National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Prevention and Treatment of Cancer-Related Infections

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

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

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

See NCCN Categories of Evidence and Consensus

Summary of the Guidelines Updates

Summary of the changes in the 2.2009 version of the Prevention and Treatment of Cancer-Related Infections Guidelines from the 1.2009 version include:
- The addition of the updated Discussion section.

Summary of the changes in the 1.2009 version of the Prevention and Treatment of Cancer-Related Infections Guidelines from the 1.2008 version include:

INF-1
- Added clofarabine and nelarabine to the intermediate overall risk of infection in cancer patients category.
- Added "Purine analogs, intermediate risk when used as single agents, when combined with intensive chemotherapy regimens the risk converts to high."
- Footnote a is new to the page: "Categories of risk are based on several factors, including underlying malignancy, whether disease is in remission, duration of neutropenia, prior exposure to chemotherapy, and intensity of immunosuppressive therapy."
- Footnote b is new to the page: "Multiple immune deficits can co-exist in the same patient."

INF-3
- Itraconazole recommendation as prophylaxis changed from a category 1 to a category 2B level of evidence and consensus.

INF-4
- Bortezomib was added as a therapy with high risk for varicella zoster reactivation for which antiviral prophylaxis should be considered.

FEV-2
- Footnote e was revised and now states: "Meta-analysis reported increased mortality associated with cefepime in randomized trials of neutropenic fever. However the FDA has concluded that cefepime remains appropriate therapy for its approved indications based on the results of the FDA's recent meta-analysis." (See Discussion)

FEV-4
Following Mouth/mucosal initial clinical presentation, added "Consider leukemic infiltrate" to the evaluation.

FEV-5
Following diarrhea added: "IV metronidazole should be used in patient who cannot take oral agents."

FEV-6
- Footnote t is new to the page: "Rapid immunofluorescent viral antigen tests may be negative for H1N1 (swine flu)."
- Footnote u is new to the page: "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."

FEV-10
- Added Influenza: Oseltamivir is approved by FDA for 5 d based on data from ambulatory otherwise healthy individuals with intact immune systems; longer courses (ie, at least 10 d) and until resolution of symptoms should be considered in the highly immunocompromised.

FEV-A (page 2 of 4)
- Added doripenem to the Antibacterial Agents Tables.

FEV-C (page 3 of 4)
- Added tenofovir DF to the Antiviral Agents Tables.

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OVERALL INFECTION RISK IN CANCER PATIENTS[a]	DISEASE / THERAPY EXAMPLES[b]	FEVER & NEUTROPENIA RISK CATEGORY (See FEV-3)	ANTIMICROBIAL PROPHYLAXIS[c,d,e,f]
Low	• Standard chemotherapy regimens for most solid tumors • Anticipated neutropenia less than 7 d	Low	• Bacterial - None • Fungal - None • Viral - None unless prior HSV episode
Intermediate	• Autologous HSCT • Lymphoma • Multiple myeloma • CLL • Purine analog therapy (ie, fludarabine, clofarabine, nelarabine, 2-CdA) • Anticipated neutropenia 7 to 10 d	Usually HIGH, but some experts suggest modifications depending on patient status. Purine analogs, intermediate risk when used as single agents; when combined with intensive chemotherapy regimens, the risk converts to high.	• Bacterial - Consider fluoroquinolone prophylaxis • Fungal - Consider fluconazole during neutropenia and for anticipated mucositis • Viral - During neutropenia and at least 30 d after HSCT
High	• Allogeneic HSCT • Acute leukemia ➤ Induction ➤ Consolidation • Alemtuzumab therapy • GVHD treated with high dose steroids • Anticipated neutropenia greater than 10 d	Usually HIGH, but significant variability exists related to duration of neutropenia, immunosuppressive agents, and status of underlying malignancy	• Bacterial - Consider fluoroquinolone prophylaxis • Fungal - See INF-3 • Viral - during neutropenia and at least 30 d after HSCT

KEY: 2-CdA = chlorodeoxyadenosine (cladribine), CLL = chronic lymphocytic leukemia, CMV = cytomegalovirus, GVHD = graft versus host disease, HSCT = hematopoietic stem cell transplant, HSV = herpes simplex virus, VZV = varicella zoster virus.

[a] Categories of risk are based on several factors, including underlying malignancy, whether disease is in remission, duration of neutropenia, prior exposure to chemotherapy, and intensity of immunosuppressive therapy.
[b] Multiple immune deficits can co-exist in the same patient.
[c] Pneumocystis prophylaxis (See INF-5).
[d] See Antibacterial Agents (FEV-A) for dosing, spectrum, and specific comments/cautions.
[e] See Antifungal Agents (FEV-B) for dosing, spectrum, and specific comments/cautions.
[f] See Antiviral Agents (FEV-C) for dosing, spectrum, and specific comments/cautions.

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OVERALL INFECTION RISK IN CANCER PATIENTS[a]	DISEASE/THERAPY EXAMPLES	ANTIBACTERIAL PROPHYLAXIS[d]	DURATION
Low	• Standard chemotherapy regimens for most solid tumors • Anticipated neutropenia less than 7 d	None[g]	
Intermediate	• Autologous HSCT • Lymphoma • CLL • Multiple myeloma • Purine analog therapy • Anticipated neutropenia 7 to 10 d	Consider fluoroquinolone prophylaxis[g] or None	
High	• Allogeneic HSCT (neutropenic) • Acute leukemia (neutropenic) • MDS (neutropenic) • Anticipated neutropenia greater than 10 d	Consider fluoroquinolone prophylaxis	
High	GVHD	Penicillin and TMP/SMX	
High	Alemtuzumab	TMP/SMX	For a minimum of 2 mo after alemtuzumab and until CD4 ≥ 200 cells/mcL

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

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

[g]Although data support levofloxacin prophylaxis for low- and intermediate-risk patients, the panel discourages this practice in low-risk patients (because of concerns about antimicrobial resistance); however, it can be considered in intermediate-risk patients.

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OVERALL INFECTION RISK IN CANCER PATIENTS[a]	DISEASE/THERAPY EXAMPLES		ANTIFUNGAL PROPHYLAXIS[e]	DURATION
Intermediate to High	ALL[h]		• Fluconazole[k] or • Amphotericin B products[l] (category 2B)	Until resolution of neutropenia
	MDS (neutropenic) AML[h] (neutropenic)		• Posaconazole (category 1)[k] or • Voriconazole (category 2B)[k] or • Amphotericin B products[l] (category 2B)	Until resolution of neutropenia
	Autologous HSCT	With mucositis[j]	• Fluconazole (category 1)[k] or • Micafungin (category1)	Until resolution of neutropenia
		Without mucositis	Consider no prophylaxis (category 2B)	
	Allogeneic HSCT (neutropenic)		Consider one of the following: • Fluconazole (category 1)[k] • Micafungin (category 1) • Itraconazole (category 2B)[k] • Voriconazole (category 2B)[k] • Posaconazole (category 2B)[k] • Amphotericin B products[l] (category 2B)	Continue during neutropenia and for at least 75 d after transplant
	Significant GVHD[i]		Consider one of the following: • Posaconazole (category 1)[k] • Voriconazole (category 2B)[k] • Echinocandin (category 2B) • Amphotericin B products[l] (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, and intensity of immunosuppressive therapy.

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

[h] Recommendations on antifungal prophylaxis in patients with acute leukemia apply to those receiving induction or re-induction chemotherapy.

[i] Consider antifungal prophylaxis in all patients with GVHD receiving immunosuppressive therapy. See Antifungal Prophylaxis section of the Discussion.

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

[k] Itraconazole, voriconazole, and posaconazole are more potent inhibitors of hepatic cytochrome P450 3A4 isoenzymes than fluconazole and may significantly decrease the clearance of vinca alkaloids.

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

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OVERALL INFECTION RISK IN CANCER PATIENTS[a]	DISEASE / THERAPY EXAMPLES	HERPES VIRUSES	ANTIVIRAL PROPHYLAXIS	DURATION OF ANTIVIRAL PROPHYLAXIS[f]
Low	• Standard chemotherapy regimens for solid tumors	HSV	None unless prior HSV episode	During neutropenia
Intermediate	• Autologous HSCT • Lymphoma • Multiple Myeloma • CLL • Purine analog therapy (ie, fludarabine)	HSV VZV	Acyclovir Famciclovir Valacyclovir	During neutropenia and at least 30 d after HSCT
High	• Acute leukemia ➤ Induction ➤ Consolidation	HSV	Acyclovir Famciclovir Valacyclovir	During neutropenia
	Bortezomib	VZV	Acyclovir Famciclovir Valacyclovir	
	• Alemtuzumab therapy • Allogeneic HSCT	HSV VZV	Acyclovir Famciclovir[m] or Valacyclovir as HSV prophylaxis[n]	HSV prophylaxis[n] • Minimum of 2 mo after alemtuzumab and until CD4 ≥ 200 cells/mcL • During neutropenia and at least 30 d after HSCT
		CMV	(See INF-6) for CMV	Pre-emptive therapy for CMV (See INF-6)

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

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

[m]Among allogeneic HSCT, there is more experience with acyclovir and valacyclovir than famciclovir.

[n]Agents used as HSV prophylaxis are also active against VZV (See FEV-C).

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INFECTION RISK IN CANCER PATIENTS[a]	DISEASE / THERAPY EXAMPLES	DURATION OF PROPHYLAXIS	ANTIPNEUMOCYSTIS PROPHYLAXIS[d]
High risk for *Pneumocystis jirovecii (Pneumocystis carinii)*	Allogeneic stem cell recipients (category 1) →	For at least 180 d	→ TMP/SMX (preferred) or Dapsone, aerosolized pentamidine, or atovaquone[q] if TMP/SMX intolerant[q]
	Acute lymphocytic leukemia (category 1) →	Throughout anti-leukemic therapy	
	Alemtuzumab →	For a minimum of 2 mo after alemtuzumab and until CD4 ≥ 200 cells/mcL	
	Consider (category 2B):		
	• Recipients of fludarabine and other T-cell depleting agents →	Until CD4 count is greater than 200 cells/mcL	
	• Patients with neoplastic disease receiving prolonged corticosteroids[o] or receiving temozolomide + radiation therapy[p] →		
	• Autologous peripheral blood stem cell transplant recipients →	3-6 mo after transplant	

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

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

[o] Risk of PCP is related to the daily dose and duration of corticosteroid therapy. Prophylaxis against PCP can be considered in patients receiving the prednisone equivalent of 20 mg or more daily for 4 or more weeks.

[p] PCP prophylaxis should be used when temozolomide is administered concomitantly with radiation therapy and should be continued until recovery from lymphocytopenia.

[q] Consider trimethoprim/sulfamethoxazole desensitization or dapsone, aerosolized pentamidine, or atovaquone when *Pneumocystis jirovecii* pneumonia prophylaxis is required, and patients are trimethoprim/sulfamethoxazole intolerant.

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PREVENTION OF CYTOMEGALOVIRUS DISEASE

INFECTION RISK IN CANCER PATIENTS[a] → **DISEASE / THERAPY EXAMPLES** → **SURVEILLANCE PERIOD[r]** → **PRE-EMPTIVE THERAPY[f,s]**

High risk for Cytomegalovirus disease

- **Allogeneic stem cell transplant recipients** →
  - 1 to 6 months after transplant
  - GVHD
  - CD4 < 100 cells/mcL
- **Alemtuzumab** →
  - For a minimum of 2 mo after alemtuzumab and until CD4 ≥ 100 cells/mcL

→ **Ganciclovir (IV)**
or
Foscarnet (IV)
or
Valganciclovir (PO)

[a] Categories of risk are based on several factors, including underlying malignancy, whether disease is in remission, duration of neutropenia, prior exposure to chemotherapy, and intensity of immunosuppressive therapy.
[f] See Antiviral Agents (FEV-C) for dosing, spectrum, and specific comments/cautions.
[r] CMV surveillance consists of at least weekly monitoring of CMV by PCR or antigen testing.
[s] Duration of prophylaxis antiviral therapy generally is for at least 2 weeks and until CMV is no longer detected.

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CLINICAL PRESENTATION

Fever:
- Single temperature ≥ 38.3°C orally or ≥ 38.0°C over 1 h

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

→

INITIAL EVALUATION OF FEVER AND NEUTROPENIA

Site specific H&P including:
- Intravascular access device
- Skin
- Lungs and sinus
- Alimentary canal (mouth, pharynx, esophagus, bowel, rectum)
- Perivaginal/perirectal

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

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

→

MICROBIOLOGIC EVALUATION

- Blood culture x 2 sets (one set consists of 2 bottles). Options include:
  - One peripheral + one catheter[a] or
  - Both peripheral or
  - Both catheter
- Urine (if symptoms, urinary catheter, abnormal urinalysis)
- Site-specific culture:
  - Diarrhea (*Clostridium difficile* assay, enteric pathogen screen)
  - Skin (aspirate/biopsy of skin lesions)
  - Vascular access cutaneous site with inflammation (consider routine/fungal/mycobacteria)
- Viral cultures:
  - Vesicular/ulcerated lesions on skin or mucosa
  - Throat or nasopharynx for respiratory virus symptoms, especially during outbreaks

See Initial Therapy (FEV-2)

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

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INITIAL THERAPY FOR FEVER AND NEUTROPENIA[b,c]

Initial antibiotic therapy should be based on:
- Infection risk assessment (See FEV-3)
- Potential infecting organisms include vancomycin-resistant enterococcus (VRE) and extended spectrum beta-lactamase (ESBL)
- Colonization with or prior infection with methicillin-resistant *Staphylococcus aureus* (MRSA)
- Site of infection
- Local antibiotic susceptibility patterns
- Organ dysfunction/drug allergy
- Broad spectrum of activity
- Previous antibiotic therapy
- Antipseudomonal coverage
- Bactericidal

→

- Intravenous antibiotic monotherapy (choose one):
  - Imipenem/cilastatin (category 1)
  - Meropenem (category 1)
  - Piperacillin/tazobactam[d] (category 1)
  - Cefepime (category 1)[e]
  - Ceftazidime[f] (category 2B)
- Intravenous antibiotic combination therapy:
  - Aminoglycoside[g] + antipseudomonal penicillin (category 1) ± beta-lactamase inhibitor (category 1)
  - Aminoglycoside + extended-spectrum cephalosporin (cefepime, ceftazidime)
  - Ciprofloxacin + antipseudomonal penicillin (category 1)
  - Use of vancomycin, linezolid, daptomycin or quinupristin/dalfopristin is not routinely recommended[h,i]
- Oral antibiotic combination therapy for low risk patients:
  - Ciprofloxacin + amoxicillin/clavulanate (category 1) (for penicillin-allergic patients, may use ciprofloxacin + clindamycin)
  - Oral antibiotic regimen recommended should not be used if quinolone prophylaxis was used

→

Site-Specific Evaluation and Therapy:

Mouth, Esophagus and Sinus/Nasal (FEV-4)

Abdominal Pain, Perirectal Pain, Diarrhea, Vascular Access Devices (FEV-5)

Lung Infiltrates (FEV-6)

Cellulitis, Wound, Vesicular Lesions, Disseminated Papules or other lesions, Urinary Tract Symptoms, Central Nervous System Symptoms (FEV-7)

OR

Follow-up (FEV-8)

[b] Consider local antibiotic susceptibility patterns when choosing empirical therapy. At hospitals where infections by antibiotic resistant bacteria (eg, MRSA or drug-resistant gram-negative rods) are commonly observed, policies on initial empirical therapy of neutropenic fever may need to be tailored accordingly.

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

[d] May interfere with galactomannan measurement.

[e] Meta-analysis reported increased mortality associated with cefepime in randomized trials of neutropenic fever. However the FDA has concluded that cefepime remains appropriate therapy for its approved indications based on the results of the FDA's recent meta-analysis. (see Discussion).

[f] Weak Gram-positive coverage and increased breakthrough infections limit utility.

[g] Some authorities recommend avoidance of aminoglycosides because of potential nephrotoxicity, which may be diminished by once-daily administration. Once-a-day aminoglycoside therapy should be avoided for treatment of meningitis or endocarditis.

[h] Although there are published studies regarding the use of some of these agents in neutropenic patients, the NCCN panel strongly recommends that these agents should not be routinely used as initial empirical therapy for neutropenic fever because of concerns about resistance and breakthrough infections.

[i] See Appropriate Use of Vancomycin and Other Agents for Gram-positive Resistant Infections (FEV-D).

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INITIAL RISK ASSESSMENT FOR FEBRILE NEUTROPENIC PATIENTS[j]

SITE OF CARE | **TREATMENT OPTIONS**

Initial evaluation

→ **High-risk (any factor listed below):**
- Inpatient status at time of development of fever
- Significant medical comorbidity or clinically unstable
- Anticipated prolonged severe neutropenia: ≤ 100 cells/mcL and ≥ 7 d
- Hepatic insufficiency (5 times ULN for aminotransferases)
- Renal insufficiency (a creatinine clearance of less than 30 mL/min)
- Uncontrolled/progressive cancer[k]
- Pneumonia or other complex infections at clinical presentation
- Alemtuzumab
- Mucositis grade 3-4

  OR
- MASCC Risk Index score of less than 21[j]

→ Hospital → IV therapy

→ **Low-risk (none of the above factors and most of the following):**
- Outpatient status at time of development of fever
- No associated acute comorbid illness, independently indicating inpatient treatment or close observation
- Anticipated short duration of severe neutropenia (≤ 100 cells/mcL for < 7 d)
- Good performance status (ECOG 0-1)
- No hepatic insufficiency
- No renal insufficiency

  OR
- A score of 21 or greater on the MASCC Risk Index[j]

→ Hospital
- → IV therapy or Sequential IV/oral therapy
- → Oral therapy (category 1)

OR

Consider ambulatory clinic

OR

Home for selected low-risk patients with adequate outpatient infrastructure established

→ See Outpatient Therapy for Low-Risk Patients (FEV-13)

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

[k]Uncontrolled/progressive cancer is defined as any leukemic patient not in complete remission, or non-leukemic patients with evidence of disease progression after more than 2 courses of chemotherapy.

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INITIAL CLINICAL PRESENTATION (DAY 0)	FINDING	EVALUATION	ADDITIONS TO INITIAL EMPIRIC REGIMEN[c,l,m] All febrile neutropenic patients should receive broad-spectrum antibiotics (FEV-2)
Mouth/ mucosal membrane	Necrotizing ulceration	• Culture and gram stains ➤ Viral - Herpes simplex virus (HSV) ➤ Fungal ➤ Consider leukemic infiltrate • Biopsy for lesions suspicious for mold	• Ensure adequate anaerobic activity • Consider anti-HSV therapy • Consider systemic antifungal therapy
	Thrush		• Antifungal therapy ➤ Fluconazole first-line therapy ➤ Voriconazole, posaconazole, or echinocandin if refractory to fluconazole
	Vesicular lesions	Viral cultures or PCR or other diagnostics and direct fluorescent antibody test for HSV and Varicella-zoster virus (VZV)	Anti-HSV therapy (category 1)
Esophagus	• Retrosternal burning • Dysphagia/ odynophagia	• Culture suspicious oral lesions ➤ HSV ➤ Fungal • Consider endoscopy, if no response to therapy • Consider CMV esophagitis in patients at high risk for CMV disease	• Initial therapy guided by clinical findings (eg, thrush or perioral HSV) • Antifungal therapy ➤ Fluconazole, first-line therapy ➤ Voriconazole, posaconazole, or echinocandin if refractory to fluconazole • Acyclovir • If at high risk for invasive CMV, consider ganciclovir or foscarnet
Sinus/ nasal	• Sinus tenderness • Periorbital cellulitis • Nasal ulceration • Unilateral eye tearing	• High resolution sinus CT/orbit MRI • ENT/ophthalmological urgent evaluation • Culture and stains/biopsy	• Add vancomycin if periorbital cellulitis noted • Add lipid amphotericin B preparation to cover possible aspergillosis and mucormycosis in high risk patients with suspicious CT/MRI findings[n] • Infectious disease consult

See Follow-up (FEV-8)

[c] 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.
[n] Posaconazole can be considered for salvage therapy or for intolerance to amphotericin B formulations. Posaconazole is not approved by the FDA as either primary or salvage therapy for invasive fungal infections.

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INITIAL CLINICAL PRESENTATION (DAY 0)	FINDING	EVALUATION[p]	ADDITIONS TO INITIAL EMPIRIC REGIMEN[c,l,m] All febrile neutropenic patients should receive broad-spectrum antibiotics (FEV-2)	
Abdominal pain[o] →		• Abdominal CT (preferred) or ultrasound • Alkaline phosphatase, transaminases, bilirubin, amylase, lipase →	• Metronidazole if *C. difficile* suspected • Ensure adequate anaerobic therapy	See Follow-up (FEV-8)
Perirectal pain →		• Perirectal inspection • Consider abdominal/pelvic CT →	• Ensure adequate anaerobic therapy • Consider enterococcal[q] coverage • Consider local care (sitz baths, stool softeners)	See Follow-up (FEV-8)
Diarrhea →		• *Clostridium difficile* assay • Consider testing for rotavirus and norovirus in winter months and during outbreaks • Consider stool bacterial cultures and/or parasite exam if travel/lifestyle history or community outbreak indicate exposure →	If *C. difficile* suspected, consider adding oral metronidazole pending assay results: IV metronidazole should be used in patient who cannot take oral agents	See Follow-up (FEV-8)
Vascular access devices (VAD)	Entry or exit site inflammation →	• Swab exit site drainage (if present) for culture • Blood culture from each port of VAD →	Vancomycin[i] initially or add it if site not responding after 48 h of empiric therapy	See Follow-up (FEV-8)
Vascular access devices (VAD)	Tunnel infection/ port pocket infection, septic phlebitis →	Blood culture from each port of VAD →	• Remove catheter and culture surgical wound • Add vancomycin[i]	See Follow-up (FEV-8)

[c] See Antibacterial Agents (FEV-A) for dosing, spectrum, and specific comments/cautions.
[i] See Appropriate Use of Vancomycin and Other Agents for Gram-positive Resistant Infections (FEV-D).
[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.
[o] Surgical and other subspecialty (eg, gastroenterology, interventional radiology) consultations should be considered for these situations as clinically indicated.
[p] Lab studies include CMV antigens/PCR and abdominal/pelvic CT.
[q] Enterococcal colonization must be differentiated from infection. Vancomycin use must be minimized because of the risk of vancomycin resistance.

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RISK CATEGORY | **EVALUATION[r,s]** | **ADDITIONS TO INITIAL EMPIRIC REGIMEN[c,l,m]**

All febrile neutropenic patients should receive broad-spectrum antibiotics (FEV-2)

Lung infiltrates

Low-risk →

Evaluation:
- Blood and sputum cultures
- Nasal wash for respiratory viruses, rapid tests[t]
- Legionella urine Ag test
- Consider BAL, particularly if no response to initial therapy or if diffuse infiltrates present

→ **Additions to initial empiric regimen:**
- Azithromycin or fluoroquinolone added to cover atypical bacteria
- Consider adding:
  - Antiviral therapy during influenza outbreaks[u]
  - Vancomycin or linezolid if MRSA suspected

Intermediate- to High-risk →

Evaluation:
- Blood and sputum cultures
- Nasal wash for respiratory viruses, rapid tests[t]
- Legionella urine Ag test
- Serum galactomannan or β-glucan test in patients at risk for mold infections
- Consider BAL, particularly if no response to initial therapy or if diffuse infiltrates present
- CT chest to better define infiltrates

→ **Additions to initial empiric regimen:**
- Azithromycin or fluoroquinolone added to cover atypical bacteria
- Consider adding:
  - Mold-active antifungal agent
  - Antiviral therapy during influenza outbreaks[u]
  - TMP-SMX if *Pneumocystis jirovecii* is possible etiology
  - Vancomycin or linezolid if MRSA suspected
- Adjunctive therapies may be considered in certain patient populations[v]

→ See Follow-up (FEV-8)

[c] 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.
[r] Other diagnoses to consider include pulmonary edema, hemorrhage, and drug toxicities.
[s] Assess for healthcare acquired pneumonia and/or resistant pathogens.
[t] Rapid immunofluorescent viral antigen tests may be negative for H1N1 (swine flu).
[u] 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.
[v] See Adjuvant Therapies (FEV-F).

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INITIAL CLINICAL PRESENTATION (DAY 0)	EVALUATION	ADDITIONS TO INITIAL EMPIRIC REGIMEN[c,l,m] All febrile neutropenic patients should receive broad-spectrum antibiotics (FEV-2)	
Cellulitis →	Consider aspirate or biopsy for culture →	Consider vancomycin[i] →	See Follow-up (FEV-8)
Wound →	Culture →	Consider vancomycin[i] →	See Follow-up (FEV-8)
Vesicular lesions →	Aspiration or scraping for VZV or HSV direct fluorescent antibody (DFA)/herpes virus cultures →	Consider acyclovir, famciclovir, or valacyclovir →	See Follow-up (FEV-8)
Disseminated papules or other lesions →	Aspiration or biopsy for bacterial, fungal, mycobacterial cultures and histopathology →	• Consider vancomycin[i] • Consider mold-active antifungal therapy in high-risk patients →	See Follow-up (FEV-8)
Urinary tract symptoms →	• Urine culture • Urinalysis →	No additional therapy until specific pathogen identified →	See Follow-up (FEV-8)
Central nervous system symptoms →	• Infectious disease (ID) consult • CT and/or MRI • Lumbar puncture (if possible) • Neurology consult →	• Empiric therapy for presumed meningitis should include an anti-pseudomonal beta-lactam agent that readily enters CSF (eg, cefepime, ceftazidime, meropenem) plus vancomycin[i], plus ampicillin (to cover listeriosis). If meropenem is used, addition of ampicillin is unnecessary because meropenem is active against *Listeria*. • For encephalitis, add high-dose acyclovir 10 mg/kg/dose 3x/d) with hydration and monitor renal function	See Follow-up (FEV-8)

[c] See Antibacterial Agents (FEV-A) for dosing, spectrum, and specific comments/cautions.
[i] See Appropriate Use of Vancomycin and Other Agents for Gram-positive Resistant Infections (FEV-D).
[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.

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PRINCIPLES OF DAILY FOLLOW-UP

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

→ Evaluate overall response to empiric therapy in 3-5 d[v] (72-120 h)

→ **RESPONDING**
- Decreasing fever trend
- Signs and symptoms of infection are stable or improving
- Patient is hemodynamically stable

→ See Follow-up Therapy (FEV-9)

→ **NONRESPONDING**
- Persistently or intermittently febrile
- Signs and symptoms of infection are not improving
- Patient may be hemodynamically unstable
- Persistent positive blood cultures

→ See Follow-up Therapy (FEV-12)

[v] See Adjunctive Therapies (FEV-F).

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FOLLOW-UP THERAPY FOR RESPONDING PATIENTS

- No change in initial empiric regimen
- If patients started on "appropriate" initial vancomycin,[i] continue course of therapy
- Initial antibiotic regimen should be continued at least until neutrophil count is ≥ 500 cells/mcL and increasing

→ Documented infection
- Bacteremia
  - Simple (no tissue site)
  - Complex (tissue infection with bacteremia)
- Pneumonia
- Skin/soft tissue
- Sinus
- Fungal
- Viral

→ See Suggested Duration of Therapy for Documented Infection (FEV-10)

→ Fever of unknown origin → See Suggested Duration of Therapy for Fever of Unknown Origin (FEV-11)

[i]See Appropriate Use of Vancomycin and Other Agents for Gram-positive Resistant Infections (FEV-D).

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FOLLOW-UP THERAPY FOR RESPONDING PATIENTS

Documented infection →

GENERAL GUIDELINES

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

→

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

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

- Skin/soft tissue: 7-14 d
- Bloodstream infection (uncomplicated)
  - Gram-negative: 10-14 d
  - Gram-positive: 7-14 d
  - *S. aureus*: at least 2 weeks after first negative blood culture and normal transesophageal echocardiogram (TEE)[w]
  - Yeast: ≥ 2 wks after first negative blood culture
  - Consider catheter removal for bloodstream infections with *Candida, S. aureus*, *Pseudomonas aeruginosa*, *Corynebacterium jeikeium*, *Acinetobacter*, *Bacillus* organisms, atypical mycobacteria, yeasts, molds, vancomycin-resistant enterococci, and *Stenotrophomonas maltophilia* (category 2B)
- Sinusitis: 10-21 d
- Catheter removal for septic phlebitis, tunnel infection, or port pocket infection
- Bacterial pneumonia: 10-21 d
- Fungal (mold and yeast):
  - *Candida*: minimum of 2 wks after first negative blood culture
  - Mold (eg, *Aspergillus*): minimum of 12 wks
- Viral:
  - HSV/VZV: 7-10 d (category 1); acyclovir, valacyclovir, or famciclovir (uncomplicated, localized disease to the skin)
  - Influenza: Oseltamivir is approved by FDA for 5 d based on data from ambulatory otherwise healthy individuals with intact immune systems; longer courses (eg, at least 10 d) and until resolution of symptoms should be considered in the highly immunocompromised

[c] 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.
[w] A TEE should be considered in all cases of *S. aureus* bacteremia. In patients with conditions that may increase the likelihood of complications (eg, neutropenia, thrombocytopenia, mucositis), a transthoracic echocardiogram (TTE) may be performed initially and, if negative, a TEE should be performed when safe. A TEE is more sensitive and preferred when compared with TTE.

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FOLLOW-UP THERAPY FOR RESPONDING PATIENTS

SUGGESTED DURATION OF THERAPY FOR FEVER OF UNKNOWN ORIGIN

Fever of unknown origin

- **Neutrophils ≥ 500 cells/mcL** → **Discontinue therapy**
- **Neutrophils < 500 cells/mcL** →
  - **Continue current regimen until neutropenia resolves**
  - **OR**
  - **Switch to oral antibiotics until neutropenia resolves (ciprofloxacin 500 mg every 8 h + amoxicillin/potassium clavulanate 500 mg every 8 h)[x]**

[x]Use clindamycin for penicillin-allergic patients.

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FOLLOW-UP THERAPY FOR NONRESPONDING PATIENTS

SUGGESTED DURATION OF THERAPY

Fever of unknown origin

- **Stable** →
  - Continue current antibacterial therapy: modification of antibacterial therapy solely on the basis of neutropenic fever not required
- **Unstable** →
  - Broaden coverage to include anaerobes, resistant Gram-negative rods, and resistant Gram-positive organisms, as clinically indicated
  - Consider adding G-CSF or GM-CSF (category 2B)
  - Ensure coverage for *Candida*
  - Infectious disease consult

→ Suggested duration of therapy (Stable and Unstable):
- Consider antifungal therapy with activity against molds for fever continuing ≥ 4 days of empiric antibiotic therapy[y]
- Duration of therapy depends on clinical course, neutropenia recovery, toxicity, and opinions of Infectious Disease consultants

Documented infection →
- Assess appropriateness of antibiotics for pathogens isolated (susceptibility testing, dosing)
- Consider adding G-CSF or GM-CSF (category 2B)
- Consider granulocyte transfusions for life-threatening refractory bacterial or fungal infections (category 2B)

[y]The timing to add empirical antifungal therapy varies with the risk of invasive mold infection but generally ranges between 4-7 d of neutropenic fever. In patients at high risk for mold infection (neutropenia > 10 d, allogeneic stem cell transplant recipients, high-dose corticosteroids), the panel recommends adding empirical antifungal therapy after 4 d unless patient is receiving prophylaxis directed against molds. See Discussion of antifungal prophylaxis versus empirical antifungal therapy.

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OUTPATIENT THERAPY FOR LOW-RISK PATIENTS

INDICATION

Patient determined to be in low-risk category on presentation with fever and neutropenia

- Outpatient status at time of development of fever
- No associated acute comorbid illness, independently indicating inpatient treatment or close observation
- Anticipated short duration of severe neutropenia (< 7 days)
- Good performance status (ECOG 0-1)
- Serum creatinine ≤ 2.0 mg/dL, liver functions ≤ 3x normal

  OR
- A score of 21 or greater on the MASCC Risk Index[j]

→

ASSESSMENT

- Careful examination
- Review lab results: no critical values
- Review social criteria for home therapy
  - Patient consents to home care
  - 24 h home caregiver available
  - Home telephone
  - Access to emergency facilities
  - Adequate home environment
  - Distance within approximately one hour of a medical center or treating physician's office
- Assess for oral antibiotic therapy
  - No nausea and vomiting
  - Able to tolerate oral medications
  - Not on prior fluoroquinolone prophylaxis

→

MANAGEMENT

Observation period (2-12 h) (category 2B) in order to:

- Confirm low-risk status and ensure stability of patient
- Observe and administer first dose of antibiotics and monitor for reaction
- Organize discharge plans to home and follow-up
- Patient education
- Telephone follow-up within 12-24 h

→ See Treatment and Follow-up (FEV-14)

[j]Risk categorization can predict outcome during the febrile episode, including complications/mortality. See Risk Assessment Resources (FEV-E).

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OUTPATIENT THERAPY FOR LOW-RISK PATIENTS

TREATMENT OPTIONS

- IV antibiotics at home
- Daily long-acting intravenous agent ± oral therapy
  - Home or office
- Oral therapy only[z]:
  - 500 mg every 8 h ciprofloxacin[aa] plus 500 mg every 8 h amoxicillin/clavulanate[x] (category 1)
  - Other oral regimens are less well-validated (eg, levofloxacin)

→

FOLLOW-UP

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

[x] Use clindamycin for penicillin-allergic patients.

[z] Criteria for oral antibiotics: no nausea or vomiting, patient able to tolerate oral medications, and patient not on prior fluoroquinolone prophylaxis.

[aa] The fluoroquinolone chosen should be based on reliable Gram-negative bacillary activity, local antibacterial susceptibilities, and the use of quinolone prophylaxis of fever and neutropenia.

[bb] Provider should be individual (eg, MD, RN, PA, NP) who has expertise in the management of patients with neutropenia and fever.

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ANTIBACTERIAL AGENTS (References are on page 4)

GRAM-POSITIVE AGENTS[a]	DOSE	SPECTRUM	COMMENTS/PRECAUTIONS
Vancomycin	15 mg/kg IV every 12 h[b]	Gram-positive organisms with exception of VRE and a number of rare Gram-positive organisms	• Should not be considered as routine therapy for neutropenia and fever unless certain risk factors present (See FEV-D)
Linezolid	600 mg PO/IV every 12 h	Gram-positive organisms including VRE	• Hematologic toxicity may occur, thrombocytopenia most common (0.3% to 10%) • Serotonin syndrome rare, use cautiously with SSRI's[1] • Not for routine use in fever and neutropenia although does not impair neutrophil recovery • Treatment option for VRE and MRSA • Peripheral/optic neuropathy with long-term use • Not recommended for line infections
Daptomycin	4-6 mg/kg IV d[b]	• Gram-positive organisms • Has in vitro activity against VRE but is not FDA-approved for this indication	• Equivalent to standard antistaphylococcal agents for *Staphylococcus aureus* bacteremia at 6 mg/kg dose in non-neutropenic patients[2] • Weekly CPK to monitor for rhabdomyolysis • Not indicated for pneumonia due to inactivation by pulmonary surfactant • Not studied in patients with fever and neutropenia • Myositis is a potential toxicity
Dalfopristin/ Quinupristin	7.5 mg/kg IV every 8 h	Gram-positive organisms including most VRE (does not have activity against *Enterococcus faecalis*) or intolerance to vancomycin	• Use limited by myalgias/arthralgias (up to 47%) • Requires central venous access delivery • Avoid use due to toxicity although coverage is good • Musculoskeletal pain syndrome is a potential toxicity

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[a] These drugs are not recommended as monotherapy for fever in the setting of neutropenia and should only be added for documented infection with resistant Gram-positive organisms or if certain risk factors are present. (See FEV-D)
[b] Requires dose adjustment in patients with renal insufficiency.

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ANTIBACTERIAL AGENTS[c] (References are on page 4)

ANTI-PSEUDOMONAL AGENTS[d]	DOSE	SPECTRUM	COMMENTS/PRECAUTIONS
Imipenem/cilastatin sodium	500 mg IV every 6 h[b]	• Broad spectrum activity against most Gram-positive, Gram-negative and anaerobic organisms • Preferred against extended spectrum beta-lactamase (ESBL) and serious *Enterobacter* infections. • Carbapenem-resistant Gram-negative rod infections are an increasing problem at a number of centers	• Use for suspected intra-abdominal source • Meropenem is preferred over imipenem for suspected /proven CNS infection • Imipenem may lower seizure threshold in patients with CNS malignancies or infection or with renal insufficiency • Empiric therapy for neutropenic fever (category 1)
Meropenem	1 gram IV every 8 h[b] (2 g IV every 8 h for meningitis)		
Doripenem	500 mg IV every 8 h[b]		• Effective in nonsocomial pneumonia and intra-abdominal infections • Lack of clinical trial experience in neutropenic patients
Piperacillin/tazobactam	4.5 grams IV every 6 h[b]	• Broad spectrum activity against most Gram-positive, Gram-negative and anaerobic organisms	• Use for suspected intra-abdominal source • Not recommended for meningitis • May result in false positive galactomannan[3] • Empiric therapy for neutropenic fever (category 1)
Cefepime	2 grams IV every 8 h[b]	• Broad spectrum activity against most Gram-positive and Gram-negative organisms	• Use for suspected/proven CNS infection with susceptible organism • Increased frequency of resistance among Gram-negative rod isolates at some centers • Empiric therapy for neutropenic fever (category 1)
Ceftazidime	2 grams IV every 8 h[b]	• Relatively poor Gram-positive activity • Breakthrough streptococcal infections reported • Not active against most anaerobes and *Enterococcus spp.*	• Use for suspected/proven CNS infection with susceptible organism • Increased frequency of resistance among Gram-negative rod isolates at some centers • Empiric therapy for neutropenic fever based on resistance among certain Gram-negative rods (category 2B)

[b]Requires dose adjustment in patients with renal insufficiency.
[c]Local antibiograms should be considered.
[d]None of these agents are active against MRSA or VRE.

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ANTIBACTERIAL AGENTS (References are on page 4)

OTHER ANTIBACTERIAL AGENTS	DOSE	SPECTRUM	COMMENTS/CAUTIONS
Ciprofloxacin	500-750 mg PO every 12 hours or 400 mg IV every 8-12 h[b]	• Good activity against Gram-negative and atypical (e.g., *Legionella spp.*) organisms • Less active than "respiratory" fluoroquinolones against Gram-positive organisms • No activity against anaerobic organisms	• Avoid for empiric therapy if patient recently treated with fluoroquinolone prophylaxis • Increasing Gram-negative resistance in many centers • Oral antibiotic combination therapy in low-risk patients (with amoxicillin/clavulanate or clindamycin) • In combination with antipseudomonal penicillin in higher risk patients
Levofloxacin	500-750 mg oral or IV daily[b]	• Good activity against Gram-negative and atypical (e.g., *Legionella spp.*) organisms • Improved Gram-positive activity compared to ciprofloxacin • Limited activity against anaerobes • Prophylaxis in neutropenic patients[5,6]	• Prophylaxis may increase bacterial resistance and superinfection[7] • Limited studies as empirical therapy in patients with fever and neutropenia
Aminoglycosides • Gentamicin • Tobramycin • Amikacin	Dosing individualized with monitoring of levels[b]	• Activity primarily against Gram-negative organisms • Gentamicin is synergistic with beta-lactams against susceptible *S. aureus* and *Enterococcus* infections	• Nephrotoxicity and ototoxicity limit use • Combination therapy with anti-pseudomonal penicillin +/- beta-lactamase inhibitor or extended spectrum cephalosporin (see FEV-2)
Trimethoprim/sulfamethoxazole (TMP/SMX)	Single or double strength daily or Double strength 3 times per wk as prophylaxis for *P. jiroveccii*		• Highly effective as prophylaxis against *P. jirovecii* in high risk patients (see INF-5)

[b]Requires dose adjustment in patients with renal insufficiency.

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ANTIBACTERIAL AGENTS REFERENCES

[1] Boyer EW, Shannon M. Serotonin syndrome. N Engl J Med 2005;352:1112-1120.

[2] Fowler VG, Boucher HW, Corey GR, et. al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus* aureus. N Engl J Med 2006;355:653-665.

[3] Aubry A, Porcher R, Bottero J, et al. Occurence and kinetics of false positive Aspergillus galactomannan test results following treatment with beta-lactam antibiotics in patients with hematological disorders. J Clin Microbio 2006;44(2):389-394.

[4] Stein GE, Craig WA. Tigecycline: A critical analysis. Clin Infect Dis 2006;43:518-524.

[5] Bucaneve G, Micozzi A, Menichetti F, et. al. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. N Engl J Med 2005;353:977-987.

[6] Cullen M, Billingham SN, Gaunt C, et. al. Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. N Engl J Med 2005;353:988-998.

[7] Baden LR. Prophylactic antimicrobial agents and the importance of fitness. N Engl J Med 2005;353:1052-1054.

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ANTIFUNGAL AGENTS (References are on page 4)

AZOLES[a]	DOSE	SPECTRUM	COMMENTS/CAUTIONS
Fluconazole	In adults with normal renal function: 400 mg IV/PO daily	• Active against *Candida* • Active against dimorphic fungi (eg, histoplasmosis, coccidioidomycosis) and *C. neoformans*	• *Candida glabrata* is associated with variable resistance in vitro and *Candida krusei* is always resistant • Inactive against molds (eg, *Aspergillus* species, Zygomycetes)
Itraconazole	Oral 400 mg daily (aim for trough of > 0.25 mcg/mL after 7 d of therapy)	• Active against *Candida, Aspergillus* species and some of the rarer molds • Active against dimorphic fungi and *C. neoformans*	• Itraconazole has negative inotropic properties and is contraindicated in patients with significant cardiac systolic dysfunction
Voriconazole	IV 6 mg/kg every 12 h x 2 doses, then 4 mg/kg every 12 h; oral 200 mg PO BID (for invasive aspergillosis);[1] IV 6 mg/kg every 12 h x 2, then 3 mg/kg every 12 h for non-neutropenic patients with candidemia[2]	• Active against *Candida, Aspergillus* species and some of the rarer molds • Active against dimorphic fungi and *C. neoformans* • Standard of care as primary therapy for invasive aspergillosis (category 1)[1,3] • Effective in candidemia in non-neutropenic patients[2]	• Poor activity against Zygomycetes • IV formulation should be used with caution in patients with significant pre-existing renal dysfunction based on potential to worsen azotemia
Posaconazole	• Prophylaxis: 200 mg PO TID among high-risk patients (See INF-3) • Salvage therapy: 200 mg PO QID followed by 400 mg PO BID once infection has stabilized	• Effective as prophylaxis in neutropenic patients with myelodysplastic syndrome and acute myelogenous leukemia,[4] and in HSCT recipients with significant GVHD[5] • Active against *Candida*, *Aspergillus* sp, some Zygomycetes sp, and some of the rarer molds • Active against dimorphic fungi and *C. neoformans*	• Evaluated as salvage therapy (but not FDA-approved) in several invasive fungal diseases. • Data on posaconazole as primary therapy for invasive fungal infections are limited. • Should be administered with a full meal or liquid nutritional supplement. For patients who cannot eat a full meal or tolerate an oral nutritional supplement alternative antifungal therapy should be considered.

[a] Azoles inhibit fungal cell membrane synthesis and inhibit cytochrome P450 isoenzymes that may lead to impaired clearance of other drugs metabolized by this pathway. Fluconazole is a less potent inhibitor of cytochrome P450 isoenzymes than the mold-active azoles. Drug-drug interactions are common and need to be closely monitored (consult package inserts for details). Reversible liver enzyme abnormalities are observed.

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ANTIFUNGAL AGENTS (References are on page 4)

AMPHOTERICIN B FORMULATIONS[b]	DOSE	SPECTRUM	COMMENTS/CAUTIONS
Amphotericin B desoxycholate (AmB-D)	Varies on indication, generally 0.5 to 1.5 mg/kg/d	Broad spectrum of antifungal activity including *Candida*, *Aspergillus* sp (excluding *Aspergillus terreus*) Zygomycetes, rarer molds, *Cryptococcus neoformans*, and dimorphic fungi	• Substantial infusional and renal toxicity including electrolyte wasting • Saline loading may reduce nephrotoxicity • Infusional toxicity may be managed with anti-pyretics, an anti-histamine, and meperidine (for rigors)
Liposomal amphotericin B (L-AMB)	3 mg/kg/d IV was as effective as, but less toxic than, 10 mg/kg/d as initial therapy for invasive mold infections[6,c]		Reduced infusional and renal toxicity compared to AmB-D
Amphotericin B lipid complex (ABLC)	5 mg/kg/d IV for invasive mold infections		Reduced infusional and renal toxicity compared to AmB-D
Amphotericin B colloidal dispersion (ABCD)	5 mg/kg/d IV for invasive mold infections		Substantial infusional toxicity; other lipid formulations of amphotericin B are generally preferred

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[b] Broad spectrum of antifungal activity. Significant infusional and renal toxicity, less so with lipid formulations.
[c] The vast majority of subjects in this trial had invasive aspergillosis; optimal dosing of L-AMB for other mold infections (such as mucormycosis) is unclear.

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ANTIFUNGAL AGENTS (References are on page 4)

ECHINOCANDINS[d]	DOSE	SPECTRUM	COMMENTS/CAUTIONS
Caspofungin	• 70 mg IV x 1 dose, then 50 mg IV daily; some investigators use 70 mg IV daily as therapy for aspergillosis • 70 mg IV x 1 dose, followed by 35 mg IV daily for patients with moderate liver disease	Active against *Candida* and *Aspergillus* sp. Not reliable or effective against other fungal pathogens.	• Primary therapy for candidemia and invasive candidiasis (category 1)[7] • Salvage therapy for aspergillosis. Similar efficacy compared to AmB-D as primary therapy for candidemia and invasive candidiasis, but significantly less toxic[7] • 45% success rate as salvage therapy for invasive aspergillosis[8] • Similar efficacy, but less toxic compared with L-AMB as empirical therapy for persistent neutropenic fever[7] • Excellent safety profile.
Micafungin	100 mg/d IV for candidemia and 50 mg/d IV as prophylaxis		• Primary therapy for candidemia and invasive candidiasis (category 1) • Similar efficacy compared to caspofungin[9] and compared to L-AMB[10] as primary therapy for candidemia and invasive candidiasis • Superior efficacy compared to fluconazole as prophylaxis during neutropenia in HSCT recipients[11] • Excellent safety profile.
Anidulafungin	200 mg IV x 1 dose, then 100 mg/d IV		• Primary therapy for candidemia and invasive candidiasis (category 1) • Superior efficacy compared to fluconazole as primary therapy for candidemia and invasive candidiasis[12] • Excellent safety profile.

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[d] A number of centers use combination voriconazole and an echinocandin for invasive aspergillosis based on in vitro, animal, and limited clinical data.

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REFERENCES FOR ANTIFUNGAL AGENTS (page 4 of 4)

[1] Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002;347:408-15.

[2] Kullberg BJ, Sobel JD, Ruhnke M, et al. Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial. Lancet 2005;366:1435-42.

[3] Walsh TJ et al. Treatment of Aspergillosis: Clinical Practice Guidelines of the Infectious Diseases Society of America. Clin Infec Dis 2008;46:327-360.

[4] Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 2007;356(4):348-59.

[5] Ullmann AJ, Lipton JH, Vesole DH, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N Engl J Med 2007;356(4):335-47.

[6] Cornely O, Maertens J, Bresnik M, et al. Liposomal amphotericin B (L-AMB) as initial therapy for invasive filamentous fungal infections (IFFI): a randomized, prospective trial of a high loading regimen vs. standard dosing (AmBiload Trial). Clin Infect Dis 2007;44:1289-97.

[7] Mora-Duarte J, Betts R, Rotstein C, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med 2002;347:2020-9.

[8] Maertens J, Raad I, Petrikkos G, et al. Efficacy and safety of caspofungin for treatment of invasive aspergillosis in patients refractory to or intolerant of conventional antifungal therapy. Clin Infect Dis 2004;39:1563-71. Epub 2004 Nov 9.

[9] Pappas PG, Rotstein CM, Betts RF, et al. Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. Clin Infect Dis 2007;45:883-93.

[10] Kuse ER, Chetchotisakd P, Da Cunha CA, et al. Micafungin Invasive Candidiasis Working Group. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomized double blind trial. Lancet 2007;369:1519-27.

[11] van Burik JA, Ratanatharathorn V, Stepan DE, et al. National Institute of Allergy and Infectious Diseases Mycoses Study Group. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. Clin Infect Dis. 2004 Nov 15;39(10):1407-16.

[12] Reboli AC, Rotstein C, Pappas PG, et al. Anidulafungin Study Group. Anidulafungin vs. fluconazole for invasive candidiasis. N Engl J Med 2007;356:2472-82.

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

ANTIVIRAL AGENTS (References are on page 4)[a]

AGENT	TREATMENT	SPECTRUM	COMMENTS/CAUTIONS
Acyclovir	Prophylaxis[b]: HSV (800-1600 mg PO BID [divided two to four times per day]; VZV in allogeneic HSCT recipients (800 mg PO BID)[1]; CMV in allogeneic HSCT recipients (800 mg PO QID)[c,2] Treatment: significant mucocutaneous HSV (5 mg/kg IV every 8H for 7-10 days); single dermatomal VZV (800 mg PO 5 times daily or 5 mg/kg IV every 8H for 7-10 days); disseminated HSV or VZV (10 mg/kg IV every 8H)[3]	HSV, VZV, CMV	Hydration to avoid crystal nephropathy with high dose
Valacyclovir	Prophylaxis[b]: HSV or VZV (500 mg PO BID or TID) CMV in allogeneic HSCT recipients (2gm PO QID)[c,4] Treatment: HSV or VZV (Valacyclovir 1 gm PO TID)[3]	HSV, VZV	
Famciclovir	Prophylaxis: HSV or VZV (250 mg PO BID) Treatment: HSV (250 mg PO TID) or VZV (500 mg PO TID)[5,6]	HSV, VZV	No data for oncologic related prophylaxis
Ganciclovir	Prophylaxis for CMV: 5-6 mg/kg IV every day for 5 days/week from engraftment until day 100 after HSCT[d,7] Pre-emptive therapy for CMV: 5 mg/kg every 12H for 2 weeks; if CMV remains detectable, treat with additional 2 weeks of ganciclovir 6 mg/kg daily 5 days per week. Therapy: CMV disease (5 mg/kg every 12H for 2 weeks followed by 5 to 6 mg/kg daily for at least an additional 2 - 4 weeks and resolution of all symptoms). Add IVIG for CMV pneumonia. Formulations and dosages of IVIG vary in different series; 400-500 mg/kg every other day for the first week is a reasonable regimen.	CMV, HSV, VZV	May cause bone marrow suppression
Valganciclovir	Prophylaxis: CMV (900 mg every day)[d] Pre-emptive therapy for CMV: 900 mg PO BID for 2 weeks; consider additional 900 mg PO daily for at least 7 days after a negative test	CMV	May cause bone marrow suppression

[a] Requires dose adjustment in patients with renal insufficiency.

[b] Antiviral prophylaxis should be targeted to specific high-risk patients (see INF-4). In non-transplant high-risk patients, prophylaxis should be administered to patients seropostive for HSV or VZV (or with a history of chicken pox). In HSCT 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 pediatrics and in patients with renal impairment. Prophylactic antiviral doses may be higher than those routinely used in immunocompetent persons (for example, for recurrent cold sores); there is substantial variability in the prophylactic doses of acyclovir used in different clinical trials in patients with hematologic malignancies and HSCT recipients.

[c] High-dose acyclovir and valacyclovir have been used as prophylaxis for CMV. Because these agents have weak activity against CMV, a strategy of CMV surveillance and pre-emptive therapy with ganciclovir, valganciclovir, or foscarnet is required among patients at high risk for CMV disease.

[d] In general, the strategy of CMV surveillance testing by antigenemia or PCR followed by pre-emptive anti-CMV therapy for a positive result is favored over universal long-term prophylaxis in allogeneic HSCT patients.

Note: All recommendations are category 2A unless otherwise indicated.
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ANTIVIRAL AGENTS (References are on page 4)[a]

AGENT	TREATMENT	SPECTRUM	COMMENTS/CAUTIONS
Foscarnet	Prophylaxis for CMV: 60 mg/kg TID or 60 mg/kg IV every 12H for 7 days, followed by 90-120 mg/kg IV every day until day 100 after HSCT.[d,7,8] Pre-emptive therapy for CMV: 60 mg/kg every 12H for 2 weeks; if CMV remains detectable, treat with additional 2 - 4 weeks of foscarnet, 90 mg/kg daily 5 days per week. Therapy: Acyclovir-resistant HSV (40 mg/kg every 8H for 7-10 days); CMV disease (90 mg/kg every 12H for 2 weeks followed by 120 mg/kg daily for at least an additional 2 - 4 weeks and resolution of all symptoms). Add IVIG for CMV pneumonia.	HSV, VZV, CMV	Drug of choice for acyclovir resistant HSV and VZV and ganciclovir resistant CMV; nephrotoxic; monitor electrolytes
Cidofovir	Prophylaxis for CMV: Cidofovir 5 mg/kg IV every other week with probenecid 2 gm PO 3H before the dose, followed by 1 gm PO 2H after the dose and 1 gm PO 8H after the dose and IV hydration Treatment: Cidofovir 5 mg/kg IV every week for 2 weeks, followed by cidofovir 5 mg/kg every 2 weeks with probenecid 2 gm PO 3H before the dose, followed by 1 gm PO 2H after the dose and 1 gm PO 8H after the dose and IV hydration	CMV, HZV, VZV	Nephrotoxicity, ocular toxicity, bone marrow toxicity, hydration and probenecid required to reduce nephrotoxicity
Oseltamivir	Prophylaxis: 75 mg PO every day[e,9] Treatment: 75 mg BID	Influenza A & B	May cause nausea (improved when taken with food)
Zanamivir	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
Amantadine		Influenza A	Not currently recommended secondary to resistance
Rimantadine		Influenza A	Not currently recommended secondary to resistance

[a] Requires dose adjustment in patients with renal insufficiency.
[d] In general, the strategy of CMV surveillance testing by antigenemia or PCR followed by pre-emptive anti-CMV therapy for a positive result is favored over universal long-term prophylaxis in allogeneic HSCT patients.
[e] Prophylaxis among highly immunocompromised persons during community and nosocomial outbreaks of influenza A should be considered.

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ANTIVIRAL AGENTS (References are on page 4)

AGENT	TREATMENT	SPECTRUM	COMMENTS/CAUTIONS
Pegylated Interferon-alpha (or peginterferon alfa-2a)	Treatment for HCV: Pegylated Interferon-alpha 1.5 mcg/kg (or peginterferon alfa-2a 180 mcg) SC weekly plus ribavirin orally (dosing based on weight: if less than 75 kg, 400 mg in the morning and 600 mg in the evening; if greater than 75 kg, 600 mg twice daily)	HCV	
Intravenous immune globulin (IVIG)	Doses of IVIG vary among different studies and different viral illnesses. A dose of 400 - 500 mg/kg administered daily for 5 days is common for parvovirus B19-associated disease.[10] For CMV and RSV disease, adjunctive IVIG (400mg/kg) every other day for 3 to 5 doses is commonly administered	RSV, Parvovirus B19, CMV	
Palivizumab	Prophylaxis: 15 mg/kg IM monthly during RSV season[f,11]	RSV	Data predominantly in pediatric population[f]
Ribavirin	Treatment for RSV disease[g]: (6 gm administered by continuous inhalation via SPAG-2 nebulizer every 12-18H daily for 7 days or 2g over 2 h TID); may be paired with IVIG (400 - 500 mg/kg every other day) or palivizumab[12]	RSV	
Lamivudine	100 mg PO every day	HBV	Concerns with resistant virus emerging when monotherapy utilized
Tenofovir DF	300 mg PO every day	HBV	Tenofovir DF is the preferred agent for chronic hepatitis B infection, but limited data in oncological populations. Adefovir and entacavir also have activity against hepatitis B.

[f]Palivizumab is an RSV-specific monoclonal antibody that has principally been evaluated in the pediatric population; there are inadequate data to judge efficacy in RSV disease in patients with hematologic malignancies and stem cell transplant recipients.

[g]Inhaled ribavirin is only FDA approved for hospitalized infants and young children with severe lower respiratory tract RSV disease. The experience in immunocompromised adults with RSV disease is limited, but should be considered given the potential morbidity and mortality associated with RSV infection. Ribvirin is teratogenic and precautions are required during administration (see Package insert).

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

ANTIVIRAL AGENTS – REFERENCES

1 Boeckh M, Kim HW, Flowers MED, Meyers JD and Bowden RA. Long-term acyclovir for prevention of varicella zoster virus disease after allogeneic hematopoietic cell transplantation -- a randomized double-blind placebo-controlled study. Blood 2006;107:1800-1805.

2 Zaia JA. Prevention and management of CMV-related problems after hematopoietic stem cell transplantation. Bone Marrow Transplant 2002;29(8):633-638.

3 Gilbert DN, Moellering RC, Sande MA. The Sanford Guide to Antimicrobial Therapy (37th ed.). Hyde Park, VT: Jeb E. Sanford Publishers. 2007

4 Ljungman P, de La Camara R, Milpied N, et al. Randomized study of valacyclovir as prophylaxis against cytomegalovirus reactivation in recipients of allogeneic bone marrow transplants. Blood 2002;99:3050-3056.

5 Frechette G, Romanowski B. Efficacy and safety of famciclovir for the treatment of HSV infection in HIV+ patients. Can J Infect Dis 1997; 8(Suppl A):44A.

6 Schacker T, Hu H, Koelle DM, et al. Famciclovir for the suppression of symptomatic and asymptomatic herpes simplex virus reactivation in HIV-infected persons: A double-blind, placebo-controlled trial. Ann Intern Med 1998;128:21-28.

7 Centers for Disease Control and Prevention. Infectious Disease Society of America. American Society of Blood and Marrow Transplantation. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. MMWR Recomm Rep 2000;49(RR-10):1-125, CE1-7.

8 Reusser P, Einsele H, Lee J, et al. Randomized multicenter trial of foscarnet versus ganciclovir for preemptive therapy of cytomegalovirus infection after allogeneic stem cell transplantation. Blood 2002;99:1159-1164.

9 Vu D, Peck AJ, Nichols WG, et al. Safety and tolerability of oseltamivir prophylaxis in hematopoietic stem cell transplant recipients: a retrospective case-control study. Clin Infect Dis 2007;45(2):187-193.

10 Heegaard Ed, Brown KE. Human parvovirus B19. Clin Microbial Rev 2002;15:485-505

11 Boeckh M, Berrey MM, Bowden RA, et al. Phase 1 evaluation of the respiratory syncytial virus-specific monoclonal antibody palivizumab in recipients of hematopoietic stem cell transplants. J Infect Dis 2001;184(3):350-354. Epub 2001 Jun 28.

12 Whimbey E, Champlin RE, Englund JA, et al. Combination therapy with aerosolized ribavirin and intravenous immunoglobulin for respiratory syncytial virus disease in adult bone marrow transplant recipients. Bone Marrow Transplant 1995;16:393-399.

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

APPROPRIATE USE OF VANCOMYCIN AND OTHER AGENTS FOR GRAM-POSITIVE RESISTANT INFECTIONS

- **Vancomycin should not be considered as a routine component of initial therapy for fever and neutropenia. Because of the emergence of vancomycin-resistant organisms, empiric vancomycin should be avoided except for serious infections associated with the following clinical situations:**
  - **Clinically apparent, serious, catheter-related infection**
  - **Blood culture positive for Gram-positive bacterium prior to final identification and susceptibility testing**
  - **Known colonization with penicillin/cephalosporin-resistant pneumococci or methicillin-resistant *Staphylococcus aureus***
  - **Hypotension or septic shock without an identified pathogen (ie, clinically unstable)**
  - **Soft tissue infection**
  - **Risk factors for viridans group streptoccocal, bacteremia (category 2B): severe mucositis (eg, associated with high-dose cytarabine) and prophylaxis with quinolones or TMP-SMX (see manuscript)[a]**
- **Vancomycin should be discontinued in 2-3 days if a resistant Gram-positive infection (eg, MRSA) is not identified.**
- **Linezolid, quinupristin/dalfopristin, and daptomycin may be used specifically for infections caused by documented vancomycin-resistant organisms (eg, VRE) or in patients for whom vancomycin is not an option. Vancomyocin or linezolid should be considered for ventilator associated MRSA pneumonia.**

(See FEV-A 1 of 4)

[a]Recent studies have shown that addition of vancomycin is likely to be unnecessary solely on the basis of neutropenic fever and mucositis when broad spectrum beta-lactam agents with activity against oral flora (eg, piperacillin/tazobactam or imipenem/cilastatin) are used.

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

RISK ASSESSMENT RESOURCES

USING THE MASCC RISK-INDEX SCORE

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

BURDEN OF ILLNESS

How sick is the patient at presentation?

←————————————————→

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

Estimate the burden of illness considering all comorbid conditions

MASCC RISK-INDEX SCORE/MODEL[1]

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

TALCOTT RISK ASSESSMENT[2]

High Risk:

Group 1- Patients hospitalized at onset of fever and neutropenia

Group 2- Outpatients with a concurrent comorbidity at presentation (hemodynamic instability, clinical bleeding, respiratory failure, altered mental status or new neurologic symptoms, dehydration)

Group 3- Outpatients with uncontrolled cancer at presentation (newly treated tumors, newly relapsed, refractory or persistent leukemia, or progressive disease)

Low Risk:

Group 4- Outpatients with comorbidity or uncontrolled cancer at presentation

[1] 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(16):3038-51.

[2] Talcott JA, Finberg R, Mayer RJ, Goldman L. The medical course of cancer patients with fever and neutropenia. Arch Intern Med 1988;148:2561-68.

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ADJUNCTIVE THERAPIES

Limited or anecdotal data are available to suggest that these interventions may be beneficial:

- G-CSF or GM-CSF should be considered in neutropenic patients with serious infectious complications, such as the following (category 2B):
  - Pneumonia
  - Invasive fungal infection
  - Progressive infection (any type)
- Granulocyte transfusions (category 2B)
  - Invasive fungal infection
  - Gram-negative rod infection unresponsive to appropriate antimicrobial therapy
- Intravenous immunoglobulin
  - Should be used in combination with ganciclovir for CMV pneumonia
  - Consider IV IgG for patients with profound hypogammaglobulinemia (category 2B)

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

Discussion

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

Infectious diseases are important causes of morbidity and mortality in patients with cancer. In certain instances, the malignancy itself can predispose patients to severe or recurrent infections. Neutropenia has been recognized for many decades as a major risk factor for the development of infections in cancer patients undergoing chemotherapy. Effective strategies to anticipate, prevent, and manage infectious complications in neutropenic cancer patients have led to improved outcomes.[1-13] Due to advances in antimicrobial therapy, it is now uncommon for patients with acute leukemia or those undergoing stem cell transplantation to die from infections during the neutropenic period.

Although neutropenia remains a key risk factor for infections, other immunocompromised states pose at least equal risk. Allogeneic hematopoietic stem cell transplant (HSCT) recipients with neutrophil recovery who require intensive immunosuppressive therapy for graft-versus-host disease (GVHD) are an example of non-neutropenic patients at great risk for common bacterial, viral, and opportunistic infections.[14-17] The spectrum of infectious diseases in allogeneic HSCT recipients with GVHD is distinct from neutropenia. These NCCN guidelines on “Prevention and Treatment of Cancer-Related Infections” discuss infections in neutropenic and immunocompromised non-neutropenic patients with cancer. Our scope also includes other highly immunocompromised patients with cancer (such as those receiving high-dose corticosteroids, purine analogues, or alemtuzumab).

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

These guidelines on “Prevention and Treatment of Cancer-Related Infections” are divided into 4 sections. The first section discusses the major host factors that predispose patients to infectious diseases. The second section addresses management of neutropenic fever. The third section addresses site-specific infections (e.g., pneumonia, abdominal infections, catheter-associated infections) and focuses on patients who have neutropenia or who are otherwise significantly immunocompromised (e.g., HSCT recipients). The fourth section addresses prevention of infectious complications, including immunization and targeted antimicrobial prophylaxis.

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 and myelodysplastic syndrome (MDS) may be leukopenic due to replacement 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*.[18] 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 and colleagues[19] noted a biphasic pattern of infection among patients with multiple myeloma. Infections by *S.pneumoniae* and *Haemophilus influenzae* occurred early in the disease and in patients responding to chemotherapy, whereas infections by *Staphylococcus aureus* and Gram-negative pathogens occurred more commonly in advanced disease and during neutropenia.

Patients with advanced or refractory malignancy have a greater risk of infectious complications than those who respond to therapy. Refractory hematologic malignancies can be associated with marrow failure from disease and from multiple cycles of chemotherapy. 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 (e.g., esophagectomy and hepatobiliary reconstruction are surgeries associated with a high risk for infection), extent of tumor burden, preoperative performance status, and previous surgery, chemotherapy, and radiation therapy. Patients with advanced malignancy are also commonly malnourished, which further increases the risk of infection.

Neutropenia

The absence of granulocytes; the disruption of the integumentary, mucosal, and mucociliary barriers; and the inherent microbial flora shifts that accompany severe illness and antimicrobial usage predispose the neutropenic patient to infection. The signs and symptoms of infection are often absent or muted in the absence of neutrophils, but fever remains an early, although nonspecific, sign.[1] Approximately 48% to 60% or more of the patients who become febrile have an established or occult infection.[20] Roughly 10% to 20% or more of patients with neutrophil counts less than 100/mcL will develop a bloodstream infection.[2] Primary sites of infection are the alimentary tract (i.e., mouth, pharynx, esophagus, large and small bowel, and rectum), sinuses, lungs, and skin.

The pathogens responsible for initial infections early in the course of fever and neutropenia (F&N) are primarily bacteria, whereas antibiotic-resistant bacteria, yeast, other fungi, and viruses are common causes of subsequent infections. Coagulase-negative staphylococci, *S.aureus,* viridans group streptococci, and enterococci are the major Gram-positive pathogens. Coliforms (e.g., *Escherichia coli*, *Klebsiella, Enterobacter* species) and *Pseudomonas aeruginosa* are the most common Gram-negative infections complicating neutropenia. Herpes simplex virus (HSV), respiratory syncytial virus (RSV), parainfluenza, and influenza A and B are also occasionally initial pathogens. Infections due to *Candida* species may occur later in the course of neutropenia, particularly as a consequence of gastrointestinal (GI) mucositis.

Aspergillus species and other filamentous fungi are an important cause of morbidity and mortality in patients with severe and prolonged neutropenia.[21] 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.[22]

Studies from more than 4 decades ago have shown that as the neutrophil count decreases below 500/mcL (defined as *neutropenia*), the susceptibility to infection increases.[2,23] The frequency and severity of infection are inversely proportional to the neutrophil count; the risks of severe infection and bloodstream infection are greatest when the neutrophil count is less than 100/mcL. The rate of decline of the neutrophil count and the duration of neutropenia are also critical factors. These latter 2 aspects are a measure of bone marrow reserve and are highly correlated with severity of infection and clinical outcome.

Disruption of Mucosal Barriers

The mucosal linings of the GI, sinopulmonary, and genitourinary tracts constitute the first line of host defense against a variety of pathogens. Chemotherapy and radiation therapy impair mucosal immunity at several different levels. When the physical protective barrier conferred by the epithelial lining is compromised, local flora may invade. Neutropenia and loss of the epithelial cell anatomic barrier may predispose patients to typhlitis (neutropenic enterocolitis). Chemotherapy-related GI mucositis predisposes patients to blood stream infections by viridans group streptococci,[24-27] Gram-negative rods, and *Candida* species.[28]

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.[29] Thus, in allogeneic HSCT recipients, fever in the late transplant period must be evaluated promptly (similar to patients with asplenia) because of the risk of overwhelming infection by encapsulated pathogens.

Asplenic patients are principally at risk for overwhelming sepsis by encapsulated bacteria. The most common pathogen is *S.pneumoniae*, but other pathogens include *H.influenzae* and *Neisseria meningitidis.* The Advisory Committee on Immunization Practices (ACIP) for the Centers for Disease Control and Prevention (CDC) recommends that asplenic persons be immunized with the pneumococcal polysaccharide and meningococcal vaccines (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5753a6.htm). The conjugated meningococcal vaccine is preferred in adults 55 years of age or younger, because it confers longer lasting immunity than the polysaccharide vaccine. Immunization of adults with the pediatric *H.influenzae* type B (Hib) vaccine is considered optional because of lack of data on efficacy in older children and adults, although studies suggest good immunogenicity in immunocompromised patients. Immunization is ideally performed at least 2 weeks in advance of splenectomy. If this is not feasible, immunization is still advisable after splenectomy, because such patients are still capable of mounting a protective antibody response. One-time re-immunization with the pneumococcal vaccine is advised in asplenic persons 5 years after the time of initial vaccination. Penicillin prophylaxis is advised in asplenic patients to prevent pneumococcal disease (see section on "Prophylaxis Against Pneumococcal Infection").

Corticosteroids and Other Lymphotoxic Agents

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

Lymphocyte-depleting agents increase the risk of common and opportunistic infectious diseases. Fludarabine is a fluorinated analogue of adenine that has been used in a variety of hematologic malignancies. Fludarabine is a lymphotoxic compound, primarily affecting CD4+ lymphocytes. 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 *Pneumocystis jirovecii* (previously *Pneumocystis carinii*) pneumonia (PCP) or listeriosis, and 3 cases occurred more than 1 year after therapy in patients who were in remission.[31] When used alone, purine analogs (such as fludarabine, clofarabine) are associated with an intermediate risk for infection; however, when combined with other immunosuppressive or cytotoxic agents, purine analogs are associated with a high risk for infection (see INF-1).[32]

Patients with hematologic malignancies and allogeneic HSCT recipients are being treated with increasing frequency using novel monoclonal antibodies that cause a depletion of lymphocyte subsets. Alemtuzumab (Campath-1H) is a humanized monoclonal antibody that targets CD52, which is abundantly expressed on most normal lymphocytes. This agent has been used most extensively in patients with CLL who have failed fludarabine therapy. Alemtuzumab causes prolonged and severe lymphopenia in all patients; it causes grade 3 or 4 neutropenia in 70% of patients.

Four weeks after initiation of alemtuzumab, the median CD4+ count was 0/mcL and 6 months after discontinuation, the count was 238/mcL in previously untreated patients (http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/103948s5070lbl.pdf). The CD8+ counts also changed in a similar manner. In some patients, CD4+ and CD8+ counts did not reach baseline levels until more than 1 year after alemtuzumab therapy. Infections are a substantial cause of morbidity and mortality in alemtuzumab recipients; most infections occurred in patients with CLL refractory to alemtuzumab.[33] Bacterial, viral, fungal, mycobacterial, and *P.jirovecii* infections are observed. Prophylaxis with trimethoprim/sulfamethoxazole (TMP/SMX) and with an antiviral agent active against HSV (acyclovir, famciclovir, or valacyclovir) should be administered from the time of alemtuzumab initiation until at least 2 months after completion of therapy or until the CD4 count is 200/mcL or more, whichever occurs later.

Cytomegalovirus (CMV) reactivation occurs in a substantial number of alemtuzumab recipients (range, 10%-50%) and occurs most commonly between 3 and 6 weeks after initiation of therapy when T-cell counts reach a nadir. The NCCN panel recommends surveillance for CMV reactivation using polymerase chain reaction (PCR) or antigen-based methods in alemtuzumab recipients from the time of initiation until at least 2 months after completion of therapy or until the CD4 count is 100/mcL or more, whichever occurs later. This CD4 count was selected based on the experience in patients with advanced acquired immunodeficiency syndrome (AIDS) where CMV disease is uncommon with a CD4 count greater than 100/mcL.[34] Pre-emptive anti-CMV therapy is recommended in those who demonstrate reactivation of the virus by surveillance methods (see INF-6). However, the Infectious

Diseases Working Party (AGIHO) of the German Society for Hematology and Oncology (DGHO) does not recommend CMV surveillance in alemtuzumab recipients.[35]

Hematopoietic Stem Cell Transplantation

Autologous HSCT recipients have fewer infectious complications than allogeneic recipients. Most infections in autologous HSCT recipients occur during neutropenia or within the first few months after transplantation before reconstitution of cellular immunity. However, CD34 enrichment of autografts leads to a substantial reduction in T-cells, natural killer cells, and monocytes, compared with unmanipulated autografts, which delays immune reconstitution. Recipients of CD34-enriched autografts appear to be at a similar level of risk as allogeneic HSCT recipients for CMV and other opportunistic infections.[36]

The spectrum of pathogens to which allogeneic HSCT recipients are most susceptible follows a time line corresponding to the predominant immune defects. In the first month after HSCT, neutropenia is the principal host defense defect, which predisposes patients to bacterial, fungal, and viral infections. 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.

Defects in cell-mediated immunity persist for several months even in uncomplicated allogeneic HSCT recipients, predisposing them to common bacterial and viral infections and to multiple opportunistic infections (e.g., candidiasis, invasive mold infections, *P.jirovecii*, *Cryptococcus neoformans*, dimorphic fungal infections [such as, histoplasmosis and coccidioidomycosis], HSV, CMV, herpes zoster, Epstein-Barr virus-associated lymphoproliferative disease, community respiratory viruses, legionellosis, listeriosis, nocardiosis, toxoplasmosis, and mycobacterial diseases). Whereas mature and cooperative T- and B-cell functions are usually reconstituted by 1 to 2 years after engraftment, chronic GVHD is associated with persistently depressed cell-mediated and humoral immunity.

Defective reconstitution of humoral immunity is a major factor contributing to increased infection susceptibility in the late transplant period. Winston and colleagues[37] noted a high frequency of pneumococcal infections between 7 and 36 months after transplantation, associated with serum opsonic deficiency for *S.pneumoniae*. Kulkarni and colleagues[38] reported that pneumococcal sepsis occurred a median of 10 months after transplant (range, 3 to 187 months) and was significantly more frequent in patients with chronic GVHD.

Guidelines from the CDC recommend that allogeneic bone marrow transplant recipients with severe hypogammaglobulinemia (IgG < 400 mg/dL) and with recurrent infections receive intravenous immunoglobulin (IVIG) prophylaxis; IVIG is not recommended in other patient groups or in autologous HSCT recipients routinely.[16] The CDC has published guidelines on vaccination of HSCT recipients and household members to prevent infections following transplantation.[16]

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 opportunistic viral[39] and fungal[40] 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.

Management of Neutropenic Patients With Fever

The definitions of F&N in these NCCN clinical guidelines are consistent with those developed by the Infectious Diseases Society of America (IDSA) and the U.S. Food and Drug Administration (FDA) for evaluating antimicrobial therapy for F&N.[3] *Fever* is defined as a single temperature 38.3°C or more orally or 38.0°C or more over 1 hour in the absence of an obvious cause. Although uncommon, a patient with neutropenia and signs or symptoms of infection (i.e., abdominal pain, severe mucositis, perirectal pain) without fever should be considered to have an active infection. The concomitant administration of corticosteroids may also blunt the fever response and any localizing signs of infection. The NCCN guidelines define *neutropenia* as either 1) an absolute neutrophil count (ANC) less than 500/mcL, or 2) an ANC less than 1000/mcL and a predicted decline to 500/mcL or less over the next 48 hours.

Initial Evaluation

The initial evaluation should focus on determining the potential sites and causative organisms of infection and on assessing the patient's risk of developing an infection-related complication (see FEV-1). A site-specific history and physical examination should be performed promptly, cultures should be obtained, and empiric antibiotics started soon after the time of presentation. The common sites of infection for patients with F&N (such as the alimentary tract, groin, skin, lungs, sinus, ears, perivagina, perirectum, and intravascular access device sites) should be thoroughly assessed. Other important historical features to consider include major comorbid illness, medications, time since last chemotherapy administration, recent antibiotic therapy, and exposure to infections from household members.

Initial laboratory/radiology evaluation should include a complete blood count with differential analysis, platelets, blood urea nitrogen, creatinine, electrolytes, total serum bilirubin, liver-associated enzymes, and renal function tests. Oxygen saturation and urinalysis should be considered, depending on symptoms. Chest radiographs should be done for all patients with respiratory signs or symptoms; however, radiographic findings may be absent in neutropenic patients with pulmonary infection.[41]

Cultures

Culture specimens should be collected during or immediately after completing the examination. Two blood samples should be cultured. When obtaining blood cultures, there are 3 options: 1) one set can be obtained peripherally and one can be obtained from a central venous catheter (if present); 2) both sets can be obtained peripherally; or 3) both sets can be obtained through the catheter (see FEV-1). The positive predictive value of a catheter culture is less than a peripheral culture. The approach of obtaining blood for culture from both the central catheter and peripherally may help determine whether the venous access device (VAD) is the source of bloodstream infection based on the differential time to positivity.[42] 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.[42] A meta-analysis has shown little clinical use for 2-site culturing in patients with cancer who have a VAD, and poor patient acceptance of peripheral venipunctures when a VAD is in place.[43] The panel consensus is that the volume of blood for culture is the most important aspect of blood culturing, but the need for the performance of cultures from both peripheral and central sites remains unclear.

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 felt to be infectious should be tested for the presence of *Clostridium difficile*.[44] In patients with diarrhea, consider testing for 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. Viral cultures of 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.[45,46] However, note that rapid immunofluorescent viral antigen tests may be negative for H1N1 (swine flu).

Initial Empiric Antibiotic Therapy

The foundation of infection management is to administer empiric antibiotics in patients with F&N. This is necessary, because currently available diagnostic tests are not sufficiently rapid, sensitive, or specific to identify or exclude microbial causes of fever from other noninfectious causes. All neutropenic patients should be treated empirically with broad spectrum antibiotics promptly at the first sign of infection (i.e., fever). This is done to avoid the mortality associated with a delay in treatment in those patients who have a serious infection.[3,22] Many highly effective antibiotic regimens are available, and those that are recommended are supported by randomized clinical trials.

Selection of initial therapy should consider the following (see FEV-2):

- The patient's infection risk assessment (see FEV-3)
- The antimicrobial susceptibilities of pathogens isolated locally
- The most common potentially infecting organisms, including antibiotic-resistant pathogens, such as extended spectrum beta-lactamase–producing Gram-negative rods, vancomycin-resistant enterococcus (VRE), and colonization with or previous infection with methicillin-resistant *S.aureus* (MRSA).
- The potential sites of infection
- The importance of a broad spectrum bactericidal antibiotic regimen that includes antipseudomonal coverage
- Clinical instability (e.g., hypotension, organ dysfunction)
- Drug allergy
- Recent antibiotic use (including prophylaxis)

Recommended Approaches

The panel considers each of the following approaches to initial empiric management of febrile neutropenia to be appropriate based on the results of large, randomized controlled clinical trials.[1,3,22]

The first approach is intravenous (IV) antibiotic monotherapy (all category 1 except where noted) with either imipenem/cilastatin, meropenem, piperacillin/tazobactam, or an extended-spectrum antipseudomonal cephalosporin (cefepime or ceftazidime [category 2B]).[4,47-50] Local institutional bacterial susceptibilities should be considered when selecting empiric antibiotic therapy. At hospitals where infections by antibiotic resistant bacteria (e.g., MRSA or drug-resistant Gram-negative rods) are commonly observed, policies on initial empirical therapy of neutropenic fever may need to be tailored accordingly.

A meta-analysis of randomized trials involving cefepime reported that cefepime was associated with increased all-cause mortality when used for empiric therapy for neutropenic fever, although no increase in infection-related mortality was noted.[51,52] A recent meta-analysis by the FDA, using additional data beyond what was used in the Yahav study, did not find a statistically significant increase in mortality for cefepime-treated patients compared with controls. Thus, the FDA has concluded that cefepime remains appropriate therapy for its approved indications based on the results of the FDA's meta-analysis (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm167254.htm). The FDA is continuing to review the safety of cefepime, but the results may not be available for at least 1 year.

The second approach is IV antibiotic combination therapy using 3 options: (1) an aminoglycoside plus an antipseudomonal penicillin (with or without a beta-lactamase inhibitor) (category 1); (2) ciprofloxacin plus an antipseudomonal penicillin (category 1);[53] or (3) an aminoglycoside plus an extended-spectrum antipseudomonal cephalosporin (ceftazidime or cefepime).[53-55]

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.[56] Once-daily aminoglycoside dosing should probably not be used for treating meningitis or endocarditis based on inadequate clinical data.

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

The third approach is the addition of IV vancomycin for specific indications either to IV monotherapy or to combination therapy (see section on "Empiric Vancomycin Therapy"). 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.* However, vancomycin should be reserved for specific indications and should not be considered as a routine component of initial therapy for F&N (see FEV-D).

Empiric Addition of Vancomycin

Considerable debate has occurred about the use of empiric vancomycin in patients with F&N. The clinical concern has been that a portion of infections caused by Gram-positive pathogens can be fulminant and lead to rapid death in patients who are not treated promptly with appropriate antibiotics. However, a large, prospective, randomized trial from the European Organization for Research and Treatment of Cancer failed to show true clinical advantages for empiric vancomycin in adults.[57] 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. A prospective randomized trial of F&N in children has reported benefit for empiric vancomycin;[58] however, another randomized study in children failed to show a benefit for the addition of vancomycin.[59]

The major concern surrounding the uncontrolled use of vancomycin has been the emergence of vancomycin-resistant organisms, especially enterococci.[60] 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.[61-63] The increase in vancomycin resistance has been associated with use of vancomycin among hospitalized patients. The 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.[64,65] Because of the increased risk of 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 F&N. Vancomycin should be considered in the following clinical situations (see FEV-D):

- Clinically apparent, IV catheter-related infection (to cover coagulase-negative staphylococcal isolates, which are usually beta-lactam antibiotic-resistant and MRSA).[66,67]

- The patient's blood cultures are positive for Gram-positive bacteria before final identification and susceptibility testing.
- Known colonization with penicillin/cephalosporin–resistant pneumococci or MRSA
- Clinical instability (e.g., hypotension or shock) develops in the patient, pending the results of cultures.[68,69]
- Soft tissue infection (particularly in regions where MRSA infection is common)[70]
- Risk factors for viridans group streptococcal bacteremia (category 2B): severe mucositis (e.g., associated with cytarabine) and prophylaxis with ciprofloxacin or TMP/SMX.

If empiric vancomycin 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 is not identified, consider discontinuing vancomycin. Recent authoritative guidelines have been published on dosing and therapeutic monitoring of vancomycin.[71]

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.[72-74] The broad spectrum, Gram-negative bacillary coverage and limited Gram-positive pathogen activity of these drugs likely predispose to GI colonization and subsequent infection with such organisms.[75,76] It is unknown whether prophylaxis with newer generation fluoroquinolones (e.g., levofloxacin), which have increased activity against Gram-positive bacteria compared to ciprofloxacin, will increase the risk of breakthrough viridans group streptococcal infections.

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.[77] Addition of vancomycin produced 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 and in HSCT recipients with neutropenic fever of unknown etiology that persisted for 48 to 60 hours after initial empiric piperacillin-tazobactam.[78,79] A smaller randomized, placebo-controlled study did not show any advantage after adding teicoplanin (a glycopeptide antibiotic similar to vancomycin) in patients with neutropenic fever that persisted after 3 to 4 days of empiric imipenem/cilastatin.[80] In patients with neutropenic fever and severe mucositis who are receiving imipenem/cilastatin, meropenem, or piperacillin/tazobactam (i.e., antibiotics with activity against oral flora), it does not appear that the addition of vancomycin is advantageous. Thus, the NCCN 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

Linezolid, daptomycin, and quinupristin/dalfopristin are active against the majority of Gram-positive organisms, including beta-lactam-resistant and vancomycin-resistant pathogens.[81-85] The panel recommends that the use of these drugs be limited to specific situations involving infections caused by documented vancomycin-resistant organisms, or for patients in whom vancomycin is not an option (see FEV-D). Although studies have been published in patients with neutropenia, the NCCN panel strongly recommends that these agents not be used routinely as empiric therapy for neutropenic fever because of concerns about emergence of resistance and toxicity.

Resistance of Gram-positive organisms to linezolid is infrequent, but this agent needs to be used cautiously in patients with compromised bone marrow function because of the marrow toxicity associated with long-term use of linezolid. Thrombocytopenia is most common (0.3% to

10%) and increases with the duration of use. In neutropenic patients with cancer, myeloid recovery does not seem to be delayed with short courses of linezolid;[86,87] however, experience with long durations of therapy (e.g., more than 14 days) is limited in cancer patients. Vancomycin or linezolid should be used for treatment of MRSA pneumonia in ventilated patients;[88-91] 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(http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126260.pdf). 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 treatment of pneumonia, because it is inactivated by pulmonary surfactant.[92,91] Daptomycin is indicated for the treatment of complicated skin and skin structure infections caused by susceptible strains of certain Gram-positive microorganisms.[93,94] A randomized study showed similar efficacy of daptomycin compared with vancomycin or anti-staphylococcal beta-lactams as therapy for *S.aureus* bacteremia and endocarditis.[95]

Quinupristin/dalfopristin is active against *S.aureus* (including MRSA) and *Enterococcus faecium* (including vancomycin-resistant strains) but is inactive against *Enterococcus faecalis*. Use of quinupristin/dalfopristin has been limited because of the high frequency of substantial musculoskeletal symptoms.[96]

Optimal therapy for VRE infections is not well defined. Linezolid, quinupristin-dalfopristin (active against *E. faecium*, but not *E. faecalis*), and daptomycin have been used in VRE bloodstream infections in patients with cancer with variable success rates.[86,96,97] 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. Other antibiotics (e.g., dalbavancin, telavancin, oritavancin, ceftobiprole [a cephalosporin]) with broad spectrum activity against Gram-positive bacteria (including MRSA) are in clinical development.

Tigecycline has activity against clinically relevant resistant Gram-positive (including VRE and MRSA) and the majority of Gram-negative pathogens but is not active against *P.aeruginosa*. It is effective in complicated skin infections, soft tissue infections, and intraabdominal infections in non-neutropenic patients. Tigecycline has not been evaluated in clinical trials in patients with cancer and specifically should not be used as single-agent therapy in neutropenic patients given its lack of anti-pseudomonal activity. The combination of tigecycline and an antipseudomonal drug may be considered in patients with cancer with refractory or multi-drug resistant infections.[98] Other antibiotics (e.g., dalbavancin, telavancin, oritavancin, ceftobiprole [a cephalosporin]) with broad spectrum activity against Gram-positive bacteria (including MRSA) have received FDA approval or are in clinical development.

Initial Empiric Therapy for Patients Who Are Clinically Unstable

Sepsis is suggested by signs of clinical instability including hypotension, tachypnea, new or worsening tachycardia, mental status changes, decreased urine output, and organ dysfunction. Initial therapy for sepsis should broadly cover pathogens that are likely to cause sepsis while minimizing the potential for inadequate treatment (see "Surviving Sepsis Campaign guidelines").[68] Unlike the stable patient with neutropenic fever, modifying antibiotics based on culture data may not be possible for the patient with sepsis if the initial regimen does not provide adequate coverage. The antibiotic regimen should be modified, if necessary, after culture results and susceptibility are known.

The initial empiric regimen for the neutropenic patient with clinical instability may include a broad spectrum beta-lactam (e.g., imipenem/cilastatin, meropenem, or piperacillin-tazobactam) plus an aminoglycoside and vancomycin. Addition of fluconazole or an echinocandin should be strongly considered in patients not receiving antifungal prophylaxis. Local susceptibility patterns and recent antibiotic use should be taken into account when devising the antibiotic regimen.[68] At hospitals where infections by antibiotic resistant bacteria (e.g., MRSA or drug-resistant Gram-negative rods) are commonly observed, policies on initial empirical therapy of neutropenic fever may need to be tailored accordingly. Some experts also suggest that patients who have a history of *P.aeruginosa* colonization or of invasive disease should receive combination therapy with an antipseudomonal beta-lactam plus an aminoglycoside or ciprofloxacin.

In septic shock, rapid interventions need to be made. 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.[99-102] Stress-dose steroids are recommended for patients with septic shock who require vasopressor support.[68,103-106] High-dose steroids may be detrimental and should not be given.[107,108]

In patients with severe sepsis, drotrecogin alfa (Xigris), or recombinant human activated protein C (APC), may provide a modest survival advantage for those at highest risk of death (APACHE II score, 25 or more), but this agent did not benefit lower risk patients or pediatric patients with shock.[68,109-111] Bleeding is the major adverse effect of drotrecogin alfa; it has not been evaluated in neutropenic patients who may have an increased risk of bleeding from concomitant thrombocytopenia. The data are currently inadequate to make a recommendation about the efficacy or safety of this agent in neutropenic patients, or more generally, in patients receiving treatment for cancer.

Prognostic Factors in Patients With Bacteremia

Elting and colleagues have developed a classification system for bacteremias in febrile neutropenic patients based on size and presence of associated tissue involvement.[112] This classification system is based on an analysis of studies from the 1970s to 1990s. Complex bacteremias are associated with the lung, liver and spleen, kidney, colon, bone and joints, veins and heart, meninges, soft tissues with necrosis, or skin/soft tissue/wound/cellulitis greater than 5 cm. Simple bacteremias are associated with less tissue involvement (bacteruria, otitis, pharyngitis, soft tissue <5 cm). Complex infections associated with bacteremia decrease survival and, thus, have prognostic significance. At 21 days, 20% of patients with complex infections were dead compared to only 5% of patients with simple bacteremias (P<.0001). Profoundly neutropenic patients with simple bacteremias had a much higher response rate to antibiotics (94% versus 70%, P<.0001) compared to patients with complex bacteremias. Response to the initial antibiotic regimen and ultimate outcome were decreased in leukemia patients (those who presented with shock or patients with serum albumin <3.5 g/dL). The median time to defervescence for patients with simple bacteremias was 50% of that observed for patients with complex bacteremias (2.5 versus 5.3 days, P<.0001).[112] Based on these and other studies, clinical criteria can be used to stratify patients with bacteremia into high- and low-risk strata shortly after the onset of the febrile neutropenic episode. These criteria in one combination or another have been used to select patients for risk-adjusted clinical trials of empiric antibiotic therapy.[5-8,10,113-119]

Empiric Antifungal Therapy in Persistent Neutropenic Fever

Empiric antifungal therapy for persistent febrile neutropenia unresponsive to broad spectrum antibacterial agents is used, because neutropenic patients are known to be at risk for invasive fungal infections, and because clinical examination and collection of cultures are not sufficiently sensitive for early detection of those infections.[17,120-123] Traditionally, empiric antifungal therapy is initiated after 4-7 days of empiric antibiotic therapy for F&N, in patients who have remained febrile or have recrudescent fever. The concept of using empiric antifungal therapy was established in the 1970s and 1980s when about 20% of patients being treated for acute leukemia or undergoing HSCT would develop an invasive fungal infection due to *Candida* or *Aspergillus* species by day 20 of neutropenia.[124] The toxicity of amphotericin B limited its use as routine prophylaxis, which would entail exposing more patients to a toxic drug over a prolonged period than does empiric therapy. With the widespread use of fluconazole prophylaxis in the 1990s among high-risk patients with acute leukemia and in HSCT recipients, the incidence of invasive candidiasis in these patients decreased substantially, although breakthrough candidemia by fluconazole-resistant strains occurred.[125] Empiric antifungal therapy for neutropenic fever principally involved switching from fluconazole to amphotericin B to broaden the antifungal spectrum to include molds such as *Aspergillus*. Subsequently, liposomal amphotericin B (L-AMB) proved to be safer than and as effective as conventional amphotericin B for empiric antifungal therapy.[126]

Based on the toxicity of amphotericin B products and the availability of safer and equally effective alternative agents, amphotericin B products were considered a category 2B recommendation for prophylaxis and empirical antifungal therapy for persistent or recurrent neutropenic fever of unknown etiology. In cases where there is a stronger clinical suspicion of mold infection than neutropenic fever alone (e.g., a new pulmonary nodule in a patient with fever and prolonged neutropenia), then use of an amphotericin B formulation (or a mold-active azole or an echinocandin) should be considered pending additional diagnostic evaluation. In general, lipid formulations of amphotericin B are generally preferred over the conventional formulation, because they are less toxic.[127] This recommendation is stronger in patients with risk factors for acute renal failure, such as pre-existing renal disease, HSCT recipients, and co-administration of nephrotoxic agents.[128-130]

Fluconazole has been used successfully as empiric therapy for neutropenic fever[131,132] in patients not receiving prophylaxis but is limited by lack of activity against molds. Intravenous followed by oral itraconazole solution was as effective as, but less toxic than, conventional amphotericin B when used as empiric therapy in an open, randomized study;[133] these results led to FDA approval of oral itraconazole solution for this indication. Intravenous itraconazole is no longer available in the United States (http://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/ucm089427.pdf).[134] Itraconazole in the capsule formulation has erratic oral bioavailability and is therefore not suitable as empiric antifungal therapy. Itraconazole has negative inotropic effects and is contraindicated in patients with significant cardiac systolic dysfunction or a history of congestive heart failure.

Voriconazole was compared with liposomal amphotericin B (L-AMB) in an open, randomized study of empiric antifungal therapy (n=837 patients, 72% with hematologic malignancies).[135] 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% versus 5.0%), with the greatest protective benefit occurring in pre-specified high-risk patients (relapsed acute leukemia and allogeneic HSCT). Because the noninferiority of voriconazole versus L-AMB was not demonstrated in this study based on prespecified criteria, voriconazole did not receive FDA approval for use as empiric therapy.[121] 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 of 1095 patients.[136] The overall success rates were 34% in both caspofungin and in L-AMB recipients. The proportion of patients who survived at least 7 days after therapy was greater in the caspofungin group (92.6% versus 89.2%, P=.05). The rates of breakthrough fungal infections and resolution of fever during neutropenia were similar in the 2 groups. In patients with a baseline invasive fungal infection, mortality was 11% in caspofungin and 44% in L-AMB recipients, respectively (P<.01). Drug-related toxicities and premature withdrawals because of drug-related adverse events were significantly lower in caspofungin recipients. This study strongly supports caspofungin as an option for empiric antifungal therapy. The other echinocandins, anidulafungin and micafungin, have not been studied specifically for empiric antifungal therapy; however, some panel members would consider them to likely be effective, based on the data for caspofungin.

It is unclear whether patients who are already receiving mold-active prophylaxis should subsequently receive empiric antifungal therapy with an additional or different antifungal solely based on persistent neutropenic fever.[137] One approach has been to evaluate such patients with a high resolution computed tomography (CT) scan of the chest, in search of lesions suspicious for invasive fungal disease. CT scanning in this setting has not been validated but it is a reasonable approach, along with careful physical examination and blood cultures, in an effort to identify a source of persistent unexplained fever in the neutropenic patient. Laboratory markers (such as serum galactomannan and beta-glucan) have important limitations, including falsely negative results in some patients already receiving prophylactic or empiric antifungals[138,139] (see "Early Diagnosis of Invasive Fungal Infections"). 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 stem cell transplant recipients; another meta-analysis assessed cut-off values.[140] However, these antigen-based assays have a high negative predictive value in the absence of mold-active antifungal therapy.

In patients receiving only yeast-active prophylaxis with fluconazole or no antifungal prophylaxis, empiric antifungal trials have shown that approximately 5% have baseline invasive fungal infections at the time of enrollment.[135,136] Empiric antifungal therapy with anti-mold activity would be expected to benefit these few patients without incurring greater risk of toxicity.

Pre-emptive antifungal therapy uses characteristic changes in chest or sinus CT scans, laboratory markers, or both to trigger modification of the antifungal regimen, rather than providing empiric antifungals to all persistently febrile neutropenic patients. Maertens and colleagues[141] evaluated the strategy of fluconazole prophylaxis in high-risk neutropenic patients followed by switching to L-AMB based on such pre-specified triggers, including serially positive serum galactomannan tests, a bronchoalveolar lavage (BAL) showing mold, and/or suggestive chest CT in patients with persistent fever or with signs of invasive fungal infection. Directed antifungal therapy was given to 7.7% (9/117) of patients rather than up to one third of patients who might have received it on the basis of fever alone. In a randomized trial of patients with neutropenic fever, a preemptive strategy was associated with an increased incidence of invasive fungal infections without an increase in overall mortality and decreased cost of antifungal drugs compared to empirical antifungal therapy.[142] Taken together, the panel considers the evidence supporting pre-emptive antifungal therapy to be too preliminary to support its routine use.

Follow-up of Patients With Neutropenic Fever

Daily evaluation by a health care professional who is experienced in treating patients with F&N is essential (see FEV-8). 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. Time to defervescence ranges from 2 to 7 days (median, 5 days) for febrile cancer patients with neutropenia who receive appropriate initial antibiotic therapy.[143] 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 additional clinical or microbiologic evidence. The expected slow defervescence of fever also complicates decisions regarding the need for repeat blood cultures. Although some experts recommend daily blood cultures until the patient becomes afebrile, increasing evidence suggests that daily blood cultures are unnecessary in stable neutropenic patients with persistent fever of unknown etiology.[144]

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, ordering additional cultures routinely before obtaining the results from the initial series is discouraged. Daily review of previously obtained cultures is critical, and the panel recommends documenting clearance of bloodstream bacterial or fungal infections with repeat blood cultures.[145]

Evaluation of Response and Duration of Therapy

The duration of antimicrobial therapy, in general, is dictated by the 1) underlying site of infection; 2) causative organism(s); and 3) the patient's clinical condition, response to treatment and neutrophil recovery. It is generally recommended that antibiotics be continued until the ANC is 500 or more cells/mcL in cases of fever of unknown etiology. Documented infections are usually treated according to the site, pathogen, and at least until ANC recovery. The panel is limited by a lack of high-level evidence to formulate consensus about duration of treatment for all situations; however, general recommendations are given.

Patients With Documented Infection Sites or Pathogens

Most experts recommend continuing antimicrobial therapy for documented infections at least until a patient's ANC recovers to 500/mcL or more (see FEV-10) but also recommend using a defined course of therapy appropriate for the specific infection. Thus, the duration of antimicrobial therapy may be longer than the duration of neutropenia in these patients. For example, most uncomplicated skin and soft tissue infections can be treated with 7 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 Gram-negative bacteremias. A longer duration (10-21 days) of treatment is also usually indicated for infections of the lungs or sinuses and for bacteremias.[112] Complex intra-abdominal infections, such as typhlitis, should be treated until all evidence of infection has resolved, and the patient has recovered from neutropenia. Invasive mold infections (e.g., Aspergillosis) generally require a minimum of 12 weeks of treatment.

For all *S.aureus* bloodstream infections, a transesophageal echocardiogram (TEE) is recommended to help define the absence or presence of heart valve vegetations, and thus, to help define the duration of therapy as short (2 weeks after first negative blood culture) or long (4 to 6 weeks).[67,146-149] A TEE is more sensitive and preferred when compared with a transthoracic echocardiogram (TTE).[67,150] In patients with conditions that may increase the likelihood of complications (e.g., neutropenia, thrombocytopenia, mucositis), a TTE may be performed initially and, if negative, a TEE should be performed when safe. If a TEE is not feasible, a minimum 4-week course of IV antibiotics should be considered for *S.aureus* bloodstream infections.

The duration of treatment for HSV (uncomplicated, localized disease to the skin) and varicella zoster virus (VZV; uncomplicated, localized disease to a single dermatome) infections is 7 to 10 days.[151] Life-threatening infections, such as invasive fungi or CMV, require individualized courses of therapy that are often prolonged. The duration of anti-infective therapy may need to be extended if further chemotherapy is required while treating a significant infection. This may occur with infections that complicate leukemia or lymphoma treatments in which multiple cycles of intensive chemotherapy are required.

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

Severe or Refractory Infections

Patients with documented infection sites or pathogens who do not respond to initial antimicrobial therapy pose a difficult management challenge and are at increased risk of infection-associated morbidity and mortality. The panel strongly recommends that an infectious disease expert be consulted for all such patients. 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 (i.e., catheter or “closed space” infection), or emergence of a second infection. Some documented infections fail to respond to appropriate therapy because of associated profound neutropenia. If possible, treatment should be optimized using broad spectrum antibiotic combinations that minimize other organ toxicity.

Both the American Society of Clinical Oncology[152] and the NCCN have guidelines for the use of prophylactic colony-stimulating factors (CSF) in neutropenic patients (see NCCN Myeloid Growth Factors Guidelines).[153] It is not clear whether these agents are useful as adjunctive therapy for established infectious diseases. Although the data supporting their use are limited, adjunctive therapy with granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) should be considered (category 2B) in neutropenic patients with serious infectious complications such as pneumonia, invasive fungal infections, or any type of progressive infection (see FEV-F). Granulocyte transfusions may be considered (category 2B) in neutropenic patients with serious infectious complications, such as invasive fungal infections or gram-negative rod infection unresponsive to appropriate antimicrobial therapy. The panel notes that the benefit versus toxicity balance associated with granulocyte transfusions has not been established.

Patients With Persistent Neutropenia and Fever of Unknown Etiology

A critical component of treating patients with fever of unknown etiology is daily clinical evaluation. Careful, daily, site-specific examinations should be performed by a health care professional who has experience and expertise in managing neutropenia and fever. Reassessment should include a review of all previous cultures and radiographs. If patients receive vancomycin as part of their initial empiric therapy, but they do not have a pathogen recovered or a site of infection identified justifying such treatment, then vancomycin should be discontinued.

Patients with fever of unknown origin who become afebrile soon after starting empiric therapy may have empiric antibiotics discontinued with ANC recovery (500 or more 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 (less than 500 neutrophils/mcL) should receive a more prolonged course of antibiotic therapy until the neutropenia resolves (see FEV-11). Lower risk patients can also be switched to oral antibiotics until their neutropenia resolves (i.e., 500 mg ciprofloxacin every 8 hours plus 500 mg of amoxicillin/potassium clavulanate every 8 hours). Patients with recurrent fever should be reassessed promptly to determine the need for a change in their antibiotic regimen or for addition of antifungal therapy.

Patients with a fever persisting beyond 4 days of initial antimicrobial therapy and with an unidentified source of infection should undergo reassessment of their antimicrobial therapy (see FEV-12). The need for a change in therapy should be based on the patient's clinical status and likelihood of imminent bone marrow recovery.

The clinically stable patient with persistent fever of unknown etiology may be safely watched without altering the initial antimicrobial therapy. Modifications of initial empiric antibiotic therapy should be based on specific new clinical findings and/or new microbiologic results; fever alone should not prompt changes in antimicrobial therapy. The major exception is the initiation of empiric antifungal therapy in patients who have persistent or recurrent fever after 4 to 7 days of empiric antibacterial therapy and who are not receiving mold-active prophylaxis (see "Empiric Antifungal Therapy"). Most experts advise continuing empiric antibiotic therapy until the absolute neutrophil count recovers.

Although fever resolution may be slow during neutropenia, persistent fever may result from a noninfectious etiology, such as drug 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 (e.g., toxoplasmosis) may complicate neutropenia, particularly if immunosuppressive agents (e.g., high-dose corticosteroids) are also used. The panel strongly recommends an infectious disease consultation for these patients.

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 to modify therapy.

New findings suggestive of sepsis (e.g., hypotension, tachycardia, mental status changes, organ dysfunction) require the following: 1) repeat physical examination to identify a source of infection; 2) repeat blood cultures; 3) consideration of radiologic studies; and 4) empiric modification of antimicrobial therapy pending culture results.[68] Information about the previous use of antibiotics and local sensitivity patterns of Gram-negative pathogens should guide empiric changes. Empiric addition of vancomycin is warranted in the unstable patient (see FEV-A, FEV-D). 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.

Outpatient Management of Patients With Neutropenic Fever

Initial Evaluation of Risk

Patients with neutropenia may be categorized into either a high- or low-risk group[10-13,113,114,154,155] using criteria that are derived either from validated clinical prediction rules based on risk models or from clinical trials eligibility criteria (see FEV-3 and FEV-E).[6,10,11,13,26,113,114,154,155] Risk assessment attempts to predict the probability that a neutropenic patient will experience serious complications during a febrile episode; risk assessment also helps determine whether the patient who is at low risk for serious complications could safely receive treatment outside of the hospital and receive initial empiric therapy with oral antibiotics.

Prospective trials have indicated that febrile neutropenic patients can be initially evaluated in the hospital, ambulatory clinic, or home and then treated effectively with broad spectrum IV, sequential IV /oral, or oral therapy.[113-115,156] Only centers with the necessary infrastructure should treat low-risk patients in an outpatient setting, preferably in an investigational context.

Risk assessment should be performed as part of the initial evaluation (see FEV-3). The most accurate and recently validated prediction rule to assess risk is from the Multinational Association of Supportive Care in Cancer (MASCC) (see FEV-E).[157,158] It is also acceptable to employ risk assessment criteria that have been identified in large clinical trials to distinguish between patients at low and high risk for complications during the course of neutropenia.

The MASCC prediction rule does not consider the duration of neutropenia to be a deciding factor that influences the clinical course during the febrile episode; however, the panel acknowledges that some consideration of the duration of anticipated neutropenia may be helpful in risk assessment.

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 on outcomes was evident. In Bodey's original work, the fatality rate was highest (80%) in patients who initially started with neutrophil counts less than 100/mcL that did not change during the first week of infection compared to the lower rate (27%) in those patients who started out with neutrophil counts less than 1000/mcL, which then rose to greater than 1000/mcL.[23] Many clinical trials since then 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% if the initial neutrophil count increased compared to 43% if it decreased or remained unchanged (P<.00001).[159] The response rate in patients who were initially profoundly neutropenic (i.e., ANC<100/mcL) but who recovered from neutropenia was 67%, compared to only 32% in patients who remained profoundly neutropenic (P<.0001).

In 1988, Rubin and colleagues examined the influence of the duration of neutropenia on the response to empiric antimicrobial therapy in patients with fever of undetermined origin.[160] Patients with less than 7 days of neutropenia had response rates to initial antimicrobial therapy of 95%, compared to only 32% in patients with more than 14 days of neutropenia (*P*<.001); however, intermediate durations between 7 and 14 days had response rates of 79%.[160]

Clearly bone marrow recovery is a very important factor that influences outcome during the febrile neutropenic episode. Delayed bone marrow recovery might be anticipated in certain patient subsets (e.g., those who have received multiple cycles of myelosuppressive chemotherapy; patients with known bone marrow metastases; or patients who have received radiation therapy to the pelvis, spine, or long bones). Most patients with solid tumors have neutropenia lasting less than 7 days and are at much lower risk. Several studies have demonstrated the ability of clinicians to predict anticipated duration of neutropenia. In prospective randomized trials of oral versus IV antibiotics for patients at low risk, the predicted expected further duration of neutropenia was used as an eligibility criteria and clinicians were accurate more than 80% of the time.[113,116] The duration of neutropenia can be one of several factors in selecting patients for outpatient management of neutropenic fever.

Evaluation of Patients for Outpatient Therapy for Neutropenic Fever

Outpatient therapy has become a common practice in low-risk patients with neutropenic fever. Several single-center clinical trials generally support the shift in care for low-risk patients to the outpatient setting; the hospital is not necessarily a safer place for low-risk patients, given the documented hazards of hospitalization.[161] However, not all centers are equipped to attempt such outpatient treatment, and some patients with fever are not appropriate candidates. Early success with this type of therapy has been predicated on the ability to accurately determine an individual patient's risk of developing complications associated with infection and on the presence of an adequate center infrastructure for the treatment and monitoring (see "Risk Assessment").

Once a patient's level of risk has been identified (see FEV-13 and FEV-E and "Risk Assessment"), it can then be used to determine the appropriate site of care and route of administration of broad spectrum antibiotics. The panel recommends that all high-risk patients receive hospital care with broad spectrum IV therapy. Low-risk patients may be treated in the hospital with oral or IV antibiotics, in an ambulatory clinic, or at home if adequate follow-up care can be provided (i.e., 24 hours per day, 7 days per week). Outpatient therapy should be considered only for low-risk patients who consent to home care, have a telephone, have access to emergency facilities, have an adequate and supportive home environment, and are within 1 hour's travel time of a medical center or physician's office. Outpatient therapy requires a period of early monitored assessment and an observation period of 2 to 12 hours (category 2B) (see FEV-13). The assessment requires a careful examination, review of laboratory results, review of social criteria for home therapy (as previously described), and assessment of whether oral antibiotics are feasible. The observation period is used to confirm the patient is low risk, to observe and administer the first dose of antibiotics, to monitor for reaction, to ensure the stability of the patient, to organize discharge plans to home and follow-up, to educate the patient, and to perform telephone follow-up 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 (e.g., a physician, nurse, physician assistant, and/or nurse practitioner) and should have experience and expertise in managing F&N.

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.[162] For selected low-risk patients, the combination of ciprofloxacin with amoxicillin/clavulanate (both at 500 mg every 8 hours) is considered the oral regimen of choice based on well-designed randomized trials (category 1) (see FEV-14). Although some of these trials were performed in an inpatient setting, they provide evidence of the efficacy of the oral combination compared with standard IV therapy in the low-risk population.[5,113] Ciprofloxacin plus clindamycin is an acceptable alternative for penicillin-allergic patients.[6] However, ciprofloxacin monotherapy is not considered by the panel to be an adequate broad spectrum agent because of the potential for serious breakthrough infections caused by viridans group streptococci.[163] Nonetheless, several small studies have used high-dose oral ciprofloxacin alone in low-risk patients with F&N.[9,164,165]

Ofloxacin was safe in low-risk patients with neutropenic fever in a randomized trial; an early death in a non-hospitalized patient in this trial underscores the need for close monitoring.[116] Presumably, levofloxacin (which is the L-isomer of ofloxacin) would be equally effective. Many oncologists (50%) are using levofloxacin as empiric therapy for low-risk patients with febrile neutropenia.[166] A preliminary study suggested that moxifloxacin (a newer generation quinolone) may also be safe in low risk patients with neutropenic fever.[167]

The panel feels that outpatient therapy with a fluoroquinolone should be based on reliable Gram-negative bacillary activity of the antibiotic that includes *P.aeruginosa* and local antibacterial susceptibilities. Ciprofloxacin plus amoxicillin/clavulanate (or ciprofloxacin plus clindamycin in penicillin-allergic patients) is the standard oral outpatient antibiotic regimen for low-risk patients with neutropenic fever. There is also evidence supporting quinolone monotherapy in this setting, but the panel feels that additional studies are required before such an approach can be routinely recommended. These recommendations for quinolone-based outpatient regimens for neutropenic fever only apply to low-risk patients who have not received a quinolone as prophylaxis. Intravenous therapy may also be used for outpatient treatment of low-risk patients with F&N with treatment given either in the home or day clinic setting. Several IV outpatient regimens for low-risk patients have been studied in nonrandomized or small open trials, including IV ceftazidime, imipenem/cilastatin, and aztreonam plus clindamycin.[6,113-115]

Once-daily ceftriaxone has been used for empiric antibiotic therapy in a few noncomparative studies in centers where *Pseudomonas* is not a common pathogen.[119] However, most *P.aeruginosa* isolates are resistant to ceftriaxone. Although ceftriaxone combined with a once-daily aminoglycoside is a convenient regimen for outpatient IV administration, an aminoglycoside without an antipseudomonal beta-lactam may not be effective against *P.aeruginosa*, which remains an infrequent but potentially lethal pathogen. Therefore, the panel cannot recommend ceftriaxone with or without an aminoglycoside as empiric therapy for neutropenic fever. If this regimen is used, it should be restricted to low-risk patients at centers where *P.aeruginosa* infection is uncommonly observed. In addition to 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 FEV-14). A return to the clinic is recommended for any positive culture, for persistent or recurrent fever at 3-5 days, if serious subsequent infections or adverse events develop, or if the patient is unable to continue the prescribed antibiotic regimen (e.g., because of oral intolerance).

Site-Specific Evaluation and Treatment of Infectious Diseases

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

Mouth and Esophageal Infections

The mouth and esophagus are common sites of infection in patients with F&N. This site predilection occurs because of the propensity of the mouth and alimentary tract mucosa to be disrupted by cytotoxic therapy, which can cause mucositis. Unfortunately, the characteristics of this disruption are not etiology specific, and important viral and fungal pathogens often can be distinguished only by microbiologic culture. Empiric antibiotic therapy must consider the endogenous anaerobic flora and the shift in oral flora, which occurs with serious illness or antibiotic use (see FEV-4). The increased frequency of HSV reactivation and severity of these infections in cancer patients are well known and preventable. The incidence of HSV reactivation in immunocompromised patients may approach 50% to 75%, but it is nearly zero in those who receive prophylaxis with appropriate antiviral agents.[151] HSV infections are associated with more extensive mucosal damage, increased secondary infections, and significantly prolonged healing time. Baglin and associates reported that patients with F&N who experienced concomitant HSV reactivation and were treated with appropriate antiviral therapy had a significant decrease in the number of days with fever.[168]

Systemic or topical antifungal agents can be used to treat thrush. Because of the risk of candidemia, systemic antifungal therapy is advised in neutropenic patients. Fluconazole is recommended as first-line therapy for thrush. If patients do not respond, the dose of fluconazole can be increased to as high as 800 mg daily (in adults with normal renal function).[169] Although cross-resistance among azoles may occur, oral voriconazole, itraconazole, or posaconazole are reasonable oral options for thrush that is refractory to fluconazole. Echinocandins (such as, caspofungin, micafungin, or anidulafungin) can be used for patients with azole-refractory mucosal candidiasis. Amphotericin B formulations are also effective but are limited by toxicity.

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

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

Ganciclovir or foscarnet may be considered for patients at high risk for CMV disease with symptoms suggestive of esophagitis.

For patients with esophagitis who do not respond to empiric therapy with these agents, careful upper endoscopy with platelet support (if required) may be considered to obtain cultures. Tissue biopsies are the gold standard of 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 done cautiously. Radiographic procedures, such as barium studies, are insensitive and add little clinically significant information; therefore, these procedures are not recommended.

Sinus or Nasal Infections

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

Initial symptoms of sinusitis may be mild. A high-resolution CT scan of the sinuses is the radiographic procedure of choice to evaluate patients with pain or tenderness of the sinuses, nasal erosions, unilateral facial swelling, unilateral eye tearing, or epistaxis. A magnetic resonance image (MRI) that includes evaluation of the orbit and cavernous sinuses is useful to evaluate proptosis of the eye or cranial nerve abnormalities. 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 scan, with biopsy and culture of any abnormal tissues. Broad spectrum coverage for aerobes and anaerobes is appropriate for neutropenic and otherwise highly immunocompromised patients with sinus infections. Vancomycin (or another anti-Gram-positive agent) should be added for periorbital cellulitis, which is frequently caused by *S.aureus*.

Sinus endoscopy with biopsy and culture are often required to definitively establish the diagnosis and should be pursued aggressively in patients at high risk for mold infection. Invasive fungal sinusitis in patients with hematologic malignancies and with prolonged neutropenia is principally caused by *Aspergillus* species (*A.flavus* and *A.fumigatus*) and Zygomycetes. In a case-control study of invasive aspergillosis and zygomycosis in patients with acute leukemia and in allogeneic HSCT recipients, fungal sinusitis and use of voriconazole each favored a diagnosis of zygomycosis.[170] A lipid formulation of amphotericin B should be used for suspected or confirmed invasive sinus mold infection, pending definitive histology and culture results (see FEV-B). Posaconazole can be considered for salvage therapy or for intolerance to amphotericin B formulations; posaconazole is not approved by the U.S. FDA as either primary or salvage therapy for invasive fungal infections. Voriconazole (category 1) is the drug of choice for invasive aspergillosis.[171-173] Urgent debridement of necrotic tissue should be performed, when feasible.[173]

Abdominal, Rectal, and Liver Infections

Most infections in the abdomen, rectum, or liver are discovered because of a combination of clinical signs and symptoms (e.g., abdominal pain, perirectal pain, and diarrhea) and of biochemical abnormalities (e.g., abnormal liver function tests) (see FEV-5). 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 on relative clinical benefit.

Antimicrobial therapy for GI infections must take into account the high likelihood of polymicrobial pathogens and the presence of the endogenous anaerobic GI flora. Acceptable therapeutic options in this setting include monotherapy with a carbapenem (imipenem/cilastatin, meropenem, doripenem, or ertapenem), piperacillin/tazobactam, or pairing ceftriaxone with metronidazole. In neutropenic patients, the antibiotic regimen should have antipseudomonal activity. Percutaneous aspiration and drainage should be performed, if feasible, for suspicious infected collections. Cholangitis may complicate obstructive tumors or previous hepatobiliary surgery. If cholangitis is suspected (patients have fever with or without abdominal tenderness and liver enzyme abnormalities compatible with obstruction), a CT scan should be performed to evaluate for biliary tract dilatation and for 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 components of the colonic flora in 30% to 60% of normal adults. Patients are susceptible to candidal bloodstream infection because of the mucosal damage induced with cytotoxic therapy and neutropenia.[28] Breaches in the GI tract after anastomotic leaks also predispose patients to candidal peritonitis and bloodstream infections, [174] and antifungal prophylaxis (e.g., with 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.[175] Diarrhea should be evaluated with at least 2 stool *C.difficile* toxin screens. The rate and severity of *C.difficile* colitis in the United States may be increasing, partly because of the emergence of a more virulent strain of *C.difficile.* Multi-institutional outbreaks of *C.difficile* colitis have been reported that were associated with high morbidity and mortality; these outbreaks were caused by a distinct strain with variations in toxin genes and with resistance to fluoroquinolones.[176,177] Early reports suggested that metronidazole cured nearly 90% of cases of *C.difficile* colitis, and the rate of recurrence was low. However, Musher and colleagues[178] reported that of 207 patients treated with metronidazole for *C.difficile* colitis, only 50% were cured and had no recurrence of disease. The panel recommends initial oral metronidazole for *C.difficile* colitis that is not severe.[179,180] IV metronidazole should be used in patients who cannot take oral agents.

Oral vancomycin is not advised as routine initial therapy for *C.difficile* colitis because of the risk of selection for VRE and because of the substantial expense. However, oral vancomycin should be considered for more complicated cases, such as severe diarrhea, dehydration, clinical instability, significant co-morbidities, or recurrent or refractory *C.difficile* colitis. Efforts should be made to deliver vancomycin by the nasogastric route in patients with severe *C.difficile* colitis.[180,181] Limited data suggest that IV metronidazole may be useful in this setting, and it is best used as an adjunct to oral vancomycin.[182,183] Intravenous vancomycin is of no value in this setting because of inadequate luminal levels. Subtotal colectomy, diverting ileostomy, or colostomy may be required in cases involving toxic dilatation or perforation of the colon. Newer therapies—including the oral agents rifaximin and nitazoxanide—are under investigation.[179,184] Multiple recurrences of

C.difficile are a challenging problem in the cancer patient and may respond to a prolonged, tapering oral vancomycin dose over several weeks.[185]

Enterocolitis

Neutropenic enterocolitis is a serious, potentially life-threatening disease characterized by fever, diarrhea, and abdominal pain. 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 or all of the colon may be involved. CT scanning is the diagnostic study of choice and usually demonstrates thickening of the bowel wall. This illness has frequently been associated with acute leukemia, neutropenia, and intensive cytotoxic therapy. The differential diagnosis for this syndrome includes *C.difficile* colitis, CMV enteritis (most common in allogeneic HSCT recipients), and GI tract GVHD. Bloodstream infections and sepsis (frequently polymicrobial), bowel perforation, and hemorrhage may occur. The natural history of typhlitis is quite variable, but all patients should be assessed for *C.difficile* infection and should be treated with bowel rest and broad spectrum antibiotics, including coverage for *C.difficile*, aerobic pathogens, and anaerobic pathogens. Parenteral nutrition should be considered if clinical signs and symptoms do not resolve promptly. Approximately 5% of patients with typhlitis develop complications requiring surgical intervention (e.g., perforation, uncontrolled sepsis or rectal bleeding).[186] Consequently, the panel recommends that surgical and other subspecialty consultations be obtained early in the course of treatment.

Vascular Access Device Infections

VAD infections are common as a consequence of the ubiquity of VADs in patients undergoing intensive or cyclic chemotherapy. The risk of infection varies with the device used (long-term implanted catheters versus short-term central catheters), duration of placement, and extent of the patient's immunosuppression. Short-term central catheters impregnated with minocycline and rifampin or silver-chlorhexidine have been associated with fewer device-related bacterial infections.[187-190] However, no studies have shown the value of these coatings for preventing infections in long-term, indwelling devices.[191] 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.[192] The panel does not currently endorse this practice because of concerns about the emergence of bacterial resistance if this approach were widely employed. The IDSA has recently published guidelines on the diagnosis and management of intravascular catheter-related infections.[67]

VAD infections are categorized as entry or exit site infections, tunnel or port pocket infections, septic phlebitis, or catheter-associated bloodstream infections (see FEV-5). The majority of these infections are caused by Gram-positive pathogens, with coagulase-negative staphylococci recovered most frequently. Accordingly, IV vancomycin is recommended for those infections that are serious and clinically obvious.

Most VAD exit site infections can be treated effectively with appropriate antimicrobial therapy without the need for catheter removal. If clinical signs of catheter infection are present, a skin swab for culture from the exit site and blood cultures should be obtained. In a patient with neutropenic fever and clinical signs of a VAD-associated infection, an appropriate initial regimen would consist of an agent recommended for neutropenic fever (see FEV-2) and vancomycin (see FEV-5). Linezolid is not advised as routine therapy for catheter-related infections nor is it FDA-approved for this indication (see FDA alert: http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126260.pdf). 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. The differential time to positivity (DTP) method is a useful diagnostic tool for detecting VAD infections. Early positivity of central venous blood cultures predicts catheter-related bacteremia and may be used to avoid unnecessary catheter removal in critically ill patients. It was shown that a DTP of 120 minutes or more (between centrally and peripherally drawn blood cultures) is highly sensitive and specific for diagnosing catheter-related bacteremia.[193-197] However, these studies were only performed in patients with removable catheters, not implanted catheters (e.g., Hickman or Mediport) that are frequently used in patients undergoing cancer treatment.

Most catheter-associated bloodstream infections respond to antimicrobial therapy alone without catheter removal, but immediate catheter removal is advisable for patients with bloodstream infections caused by fungi (yeasts or molds) or nontuberculosis mycobacteria (e.g., *Mycobacterium chelonae*, *Mycobacterium abscessus*, *Mycobacterium fortuitum*). Bloodstream infections caused by *Bacillus* organisms, *Candida, S.aureus, Acinetobacter*, *C.jeikeium*, *P.aeruginosa*, *S.maltophilia,* and vancomycin-resistant enterococci may be difficult to eradicate with antimicrobial therapy alone; therefore, catheter removal should be considered as part of initial therapy (category 2B). In patients with mucositis, the bowel is likely to be the portal of entry for bloodstream infection by GI flora such as *Candida* sp. and enterococci;[28] 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.

In all patients with *S.aureus* bloodstream infection, a TEE is recommended to evaluate for endocarditis (see “Patients With Documented Infection Sites or Pathogens” and FEV-10). Removal of the catheter should be considered to avoid a persistent nidus of infection that may predispose patients to recurrent bacteremia.

The panel recognizes that certain conditions may preclude the ability to immediately replace IV catheters, such as limited options for IV access and thrombocytopenia refractory to platelet products. Administering antibiotics through each lumen of the involved catheter has been suggested to avoid treatment failure caused by microbial sequestration. Some experts believe supplemental urokinase infusions can be helpful in patients with catheter-related infections.[198] However, the panel believes data are insufficient to recommend either of these approaches.

Lung Infections

Pulmonary infiltrates pose a difficult diagnostic challenge in patients with cancer. Noninfectious causes of pulmonary infiltrates include congestive heart failure, pulmonary hemorrhage, infarction, drug-induced pneumonitis, radiation injury, tumor, bronchiolitis obliterans, and acute respiratory distress syndrome. Common processes can have atypical radiographic appearances, and 2 or more pulmonary processes can exist simultaneously. A careful history should include the time course of respiratory symptoms, sick contacts (e.g., 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 (e.g., 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.[199] If feasible, sputum and blood cultures should be collected before starting therapy. In patients who are not neutropenic, not receiving immunosuppressive therapy, and not requiring hospital admission (based on a validated pneumonia severity index), therapy includes either 1) a respiratory fluoroquinolone (levofloxacin 750 mg/day, moxifloxacin, or gemifloxacin); or 2) a beta-lactam (e.g., high-dose amoxicillin or amoxicillin-clavulanate) plus a macrolide (e.g., azithromycin).[199] These regimens will treat most of the common community-acquired pathogens, including “atypical” pneumonia (*Chlamydia, Mycoplasma*, and *Legionella* species).

In patients requiring hospital admission, monotherapy with a respiratory fluoroquinolone or combination therapy with a macrolide plus either ceftriaxone, cefotaxime, or ertapenem) is recommended. Ertapenem has Gram-positive, Gram-negative (excluding *P.aeruginosa* and *Acinetobacter* species), and anaerobic activity useful for suspected aspiration or postobstructive pneumonia. In patients with severe community-acquired pneumonia (e.g., who require admission to an intensive care unit), we advise 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. A nasopharyngeal wash for respiratory viruses and initiation of empiric antiviral therapy should be considered during the winter, early spring, and during community outbreaks of influenza. Note that rapid immunofluorescent viral antigen tests may be negative for H1N1 (swine flu). A parapneumonic effusion should be aspirated and submitted for Gram stain, bacterial culture, protein, lactate dehydrogenase, and pH.

Community respiratory viral infections (such as, influenza, RSV, adenovirus, rhinoviruses, metapneumoviruses) have a seasonal pattern (generally November through April); however, parainfluenza viral infections can occur throughout the year. During the influenza season, consider empiric antiviral therapy for patients within 48 hours after symptoms develop that are suggestive of influenza (such as, high fever, coryza, myalgia, and dry cough), especially during community outbreaks. Pandemic influenza (e.g., swine flu) 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 (e.g., H1N1), it is necessary to be familiar with susceptibility patterns and guidelines on appropriate antiviral treatment (http://www.fda.gov/cder/drug/antivirals/influenza/default.htm).

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 of pneumonia is an important risk factor for specific pathogens that may be resistant to antibiotics.[200] 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 multi-drug resistant pathogens in patients with health-care-associated pneumonia: received antibiotics in the preceding 90 days, hospitalization for 2 days or more in the preceding 90 days, resident in nursing home or extended care facility, chronic dialysis within 30 days, home wound care, and family member with a multi-drug resistant pathogen. Late-onset hospital-acquired pneumonia (occurring after 5 days or more of hospitalization) is more likely caused by multidrug-resistant pathogens, and is associated with greater morbidity and mortality.

The population of multidrug resistant bacteria (notably, MRSA and antibiotic-resistant Gram-negative pathogens) varies among different hospitals and geographic distributions. Therefore, the selection of initial therapy for hospital-acquired pneumonia requires knowledge of the local patterns of antibiotic susceptibility. For example, at some centers, a high frequency of extended spectrum beta lactamase-producing Gram-negative bacterial infections may make a carbapenem the drug of choice as initial therapy for pneumonia. At other centers, carbapenem-resistant Gram-negative infections are an increasing problem, and an alternative class of antibiotics may be preferred based on prior local susceptibility results.[201]

In patients with late-onset hospital-associated pneumonia or risk factors for multi-drug resistant pathogens regardless of when pneumonia developed in relation to hospitalization, a broad-spectrum antibiotic regimen is recommended. An antipseudomonal beta-lactam (e.g., ceftazidime, cefepime, imipenem/cilastatin, meropenem, doripenem, or piperacillin/tazobactam) plus an antipseudomonal fluoroquinolone (e.g., ciprofloxacin or levofloxacin) or aminoglycoside, plus either linezolid or vancomycin (to cover MRSA) is a reasonable initial regimen (aim for trough vancomycin level of 15-20 mcg/mL) (see FEV-A).[200] If *Legionella* is suspected, a quinolone (ciprofloxacin or levofloxacin) should be used instead of an aminoglycoside. The antibiotic regimen should be subsequently tailored based on culture results.

Pulmonary Infiltrates in Neutropenic Patients

In patients with neutropenia for less than 1 week, pulmonary infections are likely to be caused by Enterobacteriaceae (e.g., *E.coli, Klebsiella* sp.), *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. Blood cultures, a chest radiograph, and, if possible, a sputum sample for Gram stain and culture should be obtained. In suspected acute bacterial pneumonia, appropriate empiric antibiotic therapy must be initiated promptly and the response must be closely monitored in an inpatient setting. The therapeutic regimen depends on several variables, including recent use of antibiotics, community or nosocomial pneumonia, and the local antibiotic sensitivity data.

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

If clinical improvement occurs within 48 to 72 hours of therapy, no further diagnostic measures are necessary; antibiotic therapy should be continued until neutropenia resolves and for at least 10 to 14 days.

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

Pulmonary Infiltrates in Patients With Impaired Cellular Immunity

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

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

Diffuse infiltrates have a broad differential diagnosis, including PCP, viral infections, hemorrhage, and drug-induced pneumonitis. A diagnosis of PCP should be considered in patients with significantly impaired cellular immunity not receiving PCP prophylaxis who present with diffuse pulmonary infiltrates. BAL is the standard approach for diagnosing PCP. In patients with substantial respiratory disease (e.g., labored breathing, requiring supplemental oxygen), empiric therapy should be initiated before BAL. Pending BAL results, an initial regimen can include a respiratory fluoroquinolone against community-acquired pathogens and TMP-SMX (TMP component: 5 mg/kg every 8 hours) against possible PCP. In patients with suspected PCP and with room air PaO_2 of 75 torr or less, corticosteroids (initially prednisone 40 mg twice daily, then tapered) should be added based on studies of patients with AIDS–associated PCP.[203]

Patients at the highest risk for CMV pneumonia include allogeneic HSCT recipients post-engraftment (particularly those receiving immunosuppressive therapy for GVHD) and alemtuzumab recipients. Negative results from CMV surveillance testing (antigenemia or peripheral blood PCR) make CMV pneumonia very unlikely. CMV pneumonia is uncommonly observed in non-transplanted patients receiving therapy for leukemia.[204] Community respiratory viruses can cause severe pulmonary infection in neutropenic patients and in non-neutropenic patients with impaired cellular immunity. Noninfectious etiologies must also be considered, as previously stated. BAL is sensitive in diagnosing bacterial and viral pneumonia and PCP, and is often the initial invasive diagnostic procedure (see "Invasive Diagnostic Procedures for Pulmonary Infiltrates").

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. 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, shell vial culture takes about 5 days.

Fungal pneumonia is suggested by the following: host factors predisposing the patient to invasive aspergillosis, appropriate symptoms or signs of infection, a compatible pulmonary lesion, and a positive serum galactomannan or beta-glucan assay. Host factors indicative of high risk for invasive aspergillosis include neutropenia for more than 10 days, receipt of an allogeneic HSCT, prolonged use of high-dose systemic corticosteroids, or treatment with T-cell suppressants. The galactomannan assay is specific for invasive aspergillosis, whereas the beta-glucan assay detects aspergillosis and other invasive fungal infections (including invasive candidiasis, PCP, and fusariosis).[205-207] Zygomycosis yields negative serum galactomannan or beta-glucan test results.

Antigen-based detection systems have advantages and limitations. A meta-analysis showed that the galactomannan assay had a sensitivity of 70% and specificity of 89% for proven invasive aspergillosis, and that the accuracy of the test varied.[140] The lack of consistent results likely relates to different cut-off values for a positive result, differences in patient populations, and possibly use of mold-active prophylaxis. Several variables can affect the performance of the galactomannan assay,[208,209] which may account for the different results. The sensitivity of the assay is significantly reduced by concomitant mold-active antifungal agents.[138,210] False-positive results may be more common in children and in allogeneic HSCT recipients.[211] Concomitant piperacillin/tazobactam causes false-positive galactomannan results.[212,213] False-positive beta-glucan results have been reported in patients with surgical packing who are receiving immunoglobulin therapy and in patients receiving IV amoxicillin-clavulanate.[214,215] Despite these limitations, a patient at high risk for invasive aspergillosis (e.g., prolonged neutropenia or allogeneic HSCT recipient) with clinical and radiological findings (e.g., a new pulmonary nodule of 1 cm or greater or infiltrate) compatible with invasive aspergillosis and with a positive serum galactomannan is likely to have invasive aspergillosis, and a mold-active agent (voriconazole is preferred) should be added.

The assay for serum or urine Histoplasma antigen is a sensitive and specific test in patients with disseminated histoplasmosis (histoplasmosis is endemic in the central United States). Coccidioidomycosis is endemic in the southwestern United States. Disseminated coccidioidomycosis can be diagnosed based on appropriate symptoms and signs of infection and on positive serum titers. BAL is the diagnostic gold standard for PCP. In a small series, sputum induction with hypertonic saline was diagnostic of PCP in non–HIV-infected patients in about 60% of cases.[216] A BAL should be performed if sputum induction is attempted, and the results are negative.

Invasive Diagnostic Procedures for Pulmonary Infiltrates

Invasive diagnostic procedures may be required in the following situations: 1) the clinical course does not suggest an acute bacterial process, 2) the patient has not responded to initial antibiotic therapy, and/or 3) noninvasive testing yields negative results. BAL has a high diagnostic yield in alveolar infiltrates, such as pneumonia caused by *P.jirovecii*, *M.tuberculosis,* and respiratory viruses. The sensitivity of BAL for focal lesions (such as nodules) is variable. In lesions more than 2 cm, the sensitivity of BAL ranges from 50% to 80%; however, in smaller lesions, the diagnostic yield is usually about 15%.[217] Quantitative cultures from BAL or from a protected brush catheter may increase the specificity in the diagnosis of bacterial pneumonia as distinguished from upper airway colonization in ventilated patients.

BAL cultures only detect about 50% of cases; therefore, it is relatively insensitive for diagnosing aspergillosis.[218] Galactomannan detection in BAL fluid appears to be more sensitive than serum detection[219,220] and can be used to support a diagnosis of probable aspergillosis.[221] In patients with focal peripheral lesions, percutaneous biopsy may increase the diagnostic yield; however, in thrombocytopenic patients, the risk of bleeding may be unacceptably high. The microbiologic evaluation should take into account the clinical manifestations and nature of immunocompromise. In the highly immunocompromised (e.g., those receiving chemotherapy for acute leukemia, HSCT recipients), the following studies on BAL and lung biopsies should be considered: culture and stains for bacteria, fungi, *Legionella*, mycobacteria, *Nocardia*, HSV, CMV, community respiratory viruses (both rapid antigen and shell vial culture), and cytology or immunofluorescent studies for *P.jirovecii*. In a patient with compatible host factors and radiologic findings, a positive galactomannan result from BAL is also indicative of probable invasive aspergillosis.[221]

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 diagnosis of most infectious and noninfectious etiologies. This invasive procedure may identify the causative pathogen or the presence of a noninfectious etiology (e.g., treatment-associated lung toxicity, hemorrhage, or bronchiolitis obliterans–organizing pneumonia [BOOP]), which may allow one to eliminate 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

The evaluation and recommended empiric therapy for skin and soft tissue infections in neutropenic patients are discussed in the algorithm (see FEV-7). When evaluating the potential for a skin/soft tissue infection, careful examination of all line sites and perineal areas are 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, respectively. Vancomycin may be considered for cellulitis, disseminated papules/lesions, and wound infections (see FEV-7). Acyclovir, famciclovir, or valacyclovir should be considered for vesicular lesions after appropriate diagnostic tests (scraping base of vesicle for HSV or VZV, direct fluorescent antibody tests, herpesvirus culture) have been done.

Skin lesions can be manifestations of systemic infection. Ecthyma gangrenosum is the most characteristic skin lesion associated with systemic *P.aeruginosa* infection. Similar lesions can be caused by *S.aureus*, enteric Gram-negative bacilli infection, and filamentous fungi (including *Aspergillus*, Zygomycetes, and *Fusarium* species). A rapidly progressive deep soft tissue infection with gas formation suggests clostridial myonecrosis (or polymicrobial necrotizing fascitis). Broad spectrum antibiotics and surgical debridement may be life saving if initiated early. Hematogenously disseminated candidiasis with skin involvement manifests as fever and erythematous cutaneous papules; blood cultures are expected to be positive for *Candida* species.

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

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.[222] The most common organisms infecting intraventricular devices are coagulase-negative staphylococci, *S.aureus,* and *Propionibacterium acnes*. Enterobacteriaceae and *P.aeruginosa* account for only 10% of these infections. Coagulase-negative staphylococci and *P.acnes* usually cause indolent late postoperative infections. Therapy with systemic antibiotics and removal of the entire device are the most effective approaches to eradicate infection. Use of parenteral and intraventricular instillation of antibiotics without removal of the device may not be effective, and recrudescence of infection is common. Antibiotic therapy should be tailored to the specific pathogen isolated from cerebrospinal fluid. In an acutely ill patient with suspected meningitis related to previous neurosurgery, empiric therapy can include parenteral vancomycin (which has activity against *Staphylococcus*, *Streptococcus*, and *Propionibacterium* species; dose 15 mg/kg every 8 to 12 hours to maintain serum trough concentration of 15-20 mcg/mL) in combination with ceftazidime (2 g every 8 hours), cefepime (2 g every 8 hours), or meropenem (2 g every 8 hours) (which have activity against Enterobacteriaceae and *P.aeruginosa*); these doses apply to adults with normal renal function.[222]

CNS infections unrelated to neurosurgery are relatively uncommon in patients with cancer. Initial evaluation generally involves a head CT scan to rule out intracranial bleeding and a lumbar puncture (assuming there are no contraindications). Cerebrospinal fluid studies should be tailored to specific host factors, epidemiologic exposures (e.g., 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 (e.g., associated with anti-lymphocyte immunoglobulin preparations).

Empiric therapy for presumed meningitis should include an anti-pseudomonal beta-lactam agent that readily enters the CSF (e.g., cefepime, ceftazidime, meropenem) plus vancomycin plus ampicillin (to cover listeriosis). 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 (e.g., neutropenia, neurosurgery within the past 2 months, allogeneic HSCT, history of *P.aeruginosa* infection), use of cefepime (2 g every 8 hours in adults with normal renal function) or meropenem (2 g every 8 hours in adults with normal renal function) instead of ceftriaxone in the initial empiric regimen is advised. The antibiotic regimen should be tailored based on culture results.

In patients with suspected encephalitis (fever, mental status changes, cerebrospinal fluid pleocytosis), IV acyclovir (10 mg/kg every 8 hours in patients with normal renal function) should be considered as empiric therapy for HSV in addition to an appropriate antibacterial regimen.[223] An MRI and the following cerebrospinal fluid 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 (e.g., residence in an endemic area, shelter, or prison; previous positive PPD [purified protein derivative]). In patients with severe impairment of cellular immunity (e.g., allogeneic HSCT recipients, advanced AIDS), additional cerebrospinal fluid studies should be considered (such as PCR for CMV, VZV, human herpes virus–6 [HHV-6], and toxoplasmosis). 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. Bacterial abscesses in non-immunocompromised patients are typically caused by dental flora. In patients with prolonged neutropenia and in allogeneic HSCT recipients, CNS aspergillosis must be considered. A chest CT showing a new nodule or infiltrate and a positive serum galactomannan result in this setting are highly suggestive of pulmonary aspergillosis with CNS dissemination. In patients with impaired cellular immunity, other causes of CNS abscesses include toxoplasmosis, nocardiosis, cryptococcosis, and mycobacterial infections. Noninfectious etiologies in patients with impaired cellular immunity include CNS malignancies (such as secondary lymphomas) and Epstein-Barr virus (EBV)–associated post-transplantation lymphoproliferative disorder (PTLD). Given the broad differential diagnosis of new CNS lesions in highly immuno-compromised patients, a brain biopsy is strongly recommended (if feasible) with material submitted for histology and culture. Cultures and stains should include bacteria, fungi, mycobacteria, and *Nocardia* species.

In non-immunocompromised patients with a bacterial brain abscess, initial therapy with ceftriaxone (2 g every 12 hours in adults) plus metronidazole (7.5 mg/kg every 6 hours in adults with normal renal function) is advised. In patients with prolonged neutropenia without corticosteroids or lymphocyte-depleting agents, a reasonable initial regimen consists of combination cefepime, metronidazole, and voriconazole (IV 6 mg/kg every 12 hours for 2 doses followed by 4 mg/kg every 12 hours); however, IV voriconazole (but not the oral formulation) may worsen renal disease in patients with significant pre-existing renal impairment (see FEV-B). Voriconazole (as well as itraconazole and posaconazole) has important drug-drug interactions with certain antiseizure agents (e.g., phenytoin); therefore, the voriconazole package insert should be reviewed to guide dosing of these agents (http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=7500). In allogeneic HSCT recipients and other patients with severe T-cell impairment, addition of high-dose TMP/SMX (trimethoprim component: 5 mg/kg every 8 hours) should be considered to cover toxoplasmosis and nocardiosis, pending a definitive diagnosis. An Infectious Diseases consultation is advised in all cases of suspected or documented CNS infections.

Therapy for Invasive Fungal Infections

Invasive Candidiasis

Candida species are the fourth most common cause of nosocomial bloodstream infections in the United States.[224] The crude mortality of candidemia ranges from 23% to greater than 50%. This variable mortality rate reflects serious comorbidities (such as malignancy, neutropenia) and illness requiring prolonged periods in the intensive care unit. *Candida albicans* is the most common *Candida* species isolated from the blood. The proportion of non-albicans *Candida* species varies among different centers, but accounts for approximately 50% of blood stream isolates. *Candida krusei* is always resistant to fluconazole, and *Candida glabrata* has a broad range of minimum inhibitory concentrations (MICs). *Candida parapsilosis* is mostly associated with vascular catheters and lipid formulations used for total parenteral nutrition.

A randomized study comparing IV fluconazole (400 mg daily) with amphotericin B as therapy for candidemia in non-neutropenic patients found both regimens equally effective, but fluconazole had less toxicity.[225] In a subsequent study of non-neutropenic patients with candidemia, combination therapy with a higher dose of fluconazole (800 mg daily) and amphotericin B led to improved clearance of candidemia compared with fluconazole alone, but the combination regimen was associated with significantly more nephrotoxicity and with no survival benefit.[169] Voriconazole was equally effective as, but less nephrotoxic than, a strategy of amphotericin B followed by fluconazole in non-neutropenic patients with invasive candidiasis.[226] In trials of "invasive candidiasis," most patients had candidemia, but those with deep organ involvement (e.g., 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.[227-229] When caspofungin was compared with conventional amphotericin B, there was a trend to a higher favorable response rate in the caspofungin arm (73% and 62%, respectively) in the modified intent-to-treat analysis.[227] Among patients who met eligibility criteria and received at least 5 days of study drug, caspofungin was statistically superior to amphotericin B (81% versus 65% successful outcome, respectively). Caspofungin was less toxic than amphotericin B. Micafungin was as effective as liposomal amphotericin B as therapy for invasive candidiasis.[228] fewer treatment-related adverse events (including those that led to treatment discontinuation) occurred with micafungin than with liposomal amphotericin B. Anidulafungin was not inferior to fluconazole as therapy for invasive candidiasis and was possibly more efficacious.[230] At the end of IV therapy (the primary endpoint), treatment was successful in 75.6% of patients treated with anidulafungin, as compared with 60.2% of those treated with fluconazole (95% confidence interval, 3.9 to 27.0). Finally, caspofungin and micafungin were equally safe and effective as therapy for invasive candidiasis.[229]

The IDSA has recently published detailed updated guidelines on candidiasis.[231] Fluconazole (loading dose of 800 mg [12 mg/kg], then 400 mg [6 mg/kg] daily) or an echinocandin (caspofungin: loading dose of 70 mg, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: loading dose of 200 mg, then 100 mg daily) is recommended as initial therapy for most non-neutropenic adult patients. An echinocandin is preferred in critically ill patients. Transition from an echinocandin to fluconazole is recommended for patients who have isolates that are likely to be susceptible to fluconazole (e.g., *Candida albicans*), who are clinically stable, and who have not had recent azole exposure. Fluconazole-resistant *Candida* isolates are frequently cross-resistant to other azoles;[232] therefore, if candidemia occurs in patient with recent azole exposure, a switch in class (e.g., to an echinocandin) is recommended. *Candida glabrata* strains can have variable sensitivity to azoles; an echinocandin is therefore the preferred therapy, and transition to fluconazole or voriconazole can be considered if azole susceptibility is documented. Echinocandins have reduced sensitivity to *Candida parapsilosis* compared to other candidal strains; fluconazole is recommended in this setting.

The IDSA recommends an echinocandin as initial therapy for candidemia in most neutropenic patients.[231] The NCCN panel agrees with this recommendation, but notes that because studies evaluating echinocandins have included very small numbers of neutropenic patients, the optimal therapy for invasive candidiasis in this population is not definitive. Given the availability of safer alternatives, the panel does not recommend amphotericin B products routinely for candidemia, although such agents may be considered in unusual complicated cases, such as meningitis and endocarditis.

Invasive Aspergillosis

Voriconazole is the recommended agent as primary therapy for invasive aspergillosis (see FEV-B). In an open-label, multicenter randomized trial of primary therapy for invasive aspergillosis, voriconazole was more effective than amphotericin B (53% versus 32% of subjects had a complete or partial response) and was associated with improved survival at 12 weeks (71% versus 58%, respectively).[171] Among neutropenic patients, the success rate in the voriconazole arm was 51%, which was superior to the amphotericin B arm.[171] In a retrospective analysis of 86 patients with CNS aspergillosis treated with voriconazole either as primary or salvage therapy, 35% had a complete or partial response.[233] This success rate compares very favorably to previous series in which the frequency of successful responses to amphotericin B was almost nil.[234] Based on the strength of this database, the NCCN panel and IDSA recommend voriconazole as first-line therapy for invasive aspergillosis.[173]

There can be considerable inter-individual variability in voriconazole exposure, and the utility of monitoring drug levels is controversial.[235,236] Studies with a few patients have noted a relationship between low plasma voriconazole levels and treatment failure,[237] and between high voriconazole levels and toxicity.[238,239] Voriconazole blood levels of at least 1 to 2 mcg/mL are thought to be required for efficacy. Obtaining a serum voriconazole level should be considered in cases of breakthrough or refractory fungal disease or drug toxicity.

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

Lipid formulations of amphotericin B have at least comparable efficacy and reduced renal toxicity compared to conventional amphotericin B deoxycholate (AmB-D). Some investigators have persuasively argued that lipid formulations of amphotericin B should be considered suitable replacements for AmB-D for primary therapy for many invasive fungal infections.[127] Amphotericin B colloidal dispersion (ABCD) was equally effective as, but less nephrotoxic than, AmB-D as primary therapy for invasive aspergillosis.[240] Amphotericin B lipid complex (ABLC) was safe and effective as therapy for invasive aspergillosis based on an open label data registry.[241]

A randomized study compared liposomal amphotericin B (L-AMB) at either 3 or 10 mg/kg per day for 14 days, followed by 3 mg/kg per day as therapy for invasive mold infections.[242] When compared with the 10 mg/kg/day dose, the 3 mg/kg/day dose was as effective as, but less nephrotoxic, and was associated with a trend toward superior 12-week survival (72% and 59%, respectively; 95% confidence interval, -0.2% to

26%). Because 97% of enrolled patients had invasive aspergillosis, this study does not permit conclusions about optimal L-AMB dosing in patients with other mold infections (such as zygomycosis).

Echinocandins have not been evaluated as initial monotherapy for invasive aspergillosis in clinical trials. Caspofungin as salvage therapy in patients with invasive aspergillosis led to a favorable response in 37 (45%) of 83 patients.[243] 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[244-247] but not in others.[248-250]

In small retrospective series, the combination of caspofungin and liposomal amphotericin B as salvage therapy led to a favorable outcome in approximately 40% to 60% of patients with invasive aspergillosis, although these series included cases of "possible" aspergillosis.[251,252] Marr and colleagues[253] reported a survival advantage of voriconazole plus caspofungin compared to voriconazole alone in a retrospective analysis of salvage therapy for invasive aspergillosis. This database, although encouraging, involved small numbers of patients and the 2 groups of patients evaluated were noncontemporaneous; therefore, other host and infection-related factors may have influenced the outcome. A noncomparative study of caspofungin combined with other mold-active drugs as salvage therapy for invasive aspergillosis resulted in a success rate of 49% (25/51) at 12 weeks after initiation of combination therapy,[254] which was similar to caspofungin monotherapy. In an open-label study of invasive aspergillosis, micafungin combined with other antifungals led to a successful response in 5/17 (29%) and 60/174 (35%) of the primary and salvage treatment groups, respectively.[255] The number of patients in the micafungin monotherapy arms was too small to permit comparisons. The initial micafungin dose (75 mg/day) used in this study was low by today's standards.

Although combination antifungal therapy is commonly used as therapy for invasive aspergillosis, the clinical database is inadequate to make conclusions about whether any combination regimen is more effective than voriconazole alone, which is the current gold standard. A randomized, prospective study comparing voriconazole versus voriconazole plus anidulafungin as primary therapy for invasive aspergillosis is underway.

Posaconazole has been effective as salvage therapy against a broad spectrum of invasive fungal infections.[256-259] Of patients with invasive aspergillosis that was refractory or who had intolerance to standard antifungal therapy, 42% had a complete or partial response with posaconazole.[260] Posaconazole has been approved in the European Union for treatment of invasive aspergillosis and certain other invasive fungal infections refractory to standard antifungal agents. In the United States, posaconazole is not FDA-approved as primary or salvage therapy for invasive fungal disease.

Zygomycosis and Other Invasive Mold Infections

The frequency of zygomycosis (also referred to as "mucormycosis") has increased at some centers in the setting of more frequent voriconazole usage.[170,261,262] In a case-control study of invasive aspergillosis and zygomycosis in patients with acute leukemia and allogeneic HSCT recipients, use of voriconazole and fungal sinusitis each favored a diagnosis of zygomycosis.[170] However, some transplant centers reported an increased frequency of zygomycosis that pre-dated the availability of voriconazole,[263,264] a finding that likely reflects a greater proportion of patients with severe host defense impairment. Zygomycosis typically manifests as rhinocerebral or pulmonary disease. Histopathology showing broad aseptate or hyposeptate hyphae with 90-degree branching is suggestive of zygomycosis, although culture is required for confirmation.

No randomized studies of therapy have been performed for zygomycosis and other uncommon invasive mold infections. Recommendations for therapy are based on a limited number of patients from retrospective analyses, data registries, and open-label salvage therapy antifungal trials. Treatment of zygomycosis involves amphotericin B (a lipid formulation is advised over amphotericin B deoxycholate to reduce the chance of nephrotoxicity) plus early and aggressive surgical debridement, when feasible. A gap in knowledge exists regarding optimal dosing of lipid formulations of amphotericin B for invasive non-*Aspergillus* mold infections; an initial dose of 5 mg/kg/day is commonly used. Posaconazole, a second generation antifungal azole with activity against most of the zygomycetes, has shown promising results as salvage therapy in zygomycosis refractory to or intolerant of amphotericin B formulations.[257,265] Although not approved by the U.S. FDA for this indication, posaconazole can be considered as maintenance therapy for zygomycosis following control of infection with an amphotericin B formulation and/or surgical debridement. Posaconazole has not been evaluated as primary therapy for invasive fungal diseases in clinical trials.

Fusarium species[266-268] and *Scedosporium* species became increasingly more important causes of invasive fungal infections–related mortality in leukemia and in allogeneic HSCT recipients at some centers.[263,269,270] 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.[267] Therapy for invasive fusariosis generally involves voriconazole,[271] posaconazole,[259] or a lipid formulation of amphotericin B.[272] *Scedosporium* species are resistant to amphotericin B; therapy generally involves itraconazole, voriconazole, or posaconazole. An Infectious Diseases consultation is advised in all cases of invasive mold infections and particularly in diseases by uncommon and resistant molds.

Early Diagnosis of Invasive Mold Infections

Invasive fungal pathogens have increased and remain a major concern. Computed tomography scanning of the chest may facilitate early detection of aspergillosis and other filamentous fungi.[273,274] A CT scan may show peripheral or subpleural nodules inapparent on plain chest radiographs. The “halo sign” is a characteristic, but not pathognomonic, early chest CT feature of angioinvasive organisms.[202] 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 those receiving systemic corticosteroid therapy.

Studies differ regarding whether serum galactomannan is a useful surveillance tool in asymptomatic patients at high risk for mold infections and in patients with persistent neutropenic fever of unknown etiology. In one study, prospective serial monitoring of galactomannan antigenemia in allogeneic HSCT recipients yielded positive and negative predictive values of 94.4% and 98.8%, respectively, and antigenemia preceded radiographic findings by more than 1 week in 80% of cases of invasive aspergillosis.[275] In another study, the sensitivity was only 64.5% in cases of definite invasive aspergillosis.[211]

The positive predictive value (PPV) was poor when serum galactomannan was used as a surveillance tool in patients with persistent neutropenic fever (PPV=7.1%) and in HSCT (mostly autologous) recipients (PPV=10%); the negative predictive value was 100% in both groups.

Odabasi and colleagues evaluated the beta-glucan assay (Glucatell assay, Associates of Cape Cod) as an early diagnostic marker for invasive fungal infections in patients with acute leukemia or MDS receiving antifungal prophylaxis.[205] At least one serum sample was positive at a median of 10 days before the clinical diagnosis in all patients with a proven or probable invasive fungal infection, including candidiasis, fusariosis, trichosporonosis, and aspergillosis. The negative predictive value was 100%, and the specificity of the test was 90% for a single positive test result and at least 96% for 2 or more sequential positive results. The experience of the beta-glucan assay in HSCT recipients is limited[206] and requires additional study.

Although valuable as diagnostic adjuncts to support a diagnosis of a probable invasive aspergillosis in patients with compatible host factors, clinical findings, and radiologic findings[276] (see section on Pulmonary Infiltrates), 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,[141] and more research is required. Currently, the database is inadequate to recommend any of these methods as a surveillance tool in asymptomatic immunocompromised patients or in patients with neutropenic fever alone.

Prevention of Infectious Diseases

Infection prophylaxis in cancer patients generally involves broad spectrum antimicrobial therapy directed against the most common infecting pathogens (including bacterial, viral, and fungal) in high-risk patients.

Antibacterial Prophylaxis During Neutropenia

Patients with cancer and chemotherapy-induced neutropenia are at risk for severe bacterial infections. Fluoroquinolones are the most commonly used prophylactic antibacterial agents in adults with chemotherapy-induced neutropenia. In a meta-analysis that evaluated 18 trials (n=1408 patients) in which fluoroquinolones were compared to either placebo or TMP/SMX, fluoroquinolone recipients had about 80% fewer Gram-negative infections than those without prophylaxis, leading to an overall reduction in total infections.[277] The reduction in fever was small, and in blinded trials, was not significant. Fluoroquinolone prophylaxis did not affect mortality in this meta-analysis.

The rate of Gram-positive infections and fungal infections was not significantly affected by fluoroquinolone prophylaxis in this meta-analysis.[277] This is an important consideration given the occurrence of an increased rate of Gram-positive infections in some trials of fluoroquinolone prophylaxis.[278] Viridans group streptococcal bacteremia breakthroughs have been associated with ciprofloxacin prophylaxis,[26,74] an important consideration given the potential for substantial morbidity and mortality associated with this pathogen in neutropenic patients.

Although the IDSA guidelines on management of neutropenic fever recognize the evidence that antibacterial prophylaxis in high-risk neutropenic patients reduced the frequency of Gram-negative infections, the IDSA advises against prophylaxis.[279] This recommendation is based on the concern for emergence of antibiotic-resistant bacteria and a review of previous studies that showed lack of a survival benefit associated with antibacterial prophylaxis, despite decreases in Gram-negative bacterial infections.

Studies have provided additional insight into the benefits and limitations of prophylaxis among neutropenic patients with varying degrees of risk for serious infectious complications. Gafter-Gvili and colleagues[280] conducted a meta-analysis of 95 randomized, controlled trials comparing antibiotic prophylaxis with either placebo or no intervention or with another antibiotic in afebrile neutropenic patients. Antibiotic prophylaxis significantly decreased the risk for death when compared with placebo or no treatment. The survival benefit was more substantial when the analysis was limited to fluoroquinolones. Fluoroquinolone prophylaxis reduced the risk for all-cause mortality, infection-related mortality, fever, clinically documented infections, and microbiologically documented infections. Most of the trials involved hospitalized patients with hematologic malignancies, and data were inadequate to assess the relationship between duration and degree of neutropenia and relative risk of mortality. No significant increase was observed in fluoroquinolone-resistant bacterial infections, although the length of observation may have been too short to detect the emergence of resistant bacteria. The panel recognizes the substantial limitations associated with meta-analyses. However, the panel believes that the benefit of prophylaxis in patients with hematologic malignancies on overall survival outweighs detriments related to adverse effects and development of resistance.

Two large randomized, placebo-controlled studies showed the benefit of levofloxacin prophylaxis in neutropenic patients at different levels of risk of infectious complications.[281,282] Levofloxacin has similar activity against Gram-negative pathogens compared to ciprofloxacin and ofloxacin; however, levofloxacin has improved activity against certain Gram-positive pathogens, including streptococci. Bucaneve and colleagues[282] evaluated levofloxacin prophylaxis in adult patients with cancer in whom chemotherapy-induced neutropenia (less than 1000 neutrophils/mcL) was expected to occur for more than 7 days. This protocol intentionally excluded patients anticipated to have a short duration of neutropenia who would generally be candidates for outpatient management of neutropenic fever. Levofloxacin recipients had a lower rate of microbiologically documented infections, bacteremias, and single-agent Gram-negative bacteremias than did placebo recipients. The effects of prophylaxis were also similar between patients with acute leukemia and those with solid tumors or lymphoma. Mortality and tolerability were similar in the 2 groups.

Cullen and colleagues[281] evaluated levofloxacin prophylaxis after chemotherapy for solid tumors and lymphomas for patients anticipated to have brief durations of neutropenia and typically categorized as low risk. The primary outcome was the incidence of clinically documented febrile episodes (temperature more than 38°C) attributed to infection. Secondary outcomes included the incidence of all probable infections, severe infections, and hospitalization. A total of 1565 patients underwent randomization, 87% with solid tumors and 13% with lymphoma. During the entire chemotherapy course, 10.8% of levofloxacin recipients had at least one febrile episode compared with 15.2% of placebo recipients (*P*=.01). Hospitalization was required for the treatment of infection (suspected and documented) in 15.7% of patients in the levofloxacin group and 21.6% of patients in the placebo group (*P*=.004). The incidence of severe infections, infection-related mortality, and overall mortality were similar in both groups.

Thus, the main advantage of levofloxacin prophylaxis in intermediate and higher risk patients with chemotherapy-induced neutropenia was a reduction in clinically significant bacterial infections, including Gram-negative rod bacteremia.[282] In contrast, the main advantage of prophylaxis in lower risk neutropenic patients was a small, but statistically significant, reduction in fever and hospitalization for neutropenic fever.[281] Neither study conducted a systematic long-term evaluation of antimicrobial resistance. The NCCN 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 the primary endpoint of prevention of neutropenic fever in the study by Cullen and colleagues,[281] 1000 hypothetical low-risk patients would have to receive prophylaxis during each cycle of chemotherapy-induced neutropenia to benefit only 44 patients.

An important consideration for low-risk patients with short durations of neutropenia is whether fluoroquinolone prophylaxis is of greater benefit than the option of outpatient fluoroquinolone treatment for F&N, should it occur. Both the NCCN and IDSA[279] recommend oral fluoroquinolone-based regimens as outpatient empiric therapy for neutropenic fever in adults who meet criteria for low risk of complications (see FEV-14). Use of fluoroquinolone prophylaxis may preclude their later use as empiric therapy for neutropenic fever in the same patient. The modest difference in rates of hospitalization for suspected infection in levofloxacin compared to placebo recipients (15.7% versus 21.6%, respectively) in the study by Cullen and colleagues[281] may be offset by exclusion of outpatient oral empiric therapy in patients receiving fluoroquinolone prophylaxis. To target antibacterial use, Cullen and colleagues have recently suggested more limited prophylaxis using levofloxacin only on cycle 1 of myelosuppressive cancer chemotherapy and on subsequent cycles after a fever in cycle 1.[283]

The decision whether to use antibacterial prophylaxis and the selection of the specific agent requires a balance between expected benefit and risk. The concept of risk applies to immediate adverse effects of the drug (e.g., 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 (e.g., those being treated at a cancer center). The link between fluoroquinolone use and severe *C.difficile* as well as MRSA infections provides an additional cautionary note regarding excess use of fluoroquinolones.[176,177,284,285]

The panel advises that fluoroquinolone prophylaxis (levofloxacin is preferred) be considered in patients with expected duration of neutropenia (ANC less than 1000/mcL) for more than 7 days. Trimethoprim-sulfamethoxazole should be used in patients at risk for *P.jirovecii* (formerly *P.carinii*) such as childhood acute lymphoblastic leukemia (see section on “Prophylaxis against *P.jirovecii*”). Among patients with neutropenia who are at lower risk of infectious complications (a category that includes most patients with solid tumor malignancies), the main benefit of antibacterial prophylaxis relates to a reduction in fever rather than in documented infections. In patients with neutropenia expected to last less than 7 days who are not receiving immunosuppressive regimens (e.g., systemic corticosteroids), the panel suggests no antibiotic prophylaxis.

Prophylaxis Against Pneumococcal Infection

Prophylaxis against pneumococcal infection is advised in patients who have undergone splenectomy or who are functionally asplenic and in allogeneic HSCT recipients. Most cases of pneumococcal sepsis occur within the first 2 years after splenectomy; however, a third of cases may occur up to 5 years after, and cases of fulminant sepsis have been reported more than 20 years after splenectomy. Lifelong prophylactic antibiotics have been recommended in patients who have had a splenectomy and particularly in the first 2 years after surgery, in children up to age 16 years, and in patients with other immune impairment.[286,287] However, the need for long-term antibiotic prophylaxis makes compliance extremely difficult, and resistance to penicillin is a growing concern. Penicillin prophylaxis is a reasonable approach for at least the first 5 years after splenectomy. Some experts think that prophylaxis should be continued in patients with persistent immune impairment caused by the underlying hematologic malignancy or by chemotherapy. Alternatively, patients may be provided with supplies of penicillin or amoxicillin to be taken for fever or for other early signs of sepsis. It should be emphasized that neither immunizations nor antibiotic prophylaxis will prevent all instances of overwhelming sepsis.

Allogeneic HSCT recipients are at increased risk for pneumococcal sepsis due to functional asplenia and impaired B-cell immunity. Pneumococcal sepsis is most common in the late transplant period, between 3 months to years after HSCT. Immunosuppressive therapy for GVHD delays reconstitution of B-cell immunity and significantly increases the risk of post-transplant pneumococcal sepsis.[38,288]

The NCCN panel advises that penicillin prophylaxis be initiated at 3 months after HSCT and be continued until at least 1 year after transplant. Prophylaxis should be continued in patients with chronic GVHD until immunosuppressive therapy has been discontinued. Post-transplant pneumococcal infection is generally community-acquired, and the frequency of resistance to antibiotics reflects regional antibiotic susceptibility patterns. In some areas, as many as 35% of pneumococcal isolates have intermediate- or high-level resistance to penicillin, and cross-resistance to other classes of antibiotics is common. Breakthrough pneumococcal sepsis in HSCT recipients receiving penicillin prophylaxis is well described.[289] Thus, in areas with a significant frequency of penicillin-resistant pneumococcal isolates, alternative agents should be considered based on local susceptibility patterns. Daily TMP/SMX used as prophylaxis for PCP is likely to be protective against pneumococcal disease. Vaccination with the polysaccharide pneumococcal vaccine is also strongly recommended at 1 year after cessation of immunosuppression in HSCT patients, or before a planned splenectomy, with revaccination after 5 years.

Antifungal Prophylaxis

Antifungal prophylaxis should not be used routinely in all patients with neutropenia. The rationale for antifungal prophylaxis is to prevent fungal infections in a targeted group of high-risk patients, especially those with longer durations of neutropenia or with GVHD after allogeneic HSCT. In neutropenic allogeneic HSCT recipients, 2 double-blind, placebo-controlled trials have shown that prophylactic fluconazole controlled yeast colonization and also decreased the rate of mucosal candidiasis and invasive *Candida* infections.[290,291] A decrease in mortality was noted in the study by Slavin and colleagues,[291] in which most of the patients were allograft recipients. Fluconazole conferred significant long-term improvement in survival, possibly by decreasing *Candida* antigen-induced GI tract GVHD.[292]

Fluconazole prophylaxis decreased fungal colonization, invasive infection, and fungal infection-related mortality in nontransplant patients with leukemia and in autologous transplant recipients in a placebo-controlled trial.[293] However, only 30% of the patients received growth factors, and the median duration of neutropenia was 14 to 16 days.[293] The benefit of fluconazole prophylaxis was greatest in autologous transplant recipients not receiving colony-stimulating growth factor support and in patients with leukemia receiving mucotoxic regimens consisting of cytarabine plus anthracycline. Therefore, no antifungal prophylaxis can be considered (category 2B) in autologous HSCT recipients who receive growth factor support and who do not have significant mucositis. Other studies of nontransplant patients with acute leukemia showed no significant benefit of fluconazole.[294,295]

The panel recognizes that strong evidence exists for the use of fluconazole as prophylaxis in allogeneic neutropenic HSCT recipients (category 1). However, fluconazole use can predispose to colonization and bloodstream infection by fluconazole-resistant *Candida* strains.[125,296]

Low-dose amphotericin B product and itraconazole have also been studied in high-risk patients and shown to provide protection against invasive molds, although they have provided no survival benefit in randomized studies with fluconazole.[297,298] Itraconazole, however, may be associated with hepatic toxicity and GI intolerance.[299] Itraconazole is contraindicated in persons 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.[300] This finding reinforces a note of caution about itraconazole (and by extension, voriconazole and posaconazole), a potent inhibitor of the cytochrome P450 3A4 isoenzyme, with regard to potential serious drug-drug interactions. Based on the toxicity of amphotericin B products and the availability of safer and equally effective alternative agents, amphotericin B products were considered a category 2B recommendation for prophylaxis. If an amphotericin B product is used, a lipid formulation is generally preferred because of less infusional and renal toxicity compared to conventional amphotericin B. This recommendation is made more strongly for patients at high risk for renal failure, such as those with pre-existing renal disease, HSCT recipients and co-administration of other nephrotoxic agents.[128,130]

Aerosolized delivery of amphotericin products has been considered for several years, and has the advantage of local delivery to lungs while avoiding systemic toxicity. A recent randomized, placebo-controlled trial found that aerosolized liposomal amphotericin B was useful for preventing invasive pulmonary aspergillosis in patients with prolonged neutropenia.[301] Limitations to aerosolized amphotericin B as prophylaxis include different nebulizers and amphotericin B formulations, lack of optimization of dosing, and lack of direct comparative data with systemically administered mold-active azoles or echinocandins.[302]

The echinocandin, micafungin is approved as prophylaxis in HSCT recipients with neutropenia (category 1). In a randomized, double-blind trial of autologous and allogeneic HSCT recipients, micafungin was superior to fluconazole based on pre-specified criteria that included absence of a breakthrough fungal infection and the absence of modifying the antifungal regimen empirically due to neutropenic fever.[303] The duration of study drug encompassed the neutropenic period, but not the period after neutrophil recovery where GVHD would be expected to occur. The frequency of breakthrough candidemia was similar in both arms, but there was a trend to fewer episodes of invasive aspergillosis in allogeneic HSCT recipients receiving micafungin. Survival and drug-related toxicity were similar in both arms.

Voriconazole was compared with fluconazole in a randomized study that included serum galactomannan surveillance in allogeneic HSCT recipients.[304] No difference was noted in the primary endpoint (180-day fungal-free survival), but a trend to reduced incidence of invasive aspergillosis was noted in voriconazole recipients. Because this study has been published in abstract form only, the NCCN panel considers the database on voriconazole as prophylaxis to be preliminary and therefore assigned a category 2B recommendation.

Posaconazole is currently only available in an oral formulation and needs to be taken with food for adequate absorption. Posaconazole is as effective as fluconazole as primary therapy for oropharyngeal candidiasis[305] but has not been evaluated as primary therapy for invasive fungal infections. In a randomized trial, prophylaxis with posaconazole led to fewer invasive fungal infections and less overall mortality compared to fluconazole or itraconazole in neutropenic patients with acute myelogenous leukemia (AML) or MDS receiving induction or re-induction chemotherapy.[306] The NCCN panel recommends posaconazole (category 1) as the drug of choice for prophylaxis in neutropenic patients with AML and MDS receiving induction or re-induction chemotherapy (see INF-3). The role of antifungal prophylaxis in patients with acute leukemia receiving consolidation chemotherapy has not been adequately evaluated.

Posaconazole as prophylaxis has not been evaluated during the neutropenic period following conditioning in allogeneic HSCT recipients, and thus the safety of this approach is unknown. Ingestion of a meal (ideally high-fat) or liquid nutritional supplement with each posaconazole dose is essential for achieving adequate posaconazole serum levels; patients who are unable to tolerate such oral intake should not receive this drug for prophylaxis.

The panel advises that prophylaxis with posaconazole, itraconazole, and voriconazole be avoided in patients receiving vinca alkaloid-based regimens (such as vincristine in acute lymphoblastic leukemia) because of the potential of these azoles to inhibit the cytochrome P450 3A4 isoenzyme, reducing clearance of vinca alkaloids. Severe vinca alkaloid-induced neurotoxicity has occurred when co-administered with itraconazole;[307] data on pairing vinca alkaloids with posaconazole and voriconazole are lacking. Although the package inserts of voriconazole and posaconazole advise caution if co-administered with vinca alkaloids and consideration of dose-reducing the vinca alkaloid, there are no data on the level of dose reduction required. Prophylaxis with fluconazole (which is a less potent inhibitor of cytochrome P450 3A4 than the mold-active azoles), an echinocandin, or an amphotericin B formulation should be considered in these patients as a safer alternative to the mold-active azoles.

Patients with chronic severe neutropenia (ANC less than 500/mcL) due to the underlying disease (such as aplastic anemia) are at substantial risk for invasive aspergillosis.[308] Although this population has not been evaluated in prophylactic antifungal trials, some panel members advise the use of a prophylactic mold-active agent (e.g., posaconazole or voriconazole) in such patients.

In patients with acute leukemia and autologous HSCT recipients, antifungal prophylaxis is administered until neutrophil recovery. Antifungal prophylaxis should be considered until at least day 75 after allogeneic HSCT (see INF-3). Although many centers reasonably use antifungal prophylaxis in non-neutropenic allogeneic HSCT recipients with GVHD, this practice was evaluated only recently in a properly designed study that focused specifically on this patient group. Posaconazole was compared with fluconazole as prophylaxis in allogeneic HSCT recipients with severe GVHD requiring intensive immunosuppressive therapy in a prospective, randomized, double-blind study.[309] The inclusion criteria included either grade II to IV GVHD, chronic extensive GVHD, or receiving intensive immunosuppressive therapy consisting of either high-dose corticosteroids, antithymocyte globulin, or a combination of 2 or more immunosuppressive agents or types of treatment. Prophylaxis with posaconazole led to a reduction in the incidence of invasive aspergillosis, the total number of invasive fungal infections while on treatment, and the number of deaths attributed to fungal infection. Posaconazole is recommended (category 1) as prophylaxis in patients with GVHD receiving intensive immunosuppressive therapy, as defined by the inclusion criteria in this trial. Prophylactic posaconazole can be considered in all patients with GVHD receiving immunosuppressive therapy, although the benefit/risk ratio of mold-active prophylaxis in patients receiving less intensive immunosuppressive regimens has not been established.

Secondary antifungal prophylaxis is defined as administration of antifungal therapy in a patient with a prior fungal infection to prevent recrudescence. The panel recommends secondary prophylaxis with an appropriate antifungal agent in patients with prior chronic disseminated candidiasis[310] or with invasive filamentous fungal infection[311] during subsequent cycles of chemotherapy or HSCT. In patients with invasive aspergillosis before HSCT, antifungal therapy for more than a month and resolution of radiologic abnormalities correlate with a lower likelihood of post-transplant recurrence of infection.[312] Secondary prophylaxis with a mold-active agent is advised for the entire period of immunosuppression. Secondary prophylaxis is generally administered for the duration of immunosuppression.

Antiviral Prophylaxis and Preemptive Antiviral Therapy

Herpes Simplex Virus

HSV is an important pathogen in patients who develop neutropenia and mucositis. These HSV infections are primarily reactivation of latent virus. The presence of latent HSV can be determined by pretreatment HSV serology. Reactivation and infection with HSV occur in 60% to 80% of HSCT recipients and in unprophylaxed patients with acute leukemia undergoing induction or re-induction therapy who are seropositive for HSV.[313,314] Among allogeneic HSCT recipients, HSV disease is most likely to occur within the first month, but may occur in later stages during intense immunosuppression. Although disseminated HSV infection is uncommon, the reactivation infection is frequently associated with increased mucosal damage, resulting in increased pain, limitation of the patient's ability to maintain oral hydration and nutrition, and an increased risk of bacterial and fungal superinfections.

Antiviral prophylaxis (acyclovir, valacyclovir, or famciclovir) against HSV is advised in HSV-seropositive patients receiving chemotherapy for acute leukemia, in all allogeneic HSCT recipients, and in some autologous HSCT recipients at high risk for mucositis during the neutropenic period (see FEV-C).[16] A longer period of prophylaxis should be considered in allogeneic HSCT recipients with GVHD or with frequent HSV reactivations before transplantation.[16]

HSV and herpes zoster infections are common in alemtuzumab recipients. Antiviral prophylaxis is advised until at least 2 months after completion of therapy or until CD4 counts are 200/mcL or more, whichever occurs later.

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 (such as, fludarabine). Once a patient has had an HSV reactivation infection requiring treatment, the panel recommends HSV prophylaxis for that patient during all future episodes of neutropenia induced by cytotoxic therapy.

Varicella Zoster Virus

Impaired cellular immunity is the principal risk factor for VZV disease. In allogeneic HSCT recipients with a history of VZV infection without antiviral prophylaxis, about 30% have VZV disease after reactivation. In patients with a history of chicken pox, acyclovir (800 mg oral twice daily)—administered from 1 to 2 months until 1 year after allogeneic HSCT—significantly decreased the incidence of VZV disease compared to placebo (5% versus 26%, respectively).[315] The frequency of VZV disease in the post-prophylactic period was similar in the 2 groups and predominantly occurred in patients who required systemic immunosuppression. This prolonged course of acyclovir prophylaxis is likely to also prevent HSV reactivations. The panel recommends acyclovir prophylaxis against VZV from the 1st to 12th month after allogeneic HSCT in patients seropositive for VZV pretransplant and recommends considering extending prophylaxis in patients who continue to receive systemic immunosuppressive therapy. Agents used as HSV prophylaxis are also active against VZV (see FEV-C).

Among autologous HSCT recipients, the highest risk period for HSV reactivation is during neutropenia following conditioning, whereas the risk of VZV reactivation encompasses the first year.[316] T-cell depleting agents (e.g., alemtuzumab, fludarabine, calcineurin inhibitors) also increase the risk of HSV and VZV reactivation. Bortezomib, a proteosomal inhibitor, is associated with an increased risk of VZV reactivation.[317-321] Prophylaxis with acyclovir, valacyclovir, or famciclovir should be protective and can be considered in these settings. Among alemtuzumab recipients, antiviral prophylaxis is recommended by the

FDA until 2 months after the drug is stopped or until the CD4 count is 200/mcL or more, whichever occurs later.

Cytomegalovirus

In allogeneic HSCT recipients at risk for CMV reactivation, the following preventative approaches have been evaluated:[322] 1) prophylaxis: antiviral agents are administered to all allogeneic HSCT recipients if either the donor or recipient is CMV seropositive; and 2) pre-emptive therapy: initiation of antiviral agents after detection of asymptomatic CMV infection by active surveillance. Antiviral agents potently active against CMV have substantial toxicity with long-term use. Ganciclovir is associated with marrow suppression that may increase the risk of common and opportunistic infections. Foscarnet can cause nephrotoxicity but is generally well tolerated. Cidofovir (a second-line anti-CMV agent) can be associated with substantial nephrotoxicity. Acyclovir and valacyclovir have an excellent safety profile but are only weakly active against CMV.

In 2 randomized studies, prophylaxis with acyclovir was associated with increased survival in allogeneic HSCT recipients, but the rates of CMV reactivation and disease were fairly high.[323,324] Ljungman and colleagues[325] compared oral valacyclovir (a valine esterified analogue of acyclovir with high oral bioavailability) with acyclovir as prophylaxis in allogeneic HSCT recipients in whom either the donor or recipient was CMV seropositive. All patients received initial IV acyclovir until day 28 after transplantation or until discharge, and then either oral valacyclovir or acyclovir until week 18 after transplantation. Valacyclovir was more effective than acyclovir in preventing CMV reactivation (28% versus 40%, respectively); no difference was observed in CMV disease, adverse events, or overall survival. Thus, acyclovir and valacyclovir are acceptable agents for CMV prophylaxis, but surveillance and pre-emptive therapy with ganciclovir or foscarnet are still necessary.

Highly sensitive methods for early CMV diagnosis include detection of the CMV pp65 antigen from peripheral blood leukocytes and of CMV DNA by PCR. Triggers for pre-emptive antiviral therapy are either a single positive CMV antigenemia or 2 consecutive positive PCR results. Foscarnet and ganciclovir had similar efficacy as pre-emptive CMV therapies in allogeneic HSCT recipients, but ganciclovir was associated with significantly more premature discontinuation because of either neutropenia or thrombocytopenia.[326] Oral valganciclovir used as pre-emptive anti-CMV therapy was shown to have acceptable oral bioavailability (including, in patients with grades I and II GI GVHD); was safe and effective in controlling CMV reactivation.[327-331] Thus, valganciclovir is a highly acceptable oral option for pre-emptive therapy for CMV in the absence of substantial GI GVHD. A randomized study showed that maribavir was effective as prophylaxis against CMV in allogeneic HSCT recipients.[332]

Late CMV disease, defined as occurring after day 100 of HSCT, remains a persistent problem in the era of CMV prophylaxis and pre-emptive therapy. In one series, 92% of patients with late CMV pneumonia had chronic GVHD or had received T cell–depleted transplants.[333] T-cell reconstitution results—at 3 months after allogeneic HSCT—appear to be useful in risk stratification for late CMV disease. At 3 months after HSCT, CD4 T-cell counts less than 50/mcL, total lymphocyte counts less than 100/mcL, undetectable CMV-specific T-cell responses, and GVHD were associated with late CMV disease or death in CMV-seropositive allogeneic HSCT recipients.[334] A CD4+ count less than 100/mcL predicted delayed recovery of CMV-specific immunity at 3 months after allogeneic HSCT.[335] In a case-control study, CMV disease was significantly delayed in nonmyeloablative compared with standard ablative allogeneic transplantation (median time, 132 versus 52 days, respectively); the overall 1-year incidence was similar between the 2 groups.[336] Tetramer technology allows quantification of CMV antigen-specific CD4+ and CD8+ cells as a marker for reconstitution of CMV-specific cellular immunity; it may more precisely stratify the risk for CMV disease and need for CMV surveillance.[337]

Based on the available data that predict risk of CMV disease, the NCCN panel recommends CMV surveillance for at least 6 months after allogeneic HSCT. Additional surveillance should be strongly considered during chronic GVHD requiring immunosuppressive therapy and until the CD4+ count is 100/mcL or more. Note that the CD4 count will be reduced by systemic corticosteroids and by lymphocyte-depleting agents. The majority of cases of late CMV disease occur within the first year of transplant and less than 5% occur after the second year.[333,334] Therefore, the value of CMV surveillance beyond 2 years after HSCT is unknown but can be considered in patients with significant chronic GVHD.

CMV reactivation is common among alemtuzumab recipients and occurs most frequently between 3 to 6 weeks after initiation of therapy when T-cell counts reach a nadir. The NCCN panel recommends surveillance for CMV reactivation using PCR or antigen-based methods and monitoring at least weekly. The panel recommends pre-emptive therapy with ganciclovir, foscarnet, or valganciclovir in alemtuzumab recipients from the time of initiation until at least 2 months after completion of alemtuzumab therapy and until the CD4 count is 100/mcL or more, whichever occurs later (see INF-6).

Hepatitis B Virus

Reactivation of latent hepatitis B virus (HBV) may occur in the setting of significant immunosuppression (e.g., HSCT). HBV carriers with lymphoid malignancies, especially those treated with anthracycline-based regimens, have a high risk of HBV reactivation.[338] Rare cases of liver failure and death associated with HBV reactivation have occurred in patients receiving rituximab-containing regimens (http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm166521.htm).

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

A positive hepatitis B surface antigen (HBsAg) is associated with active infection (or a window period before the development of protective immunity). False-negative HBsAg results may occur in chronic liver disease.[339] A positive hepatitis B surface antibody (HBsAb) is generally equated with protective immunity, although reactivated HBV disease may occur in the setting of significant immunosuppression in HBsAb-positive individuals.[340]

In patients undergoing intensive immunosuppressive therapy, evaluation of HBV surface antigen, core antibody, and surface antibody should be considered at baseline.[341] Evaluation of HBV and hepatitis C virus infection should be routine in HSCT recipients and donors.[341,342] In HBsAg-positive individuals, baseline quantitative PCR for HBV DNA should be obtained. Based on limited data, antiviral therapy (e.g., lamivudine) should be strongly considered in patients with active HBV infection undergoing HSCT or other intensive immunosuppression.[338,343,344] Tenofovir is the preferred agent for chronic HBV infection, but limited data are available regarding use in oncologic populations.[345] Adefovir and entecavir also have activity against hepatitis B.[346] Donors who have not been exposed to HBV should be considered for HBV vaccination before stem cell collection when the recipient is HBsAg-positive.

Vaccination

Both the CDC and the European Bone Marrow Transplant group have published guidelines on vaccination of HSCT recipients.[16,347] The ACIP has published general recommendations on immunization that include immunocompromised patients.[348] We discuss general principles regarding vaccination in patients with cancer, with a focus on influenza.

Live attenuated viral vaccines have the potential to cause disease in immunocompromised patients. Vaccines that are not live attenuated organisms can be safely administered to the immunocompromised. However, the immunogenicity of the vaccines may be attenuated in immunocompromised patients. The potential for protection conferred by antigen-derived vaccines, even if incomplete, is better than no protection if the vaccine is withheld. Persons receiving chemotherapy or radiation therapy for malignancies should not receive live attenuated vaccines for at least 3 months after therapy has been stopped and the patient is presumed to be immunocompetent.[348] Certain live viral vaccines can be safely administered to household members of severely immunocompromised patients (e.g., measles, mumps, and rubella [MMR]), whereas others can not (e.g., small pox vaccine) because of the potential risk of transmission. The package insert for the vaccine should be reviewed before administration.

Ideally, patients should be vaccinated at least 2 weeks before receiving cytotoxic or immunosuppressive therapy; however, this timing is often not feasible in patients with cancer. Administering vaccines on the same day as cytotoxic therapy is not advised, because proliferative lymphocytic responses are required for protective immunity. Immunization between cytotoxic chemotherapy courses is likely to be associated with higher response rates than during chemotherapy administration.[349,350] Patients should be considered unprotected if they were vaccinated less than 2 weeks before starting cytotoxic or immunosuppressive therapy or while receiving these agents. These patients should be revaccinated at least 3 months after therapy is discontinued if immune competence has been restored.[348] Pneumococcal, meningococcal, and Hib vaccines should be administered at least 2 weeks before elective splenectomy.[348]

Influenza infections cause significant morbidity and mortality in cancer patients. Among bone marrow transplant recipients, influenza accounts for 11% to 42% of all community-acquired viral respiratory infections.[351-353] An increased incidence and duration of influenza infections have also been observed in immunosuppressed cancer patients when compared to healthy controls.[354,355] During community outbreaks, influenza infections may represent a significant proportion of episodes of febrile neutropenia.[356] Influenza infections in severely immunocompromised cancer patients are often associated with hospitalizations, delays in potentially life-saving chemotherapy, and occasionally, death.[354-356] As a result, annual vaccination against influenza with the inactivated influenza virus is currently recommended for all individuals at increased risk from immunosuppressive disease in several countries, including the United States, Canada, and United Kingdom.[357-359] The United States and Canadian guidelines also include health care workers and household contacts in their target group for annual immunization, because they can transmit influenza to high-risk patients.[357,358]

The intranasal attenuated influenza vaccine (FluMist) should be avoided in patients with immunosuppression, because FluMist contains live attenuated influenza viruses still capable of replication, which could theoretically lead to infection in immunocompromised individuals.[360] As a result, the CDC recommends that persons with known or suspected immunodeficiency diseases or those who are receiving immunosuppressive therapies should not be immunized with the live influenza vaccine.[360] In addition, because no data are available assessing the risk for person-to-person transmission of FluMist from vaccine recipients to immunosuppressed contacts, the CDC also recommends that inactivated influenza vaccine should be used in household contacts, health-care workers, and others who have close contact with immunocompromised patients.[360]

Prophylaxis for *Pneumocystis jirovecii* (formerly *Pneumocystis carinii*)

Trimethoprim/sulfamethoxazole prophylaxis for *P.jirovecii* is highly effective.[361] Studies have documented the efficacy of this prophylactic therapy in patients with acute lymphocytic leukemia, and similar results have been found in bone marrow transplant recipients. TMP/SMX also has the potential advantage of protecting against other infectious complications (such as common bacterial infections, listeriosis, nocardiosis, and toxoplasmosis) that afflict patients with severe T-cell impairment. The more difficult questions include: (1) What prophylactic regimen should be used in patients who are truly intolerant of TMP/SMX? and (2) Besides acute leukemia patients, which other patients warrant *P.jirovecii* prophylaxis? TMP/SMX is preferred; TMP/SMX desensitization can be considered in patients who are intolerant to TMP/SMX. Daily dapsone and aerosolized pentamidine are thought to be effective alternatives to TMP/SMX, although data suggest aerosolized pentamidine may be inferior when used prophylactically in allogeneic transplant recipients.[362] Atovaquone appears to be equivalent to dapsone in HIV patients who cannot tolerate TMP/SMX. Thus, atovaquone is another alternative for oncology patients who require prophylaxis.[363]

Prophylaxis against PCP should be used in allogeneic transplant recipients, alemtuzumab recipients (http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/103948s5070lbl.pdf), and patients with acute lymphocytic leukemia (category 1). Prophylaxis against PCP is also advised in patients receiving concomitant temozolomide and radiotherapy and should be continued until recovery from lymphocytopenia (see Warnings) (http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021029s012lbl.pdf).[16] Some panel members advise prophylaxis against PCP (category 2B) for the following patients: 1) patients receiving fludarabine therapy and other T-cell depleting agents (e.g., cladribine [2-CdA]); 2) autologous hematopoietic cell transplant recipients; and 3) patients with neoplastic diseases receiving intensive corticosteroid treatment (e.g., the equivalent of 20 mg or more of prednisone daily for 4 weeks or more).[364]

Protected Environments

Although well-designed clinical trials have not validated the use of high-efficiency particulate air (HEPA) filtration, the CDC recommends that allogeneic HSCT recipients be placed in rooms with HEPA filters.[16] It is also reasonable to use HEPA filtration in nontransplant patients with prolonged neutropenia. The principal benefit of HEPA filtration is likely to be related to prevention of mold infections. In a retrospective analysis, HEPA filters were protective in highly immunocompromised patients with hematologic malignancies in the setting of an outbreak of aspergillosis.[365] The value of laminar air flow in preventing infections is unclear and is not generally recommended.

Summary

Previous NCCN guidelines related to infectious complications of cancer were primarily focused on F&N. However, the guidelines were revised in 2007 to address prevention and treatment of infections in both neutropenic and non-neutropenic immunocompromised patients with cancer. The current NCCN guidelines on “Prevention and Treatment of Cancer-Related Infections,” replace the previous “Fever and Neutropenia” guidelines.

Substantial progress has been made in preventing and treating infectious complications of neutropenia and immunosuppressive therapy in patients with cancer. It is essential to know the patient’s quantitative and qualitative immune defects and to stratify the risk for specific pathogens in the context of the history, physical examination, radiologic, and laboratory data. The development of antipseudomonal beta-lactam agents and the routine use of empiric antibacterial therapy at the onset of neutropenic fever reduced mortality from bacterial infections.[366] More patients were treated with potent cytotoxic regimens (e.g., for acute leukemia) and received allogeneic stem cell transplants; opportunistic viral and fungal infections became an important cause of mortality in these patients. In addition, the increasing prevalence of antibiotic-resistant pathogens has challenged the clinician to use antimicrobial therapy wisely. Infection control should not rely exclusively on antimicrobial prophylaxis but, rather, should continue to incorporate standard infection control measures and demand careful hand-washing by all health care professionals who come into contact with immunocompromised patients.

References

1. Pizzo PA. Management of fever in patients with cancer and treatment-induced neutropenia. N Engl J Med 1993;328:1323-1332.

2. Schimpff SC. Empiric antibiotic therapy for granulocytopenic cancer patients. Am J Med 1986;80[suppl 5c]:13-20.

3. Hughes WT, Armstrong D, Bodey GP, et al. 2002 Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis 2002;34:730-751.

4. Freifeld AG, Walsh T, Marshall D, et al. Monotherapy for fever and neutropenia in cancer patients: A randomized comparison of ceftazidime vs imipenem. J Clin Oncol 1995;13:165-176.

5. Kern WV, Cometta A, De Bock R, et al. Oral versus intravenous empirical antimicrobial therapy for fever in patients with granulocytopenia who are receiving cancer chemotherapy: International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer. N Engl J Med 1999;341:312-318.

6. Rolston KV, Rubenstein EB, Freifeld A. Early empiric antibiotic therapy for febrile neutropenia patients at low risk. Infect Dis Clin North Am 1996;10(2):223-237.

7. Malik IA, Abbas Z, Karim M. Randomised comparison of oral ofloxacin alone with combination of parenteral antibiotics in neutropenic febrile patients. Lancet 1992;339:1092-1096.

8. Hidalgo M, Hornedo J, Lumbreras C. Outpatient therapy with oral ofloxacin for patients with low risk neutropenia and fever, a prospective randomized clinical trial. Cancer 1999;85:213-219.

9. Aquino VM, Herrera L, Sandler ES, et al. Feasibility of oral ciprofloxacin for the outpatient management of febrile neutropenia in selected children with cancer. Cancer 2000;88:1710-1714.

10. Talcott JA, Whalen A, Clark J, et al. Home antibiotic therapy for low-risk cancer patients with fever and neutropenia: A pilot study of 30 patients, based on a validated prediction rule. J Clin Oncol 1994;12:107-114.

11. Talcott J, Siegel R, Finberg R, et al. Risk assessment in cancer patients with fever and neutropenia: A prospective, two-center validation of a prediction rule. J Clin Oncol 1992;10:316-322.

12. Talcott J, Finberg R, Mayer RJ, et al. The medical course of cancer patients with fever and neutropenia. Arch Intern Med 1988;148:2561-2568.

13. Rolston KV. Outpatient management of febrile, neutropenic patients. Infections in Medicine 1995;12:5.

14. Mihu CN, Schaub J, Kesh S, et al. Risk factors for late Staphylococcus aureus bacteremia after allogeneic hematopoietic stem cell transplantation: a single-institution, nested case-controlled study. Biol Blood Marrow Transplant 2008;14(12):1429-1433.

15. Rizzo JD, Wingard JR, Tichelli A, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation: joint recommendations of the European Group for Blood and Marrow Transplantation, the Center for International Blood and Marrow Transplant Research, and the American Society of Blood and Marrow Transplantation. Biol Blood Marrow Transplant 2006;12(2):138-151.

16. Sullivan KM, Dykewicz CA, Longworth DL, et al. Preventing opportunistic infections after hematopoietic stem cell transplantation: the Centers for Disease Control and Prevention, Infectious Diseases Society of America, and American Society for Blood and Marrow Transplantation Practice Guidelines and beyond. Hematology (Am Soc Hematol Educ Program) 2001:392-421.

17. Neofytos D, Horn D, Anaissie E, et al. Epidemiology and outcome of invasive fungal infection in adult hematopoietic stem cell transplant recipients: analysis of Multicenter Prospective Antifungal Therapy (PATH) Alliance registry. Clin Infect Dis 2009;48(3):265-273.

18. Griffiths H, Lea J, Bunch C, et al. Predictors of infection in chronic lymphocytic leukaemia (CLL). Clin Exp Immunol 1992;89:374-377.

19. Savage DG, Lindenbaum J, Garrett TJ. Biphasic pattern of bacterial infection in multiple myeloma. Ann Intern Med 1982;96:47-50.

20. DiNubile MJ. Fever and neutropenia: still a challenge. Contemp Intern Med 1995;7(1):35-37, 41-45.

21. Gerson SL, Talbot GH, Hurwitz S, et al. Prolonged granulocytopenia: the major risk factor for invasive pulmonary aspergillosis in patients with acute leukemia. Ann Intern Med 1984;100:345-351.

22. Wade JC. Management of infection in patients with acute leukemia. Hematol Oncol Clin North Am 1993;7:293-315.

23. Bodey GP, Buckley M, Sathe YS, et al. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med 1966;64:328-340.

24. Gonzalez-Barca E, Fernandez-Sevilla A, Carratala J, et al. Prospective study of 288 episodes of bacteremia in neutropenic cancer patients in a single institution. Eur J Clin Microbiol Infect Dis 1996;15:291-296.

25. Engelhard D, Elishoov H, Or R, et al. Cytosine arabinoside as a major risk factor for Streptococcus viridans septicemia following bone marrow transplantation: a 5-year prospective study. Bone Marrow Transplant 1995;16:565-570.

26. Bochud PY, Calandra T, Francioli P. Bacteremia due to viridans streptococci in neutropenic patients: a review. Am J Med 1994;97:256-264.

27. Rossetti F, Cesaro S, Putti MC, Zanesco L. High-dose cytosine arabinoside and viridans streptococcus sepsis in children with leukemia. Pediatr Hematol Oncol 1995;12:387-392.

28. Bow EJ, Loewen R, Cheang MS, et al. Cytotoxic therapy-induced D-xylose malabsorption and invasive infection during remission-induction therapy for acute myeloid leukemia in adults. J Clin Oncol 1997;15:2254-2261.

29. Kalhs P, Kier P, Lechner K. Functional asplenia after bone marrow transplantation [letter]. Ann Intern Med 1990;113:805-806.

30. Anaissie E, Kontoyiannis DP, Kantarjian H, et al. Listeriosis in patients with chronic lymphocytic leukemia who were treated with fludarabine and prednisone. Ann Intern Med 1992;117:466-469.

31. O'Brien S, Kantarjian H, Beran M, et al. Results of fludarabine and prednisone therapy in 264 patients with chronic lymphocytic leukemia with multivariate analysis-derived prognostic model for response to treatment [see comments]. Blood 1993;82:1695-1700.

32. Morrison VA, Rai KR, Peterson BL, et al. Impact of therapy With chlorambucil, fludarabine, or fludarabine plus chlorambucil on infections in patients with chronic lymphocytic leukemia: Intergroup Study Cancer and Leukemia Group B 9011. J Clin Oncol 2001;19(16):3611-3621.

33. Keating MJ, O'Brien S, Kontoyiannis D, et al. Results of first salvage therapy for patients refractory to a fludarabine regimen in chronic lymphocytic leukemia. Leuk Lymphoma 2002;43:1755-1762.

34. Buhles WC Jr, Mastre BJ, Tinker AJ, et al. Ganciclovir treatment of life- or sight-threatening cytomegalovirus infection: experience in 314 immunocompromised patients. Rev Infect Dis 1988 Jul-Aug;10 Suppl 3:S495-506.

35. Sandherr M, Einsele H, Hebart H, et al; Infectious Diseases Working Party, German Society for Hematology and Oncology. Antiviral prophylaxis in patients with haematological malignancies and solid tumours: Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Oncology (DGHO). Ann Oncol 2006;17(7):1051-1059. Epub 2006 Jan 12.

36. Crippa F, Holmberg L, Carter RA, et al. Infectious complications after autologous CD34-selected peripheral blood stem cell transplantation. Biol Blood Marrow Transplant 2002;8:281-289.

37. Winston DJ, Schiffman G, Wang DC, et al. Pneumococcal infections after human bone-marrow transplantation. Ann Intern Med 1979;91:835-841.

38. Kulkarni S, Powles R, Treleaven J, et al. Chronic graft versus host disease is associated with long-term risk fro pneumococcal infections in recipients of bone marrow transplants. Blood 2000;95:3683-3686.

39. Meijer E, Dekker AW, Rozenberg-Arska M, et al. Influence of cytomegalovirus seropositivity on outcome after T cell-depleted bone marrow transplantation: contrasting results between recipients of grafts from related and unrelated donors. Clin Infect Dis 2002;35:703-712.

40. Marr KA, Carter RA, Boeckh M, et al. Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors. Blood 2002;100:4358-4366.

41. Donawitz GR, Harman C, Pope T. The role of the chest roentgenogram in febrile neutropenic patients. Arch Intern Med 1991;151:701-704.

42. Gaur AH, Flynn PM, Giannini MA, et al. Difference in time to detection: a simple method to differentiate catheter-related from non-catheter-related bloodstream infection in immunocompromised pediatric patients. Clin Infect Dis 2003;37:469-475.

43. Siegman-Igra Y, Anglim AM, Shapiro DE, et al. Diagnosis of vascular catheter-related bloodstream infection: A meta-analysis. J Clin Microbiol 1997;35:928-936.

44. Guerrant RL, Van Gilder T, Steiner TS, et al. Practice guidelines for the management of infectious diarrhea. Clin Infect Dis 2001;32(3):331-351. Epub 2001 Jan 30.

45. Englund JA, Sullivan CJ, Jordan MC, et al. Respiratory syncytial virus infection in immunocompromised adults. Ann Intern Med 1988;109:203-208.

46. Harrington RD, Hooton TM, Hackman RC, et al. An outbreak of respiratory syncytial virus in a bone marrow transplant center. J Infect Dis 1992;165:987-993.

47. Oblon D, Ramphal R. A randomized trial of cefepime vs ceftazidime as initial therapy for patients with prolonged fever and neutropenia after intensive chemotherapy (abstract). Proc Ann Mtg Am Assoc Cancer Res 1993;34:A1362.

48. De Pauw BE, Deresinski SC, Feld R, et al. Ceftazidime compared with piperacillin and tobramycin for the empiric treatment of fever in neutropenic patients with cancer: A multicenter randomized trial. Ann Intern Med 1994;120:834-844.

49. Cometta A, Calandra T, Gaya H, et al. Monotherapy with meropenem vs combination therapy with ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. Antimicrob Agents Chemother 1996;40:1108-1115.

50. Bow EJ, Rotstein C, Noskin GA, et al. A randomized, open-label, multicenter comparative study of the efficacy and safety of piperacillin-tazobactam and cefepime for the empirical treatment of febrile neutropenic episodes in patients with hematologic malignancies. Clin Infect Dis 2006;43:447-459.

51. Yahav D, Paul M, Fraser A, et al. Efficacy and safety of cefepime: a systematic review and meta-analysis. Lancet Infect Dis 2007;7(5):338-348.

52. Paul M, Yahav D, Fraser A, et al. Empirical antibiotic monotherapy for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother 2006;57(2):176-189. Epub 2005 Dec 12.

53. Flaherty JP, Waitley D. Multicenter randomized trial of ciprofloxacin plus azlocillin vs ceftazidime plus amikacin for empiric treatment of febrile neutropenic patients. Am J Med 1989;87[suppl 5A]:278S-282S.

54. Cometta A, Zinner S, de Bock R, et al. Piperacillin\tazobactam plus amikacin vs ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer: The International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer. Antimicrob Agents Chemother 1995;39:445-452.

55. Cordonnier C, Herbrecht R, Pico JL, et al. Cefepime/amikacin vs ceftazidime/amikacin as empirical therapy for febrile episodes in neutropenic patients: a comparative study. Clin Infect Dis 1997;24:41-51.

56. Rybak MJ, Abate BJ, Kang SL, et al. Prospective evaluation of the effect of an aminoglycoside dosing regimen on rates of observed nephrotoxicity and ototoxicity. Antimicrob Agents Chemother 1999;43:1549-1555.

57. European Organization for Research and Treatment of Cancer (EORTC), International Antimicrobial Therapy Cooperative Group, and the National Cancer Institute of Canada - Clinical Trails Group: Vancomycin added to empirical combination antibiotic therapy for fever in granulocytopenic cancer patients. J Infect Dis 1991;163:951-958.

58. Shenep JL, Hughes WT, Roberson PK, et al. Vancomycin, ticarcillin, and amikacin compared with ticarcillin-clavulanate and amikacin in the empirical treatment of febrile, neutropenic children with cancer. N Engl J Med 1988;319:1053-1058.

59. Granowetter L, Wells H, Lange BJ. Ceftazidime with or without vancomycin vs. cephalothin, carbenicillin and gentamicin as the initial therapy of the febrile neutropenic pediatric cancer patient. Pediatr Infect Dis J 1988;7:165-170.

60. Brown AE, Kiehn TE, Armstrong D. Bacterial resistance in the patient with neoplastic disease. Infect Dis Clin Pract 1995;4[suppl 3]:S136-144.

61. Centers for Disease Control and Prevention. Staphylococcus aureus resistant to vancomycin - United States, 2002. MMWR 2002;51:565-567.

62. Sievert DM, Rudrik JT, Patel JB, et al. Vancomycin-resistant Staphylococcus aureus in the United States, 2002-2006. Clin Infect Dis 2008;46(5):668-674.

63. Finks J, Wells E, Dyke TL, Husain N, Plizga L, Heddurshetti R, et al. Vancomycin-resistant Staphylococcus aureus, Michigan, USA, 2007. Emerg Infect Dis [serial on the Internet]. 2009 Jun [date cited]. Available from http://www.cdc.gov/EID/content/15/6/943.htm

64. Siegel JD, Rhinehart E, Jackson M, Chiarello L; Healthcare Infection Control Practices Advisory Committee. Management of multidrug-resistant organisms in health care settings, 2006. Atlanta: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2006. Available from http://www.cdc.gov/ncidod/dhqp/pdf/ar/mdroguideline2006.pdf

65. Siegel JD, Rhinehart E, Jackson M, Chiarello L; Healthcare Infection Control Practices Advisory Committee. 2007 guideline for isolation precautions: preventing transmission of infectious agents in healthcare settings. Atlanta: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2007 [cited 2008 Sep 16]. Available from http://www.cdc.gov/ncidod/dhqp/pdf/guidelines/Isolation2007.pdf

66. Wade JC, Schimpff SC, Newman KA, et al. Staphylococcus epidermidis: An increasing but frequently unrecognized cause of infection in granulocytopenic patients. Ann Intern Med 1982;97:503-508.

67. Mermel LA, Allon M, Bouza E, et al. Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis 2009 Jun 2. [Epub ahead of print]

68. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Med 2008;34(1):17-60. Epub 2007 Dec 4.

69. Kaul DR, Collins CD, Hyzy RC. New developments in antimicrobial use in sepsis. Curr Pharm Des 2008;14(19):1912-1920.

70. Daum RS. Clinical practice. Skin and soft-tissue infections caused by methicillin-resistant Staphylococcus aureus. N Engl J Med 2007;357(4):380-390.

71. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm 2009;66(1):82-98.

72. International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer: Reduction of fever and streptococcal bacteremia in granulocytopenic patients with cancer: A trial of oral penicillin V or placebo combined with pefloxacin. JAMA 1994;272:1183-1189.

73. Arning M, Wolf HH, Aul C, et al. Infection prophylaxis in neutropenic patients with acute leukemia–a randomized, comparative study with ofloxacin, ciprofloxacin and cotrimoxazole/colistin. J Antimicrob Chemother 1990;26[suppl D]:137-142.

74. Elting LS, Bodey GP, Keefe BH. Septicemia and shock syndrome due to viridans streptococci: a case-control study of predisposing factors. Clin Infect Dis 1992;14:1201-1207.

75. Kerr KG, Armitage HT, McWhinney PH. Activity of quinolones against viridans group streptococci isolated from blood cultures of patients with haematological malignancy. Support Care Cancer 1999;7:28-30.

76. McWhinney PH, Patel S, Whiley RA, et al. Activities of potential therapeutic and prophylactic antibiotics against blood culture isolates of viridans group streptococci from neutropenic patients receiving ciprofloxacin. Antimicrob Agents Chemother 1993;37(11):2493-2495.

77. Tunkell AR, Sepkowitz KA. Infections caused by viridans streptococci in patients with neutropenia. Clin Infect Dis 2002;34:1524-1529.

78. Cometta A, Kern WV, De Bock R, et al. Vancomycin versus placebo for treating persistent fever in patients with neutropenic cancer receiving piperacillin-tazobactam monotherapy. Clin Infect Dis 2003;37:382-389.

79. Viscoli C, Cometta A, Kern WV, et al. Piperacillin-tazobactam monotherapy in high-risk febrile and neutropenic cancer patients. Clin Microbiol Infect 2006;12:212-216.

80. Erjavec Z, de Vries-Hospers HG, Laseur M, et al. A prospective, randomized, double-blinded, placebo-controlled trial of empirical teicoplanin in febrile neutropenia with persistent fever after imipenem monotherapy. J Antimicrob Chemother 2000;45:843-849.

81. Moellering RC. Linezolid: the first oxazolidinone antimicrobial. Ann Intern Med 2003;138:135-142.

82. Linden PK, Moellering RC Jr, Wood CA, et al. Synercid Emergency-Use Study Group. Treatment of vancomycin-resistant Enterococcus faecium infections with quinupristin/dalfopristin. Clin Infect Dis 2001;33:1816-1823.

83. Mave V, Garcia-Diaz J, Islam T, Hasbun R. Vancomycin-resistant enterococcal bacteraemia: is daptomycin as effective as linezolid? J Antimicrob Chemother. 2009 May 7. [Epub ahead of print]

84. Moise PA, Forrest A, Birmingham MC, Schentag JJ. The efficacy and safety of linezolid as treatment for Staphylococcus aureus infections in compassionate use patients who are intolerant of, or who have failed to respond to, vancomycin. J Antimicrob Chemother 2002;50(6):1017-1026.

85. Shorr AF, Kunkel MJ, Kollef M. Linezolid versus vancomycin for Staphylococcus aureus bacteraemia: pooled analysis of randomized studies. J Antimicrob Chemother 2005;56(5):923-929. Epub 2005 Sep 29.

86. Smith PF, Birmingham MC, Noskin GA, et al. Safety, efficacy and pharmacokinetics of linezolid for treatment of resistant Gram-positive infections in cancer patients with neutropenia. Ann Oncol 2003;14:795-801.

87. Jaksic B, Martinelli G, Perez-Oteyza J, et al. Efficacy and safety of linezolid compared with vancomycin in a randomized, double-blind

study of febrile neutropenic patients with cancer. Clin Infect Dis 2006;42:597-607.

88. Wunderink RG, Rello J, Cammarata SK, et al. Linezolid vs vancomycin: analysis of two double-blind studies of patients with methicillin-resistant Staphylococcus aureus nosocomial pneumonia. Chest 2003;124(5):1789-1797.

89. Powers JH, Ross DB, Lin D, Soreth J. Linezolid and vancomycin for methicillin-resistant Staphylococcus aureus nosocomial pneumonia: the subtleties of subgroup analyses. Chest 2004;126(1):314-315; author reply 315-316.

90. Wunderink RG, Mendelson MH, Somero MS, et al. Early microbiological response to linezolid vs vancomycin in ventilator-associated pneumonia due to methicillin-resistant Staphylococcus aureus. Chest 2008;134(6):1200-1207. Epub 2008 Aug 21.

91. Silverman JA, Mortin LI, Vanpraagh AD, et al. Inhibition of daptomycin by pulmonary surfactant: in vitro modeling and clinical impact. J Infect Dis 2005;191(12):2149-2152. Epub 2005 May 5.

92. Jones T, Yeaman MR, Sakoulas G, et al. Failures in clinical treatment of Staphylococcus aureus Infection with daptomycin are associated with alterations in surface charge, membrane phospholipid asymmetry, and drug binding. Antimicrob Agents Chemother 2008;52(1):269-278. Epub 2007 Oct 22.

93. Abbanat D, Macielag M, Bush K. Novel antibacterial agents for the treatment of serious Gram-positive infections. Expert Opin Investig Drugs 2003;12:379-399.

94. Bozdogan B, Esel D, Whitener C, et al. Antibacterial susceptibility of a vancomycin-resistant Staphylococcus aureus strain isolated at the Hershey Medical Center. J Antimicrob Chemother 2003;52:864-868.

95. Fowler VG, Jr., Boucher HW, Corey GR, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by Staphylococcus aureus. N Engl J Med 2006;355:653-665.

96. Raad II, Hachem R, Hanna H, et al. Prospective, randomized study comparing quinupristin-dalfoprisitin with linezolid in the treatment of vancomycin-resistant Enterococcus faecium infections. J Antimicrob Chemother 2004;53:646-649.

97. Poutsiaka DD, Skiffington S, Miller KB, et al. Daptomycin in the treatment of vancomycin-resistant Enterococcus faecium bacteremia in neutropenic patients. J Infect 2007;54(6):567-571. Epub 2006 Dec 26.

98. Chemaly RF, Hanmod SS, Jiang Y, et al. Tigecycline use in cancer patients with serious infections: a report on 110 cases from a single institution. Medicine (Baltimore) 2009;88(4):211-220.

99. Finfer S. Corticosteroids in septic shock. N Engl J Med 2008;358:188-190.

100. Groeneveld AB, Molenaar N, Beishuizen B. Should we abandon corticosteroids during septic shock? No. Curr Opin Crit Care 2008;14(4):384-389.

101. Bauer W, Ball J, Grounds M. Unanswered questions from Corticus and pragmatic suggestions. Crit Care 2008;12(4):426; discussion 426. Epub 2008 Aug 14.

102. Sprung CL, Annane D, Keh D, et al; the CORTICUS Study Group, Hydrocortisone therapy for patients with septic shock. N Engl J Med 2008;358:111-124.

103. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002;288:862-871.

104. Bollaert PE, Charpentier C, Levy B, et al. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. Crit Care Med 1998;26:645-650.

105. Briegel J, Forst H, Haller M, et al. Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, single-center study. Crit Care Med 1999;27:723-732.

106. Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. N Engl J Med 2003;348:727-734.

107. Slotman GJ, Fisher CJ Jr, Bone RC, et al. Detrimental effects of high-dose methylprednisolone sodium succinate on serum concentrations of hepatic and renal function indicators in severe sepsis and septic shock. The Methylprednisolone Severe Sepsis Study Group. Crit Care Med 1993;21(2):191-195.

108. Cronin L, Cook DJ, Carlet J, et al. Corticosteroid treatment for sepsis: a critical appraisal and meta-analysis of the literature. Crit Care Med 1995;23(8):1430-1439.

109. Abraham E, Laterre PF, Garg R, et al; Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) Study Group. Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. N Engl J Med 2005;353(13):1332-1341.

110. Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001;344:699-709.

111. Nadel S, Goldstein B, Williams MD, et al; REsearching severe Sepsis and Organ dysfunction in children: a gLobal perspective (RESOLVE) study group. Drotrecogin alfa (activated) in children with severe sepsis: a multicentre phase III randomised controlled trial. Lancet 2007;369(9564):836-843.

112. Elting LS, Rubenstein EB, Rolston KV, et al. Outcomes of bacteremia in neutropenic cancer patients: observations from two decades of epidemiologic and clinical trials. Clin Infect Dis 1997;25:247-259.

113. Freifeld A, Marchigiani D, Walsh T, et al. A double-blind comparison of empirical oral and intravenous antibiotic therapy for low-risk febrile patients with neutropenia during cancer chemotherapy. N Engl J Med 1999;341:305-311.

114. Rubenstein EB, Rolston K, Benjamin RS, et al. Outpatient treatment of febrile episodes in low-risk neutropenic patients with cancer. Cancer 1993;7:3640-3646.

115. Mullen CA, Petropoulos D, Roberts WM, et al. Outpatient treatment of fever and neutropenia for low risk pediatric cancer patients. Cancer 1999;86:126-134.

116. Malik IA, Kahn WA, Karim M, et al. Feasibility of outpatient management of fever in cancer patients with low-risk neutropenia: Results of a prospective randomized trial. Am J Med 1995;98:224-231.

117. Klastersky J. Supportive Care in Cancer. Abstracts of the 14th MASCC International Symposium 2001;10(4).

118. Mustafa MM, Aquino VM, Pappo A, et al. A pilot study of outpatient management of febrile neutropenic children with cancer at low risk of bacteremia. J Pediatr 1996;128:847-849.

119. Karthaus M, Wolf HH, Kampfe D, et al. Ceftriaxone monotherapy in the treatment of low-risk febrile neutropenia. Chemotherapy 1998;44:343-354.

120. Pizzo PA, Robichaud KJ, Gill FA, et al. Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. Am J Med 1982;72:101-111.

121. Michallet M, Ito JI. Approaches to the management of invasive fungal infections in hematologic malignancy and hematopoietic cell transplantation. J Clin Oncol 2009;27:3398-3409.

122. Staber P, Langner S, Dornbusch HJ, Neumeister P. Antifungal management in cancer patients. Wien Med Wochenschr 2007;157(19-20):503-510.

123. Bhatti Z, Shaukat A, Almyroudis NG, Segal BH. Review of epidemiology, diagnosis, and treatment of invasive mould infections in allogeneic hematopoietic stem cell transplant recipients. Mycopathologia 2006;162(1):1-15.

124. Wingard JR. Empirical antifungal therapy in treating febrile neutropenic patients. Clin Infect Dis 2004;39:S38-S43.

125. Marr KA, Seidel K, White TC, et al. Candidemia in allogeneic blood and marrow transplant recipients: evolution of risk factors after the adoption of prophylactic fluconazole. J Infect Dis 2000;181(1):309-316.

126. Walsh TJ, Finberg RW, Arndt C, et al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institute of Allergy and Infectious Diseases Mycoses Study Group. N Engl J Med 1999;340:764-771.

127. Ostrosky-Zeichner L, Marr KA, Rex JH, Cohen SH. Amphotericin B: time for a new "gold standard". Clin Infect Dis 2003;37:415-425. Epub 2003 Jul 22.

128. Bates DW, Su L, Yu DT, et al. Correlates of acute renal failure in patients receiving parenteral amphotericin B. Kidney Int 2001;60(4):1452-1459.

129. Bates DW, Su L, Yu DT, et al. Mortality and costs of acute renal failure associated with amphotericin B therapy. Clin Infect Dis. 2001;32(5):686-693. Epub 2001 Feb 21.

130. Wingard JR, Kubilis P, Lee L, et al. Clinical significance of nephrotoxicity in patients treated with amphotericin B for suspected or proven aspergillosis. Clin Infect Dis 1999;29(6):1402-1407.

131. Winston DJ, Hathorn JW, Schuster MG, et al. A multicenter, randomized trial of fluconazole versus amphotericin B for empiric antifungal therapy of febrile neutropenic patients with cancer. Am J Med 2000;108:282-289.

132. Viscoli C, Castagnola E, Van Lint MT, et al. Fluconazole versus amphotericin B as empirical antifungal therapy of unexplained fever in granulocytopenic cancer patients: a pragmatic, multicentre, prospective and randomised clinical trial. Eur J Cancer 1996;32A:814-820.

133. Boogaerts M, Winston DJ, Bow EJ, et al. Intravenous and oral itraconazole versus intravenous amphotericin B deoxycholate as empirical antifungal therapy for persistent fever in neutropenic patients with cancer who are receiving broad-spectrum antibacterial therapy. A randomized, controlled trial. Ann Intern Med 2001;135:412-422.

134. Segal BH. Aspergillosis. N Engl J Med 2009;360:1870-1884.

135. Walsh TJ, Pappas P, Winston DJ, et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. N Engl J Med 2002;346:225-234.

136. Walsh TJ, Teppler H, Donowitz GR, et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. N Engl J Med 2004;351(14):1391-1402.

137. Segal BH, Almyroudis NG, Battiwalla M, et al. Prevention and early treatment of invasive fungal infection in patients with cancer and neutropenia and in stem cell transplant recipients in the era of newer broad-spectrum antifungal agents and diagnostic adjuncts. Clin Infect Dis 2007;44(3):402-409. Epub 2007 Jan 2.

138. Marr KA, Laverdiere M, Gugel A, Leisenring W. Antifungal therapy decreases sensitivity of the Aspergillus galactomannan enzyme immunoassay. Clin Infect Dis 2005;40:1762-1769.

139. Foy PC, van Burik JA, Weisdorf DJ. Galactomannan antigen enzyme-linked immunosorbent assay for diagnosis of invasive aspergillosis after hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2007;13(4):440-443. Epub 2007 Feb 1.

140. Pfeiffer CD, Fine JP, Safdar N. Diagnosis of invasive aspergillosis using a galactomannan assay: a meta-analysis. Clin Infect Dis 2006;42:1417-1727.

141. Maertens J, Theunissen K, Verhoef G, et al. Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: a prospective feasibility study. Clin Infect Dis 2005;41:1242-1250.

142. Cordonnier C, Pautas C, Maury S, et al. Empirical versus preemptive antifungal therapy for high-risk, febrile, neutropenic patients: a randomized, controlled trial. Clin Infect Dis 2009;48(8):1042-1051.

143. Elting LS, Rubenstein EB, Rolston K, et al. Time to clinical response: An outcome of antibiotic therapy of febrile neutropenia with implications for quality and cost of care. J Clin Oncol 2000;18:3699-3706.

144. Serody JS, Berry MM, Albritton K, et al. Utility of obtaining blood cultures in febrile neutropenic patients undergoing bone marrow transplantation. Bone Marrow Transplant 2000;26:533-538.

145. Pizzo PA, Robichaud KJ, Gill FA, et al. Duration of empiric antibiotic therapy in granulocytopenic patients with cancer. Am J Med 1979;67:194-200.

146. Mugge A, Daniel WG, Frank G, et al. Echocardiography in infective endocarditis: Reassessment of the prognostic implications of vegetation size determined by transthoracic and transesophageal approach. J Am Coll Cardiol 1989;14:631-638.

147. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000;30:633-638.

148. Daniel WG, Mugge A, Martin RP, et al. Improvement in the diagnosis of abscesses associated with endocarditis by transesophageal echocardiography. N Engl J Med 1991;324:795-800.

149. Rosen AB, Fowler VG, Corey GR, et al. Cost-effectiveness of transesophageal echocardiography to determine duration of therapy for intravascular catheter associated Staphylococcus aureus bacteremia. Ann Intern Med 1999;130:810-820.

150. Baddour LM, Wilson WR, Bayer AS, et al. Infective Endocarditis: diagnosis, antimicrobial therapy, and management of complications: A Statement for Healthcare Professionals From the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: Endorsed by the Infectious Diseases Society of America. Circulation 2005;111:e394-e434e.

151. Wade JC, Newton B, McLaren C, et al. Intravenous acyclovir to treat mucocutaneous herpes simplex virus infection after marrow transplantation: A double-blind trial. Ann Intern Med 1982;96:265-269.

152. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006;24:3187-3205.

153. Heuser M, Ganser A, Bokemeyer C. Use of colony-stimulating factors for chemotherapy-associated neutropenia: review of current guidelines. Semin Hematol 2007;44(3):148-156.

154. Klastersky J, Paesmans M, Rubenstein EB, 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.

155. Rubenstein EB, Rolston KVI. Risk-adjusted management of the febrile neutropenic cancer patient. In: Rolston KVI, Rubenstein EB, eds. Textbook of Febrile Neutropenia. Martin Dunitz: London 2001:167-187.

156. Niho S, Ohe Y, Goto K, et al. Randomized trial of oral versus intravenous antibiotics in low-risk febrile neutropenic patients with lung cancer. Jpn J Clin Oncol 2004;34(2):69-73.

157. Uys A, Rapoport BL, Anderson R. Febrile neutropenia: A prospective study to validate the Multinational Association of Supportive Care of Cancer (MASCC) risk-index score. Support Care Cancer 2004;12:555-560.

158. Klastersky J, Paesmans M, Georgala A, et al. Outpatient oral antibiotics for febrile neutropenic cancer patients using a score predictive for complications. J Clin Oncol 2006;24:4129-4134.

159. Rolston KV, Berkey P, Bodey GP, et al. A comparison of imipenem to ceftazidime with or without amikacin as empiric therapy in febrile neutropenic patients. Arch Intern Med 1992;152:283-291.

160. Rubin M, Hathorn JW, Pizzo PA. Controversies in the management of febrile neutropenic cancer patients. Cancer Invest 1988;6:167-184.

161. Kohn L, Corrigan J, Donaldson M, eds. Committee on Quality of Health Care in America: To err is human: building a safer health system. Institute of Medicine Report. National Academy Press: Washington, D.C., 2000.

162. Carstensen M, Sørensen JB. Outpatient management of febrile neutropenia: time to revise the present treatment strategy. J Support Oncol 2008;6(5):199-208.

163. Kerr KG, Armitage HT, McWhinney PH. Activity of quinolones against viridans group streptococci isolated from blood cultures of patients with haematological malignancy. Support Care Cancer 1999;7:28-30.

164. Giamarellou H, Bassaris HP, Petrikkos G, et al. Monotherapy with intravenous followed by oral high-dose ciprofloxacin versus combination therapy with ceftazidime plus amikacin as initial empiric therapy for granulocytopenic patients with fever. Antimicrob Agents Chemother 2000;44:3264-3271.

165. Paganini H, Rodriguez-Brieshcke T, Zubizarreta P, et al. Oral ciprofloxacin in the management of children with cancer with lower risk febrile neutropenia. Cancer 2001;91:1563-1567.

166. Freifeld A, Sankaranarayanan J, Ullrich F, Sun J. Clinical practice patterns of managing low-risk adult febrile neutropenia during cancer chemotherapy in the USA. Support Care Cancer 2008;16(2):181-191. Epub 2007 Oct 18.

167. Rolston KV, Frisbee-Hume SE, Patel S, et al. Oral moxifloxacin for outpatient treatment of low-risk, febrile neutropenic patients. Support Care Cancer. 2009 Apr 22. [Epub ahead of print]

168. Baglin TP, Gray JJ, Marcus RE, et al. Antibiotic resistant fever associated with herpes simplex virus infection in neutropenic cancer patients with haematological malignancy. J Clin Pathol 1989;42:1255-1258.

169. Rex JH, Pappas PG, Karchmer AW, et al. A randomized and blinded multicenter trial of high-dose fluconazole plus placebo versus fluconazole plus amphotericin B as therapy for candidemia and its consequences in non-neutropenic subjects. Clin Infect Dis 2003;36:1221-1228.

170. Kontoyiannis DP, Lionakis MS, Lewis RE, et al. Zygomycosis in a tertiary care cancer center in the era of Aspergillus-active antifungal therapy: a case control observational study of 27 recent cases. J Infect Dis 2005;191:1350-1360.

171. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002;347:408-415.

172. Denning DW, Ribaud P, Milpied N, et al. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. Clin Infect Dis 2002;34(5):563-571. Epub 2002 Jan 22.

173. Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2008;46:327-360.

174. Eggimann P, Francioli P, Bille J, et al. Fluconazole prophylaxis prevents intra-abdominal candidiasis in high-risk surgical patients. Crit Care Med 1999;27:1066-1072.

175. Gorschluter M, Glasmacher A, Hahn C, et al. Clostridium difficile infection in patients with neutropenia. Clin Infect Dis 2001;33:786-791.

176. McDonald LC, Killgore GE, Thompson A, et al. An epidemic, toxin gene-variant strain of Clostridium difficile. N Engl J Med 2005;353:2433-2441.

177. Loo VG, Poirier L, Miller MA, et al. A predominantly clonal multi-institutional outbreak of Clostridium difficile-associated diarrhea with high morbidity and mortality. N Engl J Med 2005;353:2442-2449.

178. Musher DM, Aslam S, Logan N, et al. Relatively poor outcome after treatment of Clostridium difficile colitis with metronidazole. Clin Infect Dis 2005;40:1586-1590.

179. Halsey J. Current and future treatment modalities for Clostridium difficile-associated disease. Am J Health Syst Pharm 2008;65(8):705-715.

180. Gerding DN, Johnson S, Peterson LR, et al. Clostridium difficile-associated diarrhea and colitis. Infect Control Hosp Epidemiol 1995;16(8):459-477.

181. Olson MM, Shanholtzer CJ, Lee JT Jr, Gerding DN. Ten years of prospective Clostridium difficile-associated disease surveillance and treatment at the Minneapolis VA Medical Center, 1982-1991. Infect Control Hosp Epidemiol 1994;15(6):371-381.

182. Aslam S, Hamill RJ, Musher DM. Treatment of Clostridium difficile-associated disease: old therapies and new strategies. Lancet Infect Dis 2005;5(9):549-557.

183. Bartlett JG. Narrative review: the new epidemic of Clostridium difficile-associated enteric disease. Ann Intern Med 2006;145(10):758-764.

184. Bartlett JG. New antimicrobial agents for patients with Clostridium difficile Infections. Curr Infect Dis Rep 2009;11(1):21-28.

185. Blossom DB, McDonald LC. The challenges posed by reemerging Clostridium difficile infection. Clin Infect Dis 2007;45(2):222-227. Epub 2007 Jun 4.

186. Song HK, Kreisel D, Canter R, et al. Changing presentation and management of neutropenic enterocolitis. Arch Surg 1998;133:979-982.

187. Darouiche RO, Raad II, Heard SO, et al. A comparison of two antimicrobial-impregnated central venous catheters. Catheter Study Group. N Engl J Med 1999;340(1):1-8.

188. Veenstra DL, Saint S, Saha S, et al. Efficacy of antiseptic-impregnated central venous catheters in preventing catheter-related bloodstream infection: a meta-analysis. JAMA 1999;281(3):261-267.

189. Veenstra DL, Saint S, Sullivan SD. Cost-effectiveness of antiseptic-impregnated central venous catheters for the prevention of catheter-related bloodstream infection. JAMA 1999;282(6):554-560.

190. Rupp ME, Lisco SJ, Lipsett PA, et al. Effect of a second-generation venous catheter impregnated with chlorhexidine and silver sulfadiazine on central catheter-related infections: a randomized, controlled trial. Ann Intern Med 2005;143(8):570-580.

191. Pittet D, Walder B, Tramèr MR. Prevention of bloodstream infections with central venous catheters treated with anti-infective agents depends on catheter type and insertion time: evidence from a meta-analysis. ICHE 2002;23:748-756.

192. Safdar N, Maki DG. Use of vancomycin-containing lock or flush solutions for prevention of bloodstream infection associated with central venous access devices: a meta-analysis of prospective, randomized trials. Clin Infect Dis 2006;43(4):474-484. Epub 2006 Jul 11.

193. Blot F, Nitenberg G, Chachaty E, et al. Diagnosis of catheter-related bacteraemia: a prospective comparison of the time to positivity of hub-blood versus peripheral-blood cultures. Lancet 1999;354(9184):1071-1077.

194. Raad I, Hanna HA, Alakech B, et al. Differential time to positivity: a useful method for diagnosing catheter-related bloodstream infections. Ann Intern Med 2004;140(1):18-25.

195. Krause R, Auner HW, Gorkiewicz G, et al. Detection of catheter-related bloodstream infections by the differential-time-to-positivity method and gram stain-acridine orange leukocyte cytospin test in

neutropenic patients after hematopoietic stem cell transplantation. J Clin Microbiol 2004;42(10):4835-4837.

196. Abdelkefi A, Achour W, Ben Othman T, et al. Difference in time to positivity is useful for the diagnosis of catheter-related bloodstream infection in hematopoietic stem cell transplant recipients. Bone Marrow Transplant 2005;35(4):397-401.

197. Blot F, Schmidt E, Nitenberg G, Tancrede C, et al. Earlier positivity of central-venous- versus peripheral-blood cultures is highly predictive of catheter-related sepsis. J Clin Microbiol 1998;36(1):105-109.

198. La Quaglia MP, Caldwell C, Lucas A, et al. A prospective randomized double-blind trial of bolus urokinase in the treatment of established Hickman catheter sepsis in children. J Pediatr Surg 1994;29:742-745.

199. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia. Clin Infect Dis 2007;44:S27-S72.

200. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and health-care associated pneumonia. Am J Respir Crit Care Med 2005;171:388-416.

201. Nordmann P, Cuzon G, Naas T. The real threat of Klebsiella pneumoniae carbapenemase-producing bacteria. Lancet Infect Dis 2009;9(4):228-236.

202. Greene RE, Schlamm HT, Oestmann JW, et al. Imaging findings in acute invasive pulmonary aspergillosis: clinical significance of the halo sign. Clin Infect Dis 2007;44(3):373-379. Epub 2006 Dec 29.

203. Bozzette SA, Sattler FR, Chiu J, et al. A controlled trial of early adjunctive treatment with corticosteroids for Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. California Collaborative Treatment Group [see comments]. N Engl J Med 1990;323:1451-1457.

204. Nguyen Q, Estey E, Raad I, et al. Cytomegalovirus pneumonia in adults with leukemia: an emerging problem. Clin Infect Dis 2001;32:539-545.

205. Odabasi Z, Mattiuzzi G, Estey E, et al. Beta-d-glucan as a diagnostic adjunct for invasive fungal infections: validation, cutoff development, and performance in patients with acute myelogenous leukemia and myelodysplastic syndrome. Clin Infect Dis 2004;39:199-205. Epub 2004 Jun 28.

206. Ostrosky-Zeichner L, Alexander BD, Kett DH, et al. Multicenter clinical evaluation of the (1-->3) beta-d-glucan assay as an aid to diagnosis of fungal infections in humans. Clin Infect Dis 2005;41:654-659.

207. Tasaka S, Hasegawa N, Kobayashi S, et al. Serum indicators for the diagnosis of pneumocystis pneumonia. Chest 2007;131:1173-1180.

208. Wheat LJ. Rapid diagnosis of invasive aspergillosis by antigen detection. Transpl Infect Dis 2003;5:158-166.

209. Mennink-Kersten MA, Donnelly JP, Verweij PE. Detection of circulating galactomannan for the diagnosis and management of invasive aspergillosis. Lancet Infect Dis 2004;4:349-357.

210. Marr KA, Balajee SA, McLaughlin L, et al. Detection of galactomannan antigenemia by enzyme immunoassay for the diagnosis of invasive aspergillosis: variables that affect performance. J Infect Dis 2004;190:641-649. Epub 2004 Jul 1.

211. Herbrecht R, Letscher-Bru V, Oprea C, et al. Aspergillus galactomannan detection in the diagnosis of invasive aspergillosis in cancer patients. J Clin Oncol 2002;20:1898-1906.

212. Walsh TJ, Shoham S, Petraitiene R, et al. Detection of galactomannan antigenemia in patients receiving piperacillin-tazobactam and correlations between in vitro, in vivo, and clinical properties of the drug-antigen interaction. J Clin Microbiol 2004;42:4744-4748.

213. Sulahian A, Touratier S, Ribaud P. False positive test for Aspergillus antigenemia related to concomitant administration of piperacillin and tazobactam. N Engl J Med 2003;349:2366-2367.

214. Mennink-Kersten MA, Warris A, Verweij PE. 1,3-beta-d-glucan in patients receiving intravenous amoxicillin-clavulanic acid. N Engl J Med 2006;354:2834-2835.

215. Ogawa M, Hori H, Niiguchi S, et al. False-positive plasma (1-->3)-beta-D-glucan test following immunoglobulin product replacement in an adult bone marrow recipient. Int J Hematol 2004;80:97-98.

216. Masur H, Gill VJ, Ognibene FP, et al. Diagnosis of Pneumocystis pneumonia by induced sputum technique in patients without the acquired immunodeficiency syndrome. Ann Intern Med 1988;109:755-756.

217. Shelhamer JH, Toews GB, Masur H, et al. NIH conference. Respiratory disease in the immunosuppressed patient. Ann Intern Med 1992;117:415-431.

218. Levine SJ. An approach to the diagnosis of pulmonary infections in immunosuppressed patients. Semin Respir Infect 1992;7:81-95.

219. Wheat LJ, Walsh TJ. Diagnosis of invasive aspergillosis by galactomannan antigenemia detection using an enzyme immunoassay. Eur J Clin Microbiol Infect Dis 2008;27(4):245-251. Epub 2008 Jan 9.

220. Meersseman W, Lagrou K, Maertens J, et al. Galactomannan in bronchoalveolar lavage fluid: a tool for diagnosing aspergillosis in intensive care unit patients. Am J Respir Crit Care Med 2008;177(1):27-34. Epub 2007 Sep 20.

221. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 2008;46(12):1813-1821.

222. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004;39(9):1267-1284. Epub 2004 Oct 6.

223. Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2008;47(3):303-327.

224. Edmond MB, Wallace SE, McClish DK, et al. Nosocomial bloodstream infections in United States hospitals: a three-year analysis. Clin Infect Dis 1999;29:239-244.

225. Rex JH, Bennett JE, Sugar AM, et al. A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia. Candidemia Study Group and the National Institute [see comments]. N Engl J Med 1994;331:1325-1330.

226. Kullberg BJ, Sobel JD, Ruhnke M, et al. Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial. Lancet 2005;366:1435-1442.

227. Mora-Duarte J, Betts R, Rotstein C, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med 2002;347:2020-2029.

228. Kuse ER, Chetchotisakd P, da Cunha CA, et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial. Lancet 2007;369(9572):1519-1527.

229. Pappas PG, Rotstein CM, Betts RF, et al. Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. Clin Infect Dis 2007;45(7):883-893. Epub 2007 Aug 29.

230. Reboli AC, Rotstein C, Pappas PG, et al. Anidulafungin versus fluconazole for invasive candidiasis. N Engl J Med 2007;356(24):2472-2482.

231. Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 2009;48(5):503-535.

232. Pfaller MA, Messer SA, Boyken L, et al. Selection of a surrogate agent (fluconazole or voriconazole) for initial susceptibility testing of posaconazole against Candida spp.: results from a global antifungal surveillance program. J Clin Microbiol 2008;46(2):551-559. Epub 2007 Dec 19.

233. Schwartz S, Ruhnke M, Ribaud P, et al. Improved outcome in central nervous system aspergillosis, using voriconazole treatment. Blood 2005;106:2641-2645.

234. Denning DW. Therapeutic outcome in invasive aspergillosis. Clin Infect Dis 1996;23:608-615.

235. Pascual A, Nieth V, Calandra T, et al. Variability of voriconazole plasma levels measured by new high-performance liquid chromatography and bioassay methods. Antimicrob Agents Chemother 2007;51(1):137-143. Epub 2006 Nov 6.

236. Trifilio S, Pennick G, Pi J, et al. Monitoring plasma voriconazole levels may be necessary to avoid subtherapeutic levels in hematopoietic stem cell transplant recipients. Cancer 2007;109(8):1532-1535.

237. Smith J, Safdar N, Knasinski V, et al. Voriconazole therapeutic drug monitoring. Antimicrob Agents Chemother 2006;50(4):1570-1572.

238. Pascual A, Calandra T, Bolay S, et al. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. Clin Infect Dis 2008;46(2):201-211.

239. Tan K, Brayshaw N, Tomaszewski K, et al. Investigation of the potential relationships between plasma voriconazole concentrations and visual adverse events or liver function test abnormalities. Clin Pharmacol 2006;46(2):235-243.

240. Bowden R, Chandrasekar P, White MH, et al. A double-blind, randomized, controlled trial of amphotericin B colloidal dispersion versus amphotericin B for treatment of invasive aspergillosis in immunocompromised patients. Clin Infect Dis 2002;35:359-366. Epub 2002 Jul 25.

241. Chandrasekar PH, Ito JI. Amphotericin B lipid complex in the management of invasive aspergillosis in immunocompromised patients. Clin Infect Dis 2005;40:Suppl 6:S392-S400.

242. Cornely OA, Maertens J, Bresnik M, et al. Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized trial comparing a high-loading dose regimen with standard dosing (AmBiLoad trial). Clin Infect Dis 2007;44(10):1289-1297. Epub 2007 Apr 9.

243. Maertens J, Raad I, Petrikkos G, et al. Efficacy and safety of caspofungin for treatment of invasive aspergillosis in patients refractory to or intolerant of conventional antifungal therapy. Clin Infect Dis 2004;39:1563-1571. Epub 2004 Nov 9.

244. Dennis CG, Greco WR, Brun Y, et al. Effect of amphotericin B and micafungin combination on survival, histopathology, and fungal burden in experimental aspergillosis in the p47phox-/- mouse model of chronic granulomatous disease. Antimicrob Agents Chemother 2006;50:422-427.

245. Kirkpatrick WR, Perea S, Coco BJ, Patterson TF. Efficacy of caspofungin alone and in combination with voriconazole in a Guinea pig model of invasive aspergillosis. Antimicrob Agents Chemother 2002;46:2564-2568.

246. Petraitis V, Petraitiene R, Sarafandi AA, et al. Combination therapy in treatment of experimental pulmonary aspergillosis: synergistic interaction between an antifungal triazole and an echinocandin. J Infect Dis 2003;187:1834-1843.

247. Luque JC, Clemons KV, Stevens DA. Efficacy of micafungin alone or in combination against systemic murine aspergillosis. Antimicrob Agents Chemother 2003;47:1452-1455.

248. Chandrasekar PH, Cutright JL, Manavathu EK. Efficacy of voriconazole plus amphotericin B or micafungin in a guinea-pig model of invasive aspergillosis. Clin Microbiol Infect 2004;10:925-928.

249. Sivak O, Bartlett K, Risovic V, et al. Assessing the antifungal activity and toxicity profile of amphotericin B lipid complex (ABLC; Abelcet) in combination with caspofungin in experimental systemic aspergillosis. J Pharm Sci 2004;93:1382-1389.

250. Graybill JR, Bocanegra R, Gonzalez GM, Najvar LK. Combination antifungal therapy of murine aspergillosis: liposomal amphotericin B and micafungin. J Antimicrob Chemother 2003;52:656-662.

251. Aliff TB, Maslak PG, Jurcic JG, et al. Refractory Aspergillus pneumonia in patients with acute leukemia: successful therapy with combination caspofungin and liposomal amphotericin. Cancer 2003;97:1025-1032.

252. Kontoyiannis DP, Hachem R, Lewis RE, et al. Efficacy and toxicity of caspofungin in combination with liposomal amphotericin B as primary or salvage treatment of invasive aspergillosis in patients with hematologic malignancies. Cancer 2003;98:292-299.

253. Marr KA, Boeckh M, Carter RA, et al. Combination antifungal therapy for invasive aspergillosis. Clin Infect Dis 2004;39:797-802. Epub 2004 Aug 27.

254. Maertens J, Glasmacher A, Herbrecht R, et al. Multicenter, noncomparative study of caspofungin in combination with other antifungals as salvage therapy in adults with invasive aspergillosis. Cancer 2006;107:2888-2897.

255. Denning DW, Marr KA, Lau WM, et al. Micafungin (FK463), alone or in combination with other systemic antifungal agents, for the treatment of acute invasive aspergillosis. J Infect 2006;53(5):337-349. Epub 2006 May 6.

256. Raad II, Graybill JR, Bustamante AB, et al. Safety of long-term oral posaconazole use in the treatment of refractory invasive fungal infections. Clin Infect Dis 2006;42(12):1726-1734. Epub 2006 May 8.

257. Greenberg RN, Mullane K, van Burik JA, et al. Posaconazole as salvage therapy for zygomycosis. Antimicrob Agents Chemother 2006;50:126-133.

258. Pitisuttithum P, Negroni R, Graybill JR, et al. Activity of posaconazole in the treatment of central nervous system infections. J Antimicrob Chemother 2005;56:745-755.

259. Raad II, Hachem RY, Herbrecht R, et al. Posaconazole as salvage treatment for invasive fusariosis in patients with underlying hematologic malignancy and other conditions. Clin Infect Dis 2006;42:1398-1403.

260. Walsh TJ, Raad I, Patterson TF, et al. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. Clin Infect Dis 2007;44(1):2-12. Epub 2006 Nov 28.

261. Imhof A, Balajee SA, Fredricks DN, et al. Breakthrough fungal infections in stem cell transplant recipients receiving voriconazole. Clin Infect Dis 2004;39:743-746. Epub 2004 Aug 13.

262. Marty FM, Cosimi LA, Baden LR. Breakthrough zygomycosis after voriconazole treatment in recipients of hematopoietic stem-cell transplants. N Engl J Med 2004;350(9):950-952.

263. Marr KA, Carter RA, Crippa F, et al. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. Clin Infect Dis 2002;34:909-917.

264. Kontoyiannis DP, Wessel VC, Bodey GP, Rolston KV. Zygomycosis in the 1990s in a tertiary-care cancer center. Clin Infect Dis 2000;30:851-856.

265. van Burik JA, Hare RS, Solomon HF, et al. Posaconazole is effective as salvage therapy in zygomycosis: a retrospective summary of 91 cases. Clin Infect Dis 2006 Apr 1;42(7):e61-65. Epub 2006 Feb 21. Erratum in: Clin Infect Dis 2006;43(10):1376.

266. Nucci M, Marr KA, Queiroz-Telles F, et al. Fusarium infection in hematopoietic stem cell transplant recipients. Clin Infect Dis 2004;38:1237-1242. Epub 2004 Apr 15.

267. Boutati EI, Anaissie EJ. Fusarium, a significant emerging pathogen in patients with hematologic malignancy: ten years' experience at a cancer center and implications for management. Blood 1997;90:999-1008.

268. Kontoyiannis DP, Bodey GP, Hanna H, et al. Outcome determinants of fusariosis in a tertiary care cancer center: the impact of neutrophil recovery. Leuk Lymphoma 2004;45:139-141.

269. Walsh TJ, Groll A, Hiemenz J, et al. Infections due to emerging and uncommon medically important fungal pathogens. Clin Microbiol Infect 2004;10 Suppl 1:48-66.

270. Jahagirdar BN, Morrison VA. Emerging fungal pathogens in patients with hematologic malignancies and marrow/stem-cell transplant recipients. Semin Respir Infect 2002;17:113-120.

271. Perfect JR, Marr KA, Walsh TJ, et al. Voriconazole treatment for less-common, emerging, or refractory fungal infections. Clin Infect Dis 2003;36:1122-1131.

272. Perfect JR. Treatment of non-Aspergillus moulds in immunocompromised patients, with amphotericin B lipid complex. Clin Infect Dis 2005;40:Suppl 6:S401-408.

273. Kuhlman JE, Fishman EK, Burch PA, et al. Invasive pulmonary aspergillosis in acute leukemia. The contribution of CT to early diagnosis and aggressive management. Chest 1987;92:95-99.

274. Caillot D, Casasnovas O, Bernard A, et al. Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. J Clin Oncol 1997;15:139-147.

275. Maertens J, Van Eldere J, Verhaegen J, et al. Use of circulating galactomannan screening for early diagnosis of invasive aspergillosis in allogeneic stem cell transplant recipients. J Infect Dis 2002;186:1297-1306.

276. Ascioglu S, Rex JH, de Pauw B, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clin Infect Dis 2002;34:7-14.

277. Engels EA, Lau J, Barza M. Efficacy of quinolone prophylaxis in neutropenic cancer patients: a meta-analysis. J Clin Oncol 1998;16:1179-1187.

278. Bow EJ, Rayner E, Louie TJ. Comparison of norfloxacin with cotrimoxazole for infection prophylaxis in acute leukemia. The trade-off for reduced gram-negative sepsis. Am J Med 1988;84:847-854.

279. Hughes WT, Armstrong D, Bodey GP, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis 2002;34:730-751.

280. Gafter-Gvili A, Fraser A, Paul M, Leibovici L. Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. Ann Intern Med 2005;142:979-995.

281. Cullen M, Steven N, Billingham L, et al. Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. N Engl J Med 2005;353:988-998.

282. Bucaneve G, Micozzi A, Menichetti F, et al. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. N Engl J Med 2005;353:977-987.

283. Cullen MH, Billingham LJ, Gaunt CH, Steven NM. Rational selection of patients for antibacterial prophylaxis after chemotherapy. J Clin Oncol 2007;25(30):4821-4828.

284. Bartlett JG, Perl TM. The new Clostridium difficile – what does it mean? N Engl J Med 2005;353:2503-2505.

285. Cook PP, Catrou P, Gooch M, Holbert D. Effect of reduction in ciprofloxacin use on prevalence of methicillin-resistant Staphylococcus aureus rates within individual units of a tertiary care hospital. J Hosp Infect 2006;64(4):348-351. Epub 2006 Oct 12.

286. British Committee for Standards in Haematology Guideline 2001; update of guidelines initially published in 1996: http://www.bmj.com/cgi/eletters/312/7028/430#EL1)

287. Working Party of the British Committee for Standards in Haematology Clinical Haematology Task Force. Guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen. BMJ 1996;312:430-434.

288. Youssef S, Rodriguez G, Rolston KV, et al. Streptococcus pneumoniae infections in 47 hematopoietic stem cell transplantation recipients: clinical characteristics of infections and vaccine-breakthrough infections, 1989-2005. Medicine (Baltimore) 2007;86(2):69-77.

289. Kumashi P, Girgawy E, Tarrand JJ, et al. Streptococcus pneumoniae bacteremia in patients with cancer: disease characteristics and outcomes in the era of escalating drug resistance (1998-2002). Medicine (Baltimore) 2005;84(5):303-312.

290. Goodman JL, Winston DJ, Greenfield RA, et al. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation [see comments]. N Engl J Med 1992;326:845-851.

291. Slavin MA, Osborne B, Adams R, et al. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation–a prospective, randomized, double-blind study. J Infect Dis 1995;171:1545-1552.

292. Marr KA, Seidel K, Slavin MA, et al. Prolonged fluconazole prophylaxis is associated with persistent protection against candidiasis-related death in allogeneic marrow transplant recipients: long-term follow-up of a randomized, placebo- controlled trial. Blood 2000;96:2055-2061.

293. Rotstein C, Bow EJ, Laverdiere M, et al. Randomized placebo-controlled trial of fluconazole prophylaxis for neutropenic cancer patients: benefit based on purpose and intensity of cytotoxic therapy. The Canadian Fluconazole Prophylaxis Study Group [In Process Citation]. Clin Infect Dis 1999;28:331-340.

294. Winston DJ, Chandrasekar PH, Lazarus HM, et al. Fluconazole prophylaxis of fungal infections in patients with acute leukemia. Results of a randomized placebo-controlled, double-blind, multicenter trial [see comments]. Ann Intern Med 1993;118:495-503.

295. Kern W, Behre G, Rudolf T, et al. Failure of fluconazole prophylaxis to reduce mortality or the requirement of systemic amphotericin B therapy during treatment for refractory acute myeloid leukemia: results of a prospective randomized phase III study. German AML Cooperative Group. Cancer 1998;83:291-301.

296. Bodey GP, Mardani M, Hanna HA, et al. The epidemiology of Candida glabrata and Candida albicans fungemia in immunocompromised patients with cancer. Am J Med 2002;112(5):380-385.

297. Winston DJ, Maziarz RT, Chandrasekar PH, et al. Intravenous and oral itraconazole versus intravenous and oral fluconazole for long-term antifungal prophylaxis in allogeneic hematopoietic stem-cell transplant recipients. A multicenter, randomized trial. Ann Intern Med 2003;138:705-713.

298. Koh LP, Kurup A, Goh YT, et al. Randomized trial of fluconazole versus low-dose amphotericin B in prophylaxis against fungal infections in patients undergoing hematopoietic stem cell transplantation. Am J Hematol 2002;71(4):260-267.

299. Marr KA, Crippa F, Leisenring W, et al. Itraconazole versus fluconazole for prevention of fungal infections in allogeneic stem cell transplant patients. Blood 2004;103(4):1527-1533.

300. Marr KA, Leisenring W, Crippa F, et al. Cyclophosphamide metabolism is impacted by azole antifungals. Blood 2004;103(4):1557-1559.

301. Rijnders BJ, Cornelissen JJ, Slobbe L, et al. Aerosolized liposomal amphotericin B for the prevention of invasive pulmonary aspergillosis

during prolonged neutropenia: a randomized, placebo-controlled trial. Clin Infect Dis 2008;46(9):1401-1408.

302. Perfect JR. Aerosolized antifungal prophylaxis: the winds of change? Clin Infect Dis 2008;46(9):1409-1411.

303. van Burik JA, Ratanatharathorn V, Stepan DE, et al. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. Clin Infect Dis 2004;39(10):1407-1416.

304. Wingard JR, Carter SL, Walsh TJ, et al; The Blood and Marrow Transplant Clinical Trials Network. Results of a randomized, double-blind trial of fluconazole (FLU) vs. voriconazole (VORI) for the prevention of invasive fungal infections (IFI) in 600 allogeneic blood and marrow transplant (BMT) patients. Blood 2007;110:abstract 163. http://www.mykosen-online.de/infos/ash_2007_abstract_wingard.pdf

305. Vazquez JA, Skiest DJ, Nieto L, et al. A multicenter randomized trial evaluating posaconazole versus fluconazole for the treatment of oropharyngeal candidiasis in subjects with HIV/AIDS. Clin Infect Dis 2006;42:1179-1186.

306. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 2007;356:348-359.

307. Böhme A, Just-Nübling G, Bergmann L, et al. Itraconazole for prophylaxis of systemic mycoses in neutropenic patients with haematological malignancies. J Antimicrob Chemother 1996;38(6):953-961.

308. Weinberger M, Elattar I, Marshall D, et al. Patterns of infection in patients with aplastic anemia and the emergence of Aspergillus as a major cause of death. Medicine (Baltimore) 1992;71:24-43.

309. Ullmann AJ, Lipton JH, Vesole DH, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N Engl J Med 2007;356:335-347.

310. Walsh TJ, Whitcomb PO, Revankar SG, et al. Successful treatment of hepatosplenic candidiasis through repeated cycles of chemotherapy and neutropenia. Cancer 1995;76:2357-2362.

311. Offner F, Cordonnier C, Ljungman P, et al. Impact of previous aspergillosis on the outcome of bone marrow transplantation. Clin Infect Dis 1998;26:1098-1103.

312. Fukuda T, Boeckh M, Guthrie KA, et al. Invasive aspergillosis before allogeneic hematopoietic stem cell transplantation: 10-year experience at a single transplant center. Biol Blood Marrow Transplant 2004;10:494-503.

313. Meyers JD, Flournoy N, Thomas ED. Infection with herpes simplex virus and cell-mediated immunity after marrow transplant. J Infect Dis 1980;142:338-346.

314. Saral R, Ambinder RF, Burns WH, et al. Acyclovir prophylaxis against herpes simplex virus infection in patients with leukemia. A randomized, double-blind, placebo-controlled study. Ann Intern Med 1983;99:773-776.

315. Boeckh M, Kim HW, Flowers MED, et al. Long-term acyclovir for prevention of varicella zoster virus disease after allogeneic hematopoietic cell transplantation – a randomized double-blind placebo-controlled study. Blood 2006;107:1800-1805.

316. Schuchter LM, Wingard JR, Piantadosi S, et al. Herpes zoster infection after autologous bone marrow transplantation. Blood 1989;74(4):1424-1427.

317. Tong Y, Qian J, Li Y, et al. The high incidence of varicella herpes zoster with the use of bortezomib in 10 patients. Am J Hematol 2007;82(5):403-404.

318. Varettoni M, Vassallo C, Borroni G, et al. Late onset of bortezomib-associated cutaneous reaction following herpes zoster. Ann Hematol 2007;86:301-302.

319. Reece DE, Rodriguez GP, Chen C, et al. Phase I-II trial of bortezomib plus oral cyclophosphamide and prednisone in relapsed

and refractory multiple myeloma. J Clin Oncol 2008;26(29):4777-4783. Epub 2008 Jul 21.

320. Curran MP, McKeage K. Bortezomib: a review of its use in patients with multiple myeloma. Drugs 2009;69(7):859-888. doi: 10.2165/00003495-200969070-00006.

321. Chanan-Khan A, Sonneveld P, Schuster MW, et al. Analysis of herpes zoster events among bortezomib-treated patients in the phase III APEX study. J Clin Oncol 2008;26(29):4784-4790. Epub 2008 Aug 18.

322. Prentice HG, Kho P. Clinical strategies for the management of cytomegalovirus infection and disease in allogeneic bone marrow transplant. Bone Marrow Transplant 1997;19:135-142.

323. Prentice HG, Gluckman E, Powles RL, et al. Impact of long-term acyclovir on cytomegalovirus infection and survival after allogeneic bone marrow transplantation. European Acyclovir for CMV Prophylaxis Study Group. Lancet 1994;343:749-753.

324. Meyers JD, Reed EC, Shepp DH, et al. Acyclovir for prevention of cytomegalovirus infection and disease after allogeneic marrow transplantation. N Engl J Med 1988;318:70-75.

325. Ljungman P, de La Camara R, Milpied N, et al. Randomized study of valacyclovir as prophylaxis against cytomegalovirus reactivation in recipients of allogeneic bone marrow transplants. Blood 2002;99:3050-3056.

326. Reusser P, Einsele H, Lee J, et al. Randomized multicenter trial of foscarnet versus ganciclovir for preemptive therapy of cytomegalovirus infection after allogeneic stem cell transplantation. Blood 2002;99:1159-1164.

327. Winston DJ, Baden LR, Gabriel DA, et al. Pharmacokinetics of ganciclovir after oral valganciclovir versus intravenous ganciclovir in allogeneic stem cell transplant patients with graft-versus-host disease of the gastrointestinal tract. Biol Blood Marrow Transplant 2006;12:635-640.

328. Ayala E, Greene J, Sandin R, et al. Valganciclovir is safe and effective as pre-emptive therapy for CMV infection in allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 2006;37:851-856.

329. van der Heiden PL, Kalpoe JS, Barge RM, et al. Oral valganciclovir as pre-emptive therapy has similar efficacy on cytomegalovirus DNA load reduction as intravenous ganciclovir in allogeneic stem cell transplantation recipients. Bone Marrow Transplant 2006;37:693-698.

330. Einsele H, Reusser P, Bornhauser M, et al. Oral valganciclovir leads to higher exposure to ganciclovir than intravenous ganciclovir in patients following allogeneic stem cell transplantation. Blood 2006;107:3002-3008.

331. O'Brien S, Ravandi F, Riehl T, et al. Valganciclovir prevents cytomegalovirus reactivation in patients receiving alemtuzumab-based therapy. Blood 2008;111(4):1816-1819. Epub 2007 Nov 26.

332. Winston DJ, Young JA, Pullarkat V, et al. Maribavir prophylaxis for prevention of cytomegalovirus infection in allogeneic stem cell transplant recipients: a multicenter, randomized, double-blind, placebo-controlled, dose-ranging study. Blood 2008;111(11):5403-5410. Epub 2008 Feb 19.

333. Nguyen Q, Champlin R, Giralt S, et al. Late cytomegalovirus pneumonia in adult allogeneic blood and marrow transplant recipients. Clin Infect Dis 1999;28(3):618-623.

334. Boeckh M, Leisenring W, Riddell SR, et al. Late cytomegalovirus disease and mortality in recipients of allogeneic hematopoietic stem cell transplants: importance of viral load and T-cell immunity. Blood 2003;101:407-414.

335. Hakki M, Riddell SR, Storek J, et al. Immune reconstitution to cytomegalovirus after allogeneic hematopoietic stem cell transplantation: impact of host factors, drug therapy, and subclinical reactivation. Blood 2003;102(8):3060-3067. Epub 2003 Jul 3.

336. Junghanss C, Boeckh M, Carter RA, et al. Incidence and outcome of cytomegalovirus infections following nonmyeloablative compared with myeloablative allogeneic stem cell transplantation, a matched control study. Blood 2002;99:1978-1985.

337. Gratama JW, van Esser JW, Lamers CH, et al. Tetramer-based quantification of cytomegalovirus (CMV)-specific CD8+ T lymphocytes in T-cell-depleted stem cell grafts and after transplantation may identify patients at risk for progressive CMV infection. Blood 2001;98:1358-1364.

338. Yeo W, Chan PK, Ho WM, et al. Lamivudine for the prevention of hepatitis B virus reactivation in hepatitis Bs-antigen seropositive cancer patients undergoing cytotoxic chemotherapy. J Clin Oncol 2004;22;927-934.

339. Bréchot C, Degos F, Lugassy C, et al. Hepatitis B virus DNA in patients with chronic liver disease and negative tests for hepatitis B surface antigen. N Engl J Med 1985;312(5):270-276.

340. Dhédin N, Douvin C, Kuentz M, et al. Reverse seroconversion of hepatitis B after allogeneic bone marrow transplantation: a retrospective study of 37 patients with pretransplant anti-HBs and anti-HBc. Transplantation 1998;66(5):616-619.

341. Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology 2007;45(2):507-539.

342. Ghany MG, Strader DB, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009;49(4):1335-1374.

343. Lau GK, He ML, Fong DY, et al. Preemptive use of lamivudine reduces hepatitis B exacerbation after allogeneic hematopoietic cell transplantation. Hepatology 2002;36(3):702-709.

344. Rossi G, Pelizzari A, Motta M, Puoti M. Primary prophylaxis with lamivudine of hepatitis B virus reactivation in chronic HbsAg carriers with lymphoid malignancies treated with chemotherapy. Br J Haematol 2001;115(1):58-62.

345. Marcellin P, Heathcote EJ, Buti M, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. N Engl J Med 2008;359(23):2442-2455.

346. Leung N, Peng CY, Hann HW, et al. Early hepatitis B virus DNA reduction in hepatitis B e antigen-positive patients with chronic hepatitis B: A randomized international study of entecavir versus adefovir. Hepatology 2009;49(1):72-79.

347. Ljungman P, Engelhard D, de la Cámara R, et al; Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. Vaccination of stem cell transplant recipients: recommendations of the Infectious Diseases Working Party of the EBMT. Bone Marrow Transplant 2005;35(8):737-746.

348. Kroger AT, Atkinson WL, Marcuse EK, Pickering LK. General recommendations on immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2006;55(RR15):1-48.

349. Ortbals DW, Liebhaber H, Presant CA, et al. Influenza immunization of adult patients with malignant diseases. Ann Intern Med 1977;87(5):552-557.

350. Sommer AL, Wachel BK, Smith JA. Evaluation of vaccine dosing in patients with solid tumors receiving myelosuppressive chemotherapy. J Oncol Pharm Pract 2006;12(3):143-154.

351. Whimbey E, Champlin RE, Couch RB, et al. Community respiratory virus infections among hospitalized adult bone marrow transplant recipients. Clin Infect Dis 1996;22:778-782.

352. Ljungman P. Respiratory virus infections in stem cell transplant patients: The European experience. Biol Blood Marrow Transplant 2001;[7 suppl]:5S-7S.

353. Bowden RA. Respiratory virus infections after marrow transplant: The Fred Hutchinson Cancer Research Center experience. Am J Med 1997;102:27-30.

354. Feldman S, Webster RG, Sugg M. Influenza in children and young adults with cancer: 20 cases. Cancer 1977;39:350-353.

355. Kempe A, Hall CB, MacDonald NE, et al. Influenza in children with cancer. Journal of Pediatrics 1989;115:33-39.

356. Elting LS, Whimbey E, Lo W, et al. Epidemiology of influenza A virus infection in patients with acute or chronic leukemia. Support Care Cancer 1995;3:198-202.

357. Centers for Disease Control and Prevention. Prevention and control of influenza: recommendations of the advisory Committee on Immunization Practices (ACIP). MMWR 2003;52 (RR-8):1-34.

358. Health Canada. Statement on influenza vaccination for the 2003-2004 season: an Advisory Committee Statement (ACS) from the National Advisory Committee on Immunization (NACI). Canada Communicable Disease Report. 2003;29 (ACS-4):1-20.

359. Department of Health, UK. Summary of flu immunisation policy. Key points about flu immunisation policy in England. (http://www.dh.gov.uk/en/Policyandguidance/Healthandsocialcaretopics/Flu/Flugeneralinformation/DH_4001688) (Accessed July 8, 2009).

360. Harper SA, Fukuda K, Cox NJ, et al; Centers for Disease Control and Prevention. Using live, attenuated influenza vaccine for prevention and control of influenza: supplemental recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2003;52(RR-13):1-8.

361. Hughes WT, Rivera GK, Schell MJ, et al. Successful intermittent chemoprophylaxis for Pneumocystis carinii pneumonitis. N Engl J Med 1987;316:1627-1632.

362. Vasconcelles MJ, Bernardo MV, King C, et al. Aerosolized pentamidine as Pneumocystis prophylaxis after bone marrow transplantation is inferior to other regimens and is associated with decreased survival and an increased risk of other infections. Biol Blood Marrow Transplant 2000;6(1):35-43.

363. El-Sadr WM, Murphy RL, Yurik TM, et al. Atovaquone compared with dapsone for the prevention of Pneumocystis carinii pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. N Engl J Med 1998;339:1889-1895.

364. Sepkowitz KA. Pneumocystis carinii pneumonia among patients with neoplastic disease. Semin Respir Infect 1992;7(2):114-121.

365. Hahn T, Cummings KM, Michalek AM, et al. Efficacy of high-efficiency particulate air filtration in preventing aspergillosis in immunocompromised patients with hematologic malignancies. Infect Control Hosp Epidemiol 2002;23:525-531.

366. Schimpff S, Satterlee W, Young VM, Serpick A. Empiric therapy with carbenicillin and gentamicin for febrile patients with cancer and granulocytopenia. N Engl J Med 1971;284:1061-1065.