National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Prevention and Treatment of Cancer-Related Infections

Version 3.2024 — September 23, 2024

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National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
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 patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

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

See NCCN Categories of Evidence and Consensus.

Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.

Updates in Version 3.2024 of the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections from Version 2.2024 include:

MS-1

• Discussion section updated to reflect changes in the algorithm

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Updates in Version 2.2024 of the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections from Version 1.2024 include:

INF-A

• Section extensively modified

Updates in Version 1.2024 of the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections from Version 2.2023 include:

INF-1

• Header line added: See Antibacterial Agents (FEV-A) for dosing, spectrum, and specific comments/cautions
• Antimicrobial Prophylaxis, High, bullet 4 added: Length of prophylaxis depends on immune reconstitution.
• Footnotes modified:
  ▸ a: Categories of risk are based on several factors, including underlying malignancy, whether disease is in remission, duration of neutropenia, prior exposure to chemotherapy, ~~recipient or donor CMV status~~ *CMV serostatus*, and intensity of immunosuppressive therapy (IST). For infection concerns and recommended prophylaxis for immune-targeted agents, see INF-A.
  ▸ d: For patients who are intolerant to fluoroquinolone, consider TMP/SMX or an oral third-generation cephalosporin (category 2B). ~~The emergence of multidrug-resistant organisms (MDROs), disruption of the microbiome, and antibiotic toxicities must be taken into consideration when choosing an antimicrobial prophylactic agent.~~
• Footnote removed: Pneumocystis prophylaxis (INF-6). For dosing, spectrum, and specific comments/cautions, see Antibacterial Agents (FEV-A), Antifungal Agents (FEV-B), and Antiviral Agents (FEV-C) as indicated.
• Asterisk added under table: Neutropenia: ≤500 neutrophils/mcL or ≤1000 neutrophils/mcL and a predicted decline to ≤500/ mcL over the next 48 hours

INF-2

• Row added: Immune and targeted treatments

INF-4

• Footnote m modified: Some centers consider the use of letermovir through day 100 post-HCT and continue CMV surveillance for patients at high risk for CMV reactivation. See Antiviral Agents (FEV-C 2 of 4). Letermovir lacks HSV and VZV coverage and HSV/VZV prophylaxis should be continued. *In certain circumstances, up to day 200 can be considered.*

INF-5

• Footnote removed: Diagnostic monitoring and treatment for HBV, HCV, and HIV are evolving fields; consultation with an ID expert or hepatologist should be sought in the treatment of all patients with reactivation or disease.
• Footnotes modified:
  ▸ y: ~~If viral load is consistently undetectable, treatment is considered prophylactic.~~ If viral load fails to drop or previously undetectable PCR becomes positive, consult hepatologist and discontinue anti-CD20 antibody therapy.
  ▸ x: ~~Lamivudine may be considered in certain circumstances with expert consultation~~ *Lamivudine is inferior to entecavir and tenofovir, but may be considered when other agents are unavailable.*

INF-7

• Statement added: For prevention of infections in cancer survivors, including vaccination recommendations, see the NCCN Guidelines for Survivorship.

Continued

Updates in Version 1.2024 of the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections from Version 2.2023 include:

For prevention of infections in pediatric patients, refer to guidance from the CDC.

- General recommendations bullet removed: The safety of vaccines in patients receiving immunostimulatory drugs is unclear. Some emerging data suggest vaccines (eg, influenza) can be given safely.
- Pneumococcal recommendation modified: The pneumococcal conjugate vaccine (PCV20 ~~or PCV15~~) should be administered to adults who are newly diagnosed with cancer who are pneumococcal vaccine-naïve. ~~If PCV15 is used it should be followed by the polysaccharide pneumococcal vaccine (PPSV23) at least 8 weeks later. Additional PPSV23 is not needed for those receiving PCV20. For patients who have previously received PPSV23, the PCV20 or PCV15 dose should be given at least 1 year after the last PPSV23 dose. Regardless of if PCV15 or PCV20 is given, an additional dose of PPSV23 is not recommended. For those who have received PCV13 with or without PPSV23, give PPSV23 as previously recommendedkk. See Pneumococcal Vaccine Timing for Adults for specific guidance. The incremental public health benefits of providing PCV15 or PCV20 to adults who have received PCV13 only or both PCV13 and PPSV23 have not been evaluated.~~ *According to the CDC, additional pneumococcal polysaccharide vaccine (PPSV23) is not needed for those receiving PCV20. Alternatively, PCV15 can be given, followed by PPSV23 at least 8 weeks later. For patients who have previously received PPSV23, PCV20 (preferred) or PCV15 can be given. For patients who have previously received PCV13 only, they can receive PCV20 at least 1 year later, rather than PPSV23. For patients who have previously received PCV13 and 1 or 2 doses of PPSV23, they can receive PCV20 at least 5 years later. See CDC recommendations for pneumococcal vaccination*.
- Meningococcal recommendation modified: ... MenACWY vaccine is given in 2 doses ≥8 weeks apart; serogroup B vaccine is available in a 2- or 3-dose series, depending on the vaccine formulation used. *Patients with ongoing risk for meningococcal disease should receive a booster dose 5 years after completion of the primary series and every 5 years thereafter.*
- Respiratory Syncytial Virus (RSV), recommendation modified: The RSV vaccine is approved by the FDA and available for those ≥60 y. Its effectiveness in patients with cancer is unknown. The *long-acting* RSV monoclonal antibody (mAb) (nirsevimab) is approved for infants <24 months of age to prevent RSV infection.
- Vaccination modified: Travel *and Other Vaccines*
- Travel and Other Vaccines, Recommendation, bullet added: For recommendations on travel vaccines, refer to the CDC Yellow Book.

INF-7A

- Footnotes removed:
  - For prevention of infection in cancer survivors, including vaccination recommendations, see the NCCN Guidelines for Survivorship.
  - See Centers for Disease Control and Prevention (CDC) website for more updated recommendations.
  - For adults who have received PCV13 but have not completed their recommended pneumococcal vaccine series with PPSV23, one dose of PCV20 may be used if PPSV23 is not available. If PCV20 is used, their pneumococcal vaccinations are complete.
- Footnote ff modified: ~~Pneumococcal antibody responses to some serotypes in PCV13 were decreased following co-administration of the meningococcal conjugate vaccine, MenACWY-D, and PCV13. Therefore, PCV13 should not be given with MenACWY-D but can be given with MenACWY-CRM. Similar precautions should be used for PCV15.~~ *PCV20 or PCV15 should not be given with meningococcal conjugate vaccine, quadrivalent (MenACWY-D) but can be given with MenACWY-CRM.*

INF-8

- Inactivated, Subunit, or Toxoid Vaccines, row 1 modified: ~~DTaP (Diphtheria/Tetanus/Acellular Pertussis)~~ *Tdap.*
- Pneumococcal vaccination
  - Recommended timing after HCT modified: ~~6–12 months ≥12 months~~ *3-6 months*
  - Number of doses modified: ~~3,1~~ *3-4*

INF-8A

- Footnotes modified:
  - gg: Emerging therapies such as CAR T-cell therapy appear to behave similar to ~~patients who have undergone~~ allogenic transplant in terms of vaccine

Continued

UPDATES

Updates in Version 1.2024 of the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections from Version 2.2023 include:

boosting recommendations.
- ii: DTaP (diphtheria, tetanus, and acellular pertussis) is not approved for use in ages >7 (FDA/ACIP-approved 3-dose series for ≥7 year olds is Tdap/Td/Td (tetanus-diphtheria) ~~vs. considerations of Tdap/Tdap/Tdap~~). ~~Other than 3 doses of DTaP as stated, 3 doses of Tdap, or 1 dose of Tdap followed by 2 doses of Td are also acceptable options.~~
- jj ~~For patients with GVHD, PCV15 or PCV20 may be considered instead of PPSV23 as a fourth dose. The CDC is currently evaluating the use of a primary series of PCV20 and PCV15 post-HCT.~~ If PCV20 is used, 4 doses should be administered. First 3 doses are generally 1-2 months apart, with the fourth dose 6 months after the third dose. There is no need to give PPSV23. If PCV15 is used, 3 doses should be administered, followed by PPSV23 6-12 months post primary series. Following the primary series of 3 PCV doses, a dose of the PPSV23 to broaden the immune response might be given. For patients with chronic GVHD who are likely to respond poorly to PPSV23, a fourth dose of PCV20 or PCV15 should be considered instead of PPSV23.
- ll: Meningococcal B vaccine should be considered for patients at high risk, such as patients with *chronic GVHD,* asplenia, or complement deficiency or patients receiving a complement C5 inhibitor (eg, eculizumab, ravulizumab).

• Footnote qq added: Pergam SA, et al. Biol Blood Marrow Transplant 2019;25: e321-e330.

INF-A 1 of 13
• Column 1 modified: *Drug Class*/Mechanism of Action (Also for INF-A 2 of 12 through 10 of 12)
• Major Uses column removed from Table (Also for INF-A 2 of 12 through 10 of 12)
• Phosphatidylinositol-3-kinase (PI3K) inhibitors, Recommendations and Comments, bullet 1 modified: ~~Consider CMV surveillance in CMV seropositive patients~~ *Monitor for CMV reactivation in patients at high risk.*

INF-A 6 of 13
• CD30 target, Recommendations and Comments, bullet 1 modified: ~~Consider CMV monitoring in CMV-seropositive patients~~ *Severe or fatal CMV infections reported. Monitor for CMV reactivation in patients at high risk.* (Also for CCR4 target on INF-A 7 of 12)

INF-A 9 of 13
• Recommendations and Comments, bullet 5 modified: *Consider* PJP prophylaxis if high-dose steroid use (≥20 mg per day of prednisone x4 weeks).

INF-A 10 of 13
• Recommendations and Comments, bullets added:
- Consider immunoglobulin replacement therapy in the setting of low IgG and recurrent or severe sinopulmonary infections.
- For vaccine recommendations, see INF-7 and INF-8.

FEV-6
• Mouth/mucosal membrane, necrotizing ulceration, evaluation, sub-bullet removed: Consider leukemic infiltrate
• Esophagus, evaluation
- Bullet removed: Consider CMV esophagitis in patients at high risk for CMV disease
- Bullet added: Histopathologic examination for viral and fungal pathogens

• Footnote n modified: Posaconazole or isavuconazonium sulfate 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 primary therapy or secondary therapy for refractory invasive fungal infections.~~

FEV-7
• Diarrhea, evaluation, bullet 4 modified: Depending on clinical circumstances, consider *diagnostic* testing for viral, *bacterial, and/or parasitic* pathogens ~~(eg, adenovirus, rotavirus, norovirus, CMV), bacterial cultures, and/or parasite exam~~

Continued
UPDATES

Updates in Version 1.2024 of the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections from Version 2.2023 include:

FEV-8
- Vesicular lesions, evaluation modified: Aspiration or scraping for PCR/DFA, ~~and/or herpes virus cultures if PCR unavailable~~ *and/or HSV cultures if PCR unavailable.*
- CNS symptoms
  - Evaluation, bullet 3 added: Infectious disease (ID) consult
  - Treatment Modifications, bullet 1 modified: Initial empiric therapy ~~pending ID consult~~

FEV-9
- Title added: Evaluation of Patients with Possible Respiratory Infection
- Evaluation column extensively modified

FEV-12
- Follow-up therapy, bullet 4, sub-bullet added: Catheter removal highly recommended if persistent positivity
- Suggested minimum duration...,bullet 2, sub-bullet 3 modified: S. aureus: typically requires 4 weeks *(some institutions may use a shorter duration based on ID consultation)* after first negative blood culture; ID consult strongly recommended *(ID consult is associated with decreased mortality)*

FEV-A 1 of 3
- Daptomycin, Comments/Precautions, bullet removed: ID consult strongly recommended
- Tedizolid row added

FEV-B 1 of 5
- Itraconazole, Comments/Precautions, bullet 2 modified: H2 blockers and proton pump inhibitors (PPIs) may inhibit absorption of capsule formulation. Oral liquid *formulation* is preferred for improved absorption.
- Footnote b modified: TDM is routinely used in managing *itraconazole, posaconazole, and voriconazole*. *TDM is not routinely used for isavuconazole.*

FEV-B 2 of 5
- Posaconazole, Comments/Cautions
  - Bullet 1 modified: ~~Evaluated as treatment of refractory infection (but not FDA-approved) in several invasive fungal diseases~~ *Used for treatment of refractory infection (but not FDA-approved) in several invasive fungal diseases.*
  - Bullet 3 modified: *IV posaconazole or* alternative antifungal therapy should be considered for patients who cannot eat a full meal or tolerate an oral nutritional supplement.
  - Bullet added: FDA-approved for invasive aspergillosis
- Voriconazole, Comments/Cautions, bullet 2 modified: Long-term complications ~~resulting from metabolic irregularities~~ may include increased risk for squamous cell carcinoma and hyperphosphatemia

FEV-B 3 of 5
- Footnote d added: AmB-D is not preferred whenever L-AMB or ABLC is available.

FEV-C 1 of 4
- Valacyclovir: Comments/Cautions, statement removed: CMV in allogeneic HCT recipients (2 gm PO QID).
- Valganciclovir, Typical Dosing Based on Indication, bullet modified: Preemptive therapy *and treatment* for CMV...

FEV-C 4 of 4
- Footnote removed: 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 patients receiving allogeneic HCT.

COV-5
- Bullet added: For unresolved COVID-19, ID consult is recommended.

Continued
UPDATES

Updates in Version 1.2024 of the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections from Version 2.2023 include:

COV-6
- Footnote g modified: COVID-19 convalescent plasma obtained from those who have recovered from the ~~Omicron variant~~ *recent circulating variants* and have been previously vaccinated is preferred. COVID-19 convalescent plasma can be acquired via the Blood Centers of America.

COV-7
- Patient hospitalized for acute symptomatic COVID-19, Comments, bullet 2, sub-sub bullet modified: Although investigational (not standard of care), consider extending remdesivir duration to 10 days *for patients hospitalized for COVID-19* if PCR Ct is still low after 5 days and the patient remains symptomatic or is not improving.

COV-8
- Persistent symptomatic COVID-19 infection; particularly B-cell impairment, Comments
  - Bullet 2 modified: To determine potential benefit of COVID-19 convalescent plasma ~~or monoclonal antibody therapies~~, some providers (via clinical investigational approach) will first check:
  - Bullet 2, sub-bullet 2 modified: ~~SARS-CoV-2 PCR Ct for determination of viral load/burden (higher viral load corresponding to lower PCR Ct).~~ *Consult ID to assess viral load burden by PCR.*
- Persistent asymptomatic SARS-CoV-2–positive testing, Comments, bullet 3, sub-bullet removed: Low SARS-CoV-2 PCR Ct correlates with high viral load and may further suggest potential for subclinical active disease, although is currently not validated for clinical use and is considered investigational.

COV-9
- Remdesivir, Dosing/Duration, bullet removed: Caution with moderate-severe renal dysfunction (eg, CrCl <30 mL/min)

Removed from Guidelines
- COV-10 through COV-15, and COV-A 4 of 4

COV-A 3 of 3
- References 16–19 removed

ANTIMICROBIAL PROPHYLAXIS BASED ON OVERALL INFECTION RISK IN PATIENTS WITH CANCER
See Antibacterial Agents (FEV-A) for dosing, spectrum, and specific comments/cautions

Overall Infection Risk in Patients with Cancer[a]	Disease/Therapy Examples	Antimicrobial Prophylaxis
Low	• Standard chemotherapy regimens for most solid tumors • Anticipated neutropenia* <7 days	• 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 days • CAR T-cell therapy	• Bacterial - Consider fluoroquinolone prophylaxis during neutropenia[d] • Fungal - Consider prophylaxis during neutropenia and for anticipated mucositis (INF-2); consider PJP prophylaxis (INF-6) • Viral - During neutropenia and longer depending on risk (INF-3, INF-4, INF-5) • See Immune and Targeted Treatments (INF-A 11 of 13)
High[b]	• Allogeneic HCT including cord blood • Acute leukemia ▸ Induction ▸ Consolidation/maintenance • Alemtuzumab therapy • Moderate to severe GVHD • Anticipated neutropenia* >10 days	• Bacterial - Consider fluoroquinolone prophylaxis during neutropenia[d] • Fungal - Consider prophylaxis during neutropenia (INF-2); consider PJP prophylaxis (INF-6) • Viral - During neutropenia and longer depending on risk (INF-3, INF-4, INF-5) • Length of prophylaxis depends on immune reconstitution.

*Neutropenia: ≤500 neutrophils/mcL or ≤1000 neutrophils/mcL and a predicted decline to ≤500/ mcL over the next 48 hours.

[a] Categories of risk are based on several factors, including underlying malignancy, whether disease is in remission, duration of neutropenia, prior exposure to chemotherapy, cytomegalovirus (CMV) serostatus, and intensity of immunosuppressive therapy (IST). For infection concerns and recommended prophylaxis for immune-targeted agents, see INF-A.
[b] In patients at high risk, additional prophylaxis may be necessary; for example, consider penicillin and trimethoprim/sulfamethoxazole (TMP/SMX) for allogeneic hematopoietic cell transplant (HCT) recipients with chronic graft-versus-host disease (GVHD). In those with an allergy history, a careful reassessment of the allergy is recommended.
[c] This is a heterogenous disease. Therefore, treatment modalities and the type of malignancy affect risk level.
[d] For patients who are intolerant to fluoroquinolone, consider TMP/SMX or an oral third-generation cephalosporin (category 2B).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PREVENTION OF FUNGAL INFECTIONS

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

Overall Infection Risk in Patients with Cancer[a]	Disease/Therapy Examples	Consider Antifungal Prophylaxis Based on Patient- and Center-Specific Risk Factors See Antipneumocystis Prophylaxis (INF-6)	Duration
Intermediate to high	ALL	• Fluconazole[f] or an echinocandin[g] • Amphotericin B products[h] (category 2B)	Typically until resolution of neutropenia
	MDS (neutropenic)	• Posaconazole[f] (category 1) • Voriconazole,[f] isavuconazole,[f] an echinocandin,[g] amphotericin B products[i], or fluconazole (if mold activity not needed)[f] (all category 2B)	
	AML (neutropenic)		
	Autologous HCT with mucositis[e]	• Fluconazole[f] or an echinocandin[g] (both category 1)	
	Autologous HCT without mucositis	No prophylaxis (category 2B)	N/A
	Allogeneic HCT (neutropenic)[a]	• Fluconazole[f] or an echinocandin[g] (both category 1) • Voriconazole,[f] posaconazole,[f] isavuconazole,[f] or amphotericin B products[i] (all category 2B)	Continue during neutropenia[h]
	Immune and targeted treatments	See Immune and Targeted Treatments (INF-A)	Depends on nature and duration of treatment
	Significant acute GVHD (especially grade 3/4) receiving IST	• Posaconazole[f] (category 1) • Voriconazole,[f] echinocandin,[g] amphotericin B products,[i] or isavuconazole,[f] (all category 2B)	Until resolution of significant GVHD

[a] Categories of risk are based on several factors, including underlying malignancy, whether disease is in remission, duration of neutropenia, prior exposure to chemotherapy, CMV serostatus, and intensity of IST. For infection concerns and recommended prophylaxis for immune-targeted agents, see INF-A.
[e] Mucositis is a risk factor for candidemia in patients with hematologic malignancies and HCT recipients not receiving antifungal prophylaxis.
[f] 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). In select circumstances when standard therapy is contraindicated, due to drug interactions or the risk of QTc prolongation, some centers consider using echinocandins, amphotericin B at prophylactic doses, or isavuconazole.
[g] All three agents in the echinocandin class (micafungin, caspofungin, and anidulafungin) are considered by many to be interchangeable. Echinocandins are active against *Candida* and *Aspergillus*.
[h] Some studies/centers continue prophylaxis for up to day 75. Prophylaxis may be extended based on individual risk.
[i] A lipid formulation of amphotericin is generally preferred based on less toxicity.

Note: All recommendations are category 2A unless otherwise indicated.
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PREVENTION OF HERPES SIMPLEX VIRUS (HSV) AND VARICELLA ZOSTER VIRUS (VZV) REACTIVATION OR DISEASE

See Antiviral Agents (FEV-C) for dosing, spectrum, and specific comments/cautions

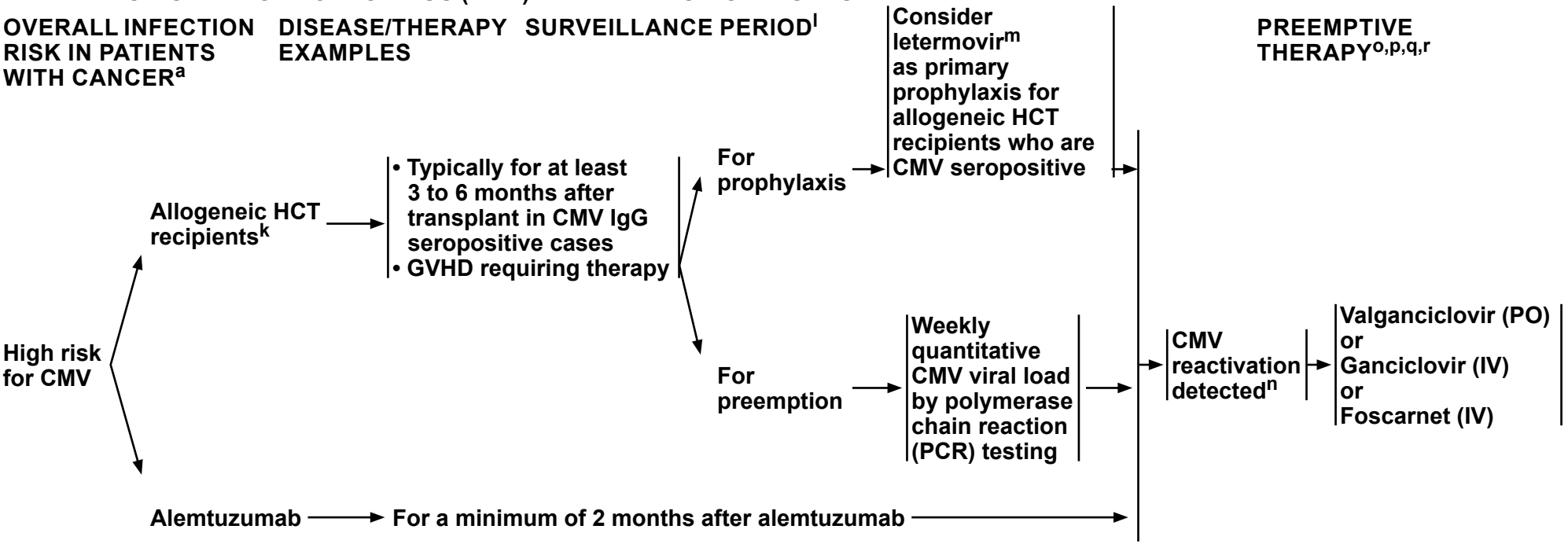
For CMV prophylaxis, see INF-4. For HBV, HCV, and HIV prophylaxis, see INF-5. For general vaccine recommendations, see INF-7.

Overall Infection Risk in Patients with Cancer[a]	Disease/Therapy Examples	Minimum Duration of Antiviral Prophylaxis
Low	• Standard chemotherapy regimens for solid tumors	No prophylaxis unless prior HSV episode; if needed, treat during active therapy including periods of neutropenia
Intermediate	• Autologous HCT • Lymphoma[b] • Multiple myeloma[b] • CLL[b] • Purine analog therapy (eg, fludarabine)	HSV prophylaxis[j] • Consider during active therapy and possibly longer depending on degree of immunosuppression VZV prophylaxis[j] • Consider for at least 6–12 months after autologous HCT
High	• Acute leukemia	HSV prophylaxis during active therapy including periods of neutropenia[j]
	• Proteasome inhibitors	VZV prophylaxis during active therapy including periods of neutropenia[j]
	• Alemtuzumab therapy • Allogeneic HCT • GVHD requiring significant escalation of immunosuppression	HSV prophylaxis[j] • Minimum of 2 months after alemtuzumab and until CD4 ≥200 cells/mcL VZV prophylaxis[j] • Prophylaxis should be considered for at least 1 year after allogeneic HCT

[a] Categories of risk are based on several factors, including underlying malignancy, whether disease is in remission, duration of neutropenia, prior exposure to chemotherapy, CMV serostatus, and intensity of IST. For infection concerns and recommended prophylaxis for immune-targeted agents, see INF-A.
[b] This is a heterogenous disease. Therefore, treatment modalities and the type of malignancy affect risk level.
[j] In pediatrics, HSV prophylaxis is indicated in children who are seropositive and prophylaxis for VZV is not routinely given unless there is a history of recurrent zoster infections or after first zoster episode while on myelosuppressive therapy, even if they are seropositive or vaccinated.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

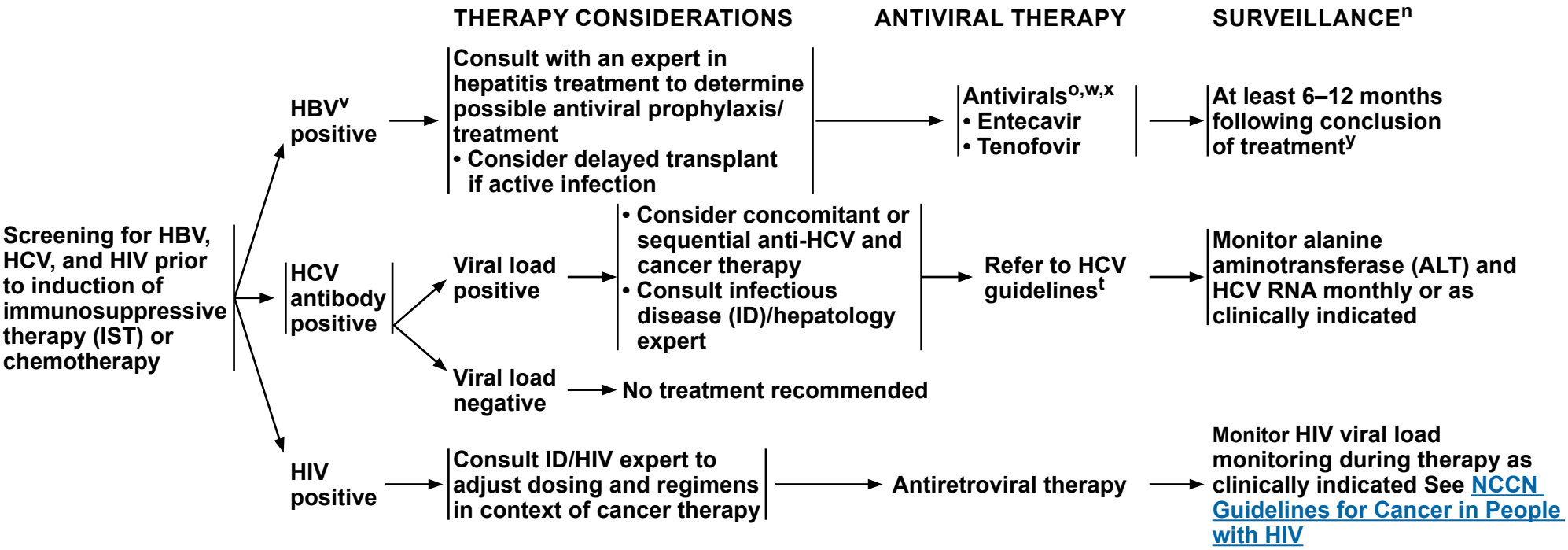
PREVENTION OF CYTOMEGALOVIRUS (CMV) REACTIVATION OR DISEASE



[a] Categories of risk are based on several factors, including underlying malignancy, whether disease is in remission, duration of neutropenia, prior exposure to chemotherapy, CMV serostatus, and intensity of IST. For infection concerns and recommended prophylaxis for immune-targeted agents, see INF-A.
[k] Higher risk transplant subgroups may exist and require different management strategies.
[l] CMV surveillance consists of weekly monitoring by PCR (thresholds for treatment vary at individual sites).
[m] Some centers consider the use of letermovir through day 100 post-HCT and continue CMV surveillance for patients at high risk for CMV reactivation. See Antiviral Agents (FEV-C 2 of 4). Letermovir lacks HSV and VZV coverage and HSV/VZV prophylaxis should be continued. In certain circumstances, up to day 200 can be considered.
[n] Consider testing for drug resistance if clinically significant breakthrough infection is detected.
[o] See Antiviral Agents (FEV-C) for dosing, spectrum, and specific comments/cautions.
[p] Preemptive therapy is defined as administration of antiviral agents to patients who are asymptomatic with laboratory markers of viremia in order to prevent CMV disease in patients who are at high risk. Duration of antiviral therapy is for at least 2 weeks and until CMV is no longer detected.
[q] Typically therapy is initiated with oral valganciclovir unless there are absorption or toxicity issues. However, some centers prefer ganciclovir over valganciclovir. Choice of agent may depend on institutional preference and/or concern for myelosuppression and nephrotoxicity.
[r] For refractory or resistant infections, an infectious disease (ID) consultation is recommended.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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



[n] Consider testing for drug resistance if clinically significant breakthrough infection is detected.
[o] See Antiviral Agents (FEV-C) for dosing, spectrum, and specific comments/ cautions.
[s] Hepatitis B Virus Screening and Management for Patients With Cancer Prior to Therapy: ASCO Provisional Clinical Opinion Update | Journal of Clinical Oncology (ascopubs.org).
[t] Therapy should be given by a provider experienced in treating hepatitis C. See American Association for the Study of Liver Diseases/Infectious Diseases Society of America HCV Guidelines.
[u] See current HIV management Guidelines: https://www.iasusa.org/resources/guidelines and https://clinicalinfo.hiv.gov/en/guidelines.
[v] High risk of HBV is defined as patients with HBsAg+ serology or HBcAb+ serology or with increasing HBV viral load in patients planned for allogeneic HCT or B-cell–depleting therapy.
[w] Duration of therapy may depend on various factors and typically needs to be continued beyond the completion of immunosuppression.
[x] Lamivudine is inferior to entecavir and tenofovir, but may be considered when other agents are unavailable.
[y] If viral load fails to drop or previously undetectable PCR becomes positive, consult hepatologist and discontinue anti-CD20 antibody therapy.

Note: All recommendations are category 2A unless otherwise indicated.
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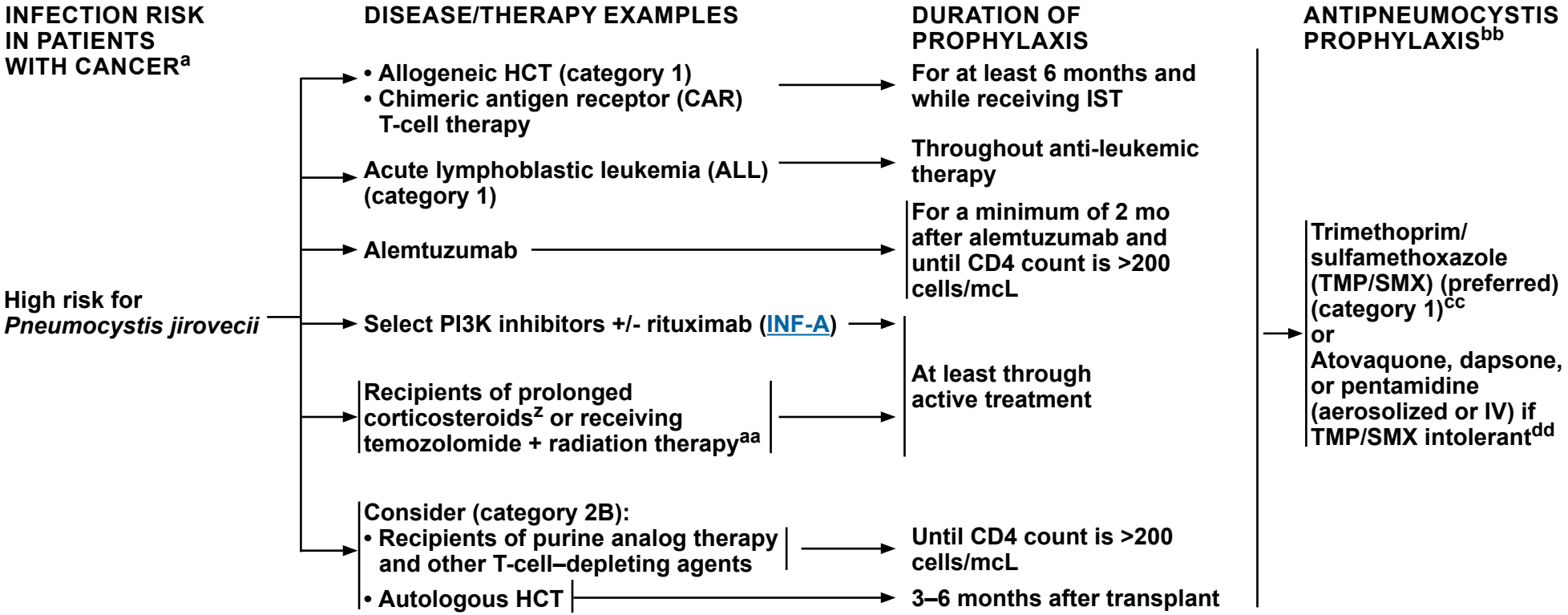
PREVENTION OF *PNEUMOCYSTIS JIROVECII (PNEUMOCYSTIS CARINII)* INFECTION



[a] Categories of risk are based on several factors, including underlying malignancy, whether disease is in remission, duration of neutropenia, prior exposure to chemotherapy, CMV serostatus, and intensity of IST. For infection concerns and recommended prophylaxis for immune-targeted agents, see INF-A.

[z] Risk of *Pneumocystis jirovecii* pneumonia (PJP) is related to the daily dose and duration of corticosteroid therapy. Prophylaxis against PJP can be considered in patients receiving the prednisone equivalent of 20 mg or more daily for 4 or more weeks.

[aa] PJP prophylaxis should be continued until recovery from lymphocytopenia.

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

[cc] TMP/SMX, when appropriately dosed, may have activity against other pathogens including *Nocardia, Toxoplasma*, and *Listeria.* Atovaquone may have activity against *Toxoplasma*.

[dd] The list of agents is alphabetical and does not reflect preference. Consider TMP/SMX desensitization or atovaquone, dapsone, or pentamidine (aerosolized or IV) when PJP prophylaxis is required in patients who are TMP/SMX-intolerant. For patients receiving dapsone, assessing G6PD levels prior to initiating therapy is recommended.

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GENERAL RECOMMENDATIONS FOR VACCINATION IN PATIENTS WITH CANCER[ee]

For prevention of infections in cancer survivors, including vaccination recommendations, see the NCCN Guidelines for Survivorship. For prevention of infections in pediatric patients, refer to guidance from the CDC.

VACCINATION	RECOMMENDATION
General	• Live vaccines should NOT be administered during chemotherapy or periods of significant immunosuppression, such as treatment of GVHD. • All household members should be up-to-date with vaccines.
Influenza	• Patients with hematologic or solid tumor malignancies should receive inactivated or recombinant influenza vaccine annually. See Key Facts about Seasonal Flu Vaccine for specific guidance.
COVID-19	• All persons with cancer, or who have been previously treated for cancer, should receive COVID-19 vaccination. See The CDC's Stay Up to Date with COVID-19 Vaccines for specific guidance. For additional information on COVID-19 vaccinations and their use, also see the CDC for Use of COVID-19 Vaccines in the United States.
Pneumococcal[ff]	• The pneumococcal conjugate vaccine (PCV20) should be administered to adults who are newly diagnosed with cancer who are pneumococcal vaccine-naïve. According to the CDC, additional pneumococcal polysaccharide vaccine (PPSV23) is not needed for those receiving PCV20. Alternatively, PCV15 can be given, followed by PPSV23 at least 8 weeks later. For patients who have previously received PPSV23, PCV20 (preferred) or PCV15 can be given. For patients who have previously received PCV13 only, they can receive PCV20 at least 1 year later, rather than PPSV23. For patients who have previously received PCV13 and 1 or 2 doses of PPSV23, they can receive PCV20 at least 5 years later. See CDC recommendations for pneumococcal vaccination.
Meningococcal[ff]	• The addition of serogroup B meningococcal vaccination has been recommended for patients at increased risk for meningococcal disease. Patients at increased risk for meningococcal disease should receive quadrivalent MenACWY vaccine series and monovalent meningococcal serogroup B vaccine series. Patients at risk include those with persistent complement component deficiencies, those taking a complement C5 inhibitor (eg, eculizumab, ravulizumab), or those with anatomic or functional asplenia. MenACWY vaccine is given in 2 doses ≥8 weeks apart; serogroup B vaccine is available in a 2- or 3-dose series, depending on the vaccine formulation used. Patients with ongoing risk for meningococcal disease should receive a booster dose 5 years after completion of the primary series and every 5 years thereafter.
Human papillomavirus (HPV) vaccination	• The recombinant 3-dose HPV vaccine should be offered to patients of all sexes up to 26 years of age and may be considered in patients up to 45 years of age.
Recombinant zoster vaccine	• The administration of recombinant zoster vaccine (RZV) is recommended for adult patients aged ≥50 years and those ≥18 years who are at increased risk for herpes zoster (HZ). The RZV vaccine is given in 2 doses ≥2–6 months apart. For adults who are at risk and ≥18 years of age, a second dose can be given 1–2 months after the first dose if they will benefit from a shorter vaccination schedule. For patients who have previously received the live-attenuated zoster vaccine live (ZVL), RZV should be given at least 2 months after the last ZVL dose.
Tdap (tetanus/ diphtheria/pertussis)	• Given every 10 years. See CDC recommendations for Tdap vaccinations.
Respiratory syncytial virus (RSV)	• The RSV vaccine is approved by the FDA and is available for those ≥60 years. Its effectiveness in patients with cancer is unknown. The long-acting RSV monoclonal antibody (mAb) (nirsevimab) is approved for infants <24 months of age to prevent RSV infection.
Travel and other vaccines	• ID consult for travel vaccines is recommended. • For recommendations on travel vaccines, refer to the CDC Yellow Book.

Footnotes on INF-7A

Note: All recommendations are category 2A unless otherwise indicated.
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GENERAL RECOMMENDATIONS FOR VACCINATION IN PATIENTS WITH CANCER
FOOTNOTES

[ee] Appropriate timing of vaccination should be assessed in patients whose disease is unlikely to respond (eg, patients who received anti–B-cell antibodies within 6 months, induction and consolidation chemotherapy for acute leukemia).

[ff] PCV20 or PCV15 should not be given with meningococcal conjugate vaccine, quadrivalent (MenACWY-D) but can be given with MenACWY-CRM.

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RECOMMENDED VACCINATION SCHEDULE AFTER AUTOLOGOUS OR ALLOGENEIC HCT[gg]

Inactivated, Subunit, or Toxoid Vaccines[hh]	Recommended Timing After HCT	Number of Doses[nn]
Tdap[ii]	6–12 months	3
Haemophilus influenzae type b (Hib)	6–12 months	3
Pneumococcal vaccination[jj]	3–6 months	3–4
Hepatitis A[kk] (Hep A)	6–12 months	2
Hepatitis B[kk] (Hep B)	6–12 months	2–3
Meningococcal conjugate vaccine[ll]	6–12 months	2–3
Influenza (injectable)	6 months	1, annually[oo]
Inactivated polio vaccine	6–12 months	3
Recombinant zoster vaccine[mm]	50–70 days after autologous HCT May be considered after allogeneic HCT	2
HPV vaccine	>6–12 months For patients ≤26 years, consider up to age 45	3
COVID-19	6 months	1 or more doses per CDC recommendations[pp]

Live Vaccines[mm]	Recommended Timing After HCT	Number of Doses[jj]
Measles/mumps/rubella (MMR)	≥24 months (may vaccinate earlier when risk:benefit ratio suggests)[qq]	1–2
Varicella vaccine	≥24 months (if no GVHD or ongoing immunosuppression and patient was seronegative for varicella pretransplant)	2

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Footnotes on INF-8A

RECOMMENDED VACCINATION SCHEDULE AFTER AUTOLOGOUS OR ALLOGENEIC HCT
FOOTNOTES

[gg] Emerging therapies such as CAR T-cell therapy appear to behave similar to allogenic transplant in terms of vaccine boosting recommendations.
[hh] Inactivated, subunit, or toxoid vaccines may be given as a combined vaccine. Vaccination may be postponed for patients receiving >20 mg of prednisone.
[ii] DTaP (diphtheria, tetanus, and acellular pertussis) is not approved for use in ages >7 (FDA/ACIP-approved 3-dose series for ≥7 year olds is Tdap/Td (tetanus-diphtheria)/Td).
[jj] If PCV20 is used, 4 doses should be administered. First 3 doses are generally 1-2 months apart, with the fourth dose 6 months after the third dose. There is no need to give PPSV23. If PCV15 is used, 3 doses should be administered, followed by PPSV23 6-12 months post primary series. Following the primary series of 3 PCV doses, a dose of the PPSV23 to broaden the immune response might be given. For patients with chronic GVHD who are likely to respond poorly to PPSV23, a fourth dose of PCV20 or PCV15 should be considered instead of PPSV23.
[kk] Strongly consider if clinically indicated. May consider Hep A and B combined vaccine if immunization for both is needed.
[ll] Meningococcal B vaccine should be considered for patients at high risk, such as patients with chronic GVHD, asplenia, or complement deficiency or patients receiving a complement C5 inhibitor (eg, eculizumab, ravulizumab).
[mm] Efficacy in allogeneic HCT, in the presence of GVHD, or ongoing immunosuppression has not been established.
[nn] Number of doses depends on which vaccine formulation is used.
[oo] Refer to 2-1-8 rule as proposed by Carpenter and Englund. Carpenter PA, et al. Blood 2016;127:2824-2832.
[pp] May consider early vaccination at 3 months during community outbreaks and high disease activity. See INF-7 for additional information.
[qq] Pergam SA, et al. Biol Blood Marrow Transplant 2019;25: e321-e330.

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IMMUNE AND TARGETED TREATMENTS[a,b]

Table 1. Targeted Therapies[i]

Drug Class/Mechanism of Action	Agents	Infection Concerns	Recommendations and Comments[c,d,e,g,h]
Ubiquitin-proteasome pathway inhibitors[1]	Bortezomib Carfilzomib Ixazomib	• Respiratory tract infection • VZV • HBV • PML	• Recommend VZV prophylaxis • VZV vaccination in patients seronegative for VZV at least 1 month prior to initiation • Consider HZ vaccination in patients seropositive for VZV • Drug-induced neutropenia and pneumonitis
Bruton tyrosine kinase (BTK) inhibitors[2]	Acalabrutinib Ibrutinib Pirtobrutinib Zanubrutinib	• VZV • HBV • PJP	• Consider HSV/VZV prophylaxis • Consider prophylaxis against PJP and opportunistic fungal infections in patients with additional risk factors • Drug-induced neutropenia
BCR::ABL tyrosine kinase inhibitors[2,3,5]	Asciminib Bosutinib Nilotinib Imatinib Dasatinib Ponatinib	• CMV (dasatinib) • VZV •HBV	• Second-generation agents are associated with greater risk of drug-induced pancreatitis and hepatotoxicity • Drug-induced neutropenia • Drug-induced pleural effusion (most frequently dasatinib)
Phosphatidylinositol-3-kinase (PI3K) inhibitors[3]	Copanlisib Idelalisib Duvelisib Alpelisib	• CMV • VZV • PML • Opportunistic fungal infections • PJP	• Consider CMV surveillance in patients seropositive for CMV • Consider PJP prophylaxis • Drug-induced neutropenia • Drug-induced pneumonitis, colitis, and hepatitis • Alpelisib has not been associated with PJP risks.

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Footnotes on INF-A 12 of 13
References

IMMUNE AND TARGETED TREATMENTS[a,b]

Table 1. Targeted Therapies (continued)[i]

Drug Class/Mechanism of Action	Agents	Infection Concerns	Recommendations and Comments[c,d,e,g,h]
KRAS G12C inhibitors	Adagrasib Sotorasib	• No significantly increased risks for infection	• Drug-induced gastrointestinal (GI) side effects (nausea, vomiting, diarrhea, hepatoxicity) • Drug-induced pneumonitis and interstitial lung disease
mTOR inhibitors[2]	Everolimus Temsirolimus Sirolimus	• VZV • HBV • HCV • PML • PJP • TB	• Screen for latent TB, treat as indicated • Consider PJP prophylaxis in patients with additional risk factors • Drug-induced pneumonitis and stomatitis • Associated with impaired wound healing
Histone deacetylase inhibitors	Vorinostat Romidepsin Belinostat	• HBV • HIV	• May reverse HIV and HBV latency
Janus kinase (JAK) inhibitors[2,3,5]	Momelotinib Fedratinib Pacritinib Ruxolitinib	• CMV • HBV • HSV • Opportunistic fungal infections • PJP • PML • TB • VZV	• Screen for latent TB and HBV, treat as indicated • Consider PJP prophylaxis (depending on additional risk factors) and HSV/VZV prophylaxis • Monitor for drug withdrawal syndrome with taper or discontinuation when used for PV or myelofibrosis. • Fedratinib can be associated with serious and sometimes fatal Wernicke-like encephalopathy • Drug-induced neutropenia
Isocitrate dehydrogenase 1 (IDH1) and isocitrate dehydrogenase 2 (IDH2) inhibitors	Enasidenib Ivosidenib Olutasidenib	No significantly increased risks for infections	• Monitor for differentiation syndrome[f] when used for AML • Drug-induced hepatotoxicity
BRAF kinase inhibitors[2]	Dabrafenib Encorafenib Vemurafenib	No significantly increased risks for infections	• Drug-induced rash (including serious hypersensitivity reactions), fever, arthralgias, neutropenia, and lymphopenia • Drug-induced pneumonitis and interstitial lung disease reported with single and combination therapies (eg, BRAF kinase + MEK kinase inhibitors) • Drug-induced hepatotoxicity, especially with vemurafenib • Adverse effect profile impacted by combination MEK kinase inhibitor therapy

Footnotes on INF-A 12 of 13
References

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Table 1. Targeted Therapies (continued)[i]

IMMUNE AND TARGETED TREATMENTS[a,b]

Drug Class/ Mechanism of Action	Agents	Infection Concerns	Recommendations and Comments[c,d,e,g,h]
MEK kinase inhibitors[2]	Binimetinib Cobimetinib Trametinib Selumetinib	No significantly increased risks for infections	• Drug-induced rash (including serious hypersensitivity reactions) and fever • Drug-induced hepatotoxicity, neutropenia, and lymphopenia • Drug-induced pneumonitis and interstitial lung disease reported with single and combination therapies (eg, BRAF kinase + MEK kinase inhibitors) • Adverse effect profile impacted by combination BRAF kinase inhibitor therapy
Bcl-2 (B-cell lymphoma 2) inhibitors[2]	Venetoclax	No significantly increased risks for infections	• Drug-induced neutropenia and lymphopenia • Dose reduction is required when used with P-gp inhibitors or strong/moderate CYP3A inhibitors (eg, posaconazole and other azoles) • Consider monitoring for fungal infections depending on additional risk factors
FLT3 (FMS-like tyrosine kinase 3) inhibitors	Gilteritinib Midostaurin Quizartinib	No significantly increased risks for infections	• Monitor for differentiation syndrome with gilteritinib[f] • Drug-induced neutropenia • Drug-induced pneumonitis
Nuclear export inhibitor	Selinexor	No significantly increased risks for infections	• Drug-induced side effects (nausea, vomiting, and diarrhea) and neutropenia
Multi-target protein kinase inhibitors	Pralsetinib Entrectinib Repotrectinib	No significantly increased risks for infections	• Toxicities vary with agent but include drug-induced neutropenia, lymphopenia, skin rash, hepatotoxicity, CNS effects, pneumonitis, interstitial lung disease, and GI effects including perforation • Pralsetinib is associated with impaired wound healing
Rho-associated coiled-coil–containing protein kinase 2 (ROCK2) inhibitor	Belumosudil	No significantly increased risks for infections	• Drug-induced neutropenia and lymphopenia • Associated with impaired wound healing

Footnotes on INF-A 12 of 13
References

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IMMUNE AND TARGETED TREATMENTS[a,b]

Table 1. Targeted Therapies (continued)[i]

Drug Class/Mechanism of Action	Agents	Infection Concerns	Recommendations and Comments[c,d,e,g,h]
Vascular endothelial growth factor receptor (VEGFR) inhibitors	Axitinib	• Increased risk of infections, including fatal infections, reported with some agents	• May impair wound healing • GI perforation and fistula formation may rarely occur
	Fruquintinib		
	Sorafenib		
	Sunitinib		
	Pazopanib		
	Vandetanib		
	Regorafenib		
	Lenvatinib		
	Tivozanib		
	Cabozantinib		
ALK inhibitors[3]	Alectinib	No significantly increased risks for infections	• Drug-induced pneumonitis and hepatotoxicity • Development of renal cysts with potential secondary infection seen with crizotinib
	Brigatinib		
	Ceritinib		
	Crizotinib		
	Lorlatinib		
CDK4/6 inhibitors	Abemaciclib	No significantly increased risks for infections	• Drug-induced neutropenia, hepatotoxicity, and rash
	Palbociclib		
	Ribociclib		
	Trilaciclib		
Fibroblast growth factor receptor (FGFR) kinase inhibitor	Futibatinib	No significantly increased risks for infections	• Monitor for hyperphosphatemia and ocular toxicity including retinal pigment epithelial detachment
	Pemigatinib		
	Erdafitinib		

Footnotes on INF-A 12 of 13
References

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Table 2. Monoclonal Antibodies and Fusion Proteins[i] IMMUNE AND TARGETED TREATMENTS[a,b]

Drug Class/ Mechanism of Action	Agents	Infection Concerns	Recommendations and Comments[c,d,e,g,h]
Bispecific CD19-directed CD3 T-cell engager (BiTE)[8]	Blinatumomab	• Bacterial infection • CMV • HSV/VZV • HBV • PML • Opportunistic fungal infections • PJP	• Consider PJP and HSV/VZV prophylaxis • Monitor for cytokine release syndrome • Drug-induced neurotoxicity, leukoencephalopathy, pancreatitis, hepatoxicity, neutropenia, and hypogammaglobulinemia
	Tafasitamab-cxix	• Bacterial infections • HBV	• Drug-induced neutropenia
Bispecific BCMA-directed CD3 T-cell engager (BiTE)	Teclistamab-cgyv Elranatamab-bcmm	• Bacterial infection • HSV/VZV • Adenovirus • CMV • PML • HBV • PJP • Opportunistic fungal infection	• Recommend PJP and HSV/VZV prophylaxis • Consider CMV screening based on epidemiologic risks • Monitor for CRS, drug-induced neutropenia, neurotoxicity, and hepatotoxicity
Bispecific C20-directed CD3 T-cell engager (BiTE)	Epcoritamab-bysp Glofitamab-gxbm Mosunetuzumab-axgb	• Bacterial infections • HBV (high risk)	• Recommend PJP and HSV/VZV prophylaxis • Consider CMV screening based on epidemiologic risks • Monitor for CRS, drug-induced neutropenia and neurotoxicity
Bispecific G protein coupled receptor class C group 5 member D (GPRC5d) directed CD3 T-cell engager (BiTE)	Talquetamab-tgvs	• Bacterial infections • HSV/VZV • CMV • Adenovirus • HBV • Candidiasis	• Recommend PJP and HSV/VZV prophylaxis • Consider CMV screening based on epidemiologic risks • Skin and nail toxicities • Monitor for CRS, drug-induced neutropenia, neurotoxicity, and hepatotoxicity
CD19 target	Loncastuximab tesirine-lpyl	• Limited data, but severe or fatal infections reported • Likely HBV risk based on effects on B-cells	• Drug-induced pleural effusion, pericardial effusion, ascites, and myelosuppression (ie, neutropenia, lymphocytopenia)

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Table 2. Monoclonal Antibodies and Fusion Proteins[i] IMMUNE AND TARGETED TREATMENTS[a,b]

Drug Class/ Mechanism of Action	Agents	Infection Concerns	Recommendations and Comments[c,d,e,g,h]
CD20 target[8]	Obinutuzumab Ofatumumab Rituximab	• HBV (high risk) • HCV • HSV/VZV • PML	• Screen for HBV[c], treat as indicated • Consider prophylaxis for VZV/HSV • Consider prophylaxis for PJP, especially if concomitant therapy further increases PJP risk • Drug-induced neutropenia, lymphocytopenia, and hypogammaglobulinemia
CD22 target[9]	Inotuzumab ozogamicin Moxetumomab pasudotox	Limited data on specific infections	• Risk for capillary leak syndrome (moxetumomab) and VOD/ hepatotoxicity (inotuzumab)
CD30 target[9]	Brentuximab vedotin	• PML • CMV • PJP • HSV/VZV	• Consider CMV monitoring in patients seropositive for CMV • Consider PJP and HSV/VZV prophylaxis • Drug-induced neutropenia and lymphocytopenia
CD33 target[9]	Gemtuzumab ozogamicin	• Bacterial infections • Opportunistic fungal infections • PJP	• Drug-induced VOD/hepatotoxicity, neutropenic colitis, and interstitial pneumonitis
CD38 target[9]	Daratumumab Isatuximab	• *Listeria* • HBV • HSV/VZV • CMV • PJP • *Cryptococcus*	• Recommend HSV/VZV prophylaxis • Consider PJP prophylaxis • Drug-induced neutropenia
CD52 target[8]	Alemtuzumab	• *Nocardia* • TB • *Listeria* • HSV/VZV • CMV • ADV • BKV • PML • Opportunistic fungal infections	• Consider CMV monitoring in patients seropositive for CMV • Recommend PJP prophylaxis if CD4 <200 • Recommend VZV/HSV prophylaxis • Risk for prolonged lymphocytopenia

Footnotes on INF-A 12 of 13
References

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Table 2. Monoclonal Antibodies and Fusion Proteins[i] IMMUNE AND TARGETED TREATMENTS[a,b]

Drug Class/ Mechanism of Action	Agents	Infection Concerns	Recommendations and Comments[c,d,e,g,h]
CD319 (SLAMF-7) target[9]	Elotuzumab	• VZV	• Recommend HSV/VZV prophylaxis • CCR4 target[9]; drug-induced interstitial pneumonitis
CCR4 target[9]	Mogamulizumab	• *Mycobacterium spp.* • CMV • HSV/VZV • HBV • *Candida* • PJP	• Consider CMV monitoring in patients seropositivefor CMV • Recommend PJP and HSV/VZV prophylaxis • Drug-induced dermatologic toxicity
Complement C1s target	Sutimlimab	• Encapsulated bacteria	• Vaccinate against encapsulated bacteria including *Streptococcus pneumoniae, Neisseria meningitidis* (serogroups A, C, W, Y and B) and *Hemophilus influenzae* at least 2 weeks prior to starting treatment.
Complement C5 inhibitor[10]	Eculizumab Ravulizumab	• Encapsultated bacteria, but in particular, *Neisseria spp* (eg, *N. meningitidis, N. gonorrhoeae*) • Opportunistic fungal infections in patients with neutropenia	• Screen for gonorrhea in patients who are at high risk for STIs • Consider prophylaxis with PCN (ciprofloxacin or azithromycin if allergic to PCN) in addition to vaccination. Duration of prophylaxis is to be guided by drug half-life, sC5b-C9/sMAC levels, sC5a, and CH50 complement activity recovery[11] • Vaccinate with both MenACWY and MenB vaccines at least 2 weeks prior to starting treatment (if possible) • Risk for other encapsulated bacterial infections (*Streptococcus pneumoniae* and *Haemophilus influenzae*) is lower. Patients who are not vaccinated should be immunized according to ACIP recommendations. • Non-groupable *Neisseria meningitidis* infection can occur despite vaccination

Footnotes on INF-A 12 of 13
References

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Table 2. Monoclonal Antibodies and Fusion Proteins[i] IMMUNE AND TARGETED TREATMENTS[a,b]

Drug Class/ Mechanism of Action	Agents	Infection Concerns	Recommendations and Comments[c,d,e,g,h]
IL-6 inhibitor[10]	Tocilizumab Siltuximab	• Bacterial infections • Mycobacteria (TB, non- TB) • VZV • HBV • Opportunistic fungal infections • PJP	• Screen for latent TB when combined with other immunosuppressive agents in patients at high risk and if epidemiologically indicated • Monitor closely for signs of infection as fever and CRP can be blunted • Drug-induced hepatotoxicity
VEGF inhibitor[6]	Bevacizumab Aflibercept	No significantly increased risks for infection	• Drug-induced neutropenia, bowel perforation, and GI hemorrhage • Associated with impaired wound healing
VEGFR inhibitor[6]	Ramucirumab		
Bispecific EGFR and MET receptor-directed antibody (with EGFR exon 20 insertion mutation)	Amivantamab-vmjw		• Drug-induced skin rash including acneiform dermatitis and interstitial pneumonitis
Epidermal growth factor receptor (EGFR/HER1) inhibitor[6]	Cetuximab Panitumumab		• Avoid sun exposure; use sunscreen • Dermatology consultation for severe rash • Drug-induced neutropenia, severe rash, and acneiform eruptions
HER2 inhibitor[6]	Pertuzumab	Bacterial infections	• Risk for skin and nail infections • Drug-induced rash including acneiform dermatitis

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Footnotes on INF-A 12 of 13
References

Table 2. Monoclonal Antibodies and Fusion Proteins[i] IMMUNE AND TARGETED TREATMENTS[a,b]

Drug Class/Mechanism of Action	Agents	Infection Concerns	Recommendations and Comments[c,d,e,g,h]
Monomethylauristatin E linked to IgG1 antibody targeting CD79b	Polatuzumab vedotin-piiq	• PJP • HSV/VZV • CMV • PML • Fungal infections • Hepatitis B reactivation	• Drug-induced myelosuppression • Drug-induced hepatotoxicity • Consider PJP and HSV/VZV prophylaxis, based on concomitant immunosuppression
Microtubule inhibitor linked to IgG1 folate receptor alpha (FRα) targeting antibody	Mirvetuximab soravtansine- gnyx	• No significantly increased risks for infection	• Monitor for drug-induced ocular disorders, interstitial lung disease/pneumonitis, and peripheral neuropathy

Footnotes on INF-A 12 of 13
References

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IMMUNE AND TARGETED TREATMENTS[a,b]

Table 3. Checkpoint Inhibitors (Monoclonal Antibodies)[1,i]

Drug Class/ Mechanism of Action	Agents	Infection Concerns[12]	Recommendations and Comments[c,d,e,g,h]
Cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) inhibitor	Ipilimumab	Increased infection risks from checkpoint inhibitors are thought to be mostly due to immunosuppressive treatment of irAEs (eg, with corticosteroids and/or TNF-alpha antagonists, alemtuzumab, abatacept), but emerging data suggest that dysregulated immunity pathways critical for infection surveillance from checkpoint inhibitors can directly increase infection risks. Infections which simulate irAEs can occur without additional immunosuppression	• Examples of irAEs: colitis, hepatitis, pneumonitis, thyroiditis, myositis, myasthenia gravis, rash, and many others. See NCCN Guidelines for Management of Immunotherapy-Related Toxicities. • Reactivation of latent TB and HBV, and invasive fungal infections have been reported with or without additional immunosuppression for treatment of irAEs ▸ Consider screening for CMV infection in patients with colitis who are not responding to corticosteroids ▸ Corticosteroids risk factor for bacterial infection: most commonly pulmonary, genitourinary, and intraabdominal ▸ Unusual CNS infections, *Listeria*, CMV, VZV have been reported • Screen for HBV and latent TB, treat as indicated • Based on epidemiologic factors, screening for *Coccidioides* and *Strongyloides* may be indicated • Consider PJP prophylaxis if high-dose steroid use (e.g., ≥ 20mg per day of prednisone for 4 weeks), or lower steroid doses but with other concomitant immunosuppression or risk factors
	Tremelimumab-actl		
Programmed death-1 (PD-1) inhibitors	Nivolumab		
	Pembrolizumab		
	Cemiplimab-rwlc		
	Dostarlimab-gxly		
	Retifanlimab-dlwr		
	Toripalimab-tpi		
PD ligand-1 (PD-L1) inhibitor	Atezolizumab		
	Durvalumab		
	Avelumab		

Footnotes on INF-A 12 of 13
References

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IMMUNE AND TARGETED TREATMENTS[a,b]

Table 4. Chimeric Antigen Receptor-Engineered T-Cell (CAR T-Cell) Therapy[13-15,i]

Drug Class/ Mechanism of Action	Agents	Infection Concerns	Recommendations and Comments[c,d,e,g,h]
CD19-directed	Axicabtagene ciloleucel	**Risk factors for infection:** • Pre-infusion: underlying malignancy, prior chemotherapy +/- HCT, antecedent infection, neutropenia • Post-infusion: CRS/ICANS and associated treatment (e.g. high-dose steroids, IL-6 inhibitors), neutropenia, lymphopenia, and hypogammaglobulinemia **Infection Timeline** Within 30 days: • Bacterial infections predominate • Highest risk period Beyond 30 days: • Respiratory tract viral infections common Fungal infection risk low but varies based upon prior therapies and degree of immunosuppression as well as other relevant risks	• Relevant serologic screening includes HIV, HBV and HCV. Consider CMV and additional screening based on epidemiologic risks. • Consider antibacterial and antifungal prophylaxis while neutropenic. • Consider mold-active antifungal prophylaxis if additional risks such as prolonged neutropenia, previous allogeneic HCT or augmented IST for CRS/ICANS. • PJP and HSV/VZV prophylaxis are recommended. • Monitor for CRS, which may mimic sepsis. See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
	Brexucabtagene autoleucel		
	Tisagenlecleucel		
	Lisocabtagene maraleucel		
B-cell maturation antigen (BCMA)-directed	Idecabtagene vicleucel		
	Ciltacabtagene autoleucel		

Footnotes on INF-A 12 of 13
References

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IMMUNE AND TARGETED TREATMENTS
FOOTNOTES

[a] The information in this table is continuously evolving and is not an exhaustive list. Refer to the FDA-approved labeling for these agents for further information on the appropriate use and further details on potential toxicities and drug interactions. The infection risk of these agents should be weighed according to the cancer being treated, the patient's relative medical comorbidities, and other antineoplastic therapies used during treatment.

[b] Additional agents in these and other categories have been FDA-approved, but their infection risk profile has not been fully established.

[c] All patients anticipating systemic anticancer therapy should be tested for HBV prior to the start of therapy. Risk assessment, including the need for HBV-directed treatment and prophylaxis, should be undertaken in patients with findings of chronic or past HBV infection (INF-5).[7]

[d] Tuberculosis (TB) screening should at minimum be performed in those with risk factors (eg, individuals [or caregivers and household members] from high-incidence TB countries, recent exposure, health care workers, residents and employees of homeless shelters/correctional facilities) and with planned use of agents associated with an increased risk for TB infection.

[e] Vaccination history should be assessed and updated (when relevant) in all patients (INF-7 and INF-8).

[f] Clinical features of differentiation syndrome can include fever, shortness of breath, rapid weight gain, pleuro-pericardial effusions, lung infiltrates, hypoxia, and hypotension.

[g] Consider monitoring and/or prophylaxis for opportunistic fungal infections.

[h] Many of these agents can cause QTc prolongation.

[i] Agents listed in this table may be used either as monotherapy or in combination regimens. Please refer to the full prescribing information and/or other cancer-specific NCCN Guidelines for the appropriate use of these agents.

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IMMUNE AND TARGETED TREATMENTS
REFERENCES

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CLINICAL PRESENTATION

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

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

Neutropenia:
- **≤500 neutrophils/mcL or**
- **≤1000 neutrophils/mcL and a predicted decline to ≤500/mcL over the next 48 hours**

→

INITIAL EVALUATION OF FEVER AND NEUTROPENIA

- **Complete history and physical (H&P) including supplemental history:**
  - **Major comorbid illness**
  - **Type and time since last chemotherapy**
  - **History of prior significant infections**
  - **Recent antibiotic therapy/prophylaxis**
  - **Medications**
  - **Use of devices**
- **Epidemiologically relevant exposures**

- **Laboratory/radiology assessment:**
  - **Complete blood count (CBC) with differential, comprehensive metabolic panel**
  - **Consider chest x-ray and urinalysis**

→

MICROBIOLOGIC EVALUATION

- **Blood culture x at least 2 sets (one set = 2 bottles)**
  - **One peripheral + one catheter (preferred but not required)[a]**
- **Urine culture (only if patient has symptoms or abnormal urinalysis; exercise caution in interpreting results if urinary catheter is present)**
- **Site-specific diagnostics:**
  - **Diarrhea (*Clostridioides difficile* [*C. difficile*] assay, enteric pathogen screen)**
  - **Skin (aspirate/biopsy of skin lesions or drainage)**
- **Viral diagnostics:**
  - **PCR- and/or direct fluorescence antibody (DFA)-based tests for vesicular/ulcerated lesions on skin or mucosa**
  - **Throat or nasopharynx for respiratory virus symptoms, especially during outbreaks**

→ **Initial Risk Assessment (FEV-2)**

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

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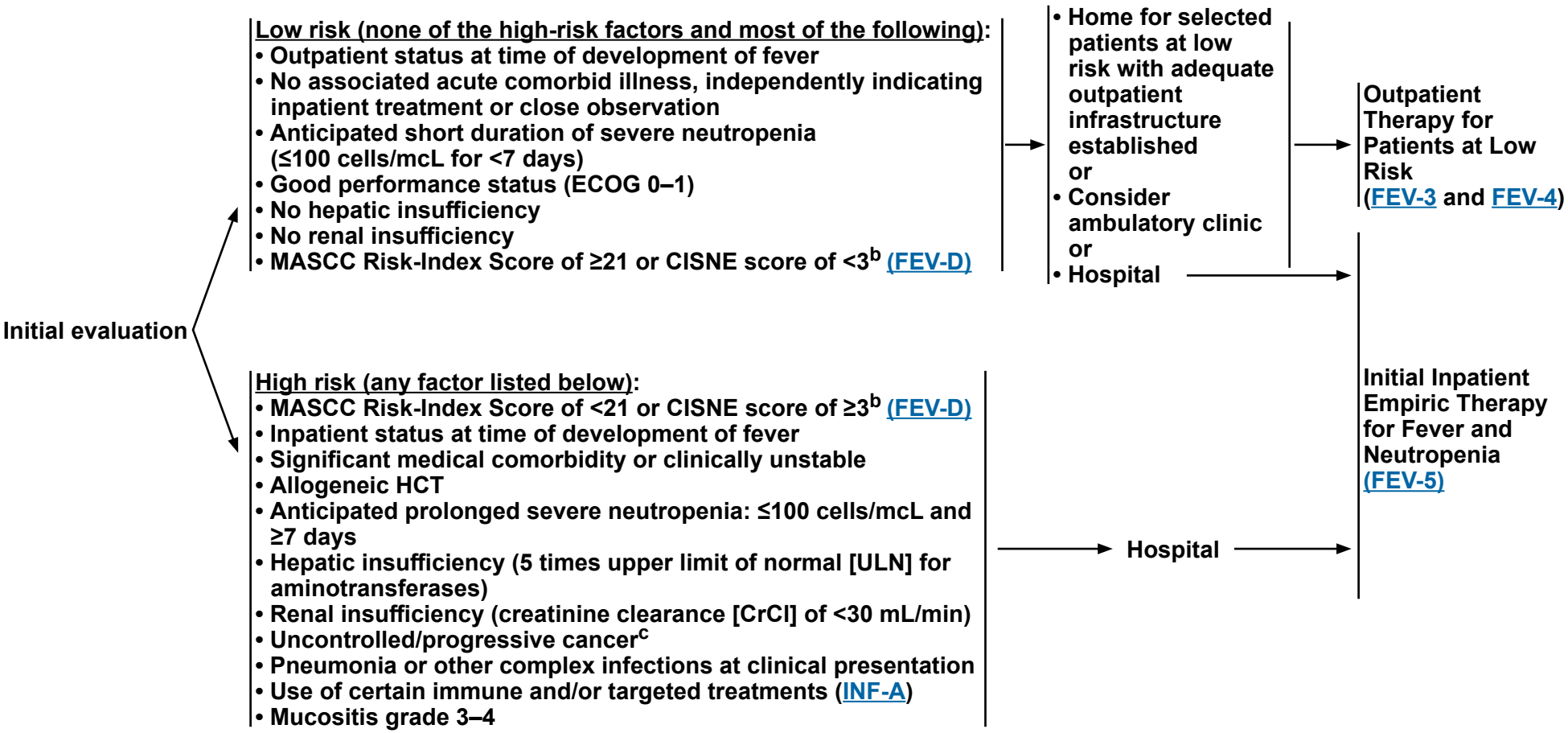

[b] Risk categorization refers to risk of serious complications, including mortality, in patients with neutropenic fever. Risk stratification is validated in adults; no generalizable, cross-validated, risk-stratified management exists for pediatric patients with febrile neutropenia. See Risk Assessment Resources (FEV-D).

[c] Uncontrolled/progressive cancer is defined as any patients with leukemia not in complete remission, or patients with other cancers and evidence of disease progression after more than 2 courses of chemotherapy.

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OUTPATIENT THERAPY FOR PATIENTS AT LOW RISK

INDICATION	ASSESSMENT	MANAGEMENT

Patient at low risk 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-hour home caregiver available
	  ▸ 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
		See Treatment and Follow-up (FEV-4)
		
		OR
		
		Consider observation period (2–12 hours) (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
		• Provide patient education
		• Follow up by telephone within 12–24 hours

[b] Risk categorization refers to risk of serious complications, including mortality, in patients with neutropenic fever. Risk stratification is validated in adults; no generalizable, cross-validated, risk-stratified management exists for pediatric patients with febrile neutropenia. See Risk Assessment Resources (FEV-D).

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OUTPATIENT THERAPY FOR PATIENTS AT LOW RISK

TREATMENT OPTIONS	FOLLOW-UP

• Intravenous (IV) antibiotics at home
• Daily long-acting IV agent ± oral therapy
  ▸ Home or office
• Oral therapy only[d]:
  ▸ Ciprofloxacin plus amoxicillin/clavulanate[e] (category 1)
  ▸ Levofloxacin
  ▸ Moxifloxacin[f] (category 1)
	→ • Patient should be monitored daily
	• Daily assessment for the first 72 hours to assess response, toxicity, and adherence; if responding, then telephone follow-up daily thereafter.
	• Specific reasons to return to clinic:
	  ▸ Any positive culture from blood or other sterile source
	  ▸ New signs/symptoms reported by the patient
	  ▸ Persistent or recurrent fever at 3–5 days
	  ▸ 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] Use clindamycin in place of amoxicillin-clavulanate for patients who are allergic to penicillin.
[f] Insufficient activity against *Pseudomonas aeruginosa*. Recommended for patients at low risk who may not require *Pseudomonas aeruginosa* coverage.

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INITIAL INPATIENT EMPIRIC THERAPY FOR UNCOMPLICATED FEVER AND NEUTROPENIA[g]

Initial antibiotic therapy should be based on:
- Infection risk assessment (FEV-2)
- Broad-spectrum coverage including antipseudomonal activity
- Colonization with or prior infection with multidrug-resistant organisms (MDROs)[h]
- Site of infection
- Local antibiotic susceptibility patterns
- Organ dysfunction/drug allergy
- Previous antibiotic therapy

IV antibiotic therapy[i]
- Typically monotherapy
  - Cefepime (category 1)
  - Imipenem/cilastatin (category 1)
  - Meropenem (category 1)
  - Piperacillin/tazobactam (category 1)
  - Ceftazidime[j] (category 2B)
- IV combination therapy could be considered where antimicrobial resistance is suspected
- Patients with high risk of anaphylaxis, consider ID/allergy consultation[k]

Site-specific evaluation and therapy:

Mouth, esophagus, and sinus/nasal (FEV-6)

Abdominal pain, perirectal pain, diarrhea, and urinary tract symptoms (FEV-7)

Lung infiltrates (FEV-9)

Cellulitis, vascular access devices (VADs), vesicular lesions, disseminated papules or other lesions, and central nervous system [CNS] symptoms (FEV-8)

OR

Follow-up (FEV-11)

- Consider oral antibiotic therapy for select patients at low risk:
- Ciprofloxacin + amoxicillin/clavulanate (category 1)[e]
- Moxifloxacin[f] (category 1)
- Levofloxacin
- Oral antibiotic regimen not recommended if patient received prior quinolone prophylaxis

Follow-up (FEV-4)

[e] Use clindamycin in place of amoxicillin-clavulanate for patients who are allergic to penicillin.
[f] Insufficient activity against *Pseudomonas aeruginosa*. Recommended for patients at low risk who may not require *Pseudomonas aeruginosa* coverage.
[g] See Antibacterial Agents (FEV-A) for dosing, spectrum, and specific comments/cautions.
[h] The CDC defines MDROs as microorganisms that are resistant to one or more classes of antimicrobial agents. Methicillin-resistant *Staphylococcus aureus* (MRSA) is an example of an MDRO.
[i] Choice of antibiotic may depend on local antibiotic susceptibility patterns and individual patient syndromes.
[j] Weak Gram-positive coverage and increased breakthrough infections limit utility.
[k] For severe beta-lactam allergy, consider vancomycin and aztreonam while further evaluation is carried out with ID/allergy consultation.

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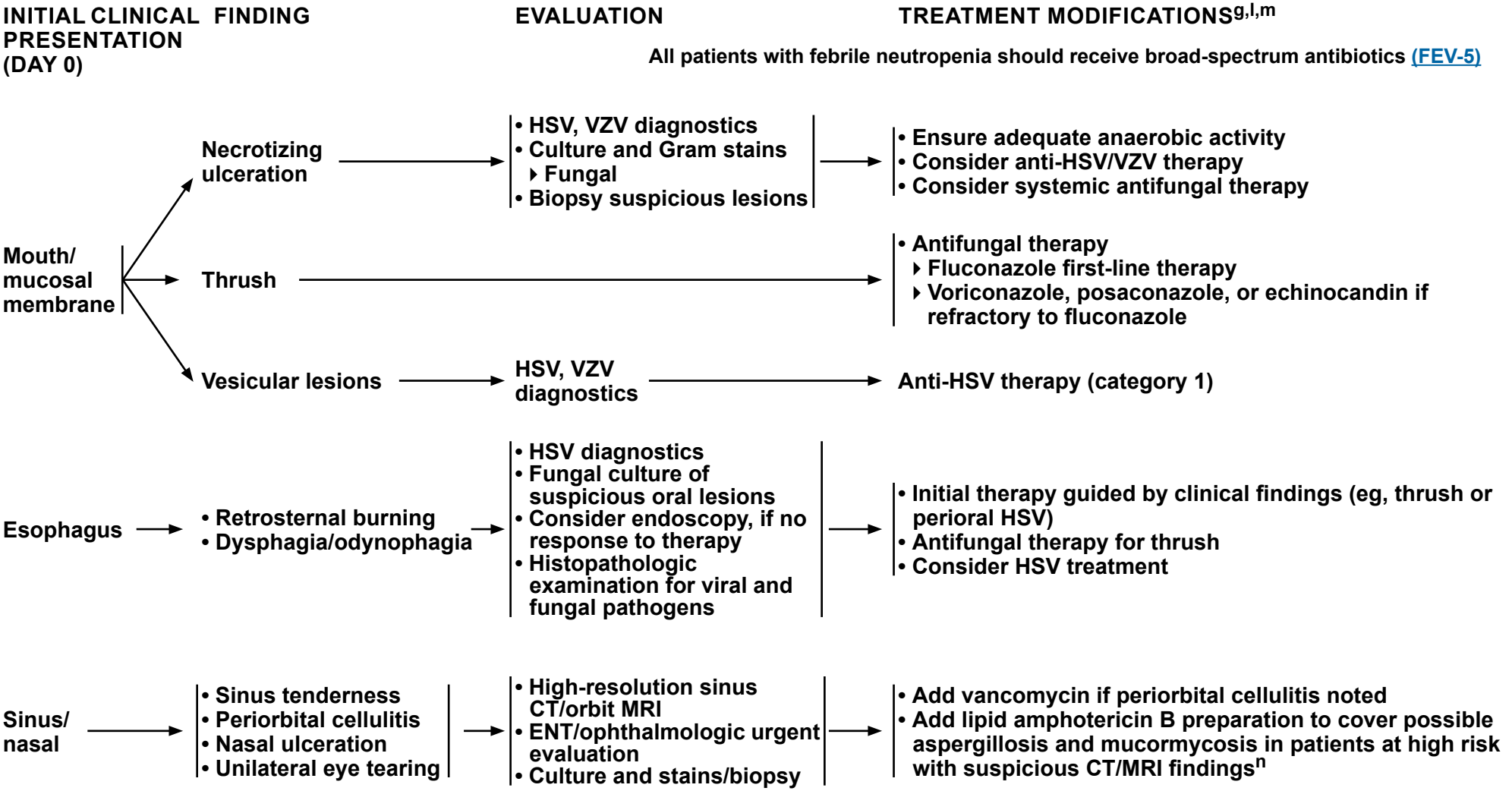

[g] See Antibacterial Agents (FEV-A) for dosing, spectrum, and specific comments/cautions.
[l] See Antifungal Agents (FEV-B) for dosing, spectrum, and specific comments/cautions.
[m] See Antiviral Agents (FEV-C) for dosing, spectrum, and specific comments/cautions. The antivirals are not equal in terms of efficacy, side effects, and resistance.
[n] Posaconazole or isavuconazonium sulfate can be considered for patients who have invasive, refractory infections or who have intolerance to amphotericin B formulations.

Follow-up (FEV-11)

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INITIAL CLINICAL PRESENTATION (DAY 0)	EVALUATION	TREATMENT MODIFICATIONS[g,l,m]
		All patients with febrile neutropenia should receive broad-spectrum antibiotics (FEV-5)
Abdominal pain	• Abdominal exam • Abdominal CT (preferred) or ultrasound • Alkaline phosphatase, transaminases, bilirubin, amylase, lipase	• Consider adding anaerobic therapy • Consider early surgical and other subspecialty (eg, gastroenterology, interventional radiology) consultations as clinically indicated
Perirectal pain	• Perirectal inspection • Consider imaging such as abdominal/pelvic CT or MRI	• Ensure adequate anaerobic therapy • Consider local care
Diarrhea[o]	• *C. difficile* testing (if not on laxatives/stool softeners/tube feeds, which may cause diarrhea) • Consider other medical causes of diarrhea: neutropenic enterocolitis, GI GVHD, mucositis • Colonoscopy may be required to evaluate for colitis and determine etiology of diarrhea • Depending on clinical circumstances, consider diagnostic testing for viral, bacterial, and/or parasitic pathogens.	*C. difficile* infection (CDI) confirmed → FEV-10 CDI negative/other cause identified → Treat as appropriate for clinical diagnosis
Urinary tract symptoms	Urine culture	No additional therapy until specific pathogen identified

[g] See Antibacterial Agents (FEV-A) for dosing, spectrum, and specific comments/cautions.
[l] See Antifungal Agents (FEV-B) for dosing, spectrum, and specific comments/cautions.
[m] 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.
[o] Diarrhea from chemotherapy or antibiotic-associated diarrhea can be confused with true CDI.

Follow-up (FEV-11)

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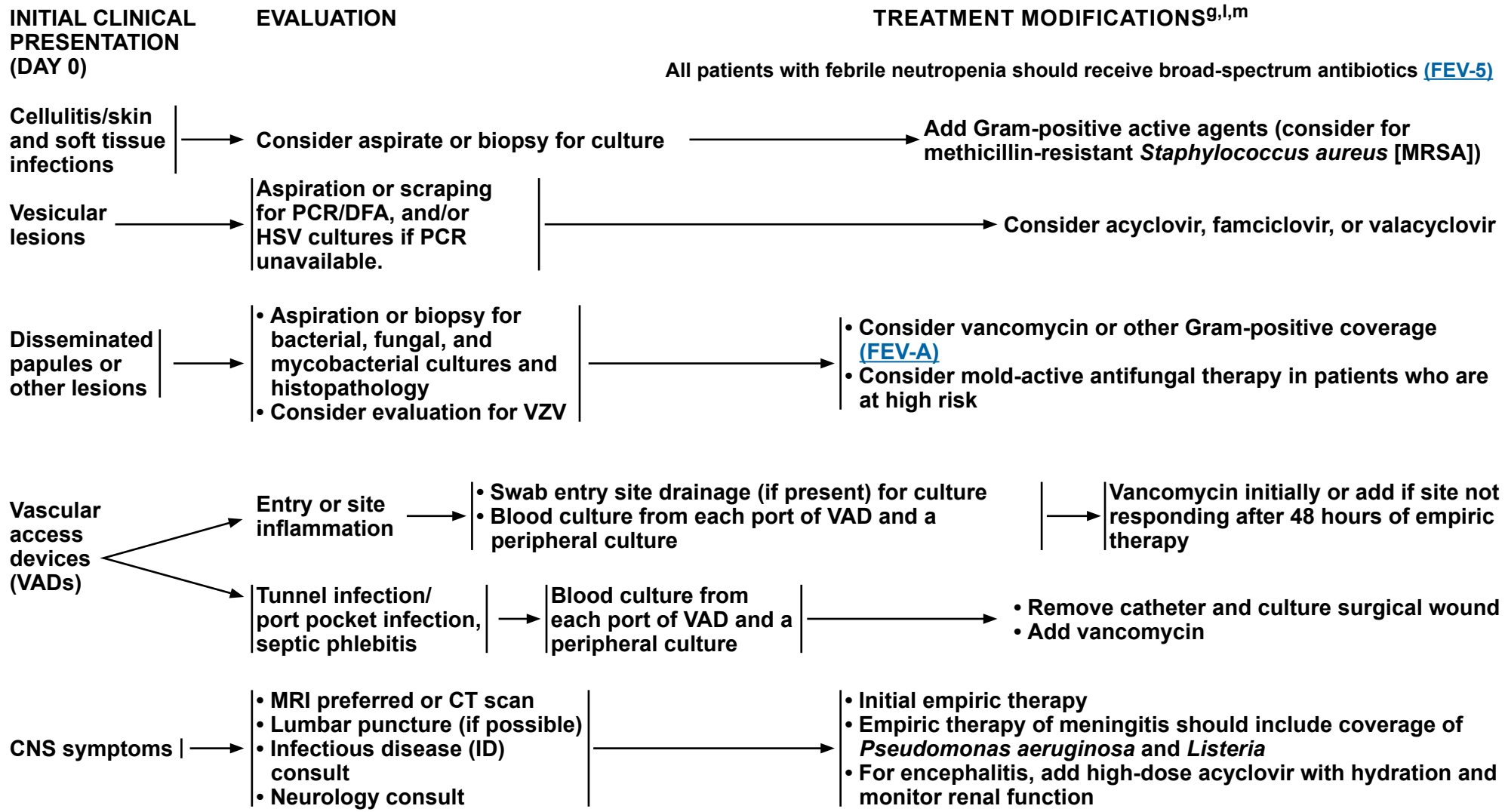

[g] See Antibacterial Agents (FEV-A) for dosing, spectrum, and specific comments/cautions.
[l] See Antifungal Agents (FEV-B) for dosing, spectrum, and specific comments/cautions.
[m] See Antiviral Agents (FEV-C) for dosing, spectrum, and specific comments/cautions. The antivirals are not equal in terms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

Follow-up (FEV-11)

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EVALUATION OF PATIENTS WITH POSSIBLE RESPIRATORY INFECTION

INITIAL CLINICAL PRESENTATION (DAY 0)	EVALUATION[p,q]	TREATMENT MODIFICATIONS[g,l,m]
		All patients with febrile neutropenia should receive broad-spectrum antibiotics (FEV-5)
Lung infiltrates →	The potential diagnoses and useful tests are extensive. CT scan to define nature and extent of infiltrates and culture of blood and sputum (if available) should be performed. Consider bronchoalveolar lavage (BAL), especially if no response to initial therapy. Based on the nature of the radiologic appearance, epidemiology, risk factors, patient history, and clinical presentation, consider: Diagnostic tests[r]: • Blood ▸ *Aspergillus* galactomannan ▸ *Cryptococcal* antigen ▸ *Coccidioides* serology ▸ *Blastomyces* and/or *Histoplasma* antigen • Urine ▸ *Blastomyces* and/or *Histoplasma* antigen ▸ *Legionella* and pneumococcal antigen • Respiratory/bronchoscopy specimens ▸ *Aspergillus* galactomannan ▸ *Pneumocystis jiroveci* PCR or DFA ▸ Mycobacterial PCR ▸ *Mycoplasma* and *Chlamydia* PCR ▸ Nucleic acid amplification testing (NAAT) for viral respiratory pathogens via nasopharyngeal swab or BAL fluid	→ • Consider adding coverage for atypical bacteria (azithromycin, doxycycline,[s] or fluoroquinolone) (see General Recommendations for Vaccination in Patients with Cancer: Pneumococcal Vaccination [INF-7]) • Consider adding: ▸ Mold-active antifungal agent [see Patients at Intermediate to High Risk on (INF-1)] ▸ Antiviral therapy during influenza season in local area[t] ▸ TMP/SMX if possible *Pneumocystis jirovecii* etiology ▸ Vancomycin or linezolid if MRSA suspected • Re-evaluate for ability to de-escalate

[g] See Antibacterial Agents (FEV-A) for dosing, spectrum, and specific comments/cautions.
[l] See Antifungal Agents (FEV-B) for dosing, spectrum, and specific comments/cautions.
[m] 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] Other diagnoses to consider include pulmonary edema, hemorrhage, and drug toxicities.
[q] Assess for health care-acquired pneumonia and/or resistant pathogens.
[r] Rapid immunofluorescent viral antigen tests may be negative for H1N1.
[s] Doxycycline can be used for *Mycoplasma* or *Chlamydia*, but is not recommended for legionellosis as some non-pneumophila *Legionella* species can be resistant to tetracyclines.
[t] 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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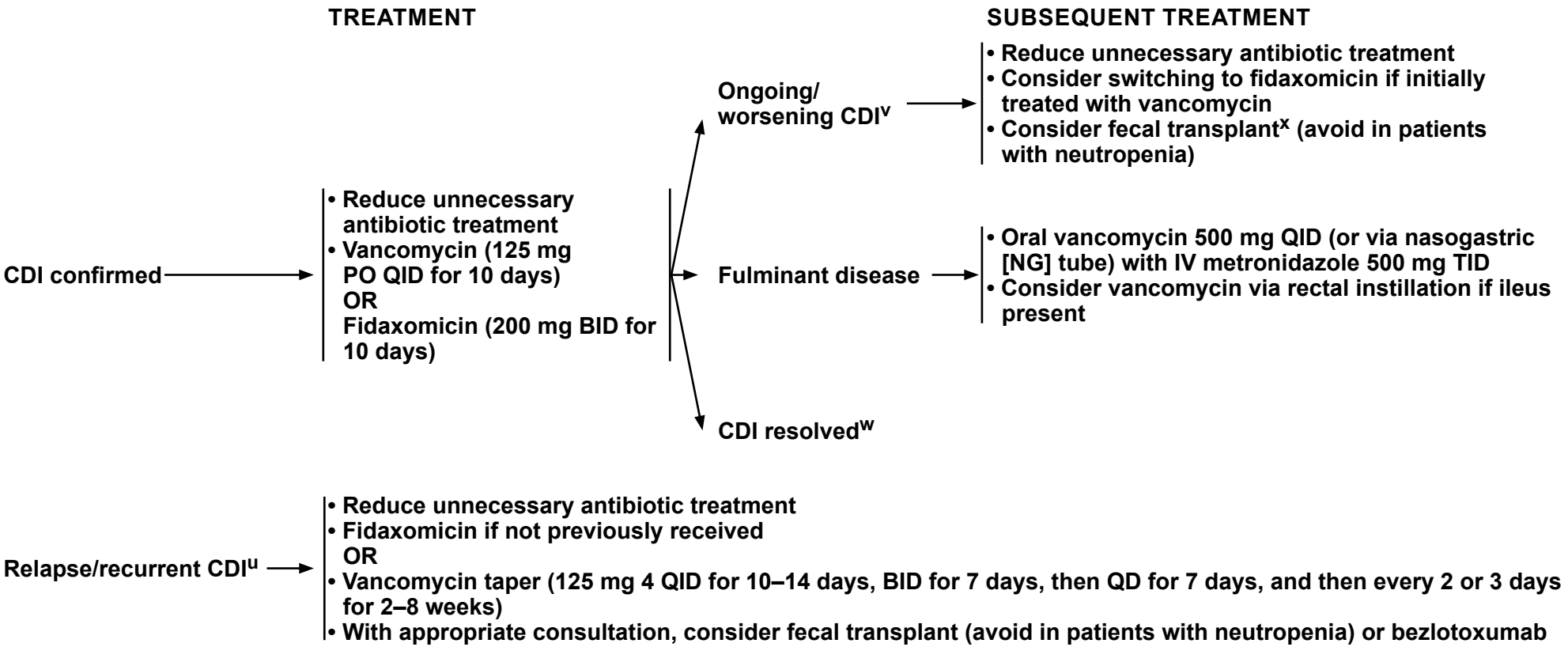
Follow-up (FEV-11)

TREATMENT OF *CLOSTRIDIOIDES DIFFICILE* INFECTIONS (CDI) IN PATIENTS WITH CANCER



[u] Recurrent CDI is defined as symptom onset and positive assay result following an episode with positive assay result in previous 2–8 weeks.
[v] For subsequent treatment options for ongoing CDI, also see the *Clostridium difficile* Practice Guidelines provided by the Infectious Diseases Society of America: https://www.idsociety.org/practice-guideline/clostridioides-difficile-2021-focused-update.
[w] If continuing antibiotics, may consider secondary prophylaxis.
[x] This treatment has not been proven to be effective in this patient population.

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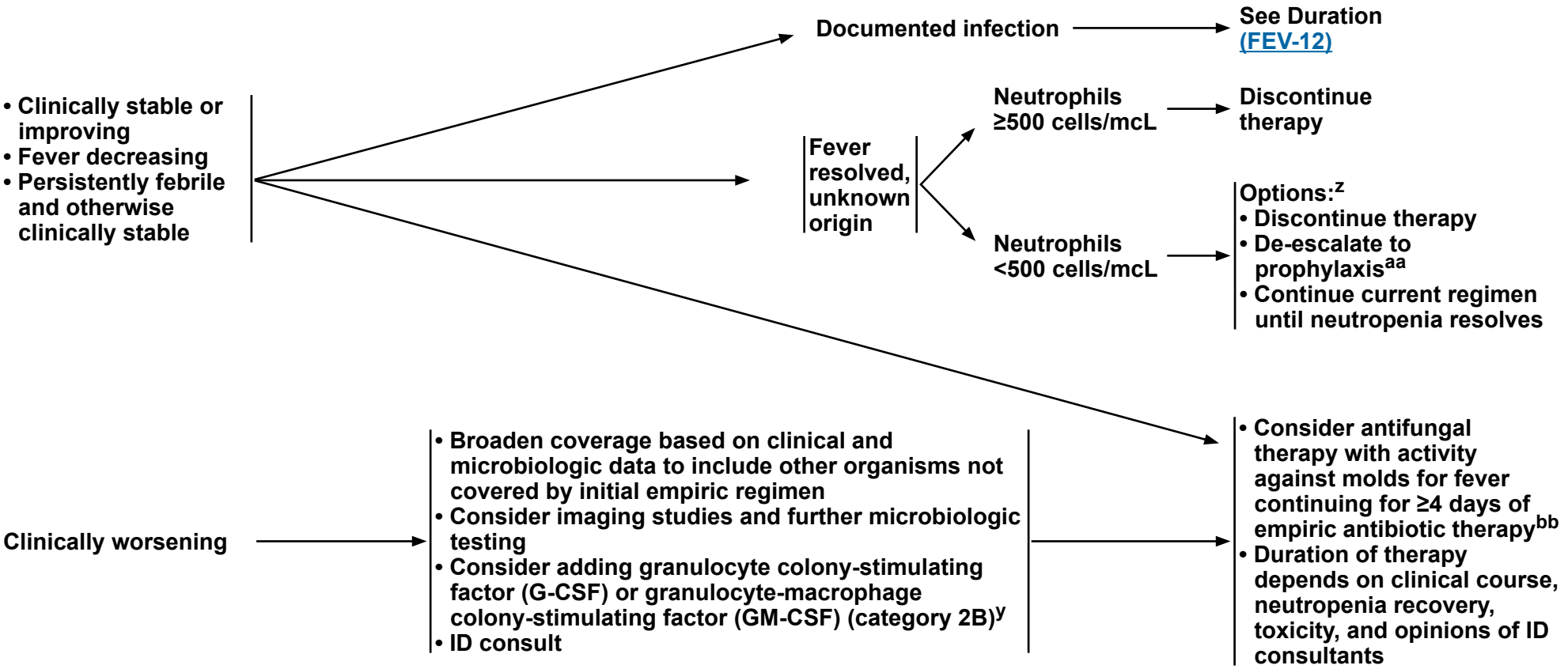
Follow-up (FEV-11)



y NCCN Guidelines for Hematopoietic Growth Factors.

z The choice will depend on particular patient details; see Discussion for additional information.

aa In patients who defervesce for at least 48 hours, it may be appropriate in some cases to de-escalate to fluoroquinolone.

bb The timing to add empiric 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 (ie, neutropenia >10 days, allogeneic HCT recipients, high-dose corticosteroids), the panel recommends adding empiric antifungal therapy after the fourth day unless patient is receiving prophylaxis directed against molds.

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FOLLOW-UP THERAPY FOR RESPONDING DISEASE

SUGGESTED MINIMUM DURATION OF THERAPY FOR DOCUMENTED INFECTION[g,l,m]

These are general guidelines for patients with uncomplicated disease and may need to be revised for individual patients. Treatment duration can be modified depending on infection severity and patient factors.

Documented infection →

- Targeted treatment of documented infections should be done
- Reassessment of empiric broad-spectrum therapy
- De-escalation and duration of antimicrobial therapy may be individualized based on:
  - Neutrophil recovery
  - Rapidity of defervescence
  - Specific site of infection
  - Infecting pathogen
  - Patient's underlying illness
- Catheter removal for septic phlebitis, tunnel infection, or port pocket infection
  - Catheter removal highly recommended if persistent positivity

→

- Skin/soft tissue: 5–14 days
- Bloodstream infection
  - Gram-negative: 7–14 days
  - Gram-positive: 7–14 days
  - *S. aureus*: typically requires 4 weeks (some institutions may use a shorter duration based on ID consultation) after first negative blood culture; ID consult strongly recommended (ID consult is associated with decreased mortality)
  - Yeast: ≥2 weeks after first negative blood culture
  - Catheter removal favored for bloodstream infections with *Candida* or other yeasts, *S. aureus*, *Pseudomonas aeruginosa*, *Corynebacterium jeikeium*, *Acinetobacter* spp., nontuberculous mycobacteria, molds, vancomycin-resistant enterococci (VRE), *Stenotrophomonas maltophilia*, and other MDROs
- Bacterial sinusitis: 7–14 days
- Bacterial pneumonia: 5–14 days
- Fungal (mold and yeast):
  - *Candida*: minimum of 2 weeks after first negative blood culture
  - Mold: minimum of 12 weeks
- Viral:
  - HSV/VZV: 7–10 days (category 1); acyclovir, valacyclovir, or famciclovir (uncomplicated, localized disease to the skin)
  - Influenza: a minimum 5-day course of oseltamivir[cc]

[g] See Antibacterial Agents (FEV-A) for dosing, spectrum, and specific comments/cautions.
[l] See Antifungal Agents (FEV-B) for dosing, spectrum, and specific comments/cautions.
[m] 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] A minimum 5-day course is standard based on data from ambulatory and otherwise healthy individuals with intact immune systems; some centers consider longer courses or higher doses (eg, 150 mg) for the highly immunocompromised, but there is no proven benefit to prolonged therapy.

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ANTIBACTERIAL AGENTS: GRAM-POSITIVE ACTIVITY ONLY[a]

Agents[b]	Dose[c]	Spectrum[e]	Comments/Precautions
Vancomycin	15 mg/kg IV every 12 hours, Loading dose[c] may be considered	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 are present • Dosing individualized with therapeutic drug monitoring (TDM)
Daptomycin	6–10 mg/kg/day IV[d] with higher doses indicated for specific infections	• Gram-positive organisms • Has in vitro activity against VRE	• Weekly creatine phosphokinase (CPK) to monitor for rhabdomyolysis • Not indicated for pneumonia due to inactivation by pulmonary surfactant
Linezolid	600 mg PO/IV every 12 hours	Gram-positive organisms, including VRE	• Hematologic toxicity (typically with prolonged cases, >2 weeks) may occur; thrombocytopenia most common (0.3%–10%) • Serotonin syndrome is rare; use cautiously with selective serotonin reuptake inhibitors (SSRIs)[1] • Treatment option for VRE and MRSA • Peripheral/optic neuropathy with long-term use
Tedizolid	200 mg QD	Gram-positive organisms, including VRE	Less hematologic toxicity compared to linezolid with prolonged use

Footnotes

[a] Drug resistance or clinical failure may dictate the use of newer restricted antibiotics, and an ID consult is recommended.

[b] These drugs are not recommended as monotherapy for fever in the setting of neutropenia and should only be added if there is high suspicion of infection with resistant Gram-positive organisms or if certain risk factors are present (FEV-D).

[c] These are standard dosing recommendations for adult patients; there are other situations where dose adjustments are required. Consult pediatric guidelines for recommended dosing in pediatric patients. Adjustments should also be made for patients with renal insufficiency and obesity according to institutional guidelines.

[d] Higher doses of daptomycin (8–12 mg/kg) are recommended for certain bloodstream infections (eg, enterococci). ID consult is strongly recommended.

[e] Once culture data are available, directed therapy may be initiated following an ID consult as appropriate for Gram-positive pathogens.

References

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Note: All recommendations are category 2A unless otherwise indicated.
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ANTIBACTERIAL AGENTS: ANTI-PSEUDOMONAL[f]

Agents	Dose[c]	Spectrum[g]	Comments/Precautions[h]
Cefepime	2 g IV every 8 hours	• 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 • Empiric therapy for neutropenic fever (category 1) • Mental status changes may occur, especially in the setting of renal dysfunction
Ceftazidime	2 g IV every 8 hours	• Poor Gram-positive activity ▸ Breakthrough streptococcal infections reported; add Gram-positive agent to empiric neutropenic fever treatment • Not active against most anaerobes and *Enterococcus* spp.	• Use for suspected/proven CNS infection with susceptible organism • Empiric therapy for neutropenic fever (category 2B; due to resistance among certain Gram-negative rods)
Imipenem/ cilastatin sodium	500 mg IV every 6 hours	• Broad-spectrum activity against most Gram-positive, Gram-negative, and anaerobic organisms • Preferred against extended-spectrum beta-lactamase (ESBL)–producing organisms 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 • Ertapenem does not have anti-pseudomonal activity • Empiric therapy for neutropenic fever (category 1) • Data are limited, but it is expected that doripenem, like meropenem, would be efficacious
Meropenem	1–2 g IV every 8 hours or 500 mg IV every 6 hours		
Piperacillin/ tazobactam	3.375 g IV every 6 hours (mild-moderate infections) or 4.5 g IV every 6 hours (severe infections including fever and neutropenia) Administered over 30 min (Some institutions use extended infusion: 3.375 g or 4.5 g every 8 hours administered over 4 hours)	• Broad-spectrum activity against most Gram-positive, Gram-negative, and anaerobic organisms	• Use for suspected intra-abdominal source • Not recommended for meningitis • Empiric therapy for neutropenic fever (category 1)

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Footnotes on FEV-A 3 OF 3

ANTIBACTERIAL AGENTS: OTHER

Agents[h]	Dose[c]	Spectrum	Comments/Cautions
Aminoglycosides • Amikacin • Gentamicin • Tobramycin	Consider extended interval dosing for patients with normal renal function (eg, 5–7 mg/kg every 24 hours)	Activity primarily against Gram-negative organisms	Sometimes used as part of combination therapy in patients who are seriously ill or hemodynamically unstable
Ciprofloxacin	500–750 mg PO every 12 hours or 400 mg IV every 8–12 hours	• Ciprofloxacin has good activity against Gram-negative and atypical organisms (eg, *Legionella* spp.) but less activity than levofloxacin or moxifloxacin 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 • Fluoroquinolone side effects should be taken into consideration (see the FDA warnings)
Levofloxacin	500–750 mg PO or IV daily	• Good activity against Gram-negative and atypical organisms (eg, *Legionella* spp.) • Improved Gram-positive activity compared to ciprofloxacin • Levofloxacin has no activity against anaerobes • Moxifloxacin is more active against anaerobes than other fluoroquinolones, but has insufficient activity against some gram-negative organisms, including *Pseudomonas*	• Prophylaxis may increase bacterial resistance and superinfection[2] • Limited studies as empiric therapy in patients with fever and neutropenia • Prophylaxis in patients with neutropenia[3,4] • Data support fluoroquinolones for prophylaxis; fluoroquinolone side effects should be taken into consideration (see the FDA warnings)
Moxifloxacin	400 mg PO or IV daily		
Metronidazole	500 mg PO (preferred) every 8–12 hours	Good activity against anaerobic organisms	• Associated with peripheral neuropathy with prolonged use (>4 weeks)
Trimethoprim/ sulfamethoxazole (TMP/SMX)	Prophylaxis: Single strength daily or double strength 3 times per week Therapy: 15 mg/kg/d in divided doses every 6–8 hours based on the trimethoprim component	Activity against *P. jirovecii* and other relevant pathogens, including *Toxoplasma gondii* and *Nocardia*	• Highly effective as prophylaxis against *P. jirovecii* in patients at high risk (INF-6) • Monitor for renal insufficiency, myelosuppression, hepatotoxicity, and hyperkalemia • Interactions with methotrexate

Footnotes

[c] These are standard dosing recommendations for adult patients; there are other situations where dose adjustments are required. Consult pediatric guidelines for recommended dosing in pediatric patients. Adjustments should also be made for renal insufficiency and patients with obesity according to institutional guidelines.

[f] Emerging data may support extended or continuous infusion of beta-lactam therapies. For highly resistant infections, see Discussion for recommendations regarding alternative antibiotics with restricted availability.

[g] No agents listed are active against MRSA or VRE.

[h] There are multiple new agents that may be useful against multiply drug-resistant bacteria including ceftolozane-tazobactam, ceftazidime/avibactam, meropenem-vaborbactam, imipenem/cilastatin/relebactam, and cefiderocol. These agents have variable spectrum and activity and should only be used with expert consultation.

References

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ANTIFUNGAL AGENTS: AZOLES

Azoles as a class have important drug interactions, especially with the newer therapeutic agents. Please carefully review. Drug-drug interactions are common and need to be closely monitored (consult package inserts for details).

Azoles[a]	Dose	Spectrum	Comments/Cautions
Fluconazole	In adults with normal renal function: typical dosing is 400 mg IV/PO daily. May vary depending on indication and *Candida* susceptibility.	• Active against most *Candida* species • Active against coccidioidomycosis and *C. neoformans* • *Candida* susceptibility testing is recommended and should guide treatment decisions	• *C. glabrata* is associated with variable resistance in vitro, *C. krusei* is intrinsically resistant, and *C. auris* is typically resistant • Inactive against molds (eg, *Aspergillus* spp., *Mucorales*)
Isavuconazonium sulfate[b]	Loading dose 372 mg IV/PO every 8 hours x 6 doses then maintenance dose 372 mg IV/PO daily	• Active against invasive aspergillosis and mucormycosis in patients with cancer and in HCT recipients[1,2,3]	• Can be considered in patients intolerant or refractory to first-line anti-mold therapy • May shorten QTc interval • Moderate inhibitor of CYP3A4, may be less clinically significant than voriconazole, itraconazole, or posaconazole
Itraconazole[b]	Loading dose 200 mg PO TID x 3 days, then maintenance dose 200 mg PO BID	• Active against *Candida, Aspergillus* spp., and some of the rarer molds • Active against dimorphic fungi and *C. neoformans* • *Candida* susceptibility testing is recommended and should guide treatment decisions	• Itraconazole has negative inotropic properties and is contraindicated in patients with significant cardiac systolic dysfunction • H2 blockers and proton pump inhibitors (PPIs) may inhibit absorption of capsule formulation. Oral liquid formulation is preferred for improved absorption. • SUBA-itraconazole has improved absorption

[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. QTc prolongation has been reported with all azole antifungals except isavuconazole. With broad use, antimicrobial-resistant organisms may emerge and may have implications for future activity of these agents.

[b] TDM is routinely used in managing itraconazole, posaconazole, and voriconazole. TDM is not routinely used for isavuconazole.

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References

ANTIFUNGAL AGENTS: AZOLES

Azoles as a class have important drug interactions, especially with the newer therapeutic agents. Please carefully review. Drug-drug interactions are common and need to be closely monitored (consult package inserts for details).

Azoles[a]	Dose	Spectrum	Comments/Cautions
Posaconazole[b]	Prophylaxis or treatment: ▸ IV injection and delayed-release (DR) tablet: Loading dose 300 mg DR tablet PO BID OR 300 mg IV BID on Day 1 and then maintenance dose 300 mg PO daily	• Effective as prophylaxis in patients with neutropenia with myelodysplastic syndrome and AML,[6] and in HCT recipients with significant GVHD[7] • Active against *Candida*, *Aspergillus* spp., some *Mucorales* spp., and some of the rarer molds • Active against dimorphic fungi and *C. neoformans* • Limited data for histoplasmosis	• Used for treatment of refractory infection (but not FDA-approved) in several invasive fungal diseases • Tablets are better absorbed and preferred, except in circumstances where alternative dosing is needed • IV posaconazole or alternative antifungal therapy should be considered for patients who cannot eat a full meal or tolerate an oral nutritional supplement • PPIs decrease posaconazole plasma concentration with oral suspension. Liquid formulation should be administered with a full meal or liquid nutritional supplement or an acidic carbonated beverage. • IV formulation should be used with caution in patients with significant renal dysfunction • FDA-approved for invasive aspergillosis
Voriconazole[b]	• Treatment of invasive aspergillosis[4] ▸ Loading dose: 6 mg/kg IV or 400 mg PO BID x 2 doses on Day 1 ▸ Maintenance: 4 mg/kg IV BID OR the following oral maintenance dosing ◊ ≥40 kg: 200 mg PO BID ◊ <40 kg: 100 mg PO BID • Treatment of candidemia in patients without neutropenia[5] ▸ Loading dose: 6 mg/kg IV or 400 mg PO BID x 2 doses on Day 1 ▸ Maintenance: 3–4 mg/kg IV BID OR the following oral maintenance dosing ◊ ≥40 kg: 200 mg PO BID ◊ <40 kg: 100 mg PO BID	• Active against *Candida, Aspergillus* spp., and some of the rarer molds • Active against dimorphic fungi and *C. neoformans* • Standard of care as primary therapy for invasive aspergillosis (category 1)[4,8] • Effective in candidemia in patients without neutropenia[5]	• Poor activity against *Mucorales* • Long-term complications 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 with an echinocandin remains limited[9] • IV formulation should be used with caution in patients with significant renal dysfunction • Visual disturbances and hallucinations may occur on therapy

[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. QTc prolongation has been reported with all azole antifungals except isavuconazole. With broad use, antimicrobial-resistant organisms may emerge and may have implications for future activity of these agents.

[b] TDM is routinely used in managing itraconazole, posaconazole, and voriconazole. TDM is not routinely used for isavuconazole.

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References

ANTIFUNGAL AGENTS: AMPHOTERICIN B FORMULATIONS[c]

Amphotericin B Formulations	Dose	Spectrum	Comments/Cautions
Amphotericin B deoxycholate (AmB-D)[d]	Varies by indication, generally 0.5–1.5 mg/kg IV daily	• Broad spectrum of antifungal activity including *Candida*, *Aspergillus* spp. (excluding *A. terreus*), *Mucorales*, rarer molds, *C. neoformans*, and dimorphic fungi • Several species of fungi may be intrinsically resistant to amphotericin (see Discussion) (eg, *Scedosporium, Lomentospora*)	• Substantial infusional and renal toxicity including electrolyte wasting • Saline loading may reduce nephrotoxicity • Infusional toxicity may be managed with antipyretics, an antihistamine, and meperidine (for rigors) • Slowing the rate of infusion is an additional way to manage amphotericin infusion reactions
Amphotericin B lipid complex (ABLC)	5 mg/kg IV daily		Reduced infusional and renal toxicity compared to AmB-D
Liposomal amphotericin B (L-AMB)	3–5 mg/kg IV daily[10,e]		

[c] Can be considered for prophylaxis with ID consult for appropriate dosing recommendations.
[d] AmB-D is not preferred whenever L-AMB or ABLC is available.
[e] In patients who are highly immunocompromised, 3 mg/kg liposomal amphotericin B was just as effective against aspergillosis compared to 10 mg/kg with significantly less toxicities. Optimal dosing for mucormycosis may require higher dosing based on other literature.

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References

ANTIFUNGAL AGENTS: ECHINOCANDINS

Echinocandins[9,f]	Dose	Spectrum	Comments/Cautions
Anidulafungin	200 mg IV x 1 dose, then 100 mg/IV daily	• Primary therapy for candidemia and invasive candidiasis (category 1)[11] • *C. auris* may be resistant to echinocandins • May be used as part of a second-line or subsequent regimen for invasive aspergillosis • Not reliable or effective against most other fungal pathogens (eg, *Trichophyton, Cryptococcus, Mucorales*)	• Echinocandins have poor CNS, urinary tract, and eye penetration • 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 second-line therapy		
Micafungin	• 100 mg IV daily for candidemia and 50–100 mg/d IV as prophylaxis • 150 mg IV daily used at some centers for *Aspergillus* spp. infection as second-line therapy		

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

References

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ANTIFUNGAL AGENTS – REFERENCES

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ANTIVIRAL AGENTS[a]

Agent	Typical Dosing Based on Indication[c]	Spectrum	Comments/Cautions
Acyclovir[b]	• Prophylaxis[d]: HSV (400–800 mg PO BID); VZV in allogeneic HCT recipients (400–800 mg PO BID)[1] • Post-VZV exposure prophylaxis: 800 mg PO 5 times daily • Treatment: Significant mucocutaneous HSV (5 mg/kg IV every 8 h for 7–10 d); single dermatomal VZV (800 mg PO 5 times daily or 10 mg/kg IV every 8 h for 7–10 d); disseminated HSV or VZV including viral encephalitis (10 mg/kg IV every 8 h)[2]	HSV VZV	• Hydration to avoid crystal nephropathy with high dose • Dosing based on ideal body weight
Famciclovir	• Prophylaxis: HSV or VZV (250 mg PO BID) • Treatment: HSV (250 mg PO TID) or VZV (500 mg PO TID)[3,4]	HSV VZV	No data for oncologic-related prophylaxis
Ganciclovir	• Preemptive therapy for CMV: 5 mg/kg every 12 h; if CMV remains detectable, further ID evaluation may be required • Treatment: CMV disease (5 mg/kg every 12 h for induction followed by 5 mg/kg daily for maintenance and resolution of all symptoms)	CMV HSV VZV	• May cause bone marrow suppression • Clinical data are limited for HHV-6 and HHV-8
Valacyclovir[b]	• Prophylaxis[d]: HSV or VZV (500 mg PO BID) preferred over oral acyclovir for VZV • Treatment: HSV or VZV (1 g PO TID)[2] preferred over oral acyclovir for HSV or VZV	HSV VZV	
Valganciclovir	• Preemptive therapy and treatment for CMV: Induction with 900 mg PO BID for induction and until negative test; consider additional 900 mg PO daily for maintenance after a negative test	CMV HSV VZV	• May cause bone marrow suppression • Clinical data are limited for HHV-6 and HHV-8

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Footnotes and References FEV-C (4 of 4)

ANTIVIRAL AGENTS[a]

Agent	Typical Dosing Based on Indication[c]	Spectrum	Comments/Cautions
Cidofovir	• 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. • Evidence is limited for treatment of adenovirus; when used, ID consult is strongly recommended.	CMV HSV VZV Adenovirus	• Hydration and probenecid required to reduce nephrotoxicity • Ocular toxicity, bone marrow toxicity
Foscarnet	• Prophylaxis for CMV: 60 mg/kg IV every 8–12 h for induction, followed by 90–120 mg/kg IV daily for maintenance after HCT.[5,6] • Preemptive therapy for CMV: Induction; 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 induction followed by 90–120 mg/kg daily for maintenance and resolution of all symptoms).	HSV VZV CMV HHV-6	Drug of choice for acyclovir-resistant HSV and VZV and ganciclovir-resistant CMV • Nephrotoxic; monitor electrolytes Clinical data are limited for HHV-6 and HHV-8. Treatment should be reserved for clinically documented disease; ID consult is highly recommended.
Letermovir	• Primary prophylaxis for allogeneic HCT recipients who are CMV seropositive (R+): 480 mg PO daily or daily IV infusion over 1 h post-transplantation. Reduce dose to 240 mg PO/IV daily if co-administered with cyclosporine.	CMV	• Has not been studied as an agent for treatment • Has multiple drug interactions, including azoles, cyclosporine, and tacrolimus; see package insert (TDM is important) • Not active against other herpes group viruses. Acyclovir is also needed for HSV and VZV.
Maribavir	• Treatment: 400 mg PO BID	CMV	• Indicated for post-transplant CMV infection refractory to ganciclovir/valganciclovir, foscarnet, and cidofovir. ID consult is highly recommended. • No activities against HSV, VZV, or HHV-6 • Inhibitor of HCMV-encoded kinase UL97 • Virologic failure due to resistance can occur and cross-resistance between maribavir and ganciclovir/valganciclovir has been observed • Not recommended to be co-administered with ganciclovir/valganciclovir • Monitor for drug interactions (may increase level of immunosuppressants such as cyclosporine, tacrolimus, sirolimus, etc.) • May cause dysgeusia
Baloxavir[e]	• Treatment: 40 mg or 80 mg PO based on weight	Influenza A & B	• There are limited data for use in patients who are immunosuppressed. • Data show an emergence of resistance in people who are healthy.
Oseltamivir[f]	• Prophylaxis: 75 mg PO daily[g,7] • Treatment: 75 mg BID (typically for 5 days)	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

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Footnotes and References FEV-C (4 of 4)

ANTIVIRAL AGENTS

Agent	Common Indication[c]	Spectrum	Comments/Cautions
Intravenous immuno-globulin (IVIG)	Doses of IVIG vary among different studies and different viral illnesses. Some data exist for use in the following: • Parvovirus B19,[8] 400–500 mg/kg IV daily for 5 days • Adjunctive therapy for CMV and RSV pneumonitis, 400 mg/kg IV every other day for 3–5 doses	RSV Parvovirus B19 CMV	• Pathogen-specific immunoglobulin or monoclonal antibodies may be considered. • CMV-specific IVIG is not more efficacious than standard IVIG. IVIG use as an antiviral is controversial.
Ribavirin (category 3)	Consider for treatment of lower respiratory tract RSV disease[h,9,10]: • 600–800 mg PO BID or TID • 6 gm administered by continuous inhalation via SPAG-2 nebulizer over 12–18 h daily or 2 g over 2 h TID	RSV	• Limit to patients undergoing HCT or with leukemia. • Experience in adults who are immunocompromised with RSV disease is limited. Ribavirin is teratogenic; precautions are required during administration (see package insert).
Entecavir	0.5 mg PO daily (nucleoside-treatment-naïve with compensated liver disease); or 1 mg PO daily (lamivudine-refractory or known lamivudine-resistant mutations or decompensated liver disease)	HBV	• Entecavir and tenofovir monotherapy are generally preferred. Choice of agent is heavily influenced by the overall condition of the patient, renal insufficiency, and the type of chemotherapy planned. Combination therapy is not generally recommended unless viral load is significantly elevated. • 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 (TDF more than TAF) has potential for nephrotoxicity; monitor for renal function
Lamivudine	100 mg PO daily		
Tenofovir	Tenofovir disoproxil fumarate (TDF) 300 mg PO daily Tenofovir alafenamide (TAF) 25 mg PO daily		

Footnotes and References
FEV-C (4 of 4)

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ANTIVIRAL AGENTS – FOOTNOTES

[a] Requires dose adjustment in patients with renal insufficiency.
[b] 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.
[c] Dosing is for adult patients. Consult pediatric guidelines for recommended dosing in these patients.
[d] Antiviral prophylaxis should be targeted to specific patients at high risk (INF-3). In patients who are at high risk and not receiving transplant, 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, in patients with renal impairment, and in patients with obesity. Prophylactic antiviral doses may be higher than those routinely used in persons who are immunocompetent (eg, 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.
[e] Not routinely recommended by the CDC
[f] Consider IV peramivir for patients who cannot have oral oseltamivir or inhaled zanamivir.
[g] During community and nosocomial outbreaks of influenza A, prophylaxis among persons who are highly immunocompromised should be considered.
[h] Inhaled ribavirin is only FDA approved for infants and young children who are hospitalized with severe lower respiratory tract RSV disease.

ANTIVIRAL AGENTS – REFERENCES

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RISK ASSESSMENT RESOURCES

Using the Multinational Association for Supportive Care in Cancer (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[1,2]

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

CISNE Score/Model[3]

Characteristic	Points
ECOG PS ≥2	2
Stress-induced hyperglycemia	2
COPD	1
Chronic cardiovascular disease	1
Mucositis NCI grade ≥2	1
Monocytes <200/µL	1

[1] The MASCC Risk-Index Score is for adults only. It does not apply to pediatric patients.

[2] Klastersky J, Paesmans M, Rubenstein EJ, et al. The Multinational Association for Supportive Care in Cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. J Clin Oncol 2000;18:3038-3051.

[3] Carmona-Bayonas A, Jimenez-Fonesca P, Virizuela Echaburu J, et al. Prediction of serious complications in patients with seemingly stable febrile neutropenia: validation of the Clinical Index of Stable Febrile Neutropenia in a prospective cohort of patients from the FINITE study. J Clin Oncol 2015;33:465-471.

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TABLE 1: SARS-COV-2 TESTING INTERPRETATION AND INFECTIVITY IN PATIENTS WITH CANCER

The following table is recommended for interpreting SARS-CoV-2 PCR/antigen testing for patients considered to be moderately/severely immunocompromised. These patients may produce replication-competent virus beyond 20 days. Ending isolation in conjunction with consultation of an ID specialist is recommended.

Asymptomatic	Discontinue isolation at **Day 20** OR Two negative consecutive respiratory specimens collected ≥24 hours apart if within 20 days
Symptomatic at time of original COVID-19 diagnosis	Resolution of fever for at least 24 hours without fever-reducing medication + Improvement of symptoms + **20 days** since symptom onset OR two negative consecutive respiratory specimens collected ≥24 hours
Continued symptoms on or after day 20 OR symptoms worsening after ending isolation (reactivation of symptoms)	Recommend repeat SARS-CoV-2 testing and consider consultation with an ID specialist

- **Detection of sub-genomic SARS-CoV-2 RNA or recovery of replication-competent virus has been reported in patients who are moderately or severely immunocompromised beyond 20 days, and as long as >140 days after a positive SARS-CoV-2 test result. Patients who recover from COVID-19 can continue to have detectable SARS-CoV-2 RNA and upper respiratory symptoms for up to 3 months after illness onset. However, prolonged detection of viral RNA may not indicate higher infectious risk and risk of transmission. If a patient has persistently positive nucleic acid amplification tests beyond 30 days, additional testing could include molecular studies, determination of PCR cycle threshold (Ct), or attempt to identify replication of the competent virus in conjunction with ID consultation.**
- **Immunocompromising conditions that have been associated with shedding of replication-competent virus beyond 20 days include active treatment for solid tumor and hematologic malignancies, solid organ transplant and taking IST, receipt of CAR T-cell therapy or HCT (within 2 years of transplantation or taking immunosuppression therapy), moderate or severe primary immunodeficiency, and active treatment with high-dose corticosteroids (ie, ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, and other biologic agents that are immunosuppressive or immunomodulatory.**

Table 1 References (COV-A 1 of 3)

Note: All recommendations are category 2A unless otherwise indicated.
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TABLE 2: CONSIDERATIONS FOR CANCER-DIRECTED THERAPY IN PATIENTS WITH POSITIVE SARS-COV-2

- **Duration of delaying the cancer-directed therapy depends on the severity of clinical SARS-CoV-2 infection (ie, mild, moderate, severe, asymptomatic), type and status of malignancy, risk of cancer relapse and progression as a result of delaying therapy, comorbidities, type and intensity of treatment, and adverse effects of treatment regimen.**
- **If cancer-directed therapy is urgently required due to uncontrolled cancer, it should be administered at the judgment of the oncologist.**

COVID-19 Severity[a]	High Risk for Progression of COVID-19	Cancer-Directed Therapy	General Recommendations for Timing of Initiation or Resumption of Cancer-Directed Therapy[c]
Patients who are hospitalized with severe to critical COVID-19	N/A	Any	• If feasible, hold therapy for at least 20 days and until improvement of symptoms and at least 24 hours have passed since resolution of fever without use of fever-reducing medications.
Mild to moderate COVID-19 or asymptomatic positive SARS-CoV-2[b]	• Prolonged neutropenia • T-cell deficiency (lymphopenia) or dysfunction • Hematologic malignancy • Tumor pulmonary involvement See complete listing of underlying medical conditions posing higher risk for severe COVID-19 at: Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19.	Cytotoxic therapy directed at lymphocytes	• If feasible, hold therapy for at least 14 days and until improvement of symptoms and at least 24 hours have passed since resolution of fever without use of fever-reducing medications. • If the patient remained asymptomatic, hold therapy for at least 10 days after the date of the first positive test.
		• Prior to planned HCT • Prior to planned CAR T-cell therapy	• If feasible, hold therapy for at least 14 days and until improvement of symptoms and at least 24 hours have passed since resolution of fever without use of fever-reducing medications; or if the patient remained asymptomatic, hold for at least 14 days after the date of the first positive test.
		• Targeted therapy • Long-acting biologic therapy • Immune checkpoint inhibitors • Radiation therapy • Immune therapy • Hormonal therapy	• Consider holding therapy for at least 10 days and until improvement of symptoms and at least 24 hours have passed since resolution of fever without use of fever-reducing medications. • If the patient remained asymptomatic, hold therapy for 10 days after the date of the first positive test.

[a] Mild illness is defined as patients with signs and symptoms of COVID-19 (eg, fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging. Moderate illness is defined as patients with lower respiratory disease during clinical assessment or imaging and an oxygen saturation (SpO_2) ≥94% on room air. Severe illness is defined as patients with SpO_2 <94% on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%, including patients on supplemental oxygen, oxygen through a high-flow device, or noninvasive ventilation. Critical illness is defined as patients with respiratory failure, septic shock, and/or multiple organ dysfunction, including patients on mechanical ventilation and extracorporeal mechanical oxygenation (ECMO) and end-organ dysfunction.

[b] Some providers delay cancer-directed therapy for shorter periods of time among patients who are asymptomatic who test positive for SARS-CoV-2.

[c] If feasible, consider doing test-based strategy with two negative tests separated by 24 hours.

Table 2 References (COV-A 1 of 3 and COV-A 2 of 3)

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TABLE 2: CONSIDERATIONS FOR CANCER-DIRECTED THERAPY IN PATIENTS WITH POSITIVE SARS-COV-2 (CONTINUED)

COVID-19 Severity[a]	High Risk for Progression of COVID-19	Cancer-Directed Therapy	General Recommendations for Timing of Initiation or Resumption of Cancer-Directed Therapy
Mild to moderate COVID-19 or asymptomatic positive SARS-CoV-2 (cont.)	No high-risk factors	• Targeted therapy • Long-acting biologic therapy • Immune checkpoint inhibitors • Radiation therapy • Immune therapy • Hormonal therapy	• Consider holding therapy for at least 10 days and until improvement of symptoms and at least 24 hours have passed since resolution of fever without use of fever-reducing medications. • If the patient remained asymptomatic, hold therapy for 10 days after the date of the first positive test.

[a] Mild illness is defined as patients with signs and symptoms of COVID-19 (eg, fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging. Moderate illness is defined as patients with lower respiratory disease during clinical assessment or imaging and an SpO_2 ≥94% on room air. Severe illness is defined as patients with SpO_2 <94% on room air, a ratio of PaO_2/FiO_2 <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%, including patients on supplemental oxygen, oxygen through a high-flow device, or noninvasive ventilation. Critical illness is defined as patients with respiratory failure, septic shock, and/or multiple organ dysfunction, including patients on mechanical ventilation and ECMO and end-organ dysfunction.

Table 2 References (COV-A 1 of 3 and COV-A 2 of 3)

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TABLE 3: CONSIDERATIONS FOR CANCER-DIRECTED THERAPY IN PATIENTS WITH SIGNIFICANT EXPOSURE TO SARS-COV-2

- **The exact risk of viral transmission after significant exposure to SARS-CoV-2 is unknown and depends upon many variables (eg, symptoms of infected person, duration and proximity of contact, room ventilation, host susceptibility, viral variant). Household contacts pose the highest risk of SARS-CoV-2 transmission.**
- **If viral transmission occurs to the patient, the upper bound of COVID-19 incubation period is 14 days.**
- **The duration of cancer-directed therapy delay depends on the type and status of malignancy and risk of cancer relapse and progression as a result of delaying therapy. If cancer-directed therapy is urgently required due to uncontrolled cancer, it should be administered at the judgment of the oncologist.**

Significant Exposure to SARS-CoV-2[d] Recommendations
• Cancer-directed therapy of patients who are asymptomatic who have had a significant exposure to SARS-CoV-2 should be delayed for 14 days since exposure. • While the Centers for Disease Control and Prevention (CDC) does not recommend quarantine or routine empiric transmission-based isolation precautions of people who have been exposed, patients who are immunocompromised who are at high risk for severe COVID-19 (Table 2) and have had a significant exposure to a person with known SARS-CoV-2 infection should consider quarantining for 14 days after last exposure. • During the quarantine period, these patients should be masked and closely monitored for development of symptoms.

Table 2 References (COV-A 1 of 3 and COV-A 2 OF 3)

[d] Per CDC definition, significant SARS-CoV-2 exposure is defined as a patient who has had a close contact (within 6 feet for a total of 15 minutes or more in 24 hours) with a person known to be infected with SARS-CoV-2. More infectious agents are likely to require lesser exposure time for transmission.

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COVID-19 MANAGEMENT IN PATIENTS WITH CANCER

- **The heterogeneity of cancers, the complexity and number of different cancer treatment regimens, and variability in the COVID-19 clinical course among patients preclude a single management approach of COVID-19 in all patients with cancer.**
- **Treatment recommendations for COVID-19 among patients with cancer are largely similar to those without cancer (see Table 3); however, several new therapies have become available that demonstrate corresponding benefits for patients with cancer and/or other risk factors for more severe disease.**
- **Table 4 lists currently available COVID-19 treatment options, dosing, and clinical indications.**
- **Comprehensive information on COVID-19–based testing, infection control measures, and evidence-based data for current treatment recommendations can be accessed at: The Centers for Disease Control and Prevention and Infectious Disease Society of America, COVID-19 Guidelines.**
- **For unresolved COVID-19, ID consult is recommended.**

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TABLE 4: COVID-19 TREATMENT IN PATIENTS WITH CANCER[e]

Clinical Scenario	Antiviral Options	Comments
• Outpatient with acute infection, recent symptom onset, and high risk of progression: ▸ Prolonged neutropenia ▸ T-cell deficiency (lymphopenia) or dysfunction ▸ Hematologic malignancy ▸ Tumor pulmonary involvement ▸ See complete list of underlying medical conditions posing higher risk for severe COVID-19 by the CDC: Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19 • See Table 2: Considerations for Cancer-Directed Therapy in Patients with Positive SARS-CoV-2	Preferred • Nirmatrelvir/ritonavir[1] • Remdesivir[2] Other • Molnupiravir[3] • High-titer COVID-19 convalescent plasma[4,f,g,h]	• Nirmatrelvir/ritonavir is the favored oral treatment for outpatients with mild to moderate COVID-19 symptoms who are at highest risk of progressing to severe disease and who do not have adverse drug-drug interactions with ritonavir. ▸ Nirmatrelvir/ritonavir use has been shown to reduce risk of hospitalization and death by up to 88%.[5] ▸ Must review potential drug interactions with ritonavir before use. • IV remdesivir is favored when oral nirmatrelvir/ritonavir is not available or suitable because of adverse drug interactions. ▸ 3-day course IV remdesivir has been shown to reduce the risk of hospitalization and death by up to 87%.[2] ▸ Requires IV administration in an infusion center, emergency department, or outpatient clinic; may limit feasibility in outpatient setting. • Oral molnupiravir has decreased efficacy for reducing hospitalization and death (30%)[3] compared with other treatment options, and concerns exist for potential mutagenicity in animal studies. ▸ It is unclear if molnupiravir is a teratogen; however, it is not recommended for use in patients who are pregnant. ▸ Please see Table 5 for recommendations regarding the use of contraception. • High-titer COVID-19 convalescent plasma is under evaluation in the outpatient setting and has been shown to reduce outpatient hospitalizations by >50%.[4] ▸ High-titer COVID-19 convalescent plasma against prevalent circulating viral variants may not be uniformly available and requires transfusion capacity by a local center. • Post-treatment recurrence of symptoms should be treated as a new possible infection with an appropriate evaluation.

[e] This is a rapidly changing field. For links to routinely updated guidance, see the Centers for Disease Control and Prevention and Infectious Diseases Society of America guidelines for updated information: CDC and IDSA.

[f] Antibody therapy should not be used as an alternative to COVID-19 vaccination. COVID-19 vaccination can be given at any interval following receipt of passive antibody therapy. Note that COVID-19 vaccination status should not affect decisions regarding the use or timing of antibody therapy for treatment of breakthrough COVID-19 disease. All mAb FDA approvals have been suspended due to emergence of viral resistance as availability of mAb for treatment depends on susceptibility to circulating strains.[5,6]

[g] COVID-19 convalescent plasma obtained from those who have recovered from the recent circulating variants and have been previously vaccinated is preferred. COVID-19 convalescent plasma can be acquired via the Blood Centers of America.

[h] There is emerging evidence that high-titer COVID-19 convalescent plasma may be beneficial in patients who are immunocompromised (particularly with B-cell impairment) with persistent SARS-Cov-2 infection.

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Table 4 References (COV-A 3 of 3)

TABLE 4: COVID-19 TREATMENT IN PATIENTS WITH CANCER (CONTINUED)[e]

Clinical Scenario	Antiviral Options	Comments
Patient hospitalized for non–COVID-19 indication but with acute symptomatic COVID-19	Preferred • IV remdesivir[2] Other • COVID-19 convalescent plasma[4,f,g,h]	• IV remdesivir x 3 days (extending to 5 days can be considered for patients with more significant disease or concurrent immunosuppression). • Consider high-titer COVID-19 convalescent plasma. Pre-BA[4,5] plasma may not be as effective.[f] ▸ High-titer COVID-19 convalescent plasma active against circulating viral variants may not be uniformly available and requires transfusion capacity by a local center. • Although a mechanistic rationale exists for use of oral antivirals, they are currently not authorized by the FDA for use in patients who are hospitalized.
Patient hospitalized for acute symptomatic COVID-19	Preferred • IV remdesivir x 5 days[6,7] Other • Consider COVID-19 convalescent plasma if meets criteria per treatment benefit index (TBI)[8] or hematologic malignancy.[f] There is emerging evidence that high-titer COVID-19 convalescent plasma may be beneficial in patients who are immunocompromised (particularly with B-cell impairment) with persistent SARS-Cov-2 infection.[f]	• Mild to moderate COVID-19 disease (Table 2) ▸ IV remdesivir x 5 days • Severe COVID-19 disease (Table 2) ▸ IV remdesivir x 5 days with dexamethasone ◊ Although investigational (not standard of care), consider extending remdesivir duration to 10 days for patients hospitalized for COVID-19 if PCR Ct is still low after 5 days and the patient remains symptomatic or is not improving. ▸ The benefit of adding IV remdesivir to dexamethasone in patients who require mechanical ventilation or ECMO is unclear, although completion of 5 days of remdesivir is favored if already started before admission to intensive care unit (ICU). • A second immunomodulatory agent (eg, IL-6 inhibitor, JAK inhibitor) is often added for patients with rapidly or progressively declining oxygen saturation (SpO_2) (Table 2). ▸ Use of IL-6 inhibitor and JAK inhibitor is generally avoided in combination, in patients with uncontrolled active infection (bacterial, fungal, mycobacterial, or non-SARS-CoV-2 viral), or in patients with significant concurrent immunosuppression (eg, neutropenia, antineoplastic chemotherapy). ▸ Further details of immunomodulatory therapeutic options and indications for patients with moderate to severe COVID-19 are available on the NIH and IDSA COVID-19 websites.[5,9] • Additional information for COVID-19 convalescent plasma use is available at: https://covid-convalescentplasma-tbi-calc.org.

Table 4 References (COV-A 3 of 3)
Table 4 Footnotes (COV-6)

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TABLE 4: COVID-19 TREATMENT IN PATIENTS WITH CANCER (CONTINUED)[e]

Clinical Scenario	Antiviral Options	Comments
Persistent symptomatic COVID-19 infection; particularly B-cell impairment	Remdesivir or nirmatrelvir/ritonavir. Immunotherapy (COVID-19 convalescent plasma) may be added in combination.	• There are no uniform treatment recommendations, but clinical investigational approaches include use of: ▸ High-titer COVID-19 convalescent plasma[10,11] • To determine potential benefit of COVID-19 convalescent plasma, some providers (via clinical investigational approach) will first check: ▸ SARS-CoV-2 antibodies to nucleocapsid antigens to confirm lack of adequate humoral response post-infection ▸ Viral load burden by PCR after ID consult • Consider avoiding molnupiravir due to concerns for risk of producing escape viral mutants.
Persistent asymptomatic SARS-CoV-2–positive testing	Unclear if therapy indicated	• Clinical significance and role for supplemental therapy remain unclear. • SARS-CoV-2 RT-PCR testing does not distinguish replication-competent and infectious virus (eg, growth in cell-line culture) from inactive virus. ▸ In a prior review of 28 studies, the pooled median duration of RNA shedding from respiratory sources was 18.4 days with wide heterogeneity (range, 1–63 days) and relatively little difference based on disease severity.[12,13] ▸ Prolonged SARS-CoV-2 detection of replication of the competent virus (>100 days) has been reported in patients who are immunocompromised and has often been associated with a weak or absent antibody response to the virus.[14,15] • Clinical decisions can be influenced by viral load interpretation (PCR Ct), patient immunologic status, cancer response/lack of response to current therapeutics, etc.
Pre-exposure prophylaxis	None	• Please see the CDC for Use of COVID-19 Vaccines in the United States for more information.

Table 4 References (COV-A 3 of 3)

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TABLE 5: COVID-19 TREATMENT OPTIONS[i]

Treatment	Dosing/Duration	Comments
Antiviral Agents		
Remdesivir	• 200 mg IV on day 1; followed by 100 mg IV daily on days 2–5	• A nucleoside analogue that inhibits SARS-CoV-2 replication by interfering with the viral RNA-dependent RNA polymerase • 5-day treatment for patients who are hospitalized with symptomatic COVID-19 • 3-day treatment for patients who are not hospitalized with mild to moderate disease and high risk of disease progression within 7 days of symptom onset • If the patient is hospitalized for reasons other than severe COVID-19, give a 3-day course of remdesivir to inpatients incidentally diagnosed with COVID-19 who are at high risk for disease progression. • Avoid if ALT >10 x ULN or ALT elevated with signs of active hepatitis. • Can be extended up to 10 days
Nirmatrelvir/ ritonavir	• 300 mg nirmatrelvir / 100 mg ritonavir orally twice daily for 5 days • Renal impairment (estimated glomerular filtration rate [eGFR] eGFR <60 to ≥30 mL/ min): 150 mg nirmatrelvir / 100 mg ritonavir twice daily for 5 days • Avoid with severe renal impairment (eGFR <30 mL/min) • Avoid with severe hepatic (Child-Pugh Class C) impairment	• A SARS-CoV-2 protease inhibitor; ritonavir boosts plasma nirmatrelvir concentrations through hepatic cytochrome 3A inhibition • Review potential for drug-drug interactions. Co-administration of ritonavir is contraindicated for many drugs. • For outpatient use only • Start within 5 days of symptom onset. • Ritonavir is a weak HIV protease inhibitor and may lead to HIV protease inhibitor resistance in uncontrolled HIV infection.
Molnupiravir	800 mg orally twice daily for 5 days	• A nucleoside analogue that causes replication failure of SARS CoV-2 replication by lethal mutagenesis • For outpatient use only • Start within 5 days of symptom onset. • Use only when nirmatrelvir and remdesivir are not available. • May cause fetal harm. Patients who may become pregnant should use reliable contraception during therapy and for 4 days after the last dose of molnupiravir. Sexually active males with partners who may become pregnant should also use effective contraception during therapy and for at least 3 months after the last molnupiravir dose.

[i] Dosing is for adults only. For pediatric dosing, consult with pharmacist. See CDC and American Academy of Pediatrics (AAP).

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Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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

ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
ADV	adenovirus
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AML	acute myeloid leukemia
BAL	bronchoalveolar lavage
BCMA	B-cell maturation antigen
CAR	chimeric antigen receptor
CBC	complete blood count
CDI	*Clostridioides difficile* infection
CISNE	clinical index of stable febrile neutropenia
CLL	chronic lymphocytic leukemia
CMV	cytomegalovirus
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CPK	creatine phosphokinase
CrCl	creatinine clearance
CRS	cytokine release syndrome
Ct	cycle threshold
CTLA-4	cytotoxic T-lymphocyte–associated antigen 4
DFA	direct fluorescence antibody
DR	delayed release
DTaP	diphtheria, tetanus, and acellular pertussis
ECMO	extracorporeal mechanical oxygenation
eGFR	estimated glomerular filtration rate
ENT	ear, nose, and throat
ESBL	extended-spectrum beta-lactamase
FiO_2	fraction of inspired oxygen
FRα	folate receptor alpha
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
GI	gastrointestinal
GVHD	graft-versus-host disease
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCT	hematopoietic cell transplant
HCV	hepatitis C virus
HHV	human herpes virus
Hib	haemophilus influenzae type b
HIV	human immunodeficiency virus
HPV	human papillomavirus
HSV	herpes simplex virus
HZ	herpes zoster
H&P	history and physical
ICU	intensive care unit
ID	infectious disease
IL-6	interleukin-6
irAE	immune-related adverse event
IST	immunosuppressive therapy
IVIG	intravenous immunoglobulin
mAb	monoclonal antibody
MDRO	multidrug-resistant organism
MDS	myelodysplastic syndromes
MenACWY	meningococcal conjugate vaccine, quadrivalent
MMR	measles, mumps, rubella
MRSA	methicillin-resistant *Staphylococcus aureus*
NAAT	nucleic acid amplification testing
NG	nasogastric
PaO2	partial pressure of oxygen
PCR	polymerase chain reaction
PCV	pneumococcal conjugate vaccine
PD-1	programmed cell death protein 1
PD-L1	programmed death ligand 1
PJP	*pneumocystis jirovecii* pneumonia
PML	progressive multifocal leukoencephalopathy
PPI	proton pump inhibitor
PPSV23	pneumococcal polysaccharide vaccine
RCC	renal cell carcinoma
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase polymerase chain reaction
RZV	recombinant zoster vaccine
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SSRI	selective serotonin reuptake inhibitor
STI	sexually transmitted infection
SpO_2	oxygen saturation
TB	tuberculosis
TBI	treatment benefit index

ABBREVIATIONS

Td	**tetanus-diphtheria**
Tdap	**tetanus, diphtheria, pertussis**
TDM	**therapeutic drug monitoring**
ULN	**upper limit of normal**
VADs	**vascular access devices**
VEGF	**vascular endothelial growth factor**
VOD	**veno-occlusive disease**
VRE	**vancomycin-resistant enterococci**
VZV	**varicella zoster virus**
ZVL	**herpes zoster vaccine**

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 indicated.

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Prevention and Treatment of Cancer-Related Infections

Discussion

This discussion corresponds to the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
Last updated September 23, 2024.

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NCCN Guidelines Version 3.2024
Prevention and Treatment of Cancer-Related Infections

Overview

There is an increased risk of infection in patients with cancer that results in higher morbidity and mortality. In certain instances, the malignancy itself can predispose patients to severe or recurrent infections. Neutropenia has been recognized as a major risk factor for the development of infections in patients with cancer undergoing chemotherapy. Effective strategies to anticipate, prevent, and manage these infectious complications have led to improved outcomes.[1-4] Due to advances in antimicrobial therapy, it is less common for patients with acute leukemia or patients undergoing hematopoietic cell transplantation (HCT) 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 HCT recipients with neutrophil recovery who require intensive immunosuppressive therapy (IST) for graft-versus-host disease (GVHD) are an example of patients who do not have neutropenia, but are at great risk for common bacterial, viral, and opportunistic infections.[5-8] The spectrum of infectious diseases in allogeneic HCT recipients with GVHD is distinct from neutropenia. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prevention and Treatment of Cancer-Related Infections discuss infections in patients who are neutropenic and immunocompromised non-neutropenic with cancer. In addition to corticosteroids and purine analogs, the increased use of monoclonal antibodies, proteasome inhibitors, and other emerging cancer therapeutics like CAR-T cell therapy has generated an ever more complex assessment of those who are immunocompromised. The scope of these guidelines is to address infections that may be seen in all of these immunocompromised populations.

The NCCN Guidelines® for the Prevention and Treatment of Cancer-Related Infections characterize the major pathogens to which patients with cancer are susceptible, with a focus on the prevention, diagnosis, and treatment of major common and opportunistic infections. The guidelines are largely divided into 5 sections comprising discussions on the following: 1) risk factors for infection (major host factors that predispose patients to infectious diseases); 2) prevention of infectious complications (including the use of antimicrobial prophylaxis and preemptive therapy); 3) infection concerns and recommendations regarding immune and targeted treatments; 4) management of neutropenic fever; and 5) management of site-specific infections (eg, pneumonia, abdominal infections, catheter-associated infections). These guidelines provide a framework for prevention and treatment of infections that 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. Additionally, the guidelines are based primarily on studies with adult patients and application of these recommendations to pediatric patients may differ. Consultation with an infectious disease expert is highly recommended.

Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Literature Search Criteria

Prior to the update of this version of the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections, an electronic search of the PubMed database was performed to obtain key literature in Prevention and Treatment of Cancer-Related Infections published since the previous Guidelines updates, using the following search terms: cancer related infections; cancer infections; cancer induced infections; prevention of cancer related infections; cancer and virus; cancer and bacterial; cancer and fungal; cancer and microbial; cancer and hepatitis; cancer and influenza; cancer and candida; cancer and aspergillus; cancer and

clostridium; cancer and staphylococcus; cancer and pseudomonas; cancer and pneumocystis; cancer and herpes; cancer and varicella zoster; or cancer and HIV. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[9]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; Validation Studies; and Practice Guidelines.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines and discussed by the Panel have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation.[10] NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

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 lymphomas [NHL], myelodysplastic syndromes [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*.[11] 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[12] noted a biphasic pattern of infection among patients with multiple myeloma. Infections by *Streptococcus pneumoniae* and *Haemophilus influenzae* occurred early in the disease and in patients with disease that responds 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 on earlier lines of therapy. Refractory hematologic malignancies can be associated with marrow failure caused by the underlying disease or from the multiple lines of prior cytotoxic therapy or IST. Patients with CLL who receive multiple chemotherapeutic

regimens are at a significantly increased risk of developing severe infections.[13] A retrospective study showed that nearly 90% of patients who are heavily pretreated (median number of prior regimens, 3; range, 1–8) with fludarabine-refractory CLL experienced serious infectious complications requiring hospitalization.[14] These infections resulted from bacterial, viral, fungal, and opportunistic pathogens, including *Pneumocystis jirovecii* (formerly called *Pneumocystis carinii)*.[14]

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, hepatobiliary reconstruction), the extent of tumor burden, their preoperative performance status, and any previous surgery, chemotherapy, or radiation therapy. Patients with advanced malignancy are also commonly malnourished, which further increases the risk of infection.

Neutropenia

Factors that predispose the patients who are neutropenic to infection include 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. The signs and symptoms of infection are often absent or muted in the absence of neutrophils, but fever remains an early, although nonspecific, sign.[2] Approximately 50% to 60% of patients who become febrile have an established or occult infection.[15] Roughly 10% to 20% of patients with neutrophil counts <100 cells/mcL will develop a bloodstream infection.[16] Primary sites of infection are the alimentary tract (ie, mouth, pharynx, esophagus, large and small bowel, 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.[17,18] 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* (*P aeruginosa*) are the most common gram-negative infections complicating neutropenia.[17] Herpes simplex virus (HSV), respiratory syncytial virus (RSV), parainfluenza, and influenza A and B are occasionally initial pathogens.[18] 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 important causes of morbidity and mortality in patients with severe and prolonged neutropenia.[17,19] 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.

A seminal study demonstrated that as the neutrophil count decreases to <500 cells/mcL (defined as *neutropenia*), the susceptibility to infection increases.[20] 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 <100 cells/mcL. The rate of decline of the neutrophil count and the duration of neutropenia are also critical factors that measure 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. Mucosal immunity is impaired by chemotherapy and radiation therapy. When the physical protective barrier conferred by the epithelial lining is compromised, local flora may invade. Furthermore, 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,[21-24] gram-negative rods, and *Candida* species.[25,26]

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.[27] Thus, in allogeneic HCT 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 principal risk factor for infection in patients who are asplenic. The most common pathogen is *Streptococcus pneumoniae*, but other pathogens include *H influenzae* and *Neisseria meningitidis.* The NCCN Guidelines provide recommendations for immunization with the pneumococcal polysaccharide and meningococcal vaccines (see *Vaccination*).

Corticosteroids and Other Immunosuppressive Agents

While many agents administered to patients with cancer can cause some degree of immunosuppression, certain agents (detailed in this section) are more likely to put patients at a risk for serious infection. When assessing a possible infection, it is important to note that many of the newer immunotherapies (eg, nivolumab, ipilimumab, pembrolizumab) can cause inflammation-related side effects that may be mistaken for infection.

Corticosteroids

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, coexisting immunodeficiencies (such as neutropenia and use of other immunosuppressive agents), and the status of the malignancy. Corticosteroids blunt fever and local signs of infection, such as peritonitis.

Purine Analogue Therapies

Purine analogues (including fludarabine, clofarabine, nelarabine, and cladribine [2-CdA]) are used to treat a variety of hematologic malignancies. These therapies are lymphocytotoxic, primarily affecting CD4+ lymphocytes. In previously treated patients with CLL, fludarabine treatment (especially in combination with other IST) was associated with infections such as listeriosis, mycobacterial infections, and opportunistic fungal and viral infections.[28] Additionally, fludarabine was associated with infections caused by *Pneumocystis jirovecii,* which is the causative agent of pneumocystis pneumonia (PJP), also known as pneumocystosis. When used alone, purine analogs 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.[29] The combination of fludarabine and corticosteroids is more immunosuppressive than either agent alone.[30] Fludarabine plus

prednisone results in a uniform depression of CD4+ cells that may persist for several months after completion of therapy.[31] In one series, 14 of 264 patients (5%) with CLL developed either PJP or listeriosis, and 3 cases occurred >1 year after therapy in patients who were in remission.[31]

Alemtuzumab

An increasing number of allogeneic HCT recipients and patients with hematologic malignancies 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 disease that has progressed on fludarabine therapy. Alemtuzumab has been associated with grade 3 or 4 neutropenia in about 40% of patients with previously untreated CLL and in 56% to 78% of patients with fludarabine-refractory disease.[32-34] Alemtuzumab is associated with prolonged and severe lymphopenia in most patients. Prescribing information indicates that 4 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. The CD8+ cell counts changed in a similar manner. In patients who are previously treated and are receiving alemtuzumab, CD4+ and CD8+ counts may not recover to baseline levels until >1 year after completion of therapy. Infections pose a concern for morbidity and/or mortality in alemtuzumab recipients, particularly for patients with heavily pretreated, fludarabine-refractory disease.[14,33,35] Bacterial, viral, fungal, mycobacterial, and *Pneumocystis jirovecii* infections have been reported with alemtuzumab.[33,35,36]

Anti-infective prophylaxis against herpes viruses and PJP is recommended in patients receiving alemtuzumab treatment (see *Antiviral Prophylaxis and Preemptive Antiviral Therapy* and *Prophylaxis for Pneumocystis jirovecii*). Several studies have shown that patients treated with alemtuzumab have increased susceptibility to cytomegalovirus (CMV) reactivation and disease.[32,33,37-39] In the absence of a large randomized controlled trial, the Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology does not currently recommend CMV surveillance in alemtuzumab recipients.[40] 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 CLL on behalf of the National Cancer Institute (NCI) recommend routine monitoring for CMV in patients with CLL who have therapies associated with the potential for CMV reactivation (eg, alemtuzumab or HCT).[41,42] The NCCN Panel recommends that surveillance for CMV reactivation is conducted at least weekly using polymerase chain reaction (PCR) in alemtuzumab recipients (see *Antiviral Prophylaxis and Preemptive Antiviral Therapy: Cytomegalovirus)*. Other compounds known to cause lymphopenia (eg, proteasome inhibitors) are associated with an increased risk of herpes zoster reactivation; therefore, prophylaxis with acyclovir, famciclovir, or valacyclovir is recommended.

Anti-CD20 Monoclonal Antibodies

Anti-CD20 monoclonal antibodies (eg, rituximab, ofatumumab, obinutuzumab) are widely used in the treatment of patients with B-cell lymphoid malignancies. The use of these monoclonal antibodies has been associated with increased risks for hepatitis B virus (HBV) reactivation, which can lead to fulminant hepatitis, liver failure, and/or death.[43-48] Antiviral prophylaxis is generally recommended for patients who test positive for HBV surface antigen (see *Antiviral Prophylaxis and Preemptive Antiviral Therapy: Hepatitis B virus*).

The use of anti-CD20 monoclonal antibodies in patients with B-cell malignancies has been associated with rare instances of progressive multifocal leukoencephalopathy (PML). PML is a demyelinating disease of

the central nervous system (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 in patients who had received prior immunosuppressive regimens.[49-56] Moreover, patients who developed PML often presented with low CD4+ counts or abnormal (low) CD4+/CD8+ ratio,[49,51,54,56] which points to a critical role of T-cell immunity in suppressing reactivation of the JC virus.

Other Immunosuppressive Therapies

In addition to the agents mentioned above, there are other immunosuppressive therapies associated with a greater risk of infection in patients with cancer. For example, temozolomide (often administered in conjunction with radiation therapy) is associated with an increased risk of infection, particularly with *Pneumocystis jirovecii*, the causative agent for PJP.[57] Likewise, idelalisib with or without rituximab is associated with an increased risk of infections including *Pneumocystis jirovecii.* Treatment with other therapies, including ibrutinib and bendamustine, have also been reported to increase susceptibility to infection, including *Pneumocystis jirovecii*.[58,59]

Hematopoietic Cell Transplantation

Autologous HCT

Autologous HCT recipients generally have fewer infectious complications than allogeneic transplant recipients. Most infections in autologous HCT recipients occur during neutropenia or within the first few months after transplantation before reconstitution of cellular immunity. However, compared to unmanipulated autologous HCTs, CD34+ cell enrichment leads to a substantial reduction in T cells, natural killer cells, and monocytes, which delays immune reconstitution.[60] Recipients of CD34+ cell-enriched autologous HCT appear to have a similar level of risk as allogeneic HCT recipients for contracting CMV and other opportunistic infections.[60] Severe or ulcerative mucositis, which develops as a result of myeloablative high-dose therapy administered prior to HCT, is associated with the occurrence of bacteremia in autologous HCT recipients.[61-63]

A multicenter prospective study evaluated the potential role of granulocyte-colony stimulating factor (G-CSF) responsiveness in predicting the occurrence of infections in patients with hematologic malignancies undergoing high-dose therapy and autologous HCT.[64] 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 HCT), and measuring the induced leukocyte peak occurring 12 to 14 hours after the G-CSF dose. G-CSF responsiveness showed a significant inverse correlation with incidences of febrile neutropenia and infections (ie, higher responsiveness associated with lower infection rates), and was shown to be the only independent predictor of infections based on multivariate analysis.[64]

Allogeneic HCT

The spectrum of pathogens to which allogeneic HCT recipients are most susceptible follows a timeline corresponding to the predominant immune defects. In the first month after allogeneic HCT (pre-engraftment period), neutropenia and breakdown of the mucocutaneous barrier comprise the principal host defense defect, which predisposes patients to bacterial and fungal infections.[65,66] 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 HCT 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), *Pneumocystis jirovecii*, and invasive molds such as *Aspergillus*.[65,66] Prophylaxis against pneumococcal infection is advised in allogeneic HCT recipients (see *Prophylaxis for Pneumococcal Infection*).

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[67] and fungal[68-70] 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.

Guidelines from the Centers for Disease Control and Prevention (CDC) recommend that allogeneic HCT recipients with severe hypogammaglobulinemia (IgG <400 mg/dL) and with recurrent infections receive intravenous immunoglobulin (IVIG) prophylaxis; IVIG is not routinely recommended in other patient groups or in autologous HCT recipients.[8] The 2009 guidelines on the prevention of infections in HCT recipients (jointly sponsored by the CDC, Infectious Diseases Society of America [IDSA], American Society for Blood and Marrow Transplantation, and European Society for Blood and Marrow Transplantation, among other organizations) reported similar recommendations on the use of IVIG.[66]

Chronic GVHD

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[71] noted a high frequency of pneumococcal infections between 7 and 36 months after transplantation, associated with serum opsonic deficiency for *Streptococcus pneumoniae*. Kulkarni et al[72] reported that pneumococcal sepsis occurred a median of 10 months after transplant (range, 3–187 months) and was significantly more frequent in patients with chronic GVHD.

CAR T-Cell Therapy

Several chimeric antigen receptor (CAR) T-cell products targeting CD19 (e.g., axicabtagene ciloleucel, tisagenlecleucel, lisocabtagene maraleucel) or B-cell maturation antigen (BCMA) (e.g., idecabtagene vicleucel, ciltacabtagene autoleucel) have been approved for hematologic malignancies. However, CAR T-cell products confer a risk of potentially life-threatening immunological toxicities, like neutropenia, lymphopenia, and hypogammaglobulinemia, and thus may increase the risk of infection in patients.[73] The highest risk for infection occurs within the first 30 days of administration of CAR T-cell therapy, and bacterial infections predominate during this period. Opportunistic infections can be expected, and prophylaxis, particularly for the prevention of *Pneumocystis jirovecii*, herpes simplex virus (HSV), and varicella zoster virus (VZV), is warranted until immune reconstitution. Pre-infusion risk factors for infection include certain underlying malignancies, prior lines of therapy with or without autologous/allogeneic HCT, antecedent infection, and neutropenia. Risk factors post-infusion may include prolonged neutropenia, cytokine release syndrome/immune effector cell-associated

neurotoxicity syndrome (CRS/ICANS) and associated treatment (eg, high-dose steroids, IL-6 inhibitors), lymphopenia, and hypogammaglobulinemia. Beyond day +30, respiratory viral infections predominate. Fungal infection risk remains low but may vary based on prior therapies, degree of immunosuppression, and other relevant risk factors.

Relevant serologic screening for human immunodeficiency virus (HIV), HBV, and hepatitis C virus (HCV) is recommended. Moreover, CMV and additional screening may be considered based on epidemiologic risks. Antibacterial and antifungal prophylaxis can be considered for patients who are neutropenic. PJP and HSV/VZV prophylaxis are recommended. The specific risk profile of the patient (duration of neutropenia, prior allogeneic HCT, previous infections, and local antibiotic resistance profiles) should guide diagnostic workup and selection of antimicrobial agents. In patients with additional risk factors, such as prolonged neutropenia, prior allogeneic HCT, or augmented immunosuppressive therapy (IST) for CRS/ICANS, mold-active antifungal prophylaxis can be considered (see *Immune And Targeted Treatments: Chimeric Antigen Receptor-Engineered T-Cell Therapy* in the algorithm).[73-76] Patients should also be monitored for CRS, which may mimic sepsis. The incidence of CRS depends on the CAR T-cell product, disease characteristics, and CRS grading system used.[73-76]

NCCN Recommendations for Categories of Infection Risk

The Panel acknowledges that there are multiple definitions of risk related to infection in patients with cancer.[36,77,78] This section is specific to the overall risk of developing infection and recommendations for prophylaxis are based on this risk characterization. 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 IST. Development of the categories of risk is further based on the expert opinion of the Panel. An overview of the antimicrobial recommendations based on risk for infection is presented below. For more details, refer to the *Prevention of Infectious Diseases* section in the discussion and *Antimicrobial Prophylaxis Based on Overall Infection Risk in Patients with Cancer* in the algorithm.

Briefly, patients with solid tumors receiving standard chemotherapy regimens and who have an anticipated duration of neutropenia <7 days are generally considered at low risk for infectious complications; thus, antimicrobial prophylaxis is not routinely recommended in these patients.[17] 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 to 10 days are considered to be at intermediate risk for infections. In addition, patients with lymphoma, multiple myeloma, CLL, autologous HCT recipients, or those receiving CAR T-cell therapy or treatment with purine analog-containing regimens (most often for hematologic malignancies such as NHL or CLL) are also considered to be at intermediate risk. For those who are at intermediate risk, prophylaxis with antibacterials (eg, fluoroquinolones) should be considered during neutropenia. Antivirals should be given during periods of neutropenia, and for autologous HCT recipients, until at least 30 days following transplant (however, consider antiviral prophylaxis for VZV for at least 6–12 months after HCT). Antifungals should be considered during periods of neutropenia and for anticipated mucositis (with the latter pertaining to autologous HCT) for intermediate risk. PJP prophylaxis should be considered in patients with intermediate risk.

Patients with anticipated duration of neutropenia >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 HCT recipients, and those with GVHD following allogeneic HCT are considered at high risk for infectious complications. 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 these patients who are at high risk for infections, prophylaxis with antibacterials (eg, fluoroquinolones) should be considered during neutropenia. These patients should receive antiviral prophylaxis during periods of neutropenia, and antiviral prophylaxis for VZV for at least 1 year after HCT. In addition, prophylaxis with antifungals can be considered for patients with ALL and for patients with neutropenia with AML/MDS.[17] For allogeneic HCT recipients or those with chronic GVHD receiving IST, antifungal prophylaxis can also be considered during periods of neutropenia and until resolution of GVHD. PJP prophylaxis should be considered in those who are at high risk for infections.

Prevention of Infectious Diseases

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

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.

Two large, randomized, placebo-controlled studies showed the benefit of levofloxacin prophylaxis in neutropenia at different levels of risk for infectious complications.[79,80] The main advantage of levofloxacin prophylaxis (in patients with intermediate and higher risk of infections) with chemotherapy-induced neutropenia was a reduction in clinically significant bacterial infections, including gram-negative rod bacteremia.[79] In contrast, the main advantage of prophylaxis in lower risk neutropenia was a small, but statistically significant, reduction in fever and hospitalization for neutropenic fever.[80] 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,[80] 1000 hypothetical patients with low risk of infections would have to receive prophylaxis during each cycle of chemotherapy-induced neutropenia to benefit only 44 patients.

In a single-center randomized study in patients undergoing high-dose therapy followed by autologous HCT (N = 157), patients were randomized to receive prophylaxis (with oral ciprofloxacin 500mg twice daily and intravenous [IV] vancomycin 1000mg once daily) or no prophylaxis; all patients received antifungal prophylaxis with fluconazole.[81] Empiric 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 response to first-line empiric therapy (66% vs. 84%; $P = .025$). 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 HCT.[81] It should be noted, however, that the prophylactic regimen in this study included vancomycin (albeit at a lower dose), is not supported by the NCCN or IDSA Panels for use as either antimicrobial prophylaxis or standard initial empiric therapy for fever and neutropenia. [17]

In a systematic review and meta-analysis by Gafter-Gvili et al (based on 109 trials, N = 13,579 patients) comparing antibacterial prophylaxis with placebo, no intervention, or prevention with another agent in patients with afebrile neutropenia, 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.[82] 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 trimethoprim/sulfamethoxazole (TMP/SMX), the use of quinolones was associated with decreased drug resistance and fewer adverse events that subsequently reduced the incidence of drug discontinuation.[82]

A systematic review and meta-analysis evaluated the risks associated with colonization and infections by fluoroquinolone-resistant bacteria.[83] Most of the studies (48 of 56 trials) included patients with hematologic malignancies or HCT recipients. Results of the analysis (based on 56 trials, N = 7878 patients; data on colonization by resistant bacteria based on 27 trials) showed that quinolone prophylaxis was associated with an increase in colonization with quinolone-resistant organisms compared with placebo or no intervention, although the increase was not statistically significant (relative risk [RR], 1.68; 95% CI, 0.71–4.00). However, no difference was 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.[83] 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.[83] This analysis suggests that prophylaxis with quinolones does not appear to increase the rate of infections by resistant organisms.

A 2017 prospective intercontinental study assessed gram-negative rod (GNR) resistance to fluoroquinolones, non-carbapenem β-lactams (including ceftazidime, cefepime or β-lactam/β-lactamase inhibitors), and carbapenems (meropenem/imipenem/doripenem) in HCT recipients. Of 655 GNR bacteremia episodes, half were found to be fluoroquinolone and non-carbapenem resistant. The total resistance rates were higher in patients with allogeneic HCT than in those with autologous HCT. Risk factors for fluoroquinolone resistance in allogeneic HCT included prolonged neutropenia and breakthrough on fluoroquinolones. Mortality was found to be significantly more common in infections caused by resistant bacteria.[84]

A 2018 meta-analysis of studies published in the years 2006–2014 assessed the role of fluoroquinolone prophylaxis during neutropenia in consideration of increasing antibiotic resistance globally.[85] The meta-analysis found no effect of the background rate of fluoroquinolone resistance on the efficacy of fluoroquinolone prophylaxis. However, in few studies, fluoroquinolone prophylaxis resulted in an increased colonization or infection with fluoroquinolone- or multidrug-resistant strains.

Fluoroquinolone prophylaxis had no effect on mortality, but it reduced the rate of bloodstream infections and episodes of fever.[85]

An important consideration for those with low risk 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 and IDSA[17] Panels 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[86] have suggested prophylaxis with levofloxacin on cycle 1 of myelosuppressive cancer chemotherapy and only in subsequent cycles if a febrile episode occurs.

The decision whether to use antibacterial prophylaxis and the selection of the specific agent requires a balance between expected benefit and risk (explained in greater detail in a review by Hoffman et al[87]). 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). Thus, the emergence of multidrug-resistant organisms (MDROs), disruption of the microbiome, and antibiotic toxicities must be taken into consideration when choosing an antimicrobial prophylactic agent. The link between fluoroquinolone use and severe *Clostridium difficile* as well as methicillin-resistant *S aureus* (MRSA) infections provides an additional cautionary note regarding excess use of fluoroquinolones.[88-91]

NCCN Recommendations for Antibacterial Prophylaxis

Antibacterial prophylaxis is not recommended for patients with a low risk of overall infection (see *Antimicrobial Prophylaxis Based On Overall Infection Risk In Patients With Cancer* in the algorithm). In 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 <7 days who are not receiving immunosuppressive regimens (eg, systemic corticosteroids), the Panel suggests no antibiotic prophylaxis.[17] In patients deemed at intermediate or high risk, the NCCN Guidelines Panel advises that fluoroquinolone prophylaxis (levofloxacin is preferred) be considered in patients with an expected duration of neutropenia (absolute neutrophil count [ANC] ≤500 neutrophils/mcL or ≤1000 neutrophils/mcL and a predicted decline to ≤500/ mcL over the next 48 hours) for >7 days. This is in agreement with the recommendations of the IDSA guidelines for the use of antimicrobial agents in patients with neutropenia with cancer.[17] For patients who are intolerant to fluoroquinolone, TMP/SMX or an oral third-generation cephalosporin may be considered.

Clinical practice guidelines have also been developed for systemic antibacterial prophylaxis in pediatric patients with cancer and those undergoing HCT.[92] The Panel for these guidelines recommends consideration of antibacterial prophylaxis in children with acute myeloid leukemia (AML) and relapsed acute lymphoblastic leukemia (ALL) receiving intensive chemotherapy expected to result in severe neutropenia (ANC <500/mcL) for at least 7 days. The Panel recommends against the routine use of antibacterial prophylaxis for children undergoing induction chemotherapy for ALL, autologous HCT and allogeneic HCT. A strong

recommendation against its routine use was made for children whose therapy is not expected to result in prolonged severe neutropenia. If used, prophylaxis with levofloxacin is recommended as a preferred option during severe neutropenia.[92]

Prophylaxis for Pneumococcal Infection

Prophylaxis for pneumococcal infection is advised in allogeneic HCT recipients. Patients undergoing allogeneic HCT 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 several years after HCT.[72,93] IST for GVHD delays reconstitution of B-cell immunity and significantly increases the risk of post-transplant pneumococcal sepsis.[72,94]

The NCCN Guidelines Panel advises that penicillin prophylaxis be initiated at 3 months after HCT and be continued until at least 1 year following transplant in patients with GVHD. Patients should receive prophylaxis regardless of prior administration of pneumococcal vaccines.[95] Prophylaxis should be continued in patients with chronic GVHD until IST 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,[96] and cross-resistance to other classes of antibiotics is common. Breakthrough pneumococcal sepsis in HCT recipients receiving penicillin prophylaxis is well described.[97] 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 PJP is likely to be protective against pneumococcal disease, but depends on local susceptibility patterns. In high-risk populations (e.g., allogeneic HCT recipients with GVHD), prophylaxis with penicillin and TMP/SMX should be considered.

Vaccination with pneumococcal vaccine is also strongly recommended (see *Vaccination*) 3 to 6 months post-HCT.

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 patients with high risk, especially those with longer durations of neutropenia or with GVHD after allogeneic HCT.[17] Selection of an antifungal agent is determined by the disease or therapy and includes azoles, amphotericin B products, and echinocandins.

Azoles

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

Prophylaxis with voriconazole was compared with fluconazole in a large, randomized, double-blind study that included serum galactomannan surveillance in allogeneic HCT recipients (N = 600).[98] Patients were randomized to receive study drugs for 100 days or for 180 days in the higher risk cohort of patients. 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 seen between treatment arms.[98]

In a multicenter randomized trial, prophylaxis with posaconazole in patients with neutropenia with AML or myelodysplastic syndromes (MDS) receiving induction or re-induction chemotherapy significantly reduced the rate of invasive fungal infections during the treatment period (2% vs. 8%; $P < .001$) and during the 100 days following randomization (5% vs. 11%; $P = .003$). Posaconazole prophylaxis also reduced the incidence of invasive aspergillosis (1% vs. 7%; $P < .001$) and was associated with a significant survival benefit ($P = .04$) compared with the fluconazole/itraconazole arm.[99] Data from a prospective, randomized study showed that posaconazole was as effective as fluconazole in allogeneic HCT recipients with severe GVHD and reported reduced incidence of invasive aspergillosis and overall invasive fungal infections in patients receiving posaconazole compared to those receiving fluconazole.[100] Posaconazole is equally effective compared to fluconazole as primary therapy for oropharyngeal candidiasis.[101] Moreover, in a 2021 phase 3 randomized controlled trial, posaconazole was found to be non-inferior to voriconazole as primary therapy for invasive aspergillosis, and participants had fewer treatment-related adverse events in the posaconazole group than in the voriconazole group.[102]

A 2020 systematic review and meta-analysis of 69 randomized clinical trials compared prophylaxis with various antifungal agents in patients with hematologic disease or who received HCT. Posaconazole prophylaxis significantly reduced invasive fungal infections (RR, 0.57; 95% CI, 0.42–0.79) and invasive aspergillosis (RR, 0.36; 95% CI, 0.15–0.85) compared with placebo. Additionally, voriconazole was associated with a significant reduction in invasive candidiasis (RR, 0.15; 95% CI, 0.09–0.26) compared with placebo. However, patients taking posaconazole had a higher incidence of withdrawal due to adverse effects.[103]

Isavuconazonium sulfate is a second-generation azole that was approved in March 2015 for the treatment of invasive aspergillosis and invasive mucormycosis. Isavuconazonium sulfate may be considered for antifungal prophylaxis when standard therapy is contraindicated, due to drug interactions or the risk of QTc prolongation.[104]

Toxicities and Drug-Drug Interactions of Azoles

Experience to date suggests that fluconazole and posaconazole are generally well tolerated and serious adverse events, primarily liver toxicity, are rare. Toxicities for voriconazole include neurologic and ophthalmic adverse events. In the context of renal dysfunction, accumulation of cyclodextrin vehicle may occur when the IV formulation is used. . Data suggest that long-term use of voriconazole may be associated with severe photosensitivity and other adverse events including cutaneous malignancies, elevated serum fluoride levels, and periosteitis.[105-109] Itraconazole may be associated with hepatic toxicity and GI intolerance[110] 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.[111] Fluconazole, itraconazole, posaconazole, and voriconazole may cause QTc prolongation. Conversely, isavuconazonium sulfate has been associated with dose-dependent QTc shortening in healthy individuals.

Azole-associated drug-drug interactions are common clinical occurrences. Both the addition and withdrawal of azoles can result in either increased

uptake of these other drugs or sub-therapeutic exposure and potential transplant rejection or GVHD. Several studies demonstrate the interaction of azoles with hepatic enzymatic pathways. Administration of itraconazole with medications that are metabolized by the 3A4 isoenzyme can increase plasma concentrations causing QTc prolongation and ventricular tachyarrhythmias.[112] These findings reinforce a note of caution about itraconazole (and by extension, fluconazole, voriconazole, isavuconazonium sulfate, and posaconazole), with regard to potential serious drug-drug interactions through inhibition of the cytochrome P450 3A4 isoenzyme. Additionally, fluconazole and voriconazole have demonstrated inhibition of CYP2C9 and CYP2C19 enzymes and high interpatient variability of genetic CYP2C19 polymorphisms that may also affect dosing.

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

Therapeutic Drug Monitoring of Azoles

Therapeutic drug monitoring (TDM) for the pharmacokinetic evaluation of antifungal agents provides guidance for achieving adequate plasma drug concentration while reducing toxicity.

TDM should be considered for patients receiving triazoles; there is no current evidence to support the use of TDM for the evaluation of polyenes or echinocandins. Fluconazole and isavuconazonium sulfate are the two triazoles that do not require TDM. Fluconazole has linear pharmacokinetics that eliminate the need for TDM,[113-117] though patients in renal failure should receive a modified dose. Studies intended to define a therapeutic range for isavuconazonium sulfate have not been performed; thus, TDM is not routinely recommended for isavuconazonium sulfate. TDM should be considered for posaconazole, voriconazole, and itraconazole. Variability of therapeutic drug levels may be affected by the route of drug administration, drug formulation, timing of monitoring, location of the infection, and intrinsic patient factors (ie, age, weight).

There are three formulations of posaconazole: oral suspension, delayed-release tablet, and IV solution. Pharmacokinetic studies with the oral suspension of posaconazole in healthy individuals showed that administration with or after a high-fat meal, or with any meal or nutritional supplement, greatly enhanced its absorption up to 400%.[118] The plasma concentration of posaconazole can be reduced by proton pump inhibitors (PPIs) due to the increase in gastric pH when given orally.[118] Subtherapeutic concentrations and breakthrough fungal infections have been reported.[119,120] As reviewed by Brüggemann et al,[121] a substantial list of drug interactions with azole antifungal drugs can result in subtherapeutic effects or toxicity. The delayed-release (DR) tablet formulation of posaconazole was approved in 2013 and has improved absorption and more predictable bioavailability. Gastric pH does not affect plasma concentration of DR posaconazole,[122] nor does it have the same interaction with PPIs or metoclopramide.[123] The IV formulation has also demonstrated similar pharmacokinetics and safety compared with the DR tablet.[124] A target concentration of posaconazole for prophylactic TDM of >0.7 mcg/mL is supported by individual studies[120,125,126] as well as two phase III studies;[99,100] however, doses as low as 0.5 mcg/mL have also been reported as effective.[120,126-130] TDM may not be necessary when using either the DR tablet or IV formulation in the prophylactic setting as data indicate that a dose of 300 mg/day results in at least 0.5 ug/mL in

>95% of patients. Treatment of an established infection is recommended to have a trough concentration >1 mcg/mL with potentially higher doses based on the pathogen minimal inhibitor concentrations (MICs) and concerns for resistance.[131,132]

Studies of itraconazole demonstrate a significant rate of breakthrough infections when plasma drug concentrations are <0.5 mcg/mL;[133,134] however, increased mortality was observed at plasma drug concentrations >5 mcg/mL.[135,136] Targeting a lower itraconazole plasma concentration for prophylaxis and a higher dose if an active infection is being treated may be beneficial. Studies suggest that trough concentrations of itraconazole between 1 and 2 mcg/mL have shown the best therapeutic responses for invasive infections,[137-140] while a trough concentration of >0.5 mcg/mL may be sufficient for prophylaxis. Currently, an upper limit of 17 mcg/mL measured by bioassay has been suggested,[141] but studies for the upper limit have not been extensive. Itraconazole solution should be given either 1 hour before or 1 hour after meals based on the 43% increase in bioavailability in patients who fasted[142], while the capsule formulation should be given with a full meal. An alternative formulation, SUBA-itraconazole (for “super bioavailability”), addresses the absorption concerns of conventional itraconazole formulations with enhanced bioavailability that allows for lower dosing, while achieving similar serum concentrations. SUBA-itraconazole is FDA approved for the treatment of blastomycosis, histoplasmosis and aspergillosis.[143,144]

Target voriconazole trough values between 0.5 and 4 mcg/mL have been proposed in clinical studies.[145-152] While 0.5 mcg/mL is a suggested target for prophylaxis, a higher range of 1 to 4 mcg/mL may be necessary for active disease and for patients with disease that has a poor prognosis. Higher concentrations may also benefit the patients who are immunocompromised by reducing breakthrough infection.[153,154] Trough concentrations ≥4 mcg/mL have correlated with toxicity in various studies.[145,149,152,155-159] Voriconazole bioavailability was lowered by about 22% when taken with food and by 34% when given with a high-fat meal.[160] Therefore, voriconazole should be given either 1 hour before or 1 hour after meals.

Studies have shown a general consensus regarding a minimal level of plasma concentration necessary for the triazoles, though the lack of prospective studies has limited the adoption of formal monitoring standards. The Society of Infectious Diseases Pharmacists (SIDP) has published its guidelines for the use of TDM of antifungal agents based on available literature.[161] Consideration of TDM is recommended by the NCCN Panel in conjunction with involvement of an infectious disease expert.

Amphotericin B Formulations

Amphotericin B formulations are broad-spectrum antifungal agents that binds to ergosterol in the fungal cell membrane, leading to the formation of pores in the membrane and subsequent cell death. The original formulation, amphotericin B deoxycholate (AmB-D), was associated with dose-limiting toxicities including infusion-related reactions and nephrotoxicity. Three lipid-associated formulations, amphotericin B lipid complex (ABLC), liposomal amphotericin B (L-AmB), and amphotericin B colloidal dispersion (ABCD), have since been developed to have reduced toxicity. When available, ABLC and L-AmB are preferred over AmB-D.

Low-dose amphotericin B formulations have been studied in patients at high risk and have been shown to provide protection against invasive molds, although no survival benefit in randomized studies was seen when compared with fluconazole.[110,162,163] 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, HCT recipients, and patients who are concurrently receiving other nephrotoxic agents.[164,165]

Aerosolized delivery of amphotericin B products has been considered for several years with the advantage of local delivery to the lungs while simultaneously avoiding systemic toxicity. A randomized, placebo-controlled trial found that aerosolized L-AmB was useful for preventing invasive pulmonary aspergillosis in patients with prolonged neutropenia.[166] 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.[167]

Echinocandins

Echinocandins are a class of antifungal agents that disrupt the integrity of the fungal cell wall through noncompetitive inhibition of β-(1,3)-D-glucan synthase, an enzyme involved in the biosynthesis of β-(1,3)-D-glucan, which is a component specific to the cell wall of many fungi. Echinocandins have fungicidal activity against *Candida* species and are fungistatic towards *Aspergillus* species. Combination therapy with amphotericin B or triazoles has been proposed to improve activity against molds; however, clinical evidence for this remains quite limited. Advantages of this family of antifungals are the relatively low toxicity profiles and limited drug-drug interactions. Though echinocandins demonstrate activity against *Candida* species that are resistant to other antifungal agents,[168] there is limited or no activity against dimorphic fungi. Four echinocandins are approved for use: caspofungin, micafungin, anidulafungin, and rezafungin. Caspofungin, micafungin, and anidulafungin are all approved for the treatment of esophageal candidiasis, while rezafungin is approved for the treatment of candidemia and invasive candidiasis in adults with limited or no alternative treatment options. Caspofungin and anidulafungin have additional indications for the treatment of candidemia and other infections caused by *Candida* species. Caspofungin is indicated for treatment of candidal pleural space infections, empiric treatment of fungal infections in neutropenia, and treatment of invasive aspergillosis in patients who are refractory to or intolerant of other antifungal agents. Micafungin has the additional indication for prophylaxis of candidal infections in patients receiving HCT.

Caspofungin was evaluated in a double-blind study including 128 patients with esophageal candidiasis.[169] Patients received either caspofungin or AmB-D. Two doses of caspofungin were evaluated (50 mg or 70 mg IV once daily) with a greater response in the patients given the higher dose (96% vs. 85%). Both groups treated with caspofungin had a better response than patients receiving amphotericin B (78%). At the 2-week follow-up, a greater percentage of patients remained negative for candidiasis with the caspofungin treatment (89% in the 70 mg group, 74% in the 50 mg group, and 63% in the amphotericin B group). Furthermore, drug-related adverse events were lower with caspofungin (7%, 4%, and 24%, respectively). Several studies have evaluated the role of caspofungin in the treatment of invasive aspergillosis in patients refractory to or intolerant of other antifungals, supporting its recommendation in this capacity.[170,171]

Micafungin is an echinocandin approved for prophylaxis against *Candida* infections in patients undergoing HCT. In a randomized, double-blind trial of autologous and allogeneic HCT recipients, the success rate with micafungin was superior to fluconazole (80% vs. 73.5%; absolute difference +6.5%; 95% CI, 0.9–12%; P = .03) based on prespecified criteria for treatment success (absence of suspected, proven, or probable

invasive fungal infections during treatment period and absence of proven or probable infection during the 4-week period after treatment).[172] The duration of this study encompassed the neutropenic period, but not the period after neutrophil recovery when GVHD would be expected to occur. The frequency of breakthrough candidemia was similar in both arms, but there was a trend to fewer episodes of invasive aspergillosis in allogeneic HCT recipients receiving micafungin. Survival and drug-related toxicity were similar between treatment arms.[172] Micafungin has shown activity in the treatment of aspergillosis in patients refractory to or intolerant of other antifungal agents.[173-175]

Anidulafungin has been shown to be an effective antifungal agent against *Candida* infection in several studies. A randomized double-blind study in 601 patients with esophageal candidiasis demonstrated noninferiority of IV anidulafungin to oral fluconazole (97.2% vs. 98.8%, respectively) and lower adverse effects (9.3% vs. 12.0%) and recurring infections at the 2-week follow-up (64.4% vs. 89.5%).[176] In a smaller study of 19 patients with triazole-refractory mucosal candidiasis, anidulafungin treatment resolved infection in 18 of the patients.[177] A larger phase III trial similarly showed superiority of anidulafungin compared to fluconazole in the treatment of candidemia and invasive candidiasis (75.6% vs. 60.2%).[178] The response at 2-week follow-up was 64.6% in the anidulafungin group versus 49.2% in the fluconazole group.

Rezafungin was evaluated in a phase 3 multicentre, double-blind randomized trial.[179] 199 patients with candidemia or invasive candidiasis were randomly assigned to either the rezafungin group (50%) or to the caspofungin group (50%). Rezafungin was found to be non-inferior to caspofungin in the treatment of candidemia and invasive candidiasis (59% vs. 61%, respectively) as well as for 30-day all-cause mortality (24% vs. 21%, respectively).

NCCN Recommendations for Antifungal Prophylaxis

CYP3A4 inhibition by azoles can lead to toxicity when administered with several classes of drugs used in cancer therapy, including proteasome inhibitors, tyrosine kinase inhibitors, and vinca alkaloids.[180] Thus, mold-active azoles should be stopped several days before the potential interacting drug is given. These azoles should also not be started until the other agent has been discontinued and sufficient time has elapsed for the drug to be eliminated. Due to variations in drug pharmacokinetics, firm recommendations regarding a minimum time from drug discontinuation to azole administration cannot be made, though some institutions consider waiting at least 10 days following administration of these classes of drugs. Use of echinocandin prophylaxis may be considered in the place of azoles. Consultation with pharmacology and infectious disease experts is recommended.

The NCCN Guidelines Panel recommends posaconazole (category 1) for antifungal prophylaxis in neutropenia with AML and MDS receiving induction or re-induction chemotherapy (see *Prevention Of Fungal Infections* in the algorithm).[17] The role of antifungal prophylaxis in patients with acute leukemia receiving consolidation chemotherapy has not been adequately evaluated. Voriconazole, isavuconazole, fluconazole, echinocandin, or amphotericin B products are all category 2B recommendations in this disease setting. Antifungal prophylaxis should be continued until resolution of neutropenia.

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

The NCCN Guidelines Panel recognizes that strong evidence exists for the use of fluconazole or echinocandin as prophylaxis in neutropenic allogeneic HCT recipients (category 1).[17] However, it should be noted that

fluconazole use can predispose patients to colonization and bloodstream infection by fluconazole-resistant *Candida* strains.[69,181] Posaconazole as prophylaxis has not been evaluated during the neutropenic period following conditioning in allogeneic HCT recipients; thus, the safety of this approach is unknown. Drug-drug interactions during conditioning for HCT, specifically with posaconazole, itraconazole, or voriconazole, complicate treatment of fungal infections in these patients. Prophylaxis may need to be tailored following consultation with an infectious disease expert. Posaconazole, isavuconazole, voriconazole, echinocandins, and amphotericin B products are all considered category 2B recommendations. Antifungal prophylaxis should be considered until at least day 75 or count recovery (ANC >500) after allogeneic HCT.[17,182-184]

Patients with hematologic malignancies are at high risk of developing invasive fungal disease. The German Society of Haematology and Medical Oncology (DGHO) strongly recommends administration of antifungal prophylaxis in patients with hematologic malignancies with prolonged neutropenia (ie, <500 cells/mcL for >7 days) with posaconazole as the drug of choice for mold-active prophylaxis.[184]

Although many centers reasonably use antifungal prophylaxis in non-neutropenic allogeneic HCT recipients with GVHD, this practice was only evaluated in a single, properly designed study. In the prospective, randomized, double-blind study, posaconazole was compared with fluconazole as prophylaxis in allogeneic HCT recipients with severe GVHD requiring intensive IST.[100] Inclusion criteria included grade II to IV GVHD, chronic extensive GVHD, or intensive IST consisting of either high-dose corticosteroids, antithymocyte globulin, or a combination of two or more immunosuppressive agents or types of treatment. Prophylaxis with posaconazole resulted in reduced incidences of invasive aspergillosis, total invasive fungal infections while on treatment, and deaths attributed to fungal infection.[100] Posaconazole is recommended (category 1) as prophylaxis in patients with GVHD receiving intensive IST, as defined by the inclusion criteria in this trial, although the benefit/risk ratio of mold-active prophylaxis in patients receiving less intensive IST has not been established.

Patients with chronic severe neutropenia (ANC <500 neutrophils/mcL) due to an underlying disease (such as aplastic anemia) are at substantial risk for invasive aspergillosis.[185] Although this population has not been evaluated in clinical trials of antifungal prophylaxis, some Panel members advise the use of a prophylactic mold-active agent (eg, posaconazole or voriconazole).

Secondary antifungal prophylaxis is defined as administration of antifungal therapy in a patient with a prior fungal infection to prevent recrudescence. The Panel recommends secondary prophylaxis with an appropriate antifungal agent in patients with prior chronic disseminated candidiasis[186] or with invasive filamentous fungal infection[187] during subsequent cycles of chemotherapy or HCT. In patients with invasive aspergillosis before HCT, antifungal therapy for >1 month and resolution of radiologic abnormalities correlate with a lower likelihood of post-transplant recurrence of infection.[188] Secondary prophylaxis with a mold-active agent is advised for the entire period of immunosuppression.

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 HCT recipients and patients (without prophylaxis) with acute leukemia undergoing induction or re-induction therapy who are seropositive for HSV.[189-191] Among allogeneic HCT recipients, HSV disease is most likely

to occur within the first month post-transplant, but may occur in later stages during intense immunosuppression.[65,66] Although disseminated HSV infection is uncommon, infection from viral reactivation is frequently associated with increased mucosal damage, resulting in increased pain, limited ability to maintain oral hydration and nutrition, and an increased risk of bacterial and fungal superinfections.

NCCN Recommendations for HSV Prophylaxis

Antiviral prophylaxis against HSV is advised during the period of neutropenia in patients who are HSV-seropositive who are receiving chemotherapy (induction or consolidation) for acute leukemia, and during neutropenia and possibly longer in allogeneic and autologous HCT recipients depending on the degree of immunosuppression (see *Prevention Of Herpes Simplex Virus And Varicella Zoster Virus Reactivation Or Disease* in the algorithm). A longer period of prophylaxis should be considered in allogeneic HCT recipients with GVHD or with frequent HSV reactivations before transplantation.[8] Acyclovir, valacyclovir or famciclovir are the initial agents of choice for HSV prophylaxis.[17,192] Foscarnet is typically reserved for patients with acyclovir-resistant HSV infection.[17,192] In patients 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.[192] However, it is required in patient receiving CMV prophylaxis with letermovir as this agent lacks activity against HSV.

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 and until CD4+ cell counts are ≥200 cells/mcL.[193]

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. HSV prophylaxis is also indicated in children who are seropositive for the virus.

Varicella Zoster Virus

Impaired cellular immunity is the principal risk factor for VZV disease. In allogeneic HCT recipients with a history of VZV infection, about 30% have reactivation of VZV disease without antiviral prophylaxis.[194] In patients with a history of chicken pox, oral acyclovir administered from 1 to 2 months until 1 year after allogeneic HCT significantly decreased the incidence of VZV disease compared to placebo (5% vs. 26%, respectively).[194] The frequency of VZV disease in the post-prophylactic period was similar between the groups and predominantly occurred in patients who required systemic immunosuppression. This prolonged course of acyclovir prophylaxis is likely to also prevent HSV reactivations. Subsequent studies have consistently demonstrated the benefit of long-term antiviral prophylaxis against VZV disease in recipients of allogeneic HCT. Patients who received anti-VZV prophylaxis with acyclovir or valacyclovir for 1 year post-HCT had significantly reduced VZV disease compared with those who did not receive long-term prophylaxis (9% vs. 25%; $P < .001$); no evidence of rebound VZV disease was observed.[195] Long-term (1 year post-allogeneic HCT) prophylaxis with lower doses of acyclovir or valacyclovir was associated with a higher cumulative incidence of VZV reactivation.[196,197]

NCCN Recommendations for VZV Prophylaxis

The NCCN Guidelines Panel recommends prophylaxis against VZV for at least 1 year after allogeneic HCT in patients seropositive for VZV pretransplant (see *Prevention Of Herpes Simplex Virus And Varicella*

Zoster Virus Reactivation Or Disease in the algorithm), and recommends considering the extension of prophylaxis in patients who continue to receive systemic IST. Although higher doses are necessary, the same agents used as HSV prophylaxis are also active against VZV. For pediatric patients, prophylaxis for VZV should not be routinely given unless there is a history of recurrent zoster infections or incidence of first zoster infection while on myelosuppressive therapy, even if they are seropositive or vaccinated.

Among autologous HCT recipients, HSV reactivation is more likely to occur in the early neutropenic phase, whereas the risk of VZV reactivation extends through the first year.[198] Thus, VZV prophylaxis for at least 6 to 12 months post-transplant should be considered in autologous HCT recipients. Prophylaxis against VZV should be considered in other patients at intermediate risk for viral reactivation, including patients with hematologic malignancies with prolonged neutropenia or those receiving T-cell–depleting agents (eg, fludarabine, alemtuzumab). Bortezomib is associated with an increased risk of VZV reactivation during active therapy[199-202]; carfilzomib may also be associated with VZV reactivation. Prophylaxis with acyclovir, valacyclovir or famciclovir should be protective and can be considered in these settings.[203,204] As previously discussed, among patients with CLL receiving alemtuzumab treatment, antiviral prophylaxis is recommended until 2 months after completion of treatment and until the CD4+ cell counts reach 200 cells/mcL or more.[193]

Cytomegalovirus

CMV infections most frequently occur in patients with cancer who undergo allogeneic HCT or who receive alemtuzumab therapy or other T-cell depleting therapies. CMV is a common cause of opportunistic infections during the early post-engraftment phase following allogeneic HCT, but can also occur in the late post-engraftment phase (particularly for patients with GVHD during the latter phase).[65,66] Infection can result from viral reactivation (in patients who are immunocompromised CMV-seropositive) or primary infection (in CMV-seronegative). The risk for CMV reactivation and disease is highest among HCT recipients with CMV-seropositive status prior to transplant.[205] Among patients who are CMV-seropositive undergoing allogeneic HCT (with graft sources from peripheral blood, bone marrow, or umbilical cord blood), the incidence of CMV reactivation ranged from 50% to 60% (with CMV disease in about 10%–30% of seropositive recipients) even with routine surveillance and antiviral prophylaxis or preemptive therapy.[205-208]

In a randomized phase II prophylaxis trial, oral letermovir was administered to allogeneic HCT recipients with CMV-seropositive status daily at 60 mg, 120 mg, or 240 mg for 12 weeks post-transplant. The incidence of prophylaxis failure (defined as discontinuation of the study drug because of CMV detection, end-organ disease, or any other cause) was significantly lower in the letermovir groups than in the placebo group (32% for the 120 mg group, 29% for the 240 mg group vs. 64%). Moreover, letermovir was well tolerated, with no indication of hematologic toxicity or nephrotoxicity.[209] In a randomized, double-blind, phase III trial, prophylaxis with daily oral or IV dose of letermovir, 480 mg/day (or 240 mg/day in patients taking ciclosporin), was administered to allogeneic HCT recipients for 14 weeks after transplantation. Fewer patients developed clinically significant CMV infection in the letermovir group than in the placebo group (38% vs. 61% in placebo; $P < .001$). The frequency of adverse events, like vomiting and edema, were mildly higher in the letermovir group.[210] Despite the lower toxicity profile of letermovir compared to other CMV-targeted drugs, rapid emergence of resistant mutants under letermovir has been described in cases where treatment is interrupted or underdosed,[211] or in patients with other risk factors.[212,213]

Valganciclovir and ganciclovir are the agents of choice for first-line preemptive therapy; foscarnet is more commonly used for patients who

cannot tolerate ganciclovir or for second-line preemptive therapy.[192] Foscarnet and ganciclovir had similar efficacy as preemptive CMV therapies in allogeneic HCT recipients, but ganciclovir was associated with a higher rate of early discontinuation because of neutropenia or thrombocytopenia.[214] Although ganciclovir had a higher rate of early discontinuation, there remains a paucity of data to recommend foscarnet as first-line treatment for CMV..[215-217]

Pharmacokinetic studies have demonstrated the feasibility and safety of using oral valganciclovir, a pro-drug of ganciclovir, in place of ganciclovir in patients who underwent allogeneic HCT.[218,219] Oral valganciclovir used as preemptive anti-CMV therapy was shown to have acceptable oral bioavailability and was safe and effective in controlling CMV infection in allogeneic HCT recipients, including patients with grades I and II GI GVHD.[218,220-222] Thus, valganciclovir is a highly acceptable oral option for preemptive therapy for CMV in the absence of substantial GI GVHD. Reports of higher rates of CMV disease with oral valganciclovir compared to IV ganciclovir in patients with hepatic dysfunction restricted approval for solid tumor transplant patients by specifically excluding liver transplant patients.[223,224] It is postulated that hepatic dysfunction allows bioabsorption of valganciclovir but decreases cleavage of the valine ester, thereby limiting conversion to the active form.[224]

Cidofovir has been evaluated as both primary and secondary preemptive therapy in allogeneic HCT recipients.[225-228] In a retrospective study of allogeneic HCT recipients (N = 82) treated for CMV disease (n = 20), primary preemptive therapy (n = 24) or secondary preemptive therapy (n = 38) with cidofovir demonstrated an observed response in 50% of patients treated for CMV disease (mainly CMV pneumonia) and in 62% of patients treated with primary preemptive therapy.[227] Moreover, secondary preemptive therapy with cidofovir resulted in a response rate of 66% in patients where disease progressed or relapse occurred (defined as continued presence or recurrence of pp65 antigenemia or viral DNA after at least 1 week of antivirals) following initial preemptive therapy with ganciclovir, foscarnet, or a combination of these agents.[227]

For CMV infections that are refractory or resistant to available antivirals (valganciclovir, ganciclovir, foscarnet, cidofovir), maribavir has shown promise in some studies. In a phase II, randomized, double-blind trial, ≥400 mg of maribavir twice daily was found to be active against refractory or resistant CMV infections in transplant recipients, with a higher proportion of patients achieving undetectable CMV DNA within 6 weeks of treatment compared to placebo.[229] Dysgeusia was the most common treatment-related adverse event. In another phase III randomized trial, maribavir was superior to other anti-CMV agents in HCT and solid organ transplant recipients, with 56% of patients achieving CMV viremia clearance under maribavir compared to 24% under other agents (P < .001). Maribavir was also associated with less acute kidney injury versus foscarnet (8.5% vs. 21.3%) and with less neutropenia versus valganciclovir/ganciclovir (9.4% vs. 33.9%).[230] On the other hand, in another phase III randomized double-blind trial, noninferiority of maribavir to valganciclovir for the primary endpoint of confirmed CMV viremia clearance was not achieved based on the prespecified noninferiority margin (69.6% vs 77.4%).[231] However, maribavir demonstrated comparable CMV viremia clearance to valganciclovir during post-treatment follow-up (52.7% vs 48.5%), with fewer discontinuations due to neutropenia.

Late CMV disease, defined as occurring after day 100 of HCT, remains a persistent problem in the era of CMV prophylaxis and preemptive therapy. CMV infections are also common among patients with lymphoproliferative malignancies, patients receiving T-cell suppressive therapy with purine analogues, and patients receiving alemtuzumab therapy, and occurs most frequently between 3 to 6 weeks after initiation of therapy when T-cell

counts reach a nadir.[33,37-39,232,233] Several studies of alemtuzumab in patients with CLL have demonstrated the effectiveness of using routine CMV monitoring coupled with preemptive anti-CMV therapy with ganciclovir in preventing overt CMV disease.[33,37,38,234] 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%; $P = .004$).[39]

NCCN Recommendations for CMV Prophylaxis

Based on the available data that predict the risk of CMV disease, the NCCN Guidelines Panel recommends routine surveillance for CMV reactivation after allogeneic HCT, consisting of weekly monitoring by PCR, especially during alemtuzumab therapy and at least 2 months after completion of treatment.[235] Upon confirmation of CMV viremia (defined as PCR positivity for CMV in ≥2 consecutive samples obtained 1 week apart), the Panel recommends preemptive therapy with oral valganciclovir, IV ganciclovir or IV foscarnet for at least 2 weeks and until CMV is no longer detectable (see *Prevention of Cytomegalovirus Reactivation or Disease* in the algorithm).

In cases of ganciclovir-resistant CMV or when ganciclovir is not tolerated (eg, ganciclovir-induced myelosuppression), IV foscarnet or IV cidofovir may be used. Additionally, in cases of post-transplant CMV infection that is refractory to ganciclovir/valganciclovir, foscarnet, or cidofovir, oral maribavir may be used. However, infectious disease consult is highly recommended due to the possibility of drug resistance or interaction. Primary prophylaxis with oral or IV letermovir may be considered for CMV-seropositive recipients who undergo allogeneic HCT, with a dose reduction recommended if co-administered with cyclosporine due to drug interactions. In patients receiving allogeneic HCT, 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. Some centers consider the use of letermovir through day 100 post-HCT and continue CMV surveillance for patients at high risk for CMV reactivation. In certain circumstances, up to day 200 can be considered.[236] Letermovir lacks HSV and VZV coverage and HSV/VZV prophylaxis should be continued.

Surveillance should typically occur for at least 3 to 6 months post-transplant and during chronic GVHD requiring IST. Higher risk transplant subgroups may exist and require different management strategies. 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 <5% occur after the second year.[237] Therefore, the value of CMV surveillance beyond 2 years after HCT is unknown but can be considered in patients with significant chronic GVHD. There is debate about how to treat patients after a negative test for CMV. There are not enough data to determine whether patients should be transitioned to surveillance or continue with chronic maintenance therapy, and if so, for how long. The benefits must be weighed against the potential toxicity associated with long-term antiviral use. Ganciclovir and valganciclovir are associated with bone marrow suppression that may increase the risk of common opportunistic infections. Foscarnet can cause nephrotoxicity and electrolyte abnormalities but is tolerated.[214,238] Cidofovir can be associated with substantial nephrotoxicity; although less frequent, ocular toxicity has been reported.[227,228] Acyclovir and valacyclovir have excellent safety profiles but are only weakly active against CMV and are not recommended as prophylaxis or treatment of CMV infection.

For the prevention and treatment of CMV pneumonitis, adjunctive IVIG can be administered; however, IVIG is generally not recommended for

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

Hepatitis B Virus

The risk factors for HBV infection include personal or parental history of an intermediate to high prevalence of HBV infection in one's birthplace (defined as a prevalence of hepatitis B surface antigen [HBsAg] positivity in >2% of the population); household and sexual contact with HBsAg+ persons; individuals with multiple sexual partners or history of sexually transmitted diseases; individuals who have been inmates of correctional facilities; patients with chronically elevated AST or ALT levels; patients with a history of injection drug use; males who have sex with other males (MSM); and patients positive for HCV or HIV.

A positive HBsAg is associated with active infection or a window period before the development of protective immunity in patients 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).[239] False-negative HBsAg results may occur in patients with chronic liver disease.[240] HBsAb positivity is generally equated with protective immunity, although reactivated HBV disease may occur in the setting of significant immunosuppression in individuals who are HBcAb-positive.[241] 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, high-dose corticosteroids, tyrosine kinase inhibitors, anti-CD20/CD52 monoclonal antibodies, 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.[46,239,242-250] The risk of HBV reactivation for patients who are HBsAg negative, HBcAb positive varies widely based on the virological profile, disease, and immunosuppressive regimen. Serum HBV DNA testing prior to the initiation of therapy may help define their risk of reactivation. If viremic, they may receive similar prophylaxis as patients who are HBsAg positive.[251] Complications of HBV reactivation can range from self-limited hepatitis to fulminant hepatic failure and death.[250,252-256] HBV reactivation can lead to early discontinuation or delayed initiation of treatment.[257,258] A systematic review and meta-analysis by Zhang et al[259] revealed that patients with B-cell non-Hodgkin lymphoma (NHL) who are HBsAg+ had worse prognosis and higher incidence of hepatic dysfunction during chemotherapy. In a meta-analysis and evaluation of the U.S. Food and Drug Administration (FDA) safety reports, it was reported that HBcAb positivity correlated with increased incidence of rituximab-associated HBV reactivation.[243] After allogeneic HCT, loss of HBV-specific immunity may occur (ie, loss of HBsAb and development of HBsAg and HBV PCR positivity). This has been observed in up to 40% of susceptible individuals in one report[260] and may be confused with hepatic GVHD. A retrospective study showed that allogeneic HCT recipients who were HBsAg negative but HBcAb positive had a high risk of seroconversion to HBsAg positivity and HBV reactivation (subsequently leading to hepatitis) following allogeneic HCT.[261]

There are several nucleos(t)ide analogs approved by the FDA for the prevention and treatment of HBV. Historically, data supporting the use of these analogues have been based on lamivudine, a reverse transcriptase inhibitor. In a meta-analysis of clinical trials evaluating lamivudine prophylaxis in patients with HBsAg-positive lymphoma treated with IST,

prophylaxis resulted in a significant reduction in HBV reactivation (risk ratio, 0.21; 95% CI, 0.13–0.35) and a trend for reduced HBV-related deaths (risk ratio, 0.68; 95% CI, 0.19–2.49) compared with no prophylaxis.[262] However, despite its initial effectiveness, virologic breakthrough was high, with reports of resistance in 80% of patients after 5 years of therapy.[263] Thus, lamivudine monotherapy has fallen out of favor. Studies suggest one of the newer agents (such as entecavir or tenofovir) may be preferable or combination therapy may have a possible role for patients with lamivudine-resistant HBV infections.[264-266]

As of 2015, tenofovir is available in two different pro-drug forms, tenofovir disoproxil fumarate (DF) and tenofovir alafenamide (AF). Tenofovir AF has greater plasma stability than tenofovir DF, allowing use of a lower dose and lesser systemic exposure to the drug.[267] Tenofovir DF has demonstrated superior antiviral efficacy compared with adefovir in a phase III randomized double-blind study in patients with chronic HBV infection, making tenofovir preferred over adefovir in this setting.[268] Two randomized, phase III, double-blind studies comparing tenofovir AF to tenofovir DF in patients with HBeAg-negative[269] or HBeAg-positive[270] chronic HBV infection showed that the efficacy of tenofovir AF was non-inferior to tenofovir DF, with better bone and renal safety for tenofovir AF. While these data support the use of tenofovir for HBV infection, limited data are available regarding its use in patient populations with cancer. A systematic review and meta-analysis showed that in patients with HBV-associated hepatocellular carcinoma (HCC), tenofovir was associated with better overall survival and reduced late recurrence compared to entecavir.[271] No detectable resistance to tenofovir DF was reported in patients with chronic hepatitis B after 6 years of treatment.[272] In another study, sequencing of the HBV polymerase/reverse transcriptase indicated sequence changes at polymorphic sites, though none resulted in drug resistance.[273] In total, there were only 16 cases of virologic breakthrough, 12 of which were associated with nonadherence to study medication. Resistance for tenofovir DF remained undetectable throughout a 5-year span. By comparison, lamivudine resistance was calculated to be 24% in the first year, and this number steeply climbed to 70% by year 5.[273]

Entecavir has shown improved antiviral activity compared to adefovir in randomized open-label studies in patients with chronic hepatitis B.[274] A few small case studies have evaluated entecavir in the prevention[275] or treatment of HBV in patients with cancer (reviewed by Liu et al[276]). Entecavir had a low drug resistance of 1.2% at 5 years[277] compared to adefovir, which had an intermediate resistance that increased from 0% in the first year to 29% by year 5.[268,278,279]

In addition to drug resistance, the safety profile of the nucleos(t)ide analogues should affect drug selection. Nephrotoxicity has been seen with adefovir[280,281] and tenofovir (specifically tenofovir disoproxil fumarate [TDF]).[282] No significant side effects have been reported with lamivudine or entecavir; however, it is recommended that all patients be monitored for lactic acidosis and severe hepatomegaly with steatosis.

NCCN Recommendations for HBV Prophylaxis

Risk-based screening is recommended by the American Society of Clinical Oncology (ASCO)[283] and the American Association for the Study of Liver Disease (AASLD). [284] Although it is possible that risk-based screening may be more cost-effective than universal screening, there are currently no validated risk tools that could easily be implemented into clinical practice. Furthermore, <60% of patients with HBV infection may have obvious risk factors,[285] and only 10% to 35% of these patients may be aware of their own HBV infection.[286] Therefore, any patient expected to receive IST or chemotherapy should be screened. Implementation of universal screening, as recommended by the CDC, should be considered. [287]

In patients undergoing intensive IST, including HCT, both patient and donor should be screened for HBV, HCV, and HIV prior to treatment.

Evaluation of HBsAg, HBcAb, and HBsAb should be considered at baseline. [192,239] Vaccination against HBV should be strongly considered in patients who are HBV-naïve (ie, negative for HBsAg, HBsAb, and HBcAb) (see *Vaccination*).[192,239] In patients who are HBV-naïve undergoing allogeneic HCT, grafts from donors who are HBsAg-positive or HBV DNA-positive should be avoided wherever possible. Donors who have not been exposed to HBV should be considered for HBV vaccination before hematopoietic cell collection.

In individuals who are HBsAg-positive or HBcAb-positive, baseline quantitative PCR for HBV DNA should be obtained. In allogeneic HCT candidates with evidence of active HBV infection (chronic hepatitis based on biopsy or positive HBsAg or high levels of HBV DNA), transplant procedure should be delayed when possible, and antiviral therapy should be given for 3 to 6 months prior to conditioning.[192] In HCT candidates who are HBsAg-positive or HBcAb-positive but without evidence of active HBV replication, antiviral prophylaxis should be considered (starting shortly before the transplant procedure). All allogeneic HCT recipients should continue surveillance for at least 12 months after transplant or during GVHD (see *Management Of Hepatitis B Virus, Hepatitis C Virus, And Human Immunodeficiency Virus Reactivation Or Disease* in the algorithm). For details on the management of HBV infection in patients with B-cell NHL, see the NCCN Guidelines for B-Cell Lymphomas.

The optimal choice of antiviral agents for prophylaxis (or preemptive approaches) will primarily be driven by institutional standards. The NCCN Panel recommends consultation with an expert in hepatitis treatment to determine appropriate antiviral prophylaxis for patients who test positive for HBV. Preferred agents for HBV prophylaxis are entecavir and tenofovir. Although data were originally obtained with lamivudine, entecavir and tenofovir are preferred, especially when treating patients with active HBV infections due to the low threshold of resistance with lamivudine.

Monitoring of HBsAg and HBV DNA and transaminases should be considered for patients without active HBV infection who are not receiving prophylaxis.

Hepatitis C Virus

Studies for HCV reactivation in patients with cancer are not as expansive as studies for hepatitis B; however, an increase in mortality was reported in patients with cancer who had HCV infection compared to patients with cancer who were HCV negative.[288] A review by Yazici et al[289] summarized studies of HCV reactivation in patients receiving targeted therapies and the data correlated an increase in HCV reactivation with these therapies.[289] Differences in outcomes between patients who are HCV positive with cancer versus HCV positive without cancer were reported to include higher occurrence of occult infection, higher risk of developing early cirrhosis, higher rate of fibrosis progression, development of viral reactivation, and poorer virologic outcomes (reviewed by Borchardt et al).[290] The guidelines from the joint IDSA and AASLD Panels for the testing, management, and treatment of hepatitis C recommend that treatment for HCV be considered for patients with chronic HCV with a life expectancy of >12 months.[291]

NCCN Recommendations for HCV Screening and Management

All patients who are expected to receive chemotherapy or IST should be screened for HCV. The data are limited regarding the treatment of HCV in patients with cancer, but it is generally not recommended that HCV treatment and cancer therapy be given concurrently.[290] The IDSA/AASLD guidelines can provide additional guidance for antiviral therapy, but an infectious diseases consult is necessary to evaluate the use of concomitant or sequential anti-HCV and cancer therapy.[291] Monitoring of ALT levels and HCV viral load monthly, or as clinically indicated, should be initiated as part of surveillance (see *Management Of Hepatitis B Virus, Hepatitis C Virus, And Human Immunodeficiency Virus Reactivation Or*

Disease in the algorithm). For details on the management of HCV infection in patients with HCV-associated lymphomas, see the NCCN Guidelines for B-Cell Lymphomas.

Human Immunodeficiency Virus

The CDC surveillance report estimates that 1.1 million persons are living with HIV in the United States. This includes the estimated 166,000 persons whose infection has not yet been diagnosed.[292] There is support for HIV testing in all patients treated for cancer.[293] Patients who are HIV-positive and have cancer are classified as having either AIDS-defining cancer (ADC) or non–AIDS-defining cancer (NADC). ADC includes Kaposi sarcoma, NHL, and cervical cancer. There is a higher incidence of these cancers in those who are HIV-positive than in those who are HIV-negative.[294]

The incidence of NADC is increasing, likely due to the longer life expectancy of patients with HIV resulting from the advancement of treatment options.[295] Patients with HIV and NADC were shown to have an overall worse cancer outcome when compared to patients who are HIV-negative with the same cancer.[296] However, improvement in outcome was seen when patients with HIV received highly active antiretroviral therapy (HAART).[297] There should be caution regarding the concomitant administration of select antiretroviral therapies (including the protease inhibitors and non-nucleoside reverse transcriptase inhibitors) with cancer therapy as adverse events through cytochrome P450 3A4 have been documented.[298] A publication from MD Anderson Cancer Center retrospectively evaluated the use of HIV screening in patients prior to systemic cancer therapy.[299] Out of the 18,874 patients in this study, there were 3514 patients who tested positive for HIV at the initiation of systemic cancer therapy. Patient histories indicated a higher incidence in patients with sexually transmitted disease (37.7% vs. 18.5%; $P < .001$) or a history of illegal drug use (46.2% vs. 18.6%; $P < .001$). Patients screened for HIV included 12.1% of patients with NADC and 9.4% of patients with cervical cancer. Interestingly, a significantly higher percentage (88.4%) of patients with NHL were screened for HIV, which may be partially attributed to clinician education of the role of HIV in these patients.[299]

NCCN Recommendations for HIV Screening

In 2006, the CDC published recommendations for routine HIV testing in all patients (13–64 years of age) in the health care setting.[300] 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 will be conducted unless the patient declines testing (opt-out screening). The CDC recommends that patients at high risk for HIV infection be screened at least annually.[300] The implementation of these guidelines is largely dependent upon institutional practices and the prevalence of undiagnosed HIV infections in specific institutions. However, the NCCN Panel strongly encourages concordance with the CDC recommendations.

In addition to the CDC recommendations, the NCCN Panel emphasizes that all patients receiving chemotherapy or IST be screened for HIV.[293] Patients co-infected with hepatitis pose an additional complication. Select antiretroviral therapies including the integrase strand inhibitors and nucleoside/nucleotide reverse transcriptase inhibitors have demonstrated fewer drug-drug interactions compared with the protease inhibitors and non-nucleoside reverse transcriptase inhibitors. However, consultation with an infectious disease expert is necessary for treatment of HIV in patients with cancer as therapies continuously evolve. HIV viral load should be monitored monthly during therapy and then as clinically indicated (see *Management Of Hepatitis B Virus, Hepatitis C Virus, And Human Immunodeficiency Virus Reactivation Or Disease* in the algorithm and NCCN Guidelines for Cancer in People with HIV).

Screening for Other Viruses

Rapid PCR panels should be considered for detection of respiratory viruses including RSV, influenza, parainfluenza virus, adenovirus, rhinovirus, and metapneumovirus in patients with cough and/or shortness of breath that might indicate a viral infection. Ribavirin and IVIG have been proposed as antiviral therapies[301-305]; however, data are not sufficient to provide recommendations.

RSV is a major cause of severe infection in patients who are immunocompromised, with mortality rates ≤80% in HCT recipients.[306,307] Progression of RSV to the lower respiratory tract occurs in ≤50% of patients receiving HCT or chemotherapy.[308-310] The virulent nature of RSV requires hospitalization for treatment. Treatment options are limited to ribavirin and adjunctive IVIG. There is a diversity of practice among the institutions for the treatment of RSV disease. Based on limited data[311-313] and strong Panel disagreement regarding the use of ribavirin and the best method of delivery, ribavirin has been designated a category 3 recommendation. Recommendations for inhaled versus oral ribavirin should be based on the individual institution.

Rapid screening tests are available for detection of influenza. Clinical benefit is highest when treatment is initiated within the first 48 hours of influenza symptoms, although benefits can still be seen when initiated after the 48-hour window.[314] 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.[315,316] 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. However, longer courses of treatment (eg, 10 days) and treatment until resolution of symptoms can be considered in those who are immunocompromised, though this is controversial. Some centers have used higher doses (eg, 150 mg BID) of oseltamivir in these patients with mixed results. Pandemic influenza does not have a predictable seasonal pattern and may spread in the community concurrently with a seasonal influenza strain. Antiviral susceptibility of influenza strains is variable and cannot be predicted based on previous influenza outbreaks. In cases of seasonal influenza and pandemic strains, it is necessary to be familiar with susceptibility patterns and guidelines on appropriate antiviral treatment.[317] There are limited data on the activity of peramivir; with comparable clinical outcomes observed in comparison with oseltamivir.[318,319] Peramivir, available as an IV injection, can be considered for patients who cannot absorb oral oseltamivir or tolerate oseltamivir or inhaled zanamivir.

A few small case studies showed limited efficacy of baloxavir, a polymerase inhibitor active against both influenza A and B viruses, in immunocompromised patients with oseltamivir- or peramivir-resistant influenza.[320-322] However, due to limited data and emergence of resistant strains,[322,323] this option is not routinely recommended by the CDC.

BK virus is a common polyomavirus that remains dormant in the kidney and urinary tract. In immunosuppressed individuals, BK virus can reactivate. Patients undergoing allogeneic HCT are particularly vulnerable to BK virus, and the development of hemorrhagic cystitis and additional complications such as ureteral stenosis.[324,325] Supportive care remains the mainstay of management. While cidofovir demonstrates effectiveness as a treatment option for BK virus, renal toxicity is a significant complication.[326] There is currently a lack of data to support recommendations on the treatment of BK virus. Expert consensus on management has been published for pediatric HCT recipients.[327]

COVID-19 screening, prophylaxis and treatment is a complex and rapidly evolving area. Please see the CDC guidelines for latest recommendations.

Prophylaxis for *Pneumocystis jirovecii*

TMP/SMX prophylaxis for *Pneumocystis jirovecii* is highly effective in preventing *Pneumocystis jirovecii* pneumonia (PJP).[328-331] In a systematic review and meta-analysis of 12 randomized studies (N = 1245; primarily in patients with acute leukemias or in HCT recipients), prophylaxis with TMP/SMX resulted in a significant reduction in PJP occurrence by 91% compared with placebo, no treatment, or treatment with non-PJP antibiotics (RR, 0.09; 95% CI, 0.02–0.32). In addition, TMP/SMX prophylaxis significantly reduced PJP-related mortality (RR, 0.17; 95% CI, 0.03–0.94).[328] TMP/SMX 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.[332] TMP/SMX is considered the treatment of choice for PJP prophylaxis (preferred, category 1; see *Prevention Of Pneumocystis Jirovecii Infection* in the algorithm). In cases of intolerance, TMP/SMX desensitization should be considered. Atovaquone, dapsone and aerosolized or IV pentamidine are alternatives to TMP/SMX in cases of intolerance. [333-335] For patients receiving dapsone, measurement of G6PD levels is recommended prior to the initiation of therapy. Patients who are G6PD deficient may have an increased risk for hemolytic adverse reactions. Methemoglobinemia can also occur with dapsone therapy.[336] Atovaquone appears to be equivalent to dapsone in HIV patients who cannot tolerate TMP/SMX.[337] In pediatric patients with acute leukemias who were intolerant of TMP/SMX, atovaquone was reported to be an effective strategy for PJPprophylaxis.[338]

Prophylaxis against PJP should be used in allogeneic HCT recipients (category 1) and patients receiving CAR T-cell therapy for at least 6 months and while receiving IST, as well as in patients with ALL (category 1) throughout anti-leukemic therapy.[339,340] Patients should receive prophylaxis against PJP for a minimum of 2 months after alemtuzumab and until the CD4 count is >200 cells/mcL. Other patients who should receive PJP prophylaxis at least through active treatment include: 1) those receiving treatment with select phosphatidylinositol-3-kinase (PI3K) inhibitors (copanlisib, idelalisib, or duvelisib) +/- rituximab; 2) patients with neoplastic diseases receiving intensive corticosteroid treatment (eg, the equivalent of ≥20 mg of prednisone daily for ≥4 weeks, also depending on the patient's overall immunologic status); and 3) patients receiving temozolomide (see *Prevention Of Pneumocystis Jirovecii Infection* in the algorithm).[340-343] Some panel members advise prophylaxis against PJP (category 2B) for patients receiving purine analog therapy (eg, fludarabine, cladribine [2-CdA]) and other T-cell–depleting agents until CD4 count is >200 cells/mcL and for autologous HCT recipients until 3 to 6 months post-transplant. Prophylaxis against PJP may also be considered in patients receiving certain bispecific antibodies. For more information on infection risks associated with bispecific antibodies, see the full NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

Vaccination

Vaccination in patients with cancer can reduce the morbidity and mortality associated with infection. In general, patients with hematologic malignancies have a greater risk for infection than patients with solid tumors. Patients receiving HCT may lose immunity to pathogens post-transplant. Therefore, vaccination recommendations for these patients are more expansive than the recommendations for the general population of patients with cancer. In any patient who is immunocompromised, live vaccines, including the live attenuated influenza vaccine (LAIV), have the potential to cause disease and should not be administered during chemotherapy or periods of significant immunosuppression such as treatment for GVHD. The safety of vaccines for patients receiving immunostimulatory drugs has not been established. Inactivated vaccines

can often be safely administered to patients with cancer. Although the immunogenicity of the vaccines may be reduced in patients who are immunocompromised, the potential for protection conferred by antigen-derived vaccines, even if incomplete, is better than no protection if the vaccine is withheld. While guidelines may provide general recommendations for vaccination schedules, the efficacy and safety of each vaccine should be evaluated to optimize the schedule on a case-by-case basis. For more information on vaccination in cancer survivors, see the NCCN Guidelines for Survivorship.

Influenza Vaccine

Influenza infections cause significant morbidity and mortality in patients with cancer. Among bone marrow transplant recipients, influenza accounts for about 10% to 40% of all community-acquired viral respiratory infections.[344-346] An increase in both the incidence and duration of influenza infections has been observed in patients with cancer who are immunosuppressed compared to healthy controls.[347,348] During community outbreaks, influenza infections may represent a significant proportion of fever and neutropenia episodes.[349] Influenza infections in patients with cancer who are severely immunocompromised are often associated with hospitalizations, delays in potentially life-saving chemotherapy, and occasionally death.[347-349] As a result, annual vaccination against influenza with the inactivated influenza virus is recommended for all individuals at increased risk due to immunosuppression.[350] A randomized study of 97 patients receiving cytotoxic chemotherapy (3-week cycles) for solid tumors found that the immunogenicity of the influenza vaccine was similar when administered at the time of chemotherapy administration (day 1) or within the cytopenic period (day 11).[351] The Advisory Committee on Immunization Practices (ACIP) for the CDC guidelines includes health care professionals and household members or caregivers in their target group for annual immunization to prevent transmission of influenza to patients at high risk.[350]

The intranasal vaccine should be avoided in patients with immunosuppression, because a LAIV is still capable of replication, which could theoretically lead to infection in immunocompromised individuals.[350,352] Because no data are available assessing the risk for person-to-person transmission of the LAIV from vaccine recipients to immunosuppressed contacts, the CDC recommends that inactivated influenza vaccine should be used in household contacts, health care workers, and others who have close contact with patients who are severely immunocompromised (ie, persons requiring a protected environment). Persons with close contact to patients with a lesser degree of immunosuppression (eg, patients receiving chemotherapy or corticosteroids, patients with HIV) may receive the LAIV.[350,352]

There are not yet sufficient data for the Panel to recommend the high-dose influenza vaccine over the standard-dose influenza vaccine. Preliminary data have shown that the high-dose influenza vaccine is safe for patients with cancer and may show more immunogenicity compared to the standard-dose influenza vaccine for this patient population.[353,354] A randomized, single-blind, controlled trial of influenza vaccine in autologous HCT recipients found comparable seroprotection and seroconversion rates against all influenza strains with both the high-dose and the standard-dose vaccines when used as part of a two-dose regimen.[355] Further data are needed to assess whether the high-dose influenza vaccine confers a clinical benefit compared to the standard-dose vaccine for patients with cancer.

Pneumococcal Vaccine

The pneumococcal conjugate vaccine can be given in newly diagnosed adults with hematologic or solid tumor malignancies following assessment of their immune status. The conjugate pneumococcal vaccine (PCV20) should be administered to newly diagnosed adults with cancer who are pneumococcal vaccine-naïve. Alternatively, PCV15 can be given, followed

by the polysaccharide pneumococcal vaccine (PPSV23) at least 8 weeks later. Additional PPSV23 is not needed for those receiving PCV20. For patients who have previously received PPSV23, PCV20 (preferred) or PCV15 can be given. Patients who have previously received PCV13 only can receive PCV20 (rather than PPSV23) at least 1 year later. Patients who have previously received PCV13 and 1 to 2 doses of PPSV23 can receive PCV20 at least 5 years later.

A phase 3 randomized controlled clinical trial found that PCV15 had a comparable safety profile to PCV13 in allo-HCT recipients, and induced comparable immune responses to PCV13.[356] Based on CDC Recommendations, vaccination with the conjugated 20-valent or 15-valent vaccine 3 to 6 months after HCT is recommended. If PCV20 is used, 4 doses should be administered. The first 3 doses are generally 1 to 2 months apart, with the fourth dose 6 months after the third dose. There is no need to give PPSV23. If PCV15 is used, 3 doses should be administered, followed by PPSV23 6 to 12 months post primary series. Following the primary series of 3 PCV doses, a dose of the PPSV23 to broaden the immune response might be given. For patients with chronic GVHD in whom PPSV23 might not be as effective, a fourth dose of PCV20 or PCV15 should be considered instead of PPSV23. Patients with asplenia should receive the pneumococcal vaccine. According to the ACIP Vaccine Recommendations and Guidelines for Altered Immunocompetence, the pneumococcal vaccine should be administered at least 2 weeks before elective splenectomy. Penicillin prophylaxis is advised in patients who are asplenic to prevent pneumococcal disease.[357,358]

Meningococcal Conjugate Vaccine

The meningococcal vaccine is recommended for patients with increased risk for meningococcal disease including patients with persistent complement component deficiency, patients taking eculizumab, and patients with anatomic or functional asplenia. The ACIP recommends that asplenic persons be immunized with the meningococcal vaccine. The meningococcal vaccine should be administered at least 2 weeks before elective splenectomy. Patients at increased risk for meningococcal disease should receive quadrivalent conjugate vaccine series (MenACWY) and monovalent meningococcal serogroup B vaccine series. Patients at risk include those with persistent complement component deficiencies, those taking a complement C5 inhibitor (eg, eculizumab, ravulizumab), or those with anatomic or functional asplenia. MenACWY vaccine is given in 2 doses ≥8 weeks apart; serogroup B vaccine is available in a 2- or 3-dose series, depending on the vaccine formulation used. The meningococcal vaccine is recommended 6 to 12 months after HCT. Booster doses can be considered in those that remain at risk for meningococcal disease. This includes revaccination every 5 years with MenACWY vaccine, while for MenB vaccine, 1 booster dose is recommended 1 year after primary series with revaccination every 2–3 years if risk remains.

Human Papillomavirus Vaccine

The human papillomavirus (HPV) vaccine is a recombinant 3-dose vaccine that is recommended for patients ≤26 years of age and can be considered for those up to age 45. The lower age limit for this vaccine is 9 years of age. While it doesn't treat existing HPV infection or disease, HPV vaccination is still recommended in individuals with prior HPV since it can still provide protection against HPV serotypes not already acquired.

Haemophilus Influenzae Type b Vaccine

Immunization of adults with the pediatric *H influenzae* type b (Hib) vaccine is considered optional because of limited data on efficacy in older children and adults, although studies suggest good immunogenicity in patients who are immunocompromised. The Hib vaccine is recommended 6 to 12 months post-HCT. For patients with planned splenectomy, immunization is ideally performed at least 2 weeks in advance. If this is not feasible,

immunization is advisable after splenectomy, because such patients are still capable of mounting a protective antibody response.

Varicella/Zoster Vaccines

The recombinant zoster vaccine (RZV) should be given to patients 50 to 70 days after autologous HCT. RZV may be considered after allogeneic HCT; however, its efficacy in allogeneic HCT, in the presence of GVHD, or during ongoing immunosuppression has not been established. The CDC recommends administration of RZV for patients aged ≥50 years, and those ≥18 years who are at increased risk for herpes zoster. The RZV vaccine is given in 2 doses 2 to 6 months apart. For adults who are immunocompromised and aged ≥18 years, a second dose can be given 1 to 2 months after the first dose if they will benefit from a shorter vaccination schedule. For patients who have previously received the live-attenuated herpes zoster vaccine (ZVL), RZV should be given at least 2 months after the last ZVL dose.

COVID-19 Vaccine

The NCCN Guidelines recommend COVID-19 vaccination for all persons with cancer, or who have been previously treated for cancer. According to the CDC, individuals aged ≥6 months who are moderately or severely immunocompromised (including recipients of HCT) and not previously vaccinated against COVID-19 should get 2 or 3 doses of the same brand of updated COVID-19 vaccine. Additionally, updated vaccines should be administered at least 2 weeks before initiation or resumption of immunosuppressive therapies. The NCCN Guidelines recommend vaccination with COVID-19 vaccine 6 months post-HCT, with a consideration for early vaccination at 3 months during community outbreaks and high disease activity. For further details of the most up-to-date vaccination recommendations, refer to CDC guidance.

Tetanus/Diphtheria/Pertussis (Tdap) Vaccine

As per the CDC, individuals ≥7 years should receive one dose of Tdap every 10 years. The FDA/ACIP approved a 3-dose series of Tdap/Tdap/Tdap or Tdap/Td/Td (tetanus/diphtheria) for individuals ≥7 years. For recipients of HCT, NCCN recommends administration of the 3-dose vaccine series, with the first dose 6 to 12 months post-HCT.

Respiratory Syncytial Virus (RSV) Vaccine

The RSV vaccine is available for adults aged ≥60 years. However, its effectiveness in patients with cancer is unknown. The long-acting RSV monoclonal antibody (nirsevimab) is approved for infants <24 months of age to prevent RSV infection.

Travel Vaccines

Vaccines have variable risk and efficacy in patients receiving cancer care; therefore, the Panel recommends consultation with an infectious disease expert prior to the administration of travel vaccines (eg, typhoid, yellow fever). Additional information on travel vaccines may be found in the CDC Yellow Book.

Vaccine Summary

Although efficacy data are lacking for the use of vaccines in patients with cancer, recommendations for their use are based on the principles of immunization and safety data. Persons receiving chemotherapy or radiation therapy for malignancies should not receive live vaccines for at least 3 months after cessation of therapy and until they are presumed to be immunocompetent.[359] Live vaccines are contraindicated during treatment and for a period of at least 6 to 12 months in patients receiving IST (eg, blinatumomab, CAR T-cell therapy, monoclonal antibodies). These patients may also have a blunted response to inactivated vaccines. Certain live vaccines can be safely administered to household members of patients who are severely immunocompromised (eg, measles, mumps, rubella [MMR]), whereas others cannot (eg, smallpox vaccine) because of

the potential risk of transmission. The package insert for the vaccine should be reviewed prior to administration. The NCCN Panel recommends that all household members be up to date on vaccinations.

Ideally, patients should be vaccinated at least 2 weeks before receiving cytotoxic therapy or IST; however, this timing is often not feasible in patients with cancer. In general, vaccination should not be given on the same day as cytotoxic therapy as cytotoxic therapy may reduce the proliferative lymphocytic responses required for protective immunity. In patients receiving chemotherapy, immunization between cytotoxic chemotherapy courses is likely to be associated with higher response rates than during chemotherapy administration.[360,361] Patients vaccinated <2 weeks before starting cytotoxic therapy or IST or while receiving these agents may have a limited response to vaccination. These patients should be revaccinated at least 3 months after therapy is discontinued and once immune competence has been restored.[359]

In summary, the NCCN Panel recommends that patients with cancer receive the influenza, COVID-19, pneumococcal, meningococcal, and HPV vaccines (see *General Recommendations For Vaccination In Patients With Cancer* in the algorithm). HCT recipients should also receive the inactivated vaccines for Tdap, Hib, hepatitis A and B, RZV, and polio (see *Recommended Vaccination Schedule After Autologous Or Allogeneic HCT* in the algorithm). The live vaccines for MMR and varicella may be given if no GVHD or ongoing immunosuppression is seen 2 years post-transplant in patients who are seronegative. Consultation with an infectious disease expert is recommended prior to administration of travel vaccines.

Protected Environments

Although well-designed clinical trials have not validated the use of high-efficiency particulate air (HEPA) filtration, the CDC recommends that allogeneic HCT recipients be placed in rooms with HEPA filters.[8,362] It is also reasonable to use HEPA filtration in patients who are nontransplant recipients 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 those who are highly immunocompromised with hematologic malignancies in the setting of an outbreak of aspergillosis.[363] The value of laminar airflow in preventing infections is unclear and generally is not recommended.[364]

Management of Neutropenia and Fever

The definitions of fever and neutropenia in the NCCN Guidelines are consistent with those developed by the IDSA and FDA for evaluating antimicrobial therapy for fever and neutropenia.[1] *Fever* is defined as a single oral temperature of ≥38.3°C (or equivalent) or ≥38.0°C over 1 hour in the absence of an obvious cause. Axillary or rectal temperature measurements should be avoided.[17] 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 localized signs of infection. The NCCN Guidelines define *neutropenia* as either: 1) an ANC ≤500 neutrophils/mcL; or 2) an ANC ≤1000 neutrophils/mcL and a predicted decline to ≤500 neutrophils/mcL 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 should be started soon after the time of presentation (see *Initial Evaluation of Fever and Neutropenia* in the

algorithm). The common sites of infection for patients with fever and neutropenia (such as the alimentary tract, skin, lungs, sinus, ears, perivaginal/perirectal, urologic, neurologic, and intravascular access device sites) should be thoroughly assessed with special attention to any devices. Other important factors in patient history to consider include major comorbid illness, medications, type and time since last chemotherapy administration, recent antibiotic therapy/prophylaxis, use of invasive devices, and previously documented infections. Other epidemiologically relevant exposures that should be considered include marijuana use, cigarette smoking, infections from household members, pets, travel, and recent blood product administration (see *Initial Evaluation of Fever and Neutropenia* in the algorithm).

Initial laboratory/radiology evaluation should include a complete blood count with differential analysis and a comprehensive metabolic panel, including blood chemistry tests to assess liver function (eg, total bilirubin, albumin, alanine aminotransferase [ALT], aspartate aminotransferase [AST]) and renal function (eg, blood urea nitrogen [BUN], 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 neutropenia with pulmonary infection.[365]

Cultures

Culture specimens should be collected during or immediately after completing the examination. Two blood samples should be cultured. When obtaining blood cultures, one set can be obtained peripherally and one can be obtained from a central venous catheter (preferred but not required) (see *Initial Evaluation of Fever and Neutropenia* in the algorithm). The positive predictive value (PPV) of a catheter culture is less than of 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 (DTP).[366] 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.[366] 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.[367] The Panel consensus is that the volume of blood for culture is the most important aspect of blood culturing; however, the Panel recommends obtaining one peripheral and one catheter culture for distinguishing between catheter-related infections and those 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*.[368] 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* in the algorithm). 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.[369,370] However, note that rapid immunofluorescent viral antigen tests may still result in a false negative for H1N1 (swine flu).

Outpatient Therapy for 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 trial eligibility criteria. [4,78,371-376] Risk assessment attempts to predict the probability that a patient with neutropenia 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 which initial empiric therapy with oral antibiotics is appropriate.

Prospective trials have indicated that febrile neutropenia can be initially evaluated in the hospital, ambulatory clinic, or home and then treated effectively with broad-spectrum IV therapy, sequential IV then oral therapy, or oral therapy.[377-379] Only centers with the necessary infrastructure should treat patients at low risk 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 Patients with Febrile Neutropenia* in the algorithm). A widely used and 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, chronic obstructive pulmonary disease [COPD], dehydration), history of prior fungal infections, site of medical care (eg, 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* in the algorithm).[380-383]

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. For example, the Clinical Index of Stable Febrile Neutropenia (CISNE) is a prognostic model developed in the FINITE study from a retrospective cohort of patients with solid tumors and seemingly clinically stable febrile neutropenia episodes.[384] The CISNE model comprises six explanatory variables associated with serious complications: Eastern Cooperative Oncology Group (ECOG) performance status ≥2 (2 points); COPD (1 point); chronic cardiovascular disease (1 point); mucositis of grade ≥2 (NCI Common Toxicity Criteria; 1 point); monocytes <200 per µL (1 point); and stress-induced hyperglycemia (2 points). These factors were integrated into a score ranging from 0 to 8, which classifies patients into three prognostic classes: low (0 points), intermediate (1–2 points), and high risk (≥3 points).[384] There are risks of applying models to populations that differ from those in which they were originally validated. Thus, a two-step combination of a set of exclusion criteria (MASCC risk index) plus a validated triage-friendly scale (CISNE) might render better prognostic stratification than those of single-model approaches.

It is important to note that risk stratification generally, as well as the MASCC risk index and the CISNE index specifically, were validated in adults. No generalizable, cross-validated, risk-stratified management exists for pediatric patients with febrile neutropenia.

The MASCC prediction rule does not consider the duration of neutropenia to be a deciding factor that influences the clinical course of treatment;[382] 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 neutropenia in patients with cancer.[17]

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,[20] the fatality rate was highest (80%) among patients with initial neutrophil counts <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 <1000 cells/mcL that rose to >1000 cells/mcL with treatment.[20] 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 recovered from neutropenia was 67%, compared to only 32% in patients who remained severely neutropenic ($P < .0001$).

In 1988, Rubin et al examined the influence of the duration of neutropenia on the response to empiric antimicrobial therapy in patients with fever of undetermined origin.[385] Patients with <7 days of neutropenia had a 95% response rate to initial antimicrobial therapy, compared to a 32% response rate in patients with >14 days of neutropenia ($P < .001$); however, intermediate durations between 7 and 14 days had response rates of 79%.[385]

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, HCT recipients, patients with known bone marrow metastases, patients who have received radiation therapy to the pelvis, spine, or long bones). Most patients with solid tumors have neutropenia lasting <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 criterion. Clinicians were correctly able to identify patients with an expected short duration of neutropenia (ie, <7–10 days) in >80% of the cases,[377,378,386] 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 those at low risk with neutropenic fever. Several single-center clinical trials generally support the shift in care for patients at low risk to the outpatient setting; the hospital is not necessarily a safer place for such patients, given the documented hazards of hospitalization.[387,388] However, not all centers are equipped to manage 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 patients at high risk for infections receive hospital care with broad-spectrum IV therapy (see *Initial Risk Assessment for Patients with Febrile Neutropenia* in the algorithm). Patients at low risk 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 patients at low risk 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 can be considered (category 2B) (see *Outpatient Therapy for Patients at Low Risk* in the algorithm). 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 treating 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.[389] For selected patients at low risk, the combination of ciprofloxacin with amoxicillin/clavulanate is considered the oral regimen of choice based on well-designed randomized trials (category 1) (see *Outpatient Therapy for Patients at Low Risk* in the algorithm). 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.[371,390,391] Ciprofloxacin plus clindamycin is an acceptable alternative for those with penicillin allergies.[3,17] 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.[392] Nonetheless, several small studies have used high-dose oral ciprofloxacin alone in patients at low risk of infection with fever and neutropenia.[393-395]

Moxifloxacin (category 1) is a newer-generation fluoroquinolone that was shown to be safe in patients at low risk with neutropenic fever.[396] In a double-blind, randomized trial, single-daily moxifloxacin was compared with twice-daily ciprofloxacin plus amoxicillin/clavulanic acid in the treatment of low-risk febrile neutropenia in patients with cancer.[397] Low risk was defined as an MASCC score >20 that is equivalent to a <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%–8%; *P* = NS). Despite similar therapy success rates, the reasons for disease progression 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 disease progression. 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 those with low risk for infections with febrile neutropenia, but the choice of regimen may be influenced by local resistance and infection patterns.

Two other fluoroquinolones, levofloxacin and ofloxacin, have been tested for the treatment of patients at low risk with febrile neutropenia. Levofloxacin is a category 2A recommendation following studies demonstrating safety and efficacy[79,80] (see *Antibacterial Prophylaxis*). Data from a 2008 self-administered survey indicated that 50% of oncologists were using levofloxacin as empiric therapy for patients at low risk with febrile neutropenia.[398] Ofloxacin was safe in patients at low risk 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.[377] Ofloxacin is not currently recommended.

NCCN Recommendations for Outpatient Therapy

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 patients allergic to penicillin) is the standard oral outpatient antibiotic regimen for patients at low risk with neutropenic fever. There is also evidence supporting quinolone monotherapy in this setting.

Moxifloxacin (category 1) and levofloxacin (category 2A) are recommended quinolone monotherapies. These recommendations for quinolone-based outpatient regimens for neutropenic fever only apply to patients at low risk who have not received a quinolone as prophylaxis. Additionally, in order for these patients 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 Patients at Low Risk* in the algorithm). IV therapy may also be used for outpatient treatment of patients at low risk with fever and neutropenia when treatment is given either in the home or day clinic setting (see *Outpatient Therapy for Patients at Low Risk* in the algorithm). Several IV outpatient regimens for patients at low risk have been studied in nonrandomized or small open trials, including IV ceftazidime, imipenem/cilastatin, and aztreonam plus clindamycin.[3,371,378,379,399-401]

Once-daily ceftriaxone has been used for empiric antibiotic therapy in a few noncomparative studies in centers where *Pseudomonas* is not a common pathogen.[402] 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 patients of low risk 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 Patients at Low Risk* in the algorithm). For the first 72 hours after initiation of empiric therapy, the patient should be assessed daily at home or at the clinic for treatment response, signs of toxicity, and treatment adherence. If the disease 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 from blood or other sterile source, for persistent or recurrent fever at 3 to 5 days, if serious subsequent infections or adverse events develop, if the patient is unable

to continue the prescribed antibiotic regimen (eg, intolerance to the oral regimen), or for infusion of IV antibiotics.

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 patients with neutropenia 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.[1,403] 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 infection risk assessment of patients;
- 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 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); and
- Bactericidal nature of the antibiotic.

Recommended Approaches

The Panel recommends 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 Inpatient Empiric Therapy for Uncomplicated Fever and Neutropenia* in the algorithm).[1,2,403]

For select patients at low risk of infection with fever and neutropenia, one approach is IV antibiotic monotherapy (all category 1 except where noted) with imipenem/cilastatin, meropenem, piperacillin/tazobactam, or an extended-spectrum antipseudomonal cephalosporin (cefepime [category 1] or ceftazidime [category 2B]).[404-408] 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 empiric therapy of neutropenic fever may need to be tailored accordingly.

Meta-analyses of randomized trials have 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.[399,409,410] However, a meta-analysis by the FDA, using additional data, did not find a statistically significant increase in mortality for patients treated with cefepime compared with controls. Thus, the FDA concluded that cefepime remains an appropriate therapy for its approved indications. A randomized, dual-center study of 105 patients treated with piperacillin/tazobactam or imipenem/cilastatin as empiric therapy for febrile neutropenia reported imipenem/cilastatin to have superior efficacy, although this area of research requires further investigation.[411]

Another approach for initial empiric therapy for patients at low risk for infections with fever and neutropenia is oral antibiotic therapy (see *Initial Inpatient Empiric Therapy for Uncomplicated Fever and Neutropenia* in the

algorithm). Ciprofloxacin plus amoxicillin/clavulanate (category 1) is an option for oral antibiotic therapy, with the alternative of ciprofloxacin plus clindamycin for patients allergic to penicillin. Moxifloxacin (category 1) or levofloxacin (category 2A) are other recommended options for this approach. Fluoroquinolone regimens should not be administered in patients receiving antimicrobial prophylaxis with a fluoroquinolone. Additionally, while data support the use of fluoroquinolones for prophylaxis, the risks and benefits should be evaluated for empiric therapy or other clinical scenarios. In particular, the side effects of fluoroquinolones should be taken into consideration. In 2016, the FDA issued a warning that fluoroquinolones are associated with disabling side effects involving tendons, muscles, joints, nerves, and the CNS.[412]

IV antibiotic monotherapy is the preferred treatment option for patients at intermediate or high risk with fever and neutropenia. However, IV antibiotic combination therapy, though not routinely recommended, may be considered in higher risk or antimicrobial resistant cases. In such situations, an aminoglycoside combined with an antipseudomonal agent can be considered.[413-415] 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.[416] 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 tedizolid is not routinely recommended. Although published studies exist regarding the use of some of these agents in neutropenia, the Panel strongly recommends that these agents not be used routinely as initial empiric therapy because of concerns for resistance and breakthrough infections.

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

For specific indications, the addition of IV vancomycin either to IV monotherapy or to combination therapy (see *Empiric Addition of Vancomycin*) 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.[417,418] 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 (EORTC) did not show true clinical advantages for empiric vancomycin in adults.[419] 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.[419] A prospective randomized trial of fever and neutropenia in children has reported benefit for empiric vancomycin;[420] however, another randomized study in children did not show a benefit for the addition of vancomycin.[421]

In addition to the occurrence of 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.[422,423] The increase in vancomycin resistance has been associated with use of vancomycin among the patients who are hospitalized. 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.[424,425] 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:

- Clinically apparent, serious IV catheter-related infection (to cover coagulase-negative staphylococcal isolates, which are usually beta-lactam antibiotic-resistant and MRSA);[426,427]
- 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;[428,429] and
- Soft tissue infection (particularly in regions where MRSA infection is common).[430]

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. Authoritative guidelines have been published on the dosing and therapeutic monitoring of vancomycin.[431] For management of complicated cases of *C difficile* infections, oral vancomycin can be considered (see *Site-Specific Evaluation and Treatment of Infections: Abdominal, Rectal, and Urinary Tract Infections: Clostridium difficile Colitis*).

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.[432-434] 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.[392,435] One study has reported an increased risk of breakthrough viridans group streptococcal infection following prophylaxis with levofloxacin,[436] 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.[437] The 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.[438,439] 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.

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 tedizolid are active against the majority of gram-positive organisms, including beta-lactam–resistant and vancomycin-resistant pathogens. [440-446] 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%–10%) and increases with the duration of linezolid treatment, typically with duration of treatment >2 weeks. In neutropenic patients with cancer, myeloid recovery does not seem to be delayed with short courses of linezolid;[447,448] however, experience with long durations of therapy (eg, >14 days) is limited in patients with cancer.

Vancomycin or linezolid should be used for the treatment of MRSA pneumonia in patients who are ventilated.[449-452] 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. 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.

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.[453,454] Daptomycin is indicated for the treatment of complicated skin and skin structure infections caused by susceptible strains of certain gram-positive microorganisms.[455,456] A pharmacokinetic study of daptomycin in patients with cancer with febrile neutropenia 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.[457] A randomized study showed similar efficacy of daptomycin compared with vancomycin or anti-staphylococcal beta-lactams as therapy for *S aureus* bacteremia and endocarditis.[458] 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 symptom 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 controls.[459] 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 regard to the rate of neutropenia, complications, adverse events, length of hospital stay, and deaths.[459]

Optimal therapy for VRE infections is not well-defined. Linezolid, tedizolid, and daptomycin have been used with variable success in the treatment of patients with VRE bloodstream infections.[440,443,448,460,461] 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, ceftaroline, oritavancin, and dalbavancin have been approved for the treatment of complicated skin and skin structure infections caused by gram-positive pathogens, including MRSA.[462,463] 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*. There are no directive data on the use of these agents in the oncologic

setting. Therefore, these agents are not currently recommended as first-line therapy.

The Panel recommends that the use of linezolid, daptomycin, and tedizolid 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.

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.[428] Unlike the patients who are stable 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 neutropenia with clinical instability may include a broad-spectrum beta-lactam (eg, imipenem/cilastatin, meropenem, 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.[428] In hospitals where infections by antibiotic-resistant bacteria (eg, MRSA or drug-resistant gram-negative rods) are commonly observed, policies on initial empiric 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.[464-468] Stress-dose corticosteroids are recommended for patients with septic shock who require vasopressor support.[428,469,470] 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.[471-474]

Empiric Antifungal Therapy in Persistent Neutropenic Fever

Empiric antifungal therapy for persistent febrile neutropenia unresponsive to broad-spectrum antibacterial agents is initiated in neutropenia known to be at risk for invasive fungal infections, but who do not have early detection of those infections following clinical examination and collection of cultures.[6,475-478] 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 who have recrudescent fever (see *Results of Daily Monitoring* in the algorithm). The timing to add empiric antifungal therapy varies with the risk of invasive mold infections, but generally ranges between 7 to 10 days of neutropenic fever despite empiric antibiotic therapy. In patients at high risk for mold infections (eg, neutropenia lasting >10 days, allogeneic HCT recipients, treatment with high-dose corticosteroids), the NCCN Guidelines Panel recommends adding empiric antifungal agents after 4 days unless the patient 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 HCT would develop an invasive fungal infection due to *Candida* or *Aspergillus* species by day 20 of neutropenia.[479] 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 compared with empiric therapy. With the widespread use of fluconazole prophylaxis in the 1990s among patients at high risk of infection with acute leukemia and in HCT recipients, the incidence of invasive candidiasis in these patients decreased substantially, although breakthrough candidemia by fluconazole-resistant strains occurred.[69,182] 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, L-AmB proved to be safer than and as effective as conventional amphotericin B for empiric antifungal therapy.[480]

Amphotericin B products are considered a category 2B recommendation for prophylaxis and empiric 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), 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.[481] This recommendation is stronger in patients with risk factors for acute renal failure, such as pre-existing renal disease, HCT recipients, and coadministration of nephrotoxic agents.[164,165,482]

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.[483,484] IV itraconazole followed by oral solution was as effective as, but less toxic than, conventional amphotericin B when used as empiric therapy in an open, randomized study.[485] These results led to FDA approval of oral itraconazole solution for this indication. IV 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. Additionally, the capsule formulation should be used with caution when concurrent with histamine H2-receptor antagonists and PPIs as these medications can reduce absorption of the itraconazole capsule. Itraconazole has negative inotropic effects and is contraindicated in patients with evidence of ventricular dysfunction or a history of congestive heart failure.

Voriconazole was compared with L-AmB in an open, randomized study of empiric antifungal therapy (N = 837 patients, 72% with hematologic malignancies).[486] 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 patients who are prespecified as high risk (relapsed acute leukemia and allogeneic HCT). 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.[476,487] 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).[488] The overall success rates were 34% in both caspofungin and 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 two 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).[488] 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 empiric treatment of presumed fungal infection in patients with fever and neutropenia. Micafungin was compared to voriconazole in a randomized, cooperative group, open-label trial as empiric antifungal therapy in patients with hematologic malignancy and febrile neutropenia. This study found no significant differences in clinical efficacy between the two therapies, although discontinuation due to drug-related adverse effects occurred less frequently in patients treated with micafungin.[489] Another echinocandin, anidulafungin, was shown in a 2021 retrospective study to have similar efficacy as caspofungin and micafungin for empiric antifungal therapy.[490] Moreover, a 2022 retrospective case-control study found that patients who were critically ill and treated with anidulafungin as empiric therapy had less incidence of invasive candidiasis (5.2% vs. 29.2%; *P* = .001), and lower 30-day all-cause mortality rate (10.4% vs. 19.4%; *P* = .04) compared to the control group that did not receive empiric antifungal therapy.[491] These studies thus support the use of micafungin and anidulafungin as additional options for empiric antifungal therapy.

Posaconazole and isavuconazonium sulfate can be considered for patients who have invasive, refractory infections or who have intolerance to amphotericin B formulations, although neither is FDA-approved for refractory infections. Both agents are, however, approved by the FDA as primary therapy for invasive fungal infections.

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.[492] One approach has been to evaluate such patients with a high-resolution 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.[493,494] 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 HCT recipients.[495] 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.[496,497] Empiric antifungal therapy with anti-mold activity would be expected to benefit these few patients without incurring a greater risk of toxicity.

Preemptive 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 patients who are persistently febrile neutropenic. Maertens and colleagues[498] evaluated a preemptive strategy of incorporating L-AmB in patients at high risk with neutropenia (who received fluconazole prophylaxis) based on such prespecified 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 empiric antifungal therapy. Using the preemptive strategy, antifungal therapy was given to 7.7% (9 of 117 episodes of neutropenic fever) of patients rather than up to one third of patients who might have received it on the basis of fever alone. 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 mucormycosis (previously referred to as “zygomycosis”) resulting in death. Two cases of breakthrough candidemia were detected by conventional culture methods and successfully treated.[498] In another study by Maertens and colleagues comparing preemptive versus empiric antifungal therapy in patients with neutropenia at high risk and on fluconazole prophylaxis, preemptive antifungal therapy was found to be non-inferior to empiric therapy in terms of overall survival, halving the number of patients receiving antifungals without excess mortality or invasive fungal diseases.[499] 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 cost of antifungal drugs compared to empiric therapy.[500] A 2022 systematic study of 7 randomized controlled trials comparing preemptive antifungal therapy with empiric antifungal therapy found that in patients with cancer at high risk of febrile neutropenia, preemptive antifungal therapy may reduce the duration and rate of use of antifungal agents compared to empiric therapy, without increasing overall and invasive fungal disease-related mortality; but the evidence regarding invasive fungal infection detection and adverse events was inconsistent and uncertain.[501] Taken together, the Panel considers the evidence supporting preemptive antifungal therapy to be insufficient 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. 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.[502] 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 neutropenia with persistent fever of unknown etiology.[503] 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.

Follow-up Therapy in Responding, Clinically Stable Patients

Patients who have infections that respond to empiric therapy should exhibit decreasing fever trends, show stable or improving signs and symptoms of infection, and be hemodynamically stable. For these patients, no change is needed to the initial empiric regimen, and if patients were started appropriately on an agent for Gram-positive resistant infections, they should continue with the course of therapy. If patients received an agent for Gram-positive–resistant infections 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 treatment should be discontinued. Similarly, the appropriateness of empiric Gram-negative therapy should be reassessed. It is generally recommended that antibiotics be continued until the ANC is ≥500 cells/mcL, and is increasing (see *Results of Daily Monitoring* in the algorithm).

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, although de-escalation to prophylactic antibiotics should be considered[504] (see *Results of Daily Monitoring* in the algorithm). In patients who defervesce for at least 48 hours, it may be appropriate in some cases to de-escalate to fluoroquinolone. Patients at lower risk 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).

Follow-up Therapy in Persistently Febrile but Otherwise Hemodynamically Stable Patients

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. A hemodynamically 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 consideration 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 *Results of Daily Monitoring* in the algorithm). In patients at high risk for mold infection (ie, neutropenia >10 days, allogeneic HCT recipients, high-dose corticosteroids), the Panel recommends adding empiric antifungal therapy after the fourth day unless the patient is receiving prophylaxis directed against molds. Documented infections are usually treated according to the infection site and pathogen, and at least until ANC recovery (see *Site-Specific Evaluation and Treatment of Infections*).

Follow-up Therapy in Non-responding, Clinically Unstable 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. Antifungal therapy with activity against molds may be considered for patients with fever continuing for 4 or more days following initiation of empiric antibiotic therapy (see *Results of Daily Monitoring* in the algorithm). 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 do not 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 NCCN and ASCO[505] have guidelines for the use of prophylactic colony-stimulating factors (CSFs) in neutropenia (see NCCN Guidelines for Hematopoietic Growth Factors). 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 G-CSF or granulocyte-macrophage CSF (GM-CSF) should be considered (category 2B) in patients with neutropenia with serious infectious complications such as pneumonia, invasive fungal infections, or any type of progressive infection.

De-escalation and Duration of Therapy for Patients with Documented Infections

Targeted treatment of documented infections should be continued for patients whose infections are responding to therapy. The need to continue empiric Gram-negative therapy may be reassessed in these patients, discontinuing Gram-negative therapy if appropriate.[506] The duration and de-escalation of antimicrobial therapy 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 (see *Follow-up Therapy for Responding Disease* in the algorithm). For example, most skin and soft tissue infections can be treated with 5 to 14 days of therapy. For most bacterial bloodstream infections, 7 to 14 days of therapy is usually adequate, with longer durations (10–14 days) recommended for more complicated bacteremias. For all *S aureus* bloodstream infections, treatment should be continued for at least 4 weeks after documentation of a first negative blood culture, although some institutions may use a shorter duration based on infectious disease consultation. In cases of endovascular involvement, treatment may need to be prolonged. Treatment for bloodstream infections caused by yeast should be continued for at least 2 weeks after the first negative blood culture is obtained. Catheter removal is recommended for septic phlebitis, tunnel infection, or port pocket infection and if bloodstream infection is caused by *Candida, S aureus, P aeruginosa, Corynebacterium jeikeium, Acinetobacter, Bacillus* organisms, atypical mycobacteria, yeasts, molds, VRE, *Stenotrophomonas maltophilia*, and other MDROs. A duration of treatment lasting 7 to 14 days is usually indicated for infections of the lungs (eg, bacterial pneumonia) or sinuses.[507] 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 (category 1). 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.

In patients with influenza, oseltamivir is approved for a minimum duration of 5 days in ambulatory patients who are otherwise healthy individuals with intact immune systems. A longer course of treatment (eg, at least 10 days) or higher dose (eg, 150 mg) that continues until resolution of symptoms should be considered in the highly immunocompromised.

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.

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.[428] 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 patients who are unstable. 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 CNS. This section is tailored to patients with neutropenia or those who are otherwise significantly immunocompromised (eg, HCT 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 are often only distinguished by microbiologic culture. Empiric antibiotic therapy must consider the endogenous anaerobic flora and the shift in oral flora, which occur with serious illness or antibiotic use. The increased frequency of HSV reactivation and severity of these infections in patients with cancer are well known and preventable. The incidence of HSV reactivation in patients who are immunocompromised may approach 50% to 75%, but it is nearly zero in those who receive prophylaxis with appropriate antiviral agents.[508] HSV infections are associated with more extensive mucosal damage, increased secondary infections, and significantly prolonged healing time. Baglin et al[509] 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.[509] 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 assay) results (see *Initial Clinical Presentation: Mouth/Mucosal Membrane* in the algorithm).

Systemic or topical antifungal agents can be used to treat thrush. Because of the risk of candidemia, systemic antifungal therapy is advised in neutropenia. Fluconazole is recommended as first-line therapy for thrush (see *Initial Clinical Presentation: Mouth/Mucosal Membrane* in the algorithm). If the infection does not respond, the dose of fluconazole can be increased up to 800 mg daily (in adults with normal renal function).[510] Although cross-resistance among azoles may occur, oral voriconazole or posaconazole are reasonable oral options for thrush that is refractory to fluconazole. Echinocandins can be used for patients with azole-refractory mucosal candidiasis. Though amphotericin B formulations are also effective, they are not recommended because of 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/or acyclovir should be considered in patients with neutropenia and in other persons who are highly immunocompromised with symptoms that suggest esophagitis. CMV esophagitis is a rare complication of chemotherapy-induced neutropenia and is most commonly observed in allogeneic HCT recipients with GVHD. Negative CMV surveillance results from PCR studies would make CMV disease very unlikely. If CMV esophagitis is diagnosed, treatment with valganciclovir or ganciclovir should be initiated. Foscarnet or cidofovir should be reserved for ganciclovir-resistant CMV or for patients who cannot tolerate ganciclovir. Empiric treatment may be considered in patients at high risk for CMV disease with symptoms suggestive of esophagitis.

For patients with esophagitis that does 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, they are not recommended.

Sinus or Nasal Infections

The sinuses are a common site of bacterial infection. Patients with severe and prolonged neutropenia (eg, >10 days) and allogeneic HCT 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 (<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. An 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* in the algorithm). 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 patients who are neutropenic and otherwise highly immunocompromised 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 Mucorales (previously referred to as Zygomycetes). In a case-control study of invasive aspergillosis and mucormycosis in patients with either acute leukemia or who were allogeneic HCT recipients, the risk factors that favored the diagnosis of mucormycosis included fungal sinusitis and use of voriconazole.[511] A lipid formulation of amphotericin B should be used for suspected or confirmed invasive sinus mold infection, pending definitive histology and culture results. Isavuconazonium sulfate or posaconazole can be considered for treatment of refractory infection or if there is intolerance to amphotericin B formulations; isavuconazonium sulfate has been approved by the FDA for invasive aspergillosis and mucormycosis; and posaconazole has been approved for invasive aspergillosis. Urgent debridement of necrotic tissue should be performed, when feasible.[512]

Abdominal, Rectal, and Urinary Tract 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 patients with neutropenia, 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,[513] 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.[514] Diarrhea should be evaluated with at least 2 stool *C difficile* toxin screens. Additionally, depending on clinical circumstances, a GI multiplex panel may be considered for identification of other pathogens, including adenovirus, rotavirus, and norovirus. 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.[90,91] Early reports suggested that metronidazole cured >90% of cases of *C difficile* colitis, and the rate of recurrence was low.[515,516] However, Musher et al[517] reported that among patients (N = 207) treated with metronidazole for *C difficile* colitis, only 50% were cured and had no recurrence of disease.

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).[518] The primary endpoint 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.[518] 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).[518] 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*.[518]

Another multicenter, double-blind, randomized trial evaluated the efficacy and safety of oral fidaxomicin versus oral vancomycin in adults with acute

C difficile infection (N = 535; n = 509 evaluable).[519] The primary endpoint of this study was clinical cure; 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).[519] 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.[520] Overall, the cure rate was significantly lower among patients with cancer (n = 183) 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, 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).[520] Subtotal colectomy, diverting ileostomy, or colostomy may be required in cases involving toxic dilatation or perforation of the colon.

Multiple recurrences of *C difficile* are a challenge in the patient with cancer and may respond to a prolonged, tapered treatment with oral vancomycin dose over several weeks.[521] The use of oral vancomycin followed by duodenal infusion of donor feces (fecal microbiota transplant, FMT) may also be an effective strategy for patients with recurrent *C difficile* infection, although there is a lack of data on the safety and efficacy of FMT in patients with cancer. In one randomized study, patients with recurrent *C difficile* infection were assigned to receive treatment with a short course of initial oral vancomycin (500 mg orally 4 times daily for 4 days) followed by bowel lavage and infusion of donor feces (n = 16) or standard oral vancomycin (500 mg orally 4 times daily for 14 days) alone (n = 13) or standard oral vancomycin with bowel lavage (n = 13). Resolution was achieved in 81% of patients in the FMT group compared with 31% in the vancomycin alone group and 23% in the group treated with vancomycin plus bowel lavage (*P* < .001 for both comparisons with the infusion group).[522] Another randomized study assigned patients with recurrent *C difficile* infection to receive an initial short course of vancomycin (125 mg orally 4 times daily for 3 days) followed by FMT via colonoscopy (n = 20) or vancomycin (125 mg orally 4 times daily for 10 days, followed by 125-500 mg/day every 2–3 days for at least 3 weeks) alone (n = 19). In this study, resolution was achieved in 90% of patients in the FMT group compared with 26% of patients in the vancomycin group (*P* < .0001).[523] While these studies should be interpreted with caution as they excluded patients who had neutropenia or recent chemotherapy, some institutions consider FMT for treatment of refractory *C difficile* infection in select cases.

Another consideration for recurrent *C difficile* is bezlotoxumab, a human monoclonal antibody against *C difficile* toxin B, used in conjunction with antibiotic treatment. Bezlotoxumab was approved by the FDA in 2016 to reduce recurrence for *C difficile* for patients receiving antibacterial treatment and who are at high risk for *C difficile* recurrence. Two double-blind, randomized, placebo-controlled, phase 3 trials of 2655 patients receiving oral antibiotics for *C difficile* infection studied the efficacy and safety of bezlotoxumab. Both trials showed that the rate of recurrent *C difficile* infection was significantly lower in patients given bezlotoxumab than in those given placebo (MODIFY I: 17% vs. 28%; *P* < .001; MODIFY II: 16% vs. 26%; *P* < .001). Rates of adverse events were similar between bezlotoxumab and placebo.[524]

The NCCN Panel recommends vancomycin (preferred in adults), or metronidazole for the treatment of suspected *C difficile* colitis. Oral vancomycin has a similar efficacy rate compared to oral metronidazole and can be considered an option for initial therapy for *C difficile* colitis despite the risk of selection for VRE and the substantial expense. Oral vancomycin should be considered over metronidazole for more complicated cases, such as those associated with severe diarrhea, dehydration, clinical instability, significant comorbidities, or recurrent or refractory *C difficile* colitis. The NCCN Panel recommends maintaining good antibiotic stewardship and reducing unnecessary antibiotic therapy at each step of the treatment process. For confirmed *C difficile* infection, the Panel recommends oral vancomycin or fidaxomicin for 10 days. In case of ongoing or worsening infection, switching to fidaxomicin can be considered if the initial treatment was with vancomycin. FMT may be considered, but should be avoided in patients with neutropenia. For relapse/recurrent *C difficile* infection, fidaxomicin is recommended if not given previously. Alternatively, a vancomycin taper, FMT (with appropriate consultation and to be avoided in patients with neutropenia) or bezlotoxumab may be considered. In case of fulminant disease, vancomycin is recommended either orally or via a nasogastric (NG) tube in combination with IV metronidazole. If ileus is present, vancomycin via rectal instillation may be considered. Efforts should be made to deliver vancomycin by the NG route in patients with severe *C difficile* colitis.[525,526] Limited data suggest that IV metronidazole may be useful in this setting, and it is best used as an adjunct to oral vancomycin.[527,528] IV vancomycin is not recommended in this setting because of inadequate luminal levels. IV metronidazole should be used in patients who cannot be treated with oral agents. Upon resolution of *C difficile* infection, secondary prophylaxis may be considered if continuing antibiotic therapy.

Enterocolitis

Neutropenic enterocolitis is a serious, potentially life-threatening disease characterized by fever, diarrhea, and abdominal pain.[529,530] 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 HCT 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, rectal bleeding).[531] Consequently, the Panel recommends that surgical and other subspecialty consultations be obtained early in the course of treatment.

The NCCN Panel recommends an abdominal exam, abdominal CT scan (preferred), or ultrasound for a confirmatory diagnosis of infection in patients experiencing abdominal pain. Additional recommendations include liver function tests (eg, alkaline phosphatase, transaminases, bilirubin, amylase, lipase). The Panel also recommends consideration of early surgical and other subspecialty (eg, gastroenterology, interventional radiology) consultations based on the clinical diagnosis. In patients with perirectal pain, the Panel recommends perirectal inspection and consideration of imaging such as abdominal/pelvic CT or MRI. Addition of antimicrobial therapy with adequate anaerobic activity is recommended in

both patient populations. In patients experiencing diarrhea who are not on laxatives, stool softeners, or tube feeds, *C. difficile* testing is strongly recommended. Other medical causes of diarrhea should be considered, including neutropenic enterocolitis, GI GVHD, and mucositis. Colonoscopy may be required to evaluate for colitis and determine etiology of diarrhea. Moreover, based on clinical circumstances, diagnostic testing for viral, bacterial, and/or parasitic pathogens may be considered. In patients with symptoms of urinary tract infection, a urine culture is recommended with no additional therapy until specific pathogen identified.

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 two 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.[316] If feasible, sputum and blood cultures should be collected before starting therapy. In patients who are not neutropenic, receiving IST, or requiring hospital admission (based on a validated pneumonia severity index), therapy includes either 1) a respiratory fluoroquinolone (levofloxacin 750 mg/day, moxifloxacin); or 2) a beta-lactam (eg, high-dose amoxicillin or amoxicillin-clavulanate) plus a macrolide (eg, azithromycin).[316] These regimens will treat most of the common community-acquired pathogens, including "atypical" pneumonia (*Chlamydia, Mycoplasma*, and *Legionella* species). Although daptomycin is effective against most gram-positive pathogens, it should not be used for the treatment of pneumonia, because it is inactivated by pulmonary surfactant.[453,454]

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 *Treatment Modifications* in the algorithm).[316] A nasopharyngeal wash for respiratory viruses and initiation of empiric antiviral therapy should be considered during peak influenza season in the local area. 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, and 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 (2018) and CDC guidelines (2023) recommend antiviral treatment with the neuraminidase inhibitors oseltamivir, zanamivir, or peramivir, which are active against both influenza A and B viruses.[532,533] 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. However, longer courses of treatment (eg, 10 days) and treatment until resolution of symptoms should be considered in patients who are immunocompromised. 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 Infection* in the algorithm). 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.[317] Peramivir has been shown to have similar clinical outcomes as oral oseltamivir[318] and can be considered for patients who cannot have oral oseltamivir or inhaled zanamivir, though it is available only as an IV injection.

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.[534] 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: 1) received antibiotics in the preceding 90 days; 2) hospitalization for ≥2 days in the preceding 90 days; 3) resident in nursing home or extended care facility; 4) chronic dialysis within 30 days; 5) home wound care; and 6) family member with a multidrug-resistant pathogen.[534] Late-onset hospital-acquired pneumonia (occurring after ≥5 days of hospitalization) is more likely to be 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.[535]

In patients with late-onset hospital-associated pneumonia or risk factors for multidrug-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, 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).[534] If *Legionella* is suspected, a quinolone (ciprofloxacin, levofloxacin, or moxifloxacin) should be used instead of an aminoglycoside. The antibiotic regimen should be subsequently tailored based on culture results.

Pulmonary Infiltrates in Patients with Neutropenia

In patients with neutropenia for <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.[536] 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 (hospital-acquired) 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. RSV, parainfluenza, and influenza are significant pathogens during neutropenia in patients receiving chemotherapy for acute leukemia and in HCT 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 7 to 14 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.[536] 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;[537] 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, >10 days) receiving broad-spectrum antibacterial agents is concerning for the possibility of invasive aspergillosis or infection with other molds.[536] Consider adding an extended-spectrum azole 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 (eg, *Aspergillus* and other filamentous fungi, *Cryptococcus neoformans*,

dimorphic fungi), *Legionella*, *Pneumocystis 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 patients with neutropenia. An antipseudomonal beta-lactam plus either a respiratory fluoroquinolone or azithromycin is a reasonable initial regimen in patients with pneumonia requiring hospitalization. In allogeneic HCT 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 (eg, chronic 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,[536] including PJP, viral infections, hemorrhage, and drug-induced pneumonitis. A diagnosis of PJP should be considered in patients with significantly impaired cellular immunity not receiving PJP prophylaxis who present with diffuse pulmonary infiltrates. BAL is the standard approach for diagnosing PJP. 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 against possible PJP. TMP/SMX desensitization or atovaquone, dapsone, or pentamidine (aerosolized or IV) can be considered when PJP prophylaxis is required in patients who are TMP/SMX intolerant. For patients receiving dapsone, consider assessing G6PD levels prior to initiating therapy.

Patients at the highest risk for CMV pneumonia include allogeneic HCT recipients in the post-engraftment setting (particularly if receiving IST for GVHD) and patients receiving treatment with alemtuzumab. Negative results from CMV surveillance testing (peripheral blood PCR) make CMV pneumonia very unlikely. CMV pneumonia is uncommon in patients who have not undergone transplant but are receiving immunosuppressive chemotherapy for leukemia.[538] Community respiratory viruses can cause severe pulmonary infection in patients with neutropenia and in those who are non-neutropenic but with impaired cellular immunity. Noninfectious etiologies must also be considered, as previously stated. BAL is sensitive in diagnosing bacterial and viral pneumonia and PJP, and is often used as the initial invasive diagnostic procedure (see *Invasive Diagnostic Procedures for Pulmonary Infiltrates*).

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.[316] 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 take 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 >10 days, receipt of an allogeneic HCT, prolonged use of high-dose systemic corticosteroids, or treatment with T-cell suppressants. The galactomannan assay is specific for invasive aspergillosis,[493,539] whereas the beta-glucan assay detects aspergillosis and other invasive fungal infections (including invasive candidiasis, *Pneumocystis jirovecii*, and fusariosis).[540-542] Mucormycosis yields negative serum galactomannan and 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.[495] The lack of consistent results likely relates to different cutoff 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,[543,544] which may account for the different results. The sensitivity of the assay is significantly reduced by concomitant mold-active antifungal agents.[494,545] False-positive results may be more common in children and allogeneic HCT recipients.[546] Historically, concomitant piperacillin/tazobactam has caused false-positive galactomannan results;[547,548] however, current formulations available in the United States rarely cause false positives.[549] 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.[550,551] Despite these limitations, a patient at high risk for invasive aspergillosis (eg, prolonged neutropenia or allogeneic HCT recipient) with clinical and radiologic 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 *Pneumocystis jirovecii* as part of the noninvasive 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 to the Central United States). Coccidioidomycosis is endemic to 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 PJP. However, in a small study, sputum induction with hypertonic saline was diagnostic of PJP in patients who are not HIV-infected in about 60% of cases.[552] 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 infection 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 *Pneumocystis jirovecii*, *M tuberculosis,* and respiratory viruses. The sensitivity of BAL for focal lesions (such as nodules) is variable. In lesions >2 cm, the sensitivity of BAL ranges from 50% to 80%; however, in smaller lesions, the diagnostic yield is usually about 15%.[553] 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. It is recommended to use galactomannan and special stains or molecular techniques with BAL to aid in the identification of additional viral, protozoal, fungal, or bacterial pathogens, particularly if there is no response to the initial therapy or if diffuse infiltrates are present.

BAL cultures only detect about 50% of pulmonary infection cases; therefore, it is relatively insensitive for diagnosing aspergillosis.[554] Galactomannan detection in BAL fluid appears to be more sensitive than serum detection[555,556] and can be used to support a diagnosis of probable aspergillosis.[557] In patients with focal peripheral lesions, percutaneous biopsy may increase the diagnostic yield; however, in patients with thrombocytopenia, the risk of bleeding may be unacceptably high. The microbiologic evaluation should take into account the clinical manifestations and nature of immunosuppression. In patients who are highly immunocompromised (eg, those receiving chemotherapy for acute leukemia, HCT recipients), the following studies on BAL and lung biopsies should be considered: culture and stains for bacteria, fungi, *Legionella*, mycobacteria, *Nocardia*, HSV, CMV, and community respiratory viruses (both rapid antigen and shell vial culture), and cytology or immunofluorescent studies for *Pneumocystis jirovecii*. In a patient with compatible host factors and radiologic findings, a positive galactomannan result from BAL is also indicative of probable invasive aspergillosis.[557]

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, 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 *Treatment Modifications* in the algorithm and *Vascular Access Device Infections* in the discussion). Acyclovir, famciclovir, or valacyclovir should be considered for vesicular lesions after appropriate diagnostic tests (ie, 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.[558] Similar lesions can be caused by *S aureus*, enteric gram-negative bacilli infection, and filamentous fungi (including *Aspergillus*, Mucorales, and *Fusarium* species). A rapidly progressive deep soft tissue infection with gas formation suggests clostridial myonecrosis (or polymicrobial necrotizing fascitis).[559] 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 patients with cancer who are highly immunocompromised, the differential diagnosis of skin lesions is often broad and includes noninfectious etiologies such as drug reactions, Sweet syndrome, erythema multiforme leukemia cutis, and (in the case of allogeneic HCT recipients) GVHD. Biopsy of skin lesions for histology and culture is recommended. In allogeneic HCT 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 due to 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-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.[560-562] 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).[563] 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.[564-566] 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.[567,568] 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.[569] 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).[570] 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 >5 days, if the rate of catheter-related bloodstream infections does not decrease despite implementation of comprehensive prevention measures at the local institution.[571] 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.[572] 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.[427]

VAD infections are categorized as entry or exit site inflammation versus tunnel infection, port pocket infection, or septic phlebitis (see *Initial Clinical Presentation* in the algorithm). The majority of these infections are caused by gram-positive pathogens, with coagulase-negative staphylococci recovered most frequently.[427] 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, blood culture from each port of VAD, and a peripheral culture 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 and vancomycin (see *Initial Inpatient Empiric Therapy for Uncomplicated Fever and Neutropenia* and

Treatment Modifications in the algorithm). Linezolid is not advised as routine therapy for catheter-related infections nor is it FDA-approved for this indication. 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 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 (between centrally and peripherally drawn blood cultures) is highly sensitive and specific for diagnosing catheter-related bacteremia.[573-577] 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 favored for patients with bloodstream infections caused by fungi (yeasts or molds) or nontuberculous mycobacteria (eg, *Mycobacterium chelonae*, *Mycobacterium abscessus*, *Mycobacterium fortuitum*).[427] Bloodstream infections caused by *Bacillus* organisms, *Candida, S aureus, Acinetobacter*, *C jeikeium*, *P aeruginosa*, *S maltophilia,* and VRE 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 disease progression caused by microbial sequestration. Some experts believe supplemental urokinase infusions can be helpful in patients with catheter-related infections.[578] 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.[579] 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 *Propionibacterium 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) in combination with

ceftazidime, cefepime, or meropenem (which have activity against Enterobacteriaceae and *P aeruginosa*).[579]

CNS infections unrelated to neurosurgery are relatively uncommon in patients with cancer. Initial evaluation generally involves a head MRI (preferred) to rule out intracranial bleeding and/or a CT scan in addition to 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 *Treatment Modifications* in the algorithm). 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 HCT, history of *P aeruginosa* infection), use of cefepime or meropenem instead of ceftriaxone in the initial empiric regimen is advised. The antibiotic regimen should be tailored based on culture results.

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.[580] In patients with suspected encephalitis (ie, fever, mental status changes, CSF pleocytosis), high-dose IV acyclovir with sufficient hydration should be considered as empiric therapy for HSV in addition to an appropriate antibacterial regimen.[581] 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 HCT recipients, advanced AIDS), additional CSF studies should be considered (such as PCR for CMV, VZV, human herpesvirus–6 type B [HHV-6B], and toxoplasmosis). For cases of HHV-6B–associated encephalitis in patients who are severely immunocompromised, such as those who have received an allogeneic transplant, treatment is recommended; however, the optimal therapy is not known (with either foscarnet or ganciclovir).[581] 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.[582] Bacterial abscesses in patients who are non-immunocompromised are typically caused by dental flora. In patients with prolonged neutropenia and in allogeneic HCT 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 immunocompromised 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 plus metronidazole is advised.[17,582,583] In patients with prolonged neutropenia without corticosteroids or lymphocyte-depleting agents, a reasonable initial regimen consists of combination cefepime, metronidazole, and voriconazole; 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. In allogeneic HCT recipients and other patients with severe T-cell impairment, addition of high-dose TMP/SMX 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.[584,585] The crude mortality of candidemia ranges from 20% to 40%.[585,586] This variable mortality rate reflects the presence of serious comorbidities (such as malignancy and 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.[585] 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 patients who are non-neutropenic found both regimens equally effective, but fluconazole had less toxicity.[587] In a subsequent study of non-neutropenic cases 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.[510] Voriconazole was as equally effective as, but less nephrotoxic than a strategy of amphotericin B followed by fluconazole in non-neutropenia with invasive candidiasis.[588] 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.[178,589-591] 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.[590] Among patients who met prespecified criteria for evaluation (those who met eligibility criteria and received at least 5 days of the study drug), caspofungin resulted in a 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 L-AmB for invasive candidiasis, with fewer treatment-related adverse events (including those that led to treatment discontinuation).[589] Anidulafungin was not inferior to fluconazole as therapy for invasive candidiasis and was possibly more efficacious.[178] 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.[591]

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.[592] 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.[592] Fluconazole-resistant *Candida* isolates are frequently cross-resistant to other azoles;[593] 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;[592] however, transition to fluconazole or voriconazole can be considered if azole susceptibility is documented. *Candida auris* may be resistant to fluconazole or echinocandins. Echinocandins have reduced sensitivity to *Candida parapsilosis* compared to other candidal strains; fluconazole is recommended in this setting.[592]

The IDSA recommends an echinocandin as initial therapy for candidemia in most neutropenic patients.[592] The NCCN Guidelines Panel agrees with this recommendation (category 1), 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 has been evaluated as primary therapy for invasive aspergillosis. In an open-label, multicenter, randomized trial, voriconazole resulted in a significantly higher success rate (including 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) in this patient population.[594] Success rates were similar for the two 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 subsequent-line therapy, 35% had a complete or partial response.[595] 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.[596] Considerable inter-individual variability in voriconazole exposure can occur, and the utility of monitoring drug levels is controversial.[597,598] Studies with a few patients have noted a relationship between low plasma voriconazole levels and disease progression,[147] and between high voriconazole levels and toxicity.[145,599] Voriconazole blood levels that are 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 TDM 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 AmB-D. Some investigators have persuasively argued that lipid formulations should be considered suitable replacements for amphotericin B for primary therapy for many invasive fungal infections.[481] ABCD was equally as effective as, but less nephrotoxic than amphotericin B as primary therapy for invasive aspergillosis.[600] ABLC was shown to be as safe and efficacious as therapy for invasive aspergillosis based on an analysis of a registry database.[601]

A randomized study compared L-AmB at either 3 or 10 mg/kg/day for 14 days, followed by 3 mg/kg/day as therapy for invasive mold infections.[602] 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 rates 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.[602] 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 mucormycosis).

Echinocandins have not been evaluated as initial monotherapy for invasive aspergillosis in clinical trials. Caspofungin for treatment of refractory infections in patients with invasive aspergillosis led to a favorable response in 37 (45%) of 83 patients.[170] 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[603-606] but not in others.[607-609] In two small retrospective series, the combination of caspofungin and L-AmB for infections refractory to first-line 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.[610,611] 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 invasive aspergillosis refractory to first-line thearpy.[612] This database study, although encouraging, involved small numbers of patients and the two groups of patients evaluated were non-contemporaneous; therefore, other host and infection-related factors may have influenced the outcome. A noncomparative study of caspofungin combined with other mold-active drugs as subsequent-line therapy for invasive aspergillosis reported a success rate of 49% (25/51) at 12 weeks after initiation of combination therapy,[613] which was similar to caspofungin monotherapy.[170] In an open-label study of invasive aspergillosis, micafungin combined with other antifungals led to a successful response in 29% (5/17) of patients treated as primary therapy and 35% (60/174) of patients with infection refractory to first-line therapy.[614] These results did

not appear favorable to response rates observed with micafungin alone (50% and 41% in primary and refractory 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. More recently, data from a randomized, prospective clinical trial comparing voriconazole versus voriconazole plus anidulafungin as primary therapy for invasive aspergillosis evaluated response based on 6-week mortality (N = 454 patients with hematologic malignancies or HCT).[615] The combination therapy had a trend towards reduced mortality compared to voriconazole alone (19.3% vs. 27.5%, respectively; 95% CI, -19.0–1.5; *P* = .087).[615]

Isavuconazonium sulfate was approved in 2015 for the treatment of invasive aspergillosis and invasive mucormycosis. Unlike other azoles, isavuconazonium sulfate is dosed as a prodrug that is broken down to the active component, isavuconazole, upon infusion.[616] A phase III, randomized trial comparing isavuconazonium sulfate to voriconazole for the primary treatment of invasive aspergillosis and other filamentous fungi showed the non-inferiority of isavuconazonium sulfate compared with voriconazole (all-cause mortality of 19% vs. 20%; adjusted difference -1.0%; 95% CI, -7.8–5.7%).[617] Treatment-emergent adverse events were similar between isavuconazonium sulfate and voriconazole (96% vs. 98%; *P* = .122) with GI disorders and infections or infestations as the most common (see *Toxicities and Drug-Drug Interactions of Azoles* for more information on safety). Isavuconazonium sulfate demonstrated a lower incidence of hepatobiliary disorders, eye disorders, and skin or subcutaneous tissue disorders. Drug-related adverse events were also lower for isavuconazonium sulfate compared to voriconazole (42% vs. 60%; *P* < .001). Based on these data, isavuconazonium sulfate can be considered for patients who have invasive, refractory infections or who have intolerance to amphotericin B formulations. A 2016 update to the IDSA Practice Guidelines lists isavuconazonium sulfate as an alternative therapy option for primary treatment of invasive aspergillosis.[618]

Posaconazole has shown activity as a second-line agent against a broad spectrum of invasive fungal infections.[619-622] 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.[623] 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 United States, 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 subsequent-line therapy for invasive fungal disease.

The NCCN Guidelines Panel recommends voriconazole monotherapy (category 1) as primary therapy for invasive aspergillosis (see *Antifungal Agents: Azoles* in the algorithm). Although combination antifungal therapy is used as treatment for invasive aspergillosis in some centers, the clinical evidence is inadequate to make conclusions about whether any combination regimen is more effective than voriconazole alone, the current gold standard.

For patients receiving treatment with an echinocandin, the Panel recommends TDM following initiation of treatment to ensure adequate plasma concentrations of the drug. Ongoing TDM is generally warranted.

Mucormycosis and Other Invasive Mold Infections

A higher frequency of mucormycosis has emerged at some institutions with the increased use of voriconazole.[511,624,625] In a case-control study of invasive aspergillosis and mucormycosis in patients with acute leukemia and allogeneic HCT recipients, use of voriconazole and presence of fungal

sinusitis each favored a diagnosis of mucormycosis.[511] However, some transplant centers reported an increased frequency of mucormycosis that pre-dated the availability of voriconazole,[626,627] a finding that likely reflects a greater proportion of patients with severe host defense impairment. Mucormycosis typically manifests as rhinocerebral or pulmonary disease. Histopathology showing broad aseptate or hyposeptate hyphae with 90-degree branching is suggestive of mucormycosis, although culture is required for confirmation.

To date, there have been no positive results from randomized studies for treatment of mucormycosis and other uncommon invasive mold infections. Therefore, recommendations for therapy are based on a limited number of patients from retrospective analyses, data registries, and open-label trials for refractory infections. Treatment of mucormycosis involves amphotericin B (a lipid formulation is advised over AmB-D 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. Isavuconazonium sulfate and posaconazole have shown promising results as therapy in mucormycosis refractory to or intolerant of amphotericin B formulations and may be considered for these patients.[619,628,629] Data from an open-label, single-arm, case-control study showed that isavuconazonium sulfate had activity against rare fungi, including mucormycosis, compared to matched controls treated with amphotericin B-based treatment (crude all-cause mortality of 33% vs. 39%; 95% CIs, 14.6–57.0% and 22.9–57.9%, respectively).[629] Ninety-five percent of patients treated with isavuconazonium sulfate had one or more adverse events during treatment, most commonly GI disorders (see *Toxicities and Drug-Drug Interactions of Azoles* for more information on safety).

While isavuconazonium sulfate is approved for the treatment of invasive mucormycosis, posaconazole has not been FDA approved for this indication. Isavuconazonium sulfate and posaconazole can also be considered as maintenance therapy for mucormycosis following control of infection with an amphotericin B formulation and/or surgical debridement.

Fusarium species[630-632] and *Scedosporium* species have emerged as important causes of invasive fungal infection-related mortality in leukemia and in allogeneic HCT recipients at some centers.[627,633,634] 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.[630] Therapy for invasive fusariosis generally involves voriconazole,[635] posaconazole,[622] or a lipid formulation of amphotericin B.[636] *Scedosporium* species are resistant to amphotericin B; therapy generally involves itraconazole, voriconazole, or posaconazole.[637,638] 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

The frequency and diversity of invasive fungal pathogens have increased, and effectively treating these pathogens remains a major challenge. CT scanning of the chest may facilitate early detection of aspergillosis and other filamentous fungi.[639,640] 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.[537] 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 HCT recipients yielded positive and negative predictive values of 94.4% and 98.8%, respectively, and antigenemia preceded radiographic findings by >1 week in 80% of cases of invasive aspergillosis.[641] In another study, the sensitivity was only 64.5% in cases of definite invasive aspergillosis.[546] The PPV was poor when serum galactomannan was used as a surveillance tool in patients with persistent neutropenic fever (PPV = 7.1%) and in HCT (mostly autologous) recipients (PPV = 10%); the negative predictive value was 100% in both groups.[546]

Odabasi et al[540] evaluated the beta-glucan assay as an early diagnostic marker for invasive fungal infections in patients with acute leukemia or MDS receiving antifungal prophylaxis.[540] 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 two or more sequential positive results.[540] The experience of the beta-glucan assay in HCT 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[642] (see *Initial Clinical Presentation for Lung Infiltrates: Evaluation* in the algorithm), 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,[498] and more research is required. Currently, the evidence is inadequate to recommend any of these methods as a surveillance tool in patients who are asymptomatic immunocompromised or in patients with neutropenic fever alone.

COVID-19 Infection in Patients with Cancer

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can cause increased disease severity and mortality in patients with active cancer compared to healthy individuals. Patients with cancer who are immunocompromised, undergoing chemotherapy, older in age, or having other medical conditions are at an increased risk for severe COVID-19. Moreover, patients with hematologic malignancies may be at higher risk of prolonged infection and death from COVID-19 than patients with solid tumors. The CDC provides a comprehensive list of recommendations on testing for SARS-CoV-2 and managing COVID-19 and cancer-directed therapies in people with concurrent cancer and COVID-19. For a summary of NCCN recommendations, see *Management of Concurrent COVID-19 and Cancer in Patients* and *General Recommendations for Vaccination in Patients with Cancer* in the algorithm.

Summary

Substantial progress has been made in the prevention and treatment of infectious complications associated with neutropenia and IST in patients with cancer. Certain populations of patients are at increased risk for developing infectious complications during the course of their disease and cancer treatment. Infectious complications remain an important cause of morbidity and mortality in patients undergoing 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. Preventive measures for infection management in patients with cancer include routine surveillance to monitor for early laboratory indications of infection (especially in the context of viral reactivations) and the appropriate use of prophylaxis and/or preemptive therapy with antimicrobial agents in patient groups who are at high risk. 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 and receiving allogeneic HCT, opportunistic viral and fungal infections have become important causes of mortality in these patients. In addition, the increasing prevalence of antibiotic-resistant pathogens is a challenge. Infection control should not only rely on anti-infective prophylaxis but should continue to incorporate standard infection control measures (eg, careful hand-washing by health care professionals). When selecting antimicrobial agents for prophylaxis and/or preemptive therapy, consideration should be given to the local susceptibility and resistance patterns of pathogens.

In summary, prevention and treatment of infections in patients with cancer is a complex and continuously evolving field. However, these advances in treatment have only further emphasized the need for multidisciplinary care. 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 patient populations at high risk, and recommendations for empiric therapy, evaluation, follow-up, and monitoring in patients with signs and/or symptoms of infections. Individualized risk evaluation for infections, incorporation of preventive measures, and prompt identification and treatment of active infections are essential components of the overall spectrum of care in cancer management, and can contribute to optimizing treatment outcomes in patients with cancer.

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