usually last less than 2 weeks before spontaneously resolving in immunocompetent hosts. Immunocompromised patients, in particular patients with AIDS, can develop serious and prolonged infection. Diagnosis from stool can be pursued microscopically by visualization of oocysts with modified acid-fast staining, EIA or direct immunofluorescent antibody testing, or molecular testing. Treatment for immunocompetent patients usually consists of supportive care. When antimicrobial agents are considered for severe or prolonged infection, nitazoxanide is recommended. In HIV-infected patients, antiretroviral therapy is most effective in resolving infection.

KEY POINTS

- Municipal water supplies and swimming pools can be a source of *Cryptosporidium* infection.
- Microscopic visualization of oocysts in stool using modified acid-fast staining, enzyme immunoassay or direct immunofluorescent antibody testing, or molecular testing can provide a diagnosis of *Cryptosporidium* infection.
- Treatment of *Cryptosporidium* infection consists of supportive care for most immunocompetent hosts or nitazoxanide for severe or prolonged infection; antiretroviral therapy is most effective in resolving infection in HIV-infected patients.

Amebiasis

Entamoeba histolytica is responsible for amebiasis. In the United States, most infections are diagnosed in travelers returning from visits to unsanitary tropical or developing countries, immigrants from these areas, persons in institutionalized settings, or those who practice oral-anal sex. Amebiasis is highly infectious, with ingestion of only a small number of infective cysts needed for infection. The incubation period is 2 to 4 weeks. Clinical findings are described in Table 46. Colonic perforation, peritonitis, and death may complicate more fulminant infections. Risk factors for severe infection in adults include immunodeficiency. Microscopic visualization of cysts or trophozoites, stool antigen immunoassay testing, stool molecular testing, and serologic antibody testing can provide a diagnosis, although the latter does not distinguish current from remote infection. Treatment is recommended for all infected patients. In symptomatic patients, treatment with metronidazole or tinidazole is recommended initially for parasitic clearance followed by an intraluminal amebicide, such as paromomycin or diloxanide, for cyst clearance. In asymptomatic infections, an intraluminal agent for eradication of cysts is recommended.

KEY POINT

- Treatment is recommended for all patients with amebiasis; for symptomatic patients, metronidazole or tinidazole is recommended initially for parasitic clearance followed by an intraluminal amebicide for cyst clearance, and for asymptomatic patients, an intraluminal agent for eradication of cysts is recommended.

Cyclospora Infection

Cyclospora infections are typically acquired after consumption of food or water that is fecally contaminated with *Cyclospora* oocysts. In the United States, many of these infections have been traced to imported fresh produce from tropical and subtropical areas or have occurred in travelers to endemic areas. The incubation period is approximately 1 week. Symptoms can last for several weeks and may be more pronounced in HIV-infected patients (Table 46).

KEY POINT

- *Cyclospora* infection is typically diagnosed microscopically by visualization of oocysts with modified acid-fast staining, microscopy with ultraviolet fluorescence, or molecular testing; trimethoprim-sulfamethoxazole is recommended for treatment of symptomatic infection.

Infections in Transplant Recipients

Introduction

The occurrence of solid organ transplantation (SOT) and hematopoietic stem cell transplantation (HSCT) procedures continues to increase, as do long-term survival rates owing to improved management of rejection and decreased complications. With more patients living longer after transplantation, awareness of principles involved in the recognition and prevention of infection in transplant recipients remains important for physicians who are not transplant specialists.

Despite improvements in immunosuppression and antimicrobial therapy, infection remains a significant cause of morbidity and mortality after SOT and HSCT. Infection is the most common cause of death in the first year after SOT. Additionally, the interaction of the immune system and infection is bidirectional; although immune suppression to prevent rejection increases risk of infection, infection also raises the risk of rejection.

Antirejection Drugs in Transplant Recipients

Success after transplantation depends on modulating the immune system to prevent organ rejection in SOT and to minimize graft-versus-host disease (GVHD) in allogeneic HSCT. Antirejection regimens involve multiple agents (**Table 50**) with different mechanisms of action, which are chosen to minimize overlapping toxicities. After SOT, an induction and maintenance strategy is applied; immunosuppression is most intensive in the first month after transplantation and often includes lymphocyte depletion therapy. Immunosuppression may require intensification during episodes of rejection, with associated increased risk of infection.

TABLE 50. Immunosuppressive Agents Used in Transplantation

Class	Agents
Glucocorticoids	Prednisone, others
Cytotoxic agents (DNA synthesis inhibitors, antimetabolites)	Mycophenolate mofetil
	Mycophenolate sodium
	Azathioprine
	Methotrexate
	Cyclophosphamide
Calcineurin pathway inhibitors	Cyclosporine
	Tacrolimus
mTOR inhibitors	Sirolimus (rapamycin)
	Everolimus
Lymphocyte-depleting antibodies	
Polyclonal	Antithymocyte globulins
Monoclonal	Muromonab (anti-CD3)
	Basiliximab (anti-IL-2 receptor)
	Daclizumab (anti-IL-2 receptor)
	Rituximab (anti-CD20)
	Alemtuzumab (anti-CD52)

IL-2 = interleukin-2; mTOR = mammalian target of rapamycin.

Steroid-sparing or minimizing regimens are increasingly used to avoid the toxicities of long-term steroid therapy. Tacrolimus, cyclosporine, or sirolimus are the cornerstones, usually with mycophenolate or, less commonly, azathioprine. Drug interactions are common with these agents, and many drugs can affect antirejection medication levels. Monitoring is important to balance adequate immunosuppression with toxicity.

KEY POINT

- Glucocorticoid-sparing or minimizing regimens (with tacrolimus, cyclosporine, or sirolimus) are increasingly used to avoid the toxicities of long-term steroid therapy.

Posttransplantation Infections

Timeline and Type of Transplant

Infection may occur at any time after transplantation, but periods of highest immunosuppression, usually within the first few months after transplantation, carry the highest likelihood. Risk for infection is also affected by pre-existing conditions (such as diabetes mellitus, cirrhosis, or neutropenia) and by colonization with resistant organisms (such as *Burkholderia* in cystic fibrosis).

The specific infection risk varies depending on the time after transplantation. **Table 51** shows the typical timeline of risk for specific infections after SOT. However, the timeline restarts when treating episodes of rejection, and infection risk

TABLE 51. Timeline of Common Infections After Solid Organ Transplantation

Early Period (<1 Month after Transplantation)	Middle Period (1-6 Months after Transplantation)	Late Period (>6 Months after Transplantation)[a]
Staphylococcus aureus infection (including methicillin-resistant)	Cytomegalovirus infection	Epstein-Barr virus (including PTLD) infection
Nosocomial gram-negative bacterial infection	Epstein-Barr virus (including PTLD) infection	Varicella-zoster virus infection
Clostridioides difficile colitis	Herpes simplex virus infection	Community-acquired pneumonia
Candida infection	Varicella-zoster virus infection	Urinary tract infections
Aspergillus infection	Polyomavirus BK infection	Polyomavirus BK infection
Surgical site infections	*Pneumocystis jirovecii* infection	Cytomegalovirus infection
Hospital-acquired pneumonia	*Toxoplasma, Trypanosoma, Strongyloides*	
Catheter-related bacteremia	*Listeria* infection	
Urinary tract infections	*Nocardia* infection	
	Tuberculosis reactivation	
	Fungal infections, including *Cryptococcus*	

PTLD = posttransplant lymphoproliferative disorder.

[a]For opportunistic infections in the late period, risk depends on level of immunosuppression. Infections such as *Pneumocystis* and other fungi, *Listeria*, and *Nocardia* can be seen in the late period in patients with higher immunosuppression.

in the late period depends on the immunosuppression level required. In the first month after SOT, infections are similar to those seen in other hospitalized postsurgical patients, including a risk of resistant bacteria, and most often involve the lungs, urinary tract, and surgical sites. The middle period usually encompasses the most intensive immunosuppression, with significant risk for viral (such as cytomegalovirus) and fungal (such as *Pneumocystis*) infections owing to defects in cell-mediated immunity. If immunosuppression can be de-escalated during the late period, risk for opportunistic infections decreases overall, but patients remain at risk for certain viral infections and have increased risk for community-acquired bacterial infections.

For some infections, the risk strongly depends on donor and recipient characteristics. Standard donor and recipient pretransplantation testing includes serologies for cytomegalovirus; Epstein-Barr virus; varicella-zoster virus; HIV; hepatitis B, C, and E viruses; syphilis; toxoplasmosis; and *Strongyloides*, *Leishmania*, and *Trypanosoma* if from an endemic area; and interferon-γ release assay for latent tuberculosis infection. Immunosuppressive drugs and changed anatomy after transplantation may also contribute to altered presentations, making diagnosis of common infections more challenging.

Noninfectious complications such as GVHD or malignancy may also be confused with infection.

Risk after HSCT is much greater for allogeneic than autologous transplantation because of the myeloablative conditioning regimen. After allogeneic HSCT, patients undergo a prolonged period of intense neutropenia, putting them at risk for bacterial infections, *Candida* and mold infections, and herpes simplex and other virus reactivation. This is followed by a prolonged period of impaired cell-mediated and humoral immunity because of immunosuppression to reduce GVHD. Development of chronic GVHD can also increase risk for infections caused by immune system effects and breakdowns in mucosal and other barriers. Infections in this later period are similar to those in the later period after SOT. **Figure 33** shows the timeline of risk for specific infections after allogeneic HSCT.

KEY POINTS

- Infection may occur at any time after transplantation but is most likely at periods of highest immunosuppression; the risk for specific organisms varies depending on the time after transplantation.
- Infection risk is much greater after allogeneic than autologous hematopoietic stem cell transplantation because of myeloablative conditioning with a prolonged period of neutropenia and immunosuppression given to reduce graft-versus-host disease.

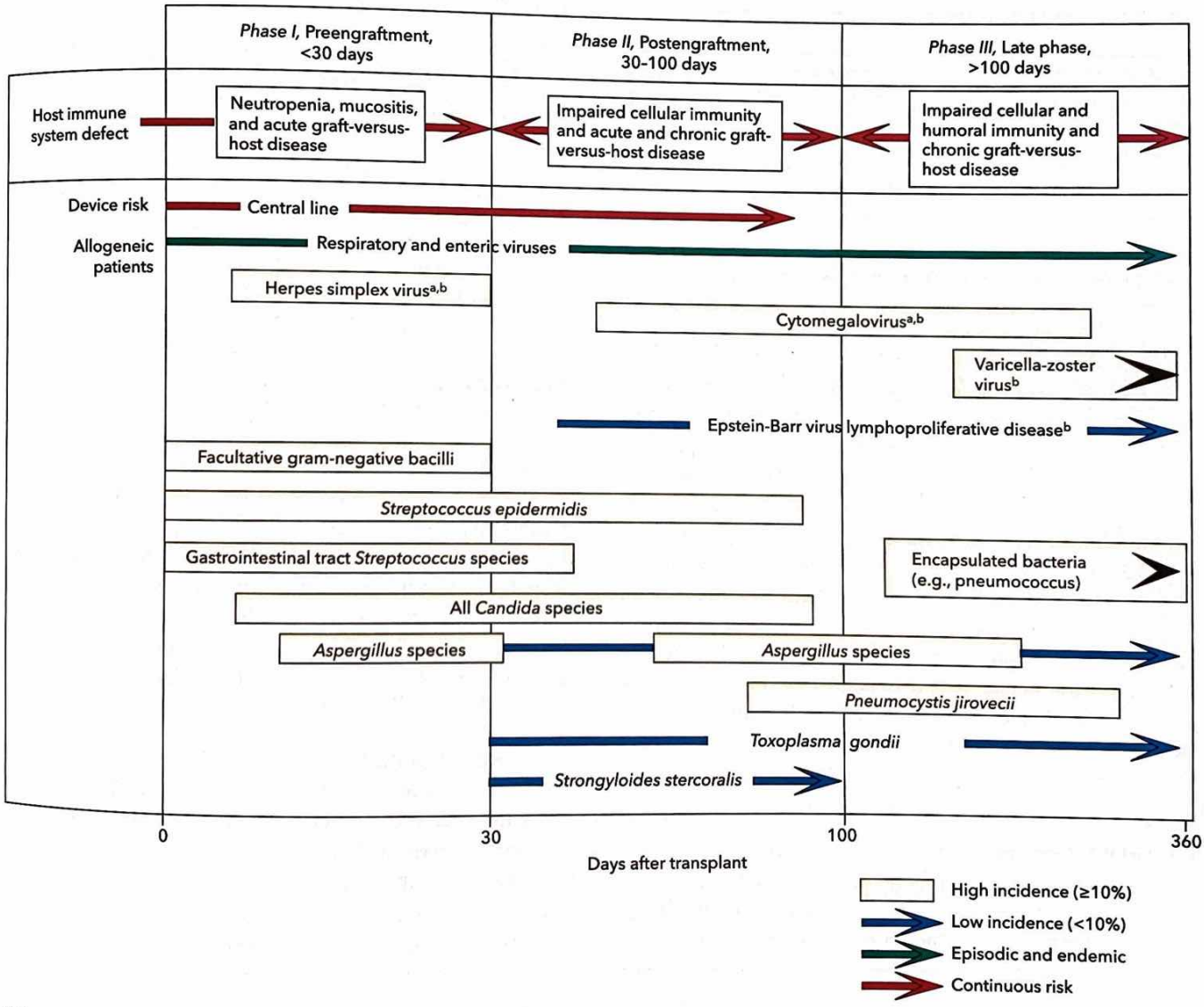

FIGURE 33. Phases of opportunistic infections in allogeneic hematopoietic stem cell transplant recipients.

[a]Without standard prophylaxis.

[b]Primarily among persons who are seropositive before transplantation.

Reprinted with permission from CDC, Infectious Disease Society of America, and the American Society of Blood and Marrow Transplantation. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Recommendations of CDC, the Infectious Disease Society of America, and the American Society of Blood and Marrow Transplantation. Cytotherapy. 2001;3:41-54. [PMID: 12028843]

Specific Posttransplantation Infections

Viral Infections

Cytomegalovirus is the most significant viral infection after transplantation, with risk for infection depending on donor and recipient serology. After SOT, the risk for cytomegalovirus is highest (>50%) for donor-positive/recipient-negative, intermediate (15%-20%) for recipient-positive, and lowest for donor-negative/recipient-negative transplantations. Risk is also significantly increased with use of lymphocyte-depleting agents. Comparatively, after allogeneic HSCT, the risk of cytomegalovirus is highest for donor-negative/recipient-positive transplantations. Cytomegalovirus is an immunomodulatory virus, and active cytomegalovirus infection after transplantation is associated with increased rates of rejection and GVHD, as well as increases in other opportunistic infections and posttransplant lymphoproliferative disorder (PTLD). Cytomegalovirus often presents as a nonspecific viral syndrome with fever and cytopenias. Specific organ disease owing to cytomegalovirus includes pneumonitis (more common in HSCT than SOT), encephalitis, hepatitis, and other gastrointestinal sites. Colitis is the most common manifestation of cytomegalovirus gastrointestinal disease after SOT, whereas esophagitis is more common after HSCT. Definitive diagnosis of organ disease depends on demonstration of cytomegalovirus in biopsy, although presumptive diagnosis can be made based on cytomegalovirus viremia, using quantitative nucleic acid amplification testing, in the appropriate clinical setting.

Epstein-Barr virus is most significant for its relationship to PTLD resulting from B-cell proliferation; PTLD should be suspected in any patient in the middle or late period presenting with lymphadenopathy or an extranodal mass, often with fever. Treatment of PTLD involves rituximab and decreasing immunosuppression. Reactivation of herpes simplex virus is especially common after HSCT and can be reduced with acyclovir prophylaxis (if the patient is not already receiving an agent for cytomegalovirus). Patients with chronic hepatitis B can have disease flares if not taking suppressive therapy (see MKSAP 19 Gastroenterology & Hepatology). Polyomavirus BK can cause nephropathy after kidney transplantation, increasing the risk of graft rejection, and hemorrhagic cystitis, particularly in HSCT.

Bacterial Infections

Bacterial infections are common in the early period after SOT and during neutropenia after HSCT. These are often typical nosocomial infections, including resistant organisms such as methicillin-resistant staphylococci, vancomycin-resistant enterococci, and multidrug-resistant gram-negative organisms. *Clostridioides difficile* colitis is common, especially with the extensive antibiotic use that accompanies transplantation. *Mycobacterium tuberculosis* can reactivate with the immunosuppression of transplantation and may present with an atypical pattern on chest radiography or with extrapulmonary disease. Related to persistently low antibody levels, encapsulated organisms such as *Streptococcus pneumoniae* remain common even late after HSCT.

Fungal Infections

Fungal infections are most common in the middle period after SOT but may also occur late, especially in the setting of increased immunosuppression for the treatment of rejection or profound T-cell depression secondary to cytomegalovirus infection. Without prophylaxis, the most common fungal infection is *Pneumocystis* pneumonia, which presents as a more acute and severe pneumonitis in patients after transplantation than in those with AIDS. Cryptococcosis usually presents as subacute meningitis with fever, headache, mental status changes, and lymphocytic pleocytosis in cerebrospinal fluid, although skin and other organ involvement may also occur; cryptococcal antigen testing is key to diagnosis. Histoplasmosis may also occur in geographically endemic areas and is more likely to present with disseminated disease after transplantation. Mucocutaneous candidiasis is common early after SOT and HSCT. Invasive *Candida* infections and candidemia can be seen, especially in the neutropenic phase after HSCT, as can aspergillosis and other invasive molds, such as *Mucor*. The risk for invasive fungal infections after HSCT is also increased in later periods by the use of immunosuppressive agents for GVHD. In SOT, pulmonary aspergillosis is most common after lung transplantation.

Protozoa and Helminths

Toxoplasma gondii, a risk particularly for heart transplant recipients, is a protozoan that can reactivate with immunosuppression, causing encephalitis with fever, headache, and focal neurologic deficits with multiple ring-enhancing brain lesions on imaging (see HIV/AIDS). *Strongyloides* can cause a hyperinfection syndrome with significant immunosuppression (especially glucocorticoid use), often with secondary pneumonia and gram-negative bacteremia. Reactivation of *Trypanosoma* or *Leishmania* can also occur after transplantation, if the recipient or donor was from an endemic area.

KEY POINTS

- Cytomegalovirus is the most significant viral infection after transplantation and may present as a nonspecific viral syndrome with fever and cytopenias or with specific organ disease, including pneumonitis, encephalitis, esophagitis, and colitis.
- *Clostridioides difficile* colitis is common after transplantation, complicating the extensive antibiotic use that accompanies transplantation.
- *Mycobacterium tuberculosis* can reactivate with the immunosuppression of transplantation and may present with an atypical pattern on chest radiography or with extrapulmonary disease.

(Continued)

KEY POINTS (continued)

- Without prophylaxis, the most common fungal infection is *Pneumocystis* pneumonia, which presents as a more acute and severe pneumonitis in patients after transplantation than in those with AIDS.

Prevention of Infections in Transplant Recipients

Prevention is preferred over treatment strategies for most common infections after transplantation because most opportunistic infections have devastating effects and the cost and toxicity of prophylaxis and immunization are relatively low. Recommended immunizations for SOT and HSCT are shown in **Table 52**. Most immunizations are safe in patients after transplantation except for live virus vaccines, which should be avoided after transplantation.

Trimethoprim-sulfamethoxazole is one of the most important prophylactic medications after transplantation. Used to prevent *Pneumocystis*, it may also reduce toxoplasmosis and certain bacteria, including *Listeria* and agents causing urinary tract infections.

Antifungal prophylaxis is indicated during the early months after HSCT and may need to be extended in the setting of GVHD. Coverage should include *Candida* and *Aspergillus*, typically with posaconazole or voriconazole.

Strategies to reduce the effects of cytomegalovirus include primary prophylaxis, usually with valganciclovir, or regular monitoring for active cytomegalovirus replication by

TABLE 52. Immunization Recommendations for Adult Recipients of Transplants[a]

Immunization	Recommendations for Solid Organ Transplantation	Recommendations for Hematopoietic Stem Cell Transplantation[b]
Pneumococcal	Before transplantation: PCV13 followed 8 weeks later by PPSV23	3-6 months after transplantation: three doses of PCV13
	After transplantation: PCV13 (if not administered pretransplantation) 2-6 months after transplantation; one dose PPSV23 at least 8 weeks after PCV13 and 5 years after any previous PPSV23	12 months after transplantation: one dose of PPSV23
Influenza (inactivated only)	Annually	Annually
Tdap	Before transplantation: complete series, including Tdap booster	6 months after transplantation: three doses Tdap
MMR	Contraindicated after transplantation	24 months after transplantation: one to two doses, only if no GVHD or immune suppression
Inactivated polio	Before transplantation: complete series	6-12 months after transplantation: three doses
Haemophilus influenzae type B	No recommendation	6-12 months after transplantation: three doses
Meningococcal	Per recommendations for nontransplant patients	6 months after transplantation: both quadrivalent conjugate vaccine and serogroup B vaccine
Hepatitis B	Before transplantation: complete series if not already immune	6-12 months after transplantation: three doses if indications for nontransplant patients are met
Hepatitis A	Before transplantation: complete series if not already immune	Per recommendations for nontransplant patients
Varicella-zoster virus		
Live attenuated vaccine	>4 weeks before transplantation: varicella if not immune	>4 weeks before transplantation: varicella if not immune
	>4 weeks before transplantation: zoster if same indications as nontransplant patients are met	24 months after transplantation: two doses varicella if seronegative and only if no GVHD or immunosuppression
	Both contraindicated after transplantation	
Recombinant adjuvanted zoster vaccine	Theoretically safe, but data in severely immunocompromised patients not yet available; no recommendations after transplantation	Theoretically safe, but data in severely immunocompromised patients not yet available except for autologous HSCT; no recommendations after transplantation
	Should be given before transplantation if possible	Should be given before transplantation if possible
Human papillomavirus	Before transplantation: per recommendations for nontransplant patients	Per recommendations for nontransplant patients

GVHD = graft-versus-host disease; MMR = measles, mumps, and rubella vaccine; PCV13 = 13-valent pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine; Tdap = tetanus, diphtheria, and acellular pertussis vaccine.

[a]See MKSAP 19 General Internal Medicine 2 for more information on vaccination recommendations and schedules.

[b]For multiple-dose immunizations, the time period between doses is generally 1-2 months.

quantitative nucleic acid amplification testing and institution of pre-emptive therapy based on results. Monitoring and pre-emptive therapy is more often used after HSCT, partially because of increased concerns for neutropenia as an adverse effect of prophylaxis and because prophylaxis was not found to be superior to pre-emptive therapy in a randomized controlled trial. Letermovir, a novel antiviral agent without the hematologic toxicities of valganciclovir, is approved for prophylaxis of cytomegalovirus infection in bone marrow transplant recipients. For SOT, prophylaxis with valganciclovir is preferred for patients at high risk (donor-positive/recipient-negative, those receiving lymphocyte-depleting agents, lung transplants) and is usually given for at least 3 to 6 months; letermovir prophylaxis is under study in SOT recipients.

KEY POINTS

HVC

- Prophylaxis and immunization are preferred over treating active infections after transplantation; live virus vaccines should not be given after transplantation.
- Monitoring by quantitative nucleic acid amplification testing for active cytomegalovirus replication and institution of pre-emptive therapy based on results is preferred to ganciclovir primary prophylaxis of cytomegalovirus infection after hematopoietic stem cell transplantation.