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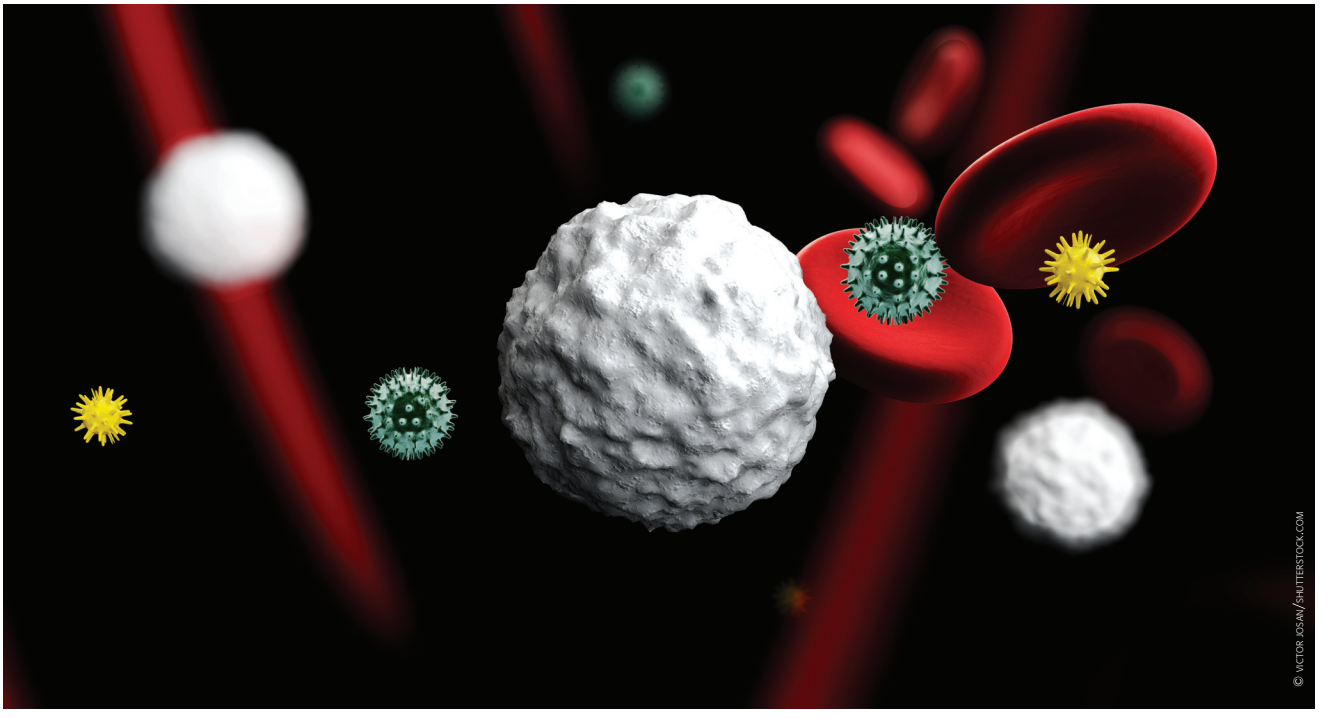

Infectious disease considerations in immunocompromised patients

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ABSTRACT

Immunocompromised patients account for about 3% of the US population. Complications arising from infection are common in these patients and can present diagnostic and therapeutic challenges. This article describes the pathophysiology of immunosuppression in five common immunocompromised states—asplenia, HIV infection, solid organ transplant, biologic use, and cancer—as well as specific infectious risks and considerations for affected patients and how to manage them.

Keywords: immunosuppression, asplenia, HIV infection, solid organ transplant, biologic use, cancer

Learning objectives

- Identify patients with immune compromise.
- Describe the specific host factors that place patients at risk for opportunistic pathogens.
- Discuss specific diagnostic and therapeutic considerations for immunocompromised patients.

The number of immunosuppressed patients in the United States has risen in recent decades. The 2013 National Health Interview Survey estimated that 2.7% of the population was immunocompromised.[1] Immunosuppression can arise from a variety of causes, including specific diseases or drugs that improve and/or extend life.

Depending on the nature of their immunosuppression, patients may be at risk for a variety of infectious complications, both common and rare. Immunosuppressed patients may not have typical symptoms of infection, which can delay care and present a diagnostic challenge. This article summarizes five common causes of immunosuppression: asplenia, HIV infection, solid organ transplant, biologic

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Key points

- Immunosuppressed patients may present with atypical signs of infection; clinicians should have a low threshold to obtain an infectious workup for these patients.
- Consider community-acquired and opportunistic infections in patients with HIV/AIDS and a CD4 count less than 500 cells/mm^3.
- CMV is one of the most common infectious complications in patients who have received solid organ transplant. Valganciclovir can be used for prophylaxis.
- Neutropenic fever is an oncologic emergency requiring prompt treatment with antibiotics.

medications for autoimmune diseases (such as inflammatory bowel disease and psoriasis), and cancer (tumor- and treatment-related). Each of these causes will be discussed with regard to the pathophysiology of immunosuppression, infectious risks and other considerations, appropriate prophylaxis and/or treatment, and vaccinations.

ASPLENIA AND FUNCTIONAL HYPOSPLENISM

This heterogeneous group comprises patients with surgical asplenia, functional hyposplenism, and (rarely) congenital asplenia. Numerous diseases may be associated with functional hyposplenia, including sickle cell disease, celiac disease, autoimmune diseases, liver cirrhosis, and graft versus host disease.[2] As of 2014, about 25,000 surgical splenectomies were performed annually in the United States, and the total number of patients with asplenia was estimated at 1 million, including 70,000 to 100,000 persons with sickle cell disease.[3]

Pathophysiology The spleen serves multiple important roles in immune system function, contributing to complex adaptive immune responses and clearing pathogens from the blood.[4] The spleen also plays an important role in the production and maturation of B-memory lymphocytes and other substances such as opsonins. These are crucial for fighting infections, specifically those caused by encapsulated organisms such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type B.[5] Because patients with asplenia lack these defensive substances, they are at risk for episodes of rapidly progressive septicemia.

Infectious risks and other considerations Overwhelming postsplenectomy infection (OPSI) refers to the development of fulminant sepsis in patients with asplenia, often due to encapsulated organisms causing meningitis or pneumonia.[6] A patient with OPSI can present with mild symptoms of infection, such as mild flu-like illness, and rapidly progress to fulminant sepsis and death.[6] Although relatively rare, OPSI is a medical emergency with a mortality of 50% to 70% if treatment is delayed or inadequate.[6]

Prophylaxis/treatment/vaccinations Patients with asplenia who have fever or other signs and symptoms of infection should be treated promptly with broad-spectrum antibiotics and observed for up to 72 hours, pending culture results. Empiric treatment can include ceftriaxone with vancomycin. Ceftriaxone targets the three most important bacterial considerations for these patients: *S. pneumoniae* strains, *H. influenzae*, and *N. meningitides*.[3] Additionally, ceftriaxone has coverage for many community-acquired Gram-negative bacilli, including *Capnocytophaga,* a pathogen often linked to animal bites.[3,6]

Prophylactic antimicrobial therapy often is recommended for children with asplenia who are under age 5 years, for 1 to 2 years following a splenectomy.[3] Lifetime antimicrobial prophylaxis can be considered for patients who have had an episode of OPSI.[3]

Clinicians should regularly review specific immunization guidelines for these patients. Coverage for encapsulated organisms and influenza virus is routinely recommended (**Table 1**).[7] Recommendations for timing of the initial vaccination series reflect the cause of asplenia: at least 14 days postoperatively for patients undergoing emergency splenectomy, 8 to 10 weeks (but no later than 14 days) before routine splenectomy, and as soon as the impairment is identified for patients with functional asplenia.[2,8]

TABLE 1. CDC-recommended vaccination schedule for patients over age 19 years who are considered asplenic[7]

Recommended vaccine	Initial vaccination schedule	Revaccination (booster)
Pneumococcal	If pneumococcal-vaccine naïve; one dose PCV 13 followed by one dose PPSV23 at least 8 weeks later	PPSV23 every 5 years
Haemophilus influenzae type B	One dose	Not applicable
Meningococcal serotype ACWY	Two-dose series; repeated at least 8 weeks apart	Every 5 years
Meningococcal serotype B	• MenB-4C: Two-dose series at least 1 month apart • MenB-FHbp: Three doses at 0, 1-2, and 6 months Note that MenB-4C and MenB-FHbp are not interchangeable	Not applicable
Influenza	One dose annually for each flu season (live attenuated vaccine, not recommended)	Repeat annually

HIV

An estimated 1.2 million people in the United States are living with HIV; about 162,500 (14.5%) of them have not been diagnosed.[9,10] Improvements in antiretroviral therapy have gradually made HIV a chronic disease requiring decades of therapy, with life expectancy approximating that of the general population.[11] Despite these improvements, a subpopulation of patients with HIV may still develop significant immunosuppression through lack of diagnosis, failure to adhere to a treatment regimen, or by developing resistance to antiretroviral therapy.

Pathophysiology HIV infection affects several components of the immune system, including B-lymphocytes, T-lymphocytes (CD4 and CD8), and lymphoid tissue; however, the immunosuppression that occurs with HIV is tied most closely to the abundance and function of CD4 T-lymphocytes.[12] CD4 cells govern a variety of immunologic activities, including inducing B lymphocytes to produce antibodies, activating macrophages, recruiting granulocytes, and producing cytokines.[13] In healthy patients, CD4 cell counts vary widely, with 500 cells/mm^3 as the lower limit of normal.[14] HIV causes a decline in the number of CD4 cells due to cell death as well as altered cellular production, differentiation, and regulation. The CD4 lymphocytes that remain are dysfunctional, with changes in cytokine production and other deviations from normal activity.[15] HIV transitions to AIDS when CD4 count drops below 200 cells/mm^3, or an HIV-infected patient develops an AIDS-defining condition or opportunistic infection (**Table 2**) irrespective of CD4 count.[16,17]

TABLE 2. Opportunistic infections based on patient CD4 count

CD4 count (cells/mm^3)	Opportunistic infection or neoplasm
>500	• Herpes zoster • TB
200-500	• Oral hairy leukoplakia • *Candida* pharyngitis (thrush) • Mucocutaneous Kaposi sarcoma • Recurrent bacterial pneumonia • Cervical or anal neoplasia
100-200	• *P. jirovecii* pneumonia • Disseminated *Histoplasmosis capsulatum* infection • Visceral Kaposi sarcoma • Progressive multifocal leukoencephalopathy • Non-Hodgkin lymphoma
<100	• *Candida esophagitis* • CMV retinitis • *Mycobacterium avium-intracellulare* • *Toxoplasma gondii encephalitis* • *Cryptosporidium parvum enteritis* • *Cryptococcus neoformans meningitis* • Herpes simplex virus, chronic, ulcerative • CMV esophagitis or colitis • Primary central nervous system lymphoma

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Infectious risks and other considerations Infections are the most common cause of fever in patients with HIV, but malignancies (predominantly lymphoma) are another important cause.[18-20] Clinicians must be aware that AIDS-defining conditions can be noninfectious, such as lymphoma, generalized lymphadenopathy, wasting syndrome, and a variety of symptoms affecting virtually every organ system.[21]

Carefully evaluate patients with HIV who present with fever. Obtain a complete history and physical examination and integrate it with diagnostic testing. Give specific consideration to the patient's most recent CD4 count.

Patients with HIV and normal CD4 counts (greater than 500 cells/mm^3) often manifest with the same types of infections as the general population. An important exception is mycobacterial infections. Multiple studies have found that tuberculosis (TB) and atypical mycobacterial pathogens cause about half of fevers in patients with HIV.[18-20]

Pneumocystis jirovecii is a common cause of opportunistic infections not only in patients with HIV, but also in many other immunocompromised patients, including those with solid organ or stem cell transplants, hematologic malignancies, and those taking biologic agents or other immunosuppressants. Patients with HIV or AIDS often develop symptoms of a *P. jirovecii* infection over the course of weeks; HIV-negative immunocompromised patients often develop symptoms over the course of days, usually presenting with only a high fever.[22] Pulmonary disease is the most common presentation of *P. jirovecii* in patients with HIV or AIDS. Patients typically manifest with subacute symptoms of worsening nonproductive cough and hypoxia. Classic chest radiograph findings of *P. jirovecii* pneumonia include bilateral perihilar interstitial infiltrates that become progressively homogenous and diffuse on serial imaging.[23] CT scan imaging historically displays extensive ground-glass infiltrates, but this can be seen with other disorders, such as interstitial lung disease and COVID-19.[23] Induced sputum or bronchoalveolar lavage will facilitate confirmatory testing.

Although cultures may not be necessary in all cases (for example, a straightforward infection in a patient with a high CD4 count), clinicians should have a low threshold for ordering blood or other cultures, including typical pathogens as well as fungal organisms and mycobacteria. Patients with low CD4 counts should be aggressively tested for opportunistic infections. Fungal and mycobacterial cultures can take weeks to yield a final result, and some fungi are difficult to culture. Additional fungal testing with serologies, complement fixation, or direct antigen testing may be needed, depending on regionally endemic infections and clinical suspicion. Consulting with infectious disease and other specialists is an important aspect of managing these complicated patients.

TABLE 3. Updates to the guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV[24]

Organism or infection	Updates	First-line prophylaxis
Pneumocystis pneumonia	Updated references for stopping PCP prophylaxis in patients with CD4 counts between 100 and 200 cells/mm^3 and plasma viral loads below detection limits of assays	Trimethoprim-sulfamethoxazole: 1 double-strength tablet daily
Disseminated *Mycobacterium avium* complex (MAC) disease	Patients with HIV infection who immediately initiate antiretroviral therapy no longer require primary prophylaxis for MAC, regardless of CD4 cell count	Azithromycin 1,200 mg weekly
Human papillomavirus (HPV)	AIII recommendation: Females and males ages 13 to 26 years with HIV infection should have 9-valent HPV recombinant vaccine as opposed to recombinant bivalent or quadrivalent vaccines (0.5 mL at 0, 1 to 2, and 6 months)	No prophylaxis indicated
Hepatitis B virus infection	CIII recommendation: (due to no data in HIV population) for administration of recently approved two-dose hepatitis B vaccine conjugated to a TLR9 agonist (Hepliisay-B)	Consider tenofovir/emtricitabine as backbone when possible for patients with HBsAg-negative/anti-HBc-positive disease to prevent hepatitis B virus reactivation during immunosuppressive therapy

Prophylaxis/treatment/vaccinations Opportunistic infections and noninfectious complications of HIV are extensively discussed in other publications, and a comprehensive overview is beyond the scope of this article (**Table 3**).[24] Vaccination of patients with HIV conforms to the 2019 adult immunization schedule published by the Advisory Committee on Immunization Practices with the exception of live vaccines. Live vaccines (live-attenuated influenza virus, measles-mumps-rubella, varicella/zoster) are contraindicated in patients with HIV and CD4 counts below 200.[25]

SOLID ORGAN TRANSPLANT

The year 2019 was the seventh consecutive record-breaking year for organ transplants in the United States, up nearly 9% from 2018.[26] Recipients are prescribed an array of immunosuppressive medications to prevent rejection of a donated organ.

Pathophysiology If the patient's immune system is unchecked, it can lead to organ damage and/or rejection. Potent immunosuppressants including glucocorticoids, calcineurin inhibitors, mTOR inhibitors, and antimetabolite drugs dramatically reduce the chance of rejection of transplanted solid organs (**Table 4**).[27,28] However, because of their altered immune systems, transplant recipients are at increased risk for infection, compared with the general population.

Infectious risks and other considerations The risk of post-transplant infection is predominantly determined by two factors: epidemiologic exposures and the degree of immunosuppression, both of which vary over time.[28,29] Therefore, when a transplant recipient presents with infection, clinicians must consider timing since transplantation, recipient/donor exposures, and current degree of immunosuppression.[28]

Bacterial and fungal infections are most common within the early post-transplant period (the first 30 days after surgery).[30] Infections during this time usually are donor-derived, recipient-derived, or due to surgical complications.[28,30] During the late transplant period (6 months or more after surgery), immunosuppressive therapy is tailored and lowers the transplant recipient's overall risk of infection. However, because of their need for lifelong immunosuppression, these patients remain at an increased risk for community-acquired infections.[28]

Invasive fungal infections are common in transplant recipients, with *Candidiasis, Cryptococcosis*, and molds such as *Aspergillus* and *Zygomycosis* most commonly reported.[31] Endemic fungi and regional species such as *Histoplasma, Coccidioides* and *Blastomyces* also are important causative agents.[31]

Viral illnesses and allograft rejection are the most common causes of fever in the intermediate post-transplant period (1 to 6 months).[29,30]

BK virus infection typically occurs in childhood, with 50% of children undergoing seroconversion by age 4 years.[32] Reactivation of latent infection often occurs after renal transplantation. Up to 10% of renal transplant patients develop BK virus nephropathy, which can result in graft loss.[33] Common complications include BK virus-associated nephropathy, ureteral stenosis, and hemorrhagic cystitis.

*Cytomegalovirus (*CMV*)* remains one of the most common complications affecting patients who have had organ transplants.[34,35] About 50% of the US population is seropositive for CMV and most patients experience an asymp-

tomatic or mild primary infection, followed by latent infection.[36] Following transplantation, patients may develop viremia without focal signs or symptoms, or localized CMV disease. CMV disease correlates with the presence of detectable CMV in clinical specimens accompanied by other clinical manifestations or invasive disease, which may lead to end-organ damage.[35] CMV disease, confirmed via quantitative serum testing, often presents with a syndrome of fever, malaise, leukopenia, and/or thrombocytopenia; many organ systems can be affected by this virus.[34,35] Common sites for an active CMV infection include the eyes, gastrointestinal (GI) tract, liver, lungs, and central nervous system. CMV can lead to an array of complications such as acute or chronic allograft rejection, and organ-specific complications such as bronchiolitis obliterans in lung transplant recipients or tubulointerstitial fibrosis in kidney transplant recipients.[35] CMV disease increases transplant recipient mortality, specifically in patients who have received lungs or small intestines.[35]

Epstein-Barr virus (EBV) primary infection and subsequent dormant disease affects up to 90% of adults.[37] EBV can be reactivated to cause a wide spectrum of disease, ranging from asymptomatic viremia to infectious mononucleosis syndrome. The latter is characterized by fever, exudative tonsillitis, cervical lymphadenopathy (particularly in the posterior chain), and splenomegaly. Atypical lymphocytosis is common, but is not specific for EBV infection. EBV also is associated with the development of certain malignancies, such as post-transplant lymphoproliferative disorder and Burkitt lymphoma.

Other viruses that can remain dormant in patients but cause disease post-transplant include varicella zoster and herpes simplex.[29] Maintain a low threshold for testing suspicious skin lesions for these viruses in transplant recipients.

Prophylaxis/treatment/vaccinations Prophylaxis and infectious treatment management are unique to each solid organ recipient, based on donor and recipient exposure, organ transplanted, and time since transplantation. Primary care providers should be familiar with the following:

Opportunistic infections. Post-transplant patients should be on low-dose trimethoprim-sulfamethoxazole (one single-strength tablet once daily or one double-strength three times weekly, with consideration for renal function) or alternative prophylactic therapy such as atovaquone or dapsone. The primary goals of prophylaxis are prevention of *P. jirovecii* pneumonia as well as other opportunistic and common urinary, respiratory, and GI bacterial infections.

BK virus. Although no specific antiviral treatment exists for BK virus, treatment consists of reducing immunosuppression with institution-dependent addition of IV immunoglobulin or other antivirals such as leflunomide or cidofovir.

CMV. Donors and recipients are screened for CMV before organ transplantation. CMV-negative transplant recipients whose donors are CMV-positive are at the greatest risk of developing CMV disease.[28] CMV prophylaxis often is started 10 days post-transplant and continued for at least 3 to 6 months.[34] Valganciclovir is the most commonly used drug for prophylaxis; acyclovir, valacyclovir, and ganciclovir also are used.[34] In case of infection, the recommended first-line treatments for CMV infection are valganciclovir or ganciclovir.[34]

EBV. Low levels of EBV viremia can be monitored with serial blood tests. Consult transplant specialists if the patient's levels continue to rise, as immunosuppression often is reduced in these patients to prevent further EBV replication.

In the case of post-transplant lymphoproliferative disorder (PTLD), resection or radiotherapy can be considered for localized disease. For systemic therapy, rituximab, a monoclonal antibody directed against CD20, and other chemotherapy agents often are used.[37]

The pneumococcal vaccine series is recommended for solid-organ recipients, starting with a single dose of pneumococcal conjugate vaccine (PCV 13) followed by a dose

TABLE 4. Immunosuppressive role of post-transplantation medications[27,28]

Category	Examples	Immunosuppressive role
Glucocorticoids	• Hydrocortisone • Methylprednisolone • Prednisolone • Prednisone	Multiple effects on gene expression, WBC number and function, and cytokine levels
Calcineurin inhibitors	• Tacrolimus • Cyclosporine	Selectively inhibit calcineurin, thereby impairing the production of cytokines in T lymphocytes
Inhibitors of mammalian (mechanistic) target of rapamycin (MTOR)	• Sirolimus • Everolimus	Block the response of T and B cell activation by cytokines
Inhibitors of purine and pyrimidine synthesis or antimetabolite drugs	• Azathioprine • Mycophenolate mofetil • Mycophenolate sodium	Exhibit a cytostatic effect on T and B lymphocytes
Antibody therapy	• Basiliximab • Daclizumab	Target B and T cells

of the pneumococcal polysaccharide vaccine (PPSV23) for patients older than age 19 years.[7] Revaccination with PPSV23 should take place every 3 to 5 years.[29] Influenza vaccination is recommended annually.[29] Live vaccines (varicella, measles, mumps, rubella, live-attenuated influenza vaccination) generally are contraindicated after transplantation because they may cause disseminated disease in immunocompromised patients.[29]

TREATMENT WITH BIOLOGICS

Autoimmune diseases such as rheumatoid arthritis, psoriasis and psoriatic arthritis, ankylosing spondylitis, inflammatory bowel disease, and multiple sclerosis affect an estimated 4.5% of the Western world.[38] Conventional therapy includes disease-modifying anti-rheumatic drugs (DMARDs) and corticosteroids, but advances in drug development have led to new therapeutic options: genetically manufactured molecules from living cells, including monoclonal antibodies. These biologic agents target specific parts of the immune system and are approved for use in several immune-mediated inflammatory diseases, as well as a few lymphoproliferative disorders.

Pathophysiology Immune-mediated inflammatory diseases are associated with overproduction of different cytokines, such as tumor necrosis factor-alpha (TNF-alpha) and the interleukins IL-1, IL-6, and IL-23).[39] These molecules have important immunologic functions, including activating macrophages, recruiting neutrophils, maintaining granulomas, stimulating immune cells, producing proinflammatory mediators, and forming immunoglobulins and inflammatory cytokines. Through these mechanisms, immune-mediated diseases cause hyperactivity of immune cells, such as T helper and B cells. Biologic agents target these molecules and cells to modulate disease. However, as a result, normal immune functions are suppressed, increasing the patient's risk for infection.[40]

The most commonly used biologics are anti-TNF-alpha agents such as etanercept, infliximab, adalimumab, certolizumab, and golimumab. Less-commonly used agents include anti-CD20/B cell agents (rituximab), T-cell costimulation modulators (abatacept), and anti-interleukin agents (anakinra, ustekinumab, and tocilizumab).

Infectious risks and other considerations All biologics are associated with an increased risk of bacterial, fungal, and viral infections, particularly anti-TNF-alpha agents, which have been the most well-studied to date.[41] In addition to an increased rate of routine community-acquired bacterial infections, invasive skin and soft-tissue infections, and septic arthritis, patients taking biologics are at risk for other opportunistic or reactivated infections (**Table 5**).[42-52] As with other immunocompromised patients, these patients may present with atypical or nonspecific symptoms. If a patient is suspected of having an invasive infection, maintain a low threshold for inpatient admission and consider routine and esoteric infections.

Prophylaxis/treatment/vaccinations According to the most recent recommendations, before starting any biologic agent, patients should be screened and treated for TB as well as hepatitis B and C.[53] Screening for TB includes either the tuberculin skin test or interferon-gamma release assay. If either test is negative, no further workup is needed and the patient may start the biologic; if positive, a chest radiograph and sputum acid-fast bacillus stain/cultures should be obtained, and the biologic withheld. Latent TB is diagnosed with either a normal or abnormal chest radiograph (for example, cavitation, fibrosis, or scarring usually in apical regions) and negative sputum acid-fast bacillus stain/cultures. Active TB is diagnosed with an abnormal chest radiograph and positive sputum acid-fast bacillus stain/cultures. Patients with either active or latent TB should start treatment immediately. In patients with latent TB, oral rifampin (10 mg/kg daily; maximum 600 mg) for 4 months is recommended; a biologic agent may be started after 1 month of treatment.[53,54] Patients with active TB should be prescribed the following oral regimen for 2 months: rifampin (10 mg/kg daily; maximum 600 mg), isoniazid (5 mg/kg daily; maximum 300 mg), pyrazinamide (1,000 to 2,000 mg daily depending on body weight), and ethambutol (800 to 1,600 mg daily depending on body weight).[55] The rifampin and isoniazid dosages should be continued for an additional 4 to 7 months, and the patient must wait to start the biologic until after this treatment is complete.[53]

In patients with chronic hepatitis B (positive HBsAg), antiviral therapy (entecavir or tenofovir) should be given concurrently with biologics. Close monitoring of liver enzymes and viral load is paramount. Patients with resolved hepatitis B (negative HBsAg and positive HBcAb) are at risk for viral reactivation and require viral load monitoring every 1 to 3 months.[56] Any patient who tests positive for hepatitis C should be treated with antivirals such as glecaprevir-pibrentasvir.[57] Optimal treatment with biologics in patients with hepatitis C is not known; however, conditional recommendations suggest concurrent therapy with an antiviral and collaboration with a hepatologist and/or gastroenterologist.[53] Screening for non-TB mycobacterium and other fungal infections (such as histoplasmosis, coccidioidomycosis, and aspergillosis) is not recommended; testing should be pursued if there is clinical suspicion for infection.

TABLE 5. Specific infectious considerations in immunosuppressed hosts receiving biologics[44-52]

Bacterial
• *Legionella pneumonia*
• Listeriosis
• *Mycobacterium*/TB
Viral
• Varicella zoster
• Hepatitis B
• Hepatitis C
Fungal
• Histoplasmosis
• Coccidioidomycosis
• Aspergillosis

In addition to screening, vaccinations—including varicella, pneumococcal, and influenza—should be updated. Live vaccinations should not be given while patients are on biologic therapy; rather, these live vaccines may be given 1 month before starting therapy or 1 month after discontinuing it. Antimicrobial prophylaxis is not routinely recommended; however, *Pneumocystis* prophylaxis with trimethoprim-sulfamethoxazole can be considered in high-risk patients on concurrent biologic therapy and corticosteroids (that is, patients receiving more than 20 mg of prednisone daily for more than 1 month).[58]

Treatment of infections in patients on biologics tends to be aggressive because of the risk of severe and disseminated disease. Despite this necessary consideration, treatment guidelines are not present in the literature due to two complex factors. First, patients on biologic therapy often are at an increased risk for infection at baseline because of their specific underlying immune-mediated disease.

> Live vaccinations should not be given while patients are on biologic therapy.

Second, biologics can alter specific immunologic targets, leading to a multitude of unique infectious risks. These intertwined, complex factors must be considered by primary care providers when developing an infectious differential in patients taking biologics for immune-mediated inflammatory diseases.[59] Management should include prompt discussion with the prescribing clinician about dose reduction or cessation, as well as referral to an infectious disease specialist.

CANCER

Cancer remains a significant health burden in the United States, claiming more than 600,000 lives annually, second only to heart disease as a leading cause of death.[60,61] Nearly 16 million people in the United States have cancer (excluding nonmelanoma skin cancers and carcinoma in situ), with an estimated 1.8 million new cancer diagnoses expected in 2020.[60] Most of these new cases are solid tumors, with cancers of the breast, lung and bronchus, prostate, and colon and rectum being the most common. Hematologic malignancies, including leukemia, lymphoma, and myeloma, account for about 10%.[60] Infection is an important complication of every type of cancer, leading to costly hospital admissions (particularly for neutropenic fever) and high mortality.[62,63]

Pathophysiology Several factors related to a malignancy itself or its treatment can increase patients' risk for infection.

Tumor-related factors. Immunosuppression caused by bone marrow infiltration occurs in hematologic malignancies in which the primary cancer cells originate in the marrow, alter blood cell lines, and thereby disrupt the normal immune response. This also can occur with nonhematologic cancers when metastases travel to the bone marrow. Solid tumors seldomly cause immunosuppression directly. Instead, these types of cancers increase the risk of infection by other methods, such as obstruction of anatomic passageways, alteration of defense mechanisms, and disruption of natural barriers in their respective locations.[64] These changes in turn may lead to local or systemic inflammation and infection.

Treatment-related factors. Chemotherapy agents target rapidly dividing cells with the goal of killing cancer cells. Unfortunately, these agents often are not cancer-specific, and may destroy rapidly dividing healthy cells, which are abundant in the hair, skin, GI tract, and bone marrow. Damage to the skin and GI tract lets pathogens breach innate immune barriers, leading to increased risk of infection. In the bone marrow, chemotherapy destroys immune cells, causing myelosuppression and immunosuppression. Although the degree of immunosuppression varies based on the chemotherapy agents used, cytotoxic antineoplastic regimens that target the bone marrow—and are used to treat leukemias and other hematologic cancers—tend to cause greater immunosuppression that can be profound and persistent. All cell lines are affected, including neutrophils, which are important mediators in the initial immune response to bacterial and fungal infections. When absolute neutrophil count falls below 1,000 cells/mcL (normal values range between 1,500 and 8,000 cells/mcL), patients are considered neutropenic. In these patients, infection risk is inversely related to the absolute neutrophil count, and the risk of invasive infections increases substantially when that level falls below 500 cells/mcL.[65] Generally, patients at high risk for infection are defined as those with prolonged and profound neutropenia (less than 100 cells/mcL for more than 7 days). Low-risk patients are those with neutropenia lasting less than 7 days.[66]

Infectious risks and other considerations *Tumor-related*. Obstruction of anatomic passageways and disruption of tissues can lead to local or systemic infection. Infections vary based on the primary tumor site, such as the lung (postobstructive pneumonia), biliary tree (ascending cholangitis), or urinary tract (pyelonephritis). These infections can be further complicated by abscess or fistula formation, as well as bacteremia. Often, the pathogens isolated from such sites are normal anatomic flora.[67]

Treatment-related. Fever is common in patients with chemotherapy-induced neutropenia. Often, no cause can be identified; only 20% to 30% of patients with febrile episodes have a documented infection.[68] Bacteremia may be the only evidence of infection, occurring in 10% to 25% of patients with neutropenic fever.[68] Recently, an epidemiologic shift has occurred, with Gram-positive

organisms such as *Staphylococcus sp*. now being more common than Gram-negative infections such as *Pseudomonas aeruginosa*.[69] Community-acquired respiratory viral infections as well as reactivated viral infections such as herpes simplex and varicella zoster are common in high-risk patients with prolonged neutropenia and/or those taking long-term high-dose corticosteroids.[70-72] Invasive fungal infections, such as those caused by *Candida sp*. and *Aspergillus sp*., also are more common in high-risk patients with neutropenia and should be considered in patients with persistent fevers after the first week of neutropenia.[68]

In patients receiving targeted cancer therapy, the risk for opportunistic infection depends on the medication. For example, the anti-CD52 monoclonal antibody alemtuzumab carries a significant risk for CMV reactivation, as well as potential for developing *Pneumocystis* pneumonia, aspergillosis, and other invasive fungal infections.[73,74] The PI3K inhibitor idelalisib is associated with an increased risk of *Pneumocystis* pneumonia and CMV.[75] Increasing evidence associates the Bruton tyrosine kinase (BTK) inhibitor ibrutinib with the threat of opportunistic infections such as *Pneumocystis* pneumonia and invasive fungal infections such as pulmonary cryptococcosis and aspergillosis.[76] Herpes simplex and varicella zoster reactivation also are associated with these medications, as well as with high-dose corticosteroids.

Prophylaxis/treatment/vaccinations *Tumor-related*. Antimicrobial prophylaxis is not routinely recommended for patients with solid tumors.[66] Reducing disease burden by way of tumor resection, chemotherapy, radiation, or a combination of these modalities is the treatment of choice for obstruction. Other options, depending on tumor location, include stent placement, percutaneous drainage, or laser therapy. Antibiotics are used alone or in conjunction with these therapies to treat secondary infection.

Chemotherapy-related. The American Society of Clinical Oncology and Infectious Disease Society of America published specific guidelines addressing the prophylactic management of patients with cancer treatment-related immunosuppression and the treatment of neutropenic syndromes.[66,68] Both guidelines stress the importance of initial risk assessment in patients with neutropenia, categorizing them into the aforementioned high-risk population (absolute neutrophil count less than 100 cells/mcL for more than 7 days) and low-risk (absolute neutrophil count less than 500 cells/mcL for less than 7 days). Early consultation with an infectious-disease specialist is emphasized. Concurrent prophylaxis with antibiotic (fluoroquinolone), antifungal (azole or echinocandin), and antiviral (nucleoside analogue) agents is recommended for high-risk patients during the neutropenic period. Additionally, patients who are at more than a 3.5% risk for *P. jirovecii* pneumonia (defined as receiving more than 20 mg prednisone daily for more than 30 days or those receiving purine analogues) also should receive appropriate prophylaxis.[66]

Although fever often is the only sign of infection, clinicians should be cognizant that severely neutropenic patients can sometimes present in an afebrile or hypothermic state.[66] Evaluation of patients presenting with fever or suspected infection includes two sets of blood cultures, chest radiographs, and urinalysis with urine culture if indicated. Additional studies and cultures from suspected sites of infection also may be warranted.[68] Treatment of high-risk patients who are febrile and neutropenic includes expeditious IV antipseudomonal antibiotics (such as cefepime) until 48 hours of negative cultures. Empiric Gram-positive coverage is not indicated (even in patients with an indwelling venous catheter), but should be considered in patients presenting with severe sepsis, pneumonia, suspected catheter-related infection, Gram-positive bacteremia, skin or soft-tissue infection, severe mucositis, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, or penicillin-resistant *Pneumococcus* colonization. Empiric antifungal agents with antimold activity (such as voriconazole, echinocandin, or amphotericin B) also are recommended for patients with hemodynamic instability, persistent fevers without clear source, or expected neutropenia of more than 7 days.[68] Adjustments to antimicrobials should be guided by clinical and microbiologic data, and documented infections treated for the appropriate duration. De-escalation to oral antibiotics in stable patients with neutropenia is recommended after the primary infection is treated and until bone marrow recovery (absolute neutrophil count greater than 500 cells/mcL).[68]

In patients receiving targeted cancer therapy, recommendations for antimicrobial prophylaxis (including for *Pneumocystis*) depend on the medication regimen. In patients who are at high risk for CMV reactivation (that is, those taking alemtuzumab or idelalisib), weekly laboratory monitoring for CMV is recommended.[73,77] At this time, no formal recommendations exist for routine antimicrobial prophylaxis in patients receiving oral BTK inhibitors.

Vaccinations are an important preventive measure in patients with solid tumors and those with hematologic malignancies. Influenza and pneumococcal (PCV13 followed by PPSV23) vaccines are recommended for all patients with cancer, except those receiving anti-B-cell antibodies (such as rituximab) and intensive chemotherapy (such as induction or consolidation therapy for leukemia).[78] Other vaccinations should be updated as needed.

Timing of vaccination is important, particularly in patients receiving chemotherapy. When possible, all indicated vaccinations should be given before chemotherapy (at least 2 weeks before for inactive vaccines and at least 4 weeks before for live vaccines). Do not administer inactive and live vaccinations during chemotherapy (with the exception of the influenza vaccine). Inactive and live vaccines may be given 3 months after completion of chemotherapy; in patients who received anti-B-cell antibodies, this period is extended to 6 months.[78]

CONCLUSION

Primary care providers are likely to be the first point of contact for immunocompromised patients experiencing infectious complications. These patients are vulnerable to uncommon pathogens and often have atypical symptoms. As a result, clinicians should have a lower threshold for expanded diagnostic testing as well as for referral and/or hospitalization when caring for these patients. Coordination with infectious disease and other specialties is another integral part of the ongoing management of immunocompromised patients.

Complications arising from infection are common in these patients and can present a diagnostic and therapeutic challenge. Appropriate prophylaxis, treatment, and vaccinations—including prompt evaluation and action—can help slow or prevent the progression of infectious complications, leading to more favorable patient outcomes. **JAAPA**

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