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79 Infections in Patients with Cancer

■ ■DIARRHEA Similar to the vomiting syndromes, chemotherapy-induced diarrhea may be immediate or can occur in a delayed fashion up to 48–72 h after the drugs. Careful attention to maintained hydration and elec trolyte repletion, intravenously if necessary, along with antimotility treatments such as “high-dose” loperamide (4 mg at the first occur rence of diarrhea, with 2 mg repeated every 2 h until 12 h without loose stools, not to exceed a total daily dose of 16 mg), are appropriate. Octreotide (100–150 µg), a somatostatin analogue, or intralumenally acting opiate-based preparations may be considered for patients not responding to loperamide.

■ ■MUCOSITIS Irritation and inflammation of the mucous membranes (mucositis) particularly afflicting the oral and anal mucosa, but potentially involv ing the entire gastrointestinal tract, may accompany cytotoxic chemo therapy. Topical therapies, including anesthetics and barrier-creating preparations, may provide symptomatic relief in mild cases. ■ ■ALOPECIA Chemotherapeutic agents vary widely in causing alopecia, with anthra cyclines, alkylating agents, and topoisomerase inhibitors reliably causing near-total alopecia when given at therapeutic doses. Antime tabolites are more variably associated with alopecia. Psychological sup port and the use of cosmetic resources are to be encouraged. “Chemo caps” that reduce scalp temperature to decrease the degree of alopecia are controversial during treatment with curative intent of neoplasms, such as leukemia or lymphoma, or in adjuvant breast cancer therapy. The richly vascularized scalp can certainly harbor micrometastatic or disseminated disease. PART 4 Oncology and Hematology ■ ■GONADAL DYSFUNCTION AND PREGNANCY All cancer treatments described in this chapter should be regarded as potentially injurious to the developing fetus and to newborns via lactation. However, there are gradations to the degree of reproductive harm. All agents tend to have increased risk of adverse outcomes when administered during the first trimester, and strategies to delay chemo therapy, if possible, until after this milestone should be considered if the pregnancy is to continue to term. Patients in their second or third trimester can be treated with most regimens for the common neo plasms afflicting women in their childbearing years, with the excep tion of antimetabolites, particularly antifolates, which have notable teratogenic or fetotoxic effects throughout pregnancy. The need for anticancer chemotherapy per se is infrequently a clear basis to recom mend termination of a concurrent pregnancy, although each treatment strategy in this circumstance must be tailored to the individual needs of the patient. Cessation of ovulation and azoospermia reliably result from regi mens that contain alkylating agents and topoisomerase poison. The duration of these effects varies with age and sex. Sperm banking before treatment may be considered. Females experience amenorrhea with anovulation after alkylating agent therapy; egg

preservation may be considered but may delay inception of urgent treatment. Recovery of normal menses is frequent if treatment is completed before age 30, but patients are unlikely to recover menses after age 35. Even those who regain menses usually experience premature menopause. Because the magnitude and extent of decreased fertility can be difficult to predict, patients should be counseled to maintain effective contraception, preferably by barrier means, during and after therapy. Resumption of efforts to conceive should be considered in the context of the patient's likely prognosis. Hormone replacement therapy should be undertaken in women who do not have a hormonally responsive tumor. For patients who have had a hormone-sensitive tumor primarily treated by a local modality, conventional practice would counsel against hormone replacement, but this issue is under investigation. ■ ■PALLIATIVE AND SUPPORTIVE CARE An important perspective the primary care provider may bring to patients and their families facing incurable cancer is that, given the limited value of chemotherapeutic approaches at some point in the natural history of

most metastatic cancers, palliative care or hospice-based approaches, with meticulous and ongoing attention to symptom relief and with family, psychological, and spiritual support, should receive prominent attention as a valuable therapeutic plan (Chaps. 13 and 73). Optimizing the quality of life rather than attempting to extend it becomes a valued intervention. Patients facing the impending progression of disease in a life-threatening way frequently choose to undertake toxic treatments of little to no poten tial value, and support provided by the primary caregiver in accessing palliative and hospice-based options in contrast to receiving toxic and ineffective regimens can be critical in providing a basis for patients to make sensible choices. Late effects of cancer and its treatment are reviewed in Chap. 100. ■ ■FURTHER READING Ascione L et al: Predicting response to antibody drug conjugates: A focus on antigens' targetability. Oncologist 28:944, 2023. Chabner BA, Longo DL: Cancer Chemotherapy, Immunotherapy, and Biotherapy; Principles and Practice, 7th ed. Philadelphia, Wolters Kluwer, 2025. Emadi A, Karp JE: Cancer Pharmacology: An Illustrated Manual of Anticancer Drugs, 2nd ed. New York, Springer Publishing Co., 2024. Federman N: Molecular pathogenesis of desmoid tumor and the role of γ-secretase inhibition. NPJ Precis Oncol 6:62, 2022. Hesketh PJ et al: Antiemetics: American Society of Clinical Oncology clinical practice update. J Clin Oncol 35:3240, 2017. Kaelin WG Jr: Von Hippel-Lindau disease: Insights into oxygen sens ing, protein degradation, and cancer J Clin Invest 132:e162480, 2022. Morad G et al: Hallmarks of response, resistance, and toxicity to immune checkpoint blockade. Cell 184:5309, 2021. Nikanjam M et al: Liquid biopsy: Current technology and clinical applications. J Hematol Oncol 15:131, 2022. Puzanov I et al: Managing toxicities associated with immune check point inhibitors: Consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer 5:95, 2017. Rosen N, Longo DL: Targeting oncogenic RAS protein. N Engl J Med 387:184, 2022. Sartor O et al: Lutetium-177–PSMA-617 for metastatic castrationresistant prostate cancer. N Engl J Med 385:1091, 2021.
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Infections in Patients

with Cancer GENERAL CONCEPTS Infection is an important complication of cancer and cancer therapy and drives excess hospitalization and mortality. Prevention, diagnosis, and treatment of infection increases survival and improves quality of life. In this regard, the infectious diseases consultant works col laboratively with multiple stakeholders to prevent infection and to effectively diagnose and treat infections when they occur. Cornerstones of infection prevention are

compliance with standard infection control guidelines, limiting exposure to pathogens, vaccination of patients and caregivers, and targeted use of antimicrobial prophylaxis. Although there have been substantial improvements in diagnostic modalities for infection including molecular and antigen-based diagnostics, the infectious diseases physician is frequently confronted with patients with suspected infection (e.g., neutropenic fever, lung lesions observed by imaging) without a definitive diagnosis. In addition, infectious and noninfectious disorders may have overlapping manifestations, such as

pneumonia versus drug-related pneumonitis and fever from infection versus cancer-associated fever. Given the broad differential diagnosis, aggressive diagnostic evaluation including biopsies may be required. Sometimes, empirical therapy must be administered based on the most likely or dangerous infections; these situations are common in patients with hematologic malignancies in whom an invasive tissue diagnosis may be unsafe due to thrombocytopenia. We provide recommendations for therapy of both documented and suspected infections. Specific treatment plans should consider several factors, such as evidence of clearance of infection, whether a persistent nidus exists (e.g., abscess or infectious phlebitis), the specific pathogen, and the immune status of the patient. A general principle of therapy is that longer courses are required in patients with persistent and severe immunocompromise (e.g., prolonged neutropenia in patients with acute leukemia or myelodysplastic syndrome). An individualized approach to the diagnosis and management of infections that is tailored to overall goals of care is recommended. For example, in the setting of uncon trolled malignancy (e.g., recurrent cholangitis from obstructive pan creatic or biliary cancers or secondary infections of tumor from bowel fistulization), source control by surgery or catheter drainage may not be feasible, and antibiotics may be used palliatively for patient comfort and to avoid unnecessary hospitalizations rather than to cure an infection. We will address the risk factors for infections and the preventive measures that may be adopted based on those risk factors. Most spe cific infections have dedicated chapters, and readers are advised to access those for in-depth discussions. We will focus here on infections associated with (or caused by) the treatment of cancer. Chemotherapyinduced neutropenia is the most important etiology, and the manage ment of neutropenic fever will be discussed in detail. We will also discuss infections associated with new treatment modalities, including biologics, immunotherapy, and cellular therapies. Infections related to hematopoietic stem cell transplant (HCT) are discussed in Chap. 148. RISK FACTORS FOR INFECTION IN PATIENTS WITH CANCER When evaluating patients with cancer and suspected infection, it is important to consider the major factors—both intrinsic and treatmentassociated—that predispose to infection. This knowledge, in turn, guides the differential diagnosis, diagnostic evaluation, and initial therapy. ■ ■RISK FACTORS INTRINSIC TO THE CANCER These are the direct consequence of the cancer. In the case of solid tumors, the most obvious risk factor for infection relates to obstruc tion. As examples, lung tumors that obstruct the airway predispose to postobstructive pneumonia, obstructive pancreatic and biliary tumors predispose to cholangitis, and tumors that result in obstructive uropa thy predispose to urinary tract infections. Tumors of the head and neck increase the risk of local infection and aspiration pneumonia. Gastro intestinal tumors can present with obstruction and local abscess pro duction by enteric flora and bloodstream infection (e.g., bloodstream infection by Streptococcus gallolyticus or Clostridium septicum in colon cancer). Direct invasion through the colonic mucosa is associated with local abscess formation and sepsis by enteric flora. Some hematologic malignancies are associated with specific immune deficits. Acute leukemia and myelodysplastic syndrome can manifest with pancytopenia at diagnosis. Patients may have a high burden of

circulating leukemic cells and lack normal circulating neutrophils. Some patients with myelodysplastic syndrome or acute myelogenous leukemia (AML) have mutations that are associated marrow failure and immunodeficiency. For example GATA2 deficiency is associated with major viral, bacterial, and fungal infections as well as hematological malignancies and solid tumors. Multiple myeloma and chronic lym phocytic leukemia are associated with impaired immunoglobulin pro duction that can manifest with recurrent sinopulmonary infections and poor antibody responses to both prior infections and vaccination. Case series suggest that patients with hairy cell leukemia are at increased risk of nontuberculous mycobacterial infections. T cell–associated leuke mias and lymphomas can be associated with human T lymphotropic

virus 1 (HTLV1) and have T cell impairment and opportunistic infec tions by Pneumocystis jirovecii, Cryptococcus neoformans, tuberculosis, or disseminated strongyloidiasis.

■ ■RISK FACTORS ASSOCIATED WITH

CANCER THERAPY There has been a dramatic expansion in cancer therapeutics, most of which influence host defense against infections (Table 79-1). Broadly speaking, cancer therapy can compromise either or both the physical barriers and immune responses that protect from infection. Examples of physical barrier disruption include central venous catheters, surgical wounds that can be a portal of entry for skin microbes, and disruption of the lymphatic drainage after mastectomy and lymphadenectomy for breast cancer. The mucosal lining of the gastrointestinal tract, respiratory tract, and other luminal surfaces constitutes the first line of host defense, both as a physical barrier and by secretion of a variety of antimicrobial products, such as immunoglobulin A (IgA), lactoferrin, and anti microbial peptides. Standard nonselective cytotoxic agents have the combined effect of both pancytopenia and mucosal disruption that predispose to infection. Radiation is sometimes administered concur rently with chemotherapy and, depending on the location of the radia tion field, can cause significant mucosal injury. Antineoplastic agents that inhibit specific pathway(s) that drive tumor cell progression are considered targeted, but they also impair specific components of the immune system whose function relies on these same pathways. For example, the anti-tumor activity of Bruton tyrosine kinase inhibitors against B-cell malignancies is by inhibiting the B-cell receptor signaling cascade, but this property can have broad immune effects that increase the risk of viral and fungal infections. CHAPTER 79 Infections in Patients with Cancer Chemotherapy-Induced Neutropenia It has been recognized for more than 50 years that the duration and degree of neutropenia drive susceptibility to infections in patients with cancer. Cytotoxic regi mens that result in prolonged neutropenia also deplete other immune cells (e.g., circulating monocytes and lymphocytes) and commonly cause mucosal injury. The risk of infection is proportional to the degree of neutropenia once the absolute neutrophil count (ANC) becomes <1000/μL. For example, standard induction chemotherapy with anthracycline plus cytarabine for AML causes prolonged neutropenia and severe mucositis. The combination of prolonged neutropenia and mucositis predisposes these patients to gastrointestinal tract infections that include ulcerations of the oral mucosa, neutropenic enterocolitis (typhlitis), and perirectal infections, as well as bloodstream infec tions by gastrointestinal flora such as viridians group streptococci, enterococci, and Enterobacterales. Reactivation of oral mucosal herpes simplex virus (HSV) is another common complication of leukemia therapy. Reflecting the fact that Candida species are endogenous gastrointestinal flora, these patients are also at risk for candidemia and chronic disseminated candidiasis. Patients with more prolonged neutropenia (e.g., ANC <500/μL for

≥2 weeks) are at risk for invasive aspergillosis and other molds. Refractory and relapsed acute leukemia further increase the risk of invasive fungal disease (Table 79-1). Antimicrobial prophylaxis tailored to the underlying immune defects has been shown to be effective in several settings, and it should be used with knowledge of the proven benefits and the direct and indirect toxicities (prevention of fever differs from prevention of infection and prolongation of survival), as well as the limitations of the available evidence. As an example, prophylaxis with a fluoroquinolone like levofloxacin should be considered in adults with prolonged neu tropenia (e.g., ANC <500/μL for ≥7 days). Multiple studies have shown decreased frequency of neutropenic fever and fewer documented infec tions, and meta-analyses suggest a survival benefit. In patients with AML receiving induction chemotherapy, prophylaxis with posacon azole was associated with less invasive fungal disease (IFD) and a survival benefit, so posaconazole is frequently recommended as prophylaxis in patients with profound, prolonged neutropenia. It is plausible that isavuconazole may be equally effective, but its efficacy in this setting has not been demonstrated.

TABLE 79-1 Immune Defects and Associated Infections in Cancer Patients HOST DEFENSE DEFECT PREDOMINANT PATHOGENS PATIENTS WITH CANCER AT GREATEST RISK Neutropenia (ANC <500/μL) Gram-negative and gram-positive bacteria Cytotoxic chemotherapy, underlying hematologic malignancy

(e.g., myelodysplasia, acute leukemia) Prolonged (≥10 days), profound neutropenia (ANC <100/μL) Increased risk of bacterial infections Candidemia Invasive aspergillosis and other molds HSV reactivation Respiratory viral infections T cell immunodeficiency Common bacterial infections Intracellular bacteria (e.g., Listeria monocytogenes, Salmonella species) Nocardia species Tuberculosis and NTM Respiratory viral infections Reactivation of herpes viruses (HSV, VZV); with severe impairment: CMV, EBV-associated lymphoproliferative disease; HHV-6-associated marrow suppression or encephalopathy, and HHV-8-associated malignancies) Mucosal candidiasis Pneumocystis jirovecii Dimorphic fungal infections (e.g., histoplasmosis, coccidioidomycosis) Cryptococcus neoformans Invasive aspergillosis and other molds Toxoplasmosis Strongyloides hyperinfection PART 4 Oncology and Hematology B cell immunodeficiency Encapsulated bacteria (Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis) Respiratory viral infections Reactivation of HSV and VZV Reactivation of HBV PML (reactivation of JC virus) Splenectomy and functional asplenia Encapsulated bacteria (can result in life-threating sepsis) Malaria, babesiosis Mucosal injury Localized infections by oral and GI flora (e.g., dental infections, neutropenic enterocolitis, perianal infection) Bacteremia (coliforms, oral streptococci, enterococci, anaerobes; can be polymicrobial) Systemic corticosteroids Broad suppressive effect on innate and adaptive immunity related to dose and duration of treatment Increased risk of common bacterial and viral infections Prolonged high-dose corticosteroids (e.g., prednisone equivalent to ≥20 mg/day for ≥28 days) increases risk of multiple opportunistic pathogens associated with impaired T cell immunity (e.g., Pneumocystis jirovecii) Abbreviations: AIDS, acquired immunodeficiency syndrome; ANC, absolute neutrophil count; BTK, Bruton tyrosine kinase; CAR, chimeric antigen receptor; CMV, cytomegalovirus; EBV, Epstein-Barr virus; GVHD, graft-versus-host disease; HBV, hepatitis B virus; HHV, human herpes virus; HSV, herpes simplex virus; MDS, myelodysplastic syndrome; NTM, nontuberculous mycobacteria; PML, progressive multifocal leukoencephalopathy; TNF, tumor necrosis factor; VZV, varicella-zoster virus. Corticosteroids Corticosteroids are part of several chemotherapy regimens used in hematologic malignancies, such as in acute lymphoid leukemias, lymphomas, and multiple myeloma. Patients with brain tumors, both primary and metastatic, are

treated with corticoste roids to control edema. In addition, corticosteroids are a mainstay of therapy to control inflammatory complications of cancer therapy. For example, immune checkpoint inhibitors are associated with pneumo nitis, colitis, and autoimmune endocrinopathies that are treated with corticosteroids, and additional agents such as tumor necrosis factor α blockade when corticosteroids alone are insufficient. Corticosteroids are also used as therapy for graft-versus-host disease (GVHD) fol lowing allogeneic stem cell transplantation and for cytokine release syndrome (CRS) following bispecific antibody therapy and adoptive cellular therapy.

Induction/reinduction therapy for acute leukemia; pancytopenia from underlying hematologic malignancy; myeloablative conditioning regimens for stem cell transplantation and lymphodepletion for adoptive cellular therapy Underlying hematologic malignancy including primary T cell malignancies AIDS-associated malignancies Corticosteroids, TNF-α blockade Janus kinase inhibitors Purine analogues Alemtuzumab GVHD Lymphodepletion for adoptive cellular therapy Lymphoid malignancies (e.g., chronic lymphocytic leukemia, multiple myeloma) B cell–depleting agents (e.g., rituximab, BTK inhibitors) Stem cell transplantation, particularly with chronic GVHD Bispecific antibodies and adoptive cellular therapy targeted against B cell antigens (e.g., CD19-directed CAR T cell regimens) Functional asplenia in chronic GVHD Cytotoxic chemotherapy that results in both neutropenia and mucosal injury Radiation (e.g., for head and neck tumors or rectal cancer) predisposes to local tissue damage, impaired blood flow, and secondary bacterial infection Corticosteroids are common components of antineoplastic regimens for hematologic cancers (e.g., for acute lymphoblastic leukemia, lymphomas, and multiple myeloma) and are administered concurrently with other immunosuppressive therapies Other common indications for corticosteroids are to reduce inflammation from central nervous system tumors and as therapy for immune-related toxicities High-dose corticosteroids have inhibitory effects on multiple com ponents of innate and adaptive immunity. The risk of infections is related to their dose and duration, the underlying malignancy, and other immunosuppressive agents that are used concurrently. For exam ple, induction therapy for acute lymphoblastic leukemia includes both cytotoxic agents that result in pancytopenia and corticosteroids that cumulatively increase infection risk. Corticosteroids can also decrease signs of infection such as fever and abdominal tenderness. The inhibi tory effect of corticosteroids on T cell immunity increases the risk of infections by viruses (e.g., HSV, varicella-zoster virus [VZV]), myco bacteria, Nocardia species, and fungal infections, including mucosal candidiasis, dimorphic fungi, and Pneumocystis jirovecii pneumonia (PJP) (Table 79-1). Prophylaxis against Pneumocystis jirovecii with trimethoprim sulfamethoxazole (TMP-SMX) (or an alternative agent if

intolerant) is recommended in patients receiving the adult equivalent of prednisone ≥20 mg per day for at least 4 weeks. Radiation Radiation causes direct tissue damage (including dam age to the vasculature) and impairs wound healing. Infectious com plications of radiation include local infection and fistulization. As an example, neoadjuvant radiation therapy for rectal tumors increases the risk of surgical site infections. Radiation to the head and neck increases the risk of infections related to the tumor and as a surgical complica tion. Osteoradionecrosis of the jaw predisposes to secondary infections of the soft tissue and bone that may require combined prolonged anti biotics and surgical removal of dead bone and reconstruction. Splenectomy Splenectomy may be performed for diagnosis or treatment of cancer. The spleen has several key immune functions including removing of bacteria from blood, antigen presentation to T cells, and housing B cells that are activated and produce antibodies. Functional asplenia is present after

splenic irradiation and with chronic GVHD. Asplenic patients are principally at risk for overwhelming sepsis by encapsulated bacteria like Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitidis. Patients should be vaccinated against these pathogens prior to planned splenectomy. Antibiotic pro phylaxis (e.g., with penicillin) should be considered for the first 2 years after splenectomy, especially in patients with active malignancy or receiv ing immunosuppressive therapy. Asplenic patients with fever should be started promptly on antibiotics active against S. pneumoniae (e.g., ceftriaxone or levofloxacin or moxifloxacin). Vancomycin should be added in areas where high-level penicillin or cephalosporin resistance is common. Asplenic individuals also have increased risk of babesiosis, malaria, and infection with Capnocytophaga canimorsus (associated with animal bites or scratches) and Salmonella spp. B Cell–Depleting Agents B cell–depleting agents are used as therapy for patients with B cell malignancies, such as B cell lymphomas and chronic lymphocytic leukemia. They are commonly used in com bination with other antineoplastic agents. Antibody-based drugs such as rituximab result in prolonged B cell depletion, while Bruton tyrosine kinase (BTK) inhibitors (e.g., ibrutinib) interrupt a key enzyme and B cell activation but have shorter-acting effects. The effects of B cell depletion include increased risk of encapsulated bacteria and respi ratory viral infections. Importantly, these patients are likely to have reduced immune responses to vaccination against bacteria and viruses, including influenza, SARS-CoV-2, and hepatitis B. The risk of severe COVID-19 is substantially increased in patients with hematologic malignancies compared with patients with solid tumors, and B cell– depleting agents are associated with increased COVID-19 severity and lack of serologic responses to SARS-CoV-2 infection and vaccination. All patients who will receive B cell–depleting agents should be screened for hepatitis B infection and receive therapy for hepatitis B (e.g., with entecavir or tenofovir alafenamide) for active or prior hepatitis B infection (see Chaps. 350 and 352 on hepatitis viruses and Chap. 208 on human immunodeficiency virus [HIV] infections). Rituximab and other B cell–depleting agents have been associated with progressive multifocal leukoencephalopathy (PML) and PJP, but the magnitude of the effect is difficult to ascertain. In addition, BTK inhibitors can have off-target effects on innate immune cells and increase the risk of other infections, including invasive aspergillosis, particularly when com bined with other immunosuppressive agents, such as corticosteroids. Bispecific Antibodies Bispecific antibodies are engineered to have dual specificity for a T cell antigen (e.g., CD3, a component of the T cell receptor complex) and a tumor antigen with the goal of stimulating T cell killing of tumor cells. When bispecific antibody con structs directed against B cell antigens (e.g., blinatumomab, a bispecific antibody against CD3 and the B cell antigen CD19) are used against B cell malignancies, the overall effect is a nonselective depletion of both tumor cells and normal B cells. Importantly, bispecific antibodies are commonly used in patients with refractory hematologic malignancies who already are at high risk for infection based on the underlying can cer and prior therapy. Bispecific antibody therapy can result in CRS,

characterized by fever and inflammatory organ damage. Treatment of CRS involves high-dose corticosteroids and interleukin 6 (IL-6) block ade, which further increases the risk of infections.

Adoptive Cellular Therapy Adoptive cellular therapy (ACT) involves administration of genetically engineered cells targeted to tumor antigens. The most commonly used ACT is chimeric antigen receptor (CAR) T cells, in which autologous T cells are genetically engi neered to express a receptor directed against a tumor antigen. Engage ment of cells expressing this antigen results in the CAR T cell activation and tumor cell killing. In contrast to bispecific antibodies, current ACT involves lymphodepletion chemotherapy (usually with fludarabine and cyclophosphamide) to deplete

immune cells and allow maximal expan sion of the engineered T cells. A major goal of immunotherapy is to make ACT more effective for a broad range of solid tumors; however, the current use of ACT largely involves refractory B cell malignancies: lymphoblastic leukemia, lymphomas, and multiple myeloma. Lym phodepletion regimens result in pancytopenia, and both neutropenia and lymphopenia can be prolonged (months to years). In the case of standard CD19-directed CAR T cells, B cell depletion is by design; the persistence of CAR T cells is required for antitumor immunity, but it is nonselective, and the duration of global B cell depletion can be for years. ACT can also be complicated by CRS and an immune effector cell–associated neurotoxicity syndrome that can be life-threatening and requires treatment with intensive high-dose corticosteroids often combined with IL-6 blockade. Additional hematologic complications can occur after ACT, such as hemophagocytic lymphohistiocytosis (HLH), which extends pancytopenia and entails additional immuno suppressive therapy. CHAPTER 79 Infections in Patients with Cancer Recommendations regarding prophylaxis following ACT are based mainly on extrapolation and expert opinion. These include levofloxa cin during neutropenia, TMP-SMX while on systemic corticosteroids or while CD4 count is <200/μL, acyclovir, and perhaps mold-active prophylaxis (e.g., posaconazole) during periods of prolonged neutro penia. Recipients of CAR T cells constitute a heterogeneous population due to the effect of multiple previous courses of therapy, sometimes including allogeneic HCT, and prophylaxis should be tailored to the degree of immunosuppression. Cancer and HIV Infection HIV-associated malignancies include Epstein-Barr virus–associated non-Hodgkin and Hodgkin lymphomas, HHV-8-associated Kaposi sarcoma and primary effusion lymphoma, and human papilloma virus–associated cervical and anal cancer. HIVpositive patients have higher risks of chronic hepatitis B and hepatitis C infections that increase the risk of hepatocellular carcinoma. Patients with HIV infection can also have cancers that are not HIV-associated. A mainstay of cancer management in patients who are HIV-positive is that the antineoplastic regimen must be concurrent with antiretroviral therapy and appropriate prophylactic antimicrobials. The goals of anti retroviral therapy are a nondetectable HIV viral load and tolerability of the regimen, which includes monitoring and avoiding drug–drug interactions with antineoplastic chemotherapy. In general, it is recom mended to test for HIV and hepatitis B and hepatitis C infection prior to starting antineoplastic therapy. DIAGNOSIS AND MANAGEMENT OF INFECTIONS IN PATIENTS WITH NEUTROPENIA Chemotherapy-induced neutropenia remains the major risk factor for infection in patients with cancer. However, patients with cancer fre quently have multiple risk factors for infection, both from the under lying malignancy and its treatment. When evaluating patients with neutropenia and suspected infection, it is important to consider these other risk factors in the diagnostic evaluation and therapy (Fig. 79-1). ■ ■NEUTROPENIC FEVER A high proportion of cancer patients who become neutropenic after receiving chemotherapy develop fever. The standard definition of neu tropenic fever (NF) is a single oral temperature ≥38.3°C or a tempera ture of ≥38.0°C sustained over 1 h, with an absolute neutrophil count

A B FIGURE 79-1 Multiple pulmonary infections in a patient with acute myelogenous leukemia (AML). A patient with AML in remission after reinduction therapy with cytarabine, granulocyte colony-stimulating factor, and fludarabine (FLAG) presented with fever and neutropenia. A chest CT demonstrated diffuse pulmonary infiltrates (A). Bronchoalveolar lavage (BAL) was unrevealing except for positive PCR for Pneumocystis jirovecii, and trimethoprim-sulfamethoxazole was instituted. After 11 days of appropriate treatment (B), a repeat CT showed resolution of the infiltrates but a conspicuous, dense, well-circumscribed pulmonary nodule that had not been appreciated initially. Targeted BAL of the left lower lobe was positive for galactomannan, providing

the diagnosis of probable invasive aspergillosis. The initial BAL had been of the right middle lobe only. Immunocompromised patients may have several infections simultaneously, and cancer patients often accumulate risk factors for infection during their treatment. PART 4 Oncology and Hematology (ANC) of <500 cells/μL, or an ANC that is expected to decrease to <500 cells/μL over the next 48 h. During neutropenia localizing signs and symptoms of infection may be subtle or altogether lacking, and infections may progress very quickly. These two basic features mandate early initiation of empiri cal antibacterial agents in neutropenic patients whenever infection is suspected. Although fever is the most common sign of infection, it is not the only one, and similar management should be used whenever infection is suspected in a neutropenic patient, such as in the presence of otherwise unexplained pain, tenderness, or erythema potentially secondary to infection. NF is considered infectious in origin, but an infection is identified in only a minority of cases. An infection may be documented micro biologically (e.g., Pseudomonas aeruginosa bacteremia identified by positive blood cultures) or only clinically (e.g., abdominal pain and bloody diarrhea with negative blood cultures, presumed to represent neutropenic enterocolitis). Using standard diagnostic methods (i.e., routine cultures, serologic tests, and imaging studies) an infection is documented in approximately 40% of episodes of NF. However, newer diagnostic modalities using plasma cell–free DNA polymerase chain reaction (PCR) identify a potential bacterial etiology most of the time. Most bacteria identified by these studies are part of the normal flora of skin and bowel (as are the bacteria isolated by standard culture methods when these are positive), since these physical barriers are often disrupted by the cancer treatments that caused the neutropenia. Infections during neutropenia are typically caused by microorganisms carried by the patient as part of their microbiome. ■ ■MANAGEMENT OF NEUTROPENIC FEVER First Neutropenic Fever There is a wealth of good-quality evi dence to support standard-of-care guidelines for the management of the initial episode of NF. After a swift history and physical exam (focused on potential portals of entry like the vascular catheter exit site, mouth, and perianal area), blood cultures are obtained and empirical antibiotic therapy is initiated using a single agent (monotherapy) with broad-spectrum activity, including coverage of P. aeruginosa. Ideally, anti biotics should be given within 1 h of the onset of NF. The diagnostic utility of chest imaging in the absence of respiratory symptoms or signs has not been established. Ceftazidime, cefepime, imipenem, meropenem, and piperacillintazobactam are the best-studied antibiotics used as monotherapy for NF. The specific choice will vary from institution to institution based on the local frequency of resistant bacteria. This “backbone regimen”

may be complemented with a second agent against resistant gramnegative or gram-positive bacteria depending on clinical features, prior history of resistant pathogens, or local trends of antimicrobial resistance. It should be emphasized that standard empirical monotherapy regimens for NF apply to clinically stable patients with NF of unclear etiology. Management of neutropenic patients with localized signs of infection (e.g., respiratory, intra-abdominal, intravascular catheter–associated) are discussed below. In patients who are clinically unstable, such as those with hypotension or signs of organ injury raising con cern for sepsis (e.g., impaired mental status, pulmonary edema, acute renal injury), a broader-spectrum antimicrobial regimen is warranted. Although the specific regimen for presumed or documented septic shock varies based on the patient’s prior history of resistant infection and local susceptibility patterns, an example of an initial regimen is vancomycin, meropenem, and possibly an aminoglycoside; in patients at risk for candidiasis, an echinocandin may be added. The standard monotherapy regimens lack activity against specific gram-positive pathogens. Gram-positive coverage with a glycopeptide antibiotic

(vancomycin in the United States) is not routinely part of the initial regimen. Instead, the addition of a glycopeptide is reserved for clinical situations in which a gram-positive pathogen resistant to the standard regimen (e.g., methicillin-resistant Staphylococcus aureus [MRSA]) is more likely. The Infectious Diseases Society of America (IDSA) guidelines recommend empirical gram-positive coverage with sepsis, clinically evident soft tissue infection, clinically suspected cath eter exit site infection, pneumonia, severe mucositis (only if ceftazi dime is used as empirical regimen, because mucositis is a risk factor for viridans group streptococci), and known carrier status of MRSA or penicillin-resistant pneumococcus. Meta-analysis has shown that the routine inclusion of vancomycin in the initial regimen is not associated with better outcomes but does result in more nephrotoxicity. After starting antibiotics, fever usually resolves in 24–72 h. If an infection was diagnosed, antibiotics are continued for the appropriate amount of time for that specific infection. When a specific microbe is isolated (e.g., from blood cultures), experts disagree regarding the need for continuing the broad-spectrum coverage versus narrowing based on susceptibility results. If no microorganism is isolated and no source is identified, the optimal strategy for antibiotic management of NF that resolves with antibiotics is debated. In the past, empirical antibiotics were continued until resolution of neutropenia. However, recent studies have suggested that de-escalation from empiric therapy to prophylaxis or discontinua tion are safe if specific criteria are met, including clinical stability. The advantage of such de-escalation or early discontinuation strategies relates to reduced antibiotic exposure and lower risk of selection of resistant pathogens; these benefits must be balanced against the poten tial for inadequately treated infection. Large, randomized, multicenter trials are required to evaluate the benefits and safety of antibiotic deescalation or discontinuation of empirical antibiotic therapy in patients with persistent neutropenia. Persistent Fever If the fever continues while receiving empirical antibiotic therapy without a diagnosis, evidence supports and guide lines recommend continuing the same antibiotic without addition or modification in the absence of clinical changes or new microbiologic data. The antibacterial regimen should be modified only if new clinical features arise (e.g., hypotension) of if new microbiologic data become available (e.g., a positive culture), and not just because of persistent fever. Although there is agreement on this issue between different guidelines, persistent, stable fever is a common reason why the anti bacterial regimen is modified in clinical practice. The longer the neu tropenic fever persists during the administration of broad-spectrum antibiotics, the higher the likelihood of IFD. Depending on prior his tory, use of antifungal prophylaxis, and local practices, one may choose to initiate empirical antifungal treatment after 5 days of fever (this was standard of care for decades and is called empirical antifungal therapy) or to perform tests focused on diagnosing an occult fungal infec tion and initiate antifungals only if these additional tests support the

possibility of IFD. This more recent approach has been named preemp tive antifungal strategy and seems to result in similar patient outcomes with less use of antifungals. The empirical antifungal of choice will vary depending on the antifungal prophylaxis used (if any). Caspofungin and liposomal amphotericin B are the best-studied empirical antifun gal treatment of NF, but expert recommendations vary. A frequently used approach is to administer posaconazole as antifungal prophylaxis in high-risk patients with neutropenia (e.g., those receiving induc tion or reinduction regimens for acute myeloid leukemia) and to not modify the antifungal regimen based solely on persistent or recurrent neutropenic fever. Recrudescent Fever and Fever at the Time of Neutrophil Recovery In addition to the initial episode of fever and persistent fever, there are two other NF scenarios that have been less well stud ied: recrudescent fever and fever at the time of neutrophil

recovery. Recrudescent fever refers to the situation in which the initial episode of fever resolves without a diagnosis, neutropenia persists, the antibi otic regimen is continued unmodified, and fever reappears after the patient has been afebrile for 48–96 h. This is not uncommon during prolonged neutropenia during induction or reinduction therapy in acute leukemia. In this case (as opposed to the first episode of NF), an infection is identified most of the time (bacterial, fungal, or viral), and the recommended approach is to empirically modify the antimicrobial regimen that had successfully controlled the fever up to this point, aiming for coverage of resistant bacteria and fungi. Intensive diagnos tic procedures, including CT imaging, should be undertaken. Where available, CT combined with positron emission tomography (CT-PET) may be considered. Finally, fever at the time of neutrophil recovery may be infectious in origin: either a preexisting infection that was silent due to lack of neutrophils (sometimes this is considered analogous to the immune reconstitution inflammatory syndrome [IRIS] seen after initiation of antiretroviral therapy in AIDS) or, less likely, a superinfection. How ever, fever is frequently noninfectious at this time and is related to myeloid engraftment. In any case, the recommended response to fever that occurs simultaneously with resolution of neutropenia is not any specific empirical antimicrobial regimen, but to pursue a thorough diagnostic evaluation. ■ ■OUTPATIENT THERAPY FOR NEUTROPENIC FEVER Outpatient therapy for neutropenic fever should be considered in patients at lower risk for infectious complications from neutropenia. These patients typically have solid rather than hematologic tumors with a short expected duration of neutropenia, usually 7 days or less. Criteria for candidates for outpatient empirical therapy include clinical stability, no localizing symptoms or signs of infection, ability to eat and drink without difficulty, absence of significant comorbidities such as chronic lung or cardiovascular disease, normal renal and liver function, and easy access to a hospital and a caregiver at home. Outpatient oral antibiotic therapy in adults typically involves a quinolone (e.g., levo floxacin or ciprofloxacin) plus amoxicillin-clavulanate; such regimens are appropriate only for patients who have not received a quinolone as prophylaxis. DOCUMENTED INFECTIONS DURING NEUTROPENIA ■ ■BACTEREMIA Bacteremia is the most common microbiologically documented infec tion in neutropenic patients with fever. NF is associated with bacte remia in only 10% of cases, but this subgroup of patients has much higher mortality than the general group of neutropenic patients with fever, particularly with gram-negative bacteremia. Most recent series show similar proportions of gram-positive (coagulase-negative Staphylococcus, Streptococcus species, Enterococcus species including vancomycin-resistant Enterococcus [VRE]) and gram-negative bacteria (Enterobacterales and P. aeruginosa).

Bacteremia in neutropenic patients may be secondary to another site of infection (e.g., pneumonia, neutropenic enterocolitis, cellulitis) or, most commonly, to mucosal barrier injury (MBI) caused by the anti neoplastic treatment. The chemotherapy and/or radiation frequently damages the mucosa of the gastrointestinal tract, facilitating translo cation of commensal bacteria during neutropenia. Clinically, one may question whether the bacteremia may be a central line–associated blood stream infection (CLABSI). If the isolate is an intestinal bacterium, it is considered related to MBI in the absence of local signs of infection involving the venous catheter. If the isolate is part of the skin flora, like coagulase-negative Staphylococcus, it is more likely to be a CLABSI, but it may also represent a contaminant or colonization of the catheter. Colonization or contamination should be presumed when only one of several blood culture bottles is positive for normal skin flora, especially if the culture takes more than 24 h to turn positive. When a blood culture becomes positive for a gram-positive organism, it is important to repeat blood cultures, ideally from both central and peripheral sites, to determine whether the blood culture isolate is recovered from more than one

bottle and at different time points. Skin flora growing from blood drawn from the catheter with negative peripheral blood cultures can reflect catheter colonization (i.e., not a true bloodstream infection) or CLABSI with low levels of bacteria in blood resulting in negative peripheral cultures. When both the peripheral and the central blood cultures are positive for the same organism, bacteremia is con firmed, and the differential time to positivity may allow establishing the diagnosis of catheter-related bacteremia if the central line culture grows at least 2 h earlier than the peripheral. However, the practice of always obtaining a peripheral blood culture may not be practical on an oncology ward, where patients may be febrile daily and are frequently thrombocytopenic.

CHAPTER 79 Infections in Patients with Cancer More important than whether blood cultures are collected from the central catheter alone or from central and peripheral venous sources is ensuring that an adequate volume of blood (as determined by the specific blood culture platform) is collected. The optimal frequency of blood cultures in NF has not been established. Similarly, the use of surveillance blood cultures in neutropenic patients has not been adequately studied. The amplification by PCR of plasma cell–free DNA, with its superior yield compared with blood cultures, is still investigational, and its place in the routine management of NF remains to be defined. If CLABSI is diagnosed, the preferred treatment is to remove the catheter. Again, this may not always be practical in the case of thrombocytopenic patients with limited access, and an attempt to salvage a permanent catheter (i.e., tunneled catheter or port) may be appropriate as long as the patient remains hemodynamically stable and

the blood cultures become negative upon initiating appropriate anti biotics. Antibiotic lock therapy should be considered, if feasible. The likelihood of success when a catheter is colonized with S. aureus, mycobacteria, or Candida species is low, and these catheters should be removed as soon as possible. It is customary to provide some time without central access (e.g., a 48-h “line holiday”) before replacing the central venous catheter, although the evidence supporting this practice is scant. Patients may require continuous central IV access, and in this case it is reasonable to use nonsurgically placed lines (e.g., a peripher ally inserted central catheter) and to place a new surgically implanted port (e.g., mediport) only when there is clear evidence of blood culture clearance. Endocarditis is rare during neutropenia, but it should be suspected with persistently positive blood cultures or with clinical findings like a new murmur or embolic phenomena. Routine echocardiogram in every case of bacteremia in neutropenic patients is not recommended, but patients with S. aureus bacteremia do require one. ■ ■RESPIRATORY INFECTIONS Sinusitis Sinusitis may manifest by pressure, facial pain, rhinor rhea, and postnasal drip but occasionally has very mild symptoms that will be elicited only by targeted questioning during the physical exam. Symptomatic sinusitis in neutropenic patients may be caused by

pathogens relatively uncommon in immunocompetent people, includ ing S. aureus, P. aeruginosa, and other gram-negative bacilli. Evaluation by CT and consultation by otolaryngology to examine the integrity of the mucosa and obtain samples for culture is recommended. Invasive fungal sinusitis may be caused by Aspergillus species, agents of mucor mycosis, Fusarium species, and relatively less virulent dematiaceous molds like Alternaria, Bipolaris, or Curvularia. CT findings sugges tive of fungal etiology include marked asymmetry, heterogeneous radiodensity of the contents of the sinuses, and, later in the disease, bony erosions. The endoscopic exam may show pale, devitalized mucosa and, sometimes, necrotic ulceration of a turbinate caused by the

angioinvasive process. Invasive fungal sinusitis during neutropenia mandates surgical resection. Repeated visits to the operating room in conjunction with optimal antifungal therapy are necessary to save the patient’s life. The empirical antifungal agent may vary depending on the preexisting antifungal prophylaxis, but, given the possibility of mucormycosis and fusariosis, many experts would recommend a lipid formulation of amphotericin B, often considered the antifungal of choice for mucormycosis, together with posaconazole, which is nonin ferior to voriconazole for Aspergillus species and has superior activity in vitro against dematiaceous molds.

Pneumonia Pulmonary infiltrates are a common diagnostic chal lenge in immunocompromised hosts. A systematic approach to the differential, which includes infections and noninfectious etiologies, is mandatory. Some important noninfectious conditions to be consid ered include heart failure, fluid overload, transfusion reactions like transfusion-associated circulatory overload (TACO) and transfusionassociated lung injury (TRALI), chemotherapy-associated pneumoni tis, organizing pneumonia, and diffuse alveolar hemorrhage, as well as dissemination of the cancer itself. The radiologic appearance is useful to separate unilateral focal processes (suggestive of bacterial or mold infection) from multifocal or diffuse infections, which may be caused in addition by viruses, atypical bacteria, and PJP. Single or multiple dense, well-circumscribed nodules suggest IFD in high-risk patients (e.g., those with leukemia and allogeneic stem cell transplant recipi ents), but Nocardia species may have the same appearance and other bacteria like P. aeruginosa and Stenotrophomonas maltophilia may cause angioinvasive infection and result in similar radiology. Unfor tunately, characteristic radiologic differences may not hold true in an individual case, and every attempt should be made to obtain a respira tory sample for microbiologic diagnosis. PART 4 Oncology and Hematology Early bronchoscopy with bronchoalveolar lavage (BAL) in neutro penic patients with pneumonia is recommended. The yield of BAL is highest for diffuse and multifocal processes. In the case of pulmonary nodules accessible to percutaneous or endobronchial biopsy, the choice of diagnostic procedure will often depend on institutional expertise, clinical status, and comorbidities. The empirical antimicrobial regi men may vary slightly depending on the radiology and the individual risk factors but should always provide optimal antibacterial coverage by combining one of the antipseudomonal β-lactams together with vancomycin and an agent active against Legionella, like azithromycin, a fluoroquinolone, or doxycycline. If the patient has risk factors for

S. maltophilia (high prevalence in the institution, previous exposure to carbapenems), the addition of TMP-SMX or levofloxacin should be considered. The empirical addition of TMP-SMX for PJP depends on the clinical scenario and risk factors. If the only immune defect of the patient is neutropenia, the main concerns are bacteria and molds, the likelihood of PJP is low, and empirical anti-Pneumocystis coverage seems unnec essary. However, patients with hematologic malignancies often have received corticosteroids or other agents that decrease cellular immu nity and put them at risk for PJP. In this case, empirical coverage until PJP has been ruled out is reasonable. The current gold standard for the diagnosis of PJP is PCR of respiratory secretions, which occasionally may detect patients who are merely colonized. Serum β-d-glucan is typically elevated in patients with PJP, and a positive result increases the likelihood of PJP in a patient with appropriate risk factors and radiologic findings. However, false-positive and -negative β-d-glucan

results occur, and this test is not specific for PJP; therefore, a positive serum β-d-glucan does not always obviate the need for BAL. Invasive fungal disease (IFD) is suggested by single or multiple

dense, well-circumscribed nodules, particularly larger than 2 cm. The halo sign (ground glass opacity surrounding a dense nodule) or the reverse halo sign (ground glass opacity seen inside a nodule, some times said to be more common in mucormycosis) may be present, but these are not diagnostic. Peripheral wedge-shaped infiltrates also may be seen. In patients at high risk for IFD, initiation or escalation of antifungal therapy is commonly begun prior to establishing a diagno sis. Such decisions must consider the antifungal prophylaxis that the patient is receiving. If the patient is on fluconazole or no antifungal prophylaxis, a mold-active azole (e.g., voriconazole, posaconazole, isavuconazole) as empirical therapy is reasonable pending a diagnosis, since Aspergillus is by far the most likely mold infection. If on the other hand, a suspected fungal infection occurs while receiving a mold-active azole, many experts would recommend switching the regimen to lipo somal amphotericin B, while aggressively pursuing a diagnosis. Evaluation of suspected pneumonia involves sputum and blood cultures, nasopharyngeal swab for PCR for respiratory viruses, urine Legionella antigen, and in patients with neutropenia, evaluation for IFD (e.g., serum galactomannan, beta-glucan) should be included. If these studies are negative and the empirical antimicrobial regimen does not lead to improvement, early BAL or image-guided percutaneous lung biopsy should be considered. If non-invasive diagnostic studies identify a pathogen, it is important to consider the potential for concurrent or secondary infection by other pathogens. For example, respiratory viral infections can be complicated by secondary bacterial pneumonias, and cases of invasive pulmonary aspergillosis following COVID-19 have been documented. It is therefore important to consider a broad differential diagnosis and to repeat imaging and diagnostic evaluation in patients with worsening pneumonia even when an initial diagnosis has been made. ■ ■INTRA-ABDOMINAL INFECTIONS Neutropenic Enterocolitis (Typhlitis) Sometimes bacteria invade the wall of the intestine and proliferate there, causing inflamma tion and even necrosis of segments of the bowel. The clinical syndrome includes fever, abdominal pain, and tenderness and diarrhea, which is occasionally bloody. The term typhlitis (inflammation of the cecum) is sometimes used, as the cecum is most commonly involved, but the terminal ileum, ascending colon, and other segments of the intestine also may be affected, so the more general term neutropenic enterocolitis is preferred. Blood cultures are frequently positive (with bowel flora), but not always. Plain films of the abdomen are not sensitive or specific, but a right lower quadrant soft tissue density, distended bowel loops, ileus, or “thumbprinting” suggesting mucosal edema may sometimes be seen. A CT scan of the abdomen and pelvis usually demonstrates a right lower quadrant inflammatory mass, with thickened bowel wall and stranding of the surrounding fat. Conservative management with broad-spectrum antibiotics, bowel rest, bowel decompression, and nutritional support is usually preferred. Surgery may be required if the patient deteriorates and intestinal perforation, peritonitis, and hemo dynamic instability ensue. Carbapenems and piperacillin-tazobactam are appropriate given their broader spectrum. If ceftazidime or cefepime is used, additional agents against anaerobic bacteria (e.g., metronidazole) must be added. In selecting an empirical regimen, it is important to note prior infections with antibiotic-resistant infections, such as VRE, and extended-spectrum β-lactamase (ESBL) of carbapenem-resistant (CRE) gram-negative infections. Similar to intra-abdominal infections, perirectal and perianal infec tions are caused by gastrointestinal flora in the context of neutropenia and mucosal injury. CT imaging is helpful to assess the extent of infec tion. These infections typically respond to broad-spectrum antibiotic therapy without the need for surgery, but follow-up imaging after neu trophil recovery may be necessary if symptoms or fever persist. Clostridioides difficile (C. difficile)–Associated Disease Cancer patients are at increased risk of C. difficile–associated disease (CDAD)

because of their frequent exposure to healthcare facilities, antibiotics, and chemotherapeutic drugs. Patients with a history of CDAD in the previous year are often treated prophylactically with oral vancomycin (125 mg daily) when empirical antibiotic therapy for neutropenic fever is begun. Every hospitalized neutropenic patient with diarrhea should be tested for C. difficile. It is unclear whether neutropenic patients with CDAD have worse outcomes, higher risk of complications, or increased frequency of neutropenic enterocolitis. First-line treatment is fidaxomicin, with oral vancomycin as an alternative. In case of ileus or overwhelming CDAD, combination of either oral fidaxomicin or van comycin with IV metronidazole (which is secreted into the intestinal lumen) is recommended. Cholecystitis Cholecystitis is a rare infection during neutropenia, and most cases have been seen during treatment of acute leukemia. The presentation is like that in nonneutropenic individuals, but bacteremia is more common. At least half of the reported cases have been acal culous cholecystitis. Conservative management, frequently including cholecystostomy, is used until resolution of neutropenia when chole cystectomy can be performed more safely. ■ ■CENTRAL NERVOUS SYSTEM INFECTIONS Bacterial central nervous system (CNS) infections are uncommon during neutropenia and usually secondary to an episode of bacteremia (which may or may not have been detected) or to extension from the paranasal sinuses. Meningitis caused by gram-negative bacilli, includ ing P. aeruginosa, may occur in this setting. Two unexpected causes of CNS infections are worth mentioning. Rothia mucilaginosa, a grampositive coccus that is part of the oral flora, may seed the meninges during a transient bacteremia that seemed to be controlled easily with appropriate antibiotic treatment. This is a rare infection, and most cases treated successfully have received meropenem and vancomycin. Similarly, Bacillus cereus, a gram-positive bacillus ubiquitous in the environment, has been reported as a cause of difficult-to-treat men ingitis and brain abscess in neutropenic patients with acute leukemia. The combination of meropenem and vancomycin also has been used successfully. Listeria monocytogenes meningitis and bacteremia are most common in patients with impaired cellular immunity, includ ing patients with cancer receiving immunosuppressive regimens. Besides meningitis, L. monocytogenes can also cause rhombencephalitis (inflammation of the brainstem and cerebellum) and brain abscess. The combination of ampicillin and gentamicin is recommended. In cases of penicillin allergy TMP-SMX may be used. Listeria monocyto genes is susceptible in vitro to meropenem and linezolid, but clinical experience is limited. In patients with hematologic cancers and prolonged neutropenia, brain lesions should raise the concern for opportunistic pathogens, usually fungi. Aspergillus and Candida brain abscesses are usually hematogenous; mucormycosis more frequently follows extension from the sinuses. Empirical treatment should be administered including antibacterial (typically meropenem plus vancomycin) and antifungal agents until the etiology is established. As mentioned for pulmonary infections, the choice of antifungal may be conditioned by preexisting antifungal prophylaxis. Voriconazole is the preferred agent for CNS aspergillosis and liposomal amphotericin B for mucormycosis. Echino candins do not achieve therapeutic levels in the brain or cerebrospinal fluid (CSF), and they should not be relied upon for the treatment of CNS infections. Nocardia species and Toxoplasma gondii are important causes of brain abscess in immunocompromised patients. The major risk factor for these infections is suppressed T cell immunity. In patients with cancer, prolonged intensive corticosteroid therapy and use of purine analogues are examples of risk factors. TMP-SMX used as prophylaxis for PJP may also confer some protection against Listeria, Nocardia, and Toxoplasma. Patients with cancer are at increased risk of viral encephali tis. Herpes simplex virus (HSV) encephalitis is characterized by fever and decreased level of consciousness. Imaging shows unilateral

involvement of the temporal lobe. Abnormalities in the CSF may be altered by radiation therapy or corticosteroids. The diagnosis is by PCR of the CSF, which may be falsely negative early in the course of the disease. Herpes zoster encephalitis is a rare but devastating complica tion in patients with defective T cell immunity. Human herpesvirus 6 (HHV-6) encephalitis is rare outside of allogeneic stem cell transplan tation (allo-HCT) (see Chap. 148). Finding a high level of HHV-6 in blood in any other setting brings up the possibility of HHV-6 chromo somal integration, which is present in around 1% of the population.

In patients who have had neurosurgery, including those with neurosurgical devices (e.g., shunts or reservoirs), infections by grampositive bacteria are most common, although gram-negative infections including coliforms and P. aeruginosa can occur. Risk factors include multiple neurosurgeries (e.g., for recurrent tumor), cranial irradiation, antiangiogenics (which disrupt blood supply), and use of immuno suppressives. Vancomycin plus an antipseudomonal cephalosporin (e.g., ceftazidime) is an appropriate initial regimen for postneuro surgical CNS infections, pending culture data. Surgical drainage and debridement of infected material and removal of hardware are usually required. CHAPTER 79 ■ ■SKIN AND SOFT TISSUE INFECTIONS As a rule, focal skin lesions in neutropenic, febrile patients should be biopsied, as the diagnostic possibilities are multiple, and some of the causes may be life-threatening and require immediate treatment. Cellulitis may be caused by streptococci or S. aureus, but also by gram-negative bacilli, and broad-spectrum coverage with an antip seudomonal β-lactam and vancomycin should be administered until an etiologic diagnosis is established. Multiple foci of erythematous tender plaques with underlying fasciitis and myositis are associated with bacteremia by Clostridium septicum, sometimes seen in patients with colorectal cancer. Ecthyma gangrenosum appears as a tender, erythematous papule that then becomes necrotic and ulcerated. It may be caused by local inoculation or by hematogenous seeding, typically of

P. aeruginosa but sometimes other gram-negative bacteria or even molds like Fusarium species. Single or multiple lesions may be seen. Disseminated candidiasis with hematogenous cutaneous disease mani fests with fever and other signs of systemic infection and multiple raised cutaneous papules. Hemorrhagic bullae are described in cel lulitis caused by gram-negative bacteria (including Vibrio vulnificus, which may be suspected with a history of liver dysfunction and expo sure to shellfish). Infections in Patients with Cancer Many noninfectious processes can cause skin lesions, but the pres ence of fever is unusual except in Sweet syndrome, also known as acute neutrophilic dermatosis (Fig. 79-2). This is characterized by fever and a variety of skin lesions including papules, nodules, plaques, and some times blisters. Skin lesions are often tender and may ulcerate. Sweet syndrome can have many causes, including underlying cancer, usually hematologic. Pathergy is characteristic, and lesions may appear at the insertion site of an intravascular catheter, mimicking infection (Fig. 79-2). Leukemia cutis may manifest as a variety of nontender papules, nodules, or plaques. Fever is unusual. Chemotherapeutic agents can cause a variety of skin reactions, including hyperpigmenta tion, hand-foot syndrome (erythema, edema, and blistering of palms and soles), and several rashes. Definitive diagnosis often requires biopsy of skin lesions with appropriate cultures and histopathology. ■ ■URINARY TRACT INFECTIONS It is common to obtain urine cultures in patients with NF regardless of urinary symptoms, and sometimes bacteriuria is detected. The question of whether it is just asymptomatic bacteriuria (common and increasing with age in both men and women), unrelated to the fever, or reflects true urinary tract infection (UTI) necessitating specific treatment may not be immediately answerable. It

is appropriate to treat bacteriuria in patients with NF, and standard empirical antibiotic regimens used for NF will cover most urinary pathogens. If UTI is believed to be the source of NF, CT imaging should be considered to

A B C D PART 4 Oncology and Hematology FIGURE 79-2 Sweet syndrome. A 47-year-old man admitted for acute myelogenous leukemia (AML) received a surgically implanted catheter and was started on idarubicin and cytosine arabinoside (Ara-C). He developed erythema and tenderness at the insertion site and the cuff site after 24 h, followed by fever. The catheter was removed and cultured (negative) and broad-spectrum antibiotics started, without effect. The catheter exit site worsened, with bullae formation (A). New skin nodules developed on his left thigh, both cheeks, and scalp. Tender induration of the sternocleidomastoid muscle was noticeable clinically and by CT (B). Skin biopsy showed a dense infiltrate of mature neutrophils consistent with Sweet syndrome (C, D). The lesions and the fever resolved promptly with oral prednisone. evaluate for complicated UTI with potential etiologies including geni tourinary tract obstruction by tumor or kidney stones, pyelonephritis, and prostatitis. PREVENTION OF INFECTIONS

IN PATIENTS WITH CANCER Prevention measures to avoid infections should be tailored to the immune status of the patient and consequent risk of infections. The most stringent measures apply to patients with hematologic malignan cies with prolonged neutropenia, to stem cell transplant and adop tive cellular therapy recipients, and to other patients who may have prolonged neutropenia for other reasons (e.g., aplastic anemia) or are receiving intensive systemic corticosteroid therapy. At the other end of the spectrum are patients with solid tumors who are in remission and not receiving active chemotherapy or only receiving hormonal agents, such as antiestrogen therapy for breast cancer. These patients should adhere to guidelines to prevent infection that apply to the general population such as hand hygiene, food safety, and guideline-based vac cines. This section is focused on prevention measures for patients with cancer at high risk for infections including opportunistic infection. ■ ■ENVIRONMENTAL PRECAUTIONS Inpatient leukemia and transplant wards are typically engineered with HEPA filters and appropriate air exchanges, and individual patient rooms are under positive pressure relative to the outside. The principal rationale for these precautions is to reduce mold spore exposure; these structural precautions were in part driven by outbreaks of aspergillosis. For similar reasons, houseplants are restricted from these wards. Con struction, which can release mold spores, must be performed under stringent infection control precautions to minimize patient exposure. In addition to limiting mold exposure, these precautions may have additional benefits to limit airborne transmission of other infections. The vast majority of chemotherapy regimens are administered to outpatients, including to patients with hematologic malignancies

receiving intensive immunosuppressive regimens. The stringent envi ronmental precautions used for inpatients are not feasible in the out patient setting or in the home. Patients should not have construction done in their homes and should avoid exposure to construction sites during periods of significant immune compromise. Patients should also not be involved in gardening, mulching, or similar activities that result in spore exposure. ■ ■PROTECTION FROM FOOD-BORNE INFECTIONS The old practice of implementing “low-microbial diets” for neutrope nic patients did not show convincing benefit in well-designed studies and carries the disadvantages of limiting nutrition and affecting quality of life. Patients should be educated about food and water safety precau tions issued by the Centers for Disease Control and Prevention (www. cdc.gov/food-safety/foods/weakened-immune-systems.html) and other authoritative bodies that are tailored to

immunocompromised persons but are less restrictive than low-microbial diets. These guidelines stress hand hygiene, washing vegetables and fruits, not consuming raw or undercooked meat, poultry, or fish or unpasteurized dairy products, avoidance of waterborne infections, and awareness of food-borne outbreaks. Travel to regions where food and water safety is not reliable should be avoided. Animals also are a potential source of infection, particularly via the fecal–oral route. Patients with cancer should avoid exposure to farm animals and wild animals (e.g., hunting and butchering). Acquiring a new pet while immunocompromised is not advisable. Existing pets can continue to live in the patient's house, but the patient should avoid direct exposure to animal waste, such as cleaning a cat litter box or bird cage. Patients should avoid dogs recently vaccinated for kennel cough, if possible. Contact with more exotic pets (e.g., reptiles) should be avoided because they can harbor more unusual pathogens (e.g., Salmonella species). ■ ■RESPIRATORY VIRAL INFECTIONS Patients with cancer should avoid contact with persons with symp toms or signs of respiratory infection to the extent feasible. Risk of viral infection is increased in congregate settings that are indoors and involve large numbers of people in close proximity. Precautions to limit infection spread, such as choosing outdoor over indoor events and avoiding crowded settings, are advisable. For example, a dinner at a restaurant in which the table is limited to a few persons carries less risk of transmissible infections than a crowded buffet-style setting. Patients with cancer should be aware of local patterns of viral infection. This point was amply demonstrated during the COVID-19 pandemic and applies to other viral infections, such as influenza and respiratory syncytial virus (RSV). If local viral outbreaks occur, patients with cancer should use additional precautions to limit exposure. In addition to avoiding crowds, masking may provide an additional layer of protection, especially in settings of high levels of community spread of respiratory viral infections. ■ ■SEXUAL INTIMACY To avoid risk of sexually transmitted infections, it is recommended that sexual intercourse be in a monogamous relationship. During neutrope nia, sexual intercourse and oral–genital or rectal stimulation may cause injury and predispose to infection. Once the ANC recovers, sexual activity usually can be resumed. ■ ■ANTIMICROBIAL PROPHYLAXIS Antimicrobial prophylaxis should be tailored to infection risk. Most patients with solid tumors require no antimicrobial prophylaxis. In addition to side effects of antibiotics, increased risk of C. difficile, and selection of antibiotic-resistant flora, there is precedent for antibiotics diminishing the efficacy of immune checkpoint inhibitors by disrup tion of the microbiome. As discussed above, prophylaxis with a quinolone should be con sidered in adults with prolonged neutropenia (e.g., ANC <500/µL for at least 7 days). Acyclovir prophylaxis to prevent HSV and VZV

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