obtaining blood cultures, there are 3 options: 1) one set can be obtained peripherally and one can be obtained from a central venous catheter (preferred); 2) both sets can be obtained peripherally; or 3) both sets can be obtained through the catheter (see *Initial Evaluation of Fever and Neutropenia* on page FEV-1). The positive predictive value of a catheter culture is less than a peripheral culture. Obtaining blood for culture from both the central venous catheter and peripherally may help determine whether the venous access device (VAD) is the source of a bloodstream infection based on the differential time to positivity.[308] However, some experts recommend that only blood from the VAD needs to be obtained for culture, without the requirement for a peripheral vein blood culture.[308] A meta-analysis has shown little clinical use for two-site culturing in patients with cancer who have a VAD, and poor patient acceptance of peripheral venipunctures when a VAD is in place.[309] The panel consensus is that the volume of blood for culture is the most important aspect of blood culturing; in addition, the panel recommends obtaining one peripheral and one catheter culture for distinguishing between catheter-related infections and from secondary sources.

In the absence of lesions or clinical signs and symptoms, routine cultures of the anterior nares, oropharynx, urine, stool, and rectum are rarely helpful. Diarrheal stools suggestive of infection, should be tested for the presence of *C difficile*.[310] In patients with diarrhea, consider screening for enteric pathogens including rotavirus and norovirus in winter months and during outbreaks. Symptoms of urinary tract infection should be evaluated with a urinalysis and culture. Vascular access site inflammation or drainage should be cultured. Biopsy with microbiologic and pathologic evaluation should be considered for new or undiagnosed skin lesions (see *Initial Evaluation of Fever and Neutropenia* on page FEV-1). Viral cultures of vesicular or ulcerated mucosal or cutaneous lesions may identify HSV infections. In patients with symptoms of respiratory viral infection, viral cultures and rapid viral antigen testing of the nasopharyngeal secretions can be useful during local outbreaks of such infections.[311,312] However, note that rapid immunofluorescent viral antigen tests may still result in a false negative for H1N1 (swine flu).

Outpatient Management of Patients With Neutropenic Fever

Initial Evaluation of Risk

Patients with neutropenia may be categorized into either a high- or low-risk group using criteria derived either from validated clinical prediction rules based on risk models or from clinical trials eligibility criteria.[8,10-12,313-315] Risk assessment attempts to predict the probability that a neutropenic patient will experience serious complications during a febrile episode. This assessment helps to determine whether a patient at low risk for serious complications could safely receive treatment outside of the hospital and initial empiric therapy with oral antibiotics.

Prospective trials have indicated that febrile neutropenic patients can be initially evaluated in the hospital, ambulatory clinic, or home and then treated effectively with broad spectrum IV, sequential IV /oral, or oral therapy.[315-317] Only centers with the necessary infrastructure should treat low-risk patients in an outpatient setting, preferably in an investigational context.

Risk assessment should be performed as part of the initial evaluation (see *Initial Risk Assessment for Febrile Neutropenic Patients* on page FEV-2). A widely used and recently validated prediction rule to assess risk was developed by the Multinational Association of Supportive Care in Cancer (MASCC). The MASCC risk index is derived from a model that includes weighted scores based on burden of illness (eg, extent of febrile neutropenia), evidence of clinical instability or comorbid conditions (eg, hypotension, COPD, dehydration), history of prior fungal infections, site of medical care (ie, inpatient, outpatient) and age (cut off of 60 years); patients with MASCC risk index scores <21 are considered at high risk for developing infectious complications (see *Risk Assessment Resources* on page FEV-D).[318-321] It is also acceptable to employ risk assessment criteria that have been identified in large clinical trials to distinguish between patients at low and high risk for complications during the course of neutropenia.

The MASCC prediction rule does not consider the duration of neutropenia to be a deciding factor that influences the clinical course of treatment;[320] however, the panel acknowledges that the duration of anticipated neutropenia may be helpful in risk assessment. A patient with severe neutropenia (ANC ≤100 neutrophils/mcL) anticipated to last ≥7 days may be considered at high risk, regardless of the MASCC risk index score or other risk factors listed in the Guidelines. This recommendation is also in agreement with those of the current IDSA guidelines on the management of neutropenic patients with cancer.[22]

Duration of Neutropenia and Risk

For decades, clinicians have regarded depth and duration of neutropenia as critical determinants of a patient's risk for infection.

Once the relationship between the ANC and incidence of infections was demonstrated, the importance of increased neutrophil counts for improved outcomes was evident. In the original study by Bodey et al,[25] the fatality rate was highest (80%) among patients with initial neutrophil counts less than 100 cells/mcL that did not change during the first week of infection compared to the lower rate (27%) seen in patients with initial neutrophil counts less than 1000 cells/mcL that rose to greater than 1000 cells/mcL with treatment.[25] Subsequently, clinical trials have reported that response rates to antibiotic regimens are highly influenced by trends in the neutrophil count during febrile episodes. In one study, the overall response rate was 73% when the initial neutrophil count increased compared to 43% when it decreased or remained unchanged ($P < .0001$). The response rate in patients who were initially profoundly neutropenic (ie, ANC<100 neutrophils/mcL) but who recovered from neutropenia was 67%, compared to only 32% in patients who remained profoundly neutropenic ($P < .0001$).

In 1988, Rubin et al[322] examined the influence of the duration of neutropenia on the response to empiric antimicrobial therapy in patients with fever of undetermined origin.[322] Patients with less than 7 days of neutropenia had response rates to initial antimicrobial therapy of 95%, compared to only 32% in patients with more than 14 days of neutropenia ($P < .001$); however, intermediate durations between 7 and 14 days had response rates of 79%.[322]

Bone marrow recovery is an important factor that influences outcome during the febrile neutropenic episode. Delayed bone marrow recovery might be anticipated in certain patient subsets (eg, patients who have received multiple cycles of myelosuppressive chemotherapy, HSCT recipients, patients with known bone marrow metastases, or patients who have received radiation therapy to the pelvis, spine, or long bones). Most patients with solid tumors have neutropenia lasting less than 7 days and are generally lower risk. Several studies have demonstrated the ability of clinicians to predict a patient's anticipated duration of neutropenia. In prospective studies of patients identified as low risk for morbidity and mortality from febrile neutropenia, the expected duration of neutropenia was used as an eligibility criteria. Clinicians were correctly able to identify patients with an expected short duration of neutropenia (ie, less than 7-10 days) in more than 80% of the cases[3,316,317] indicating that the duration of neutropenia can be one of several factors in selecting patients for outpatient management of neutropenic fever.

Evaluation of Patients for Outpatient Therapy for Neutropenic Fever

Outpatient therapy has become a common practice in low-risk patients with neutropenic fever. Several single-center clinical trials generally support the shift in care for low-risk patients to the outpatient setting; the hospital is not necessarily a safer place for low-risk patients, given the documented hazards of hospitalization.[323,324] However, not all centers are equipped to attempt such outpatient treatment, and some patients with fever are not appropriate candidates. Early success with this type of therapy has been predicated on the ability to accurately determine an individual patient's risk of developing complications associated with infection and on the presence of an adequate infrastructure for treatment and monitoring.

Once a level of risk has been identified, it can then be used to determine the appropriate site of care and route of broad spectrum antibiotics administration. The panel recommends that all high-risk patients receive hospital care with broad spectrum IV therapy (see *Initial Risk Assessment for Febrile Neutropenic Patients* on page FEV-2). Low-risk patients may be treated in the hospital with oral or IV antibiotics, in an ambulatory clinic, or at home if adequate follow-up care can be provided (ie, 24 hours per day, 7 days per week).

Outpatient therapy should be considered only for low-risk patients who consent to home care, have a telephone, have access to emergency facilities, have an adequate and supportive home environment, and are within 1-hour travel time of a medical center or physician's office. Outpatient therapy requires a period of early assessment and an observation period of 2 to 12 hours (category 2B) (see Outpatient Therapy for Low-Risk Patients on page FEV-3). The assessment requires a careful examination, review of laboratory results, review of social criteria for home therapy (as described above), and assessment of whether oral antibiotics are feasible. The observation period is used to confirm that the patient is at low risk and to ensure the clinical stability of the patient; to administer the first dose of antibiotics and monitor for any reactions; to organize discharge plans for home and follow-up care; and to provide patient education. A telephone follow-up should be performed within 12 to 24 hours. This assessment and observation can be performed during a short hospital stay or in an ambulatory facility or office staffed with qualified health care professionals. Providers who perform the early assessment and follow-up should be well trained (eg, a physician, nurse, physician assistant, and/or nurse practitioner) and should have experience and expertise in managing patients with fever and neutropenia.

Outpatient Regimens

Outpatient antimicrobial treatment may consist of broad spectrum IV antibiotics given at home or in the clinic, or an oral regimen for carefully selected patients.[325] For selected low-risk patients, the combination of ciprofloxacin with amoxicillin/clavulanate (both at 500 mg every 8 hours) is considered the oral regimen of choice based on well-designed randomized trials (category 1) (see *Outpatient Therapy for Low-Risk Patients* on page FEV-4). Although some of these trials were performed in an inpatient setting, they demonstrate the efficacy of the oral combination compared with standard IV therapy in the low-risk population.[5,313,326] Ciprofloxacin plus clindamycin is an acceptable alternative for penicillin-allergic patients.[8,22] However, ciprofloxacin monotherapy is not considered by the panel to be an adequate broad spectrum agent because of the suboptimal coverage for gram-positive organisms and potential for serious breakthrough infections caused by viridans group streptococci.[327] Nonetheless, several small studies have used high-dose oral ciprofloxacin alone in low-risk patients with fever and neutropenia.[1,328,329]

Moxifloxacin (a newer generation fluoroquinolone) was shown to be safe in low-risk patients with neutropenic fever.[330] In a recent double-blind, randomized trial, single daily moxifloxacin was compared with twice daily ciprofloxacin plus amoxicillin/clavulanic acid in the treatment of low-risk febrile neutropenic patients with cancer.[331] Low risk was defined as an MASCC score greater than 20 that is equivalent to a less than 10% complication rate. Of the 333 patients treated on this trial, 169 were given moxifloxacin and 169 patients were treated with the ciprofloxacin combination. Therapy success was observed in 80% of patients treated with moxifloxacin compared with 82% of patients given ciprofloxacin combination therapy (95% CI, -10% to 8%, *P* = NS). Despite similar therapy success rates, the reasons for failure of the treatment differed between the two groups. Moxifloxacin treated patients had greater microbial complications including persistent or breakthrough resistance, while patients given the ciprofloxacin combination had mostly drug intolerance or adverse events that resulted in treatment failure. Rates of patients treated with moxifloxacin compared to ciprofloxacin combination with serious adverse events (6% vs. 8%, *P* = .23) or any adverse event (44% vs. 52%; *P* = .13) were similar. Moxifloxacin has a longer half-life which allows for once daily dosing. It is more active against gram-negative bacteria but has limited activity against *P aeruginosa* compared to ciprofloxacin. Therefore, both

of these treatments are recommended for low-risk patients with febrile neutropenia but the choice of regimen may be influenced by local resistance and infection patterns.

Two other fluoroquinolones, ofloxacin and levofloxacin, have been tested for the treatment of low-risk patients with febrile neutropenia. Ofloxacin was safe in low-risk patients with neutropenic fever in a randomized trial though an early death in a non-hospitalized patient in this trial underscores the need for close monitoring.[316] Presumably, levofloxacin (which is the L-isomer of ofloxacin) would be equally effective and data from a 2008 self-administered survey indicated that 50% of oncologists were using levofloxacin as empiric therapy for low-risk patients with febrile neutropenia.[332]

The panel feels that outpatient therapy with a fluoroquinolone should be based on reliable gram-negative bacillary activity of the antibiotic that includes *P aeruginosa* and local antibacterial susceptibilities. Ciprofloxacin plus amoxicillin/clavulanate (or ciprofloxacin plus clindamycin in penicillin-allergic patients) is the standard oral outpatient antibiotic regimen for low-risk patients with neutropenic fever. There is also evidence supporting quinolone monotherapy in this setting. Currently only moxifloxacin is recommended as a quinolone monotherapy. Additional studies are necessary before recommendations can be made for any other monotherapy. These recommendations for quinolone-based outpatient regimens for neutropenic fever only apply to low-risk patients who have not received a quinolone as prophylaxis. Additionally, in order for a low-risk patient to receive oral antibiotics, the patient should not present with nausea or vomiting, and must be able to tolerate oral medications (see *Outpatient Therapy for Low-Risk Patients* on page FEV-3). Intravenous therapy may also be used for outpatient treatment of low-risk patients with fever and neutropenia when treatment is given either in the home or day clinic setting (see *Outpatient Therapy for Low-Risk Patients* on page FEV-4). Several IV outpatient regimens for low-risk patients have been studied in nonrandomized or small open trials, including IV ceftazidime, imipenem/cilastatin, and aztreonam plus clindamycin.[8,313,315,317,333,334]

Once-daily ceftriaxone has been used for empiric antibiotic therapy in a few noncomparative studies in centers where *Pseudomonas* is not a common pathogen.[335] However, most *P aeruginosa* isolates are resistant to ceftriaxone. Although ceftriaxone combined with a once-daily aminoglycoside is a convenient regimen for outpatient IV administration, an aminoglycoside without an antipseudomonal beta-lactam may not be effective against *P aeruginosa*, which remains an infrequent but potentially lethal pathogen. Therefore, the panel cannot recommend ceftriaxone (with or without an aminoglycoside) as empiric therapy for neutropenic fever. If this regimen is used, it should be restricted to low-risk patients at centers where *P aeruginosa* infection is uncommon. In addition to the antimicrobial spectrum, other factors to consider in the choice of an outpatient regimen include stability of the reconstituted drugs, ability to manage IV infusions, and VADs.

Follow-Up of Outpatients With Fever and Neutropenia

Follow-up management can be performed at the patient's home or in the physician's office or clinic. The panel recommends that patients be assessed daily while febrile, although some experts feel that less frequent follow-up may be appropriate after fever defervescence (see *Outpatient Therapy for Low-Risk Patients* on page FEV-4). For the first 72 hours after initiation of empirical therapy, the patient should be assessed daily at home or at the clinic for treatment response, signs of toxicity, and treatment compliance. If the patient is responding to the treatment regimen, then daily follow-up by telephone is sufficient. A return to the clinic is recommended for any positive culture, for persistent or recurrent fever at 3-5 days, if serious subsequent

infections or adverse events develop, or if the patient is unable to continue the prescribed antibiotic regimen (eg, intolerance to the oral regimen).

Initial Empiric Antibiotic Therapy

The foundation of infection management is to administer empiric antibiotics in patients with fever and neutropenia. This approach is necessary because currently available diagnostic tests are not sufficiently rapid, sensitive, or specific to identify or exclude microbial causes of fever from other noninfectious causes. All neutropenic patients should be treated empirically with broad spectrum antibiotics promptly at the first sign of infection (ie, fever). This is done to avoid the mortality associated with a delay in treatment in patients with a serious infection.[4,336] Many highly effective antibiotic regimens are available, and are recommended based on data from randomized clinical trials.

Selection of initial therapy should consider the following:

- The patient's infection risk assessment;
- The antimicrobial susceptibilities of pathogens isolated locally;
- The most common potentially infecting organisms, including antibiotic-resistant pathogens, such as extended spectrum beta-lactamase–producing gram-negative rods, vancomycin-resistant enterococcus (VRE), and colonization with or previous infection with methicillin-resistant *S aureus* (MRSA);
- The potential sites of infection;
- The importance of a broad spectrum bactericidal antibiotic regimen that includes antipseudomonal coverage;
- Clinical instability (eg, hypotension, organ dysfunction);
- Drug allergy;
- Recent antibiotic use (including prophylaxis)
- Bactericidal.

Recommended Approaches

The panel considers the following approaches to initial empiric management of febrile neutropenia to be appropriate based on the results of large, randomized controlled clinical trials (see *Initial Empiric Therapy for Uncomplicated Fever and Neutropenia* on page FEV-5).[4,7,336]

The first approach is IV antibiotic monotherapy (all category 1 except where noted) with either imipenem/cilastatin, meropenem, piperacillin/tazobactam, or an extended-spectrum antipseudomonal cephalosporin (cefepime [category 1] or ceftazidime [category 2B]).[2,337-340] Local institutional bacterial susceptibilities should be considered when selecting empiric antibiotic therapy. In hospitals where infections caused by antibiotic resistant bacteria (eg, MRSA or drug-resistant gram-negative rods) are commonly observed, policies on initial empirical therapy of neutropenic fever may need to be tailored accordingly.

A meta-analysis of randomized trials reported that cefepime was associated with increased all-cause mortality when used as empiric therapy for neutropenic fever, although no increase in infection-related mortality was noted.[333,341] However, a subsequent meta-analysis by the FDA, using additional data, did not find a statistically significant increase in mortality for cefepime-treated patients compared with controls. Thus, the FDA concluded that cefepime remains an appropriate therapy for its approved indications.[342,343]

Intravenous antibiotic combination therapy is not routinely recommended except in complicated or resistant cases. In such situations, an aminoglycoside combined with an antipseudomonal agent

can be considered. [344-346] Aminoglycoside use carries the inherent risk of renal and otic toxicity. Avoiding these toxicities requires careful monitoring and necessitates frequent reassessment, but once-daily aminoglycoside dosing is associated with less renal toxicity than shorter interval dosing.[347] Once-daily aminoglycoside dosing should probably not be used for treating meningitis or endocarditis based on inadequate clinical data. The use of vancomycin, linezolid, daptomycin, or quinupristin/dalfopristin is not routinely recommended. Although published studies exist regarding the use of some of these agents in neutropenic patients, the panel strongly recommends that these agents not be used routinely as initial empirical therapy because of concerns for resistance and breakthrough infections.

For patients at high risk for *Pseudomonas* infections (such as, history of previous *Pseudomonas* infections or presence of ecthyma gangrenosum), initial combination therapy with the most active antipseudomonal agents available in the local setting should be considered.

As discussed earlier, initial empirical therapy for low-risk patients with fever and neutropenia is oral antibiotic combination therapy (see Initial Empiric Therapy for Uncomplicated Fever and Neutropenia on page FEV-5). Ciprofloxacin plus amoxicillin/clavulanate is recommended (category 1), with the option of ciprofloxacin plus clindamycin for patients allergic to penicillin. Fluoroquinolone regimens should not be administered in patients receiving antimicrobial prophylaxis with a fluoroquinolone.

For specific indications, the addition of IV vancomycin either to IV monotherapy or to combination therapy (see *Empiric Addition of Vancomycin* in the Discussion) may be considered. Support for the judicious use of vancomycin has developed because of the increased frequency of beta-lactam–resistant gram-positive infections caused by MRSA, most coagulase-negative staphylococci, penicillin-resistant viridans group streptococci and enterococci, and *Corynebacterium jeikeium.* Vancomycin should be reserved for specific indications and should not be considered as a routine component of initial therapy for fever and neutropenia.

Empiric Addition of Vancomycin

Considerable debate has occurred about the use of empiric vancomycin in patients with fever and neutropenia, as the uncontrolled use of vancomycin has facilitated the dissemination of vancomycin-resistant organisms, especially enterococci.[348,349] The clinical concern is that a portion of infections caused by gram-positive pathogens can be fulminant and lead to rapid death in patients who are not treated promptly with appropriate antibiotics. However, a large, prospective, randomized trial from the European Organization for Research and Treatment of Cancer failed to show true clinical advantages for empiric vancomycin in adults.[350] This study reported that empiric vancomycin decreased the number of days the patients had fever but did not improve survival. The study also showed that empiric vancomycin was associated with an increased incidence of nephrotoxicity and hepatotoxicity.[350] A prospective randomized trial of fever and neutropenia in children has reported benefit for empiric vancomycin;[351] however, another randomized study in children failed to show a benefit for the addition of vancomycin.[352]

In addition to the occurrence of vancomycin-resistant enterococci (VRE), there are other vancomycin-resistant pathogens of note. Reports of vancomycin-resistant and vancomycin-intermediate sensitive *S aureus* are currently rare but are of key concern, and they underscore the need for judicious vancomycin use.[353,354] The increase in vancomycin resistance has been associated with use of vancomycin

among hospitalized patients. The NCCN Guidelines Panel advises practitioners to adopt the recommendation of the Hospital Infection Control Practices Advisory Committee (HICPAC) of the CDC for preventing the spread of vancomycin resistance.[355,356] Because of the increased risk for vancomycin-resistant organisms, empiric vancomycin use should be considered only in patients at high risk for serious gram-positive infection, and should not be considered as a routine component of initial therapy for fever and neutropenia. Vancomycin should be considered in the following clinical situations (see *Appropriate Use of Vancomycin and Other Agents for Gram-Positive Resistant Infections* on page FEV-F):

- Clinically apparent, serious IV catheter-related infection (to cover coagulase-negative staphylococcal isolates, which are usually beta-lactam antibiotic-resistant and MRSA);[357,358]
- Blood cultures positive for gram-positive bacteria before final identification and susceptibility testing;
- Known colonization with penicillin/cephalosporin–resistant pneumococci or MRSA;
- Clinical instability (eg, hypotension or shock), pending the results of cultures;[359,360]
- Soft tissue infection (particularly in regions where MRSA infection is common).[361]

If empiric vancomycin (or other agents for gram-positive resistant infection) is initiated in any of these situations, its use should be reassessed within 2 to 3 days of initiation. If a resistant gram-positive pathogen (eg, MRSA) is not identified, the panel recommends discontinuing the agent. Recent authoritative guidelines have been published on the dosing and therapeutic monitoring of vancomycin.[362] For management of complicated cases of *C difficile* infections, oral vancomycin can be considered (see *Site-Specific Evaluation and Treatment of Infectious Diseases: Abdominal, Rectal, and Liver Infections: Clostridium difficile Colitis* in the Discussion).

In patients with acute leukemia receiving mucotoxic regimens, prophylaxis with ciprofloxacin and TMP/SMX have been associated with an increased risk of viridans group streptococcal infections.[81,363,364] The broad spectrum, gram-negative bacillary coverage and limited gram-positive pathogen activity of these drugs likely predispose patients to GI colonization and subsequent infection with such organisms.[327,365] An abstract has reported an increased risk of breakthrough viridans group streptococcal infection following prophylaxis with levofloxacin,[366] which has increased activity against gram-positive bacteria compared to ciprofloxacin; however, this is a single report and more data will be necessary to fully evaluate the use of newer generation fluoroquinolones.

Although bloodstream infections by viridans group streptococci resistant to all beta-lactams are observed in patients with cancer, cefepime, imipenem/cilastatin, meropenem, and piperacillin-tazobactam have more reliable activity than ceftazidime against viridans group streptococci.[367] Addition of vancomycin provided no benefit compared to placebo with regard to defervescence, episodes of gram-positive bacteremia, or use of empiric antifungal therapy in patients with hematologic malignancies with neutropenic fever of unknown etiology that persisted for 48 to 60 hours after initial empiric piperacillin-tazobactam.[368,369] A smaller randomized, placebo-controlled study did not show any advantage after adding teicoplanin (a glycopeptide antibiotic similar to vancomycin) in patients with neutropenic fever that persisted after 3 to 4 days of empiric imipenem/cilastatin.[370] In patients with neutropenic fever and severe mucositis who are receiving imipenem/cilastatin, meropenem, or piperacillin/tazobactam (ie,

antibiotics with activity against oral flora), it does not appear that the addition of vancomycin is advantageous. Thus, the NCCN Guidelines Panel strongly recommends that vancomycin should not be routinely added to an empiric regimen solely based on persistent neutropenic fever of unknown etiology (see *Appropriate Use of Vancomycin and Other Agents for Gram-Positive Resistant Infections* on page FEV-F).

Agents With Broad Spectrum Activity Against Gram-Positive Pathogens

Decreased susceptibility to vancomycin is an increasing concern. If decreased susceptibility is found on minimum inhibitory concentration (MIC) assessment, other treatment options for resistant gram-positive infections should be considered. Linezolid, daptomycin, and quinupristin/dalfopristin are active against the majority of gram-positive organisms, including beta-lactam-resistant and vancomycin-resistant pathogens.[371-375] The panel recommends that the use of these drugs be limited to specific situations involving infections caused by documented vancomycin-resistant organisms, or for patients in whom vancomycin is not an option. Although studies have been published in patients with neutropenia, the NCCN Guidelines Panel strongly recommends that these agents not be used as routine empiric therapy for neutropenic fever because of concerns about the emergence of resistance and toxicity.

Resistance of gram-positive organisms to linezolid is infrequent, but this agent should be administered with caution in patients with compromised bone marrow function because of the marrow toxicity associated with its long-term use. Thrombocytopenia is most common (0.3% to 10%) and increases with the duration of linezolid treatment, typically with duration of treatment of more than 2 weeks. In neutropenic patients with cancer, myeloid recovery does not seem to be delayed with short courses of linezolid;[376,377] however, experience with long durations of therapy (eg, more than 14 days) is limited in cancer patients. Vancomycin or linezolid should be used for the treatment of MRSA pneumonia in ventilated patients.[378-381] The FDA issued an alert about linezolid indicating that it is not approved for treatment of catheter-related infections, catheter-site infections, or gram-negative infections.[382] In an open-label randomized study, patients treated with linezolid had a higher chance of death compared with those receiving vancomycin, oxacillin, or dicloxacillin for intravascular catheter-related infections with 1) gram-negative agents alone; 2) both gram-positive and gram-negative organisms; or 3) no infection. No mortality difference by treatment was found among those who had gram-positive infections alone.[382]

Daptomycin is effective against most gram-positive pathogens, but it should not be used for the treatment of pneumonia, because it is inactivated by pulmonary surfactant.[383,384] Daptomycin is indicated for the treatment of complicated skin and skin structure infections caused by susceptible strains of certain gram-positive microorganisms.[385-387] A pharmacokinetic study of daptomycin in febrile neutropenic patients with cancer showed that this agent was active and well tolerated in this population (N=29) with a median time to defervescence of 3 days following the start of treatment.[388] A randomized study showed similar efficacy of daptomycin compared with vancomycin or anti-staphylococcal beta-lactams as therapy for *S aureus* bacteremia and endocarditis.[389] In a prospective study in patients with cancer who were treated with daptomycin for gram-positive catheter-related bloodstream infections (N=40), the rates of symptoms resolution at 48 hours (76% vs. 53%) and microbial eradication at 48 hours (78% vs. 34%) were higher with daptomycin compared with historical vancomycin treatment in matched-control patients.[390] In addition, the overall response rate was higher with daptomycin (68% vs. 32%), and the incidence of nephrotoxicity was lower. The treatment groups were comparable with

regards to the rate of neutropenia, complications, adverse events, length of hospital stay, and deaths.[390]

Quinupristin/dalfopristin is active against *S aureus* (including MRSA) and *Enterococcus faecium* (including vancomycin-resistant strains) but is inactive against *Enterococcus faecalis*. Use of quinupristin/dalfopristin has been limited because of the high frequency of substantial musculoskeletal symptoms.[391]

Optimal therapy for VRE infections is not well defined. Linezolid, quinupristin-dalfopristin (active against *E. faecium*, but not *E. faecalis*), and daptomycin have been used with variable success in the treatment of patients with VRE bloodstream infections.[377,391,392] Removal of an infected catheter should always be strongly considered. In the absence of more definitive data, therapy with one of these agents is advised for VRE bacteremia.

Telavancin, a lipoglycopeptide antibiotic, and ceftaroline, a broad spectrum cephalosporin antibiotic, have both been approved for the treatment of complicated skin and skin structure infections caused by gram-positive pathogen, including MRSA.[393,394] However, there are no directive data on their use in the oncologic setting. Ceftaroline is also indicated for the treatment of community-acquired bacterial pneumonia caused by susceptible gram-negative and gram-positive (except for MRSA) pathogens; this agent is not active against *Enterococcus faecalis*.[394] Other glycopeptide antibiotics (eg, dalbavancin, oritavancin) are in clinical development.

Initial Empiric Therapy for Patients Who Are Clinically Unstable

Sepsis is suggested by signs of clinical instability including hypotension, tachypnea, new or worsening tachycardia, mental status changes, decreased urine output, and organ dysfunction. Initial therapy for sepsis should broadly cover pathogens that are likely to cause sepsis while minimizing the potential for inadequate treatment.[359] Unlike the stable patient with neutropenic fever, modifying antibiotics based on culture data may not be possible for the patient with sepsis if the initial regimen does not provide adequate coverage. The antibiotic regimen should be modified, if necessary, after culture results and susceptibility are known.

The initial empiric regimen for the neutropenic patient with clinical instability may include a broad spectrum beta-lactam (eg, imipenem/cilastatin, meropenem, or piperacillin-tazobactam) plus an aminoglycoside and vancomycin. Addition of fluconazole or an echinocandin should be strongly considered in patients not receiving antifungal prophylaxis. Local susceptibility patterns and recent antibiotic use should be taken into account when devising the antibiotic regimen.[359] In hospitals where infections by antibiotic resistant bacteria (eg, MRSA or drug-resistant gram-negative rods) are commonly observed, policies on initial empirical therapy of neutropenic fever may need to be tailored accordingly. Some experts also suggest that patients who have a history of *P aeruginosa* colonization or of invasive disease should receive combination therapy with an antipseudomonal beta-lactam plus an aminoglycoside or ciprofloxacin.

For cases of septic shock, rapid interventions are needed. Fluid resuscitation, oxygen, invasive hemodynamic monitoring, and vasopressor agents may be required. Stress doses of hydrocortisone (IV 50 mg every 6 hours with or without fludrocortisone oral 50 mcg daily) have been associated with decreased mortality in patients with septic shock and with insufficient adrenal reserve.[395-399] Stress-dose corticosteroids are recommended for patients with septic shock who require vasopressor support.[359,400,401] High-dose corticosteroids have not shown any benefit in the setting of septic shock or severe sepsis, and may be associated with increased risks for secondary infections.[402-405]

In patients with severe sepsis, drotrecogin alfa, a recombinant human activated protein C (APC), was FDA approved for reducing mortality in patients with the highest risk of death (APACHE II score, 25 or more); however, this agent is not beneficial in lower risk patients or in pediatric patients.[359,406-409] Moreover, based on results from a large placebo-controlled trial that showed no survival benefit in patients with severe sepsis or septic shock treated with drotrecogin alfa, the manufacturer voluntarily withdrew the drug worldwide (in October 2011).[410]

Empiric Antifungal Therapy in Persistent Neutropenic Fever

Empiric antifungal therapy for persistent febrile neutropenia unresponsive to broad spectrum antibacterial agents is used, because neutropenic patients are known to be at risk for invasive fungal infections, and clinical examination and collection of cultures are not sufficiently sensitive for early detection of those infections.[14,411-414] Traditionally, empiric antifungal therapy is initiated after 4 or more days of empiric antibiotic therapy for fever and neutropenia, in patients who have remained febrile or have recrudescent fever (see *Principles of Daily Follow-up* on page FEV-10).The timing to add empirical antifungal therapy varies with the risk of invasive mold infections, but generally ranges between 7 to 10 days of neutropenic fever despite empirical antibiotic therapy. In patients at high risk for mold infections (eg, neutropenia lasting >10 days, allogeneic HSCT recipients, treatment with high-dose corticosteroids), the NCCN Guidelines Panel recommends adding empirical antifungal agents after 4 days unless the patients is receiving prophylaxis with mold-active agents. The concept of using empiric antifungal therapy was established in the 1970s and 1980s when about 20% of patients being treated for acute leukemia or undergoing HSCT would develop an invasive fungal infection due to *Candida* or *Aspergillus* species by day 20 of neutropenia.[415] The toxicity of amphotericin B limited its use as routine prophylaxis, which would entail exposing more patients to a toxic drug over a prolonged period than does empiric therapy. With the widespread use of fluconazole prophylaxis in the 1990s among high-risk patients with acute leukemia and in HSCT recipients, the incidence of invasive candidiasis in these patients decreased substantially, although breakthrough candidemia by fluconazole-resistant strains occurred.[78,102] Empiric antifungal therapy for neutropenic fever principally involved switching from fluconazole to amphotericin B to broaden the antifungal spectrum to include molds such as *Aspergillus*. Subsequently, liposomal amphotericin B (L-AMB) proved to be safer than and as effective as conventional amphotericin B for empiric antifungal therapy.[416]

Amphotericin B products are considered a category 2B recommendation for prophylaxis and empirical antifungal therapy for persistent or recurrent neutropenic fever of unknown etiology based on their toxicity and the availability of safer and equally effective alternative agents. In cases where there is a stronger clinical suspicion of mold infection than neutropenic fever alone (eg, a new pulmonary nodule in a patient with fever and prolonged neutropenia), then use of an amphotericin B formulation (or a mold-active azole or an echinocandin) should be considered pending additional diagnostic evaluation. In general, lipid formulations of amphotericin B are preferred over the conventional formulation, because they are less toxic.[417] This recommendation is stronger in patients with risk factors for acute renal failure, such as pre-existing renal disease, HSCT recipients, and co-administration of nephrotoxic agents.[170,171,418]

Fluconazole has been used successfully as empiric therapy for neutropenic fever in patients not receiving prophylaxis but is limited by lack of activity against molds.[419,420] Intravenous followed by oral itraconazole solution was as effective as, but less toxic than, conventional amphotericin B when used as empiric therapy in an open,

randomized study;[421] these results led to FDA approval of oral itraconazole solution for this indication. Intravenous itraconazole is no longer available in the United States. Itraconazole in the capsule formulation has erratic oral bioavailability and is therefore not suitable as empiric antifungal therapy. Itraconazole has negative inotropic effects and is contraindicated in patients with evidence of ventricular dysfunction or a history of congestive heart failure.[422]

Voriconazole was compared with liposomal amphotericin B (L-AMB) in an open, randomized study of empiric antifungal therapy (N=837 patients, 72% with hematologic malignancies).[423] The overall success rates for preventing invasive fungal infections were 26% with voriconazole and 31% with L-AMB. Empiric voriconazole was associated with fewer breakthrough fungal infections (1.9% vs. 5.0%; *P* = .02), with the greatest protective benefit occurring in pre-specified high-risk patients (relapsed acute leukemia and allogeneic HSCT). Because the noninferiority of voriconazole versus L-AMB was not demonstrated in this study based on prespecified criteria, voriconazole did not receive FDA approval for use as empiric therapy.[412,424] Voriconazole is an option (category 2B) for empiric therapy in patients at high risk for invasive mold infection.

Echinocandins are active against *Candida* and *Aspergillus* species but have unreliable activity against most other opportunistic fungi. Caspofungin was compared with L-AMB as empiric therapy for fungal infections in a randomized double-blind study in patients with persistent fever and neutropenia (N=1095).[425] The overall success rates were 34% in both caspofungin and in L-AMB recipients. The proportion of patients who survived at least 7 days after therapy was greater in the caspofungin group (92.6% vs. 89.2%, *P* = .05). The rates of breakthrough fungal infections and resolution of fever during neutropenia were similar between the 2 groups. Among patients with a baseline invasive fungal infection, the success rate was higher with caspofungin versus L-AMB (52% vs. 26%; *P* = .04) and the mortality rate was lower with caspofungin (11% vs. 44% with L-AMB).[425] Drug-related toxicities and premature withdrawals because of drug-related adverse events were significantly lower in caspofungin recipients. This study supports caspofungin as an option for empiric antifungal therapy. Caspofungin is approved for use as empirical treatment of presumed fungal infection in patients with fever and neutropenia.[426] The other echinocandins, anidulafungin and micafungin, have not been studied specifically for empiric antifungal therapy; however, some panel members would consider them to likely be effective, based on the data for caspofungin.

It is unclear whether patients who are already receiving mold-active prophylaxis should subsequently receive empiric antifungal therapy with an additional or different antifungal solely based on persistent neutropenic fever.[427] One approach has been to evaluate such patients with a high resolution computed tomography (CT) scan of the chest, in search of lesions suspicious for invasive fungal disease. CT scanning in this setting has not been validated but it is a reasonable approach, in concert with careful physical examination and blood cultures, in an effort to identify a source of persistent unexplained fever in patients with neutropenia. Laboratory markers (such as serum galactomannan and beta-glucan) have important limitations, including false-negative results in some patients already receiving prophylactic or empiric antifungals.[428,429] A meta-analysis showed the sensitivity of the galactomannan test for proven aspergillosis to be only 70% among patients with hematologic malignancies and 82% among HSCT recipients..[430] However, these antigen-based assays have a high negative predictive value in the absence of mold-active antifungal therapy.

In patients undergoing chemotherapy for acute leukemias and receiving only yeast-active prophylaxis with fluconazole, 3% to 4% developed invasive fungal infections despite prophylaxis.[103,105] Empiric antifungal therapy with anti-mold activity would be expected to benefit these few patients without incurring a greater risk of toxicity.

Pre-emptive antifungal therapy uses characteristic changes in chest or sinus CT scans, laboratory markers, or both to trigger modification of the antifungal regimen, rather than providing empiric antifungals to all persistently febrile neutropenic patients. Maertens and colleagues[431] evaluated a pre-emptive strategy of incorporating L-AMB in high-risk neutropenic patients (who received fluconazole prophylaxis) based on such pre-specified triggers, including serially positive serum galactomannan tests, a bronchoalveolar lavage (BAL) showing mold, and/or suggestive chest CT in patients with persistent fever or with signs of invasive fungal infection. A total of 136 treatment episodes (among 88 patients) were evaluated. Among these, neutropenic fever developed in 117 cases, of which 35% would have met the existing criteria for empirical antifungal therapy. Using the pre-emptive strategy, antifungal therapy was given in 7.7% (9 of 117 episodes of neutropenic fever) of cases rather than up to one third of cases that might have received it on the basis of fever alone.[431] In addition, seropositivity for galactomannan led to early initiation of antifungal therapy in 10 non-febrile episodes. This approach detected all cases of invasive aspergillosis but missed 1 case of invasive fungal infection that involved disseminated zygomycosis resulting in death. Two cases of breakthrough candidemia were detected by conventional culture methods and successfully treated.[431] In a randomized trial of patients with neutropenic fever, a preemptive strategy was associated with an increased incidence of probable or proven invasive fungal infections (9% vs. 3% in empirically treated group; $P < .05$), although without an increase in overall mortality and ultimately with a decreased the cost of antifungal drugs compared to empirical therapy.[432] Taken together, the panel considers the evidence supporting pre-emptive antifungal therapy to be too preliminary to support its routine use.

Follow-up of Patients With Neutropenic Fever

Daily evaluation by a health care professional who is experienced in treating patients with fever and neutropenia is essential. The daily examination should focus on a site-specific assessment, and an infectious disease consultation should be considered for all complicated cases or progressive infections (see *Principles of Daily Follow-up* on page FEV-10). Daily follow-up should include an evaluation of response to empiric antimicrobial therapy, both in terms of fever trends and changes in signs and/or symptoms of infections. Time to defervescence ranges from 2 to 7 days (median, 5 days) for febrile patients with cancer with neutropenia who receive appropriate initial antibiotic therapy.[433] This rate of fever response should be considered when assessing the need to adjust initial antibiotics; random additions or changes for persistent fever are discouraged in the absence of clinical or microbiologic evidence. The expected slow defervescence of fever also complicates decisions regarding the need for repeat blood cultures. Although some experts recommend daily blood cultures until the patient becomes afebrile, increasing evidence suggests that daily blood cultures are unnecessary in stable neutropenic patients with persistent fever of unknown etiology.[434] As part of follow-up, patients should also be evaluated for potential drug toxicities by liver and kidney function tests (generally conducted at least twice weekly)

Current bacterial blood culture systems (such as the BACTEC™ continuous-monitoring culture system) can detect 90% to 100% of bacterial bloodstream pathogens within 48 hours of culture. For this

reason, routine ordering of additional cultures before obtaining the results from the initial series is discouraged. Daily review of previously obtained cultures is critical, and the panel recommends documenting the clearance of bloodstream bacterial or fungal infections with repeat blood cultures. The overall response to initial empiric antimicrobial therapy should be evaluated 3 to 5 days from initiation of empiric therapy. For patients with fever continuing for 4 days or more with empiric therapy, addition of antifungal therapy with activity against molds should be considered.

Evaluation and Follow-up Therapy in Responding Patients

Patients who are responding to empiric therapy should exhibit decreasing fever trends, stable or improving signs and symptoms of infection and should be hemodynamically stable. For these patients, no change is needed to the initial empiric regimen, and if patients were started appropriately on vancomycin, they should continue with the course of therapy. If patients received vancomycin as part of their initial empiric therapy, but they do not have a pathogen recovered or a site of infection identified justifying such treatment, then vancomycin should be discontinued. It is generally recommended that antibiotics be continued until the ANC is 500 cells/mcL or greater, and increasing (see *Principles of Daily Follow-up* on page FEV-10). Patients with fever of unknown origin who become afebrile soon after starting empiric therapy may have empiric antibiotics discontinued with ANC recovery (ANC ≥ 500 neutrophils/mcL) as long as the neutrophil count is likely to continue to increase (patients are often receiving a growth factor). This recommendation assumes that the patient is clinically well and afebrile for at least 24 hours before antibiotic discontinuation. Patients who become afebrile but remain persistently neutropenic (ANC <500 neutrophils/mcL) should receive a more prolonged course of antibiotic therapy until the neutropenia resolves (see *Principles of Daily Follow-up* on page FEV-10). Lower risk patients can also be switched to oral antibiotics until their neutropenia resolves (eg, 500 mg ciprofloxacin every 8 hours plus 500 mg of amoxicillin/potassium clavulanate every 8 hours). For patients that have defervesced but remain neutropenic, de-escalation to prophylactic antibiotics should be considered. Patients with recurrent fever should be reassessed promptly to determine the need for either a change in their antibiotic regimen or for the addition of antifungal therapy. The clinically stable patient with persistent fever of unknown etiology may be safely watched without altering the initial antimicrobial therapy. Modifications of initial empiric antibiotic therapy should be based on specific new clinical findings and/or new microbiologic results; fever alone should not prompt changes in antimicrobial therapy. The exception is the initiation of empiric antifungal therapy in patients who have persistent or recurrent fever after 4 to 7 days of empiric antibacterial therapy and who are not receiving mold-active prophylaxis (see *Principles of Daily Follow-up* on page FEV-10). Documented infections are usually treated according to the site, pathogen, and at least until ANC recovery (see *Site-Specific Evaluation and Treatment of Infections* in the Discussion).

Duration of Therapy for Patients With Documented Infections

The duration of antimicrobial therapy, in general, is dictated by the 1) underlying site of infection; 2) causative organism(s); and 3) patient's clinical condition, response to treatment and neutrophil recovery. Most experts recommend continuing antimicrobial therapy for documented infections at least until the ANC recovers to 500 neutrophils/mcL or greater, but also recommend using a defined course of therapy appropriate for the specific infection. Thus, the duration of antimicrobial therapy may be longer than the duration of neutropenia in these patients (see *Follow-up Therapy for Responding Patients* on page FEV-11). For example, most uncomplicated skin and soft tissue infections can be treated with 7 to 14 days of therapy. For most uncomplicated bacterial bloodstream infections, 7 to 14 days of therapy is usually

adequate, with longer durations (10-14 days) recommended for gram-negative bacteremias. A longer duration (10-21 days) of treatment is also usually indicated for infections of the lungs (eg, bacterial pneumonia) or sinuses.[435] For all *S aureus* bloodstream infections, treatment should be continued for at least 2 weeks after documentation of a first negative blood culture. In cases of endovascular involvement, treatment may need to be prolonged. Complex intra-abdominal infections, such as typhlitis, should be treated until all evidence of infection has resolved, and the patient has recovered from neutropenia. For fungal infections with *Candida*, treatment should be continued for at least 2 weeks after documentation of a first negative blood culture. Invasive mold infections (eg, aspergillosis) generally require treatment for a minimum of 12 weeks.

The duration of treatment for HSV (uncomplicated, localized disease to the skin) and VZV (uncomplicated, localized disease to a single dermatome) infections is typically 7 to 10 days.[436-438] Life-threatening infections, such as invasive fungi or CMV, require individualized courses of therapy that are often prolonged. The duration of anti-infective therapy may need to be extended if further chemotherapy is required while treating a significant infection. This may occur with infections that complicate leukemia or lymphoma treatments in which multiple cycles of intensive chemotherapy are required.

Patients with documented infections who become afebrile after the initiation of the empiric antibiotic regimen and who are at low risk for complications associated with infection may be candidates for outpatient antibiotic therapy. The regimen, whether oral or IV, should be appropriate for neutropenic fever and have activity against the specific infection.

Evaluation and Follow-up Therapy in Non-responding Patients

Although fever resolution may be slow during neutropenia, persistent fever may result from a noninfectious etiology, such as drug-induced fever. Persistent fever may also represent an inadequately treated infectious process, such as a nonbacterial infection (fungal or viral), a bacterial infection that is resistant to empiric antibiotics, a venous access or closed space infection, or inadequate antimicrobial serum levels. It is important to recognize that documented deep tissue infections may take longer than fever of unknown etiology to respond to antimicrobial therapy. In these cases, daily assessment of clinical improvement or failure depends on radiographic, culture and clinical examination data, and on the fever trends. Unusual infections (eg, toxoplasmosis) may complicate neutropenia, particularly if immunosuppressive agents (eg, high-dose corticosteroids) are also used. The panel strongly recommends an infectious disease consultation for these patients.

Patients who remain persistently or intermittently febrile, show no improvement in signs/symptoms of infections, have persistent positive blood cultures, and/or may be hemodynamically unstable, should be considered non-responsive to initial empiric antimicrobial therapy. These patients pose a serious management challenge and are at increased risk of infection-associated morbidity and mortality. For such patients, antimicrobial coverage should be broadened to include anaerobes, resistant gram-negative rods, and resistant gram-positive organisms, as clinically indicated. Coverage should also include *Candida*. In addition, the patient should be reevaluated with CT scans. Again, the panel strongly recommends that an infectious disease expert be consulted for all such patients (see *Principles of Daily Follow-up* on page FEV-10). The lack of response may suggest an infection with a pathogen resistant to the antimicrobial therapy being used, inadequate serum or tissue levels of the antibiotic(s), infection at a vascular site (ie,

catheter or “closed space” infection), or emergence of a second infection. Some documented infections fail to respond to appropriate therapy because of associated profound neutropenia. If possible, treatment should be optimized using broad spectrum antibiotic combinations that minimize other organ toxicity.

Both the American Society of Clinical Oncology[439] and the NCCN have guidelines for the use of prophylactic colony-stimulating factors (CSF) in neutropenic patients (see NCCN Myeloid Growth Factors Guidelines). It is not clear whether these agents are useful as adjunctive therapy for established infectious events. Although the data supporting their use are limited, adjunctive therapy with granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) should be considered (category 2B) in neutropenic patients with serious infectious complications such as pneumonia, invasive fungal infections, or any type of progressive infection (see *Adjunctive Therapies* on page FEV-E). Granulocyte transfusions may be considered (category 2B) in neutropenic patients with serious infectious complications, such as invasive fungal infections or gram-negative rod infection unresponsive to appropriate antimicrobial therapy (see *Adjunctive Therapies* on page FEV-E). The panel notes that the benefit versus toxicity balance associated with granulocyte transfusions has not been established.

Development of Clinical Instability While Receiving Antibacterial Therapy

It is essential to recognize the early signs of breakthrough infections after the initiation of antibacterial therapy. Although persistent neutropenic fever alone is not an indication to modify the antibacterial regimen, signs of breakthrough infection should prompt additional evaluation and consideration of therapy modification.

New findings suggestive of sepsis (eg, hypotension, tachycardia, mental status changes, organ dysfunction) require the following: 1) repeat physical examination to identify the source of infection; 2) repeat blood cultures; 3) consideration of radiologic studies; and 4) empiric modification of antimicrobial therapy pending culture results.[359] Information about previous use of antibiotics and local sensitivity patterns of gram-negative pathogens should guide empiric changes. Empiric addition of vancomycin is warranted in the unstable patient. In patients receiving ceftazidime, the possibility of breakthrough infections (either from extended spectrum beta-lactamase–producing or from cephalosporinase-producing gram-negative rods) should be considered and switching to imipenem/cilastatin or meropenem is appropriate pending culture results. *Stenotrophomonas maltophilia* or carbapenem-resistant *P aeruginosa* may cause breakthrough sepsis in patients receiving imipenem/cilastatin or meropenem; consider empiric modification to a regimen containing piperacillin-tazobactam, an aminoglycoside, and TMP/SMX. In patients not receiving a systemic antifungal agent, addition of fluconazole or an echinocandin should be strongly considered for possible candidemia. The antibiotic regimen should then be tailored based on culture and radiologic results.

Site-Specific Evaluation and Treatment of Infections

The NCCN Guidelines provide recommendations for site-specific evaluation and therapy for infections of the mouth and esophagus, sinuses, liver, abdomen, rectum, vascular access sites, lungs, skin/soft tissue, urinary tract, and central nervous system (CNS). This section is tailored to patients with neutropenia or those who are otherwise significantly immunocompromised (eg, HSCT recipients).

Mouth and Esophageal Infections

The mouth and esophagus are common sites of infection in patients with fever and neutropenia. This site predilection occurs because of the propensity of the mouth and alimentary tract mucosa to be disrupted by cytotoxic therapy, which can cause mucositis. Unfortunately, the characteristics of this disruption are not etiology specific, and important viral and fungal pathogens often can be distinguished only by microbiologic culture. Empiric antibiotic therapy must consider the endogenous anaerobic flora and the shift in oral flora, which occurs with serious illness or antibiotic use. The increased frequency of HSV reactivation and severity of these infections in cancer patients are well known and preventable. The incidence of HSV reactivation in immunocompromised patients may approach 50% to 75%, but it is nearly zero in those who receive prophylaxis with appropriate antiviral agents.[440] HSV infections are associated with more extensive mucosal damage, increased secondary infections, and significantly prolonged healing time. Baglin et al[441] reported that patients with fever and neutropenia who experienced concomitant HSV reactivation and were treated with appropriate antiviral therapy had a significant decrease in the number of days with fever.[441] Ulcerations of the oral mucosa may be due to HSV infections or fungal sources; a culture should be obtained to determine the pathogenic organism, and addition of antiviral or systemic antifungal therapy should be considered, pending results. Vesicular lesions are most often caused by herpes virus infections and should be treated with antivirals pending culture (or other diagnostic assays) results (see *Initial Clinical Presentation: Mouth/Mucosal Membrane* on page FEV-6).

Systemic or topical antifungal agents can be used to treat thrush. Because of the risk of candidemia, systemic antifungal therapy is advised in neutropenic patients. Fluconazole is recommended as first-line therapy for thrush (see *Initial Clinical Presentation: Mouth/Mucosal Membrane* on page FEV-6). If patients do not respond, the dose of fluconazole can be increased up to 800 mg daily (in adults with normal renal function).[442] Although cross-resistance among azoles may occur, oral voriconazole, itraconazole, or posaconazole are reasonable oral options for thrush that is refractory to fluconazole. Echinocandins (such as, caspofungin, micafungin, or anidulafungin) can be used for patients with azole-refractory mucosal candidiasis. Amphotericin B formulations are also effective but are limited by toxicity.

Thrush along with retrosternal burning, chronic nausea, or odynophagia should raise suspicion for *Candida* esophagitis. However, *Candida* esophagitis may occur in the absence of oral thrush, especially in patients receiving oral topical antifungal agents. Definitive diagnosis of esophageal candidiasis is made by endoscopy. Empiric systemic antifungal therapy is often used to treat presumed *Candida* esophagitis.

The presence of thrush favors esophageal candidiasis in patients with symptoms compatible with esophagitis, although the symptoms of HSV and *Candida* esophagitis are similar. Other causes of esophagitis (eg, radiation esophagitis, GVHD of the esophagus or stomach) also produce similar symptoms. A trial of fluconazole and acyclovir (5 mg/kg IV every 8 hours in patients with normal renal function) should be considered in neutropenic patients and other highly immunocompromised persons with symptoms that suggest esophagitis. CMV esophagitis is a rare complication of chemotherapy-induced neutropenia and is most commonly observed in allogeneic HSCT recipients with GVHD. Negative CMV surveillance results from antigenemia or PCR studies would make CMV disease very unlikely. Ganciclovir or foscarnet may be considered for patients at high risk for CMV disease with symptoms suggestive of esophagitis.

For patients with esophagitis who do not respond to empiric therapy with these agents, careful upper endoscopy with platelet support (if required) may be considered to obtain cultures. Tissue biopsies are the gold standard for the diagnosis of invasive esophageal infections. However, endoscopy and biopsy may be associated with complications in patients who are profoundly neutropenic and/or thrombocytopenic; therefore, the procedure should be performed with caution. Radiographic procedures, such as barium studies, lack sensitivity and add little clinically significant information; therefore, these procedures are not recommended.

Sinus or Nasal Infections

The sinuses are a common site of bacterial infection. Patients with severe and prolonged neutropenia (eg, more than 10 days) and allogeneic HSCT recipients with GVHD are particularly susceptible to invasive mold infections. Cytotoxic therapy disrupts the natural cleansing mechanisms in the nasal passages and increases colonization. A preceding chronic infection may also become active in the setting of neutropenia. Sinusitis during the early neutropenic period (less than 7 days) is principally caused by respiratory and gram-negative bacterial pathogens. In patients with longer duration neutropenia or in patients receiving concomitant high-dose corticosteroid therapy, invasive mold infections are an important concern.

Initial symptoms of sinusitis may be mild. A high-resolution CT scan of the sinuses is the radiographic procedure of choice to evaluate patients with pain or tenderness of the sinuses, nasal erosions, unilateral facial swelling, unilateral eye tearing, or epistaxis. A magnetic resonance image (MRI) that includes evaluation of the orbital and cavernous sinuses is useful to evaluate proptosis of the eye or cranial nerve abnormalities (see *Initial Clinical Presentation: Sinus/Nasal* on page FEV-6). Bony erosion on CT scan suggests invasive fungal disease. Ear, nose, and throat (ENT) and ophthalmologic examinations should be performed for symptomatic patients with abnormalities on CT scans, with biopsy and culture of any abnormal tissues. Broad spectrum coverage for aerobes and anaerobes is appropriate for neutropenic and otherwise highly immunocompromised patients with sinus infections. Vancomycin (or another gram-positive active agent) should be added for periorbital cellulitis, which is frequently caused by *S aureus*.

Sinus endoscopy with biopsy and culture are often required to definitively establish the diagnosis and should be pursued aggressively in patients at high risk for mold infection. Invasive fungal sinusitis in patients with hematologic malignancies and with prolonged neutropenia is principally caused by *Aspergillus* species (*A flavus* and *A fumigatus*) and Zygomycetes. In a case-control study of invasive aspergillosis and zygomycosis in patients with either acute leukemia or who were allogeneic HSCT recipients, the risk factors that favored the diagnosis of zygomycosis included fungal sinusitis and use of voriconazole.[443] A lipid formulation of amphotericin B should be used for suspected or confirmed invasive sinus mold infection, pending definitive histology and culture results. Posaconazole can be considered for salvage therapy or if there is intolerance to amphotericin B formulations; posaconazole is not approved by the FDA as either primary or salvage therapy for invasive fungal infections. Voriconazole (category 1) is the drug of choice for invasive aspergillosis.[444-446] Urgent debridement of necrotic tissue should be performed, when feasible.[446]

Abdominal, Rectal, and Liver Infections

Most infections in the abdomen, rectum, or liver are discovered because of a combination of clinical signs and symptoms (eg, abdominal pain,

perirectal pain, diarrhea) and of biochemical abnormalities (eg, abnormal liver function tests). These infections are usually diagnosed and managed based on the radiologic, GI, and surgical expertise of the treating oncology center. Improved imaging techniques (including ultrasonography, CT scans, MRI, and radionuclide and endoscopic procedures) have decreased the need for surgical intervention. The choice of diagnostic studies should be based on the clinical presentation and relative clinical benefit.

Antimicrobial therapy for GI infections must take into account the high likelihood of polymicrobial pathogens and the presence of the endogenous anaerobic GI flora. Acceptable therapeutic options in this setting include monotherapy with a carbapenem (imipenem/cilastatin, meropenem, doripenem, or ertapenem), piperacillin/tazobactam, or pairing ceftriaxone with metronidazole. In neutropenic patients, the antibiotic regimen should have antipseudomonal activity. Percutaneous aspiration and drainage should be performed, if feasible, for suspicious infected collections. Cholangitis may complicate obstructive tumors or previous hepatobiliary surgery. If cholangitis is suspected (ie, patients have fever with or without abdominal tenderness and liver enzyme abnormalities compatible with obstruction), a CT scan should be performed to detect biliary tract dilatation and abscess or infected collections. An endoscopic cholangiogram is useful to document the level of obstruction; if present, endoscopic stent placement may resolve the obstruction, which is a key component in managing cholangitis.

The GI tract and central venous catheters are the principal portals of entry of systemic candidiasis. *Candida* species are frequently components of the colonic flora in normal adults. Patients are susceptible to candidal bloodstream infection because of the mucosal damage induced with cytotoxic therapy and neutropenia. Breaches in the GI tract after anastomotic leaks also predispose patients to candidal peritonitis and bloodstream infections,[447] and antifungal prophylaxis (eg, fluconazole) should be considered.

***Clostridium difficile* Colitis**

Clostridium difficile colitis is principally a complication of antibiotic therapy and hospitalization, but it is also a complication of neutropenia, occurring in about 7% of patients.[448] Diarrhea should be evaluated with at least 2 stool *C difficile* toxin screens. The rate and severity of *C difficile* colitis in the United States may be increasing, partly because of the emergence of a more virulent strain of *C difficile.* Multi-institutional outbreaks of *C difficile* colitis have been reported that were associated with high morbidity and mortality; these outbreaks were caused by a distinct strain with variations in toxin genes and with resistance to fluoroquinolones.[92,93] Early reports suggested that metronidazole cured over 90% of cases of *C difficile* colitis, and the rate of recurrence was low.[449,450] However, Musher et al[451] reported that among patients (N=207) treated with metronidazole for *C difficile* colitis, only 50% were cured and had no recurrence of disease.

Oral vancomycin has a similar efficacy rate compared to oral metronidazole. More recently, it was recognized as an option for initial therapy for *C difficile* colitis despite the risk of selection for VRE and the substantial expense. Oral vancomycin should also be considered over metronidazole for more complicated cases, such as those associated with severe diarrhea, dehydration, clinical instability, significant co-morbidities, or recurrent or refractory *C difficile* colitis. Efforts should be made to deliver vancomycin by the nasogastric route in patients with severe *C difficile* colitis.[452,453] Limited data suggest that IV metronidazole may be useful in this setting, and it is best used as an adjunct to oral vancomycin.[454,455] Intravenous vancomycin is of no value in this setting because of inadequate luminal levels. The panel recommends initial oral metronidazole or oral vancomycin for *C difficile* colitis that is not

severe.[452,456,457] IV metronidazole should be used in patients who cannot be treated with oral agents (see *Initial Clinical Presentation: Additions to initial empiric regimen* on page FEV-7).

Recently, a multicenter, double-blind randomized trial was conducted to evaluate the efficacy and safety of oral fidaxomicin versus oral vancomycin in patients with *C difficile* infection (N=629).[458] The primary end point of this study was clinical cure, defined as the resolution of diarrhea and no further therapy necessary following completion of study treatment. The clinical cure rate with fidaxomicin was noninferior to vancomycin (88.2% vs. 85.8%) in the modified intent-to-treat analysis.[458] The frequency and severity of adverse events were similar between treatment arms. In addition, fidaxomicin was associated with a significantly decreased recurrence rate compared with vancomycin (15.4% vs. 25.3%; *P* = .005) and a significantly higher rate of resolution of diarrhea without recurrence (74.6% vs. 64.1%; *P* = .006).[458] A decrease in recurrence of *C difficile* diarrhea was not observed in the treatment of the current epidemic strain, NAP1/BI/027. The investigators postulate that the improved duration of infection resolution with fidaxomicin may be due to its preservation of normal intestinal anaerobic flora, which may help to prevent the reemergence of *C difficile*.[458] Another multicenter, double-blind randomized trial evaluated the efficacy and safety of oral fidaxomicin versus oral vancomycin in adult patients with acute *C difficile* infection (N=535; n=509 evaluable).[459] The primary end point of this study was clinical cure. This study also demonstrated that the clinical cure rate with fidaxomicin was noninferior to vancomycin (87.7% vs. 86.8%) in the modified intent-to-treat analysis. Interestingly, among the subgroup of patients receiving concomitant antibiotics for other infections (n=96), treatment with fidaxomicin resulted in a higher cure rate compared with vancomycin (90.2% vs. 73.3%; *P* = .031).[459] The incidence of treatment-emergent adverse events was similar between treatment arms. Both of these large randomized controlled studies showed that treatment of *C difficile* infection with fidaxomicin was noninferior to vancomycin. A subgroup analysis combining data from the two randomized studies was conducted to evaluate the efficacy of these agents in patients with a cancer diagnosis who had *C difficile* infection (n=183).[460] Overall, the cure rate was significantly lower among the patients with cancer compared with patients without cancer in these trials (n=922; 79.2% vs. 88.6%; *P* < .001). In addition, the median time to resolution of diarrhea was delayed among patients with cancer (100 hours vs. 55 hours; *P* < .001). An analysis by treatment regimen showed that among the subgroup of patients with cancer (n=183), those treated with fidaxomicin had a more rapid median time to resolution of diarrhea compared with patients treated with vancomycin (74 hours vs. 123 hours; *P* = .045).[460] Fidaxomicin was approved by the FDA in 2011 for the treatment of *C difficile*-associated diarrhea. Fidaxomicin is not generally used as first line treatment of *C difficile*; however, it should be considered in certain circumstances, particularly for the treatment of recurrent infection.

Subtotal colectomy, diverting ileostomy, or colostomy may be required in cases involving toxic dilatation or perforation of the colon. Newer therapies—including the oral agents rifaximin and nitazoxanide—are under investigation.[456,461] Multiple recurrences of *C difficile* are a challenging problem in the patient with cancer and may respond to a prolonged, tapered treatment with oral vancomycin dose over several weeks.[462] The use of oral vancomycin followed by duodenal infusion of donor feces may be an effective strategy in patients with recurrent *C difficile* infection.[463] In a recent randomized study, patients with recurrent *C difficile* infection were assigned to receive treatment with a short course of initial oral vancomycin (500 mg PO 4 times daily for 4 days) followed by bowel lavage and infusion of donor feces (n=16) or

standard oral vancomycin (500 mg PO 4 times daily for 14 days) alone (n=13) or standard oral vancomycin with bowel lavage (n=13).[463] The primary endpoint was resolution of *C difficile*-associated diarrhea without relapse for 10 weeks. Resolution was achieved in 81% of patients in the donor feces infusion group compared with 31% in the vancomycin alone group and 23% in the group treated with vancomycin with bowel lavage ($P < .001$ for both comparisons with the infusion group).[463]

Enterocolitis

Neutropenic enterocolitis is a serious, potentially life-threatening disease characterized by fever, diarrhea, and abdominal pain.[464,465] When it occurs in the cecum, it is commonly referred to as typhlitis. The cecum is more vulnerable because of its size and shape, but any portion or the entire colon may be involved. This illness has frequently been associated with acute leukemia, neutropenia, and intensive cytotoxic therapy. CT scanning is the preferred diagnostic test and usually identifies any thickening of the bowel wall. The differential diagnosis for this syndrome includes *C difficile* colitis, CMV enteritis (most common in allogeneic HSCT recipients), and GI tract GVHD. Bloodstream infections and sepsis (frequently polymicrobial), bowel perforation, and hemorrhage may occur. The natural history of typhlitis is quite variable, but all patients should be assessed for *C difficile* infection and should be treated with bowel rest and broad spectrum antibiotics, including coverage for *C difficile*, aerobic pathogens, and anaerobic pathogens. Parenteral nutrition should be considered if clinical signs and symptoms do not resolve promptly. Approximately 5% of patients with typhlitis develop complications requiring surgical intervention (eg, perforation, uncontrolled sepsis or rectal bleeding).[466] Consequently, the panel recommends that surgical and other subspecialty consultations be obtained early in the course of treatment.

Lung Infections

Pulmonary infiltrates pose a difficult diagnostic challenge in patients with cancer. Noninfectious causes of pulmonary infiltrates include congestive heart failure, pulmonary edema, hemorrhage, infarction, drug-induced pneumonitis, radiation injury, tumor, bronchiolitis obliterans, and acute respiratory distress syndrome. Common processes can have atypical radiographic appearances, and 2 or more pulmonary processes can exist simultaneously. A careful history should include the time course of respiratory symptoms, sick contacts (eg, community respiratory viral infections, tuberculosis), recent hospitalization, travel, exposure to animals, and exposure to droplets from water distribution systems (*Legionella*). Community outbreaks of specific pathogens (eg, influenza, pertussis) should be considered in the differential diagnosis and should guide initial therapy.

Community-Acquired Pneumonia in the Absence of Neutropenia and Immunosuppressive Therapy

The diagnostic evaluation and initial therapy for community-acquired pneumonia must consider host factors and previous use of antibiotics. The IDSA has published guidelines on community-acquired pneumonia.[467] If feasible, sputum and blood cultures should be collected before starting therapy. In patients who are not neutropenic, receiving immunosuppressive therapy, nor requiring hospital admission (based on a validated pneumonia severity index), therapy includes either 1) a respiratory fluoroquinolone (levofloxacin 750 mg/day, moxifloxacin, or gemifloxacin); or 2) a beta-lactam (eg, high-dose amoxicillin or amoxicillin-clavulanate) plus a macrolide (eg, azithromycin).[467] These regimens will treat most of the common community-acquired pathogens, including “atypical” pneumonia (*Chlamydia, Mycoplasma*, and *Legionella* species).

In patients requiring hospital admission, monotherapy with a respiratory fluoroquinolone or combination therapy with a macrolide plus either ceftriaxone, cefotaxime, or ertapenem is recommended. Ertapenem has gram-positive, gram-negative (excluding *P aeruginosa* and *Acinetobacter* species), and anaerobic activity useful for suspected aspiration or postobstructive pneumonia. In patients with severe community-acquired pneumonia (eg, who require admission to an intensive care unit), the panel advises broad spectrum coverage with an antipseudomonal beta-lactam plus either a respiratory fluoroquinolone or azithromycin. In patients with previous MRSA infection or known colonization with MRSA, addition of vancomycin or linezolid should be considered for pneumonia requiring hospitalization (see *Additions to Initial Empiric Regimen* on page FEV-8).[467] A nasopharyngeal wash for respiratory viruses and initiation of empiric antiviral therapy should be considered during the winter, early spring, and during community outbreaks of influenza. Note that rapid immunofluorescent viral antigen tests may result in a false negative for H1N1 (swine flu). A parapneumonic effusion should be aspirated and submitted for Gram stain, bacterial culture, protein, lactate dehydrogenase, and pH.

Community respiratory viral infections (such as, influenza, RSV, adenovirus, rhinoviruses, metapneumoviruses) have a seasonal pattern (generally November through April); however, parainfluenza viral infections can occur throughout the year. During the influenza season, consider empiric antiviral therapy for patients within 48 hours after symptoms develop that are suggestive of influenza (eg, high fever, coryza, myalgia, dry cough), especially during community outbreaks. Both the IDSA (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.[467,468] 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.[469,470] However, longer courses of treatment (eg, 10 days) and until resolution of symptoms should be considered in immunocompromised patients; some centers have used higher doses (eg, 150 mg BID) of oseltamivir in these patients with mixed results (see *Suggested Minimum Duration of Therapy for Documented Infections* on page FEV-11). 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, it is necessary to be familiar with susceptibility patterns and guidelines on appropriate antiviral treatment.[471]

Hospital-Acquired Pneumonia

Guidelines on the management of adults with hospital-acquired pneumonia from the American Thoracic Society (ATS) emphasize that the time of onset is an important risk factor for specific pathogens that may be resistant to antibiotics.[472] Early-onset hospital-acquired pneumonia (occurring within the first 4 days of hospitalization) is likely to be caused by antibiotic-sensitive bacteria and usually carries a better prognosis. However, patients with cancer may be at risk for acquisition of antibiotic-resistant bacteria based on prior hospitalizations, prior antibiotic use, and impaired immune status regardless of when pneumonia begins in the course of the current hospitalization. The ATS guidelines define the following as risk factors for multidrug-resistant pathogens in patients with health-care-associated pneumonia: received antibiotics in the preceding 90 days; hospitalization for 2 days or more in the preceding 90 days; resident in nursing home or extended care facility; chronic dialysis within 30 days; home wound care; and family member with a multidrug-resistant pathogen.[472] Late-onset hospital-acquired pneumonia (occurring after 5 days or more of hospitalization)

is more likely caused by multidrug-resistant pathogens, and is associated with greater morbidity and mortality.

The population of multidrug-resistant bacteria (notably, MRSA and antibiotic-resistant gram-negative pathogens) varies among different hospitals and geographic distributions. Therefore, the selection of initial therapy for hospital-acquired pneumonia requires knowledge of the local patterns of antibiotic susceptibility. For example, at some centers, a high frequency of extended spectrum beta lactamase-producing gram-negative bacterial infections may make a carbapenem the drug of choice as initial therapy for pneumonia. At other centers, carbapenem-resistant gram-negative infections are an increasing problem, and an alternative class of antibiotics may be preferred based on prior local susceptibility results.[473]

In patients with late-onset hospital-associated pneumonia or risk factors for multi-drug resistant pathogens regardless of when pneumonia developed in relation to hospitalization, a broad-spectrum antibiotic regimen is recommended. An antipseudomonal beta-lactam (eg, ceftazidime, cefepime, imipenem/cilastatin, meropenem, doripenem, or piperacillin/tazobactam) plus an antipseudomonal fluoroquinolone (eg, ciprofloxacin or levofloxacin) or aminoglycoside, plus either linezolid or vancomycin (to cover MRSA) is a reasonable initial regimen (aim for vancomycin trough level of 15-20 mcg/mL).[472] If *Legionella* is suspected, a quinolone (ciprofloxacin or levofloxacin) should be used instead of an aminoglycoside. The antibiotic regimen should be subsequently tailored based on culture results.

Pulmonary Infiltrates in Neutropenic Patients

In patients with neutropenia for less than 7 days, pulmonary infections are likely to be caused by Enterobacteriaceae (eg, *E coli, Klebsiella* species), *P aeruginosa*, *S aureus*, and pathogens encountered in non-immunocompromised persons (as previously described). Because of the neutropenia, consolidation and sputum production may be absent.[474] Blood cultures, a chest radiograph, and, if possible, a sputum sample for Gram stain and culture should be obtained. In suspected acute bacterial pneumonia, appropriate empiric antibiotic therapy must be initiated promptly and the response must be closely monitored in an inpatient setting. The therapeutic regimen depends on several variables, including recent use of antibiotics, community or nosocomial pneumonia, and the local antibiotic sensitivity data.

If community-acquired pneumonia is suspected (ie, pneumonia is present before admission or develops within 3 to 4 days of hospitalization), addition of a macrolide or fluoroquinolone to an antipseudomonal beta-lactam is warranted to treat atypical pathogens. For nosocomial pneumonia, therapy with an antipseudomonal beta-lactam is advised, and addition of an aminoglycoside or fluoroquinolone should be considered. For cases of nosocomial pneumonia in which hospital-acquired legionellosis is suspected, empiric addition of a macrolide or fluoroquinolone is also warranted. Vancomycin or linezolid should be added for pneumonia in patients colonized with MRSA and for nosocomial pneumonia at centers in which MRSA is common. Community respiratory viruses should also be considered, especially during winter months. Respiratory syncytial virus, parainfluenza, and influenza are significant pathogens during neutropenia in patients receiving chemotherapy for acute leukemia and in HSCT recipients.

If clinical improvement occurs within 48 to 72 hours of therapy, no further diagnostic measures are necessary; antibiotic therapy should be continued until neutropenia resolves and for at least 10 to 21 days thereafter. Once neutropenia resolves, an appropriate oral antibiotic regimen can be administered for the remainder of the course.

In cases of refractory pneumonia, bacterial infection resistant to the initial antibiotic regimen and nonbacterial pathogens should be considered, particularly filamentous fungi.[474] A CT scan of the chest is useful in defining the location and morphology of the lesions, and in guiding diagnostic procedures. A "halo sign" in a persistently febrile neutropenic patient is highly suggestive of invasive aspergillosis;[475] however, angioinvasive infections including other filamentous fungi and *P aeruginosa* may produce similar findings.

A new or progressive infiltrate developing in patients with prolonged neutropenia (eg, more than 10 days) receiving broad spectrum antibacterial agents suggests invasive aspergillosis or infection with other molds.[474] Consider adding voriconazole or a lipid formulation of amphotericin B while waiting for diagnostic results. Empiric modification of the antibacterial regimen based on the predominant local hospital pathogens (eg, MRSA, antibiotic-resistant gram-negative bacteria) is also warranted in patients with rapidly progressive pneumonia.

Pulmonary Infiltrates in Patients With Impaired Cellular Immunity

Patients with impaired cellular immunity are at increased risk for common bacterial infections and opportunistic infections, including fungi (*Aspergillus* and other filamentous fungi, *Cryptococcus neoformans*, dimorphic fungi), *Legionella*, *P jirovecii, M tuberculosis*, nontuberculous mycobacteria, *Nocardia* species, and viral pathogens.

In patients with clinical and radiographic findings suggestive of acute bacterial pneumonia (eg, acute onset fever, respiratory symptoms, focal infiltrate), the diagnosis and management are similar to the treatment of neutropenic patients. An antipseudomonal beta-lactam plus either a respiratory quinolone or azithromycin is a reasonable initial regimen in patients with pneumonia requiring hospitalization. In allogeneic HSCT recipients with GVHD not receiving mold-active prophylaxis, addition of a mold-active drug (eg, voriconazole) should be considered. Particularly among the most highly immunocompromised patients (eg, significant GVHD), the differential diagnosis is very broad, and an initial empiric regimen cannot have activity against all possible pathogens. It is critical to establish a definitive diagnosis in patients with negative diagnostic results who are deteriorating clinically after a 2 to 3 day trial of broad spectrum antibiotics.

Diffuse infiltrates have a broad differential diagnosis,[474] including PCP, viral infections, hemorrhage, and drug-induced pneumonitis. A diagnosis of PCP should be considered in patients with significantly impaired cellular immunity not receiving PCP prophylaxis who present with diffuse pulmonary infiltrates. BAL is the standard approach for diagnosing PCP. In patients with substantial respiratory disease (eg, labored breathing, requiring supplemental oxygen), empiric therapy should be initiated before BAL. Pending BAL results, an initial regimen can include a respiratory fluoroquinolone against community-acquired pathogens and TMP-SMX (TMP component: 5 mg/kg every 8 hours) against possible PCP. Based on studies of patients with AIDS–associated PCP, corticosteroids (initially prednisone 40 mg twice daily, then tapered) should be added for patients with suspected PCP and with room air PaO_2 of 75 torr or less.[476]

Patients at the highest risk for CMV pneumonia include allogeneic HSCT recipients in the post-engraftment setting (particularly if receiving immunosuppressive therapy for GVHD) and patients receiving treatment with alemtuzumab. Negative results from CMV surveillance testing (antigenemia or peripheral blood PCR) make CMV pneumonia very unlikely. CMV pneumonia is uncommon in non-transplanted patients receiving immunosuppressive chemotherapy for leukemia.[477] Community respiratory viruses can cause severe pulmonary infection in neutropenic patients and in non-neutropenic patients with impaired

cellular immunity. Noninfectious etiologies must also be considered, as previously stated. BAL is sensitive in diagnosing bacterial and viral pneumonia and PCP, and is often the initial invasive diagnostic procedure (see *Invasive Diagnostic Procedures for Pulmonary Infiltrates* in the Discussion).

Non-Invasive Diagnosis of Pneumonia

In patients with suspected pneumonia, routine sputum and blood cultures should be obtained, ideally before antibiotics are initiated or modified. Sputum cultures for *Legionella* species are sensitive if obtained before initiating antibiotics; however, specific culture conditions are required. Legionellosis can also be diagnosed based on urine antigen testing, which only detects *Legionella pneumophila* type I, the cause of most (but not all) cases of *Legionella* pneumonia.[467] A nasopharyngeal wash is useful to diagnose community respiratory viral infections. The rapid test for influenza A and B may be performed using a throat or nasopharyngeal swab. Rapid antigen detection methods can provide a diagnosis within hours; however, if results are negative, a shell vial culture will takes about 5 days.

Fungal pneumonia is suggested by the following: host factors predisposing the patient to invasive aspergillosis; appropriate symptoms or signs of infection; a compatible pulmonary lesion; and a positive serum galactomannan or beta-glucan assay. Host factors indicative of high risk for invasive aspergillosis include neutropenia for more than 10 days, receipt of an allogeneic HSCT, prolonged use of high-dose systemic corticosteroids, or treatment with T-cell suppressants. The galactomannan assay is specific for invasive aspergillosis,[428,478] whereas the beta-glucan assay detects aspergillosis and other invasive fungal infections (including invasive candidiasis, PCP, and fusariosis).[479-481] Zygomycosis yields negative serum galactomannan or beta-glucan test results.

Antigen-based detection systems have advantages and limitations. A meta-analysis showed that the galactomannan assay had a sensitivity of 70% and specificity of 89% for proven invasive aspergillosis, though the accuracy of the test varied.[430] The lack of consistent results likely relates to different cut-off values for a positive result, differences in patient populations, and possibly the use of mold-active prophylaxis. Several variables can affect the performance of the galactomannan assay[482,483] which may account for the different results. The sensitivity of the assay is significantly reduced by concomitant mold-active antifungal agents.[429,484] False-positive results may be more common in children and allogeneic HSCT recipients.[485] Moreover, concomitant piperacillin/tazobactam causes false-positive galactomannan results.[486,487] False-positive beta-glucan results have also been reported in patients with surgical packing who are receiving immunoglobulin therapy and in patients receiving IV amoxicillin-clavulanate.[488,489] Despite these limitations, a patient at high risk for invasive aspergillosis (eg, prolonged neutropenia or allogeneic HSCT recipient) with clinical and radiological findings (eg, a new pulmonary nodule ≥ 1 cm, infiltrate) compatible with invasive aspergillosis and with a positive serum galactomannan is likely to have invasive aspergillosis, and therefore a mold-active agent (voriconazole is preferred) should be added.

Additional assays can detect histoplasmosis, coccidioidomycosis and PCP as part of the non-invasive diagnosis of pneumonia. The assay for serum or urine Histoplasma antigen is a sensitive and specific test in patients with disseminated histoplasmosis (histoplasmosis is endemic in the central United States). Coccidioidomycosis is endemic in the southwestern United States. Disseminated coccidioidomycosis can be diagnosed based on appropriate symptoms and signs of infection and on positive serum titers. As previously discussed, BAL is the diagnostic gold standard for PCP. In a small series, sputum induction with

hypertonic saline was diagnostic of PCP in non–HIV-infected patients in about 60% of cases.[490] A BAL should be performed if sputum induction is attempted, and the results are negative.

Invasive Diagnostic Procedures for Pulmonary Infiltrates

Invasive diagnostic procedures may be required in the following situations: 1) the clinical course does not suggest an acute bacterial process; 2) the patient has not responded to initial antibiotic therapy and/or; 3) noninvasive testing yields negative results. BAL has a high diagnostic yield in alveolar infiltrates, such as pneumonia caused by *P jirovecii*, *M tuberculosis,* and respiratory viruses. The sensitivity of BAL for focal lesions (such as nodules) is variable. In lesions greater than 2 cm, the sensitivity of BAL ranges from 50% to 80%; however, in smaller lesions, the diagnostic yield is usually about 15%.[491] Quantitative cultures from either BAL or a protected brush catheter may increase the specificity in the diagnosis of bacterial pneumonia as distinguished from upper airway colonization in ventilated patients.

BAL cultures only detect about 50% of cases; therefore, it is relatively insensitive for diagnosing aspergillosis.[492] Galactomannan detection in BAL fluid appears to be more sensitive than serum detection[493,494] and can be used to support a diagnosis of probable aspergillosis.[495] In patients with focal peripheral lesions, percutaneous biopsy may increase the diagnostic yield; however, in thrombocytopenic patients, the risk of bleeding may be unacceptably high. The microbiologic evaluation should take into account the clinical manifestations and nature of the immunosuppression. In highly immunocompromised patients (eg, those receiving chemotherapy for acute leukemia, HSCT recipients), the following studies on BAL and lung biopsies should be considered: culture and stains for bacteria, fungi, *Legionella*, mycobacteria, *Nocardia*, HSV, CMV, community respiratory viruses (both rapid antigen and shell vial culture), and cytology or immunofluorescent studies for *P jirovecii*. In a patient with compatible host factors and radiologic findings, a positive galactomannan result from BAL is also indicative of probable invasive aspergillosis.[495]

For nondiagnostic BAL or percutaneous lung biopsy results, a thoracoscopic lung biopsy should be considered if an adequate platelet count is achievable. The thoracoscopic approach has less morbidity than an open lung biopsy and generally provides adequate tissue samples for the diagnosis of most infectious and noninfectious etiologies. This invasive procedure may identify the causative pathogen or the presence of a noninfectious etiology (eg, treatment-associated lung toxicity, hemorrhage, or bronchiolitis obliterans–organizing pneumonia [BOOP]), which may allow for the elimination of potentially toxic or unnecessary antimicrobial therapies. Thoracoscopic and open lung biopsies sometimes do not provide a definitive diagnosis, either due to sampling error or nonspecific pathologic findings.

Skin and Soft Tissue Infections

When evaluating the potential for a skin/soft tissue infection, careful examination of all line sites and perineal areas is essential. Antimicrobial therapy should be tailored to the probable organism(s): Staphylococci and streptococci for catheter-associated processes, and gram-negative and anaerobic organisms for perineal processes. Vancomycin may be considered for cellulitis, disseminated papules/lesions, and infections associated with VAD (see *Additions to Initial Empiric Regimen* on page FEV-9). Acyclovir, famciclovir, or valacyclovir should be considered for vesicular lesions after appropriate diagnostic tests (scraping base of vesicle for HSV or VZV, direct fluorescent antibody tests, herpes virus culture) have been performed.

Skin lesions can be manifestations of systemic infection. Ecthyma gangrenosum is the most characteristic skin lesion associated with

systemic *P aeruginosa* infection.[496] Similar lesions can be caused by *S aureus*, enteric gram-negative bacilli infection, and filamentous fungi (including *Aspergillus*, Zygomycetes, and *Fusarium* species). A rapidly progressive deep soft tissue infection with gas formation suggests clostridial myonecrosis (or polymicrobial necrotizing fascitis).[497] Broad spectrum antibiotics and surgical debridement may be lifesaving if initiated early. Hematogenously disseminated candidiasis with skin involvement manifests as fever and erythematous cutaneous papules; blood cultures are expected to be positive for *Candida* species.

In the highly immunocompromised patient with cancer, the differential diagnosis of skin lesions is often broad and includes noninfectious etiologies such as drug reactions, Sweet's syndrome, erythema multiforme leukemia cutis, and (in the case of allogeneic HSCT recipients) GVHD. Biopsy of skin lesions for histology and culture is recommended. In allogeneic HSCT recipients, the differential diagnosis of infectious etiologies is particularly broad, and cultures from skin biopsies for bacteria, fungi, viruses, and mycobacteria should be considered when infection is suspected.

Vascular Access Device Infections

VAD infections are common as a consequence of the ubiquity of VADs in patients undergoing intensive or cyclic chemotherapy. The risk of infection varies with the device used (long-term implanted catheters versus short-term central catheters), duration of placement, and extent of the patient's immunosuppression. Short-term central catheters coated with the antimicrobial agent chlorhexidine and silver sulfadiazine (CHSS) have been shown to significantly decrease the incidence of both catheter colonization and catheter-related bloodstream infections compared with standard (non-coated) catheters;[498,499] however, this benefit with CHSS coating was not observed in the setting of patients with hematologic malignancies requiring longer use of central catheters (eg, duration of catheterization 20 days).[500] In subsequent studies that evaluated the use of CHSS-coated short-term catheters compared with controls, CHSS-coated catheters significantly decreased the incidence of colonization but showed no difference in terms of incidence of catheter-related bloodstream infections.[501-503] The use of short-term catheters coated with minocycline and rifampin has been shown to significantly decrease the risks for catheter colonization and bloodstream infections compared with either controls or CHSS-coated catheters.[504,505] However, conflicting results were reported by another study in which minocycline- and rifampin-coated catheters reduced the risk for coagulase-negative staphylococci colonization, but they increased the risk for colonization with *Candida* spp; moreover, no significant difference was noted in the incidence of catheter-related bloodstream infections compared with controls.[506] Only limited data are available on the use of long-term catheters coated with minocycline and rifampin. In a prospective randomized double-blind study in patients with cancer requiring long-term catheterization (mean duration of catheterization 63–66 days), a significant risk reduction in catheter-related bloodstream infections was observed with the coated catheter (1.6% vs. 8%; RR for uncoated vs. coated, 1.8; 95% CI, 1.4–2.3; P = .003).[507] The recently published guidelines for the prevention of catheter-related infections (based on an interdisciplinary working group involving the IDSA and CDC) recommend the use of catheters impregnated with CHSS or minocycline/rifampin in patients requiring catheterization for greater than 5 days, if the rate of catheter-related bloodstream infections do not decrease despite implementation of comprehensive prevention measures at the local institution.[508] A meta-analysis of prospective, randomized studies showed that use of a vancomycin lock solution in patients being treated with long-term central VADs reduced the risk of bloodstream infection.[509] The panel does not

currently endorse this practice due to concerns over the emergence of bacterial resistance if this approach were widely employed. The IDSA has published guidelines on the diagnosis and management of intravascular catheter-related infections.[358]

VAD infections are categorized as entry or exit site infections versus tunnel or port pocket infections or septic phlebitis (see *Initial Clinical Presentation* on page FEV-9). The majority of these infections are caused by gram-positive pathogens, with coagulase-negative staphylococci recovered most frequently.[358] Accordingly, IV vancomycin is recommended for those infections that are serious and clinically obvious.

Most VAD exit site infections can be treated effectively with appropriate antimicrobial therapy without the need for catheter removal. If clinical signs of catheter infection are present, a skin swab for culture from the exit site and blood cultures should be obtained. In a patient with neutropenic fever and clinical signs of a VAD-associated infection, an appropriate initial regimen would consist of an agent recommended for neutropenic fever (see *Initial Empiric Therapy for Uncomplicated Fever and Neutropenia* on page FEV-5) and vancomycin (see *Additions to Initial Empiric Regimen* on page FEV-9). Linezolid is not advised as routine therapy for catheter-related infections nor is it FDA-approved for this indication.[382] For a clinically apparent, serious, catheter-related infection (such as a tunnel or port pocket infection, or septic phlebitis), catheter removal should be performed immediately.

Determining the role of the catheter in bloodstream infections is frequently difficult if local catheter inflammation is not evident. A useful diagnostic tool for detecting VAD infections is the differential time to positivity (DTP). Early positivity of central venous blood cultures predicts catheter-related bacteremia and may be used to avoid unnecessary catheter removal in critically ill patients. It was shown that a DTP of 120 minutes or more (between centrally and peripherally drawn blood cultures) is highly sensitive and specific for diagnosing catheter-related bacteremia.[382,510-514] However, these studies were only performed in patients with removable catheters, not implanted catheters (eg, Hickman or Mediport) that are frequently used in patients undergoing cancer treatment.

Most catheter-associated bloodstream infections respond to antimicrobial therapy alone without catheter removal, but immediate catheter removal is advisable for patients with bloodstream infections caused by fungi (yeasts or molds) or nontuberculosis mycobacteria (eg, *Mycobacterium chelonae*, *Mycobacterium abscessus*, *Mycobacterium fortuitum*).[358] Bloodstream infections caused by *Bacillus* organisms, *Candida, S aureus, Acinetobacter*, *C jeikeium*, *P aeruginosa*, *S maltophilia,* and vancomycin-resistant enterococci may be difficult to eradicate with antimicrobial therapy alone; therefore, catheter removal should be considered as part of initial therapy. In patients with mucositis, the bowel is likely to be the portal of entry for bloodstream infection by GI flora such as *Candida* spp. and enterococci. DTP may be useful to distinguish whether bloodstream infection by these organisms is catheter-related and to guide whether catheter removal should be performed. If not removed initially, catheter removal is advised for known or suspected VAD-associated bloodstream infections if the organism is recovered from blood obtained 48 hours after initiation of appropriate antibiotic therapy. In patients with VAD infection and clinical instability, removal of the infected catheter should be performed immediately.

The panel recognizes that certain conditions may preclude the ability to immediately replace IV catheters, such as limited options for IV access and thrombocytopenia refractory to platelet products. Administering

antibiotics through each lumen of the involved catheter has been suggested to avoid treatment failure caused by microbial sequestration. Some experts believe supplemental urokinase infusions can be helpful in patients with catheter-related infections.[515] However, the panel believes data are insufficient to recommend either of these approaches.

Central Nervous System Infections

CNS infections in patients with cancer can be divided into surgical and nonsurgical complications. The IDSA has published guidelines on the management of bacterial meningitis.[516] The most common organisms infecting intraventricular devices are coagulase-negative staphylococci, *S aureus,* and *Propionibacterium acnes*. Enterobacteriaceae and *P aeruginosa* account for only 10% of these infections. Coagulase-negative staphylococci and *P acnes* usually cause indolent late postoperative infections. Therapy with systemic antibiotics and removal of the entire device are the most effective approaches to eradicate infection. Use of parenteral and intraventricular instillation of antibiotics without removal of the device may not be effective, and recrudescence of infection is common. Antibiotic therapy should be tailored to the specific pathogen isolated from cerebrospinal fluid. In an acutely ill patient with suspected meningitis related to previous neurosurgery, empiric therapy can include parenteral vancomycin (which has activity against *Staphylococcus*, *Streptococcus*, and *Propionibacterium* species; dose 15 mg/kg every 8 to 12 hours to maintain a serum trough concentration of 15-20 mcg/mL) in combination with ceftazidime (2 g every 8 hours), cefepime (2 g every 8 hours), or meropenem (2 g every 8 hours) (which have activity against Enterobacteriaceae and *P aeruginosa*); these doses apply to adults with normal renal function.[516]

CNS infections unrelated to neurosurgery are relatively uncommon in patients with cancer. Initial evaluation generally involves a head CT scan to rule out intracranial bleeding and a lumbar puncture (assuming there are no contraindications). Cerebrospinal fluid studies should be tailored to specific host factors, epidemiologic exposures (eg, travel history), and clinical presentation. At a minimum, cell counts with differential, glucose and protein levels, Gram stain and bacterial culture, cryptococcal antigen and fungal culture on cerebrospinal fluid should be obtained. Noninfectious causes of meningitis include nonsteroidal anti-inflammatory agents, TMP/SMX, carcinomatous meningitis, and serum sickness (eg, associated with anti-lymphocyte immunoglobulin preparations).

For suspected CNS infections, infectious disease and neurology consultation is strongly recommended, and empiric therapy should be initiated pending infectious disease consult. Empiric therapy for presumed meningitis should include an anti-pseudomonal beta-lactam agent that readily enters the CSF (eg, cefepime, ceftazidime, meropenem) plus vancomycin plus ampicillin (to cover listeriosis) (see *Additions to Initial Empiric Regimen* on page FEV-9). If meropenem is used, addition of ampicillin is unnecessary because meropenem is active against *Listeria*. This regimen has activity against the common causes of bacterial meningitis, including penicillin-resistant pneumococci and listeriosis. In patients at risk for *P aeruginosa* meningitis (eg, neutropenia, neurosurgery within the past 2 months, allogeneic HSCT, history of *P aeruginosa* infection), use of cefepime (2 g every 8 hours in adults with normal renal function) or meropenem (2 g every 8 hours in adults with normal renal function) instead of ceftriaxone in the initial empiric regimen is advised. The antibiotic regimen should be tailored based on culture results.

The use of dexamethasone as adjuvant therapy in the management of bacterial meningitis has been evaluated in a number of studies, although conflicting results have been reported. In an earlier systematic

review of published data in patients with acute bacterial meningitis, adjuvant therapy with corticosteroids was associated with significantly lower risks for mortality (RR, 0.76; 95% CI, 0.59–0.98), severe hearing loss (RR, 0.36, 95% CI, 0.22-0.60), and long-term neurological sequelae (RR, 0.66; 95% CI, 0.44-0.99).[517] These outcomes mainly reflected the pediatric population, as only limited data were available for adults. In a prospective randomized double-blind study involving adult patients with acute bacterial meningitis (N=301), adjuvant dexamethasone compared with placebo significantly reduced the risks for unfavorable outcomes (defined as a score of 1-4 on the Glasgow Outcome Scale)(RR, 0.59; 95% CI, 0.37–0.94; *P* = .03) and mortality (RR, 0.48; 95% CI, 0.24–0.98; *P* = .04); this benefit was observed in patients with pneumococcal meningitis.[518] In a more recent prospective, randomized double-blinded study in adults and adolescents with suspected or confirmed bacterial meningitis (N=435), adjuvant dexamethasone significantly reduced the risks for death at 1 month (RR, 0.43; 95% CI, 0.20–0.94) and death or disability at 6 months (RR, 0.56; 95% CI, 0.32–0.98) in patients with confirmed cases of bacterial meningitis, but not for those with suspected cases.[519] Other recent prospective randomized studies in pediatric patients appear to conflict with the findings from the earlier systematic review. In these studies that evaluated the use of adjuvant dexamethasone, glycerol, or both, in children treated with ceftriaxone for bacterial meningitis, adjuvant dexamethasone alone was not associated with significant reductions in risks for death, deafness/hearing loss, or severe neurological sequelae.[520,521] Moreover, in a recent meta-analysis of 2029 patients, dexamethasone was not found to be associated with significant reductions in death or neurological sequelae, although a statistically significant reduction in hearing loss was observed among surviving patients.[522] The IDSA guidelines (2004) for the management of bacterial meningitis support the incorporation of adjuvant dexamethasone in pediatric patients with *H influenzae* type B meningitis and in adult patients with pneumococcal meningitis.[516] In patients with suspected encephalitis (fever, mental status changes, CSF pleocytosis), IV acyclovir (10 mg/kg every 8 hours in patients with normal renal function) should be considered as empiric therapy for HSV in addition to an appropriate antibacterial regimen.[523] An MRI and the following CSF studies should be performed: 1) cell count with differential; 2) glucose and protein levels; 3) Gram stain and culture for bacteria; 4) Cryptococcal antigen and fungal culture; and 5) PCR for HSV. PCR for West Nile virus and other arboviruses should be considered in patients with exposure to endemic areas. Culture and PCR for tuberculosis should be considered in patients with known or suspected exposure to tuberculosis (eg, residence in an endemic area, shelter, or prison; previous positive PPD [purified protein derivative]). In patients with severe impairment of cellular immunity (eg, allogeneic HSCT recipients, advanced AIDS), additional CSF studies should be considered (such as PCR for CMV, VZV, human herpes virus–6 type B [HHV-6B], and toxoplasmosis). For cases of HHV-6B-associated encephalitis in severely immunocompromised patients such as those who have received an allogeneic transplant, treatment is recommended, however, the optimal therapy is not known (with either foscarnet or ganciclovir).[523] Cytology to evaluate for CNS malignancy as a cause of meningitis or encephalitis should also be considered.

Brain abscesses usually manifest with headache, focal neurologic findings, or seizures. An MRI typically shows single or multiple lesions with edema and ring enhancement.[524] Bacterial abscesses in non-immunocompromised patients are typically caused by dental flora. In patients with prolonged neutropenia and in allogeneic HSCT recipients, CNS aspergillosis must be considered. A chest CT showing a new nodule or infiltrate and a positive serum galactomannan result in this

setting is highly suggestive of pulmonary aspergillosis with CNS dissemination. In patients with impaired cellular immunity, other causes of CNS abscesses include toxoplasmosis, nocardiosis, cryptococcosis, and mycobacterial infections. Noninfectious etiologies in patients with impaired cellular immunity include CNS malignancies (such as secondary lymphomas) and Epstein-Barr virus (EBV)–associated post-transplantation lymphoproliferative disorder (PTLD). Given the broad differential diagnosis of new CNS lesions in highly immuno-compromised patients, a brain biopsy is strongly recommended (if feasible) with material submitted for histology and culture. Cultures and stains should include bacteria, fungi, mycobacteria, and *Nocardia* species.

In non-immunocompromised patients with a bacterial brain abscess, initial therapy with ceftriaxone (2 g every 12 hours in adults) plus metronidazole (7.5 mg/kg every 6 hours in adults with normal renal function) is advised.[22,524,525] In patients with prolonged neutropenia without corticosteroids or lymphocyte-depleting agents, a reasonable initial regimen consists of combination cefepime, metronidazole, and voriconazole (IV 6 mg/kg every 12 hours for 2 doses followed by 4 mg/kg every 12 hours); however, IV voriconazole (but not the oral formulation) may worsen renal disease in patients with significant pre-existing renal impairment. Voriconazole (as well as itraconazole and posaconazole) has important drug-drug interactions with certain antiseizure agents (eg, phenytoin); therefore, the voriconazole package insert should be reviewed to guide dosing of these agents.[114] In allogeneic HSCT recipients and other patients with severe T-cell impairment, addition of high-dose TMP/SMX (trimethoprim component: 5 mg/kg every 8 hours) should be considered to cover toxoplasmosis and nocardiosis, pending a definitive diagnosis. An infectious disease consultation is advised in all cases of suspected or documented CNS infection.

Therapy for Invasive Fungal Infections

Invasive Candidiasis

Candida species are the fourth most common cause of nosocomial bloodstream infections in the United States.[526,527] The crude mortality of candidemia ranges from 20% to 40%.[527,528] This variable mortality rate reflects the presence of serious comorbidities (such as malignancy, neutropenia), patient population (adult versus pediatric), and illness requiring prolonged periods in the intensive care unit. *Candida albicans* is the most common *Candida* species isolated from the blood.[527] The proportion of non-albicans *Candida* species varies among different centers, but accounts for approximately 50% of blood stream isolates.

A randomized study comparing IV fluconazole (400 mg daily) with amphotericin B as therapy for candidemia in non-neutropenic patients found both regimens equally effective, but fluconazole had less toxicity.[529] In a subsequent study of non-neutropenic patients with candidemia, combination therapy with a higher dose of fluconazole (800 mg daily) and amphotericin B led to improved clearance of candidemia compared with fluconazole alone, but the combination regimen was associated with significantly more nephrotoxicity and with no survival benefit.[442] Voriconazole was as equally effective as, but less nephrotoxic than, a strategy of amphotericin B followed by fluconazole in non-neutropenic patients with invasive candidiasis.[530] In trials of "invasive candidiasis," most patients had candidemia, but those with deep organ involvement (eg, peritoneal, hepatic, or renal candidiasis) without positive blood cultures were also eligible for enrollment.

Four phase III randomized trials have been performed evaluating echinocandins as initial therapy for invasive candidiasis.[531-534] When caspofungin was compared with conventional amphotericin B, there was a trend for a higher favorable response (defined as resolution of clinical symptoms and culture-confirmed eradication) rate in the caspofungin arm (73% vs. 62%) in the modified intent-to-treat analysis.[532] Among patients who met prespecified criteria for evaluation (those who met eligibility criteria and received at least 5 days of study drug), caspofungin resulted in significantly higher success rate compared with amphotericin B (81% vs. 65%; 95.6% CI, 1.1–29.7; *P* = .03). Caspofungin was less toxic than amphotericin B. Similarly, micafungin was shown to be as effective as liposomal amphotericin B for invasive candidiasis, with fewer treatment-related adverse events (including those that led to treatment discontinuation).[531] Anidulafungin was not inferior to fluconazole as therapy for invasive candidiasis and was possibly more efficacious.[534] At the end of IV therapy, successful outcomes (based on both clinical and microbiologic responses; primary endpoint) were achieved in a higher proportion of patients treated with anidulafungin compared with fluconazole (76% vs. 60%; 95% CI, 3.9–27.0; *P* = .01), though a center effect was observed in this study. Finally, caspofungin and micafungin were shown to be equally safe and efficacious as treatment for invasive candidiasis.[533]

The IDSA has published detailed updated guidelines for the management of candidiasis recommending fluconazole or an echinocandin as initial therapy for most non-neutropenic adult patients; an echinocandin is preferred in critically ill patients.[535] Transition from an echinocandin to fluconazole is recommended for patients who have isolates that are likely to be susceptible to fluconazole (eg, *Candida albicans*), who are clinically stable, and who have not had recent azole exposure.[535] Fluconazole-resistant *Candida* isolates are frequently cross-resistant to other azoles;[536] therefore, if candidemia occurs in a patient with recent azole exposure, a switch in class (eg, to an echinocandin) is recommended. *Candida krusei* is generally resistant to fluconazole. An echinocandin is the preferred therapy for *Candida glabrata* stains due to their variable sensitivity to azoles;[535] however, transition to fluconazole or voriconazole can be considered if azole susceptibility is documented. Echinocandins have reduced sensitivity to *Candida parapsilosis* compared to other candidal strains; fluconazole is recommended in this setting.[535]

The IDSA recommends an echinocandin as initial therapy for candidemia in most neutropenic patients.[535] The NCCN Guidelines Panel agrees with this recommendation, but notes that because studies evaluating echinocandins have included very small numbers of neutropenic patients, the optimal therapy for invasive candidiasis in this population is not definitive. Given the availability of safer alternatives, the panel does not recommend amphotericin B products routinely for candidemia, although such agents may be considered in unusual or complicated cases, such as instances of meningitis and endocarditis.

Invasive Aspergillosis

Voriconazole is the recommended agent as primary therapy for invasive aspergillosis (see *Antifungal Agents: Azoles* on page FEV-B 1 of 4). In an open-label, multicenter randomized trial of primary therapy for invasive aspergillosis, voriconazole resulted in a significantly higher success rate (included complete and partial responses) compared with amphotericin B (53% vs. 32%; 95% CI, 10.4–32.9) and was associated with an improved survival rate at 12 weeks (71% vs. 58%; HR, 0.59; 95% CI, 0.40–0.88).[445] Success rates were similar for the 2 treatment arms in the subgroup of patients with neutropenia (51% with voriconazole vs. 32% with amphotericin B). In a retrospective analysis

of 86 patients with CNS aspergillosis treated with voriconazole either as primary or salvage therapy, 35% had a complete or partial response.[537] This success rate compares favorably to a previous series in which the frequency of successful responses to amphotericin B in CNS aspergillosis was almost nil.[538] Based on the strength of this database, the NCCN Guidelines Panel recommends voriconazole as first-line therapy for invasive aspergillosis, which is consistent with IDSA recommendations.[446]

Considerable inter-individual variability in voriconazole exposure can occur, and the utility of monitoring drug levels is controversial.[539,540] Studies with a few patients have noted a relationship between low plasma voriconazole levels and treatment failure,[144] and between high voriconazole levels and toxicity.[142,541] Voriconazole blood levels of at least 1 to 2 mcg/mL are thought to be required for efficacy. One week after initiating treatment with voriconazole, it is recommended that trough levels by therapeutic drug monitoring be obtained to ensure adequate plasma concentration of the drug. Obtaining a serum voriconazole level should be considered in cases of breakthrough or refractory fungal disease or drug toxicity.

It is not clear what the optimal therapy is for breakthrough invasive aspergillosis in patients receiving mold-active prophylaxis. Breakthrough invasive aspergillosis in a patient receiving oral posaconazole prophylaxis may be caused by inadequate oral bioavailability due to mucositis or poor oral intake, or possibly resistance. Some experts would advise changing to a different class of antifungals (such as a lipid formulation of amphotericin B, with or without an echinocandin). Others would use IV voriconazole with or without an echinocandin.

Lipid formulations of amphotericin B have at least comparable efficacy and reduced renal toxicity compared to conventional amphotericin B deoxycholate. Some investigators have persuasively argued that lipid formulations should be considered suitable replacements for amphotericin B for primary therapy for many invasive fungal infections.[417] Amphotericin B colloidal dispersion (ABCD) was equally effective as, but less nephrotoxic than, amphotericin B as primary therapy for invasive aspergillosis.[542] Amphotericin B lipid complex (ABLC) was shown to be safe and efficacious as therapy for invasive aspergillosis based on an analysis of a registry database.[543]

A randomized study compared liposomal amphotericin B (L-AMB) at either 3 or 10 mg/kg per day for 14 days, followed by 3 mg/kg per day as therapy for invasive mold infections.[544] Response rates (both complete and partial responses) after completion of treatment with the 3 mg/kg/day and 10 mg/kg/day dose groups were similar (50% vs. 46%); the 12-week survival rate were 72% and 59%, respectively (95% CI, -0.2–26%). The high-dose group was associated with significantly higher incidences of nephrotoxicity and hypokalemia, which suggested that the 3 mg/kg/day dosing was more optimal in this patient population.[544] Because 97% of enrolled patients had invasive aspergillosis, this study does not permit conclusions about optimal L-AMB dosing in patients with other mold infections (such as zygomycosis).

Echinocandins have not been evaluated as initial monotherapy for invasive aspergillosis in clinical trials. Caspofungin as salvage therapy in patients with invasive aspergillosis led to a favorable response in 37 (45%) of 83 patients.[545] It might be possible to use combination antifungal therapy pairing an echinocandin with either an amphotericin B preparation or an azole with activity against *Aspergillus* species. The rationale is that echinocandins target a unique site (the beta-glucan constituent of the fungal cell wall), which is distinct from the polyenes and azoles that target the fungal cell membrane. The combination of an echinocandin with an azole or amphotericin B has shown neutral to

synergistic activity in vitro. Enhanced efficacy of combination regimens pairing an echinocandin with either an azole or an amphotericin B formulation was observed in some animal models of invasive aspergillosis[546-549] but not in others.[550-552]

In two small retrospective series, the combination of caspofungin and liposomal amphotericin B as salvage therapy led to a favorable outcome in approximately 40% to 60% of patients with invasive aspergillosis, although these series included cases of "possible" or "probable" aspergillosis.[553,554] Marr et al reported a significant improvement in the 3-month survival rate with voriconazole plus caspofungin compared with voriconazole alone in a small retrospective analysis (N=47) of salvage therapy for invasive aspergillosis.[555] This database study, although encouraging, involved small numbers of patients and the 2 groups of patients evaluated were noncontemporaneous; therefore, other host and infection-related factors may have influenced the outcome. A noncomparative study of caspofungin combined with other mold-active drugs as salvage therapy for invasive aspergillosis reported a success rate of 49% (25/51) at 12 weeks after initiation of combination therapy,[556] which was similar to caspofungin monotherapy.[545] In an open-label study of invasive aspergillosis, micafungin combined with other antifungals led to a successful response in 29% (5/17) and 35% (60/174) of the primary and salvage treatment groups, respectively.[557] These results did not appear favorable to response rates observed with micafungin alone (50% and 41% in primary and salvage treatment groups, respectively); however, the patient numbers in the micafungin monotherapy arms were too small to permit comparisons. In addition, the initial micafungin dose (75 mg/day) used in this study was low by current standards.

Although combination antifungal therapy is commonly used as treatment for invasive aspergillosis, the clinical evidence is inadequate to make conclusions about whether any combination regimen is more effective than voriconazole alone, the current gold standard. A randomized, prospective clinical trial (NCT00531479) comparing voriconazole versus voriconazole plus anidulafungin as primary therapy for invasive aspergillosis has been completed though data is not yet available.

Posaconazole has shown activity as salvage therapy against a broad spectrum of invasive fungal infections.[558-561] In an open-label study in patients with invasive aspergillosis refractory to or who had intolerance to standard antifungal therapy (N=107), 42% had a complete or partial response with posaconazole.[562] Posaconazole is approved in the European Union for the treatment of invasive aspergillosis and certain other invasive fungal infections refractory to standard antifungal agents. In the U.S., posaconazole is approved by the FDA for prophylaxis of invasive *Aspergillus* and *Candida* infections, and for treatment of oropharyngeal candidiasis (including cases refractory to fluconazole or itraconazole), but is not indicated as primary or salvage therapy for invasive fungal disease.[115]

For patients receiving treatment with itraconazole, voriconazole, or posaconazole, the panel recommends therapeutic drug monitoring following initiation of treatment to ensure adequate plasma concentrations of the drug. Ongoing therapeutic drug monitoring is generally warranted.

Zygomycosis and Other Invasive Mold Infections

A higher frequency of zygomycosis (also referred to as "mucormycosis") has emerged at some with the increased use of voriconazole.[443,563,564] In a case-control study of invasive aspergillosis and zygomycosis in patients with acute leukemia and allogeneic HSCT recipients, use of voriconazole and presence of fungal sinusitis each favored a diagnosis

of zygomycosis.[443] However, some transplant centers reported an increased frequency of zygomycosis that pre-dated the availability of voriconazole,[565,566] a finding that likely reflects a greater proportion of patients with severe host defense impairment. Zygomycosis typically manifests as rhinocerebral or pulmonary disease. Histopathology showing broad aseptate or hyposeptate hyphae with 90-degree branching is suggestive of zygomycosis, although culture is required for confirmation.

No randomized studies have been performed for treatment of zygomycosis and other uncommon invasive mold infections. Recommendations for therapy are based on a limited number of patients from retrospective analyses, data registries, and open-label trials for salvage therapy. Treatment of zygomycosis involves amphotericin B (a lipid formulation is advised over amphotericin B deoxycholate to reduce the chance of nephrotoxicity) plus early and aggressive surgical debridement, when feasible. A gap in knowledge exists regarding optimal dosing of amphotericin B lipid formulations for invasive non-*Aspergillus* mold infections; an initial dose of 5 mg/kg/day is commonly used. Posaconazole, a second generation antifungal azole with activity against most of the zygomycetes, has shown promising results as salvage therapy in zygomycosis refractory to or intolerant of amphotericin B formulations.[558,567] Although not approved by the FDA for this indication, posaconazole can be considered as maintenance therapy for zygomycosis following control of infection with an amphotericin B formulation and/or surgical debridement. Posaconazole has not been evaluated as primary therapy for invasive fungal diseases in clinical trials.

Fusarium species[568-570] and *Scedosporium* species have emerged as important causes of invasive fungal infection–related mortality in leukemia and in allogeneic HSCT recipients at some centers.[566,571,572] The likelihood of infection by a *Fusarium* species is substantially increased by the presence of disseminated cutaneous lesions and isolation of a mold from blood culture.[568] Therapy for invasive fusariosis generally involves voriconazole,[573] posaconazole,[561] or a lipid formulation of amphotericin B.[574] *Scedosporium* species are resistant to amphotericin B; therapy generally involves itraconazole, voriconazole, or posaconazole.[575,576] An infectious disease consultation is advised in all cases of invasive mold infections, particularly for cases involving uncommon and resistant molds.

Early Diagnosis of Invasive Mold Infections

Invasive fungal pathogens have increased and remain a major concern. CT scanning of the chest may facilitate early detection of aspergillosis and other filamentous fungi.[577,578] A CT scan may show peripheral or subpleural nodules that are not apparent on plain chest radiographs. The “halo sign” is a characteristic, but not pathognomonic, early chest CT feature of angioinvasive organisms.[475] The hazy alveolar infiltrates surrounding the central nodule or region of consolidation appear to correspond to regions of hemorrhage and are highly suggestive of invasive mold disease, aspergillosis being the most common. The panel recommends a chest CT scan in patients with 10 to 14 days of neutropenia and with persistent or recurrent fever of unknown origin that is unresponsive to empiric antibacterial agents. A chest CT scan may be considered earlier in patients with multiple prior cycles of potently cytotoxic chemotherapy and in patients receiving systemic corticosteroid therapy.

Studies differ regarding whether serum galactomannan is a useful surveillance tool in asymptomatic patients at high risk for mold infections and in patients with persistent neutropenic fever of unknown etiology. In one study, prospective serial monitoring of galactomannan

antigenemia in allogeneic HSCT recipients yielded positive and negative predictive values of 94.4% and 98.8%, respectively, and antigenemia preceded radiographic findings by more than 1 week in 80% of cases of invasive aspergillosis.[579] In another study, the sensitivity was only 64.5% in cases of definite invasive aspergillosis.[485] The positive predictive value (PPV) was poor when serum galactomannan was used as a surveillance tool in patients with persistent neutropenic fever (PPV=7.1%) and in HSCT (mostly autologous) recipients (PPV=10%); the negative predictive value was 100% in both groups.[485]

Odabasi et al[479] evaluated the beta-glucan assay as an early diagnostic marker for invasive fungal infections in patients with acute leukemia or MDS receiving antifungal prophylaxis.[479] At least one serum sample was positive at a median of 10 days before the clinical diagnosis in all patients with a proven or probable invasive fungal infection, including candidiasis, fusariosis, trichosporonosis, and aspergillosis. The negative predictive value was 100%, and the specificity of the test was 90% for a single positive test result and at least 96% for 2 or more sequential positive results.[479] The experience of the beta-glucan assay in HSCT recipients is limited and requires additional study.

Although valuable as diagnostic adjuncts to support a diagnosis of probable invasive aspergillosis in patients with compatible host factors, clinical findings, and radiologic findings[580] (see *Initial Clinical Presentation for Lung Infiltrates: Evaluation* on page FEV-8), the value of these laboratory markers as surveillance tools for invasive fungal infections is controversial. Use of surveillance markers as a trigger for additional diagnostic evaluation or to modify antifungal therapy is at an exploratory level,[431] and more research is required. Currently, the evidence is inadequate to recommend any of these methods as a surveillance tool in asymptomatic immunocompromised patients or in patients with neutropenic fever alone.

Summary

Substantial progress has been made in the prevention and treatment of infectious complications associated with neutropenia and immunosuppressive therapy 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 anti-tumor 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 the overall status of immune function in the patient. It is therefore imperative that patients be evaluated individually for risk of infection in order to minimize the occurrence of infection-related complications. Preventative 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 pre-emptive 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 patients at high risk for specific pathogens during the high-risk period in order to avoid the emergence of resistant pathogens. The development of antipseudomonal beta-lactam agents and the routine use of empiric antimicrobial therapy at the onset of neutropenic fever have contributed to reductions in mortality from bacterial infections. With more patients undergoing treatment with potent cytotoxic regimens (eg, in acute leukemia) and receiving allogeneic HSCT, opportunistic viral and fungal

infections has become an important cause of mortality in these patients. In addition, the increasing prevalence of antibiotic-resistant pathogens has become an important challenge. Infection control should not only rely on anti-infective prophylaxis but should also continue to incorporate standard infection control measures such as careful hand-washing by all health care professionals who come into contact with immunocompromised patients. When selecting antimicrobial agents for prophylaxis and/or pre-emptive therapy, consideration should be given to the local susceptibility and resistance patterns of pathogens.

In summary, the NCCN Guidelines for Prevention and Treatment of Cancer-related Infections aim to 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 preventative 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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