

Infections in Transplant Recipients

Introduction

Despite improvements in immunosuppression and antimicrobial therapy, infection remains a significant cause of morbidity and mortality after solid organ transplantation (SOT) and hematopoietic stem cell transplantation (HSCT). Infection is the most common cause of death in the first year after SOT. Additionally, the interaction of the immune system and infection goes both ways; although immune suppression to prevent rejection increases risk of infection, infection also raises the risk of rejection.

The occurrence of SOT and 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.

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 52) with

TABLE 52. Immunosuppressive Agents Used in Transplantation

Class	Agents
Glucocorticoids	Prednisone, others
Cytotoxic agents (DNA synthesis inhibitors, antimetabolites)	Mycophenolate mofetil
	Mycophenolate sodium
	Azathioprine
	Methotrexate
Calcineurin pathway inhibitors	Cyclophosphamide
	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.

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 early period after transplantation and often includes lymphocyte depletion therapy. Immunosuppression may require intensification later for episodes of rejection, and this may again increase the risk of infection.

Glucocorticoids have historically been the cornerstone of antirejection therapy, but steroid-sparing or minimizing regimens are increasingly being used to avoid the toxicities of long-term 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 risk of specific infections varies depending on the time frame after transplantation. Table 53 shows the typical timeline of risk for specific infections after SOT. However, the timeline restarts when treating episodes of rejection, and infection risk in the late period depends on the level of immunosuppression required. Knowledge of the risk timeline and effect of the immunosuppression level can be helpful in recognizing likely infections and in preventing infections through targeted prophylaxis. 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.

Additional general considerations include the higher likelihood of infections to disseminate after transplantation and the subtle or atypical presentation of infection because of

TABLE 53. 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
<i>Staphylococcus aureus</i> 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
<i>Clostridium difficile</i> colitis	Herpes simplex virus infection	Community-acquired pneumonia
<i>Candida</i> infection	Varicella-zoster virus infection	Urinary tract infections
<i>Aspergillus</i> infection	Polyoma BK virus infection	Polyoma BK virus infection
Surgical site infections	<i>Pneumocystis jirovecii</i> infection	Cytomegalovirus infection
Nosocomial pneumonia	<i>Toxoplasma</i> , <i>Trypanosoma</i> , <i>Strongyloides</i>	
Catheter-related bacteremia	<i>Listeria</i> infection	
Urinary tract infections	<i>Nocardia</i> infection	
	Tuberculosis reactivation	
	Fungal infections, including <i>Cryptococcus</i>	

PTLD = posttransplant lymphoproliferative disorder.

^aFor 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.

changed anatomy after transplantation. Immunosuppressive drugs may also contribute to altered presentation because of reduction in fever and other inflammatory responses making the usual signs and symptoms of infection less prominent. Noninfectious complications such as GVHD or malignancy may also be confused with infection. 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.

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 21 shows the timeline of risk for specific infection 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 frame 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.

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 post-transplant 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. Although cytomegalovirus can cause disease anywhere in the gastrointestinal tract, colitis is the most common 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, demonstrated by 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

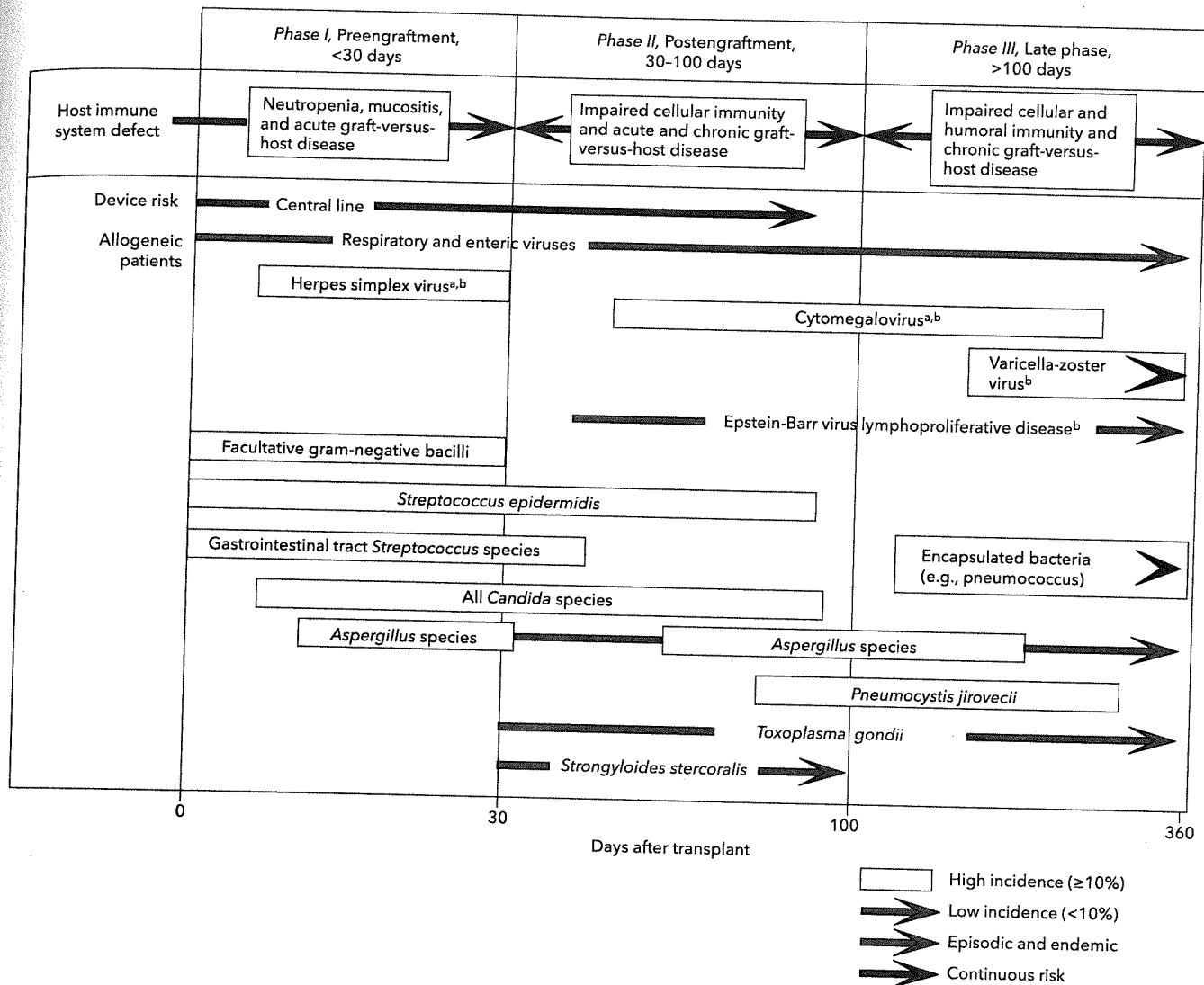


FIGURE 21. Phases of opportunistic infections in allogeneic hematopoietic stem cell transplant recipients.

^aWithout standard prophylaxis.

^bPrimarily among persons who are seropositive before transplantation.

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can have flares of disease if not taking suppressive therapy. Polyoma BK virus can cause a nephropathy in the middle or late period after transplantation.

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. *Clostridium 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 rejection or cytomegalovirus infection. The most common fungal infection without prophylaxis is *Pneumocystis pneumonia*, which is typically a more aggressive pneumonia 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 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 infection 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 is a protozoan that can reactivate with immunosuppression after transplantation, usually causing encephalitis with fever, headache, and focal neurologic deficits and with multiple ring-enhancing brain lesions on imaging. *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 were 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.
- *Clostridium 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.
- *Pneumocystis* pneumonia is the most common fungal infection without prophylaxis; it is typically a more aggressive pneumonia 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 54**. 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. Trimethoprim-sulfamethoxazole is usually given up to 1 year after transplantation and often longer if immunosuppression cannot be adequately reduced.

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 remain important and include primary prophylaxis, usually with valganciclovir, or regular monitoring for active cytomegalovirus replication by 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. The potential role of letermovir, a new antiviral agent without the hematologic toxicity of ganciclovir, is being studied for cytomegalovirus prophylaxis. 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.

KEY POINTS

- 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.

HVC

Health Care-Associated Infections



Epidemiology

Health care-associated infections (HCAI) have been linked to indwelling medical devices, prosthetic devices and materials, surgery, invasive procedures, transmission of organisms between patients and health care personnel, and environmental factors. Four percent of hospitalized patients acquire at least one HCAI, costing the U.S. health care system an estimated \$28 billion to \$45 billion annually. HCAs include pneumonia and surgical site infections (21.8% each), gastrointestinal infections (17.1%), urinary tract infections (12.9%; 67.7%