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Infections in Transplant Recipients GENERAL CONCEPTS This chapter discusses infections in recipients of solid organ transplant (SOT), vascular composite allografts (VCAs), and hematopoietic stem cell transplantation (HCT). Despite the notable differences between these procedures, they share the fact that recipients receive immu nosuppression (in the case of SOT and VCAs, for life). They become immunocompromised and, consequently, are at increased risk for infection. PART 5 Infectious Diseases Infections in immunocompromised patients may be caused by the common pathogens that affect everybody but also by opportunistic microorganisms that usually do not cause significant illness in healthy people. The physician taking care of transplant recipients should be aware of the risk of unusual pathogens, uncommon presentation of infections, and multiple concomitant infections. In addition, response to treatment may be suboptimal due to the effect of immunosup pressive medication and corticosteroids as well as coexisting medical or surgical complications. Professional societies issue and regularly update guidelines for the diagnosis and management of infections in these patients. For SOT, the reader is referred to the guidelines from the American Society of Transplantation Infectious Diseases Community of Practice and, for HCT, to the guidelines published by the American Society for Transplantation and Cellular Therapy and the European Conference on Infections in Leukemia (ECIL). In this textbook, there are chapters dedicated to SOT (Chaps. 271, 309, 325, and 356), HCT (Chap. 119), and cellular therapy (Chap. 483), as well as chapters about every one of the pathogens that will be men tioned here. Our goal is to focus on the particulars of infections as they pertain to transplant, as well as to discuss some relevant topics that are not included elsewhere. These include pretransplant evaluation of transplant candidates, assessment of potential donors, infections acquired through the transplant, and prophylaxis of infections. Understanding the similarities between transplants regarding

increased risk of infection (e.g., immunosuppressive agents) is impor tant, as is understanding some of the basic differences. An obvious and relevant difference is that SOT and VCA transplants include surgical procedures, and the operations are extremely challenging. Most early infections are related to complications of the surgery, and sometimes even late infections may have their origin in the operating room. In contrast, early infections after HCT are related to the neutropenia induced by the conditioning regimen. Another difference is that both SOT and VCA transplants require lifelong immunosuppression to prevent rejection. This means the risk of opportunistic infection never goes away. Conversely, immunosuppression is not typically

administered after autologous HCT (auto-HCT), and it is only given for a few months after allogeneic HCT (allo-HCT). Finally, both SOT and allo-HCT carry a risk of unfavorable immune reactions: rejec tion of the transplanted organ and graft-versus-host disease (GHVD), respectively. Both rejection and GVHD are treated by increasing the immunosuppression, with consequent increased risk of infection. INFECTIONS AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION HCT is a procedure in which a conditioning regimen that eliminates (partially or completely) the recipient's myeloid and lymphoid immune systems is followed by the infusion of hematopoietic stem cells, with subsequent recovery of bone marrow and immune function. It includes two distinct categories: auto-HCT and allo-HCT. Of the approximately 20,000 HCTs performed in the United States every year, 12,000 are autologous and 8000 allogeneic. In both, a conditioning regimen (vari able combinations of chemotherapy, radiation, and serotherapy) is administered. This conditioning regimen eliminates the myeloid pro genitors and the lymphoid immune system of the patient. Then, hema topoietic stem cells are administered to replenish both the myeloid and the lymphoid immune systems. In the case of autologous transplanta tion, the stem cells are from the recipient, harvested in advance and cryopreserved until the day of the transplant. This procedure does not correct defects present in the stem cells (e.g., hemoglobinopathies, primary immunodeficiencies) and, in the treatment of cancer, is not expected to cure a malignancy that is refractory to chemotherapy because the autologous stem cells have no anticancer potential. For malignancies still susceptible to chemotherapy, however, the intensive myeloablative conditioning regimen could be curative, while the infu sion of autologous cells would effectively "rescue" the bone marrow. Conversely, in allo-HCT, the donor is another person, and their stem cells are free of whatever genetic defect the recipient's stem cells had. This means allo-HCT could, in principle, cure stem cell disorders. The reconstituted myeloid system, for instance, will be free of hemoglobin opathy. The reconstituted immune system should ultimately become immunocompetent. If a malignancy is being treated, there is potential for the new immune system to fight it and even eradicate it, through a now well-defined phenomenon called graft-versus-leukemia (GVL) or graft-versus-tumor (GVT) effect. From this standpoint, allo-HCT may be considered a form of immunotherapy, and it has been used to cure chemotherapy-refractory malignancies. There is also, unfortunately, the potential for the regenerated immune system to recognize the recipient as "alien" and to mount an immune response against their organs, which is called graft-versus-host disease (GVHD) and can be severe and even fatal. GVHD is common, affecting between 35 and 50% of allo-HCT recipients with varying severity (from mild to lifethreatening). To prevent GVHD, allo-HCT recipients receive a few months of immunosuppression, which is then slowly tapered. GVHD is not expected to occur after auto-HCT, so no immunosuppression is administered after the stem cell infusion. The biological difference between auto-HCT and allo-HCT dictates the different indications of each one. The vast majority of auto-HCTs performed are for multiple myeloma and lymphoma, malignancies that do not involve

the stem cells. In this situation, the therapeutic inter vention is the conditioning regimen, and the function of the infusion of stem cells (the transplant) is to replenish the myeloid progenitors eliminated by the conditioning. A minute fraction of auto-HCT is used or is being studied in select nonmalignant conditions that could poten tially benefit from intense immunoablation. Auto-HCT was superior to standard immunosuppression for the treatment of severe systemic sclerosis in a randomized controlled trial and is also being used in selected patients with multiple sclerosis. It is also being investigated in systemic lupus erythematosus, rheumatoid arthritis, polymyositis/ dermatomyositis, and Crohn disease. The most common indication for allo-HCT is acute leukemia, fol lowed by myelodysplastic and myeloproliferative disorders. It is also increasingly used for nonmalignant conditions including aplastic anemia, hemoglobinopathies (e.g., sickle cell disease, thalassemia), and primary immunodeficiency disorders (PIDs; also called inborn errors

of immunity [IEI]) including severe combined immunodeficiencies (SCID), phagocytic disorders such as chronic granulomatous disease, diseases of immune dysregulation such as familial hemophagocytic lymphohistiocytosis, and others. Different conditioning regimens result in varying degrees of organ toxicity, including mucositis, and variable durations of neutropenia. In the case of allo-HCT, additional factors that impact the risk of infection include the source of stem cells (bone marrow, peripherally collected stem cells, or umbilical cord blood [UCB]) and the degree of human leukocyte antigen (HLA) matching and relatedness between the donor and the recipient (in increasing infection risk: matched sibling donor, matched unrelated donor, haploidentical donor, mismatched donor). Infections are common after transplant and account for between 15 and 25% of the deaths in the first 100 days after auto-HCT and between 20 and 40% after allo-HCT, depending on the type of transplant. The risk factors for infection include preexisting conditions (intimately associated with the indication for transplant), conditioning regimen with its attendant neutropenia, mucositis and immunosuppression, and (in the case of allo-HCT) immunosuppression to prevent GVHD and, if this occurs, GVHD and its treatment. As mentioned earlier, however, and in distinction to SOT, most allo-HCT recipients do not receive lifelong immunosuppression. A few years after allo-HCT, a patient without chronic GVHD has an essentially normal immune system. TIMELINE OF INFECTIONS AFTER HCT Considerable experience over decades of transplantation has resulted in learning what the expected infections are and when they are sup posed to occur. Anti-infective prophylaxis derives from this knowl edge. Nomenclature varies, but we will consider very early infections (from initiation of the conditioning regimen until resolution of neutro penia), early infections (from neutrophil engraftment until day +100), and late infections (after day +100) (Table 148-1). Very Early Infections: Preexisting Infections, Baseline Condition, and Neutropenia We consider the “very early” phase of HCT to be the period between the initiation of the conditioning regimen and recovery from neutropenia (neutrophil engraftment). The intensity of the conditioning (which is classified as myeloablative, reduced intensity, and nonmyeloablative) results in different degrees and durations of neutropenia, mucositis, and immunosuppression. During this time, bacterial infections related to neutropenia and mucosal barrier injury predominate, but one must also consider pre existing infections, both common and frequently known in patients undergoing transplant for PID (e.g., known diarrhea and cholangiopa thy caused by cryptosporidiosis in patients with SCID) and potentially unknown and acquired during therapies received prior to transplant (e.g., pulmonary aspergillosis developed during induction therapy of acute myeloid leukemia but asymptomatic pulmonary nodules at the time of transplant). A pretransplant infectious diseases consult TABLE 148-1 Common Sources of Infection After Hematopoietic Stem Cell Transplantation INFECTION SITE VERY EARLY (<1 MONTH) EARLY (BEFORE 100 DAYS) LATE

(>100 DAYS) Disseminated Aerobic bacteria (gram-negative, gram-positive) Candida, Aspergillus, CMV, EBV, Toxoplasma Skin and mucous membranes HSV, Candida HSV, VZV VZV, HPV (warts) Lungs Aerobic bacteria (gram-negative,

gram-positive), Aspergillus, other molds CMV, community-acquired respiratory viruses, Pneumocystis, Toxoplasma, molds, adenovirus Gastrointestinal tract Clostridioides difficile CMV, adenovirus, norovirus EBV, CMV, norovirus Genitourinary tract BK virus BK virus, adenovirus Brain HHV-6, Toxoplasma Toxoplasma, JC virus (rare) Bone marrow CMV, Toxoplasma CMV Abbreviations: cGVHD, chronic graft-versus-host disease; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV-6, human herpesvirus type 6; HPV, human papillomavirus; HSV, herpes simplex virus; NTM, nontuberculous mycobacteria; VZV, varicella-zoster virus.

is recommended, when possible, as a review of previous records and imaging may be extremely useful for prevention, diagnosis, and management of infection. An etiologic diagnosis for abnormal find ings should be pursued. A review of past infection or colonization with resistant pathogens may also provide actionable information, for instance, determining the choice of empirical antibiotics during neutropenic fever.

Fever during neutropenia (neutropenic fever) occurs in a large pro portion of HCT recipients, depending on the conditioning regimen. Neutropenic fever is discussed in depth in Chap. 79, but a summary follows. Fever during neutropenia is considered infectious in origin even if no infection is identified in most cases. The management cen ters on the fact that bacterial infections may progress very quickly in the absence of neutrophils, so expediency is critical. A thorough physi cal exam should be performed, with emphasis on possible bacterial portals of entry (e.g., mouth, perianal region, catheter exit site); blood cultures should be obtained; and broad-spectrum antibiotics including activity against Pseudomonas aeruginosa should be initiated. Antibiotic choice varies with prior history (e.g., previous infection with multi drug-resistant [MDR] gram-negative bacteria or methicillin-resistant Staphylococcus aureus), the clinical presentation (e.g., localizing symp toms or signs, hemodynamic instability), and the local patterns of resistance. Once antibiotics are started, they are modified depending on new microbiologic data or changes in the clinical status. In general, persistent fever alone is not an indication to modify the antibacterial regimen. However, persistent fever while receiving broad-spectrum antibiotics identifies a subset of patients with higher likelihood of har boring invasive fungal disease (IFD), and a thorough search for IFD or modification of the antifungal regimen is indicated when neutropenic fever continues for >4 days. CHAPTER 148 Bacterial infections during this time are related to the degree and duration of neutropenia and the extent of the mucositis. Consequently, milder, nonmyeloablative conditioning regimens may result in less very early infections. Antibacterial prophylaxis (typically with a fluoroqui nolone such as levofloxacin) decreases the frequency of neutropenic fever and is used by some groups, but there is growing concern about the long-term consequences of this practice (potential for worsening transplant outcome due to microbiome disruption), as well as coloniza tion with resistant bacteria and Clostridioides difficile colitis. Currently, antibacterial prophylaxis during HCT is not universal. Infections in Transplant Recipients Neutropenia during HCT is usually shorter than after induction of remission of acute leukemia. The most common early fungal infection after HCT used to be candidiasis, but now antifungal prophylaxis is almost universal. Prophylaxis with fluconazole decreases the likelihood of invasive candidiasis and improves survival in the allo-HCT setting. Fluconazole prophylaxis is most often used, but if the

likelihood of asper gillosis is considered high, an agent with activity against mold, typically posaconazole, is used instead. Aspergillus and other molds are uncom mon during short neutropenia, but there may be other factors that put the patient at risk. It should be noted that antimicrobial prophylaxis is PERIOD AFTER TRANSPLANTATION Encapsulated bacteria (Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis) Community-acquired respiratory viruses, Pneumocystis, Nocardia, S. pneumoniae, H. influenzae NTM (cGVHD)

never completely effective. Breakthrough infections may occur, such as non-albicans Candida when fluconazole is used or Fusarium, Mucorales, or other azole-resistant molds when posaconazole is used.

Risk of early Pneumocystis jirovecii pneumonia (PJP) varies with the indication for transplant and prior treatments, as well as with the conditioning regimen. For instance, a patient receiving allo-HCT for sickle cell disease is not at risk for PJP before receiving the condition ing regimen, whereas patients with immunodeficiency or heavily treated for acute lymphoblastic leukemia carry considerable risk. In most cases, prophylaxis against PJP is used. It is well accepted that trimethoprim-sulfamethoxazole (TMP-SMX) is most effective, and it can be used until the infusion of stem cells. After the stem cells are given, the potential for myelotoxicity and delayed engraftment makes other options (e.g., inhaled or intravenous pentamidine) preferable. Atovaquone may be used, but it is expensive, unpalatable, and requires a fatty meal for optimal absorption, which may be difficult during this phase of significant mucositis. Herpes simplex virus (HSV) reactivation occurs early, associated with the mucositis caused by the conditioning regimen. Acyclovir prophylaxis is standard of care, and it effectively prevents HSV and varicella-zoster virus (VZV). Breakthrough HSV must be differenti ated from mucositis caused by chemotherapy, and viral polymerase chain reaction (PCR) should be used. If HSV breaks through acyclovir prophylaxis and absorption is not an issue, acyclovir-resistant HSV should be considered. Decisions must be made clinically, since drug resistance can only be determined definitively by phenotypic testing, which takes weeks. Some instances of low-level resistance may be over come by switching to high-dose (10 mg/kg per 8 h) IV acyclovir, but if this does not result in clinical improvement, foscarnet 60 mg/kg per 12 h or cidofovir 5 mg/kg weekly should be used. PART 5 Infectious Diseases Cytomegalovirus (CMV) infection is uncommon before engraft ment and will be discussed in detail later, but in many centers, HCT recipients who are CMV seropositive start prophylaxis with the anti viral letermovir at the time of transplant. Of note, letermovir has no activity against HSV or VZV, so acyclovir should be administered concomitantly. Early Infections: Between Neutrophil Engraftment and Day 100—Reactivation of Latent Infections and Complications of GVHD and Its Treatment During this phase, the patient has neutrophils but not a functioning lymphoid immune system. Potential infections include exogenous pathogens (e.g., community-acquired respiratory viruses), acquired when the patient is discharged from the hospital and reenters the community, as well as the reactivation of latent pathogens (e.g., herpesviruses, adenovirus, JC virus, and para sites such as Toxoplasma gondii). Despite neutrophil engraftment, the patient’s lymphoid immune system was eliminated by the conditioning regimen, and the infused stem cells have not had time to create a func tioning immune system. Other factors may impact the risk of infection. In the case of allo-HCT, there is usually ongoing immunosuppression with a calcineurin inhibitor (cyclosporine A or tacrolimus), siroli mus, or mycophenolate mofetil. The conditioning regimen may have included particularly immunosuppressive strategies such as sero therapy with antithymocyte globulin or alemtuzumab, which have a long half-life and may result in prolonged T-cell depletion that persists

after engraftment. The source of the stem cells administered also plays a role: peripherally collected stem cells include more mature T cells than bone marrow, and these may offer some protection against latent pathogens. Ex vivo T-cell depletion (CD34 selection) is sometimes used and results in a product with even fewer mature T cells than bone marrow. UCB also lacks effective cellular immunity against infections latent in the recipient. Finally, if the patient develops acute GVHD, high-dose corticosteroids may be added to the immunosuppressive regimen, increasing the risk not only of latent infection reactivation but also of newly acquired bacterial and fungal infections. If GVHD does not respond to steroids, second-line agents may be added, compound ing the immunocompromise of the patient. BACTERIAL INFECTIONS Mucositis and neutropenia have resolved during this phase. Some patients still have a central venous catheter,

with the attendant risk of catheter-related bloodstream infection. How ever, in the absence of GVHD, bacterial infections are relatively uncom mon. Conversely, if acute GVHD of the bowel occurs, the patient is at risk of mucosal barrier injury–related bloodstream infection with bowel flora, particularly when high-dose corticosteroids are initiated. C. difficile infection is also common during this period and should be aggressively treated. FUNGAL INFECTIONS Because neutropenia is no longer a factor, fun gal infection during this time is usually associated with corticosteroid use, although other immunosuppressive agents used to treat acute GVHD may also increase the risk. Aspergillosis is the most common mold infection, and patients with GVHD on high-dose corticosteroids (i.e., >0.5 mg/kg of prednisone every other day) or on a combina tion of immunosuppressive agents frequently receive posaconazole prophylaxis, based on the results of a randomized controlled trial. Many authorities recommend monitoring serum posaconazole levels, particularly when absorption may be compromised by severe acute GVHD of the bowel. A level <700 ng/μL is considered subtherapeutic, but experts disagree on what levels are desirable for effective prophy laxis and/or treatment. The use of serologic markers of fungal infec tion (galactomannan and/or beta-d-glucan) is not recommended in this setting, as the sensitivity of the tests is markedly reduced when on mold-active azoles. HERPESVIRUSES Herpesviruses may reactivate during this phase, par ticularly in the setting of T-cell depletion, UCB transplant, or GVHD and its treatment. HSV and VZV are usually effectively prevented by acyclovir prophy laxis, but acyclovir-resistant HSV may occur (see the previous section). CMV disease may be prevented by prophylaxis or preemptive manage ment and is discussed separately. Human herpesvirus 6 (HHV-6), the cause of exanthem subitum (sixth disease) in children, is carried latently by most adults and reacti vates frequently after HCT. Most of the time, reactivation is asymptom atic and goes undetected, since routine monitoring of HHV-6 is not recommended. However, it can sometimes cause encephalitis, which may be severe and result in significant morbidity and even death. It presents as limbic encephalitis, typically without a fever and initially with a clear sensorium but with short-term memory loss accompa nied by tremor or other involuntary movements. It may progress to abnormal mental status, seizures, and coma. The diagnosis is made in the presence of signs and symptoms of encephalitis with detectable HHV-6 in the cerebrospinal fluid (CSF) and no other explanation for the disease. Brain magnetic resonance imaging (MRI) may be normal initially but later shows bilateral involvement of the amygdala on the temporal lobes. It is not clear whether treatment modifies the out come, as HHV-6 tends to get under control in most patients without any intervention and affected patients frequently suffer significant long-term sequelae despite antiviral treatment. Guidelines recommend treatment with ganciclovir or foscarnet, although some experts recom mend combining both antivirals. Other less well-established disease associations with HHV-6 include fever, GVHD, pneumonia, poor graft function, liver enzyme abnormalities, and

thrombocytopenia. Human herpesvirus 7 (HHV-7) is, like CMV and HHV-6, a betaherpesvirus. It may be detected by PCR in the blood of HCT recipients, but it is not known whether it causes any disease or is a co-factor in other infections such as CMV and HHV-6. BK VIRUS BK virus, a polyomavirus that infects 80–90% of people, is associated with hemorrhagic cystitis after allo-HCT and, very sel domly, nephropathy. The clinical presentation includes dysuria and bladder spasms and hematuria, usually macroscopic. High-level BK viruria is usually present, but this may also happen without symptoms. The increasing use of posttransplant cyclophosphamide as prophylaxis for GVHD may make diagnosis difficult, as cyclophosphamide can cause hemorrhagic cystitis. There is no known effective treatment for BK virus after HCT, but hemorrhagic cystitis, albeit debilitating, is almost always self-limited. In severe cases, intravesical clots may cause obstructive uropathy and require continuous bladder irrigations.

Rarely, BK virus may cause nephropathy after allo-HCT. This entity is discussed in detail in the section on infections after SOT. RESPIRATORY VIRUSES Besides the reactivation of latent viral infec tions expected during this period, once the patient is discharged after transplant, they are exposed to community-acquired respiratory viruses, which have significant mortality when they progress from upper respiratory tract infection to pneumonia. Many respiratory viruses can cause significant morbidity after HCT. SARS-CoV-2, influenza, respiratory syncytial virus (RSV), metapneu movirus, and parainfluenza 3 may cause severe disease more often, but multiple enteroviruses and non–severe acute respiratory syndrome (SARS) coronaviruses may occasionally result in pneumonia. Only a few of these infections are amenable to antiviral treatment. Diagnosis usually relies on molecular methods (PCR of nasopharyngeal swab or nasal wash), but rapid viral culture (shell vial) is still used in some centers. A general principle of viral infections is that controlling them (espe cially long term) requires the host’s specific immunity, to a degree that bacterial infections do not. In this regard, decreasing the immunosup pression, if possible, is a standard part of the management. Unfortu nately, this may not be possible in allo-HCT, particularly if the viral infection occurs in the setting of GVHD. If there is no GVHD, some consideration should be given to decreasing the dose of immunosup pressive drugs such as calcineurin inhibitors or sirolimus, which are usually carefully monitored through blood levels. Specific antiviral treatment recommendations follow. Coronavirus Disease 2019 (COVID-19) U.S. Food and Drug Administra tion (FDA)-approved antiviral treatments for SARS-CoV-2 include remdesivir and nirmatrelvir-ritonavir (Paxlovid). In nonvaccinated, never-infected, non-immunocompromised patients with comorbid conditions or older than 60 years with COVID-19, nirmatrelvirritonavir given within 3 days of the onset of symptoms resulted in a 90% decrease on the risk of hospitalization or death. More recent studies including people who have been vaccinated and are not at high risk of progression have not confirmed these results. However, many experts still recommend nirmatrelvir-ritonavir for immunocompro mised patients. Unfortunately, transplant recipients are frequently receiving medications such as tacrolimus or sirolimus that may make nirmatrelvir-ritonavir use impractical due to drug–drug interactions. The antiviral molnupiravir has an FDA emergency use authoriza tion for the treatment of adults with mild-to-moderate COVID-19 who are at high risk for progression to severe disease and for whom other COVID-19 treatment options are not accessible or clinically appropriate. Most experts would at least consider antiviral treatment of COVID-19 in HCT recipients. Depending on the clinical setting, outpatient administration of IV remdesivir may be a more practical option. Bacterial superinfection is uncommon after COVID-19, but aspergillosis has been described. Risk factors for COVID-19-associated pulmonary aspergillosis include high-dose corticosteroids and hema tologic malignancy but not necessarily transplant. Influenza Virus

Influenza may be treated with neuraminidase inhibi tors (oseltamivir, zanamivir, or peramivir) or baloxavir, an inhibitor of the polymerase acidic (PA) protein. There are limited data to choose between these two options, but more experience with the former. Amantadine and rimantadine, only active against influenza A, are not currently recommended in the United States because of widespread resistance. Respiratory Syncytial Virus RSV may be treated off-label with ribavirin, either orally or by inhalation. In RSV, lymphopenia (absolute lympho cyte count [ALC]) has been found to be a risk factor for the develop ment of pneumonia, and some experts recommend using ALC <1000/μL as a guide to initiate early treatment with ribavirin. Adenovirus Adenovirus occupies a particular place within this group, as it can represent a newly acquired community-acquired infec tion or be reactivation of latent virus from prior infection. Because adenovirus may be more common in children, some pediatric centers monitor high-risk patients by PCR of stool and/or blood and attempt

intervention before established adenovirus disease ensues. Drugs with activity against adenovirus include cidofovir, brincidofovir, and (for some species) ribavirin. The response of established adenovirus disease to antivirals is poor.

As mentioned above, all respiratory viral infections may occasionally cause lower respiratory tract disease. When there is lower respiratory tract with any respiratory virus, a search for co-pathogens (bacterial or fungal) is indicated, as these are frequently present. TOXOPLASMOSIS Toxoplasma gondii infects >2.5 billion people. The prevalence and routine monitoring after HCT vary significantly between countries. Studies from Europe suggest that allo-HCT recipi ents who have positive Toxoplasma serology reactivate frequently (8–21%) and early (95% within the first 6 months). The presentation may be just fever (this, in the presence of a positive Toxoplasma PCR, is often called toxoplasmosis infection), but also may include pneumonia (small pulmonary nodules and interstitial pneumonia predominantly at the lung bases), heart disease, brain abscess (single, multiple, or diffuse encephalitis), and disseminated disease sometimes associated with hemophagocytic lymphohistiocytosis. Diagnosis is by blood PCR and/or immunohistochemistry. The standard treatment is with pyri methamine and sulfadiazine, but TMP-SMX may be equally effective. Atovaquone is a second-line agent, and there are anecdotal reports in advanced HIV of successful use of the combination of azithromycin and clindamycin. Late Infections (After Day 100) Day 100 post-HCT remains an arbitrary boundary, as this is when tapering of immunosuppression usually begins. Conceptually, immune reconstitution takes place unim peded by immunosuppressants, so the risk of infection should become progressively less. Most infections at this time are caused by commu nity-acquired pathogens, although late CMV may also occur. The main risk factor for infection is the presence of GVHD and its treatment. Chronic GVHD (cGVHD) results in functional asplenia, and Strep tococcus pneumoniae is a particularly important pathogen. Late fatal infections are predominantly bacterial, but respiratory viral infections such as influenza are still more common than in age-matched popula tions. The group at highest risk are patients with cGVHD receiving immunosuppression. CHAPTER 148 Infections in Transplant Recipients INFECTIONS AFTER SOLID ORGAN TRANSPLANT ■ ■RISK FACTORS FOR INFECTION AFTER SOLID ORGAN TRANSPLANT Infectious complications remain a major cause of morbidity and mor tality after SOT. The risk of infection is determined by the interaction of various factors, such as age of the recipient; type of transplant and technical complexities associated with it; other invasive procedures; dose, duration, and temporal sequence of immunosuppressive drugs; epidemiologic exposures of both donor and recipient; use of antimi crobial prophylaxis; donor-recipient serostatus

to certain infections (e.g., CMV, Epstein-Barr virus [EBV], toxoplasmosis); and ongoing viral replication (so-called indirect effects). Assessment of a recipient's risk for infection helps tailor specific preventive strategies and workup when an infection is suspected. Induction immunosuppression is usually administered immediately prior to transplantation. This is followed by maintenance immunosup pression, which frequently consists of triple therapy with a calcineurin inhibitor (cyclosporine A or tacrolimus) or an mTOR inhibitor (siro limus or everolimus), mycophenolate mofetil, and corticosteroids. Maintenance immunosuppression may be intensified during periods of rejection, and it may be decreased with time, but it is usually continued for life. The amount of immunosuppression the patient is receiving is important in terms of risk of infection. Age is also an important determinant of susceptibility to infections; it impacts the likelihood of prior exposures to microbial pathogens, either by primary infection or vaccination. History of exposure can have either positive or negative effects. Older patients are more likely to have encountered pathogens that can remain latent and reactivate at the time

of transplant (e.g., tuberculosis [TB]); younger patients have a higher risk of acquiring primary infections after transplant, sometimes from the transplanted organ, which tend to be more severe than those secondary to reactivation of a latent infection (e.g., CMV). In addition, preexisting immunity can have a protective effect against clinical disease (e.g., EBVassociated posttransplant lymphoproliferative disorder [PTLD]).

The type of allograft affects the specific infectious risk due to techni cal factors associated with the transplant procedure but also inherent to the transplanted organ and risk of rejection. For example, urinary tract infections are most common after kidney transplant, either from cath eter placement or ureter stenting. BK virus is ubiquitous, but associated nephropathy (BK virus-associated nephropathy) is most common after kidney transplant and is an important cause of allograft loss. Infec tion after liver transplant frequently results from leaks of biliary and gastrointestinal anastomoses. Cardiac assist devices in heart transplant recipients are a frequent source of infection. Tracheal anastomotic infections, particularly due to fungi, are a significant complication of lung transplantation. In single-lung transplants, recurrent infections of the native lung, such as gram-negative bacilli or fungi, can extend to the transplanted lung. In small intestine transplant, opportunistic and nonopportunistic viral infections of the gastrointestinal tract are com mon; these can be severe and even life-threatening (e.g., norovirus). ■ ■TIME COURSE OF INFECTIONS AFTER SOLID ORGAN TRANSPLANT (TABLE 148-2) Despite all the differences in individual risk of infection, some general patterns of infection in the absence of antimicrobial intervention are similar among SOT recipients. This predictable temporal pattern has enabled the institution of specific prophylactic strategies and is useful when developing an infection differential diagnosis. PART 5 Infectious Diseases Early Period: Infections in the First Month After Transplant

Infections in this period are generally associated with technical compli cations of the transplant surgery and are nosocomial. Bacterial infec tions are most common during this time across all organs. Infections with prior colonizers (e.g., MDR bacteria) can occur, and bacterial prophylactic strategies should take these into account. Antimicrobial prophylaxis is usually started promptly after transplant. Hepatitis C occurs during this period when hepatitis C–positive donors are used. Opportunistic infections can happen in recipients with comorbid immunodeficiencies or those who received immunosuppression before transplant, but in the absence of these risk factors, the development of classic opportunistic infections during this early posttransplant period should alert

to the possibility of donor allograft-transmitted infections (e.g., invasive coccidioidomycosis). Intermediate Period: Infections 1–6 Months After Transplant

In the absence of routine antimicrobial prophylaxis, this period is char acterized by the presence of classic opportunistic infections, such as P. jirovecii and CMV. The incidence of these infections has been sig nificantly reduced or delayed with the use of prophylaxis or preemptive therapy. Reactivation of latent infections such as TB, Chagas' disease, endemic mycoses, and cryptococcosis can occur, so it is important to ascertain the risk before transplant and implement specific prophylactic strategies. Viral infections such as BK virus, adenovirus, RSV, hepatitis B virus, and EBV are common. Invasive fungal infections, specifically Aspergillus and other mold infections, can be problematic during this period of heightened immune suppression, but risk varies significantly by type of organ transplanted. Donor-derived infections may still occur. Late Period: Infections 6 Months After Transplant This period is less well defined. Patients with satisfactory allograft func tion may develop more severe manifestations of community-acquired infections. Prophylaxes are frequently stopped, since the risk of oppor tunistic infections is lower than in the earlier period. Patients with poor allograft function due to rejection receive increased immunosuppres sion and are at higher risk of opportunistic infections for a variable period thereafter. Frequently, antimicrobial prophylaxes are "reset" when an episode of acute rejection ensues. The type of rejection (e.g., cellular or humoral) and its specific management may influence the

infection risk. Given that all SOT recipients need lifelong immunosup pression, increased risk of infection persists. Late-onset CMV, nocar diosis, PJP, listeriosis, invasive fungal infections, and EBV-associated PTLD are some examples of opportunistic infections that can be expected in these patients. Patients with ongoing chronic viral reacti vation, particularly CMV, are also at increased risk of other opportu nistic infections. In addition, lung transplant recipients with chronic graft dysfunction are at high risk of recurrent bacterial pneumonia. Similarly, liver transplant recipients with chronic graft dysfunction fre quently develop biliary strictures and recurrent cholangitis. Over time, MDR bacteria can become a problem. VASCULAR COMPOSITE ALLOGRAFTS VCAs refer to transplantation as a single functional unit of multiple tissues, such as muscle, blood vessel and nerve bundles, and associ ated viscera or bone. Face, hand, and uterus are common examples. These procedures are increasing in frequency and complexity, but data regarding infection risk are still scarce and inferred from the known risk of SOT. Due to the highly complex anatomy of the allografts and their natural microbial colonization, bacterial infections are most common. Relevant infection prevention strategies are like those used in SOT, such as updated immunizations pretransplant, donor/recipient serologic screening, and targeted antimicrobial prophylaxis. Planning and in-depth communication between the organ procurement team, the surgical team, and an infectious disease consultant are important so that relevant cultures are obtained and results reported back. Surveil lance cultures for targeted microbiologic diagnosis will vary depending on the transplanted tissue. For example, for face transplants, in addi tion to cultures of respiratory pathogens, sinus cultures for bacteria and fungi are routinely obtained. Similarly, in penile or uterine transplants, sexually transmitted infections such Chlamydia or human papilloma virus need to be explicitly ruled out. Opportunistic infection risk is largely driven by the induction, maintenance, and intensification of immunosuppression due to the frequent rejection episodes. Systemic viral infections, in particular CMV and EBV, have been a significant problem after VCA; similar prevention strategies, as in other high-risk SOT recipients, are recom mended. Fungal

infections, such as cryptococcus or mucocutaneous candidiasis, may mimic rejection, which underscores the importance of establishing a histopathologic and/or microbiologic diagnosis and reassessing frequently. As the field of VCA continues to evolve, the risk of infectious complications needs to be continually assessed so that in the future we can better define its similarities and differences from other types of transplants. DONOR-DERIVED INFECTIONS Donor-derived infections (DDIs) can be expected or unexpected. Expected transmission to the recipient occurs with pathogens that are known to be present in the transplanted organ. Viruses such as CMV, EBV, hepatitis B virus, hepatitis C virus, and BK polyomavirus are examples. Preventive strategies such as targeted antimicrobial prophylaxis and access to highly specific molecular assays minimize the risk of end-organ disease and the overall impact on the recipient despite transmission. Global and regional health and transplantation societies provide detailed recommendations for adequate screen ing for certain blood and tissue donor-derived pathogens, such as HIV and viral hepatitis, and provide specific guidance for continued surveillance in recipients of donors with a history of IV drug use, unprotected sexual activity, multiple sexual partners, or incarceration within 30 days of potential donation. Recommendations often vary between organizations and countries. Transmission of unexpected infections occurs when pathogens not detected in an organ donor prior to organ recovery are transmitted to recipients. Screening donors for transmissible pathogens requires clinical and epidemiologic his tory as well as laboratory evaluation. Despite clinical and laboratory screening of potential donors for transmissible diseases, unexpected transmission of infection from donor to recipient remains an inherent risk of transplantation, predominantly of solid organ and composite tissue transplantation. Unexpected donor-derived diseases affect <1%

TABLE 148-2 Common Infections After Solid Organ Transplantation by Site of Infection and Transplant Type INFECTED SITE TYPE OF INFECTION RISK FACTOR MANAGEMENT Transplanted organ Bacterial and fungal infections of the graft, anastomotic site, and surgical wound Prior colonization of the donor with MDR organisms Surgical incision infection Bacterial, yeast infections are most common; NTM (rare, mostly thoracic transplants) Pain, erythema, discharge, or dehiscence of wounds, typically within the first 30 days posttransplant Intra-abdominal infections in liver transplant recipients Bacterial and yeast infections Secondary to biliary anastomoses leaks, or Roux-en-Y hepaticojejunostomy or other anastomoses that increase the risk of intestinal reflux into the biliary system; hepatic necrosis, from hepatic vascular thrombosis Intrahepatic infection in liver transplant Recurrent cholangitis (bacteria and yeast) Biliary strictures: anastomotic (acute) or nonanastomotic (chronic allograft rejection) Urinary tract infections in kidney transplant Recurrent cystitis and pyelonephritis (bacteria, in particular Enterobacteriaceae); Mycobacterium tuberculosis and yeasts are less frequent causes of UTI but should be suspected when there is pyuria and/or hematuria and negative cultures Duration of indwelling urinary tract catheters, female recipients, as well as recurrent UTI prior to the transplant Polyomavirusassociated nephropathy in kidney transplant BK, rarely JC virus Heightened immunosuppression, male recipient, older age, and a high BK viremia (>10,000 copies/mL) Pneumonia and tracheobronchitis in lung transplant Bacterial infections: severe or recalcitrant community-acquired viral pathogens (RSV, influenza, SARS-CoV-2); invasive mold infections; fungal tracheobronchial infection; NTM pulmonary disease Pretransplant colonization with resistant organisms, requiring endotracheal intubation prior to the transplant, and mucociliary dysfunction, are significant risk factors for bacterial infections; CLAD is a risk factor for and a result of recurrent viral, bacterial, fungal, and mycobacterial infections Mediastinitis in thoracic organ transplants Bacterial or Candida mediastinitis, with or without sternal osteomyelitis; less common Nocardia spp., NTM, or molds Diabetes mellitus, surgical

reoperation, and acute rejection Myocarditis, pericarditis, and cardiomyopathy in heart transplant Toxoplasma gondii infection Toxoplasma pretransplant serology D+/R– Trypanosoma cruzi Pretransplant recipient seropositivity (hearts from seropositive donors are not used) Infectious hyperammonemia syndrome in lung transplant (less commonly in other transplants) Ureaplasma spp. systemic infection (less commonly Mycoplasma spp.) that results in encephalopathy due to high ammonia levels >200 µmol/L Donor lung colonization Targeted antimicrobial treatment and direct ammonia removal through renal replacement therapy, lactulose, and reducing enteral protein intake. Prevalence in transplanted organs is roughly 10%, and screening should be considered. Abbreviations: CLAD, chronic lung allograft dysfunction; D+/R–, donor positive, recipient negative (serology); IR, interventional radiology; MDR, multidrug-resistant; NTM, nontuberculous mycobacteria; PCR, polymerase chain reaction; RSV, respiratory syncytial virus; TMP-SMX, trimethoprim-sulfamethoxazole; UTI, urinary tract infection. of all transplant recipients, and most are infections. (Besides infection, donors may also transmit unsuspected malignancies and other condi tions [e.g., hemochromatosis], but these are beyond the scope of this chapter and will not be discussed.) Unexpected DDIs occur predomi nantly in cadaveric donation, where screening of potentially transmis sible infection is hampered by the incomplete assessment of the donor’s

Institute targeted antimicrobial treatment as soon as prior colonization is known (peritransplant or immediately posttransplant). Source control (surgical or interventional radiology) and continued directed antimicrobials. Optimal duration after source control is unknown. Usual correlates of adequate treatment are clinical, laboratory, and radiologic resolution. Collection of microbiologic specimens for culture. Thorough washout and debridement. Imaging to evaluate for the presence of deeper infection. Antimicrobials should be adjusted based on microbiologic results, and duration guided by clinical response. Obtain blood cultures. Deep tissue or fluid cultures obtained intraoperatively or by IR. Source control. Antimicrobials adjusted based on microbiologic results (polymicrobial infections are the norm). Optimal duration of antimicrobials is unknown. Usual correlates of adequate treatment are clinical, laboratory, and radiologic resolution. Biliary drainage and antimicrobials. Prompt catheter and ureteral stent removal. Targeted antimicrobials. If recurrent UTI, evaluate for anatomic abnormalities (ureteral reflux, ureterovesical junction stenosis, neurogenic bladder, bladder diverticulum). CHAPTER 148 The only effective intervention is reduction in immunosuppression. An allograft kidney biopsy is necessary when there is suspicion of rejection or a different infection. Early antimicrobial therapy if possible. For viral respiratory pathogens, prevention with seasonal annual vaccination is recommended, with monoclonal antibodies when available. In patients with CLAD, respiratory rehabilitation and pulmonary toileting. Infections in Transplant Recipients Deep tissue cultures (intraoperatively). Duration of antimicrobials is unknown. Correlates of adequate treatment are clinical, laboratory, and radiologic resolution. Diagnosis is established by the identification of tachyzoites in the endomyocardial biopsy or PCR in tissue and/or pericardial fluid. Preemptive monitoring via blood PCR and TMP-SMX prophylaxis reduce incidence of disease. Clinical manifestations are fever, myocarditis, and painful skin lesions. Preemptive monitoring via blood PCR to detect early reactivation is indicated in all previously known seropositive recipients. Antitrypanosomal treatment (benznidazole or nifurtimox) for all patients with reactivation and tissueinvasive disease. risk. Almost all become apparent within 90 days of the transplant sur gery. Overall mortality is around 15%, but it is much higher (30–50%) in some fungal (e.g., aspergillosis, coccidioidomycosis) and parasitic infections (e.g., strongyloidiasis, toxoplasmosis). The risk of DDI needs to be balanced against the growing number

of patients on the trans plant waitlist and their associated risks of mortality. The early diagnosis

of a DDI requires a high index of suspicion. Clinicians should be on alert to the possibility of an unexpected transmission. DDI should be considered when opportunistic infections happen outside the expected at-risk period, in the case of infections with no clear epidemiologic risk factors in the recipient, with unusual clinical syndromes, and with persistent undiagnosed fever, especially during the first 90 days. Trans plant and infectious disease physicians should be alerted to clusters of infections in recipients from the same donor. When an unexpected DDI is suspected, besides prompt diagnosis and treatment in the recipient, immediate communication with public health authorities and the organ procurement organization is essential to decrease the risk of transmission/disease in other recipients.

Donors with a known or suspected active infection at the time of donation, such as pneumonia, urinary tract infection or bloodstream infection, may transmit the infection to the recipient. Living donors with an identified active infection should ideally be treated and transplantation delayed until infection resolves. In deceased donors, targeted antimicrobial prophylaxis for recipients is highly effective in preventing disease transmission when the infection is due to sus ceptible bacteria. Bacteremia in deceased donors is not uncommon, and studies have shown that, in adult recipients, donor bacteremia is not associated with adverse outcomes if a feasible treatment option exists. Bacterial meningitis carries a similar risk of transmission. Blood cultures should be obtained to rule out occult bacteremia in deceased donors, but bacteremia is generally not considered a contraindica tion to organ procurement and transplantation, unless no effective antimicrobial therapy is available. However, if the organ selected for transplantation is not infected or colonized and the donor is not bac teremic, the risk of transmission is low. These scenarios require careful analysis, and decisions should be individualized. The patient should be involved in deciding the acceptance of donors who may entail a higher risk for the recipient. PART 5 Infectious Diseases Meningoencephalitis in SOT recipients can be devastating. Viruses cause most cases, and effective antiviral treatments exist for only a few of these. Parasitic and fungal meningoencephalitis are also associated with significant morbidity and mortality. Development of meningoencepha litis or other neurologic syndrome in an SOT recipient, especially early after transplantation, should raise suspicion for DDI. Meningoencepha litis of unknown etiology in a donor is one of the few remaining absolute contraindications of transplantation. Even in patients in whom the etiol ogy is suspected, caution is advised, and a comprehensive evaluation for infectious causes, with special consideration for opportunistic infection when the donor is from an endemic area, should be undertaken. TB and endemic mycoses have been well-documented donortransmitted infections and are associated with significant risk of mortality or graft loss. Routine screening is recommended in areas of endemicity or in other recognized high-risk scenarios for TB, such as incarceration, displacement, or homelessness. Screening in deceased donors is frequently limited by the extent of the medical history and time constraints. IMPORTANT PATHOGENS IN

TRANSPLANT RECIPIENTS ■ ■CYTOMEGALOVIRUS CMV is the most important virus in both SOT and HCT recipients. CMV is usually acquired in early childhood and establishes latency for life in many different cell types, including endothelial cells and dendritic cells. Seropositivity for CMV (defined as positive anti-CMV IgG) varies by geographic region and ranges from 30 to 97%, increas ing with age. CMV infection is defined as detection of the virus in the blood (typically by PCR, which has replaced the old pp65 antigenemia test). CMV DNA may be quantified in whole blood or in plasma,

with results expressed in international units per microliter (IU/μL), and only results using the same test should be compared. CMV viremia is usually asymptomatic, but SOT recipients may develop a syndrome of fever, malaise, myalgias, moderate leukopenia with occasional atypical peripheral blood lymphocytes, and mild transaminitis concomitant with the detection of CMV in the peripheral blood. This is called CMV

syndrome. Tissue-invasive CMV disease is diagnosed by histopatho logic proof of invasion by the virus and tissue damage. Pneumonitis is the most feared end-organ disease after allo-HCT, and gastrointestinal disease is the most common, both after SOT and allo-HCT, but many other organs may be affected. Typically, CMV infection precedes development of disease by a few days, but sometimes CMV gastroin testinal disease occurs before the virus may be detected in the blood, or simultaneously. Clinically significant CMV infection is a term used in some clinical trials of CMV prophylaxis and includes invasive disease and/or a viremia level that triggers treatment with antivirals. Before widespread use of interventions aimed at reducing the incidence of CMV end-organ disease (i.e., pneumonitis, carditis, gastroenteritis, hepatitis), this occurred frequently during the first 1–6 months after transplantation and was associated with high morbidity and mortality. In addition, active CMV replication is associated with several “indirect effects,” including increased rates of bacterial and fungal infection, increased graft dysfunction, transplant vascular disease, acute rejec tion, and, after HCT, increased GVHD and increased nonrelapse transplant-related mortality. Avoiding CMV disease is an important part of transplant medicine. The process starts with donor selection, as the serostatuses of both donor and recipient are the main determinants of the risk of disease. In SOT, the highest risk is seen with a seropositive donor going into a seronegative recipient (D+/R–). In this setting, up to 50% of recipients may become viremic after prophylaxis is stopped, with lung, small bowel, pancreas, and combined kidney-pancreas having higher risks. After HCT, the highest risk is for seropositive recipients (who harbor the virus in many of their tissues) receiving stem cells from seronega tive donors (D–/R+), 60–70% of whom may develop CMV viremia. When several donors are available, avoiding high-risk CMV serostatus combinations is part of the selection process. Once the transplant takes place, prevention of CMV disease can be achieved by two different strategies: universal prophylaxis or preemptive management. There are two strategies to prevent CMV disease after transplant: universal prophylaxis, in which every recipient at high risk is given antivirals (usually valganciclovir after SOT or letermovir after allo-HCT) for an arbitrary period (usually 3–6 months after SOT and 100 days after allo-HCT), or preemptive management, in which CMV is monitored in the blood weekly and anti-CMV treatment initiated when a particu lar level of viremia is detected. Of note, valganciclovir (a prodrug of ganciclovir) is active against HSV and VZV, but letermovir is not, so if letermovir is used, acyclovir or valaciclovir must be added for HSV/ VZV prophylaxis. The tolerable level of viremia differs based on type of transplant, timing of the infection, and other factors that increase the risk of CMV disease. In UCB transplant or T-cell-depleted transplants, lower levels of viremia may trigger treatment, as the kinetics of viral replication and risk of progression to end-organ disease may be sig nificantly higher in these patients. Randomized trials comparing both strategies have been performed only after allo-HCT for kidney and liver transplant but are not available for SOT involving other organs. Prophylaxis and preemptive treatment seem similarly effective in terms of overall mortality, and transplant centers may choose one over the other based on considerations such as logistics (more complicated with preemptive therapy) and cost (potentially higher with letermo vir). Treatment of significant viremia is with ganciclovir or foscarnet. Cidofovir and maribavir are inferior, and the former is potentially more toxic. Ganciclovir and foscarnet are

considered equally effective but differ in toxicity: ganciclovir has significant myelotoxicity, and foscar net causes electrolyte abnormalities that usually cannot be managed in the outpatient setting, as well as nephrotoxicity. If viremia increases after 2 weeks of optimal antiviral treatment or if it does not decrease, the infection is considered “refractory” or “possibly refractory” CMV, respectively, and testing for genetic resistance to antivirals is recom mended. The antiviral maribavir is FDA approved for resistant/refractory CMV, but its efficacy is only moderate, with <20% of patients with resistant/refractory CMV maintaining control of the virus at 16 weeks. Invasive disease due to CMV varies with the type of transplant. After allo-HCT, CMV pneumonia is the most severe, but it is now uncommon with the use of prophylaxis or preemptive management.

Involvement of the gastrointestinal tract (most commonly CMV coli tis, but any segment of the bowel may be affected) is more frequent, in part because the time between asymptomatic viremia and CMV colitis is shorter. After SOT, CMV reactivation may start in the transplanted organ in CMV-seropositive donors (e.g., CMV pneumonia in lung transplant, enteritis in small-bowel transplant). Hepatitis, retinitis, and, rarely, central nervous system (CNS) involvement (myelopathy, encephalopathy) may also occur. Frequency of CMV monitoring after prophylaxis or treatment is completed is not well established. If available, immune monitoring, via commercially available CMV-specific interferon γ (IFN-γ) release assays that detect CMV-specific T cells in whole blood, may allow for more precise targeting of monitoring and prophylactic strategies. ■ ■EPSTEIN-BARR VIRUS Most adults are infected with EBV, which remains latent in B cells. When an EBV-seropositive donor provides an allograft to an EBVseronegative recipient (D+/R–), EBV infection (detection of EBV in blood or plasma) is very common. This primary EBV infection may be asymptomatic, present with end-organ disease such as hepatitis or enteritis, or cause a mononucleosis-like febrile illness with or without lymphadenopathy, atypical lymphocytes, and culture-negative exuda tive pharyngitis. EBV-associated PTLD is a heterogeneous group of clinical syndromes associated with uncontrolled lymphoproliferation (typically of B cells, but cases of natural killer– and T-cell EBV-positive PTLD occur), which ranges from polyclonal proliferation to true lymphoma containing clonal chromosomal abnormalities. The diag nosis requires tissue examination, which may show a polymorphic or monomorphic proliferation of B cells or even frank lymphoma. Risk of PTLD after SOT is greater in EBV-seronegative transplant recipients, who acquire a primary infection through the allograft. Consequently, this scenario is most common in pediatric transplant recipients. Viral burden within the lymphoid tissue of the transplanted organ appears to be a risk factor for PTLD, with intestinal transplant recipients at the highest risk and kidney lowest. EBV-positive PTLD is most frequent in the first year after SOT, but late PTLD incidence increases after 7–10 years and is related to duration of immunosuppression. Late PTLD can present as primary CNS lymphoma and gastrointestinal tract disease. EBV viral load monitoring and radiologic evaluation can assist in early diagnosis. Positron emission tomography/computed tomography (CT) imaging is useful in establishing lymph node or end-organ disease involvement, thus allowing for targeted tissue sampling to establish the diagnosis. In SOT, reduction of immunosuppression is the preferred initial treatment strategy. Rituximab is recommended next if the PTLD cells express CD20. Cytotoxic chemotherapy may be required. For refractory cases, adoptive immunotherapy with EBV-specific T cells, including chimeric antigen receptor T cells and third-party trained T cells, such as tabelecleucel, have been used. All donors and recipients should undergo EBV serologic testing before transplant. Preemptive monitor ing of EBV viral load in high-risk (EBV D+/R–) SOT recipients is sug gested, and reduction of immunosuppression is recommended in EBV viremic patients. Withdrawal of immunosuppression may trigger graft rejection. Specific viral load cutoffs that should

trigger an intervention have not been established; there is considerable interlaboratory vari ability even with commercial EBV PCR assays. Serial monitoring with the same assay (e.g., whole blood or plasma) and the same laboratory is necessary to establish a trend. Rapidly rising EBV viral load is a sig nificant risk factor for PTLD. EBV-positive PTLD is an early complication of allo-HCT, occurring in the first 2–4 months. In this case, the virus is usually present in the recipient, and the risk is highest in EBV D–/R+ pair and cord blood stem cell source, although any D/R mismatch (D+/R− or D−/R+) in the setting of T-cell-depleted grafts is recognized as a significant risk. EBV D/R matching is recommended whenever possible. The overall frequency is ~3%, varying between 1% in matched sibling donor trans plant to up to 10% in unrelated UCB transplants. The risk depends on the degree of T-cell depletion because it is the T-cell function after transplant (derived from the donor) that will control EBV. The man agement is like that described above, with the caveats that decreasing

immunosuppression after allo-HCT may be difficult or impossible if GVHD is present and that, if the stem cell donor is available and is EBV positive, administration of lymphocytes from the donor (donor lymphocyte infusion) may be a successful strategy, as a significant fraction of the T-cell repertoire is directed against EBV. Donor-derived adoptive immunotherapy with EBV-specific T cells or off-the-shelf commercially available EBV-specific T cells, such as tabelecleucel, are increasingly used as second-line therapy.

■ ■POLYOMAVIRUSES Polyomaviruses have been identified as frequent causes of allograft dysfunction in kidney transplant recipients. BK virus (BKV) and JC virus (JCV) are the most common pathogenic poliomaviruses that infect humans. BKV (most commonly) and JCV have been associated with tubulointerstitial nephritis and nephropathy, usually referred to as polyomavirus-associated nephropathy (PVAN). Ureteric stenosis and hemorrhagic cystitis can also occur. BKV infection is most common in kidney transplant recipients. Viruria is common, but some patients develop viremia, which in the absence of an intervention results in PVAN and allograft loss. The presumptive diagnosis of BKV nephropa thy can be established with renal dysfunction and viremia, but acute rejection and PVAN can coexist and can be clinically indistinguishable. Definitive histopathologic diagnosis requires identification of viral cytopathic changes and immunohistochemistry for SV40 antigen or BKV-specific antigen detection in the tissue. Reduction of immuno suppression is the mainstay of treatment. Preemptive monitoring of BKV viral load can aid in the early detection of BK viremia; increasing viral loads are predictive of PVAN, and careful reduction of immuno suppression can prevent renal dysfunction and graft loss. CHAPTER 148 BKV after allo-HCT was discussed earlier, in the section on early infections after HCT, above. After PVAN, PML caused by JCV CNS infection is the most com mon disease caused by polyomaviruses in SOT, although it is signifi cantly less common than in other immunocompromised patients, such as those with advanced HIV. Diagnosis is established by a compatible neurologic syndrome, molecular detection of JC virus in the CSF, and radiologic evidence of demyelinating disease. As with other polyoma virus infections, no effective antiviral therapy exists, and reduction of immunosuppression is commonly employed, with overall poor response rates. Directed T-cell therapies are under development, and immune checkpoint inhibition (e.g., pembrolizumab) has been used successfully in some cases. Infections in Transplant Recipients ■ ■FUNGAL INFECTIONS Invasive fungal infections are a common infectious complication in transplant recipients. Newer antifungals and corticosteroid-sparing immunosuppressive regimens have decreased the overall incidence of invasive fungal infections and improved outcomes. Invasive candidiasis is the most common

invasive fungal infection in SOT recipients. Other fungal infections such as invasive aspergillosis, cryptococcosis, and endemic mycoses are also prevalent. In HCT, almost universal antifun gal prophylaxis with activity against Candida has made mold infections relatively more frequent. Candidiasis Invasive candidiasis is most often an early compli cation after SOT. Length of hospitalization, frequent use of broadspectrum antimicrobials, intravascular catheters, renal replacement therapy, and critical illness are all risk factors for increased incidence of invasive candidiasis. Additionally, the complex nature of abdominal organ transplant surgical procedures increases the risk of invasive can didiasis. In liver transplant recipients, choledochojejunostomy, largevolume transfusion of cellular blood products (including platelets and packed red blood cells), reoperation, and retransplantation are all risk factors for invasive candidiasis. Pancreas transplantation with enteric drainage and small-bowel transplantation are particularly prone to be complicated by candidemia or invasive candidiasis. Targeted antifungal prophylaxis in liver, pancreas, and small-bowel transplant recipients is routine and decreases the incidence of invasive candidiasis. All forms of invasive candidiasis in transplant recipients merit antifungal treatment, and echinocandins are the initial treatment of

choice, except in CNS disease or urinary tract infection. In addition to antifungal treatment, source control, such as catheter removal, and mechanical drainage of abdominal or surgical collections are the mainstay of successful treatment. Lung transplant recipients are at risk of invasive disease at the site of tracheal anastomosis, which can lead to anastomotic leak. Mycotic aneurisms of the main vessel of the allograft are associated with a high risk of rupture and usually represent a DDI or result from contamination of the preservation fluid. Early diagnosis and aggressive medical and surgical treatment are indispensable for overall survival.

Aspergillus and Other Molds Invasive pulmonary aspergillosis is the most common invasive mold infection in transplant recipients and the overall most common invasive fungal infection in lung trans plant recipients. Airway and allograft colonization with Aspergillus spp. is a common but also invasive disease. Lung transplant recipients experience the full spectrum of Aspergillus spp. pathology, including tracheobronchitis, bronchial anastomotic infections, invasive pulmo nary aspergillosis, and disseminated disease. Tracheobronchitis and bronchial anastomotic infections are characterized by ulceration and cartilage invasion. Dissemination, including to the brain, can occur and should be ruled out in all transplant recipients. Risk factors are single-lung transplant, lung transplant for cystic fibrosis, airway isch emia, rejection with increased immunosuppression, and chronic lung allograft dysfunction (CLAD). Risk factors for invasive aspergillosis (IA) in other SOTs include CMV infection and disease and degree of immunosuppression, such as high-dose corticosteroids for rejection. Retransplantation and posttransplant liver or renal hepatic failure, as well as prolonged neutropenia, increase the overall risk of IA. Targeted antimold prophylaxis in those at high risk of IA is recom mended. Monitoring serum galactomannan (GMN) does not perform well in SOT recipients. Targeted diagnostic bronchoalveolar lavage (BAL) GMN and serum GMN are preferred when there is suspicion of invasive disease. CT imaging can assist in the early diagnosis of IA. The CT findings are variable (Fig. 148-1). Whereas dense, wellcircumscribed pulmonary nodules, sometimes with halo sign, are char acteristic in patients with hematologic malignancies, SOT recipients more frequently present with nonspecific pulmonary findings such as alveolar and centrilobular infiltrates, and the halo sign is almost never seen. Despite early diagnosis and treatment, the mortality associated with IA is still high. Other mold infections in SOT are less frequent but significantly more common than in nontransplant populations. PART 5

Infectious Diseases Aspergillosis after HCT is a complication of prolonged neutropenia or the use of high-dose corticosteroids for the treatment of GVHD. Prophylaxis with posaconazole is frequently used in patients receiving

> 0.5 mg/kg of prednisone every day or being treated for GVHD with two or more immunosuppressants. Some of the newer treatments for GVHD, such as ibrutinib and ruxolitinib, seem to significantly increase the risk of IA. Presentation is nonspecific with dyspnea, cough, and chest pain. Fever may be absent. Lack of systemic toxicity is frequent A B C FIGURE 148-1 Radiologic findings are often nonspecific in transplant recipients. A. Nocardia 3 months after kidney transplant in a patient who was not receiving trimethoprim-sulfamethoxazole. A fine-needle aspirate showed only necrosis, but the bronchoalveolar lavage (BAL) grew Nocardia cyriacigeorgica. B. Tuberculosis 3 months after heart transplant in a patient with known latent tuberculosis infection who was receiving isoniazid prophylaxis. The isolate of Mycobacterium tuberculosis was resistant to isoniazid. C. Aspergillosis in a neutropenic patient receiving allogeneic hematopoietic stem cell transplant for acute myelogenous leukemia. The BAL was positive for galactomannan, but the culture was negative. The mold was later identified as a non-fumigatus Aspergillus by next-generation sequencing of a surgical specimen.

in mold infections. Establishing an accurate diagnosis is essential, since most mold infections can have similar presentations, and antifungal susceptibility varies significantly between molds. Cryptococcosis With prolonged immunosuppression, SOTs are at risk of cryptococcal infection and disease. These tend to occur later after SOT, with most cases occurring between 1 and 3 years after the transplant. Earlier presentation should alert to the possibility of donorderived cryptococcosis. Advanced liver disease is a risk factor for cryptococcosis, and liver transplant recipients may present earlier after transplant, especially if mental status changes peri-transplant were attributed to hepatic encephalopathy but no microbiologic workup was completed. Other presentations include skin papules or cellulitis, pneumonia, and asymptomatic or minimally symptomatic lung nod ules. Both Cryptococcus neoformans and Cryptococcus gattii are known pathogens in SOT recipients. Serum cryptococcal antigen assay allows early noninvasive diagnosis but requires a high index of suspicion. In patients with CNS disease, both serum and CSF cryptococcal antigen are extremely useful in the early diagnosis of cryptococcal disease. In the evaluation of patients with mental status changes with or without fever or with cryptococcal disease outside of the CNS, patients should undergo a lumbar puncture with CSF opening pressure, as well as cell count and culture. These are useful for the diagnosis of CSF involve ment, but also to evaluate the appropriate treatment response. Moni toring of cryptococcal antigen to determine the duration of therapy is not recommended because it may persist despite microbiologic and clinical resolution. Immune reconstitution inflammatory syndrome has been described in SOT recipients when immunosuppression is tapered aggressively in cryptococcal meningitis and may result in worsening of the initial symptoms despite microbiologic cure. Cryptococcosis is less common after allo-HCT, probably due to the prevalence of antifungal prophylaxis. Endemic Mycoses SOT recipients are second only to people with advanced HIV in terms of risk of disseminated endemic

mycoses. Given its worldwide endemicity, histoplasmosis is the most common, but disseminated coccidioidomycosis, in particular CNS disease, is associated with higher mortality, and patients who survive usually require lifelong antifungal therapy. Invasive forms of all endemic myco ses have been described in transplant recipients. Pneumocystis jirovecii PJP is an important complication of SOT and allo-HCT, and prophylaxis early after transplant is used routinely. Breakthroughs are uncommon if patients are receiving TMP-SMX but may be seen with second-line prophylaxis such as inhaled pentamidine or atovaquone. Lung transplant recipients retain a lifelong risk of infec tion. Acute or subacute shortness of breath, with significant hypox emia, is the most common presentation. Radiologic changes may be subtle and out of proportion to the hypoxemia, with a broad alveolararterial gradient. Many radiologic presentations have been described, but the most common are ground-glass opacities. Nodules and atypical

consolidations have also been described, especially in patients who receive less effective prophylactic agents, such as inhaled pentamidine or atovaquone. Most patients with PJP have elevated β-d-glucan in serum. The definitive diagnosis is established by identification of Pneu mocystis trophozoites in a respiratory sample from an induced sputum, a BAL, or a lung biopsy, but microscopy has low sensitivity, and increas ingly, PCR in the BAL has become the diagnostic modality of choice. A positive PCR requires clinical interpretation because some patients may be merely colonized. During treatment, an immune reconstitution inflammatory syndrome (IRIS)-like condition can occur, so tapering of immunosuppression is usually not advised in transplant recipients newly diagnosed with PJP. The use of adjuvant corticosteroids in nonHIV patients with severe PJP remains controversial. ■ ■MYCOBACTERIAL INFECTIONS Mycobacterium tuberculosis TB remains a major challenge and public health threat in transplant recipients. Incidence of active TB among SOT recipients is estimated to be 20–75 times higher than in the general population. Incidence varies significantly among different geographic regions and ethnic groups. Most cases occur between 6 and 12 months after the transplant and are associated with very high mortality; many more cases result in graft loss. Donor-derived TB has been also well documented after SOT, and these cases can present earlier after transplant. In contrast, TB after HCT is relatively uncom mon and presents early within the first year after allo-HCT. In areas of medium or high endemicity, cases of active TB develop most com monly from reactivation of old foci of infection, but primary infection after transplant can also occur. Disseminated disease is common, and fever is the most common presenting symptom (>90%). In those with only pulmonary involvement, fever is present in ~60%. Involvement of every organ and atypical presentations have been reported (Fig. 148-1). Good-quality data regarding the optimal combinations of drugs and length of therapy are lacking in organ transplant recipients. Decisions are based on case series, recommendations for the general population and other immunocompromised individuals such as people living with HIV, and expert opinion. Most cases require 6–9 months of treatment, but in disseminated disease with CNS involvement, extrapulmonary TB, cavitary TB, or culture positivity after 2 months of treatment, 12–18 months of treatment are recommended. Daily therapy is recom mended over intermittent dosing, given signals of higher relapse rates with intermittent dosing and concerns of less reliable immunosup pressive drug levels due to drug–drug interactions that may ultimately result in higher rejection rates or graft loss. Rifamycin-containing regimens are preferred for all types of TB due to the potent sterilizing activity of such regimens. Rifampin, the most used rifamycin, is a potent inducer of the cytochrome P450 enzyme, which increases the metabolism of many drugs, including calcineurin inhibitors (cyclo sporine and tacrolimus), mTOR inhibitors (sirolimus and everolimus), and corticosteroids; its use has been frequently associated with acute rejection. Rifampin-based

treatment is extremely problematic. Even though there is less experience with the use of rifabutin and it is not available worldwide, rifabutin is a weaker inducer of cytochrome p450, and drug interactions are significantly easier to manage than with rifampin. Other rifamycin-sparing treatment protocols can be used in organ transplant recipients to avoid drug–drug interactions; however, when a rifamycin is not used, shorter courses (6–9 months) should not be used. Use of a rifamycin is also highly desirable in patients with severe, disseminated, or cavitary disease. The initial treatment regimen should follow local recommendations based on local resistance pat terns and tailored to available susceptibility data. Newer antitubercu lous antimicrobials have not been studied in transplant recipients but are promising. Reduction of immunosuppressive therapies, which help control the infection, should be done slowly if at all, as IRIS is a wellknown complication of mycobacterial disease. If symptoms worsen with lowering immunosuppression, IRIS should be considered. Prevention of TB after transplantation relies on adequately iden tifying those at risk of reactivation or recipients of an organ from a donor who has latent TB infection (LTBI) and treating LTBI. Screening

relies on known epidemiologic exposures and probing the individual's immune response to TB antigens. There are two methods available for screening for prior TB exposure (for additional information, see Chap. 183), the tuberculin skin test (TST) and the IFN-γ release assays (IGRAs); both assays are less sensitive in immunocompromised hosts. In transplant candidates or recipients, a TST >5 mm is consistent with LTBI. Patients with prior positive bacillus Calmette-Guérin vaccina tion can have a positive TST from prior vaccination. In these patients, IGRA is preferable. End-stage renal disease, end-stage liver disease, and receipt of prior chemotherapies are all well-known risk factors that can lead to a false-negative TST or indeterminate results in the IGRAs. In patients with indeterminate results, the decision to treat LTBI should be made clinically, according to epidemiologic risk factors based on history. In patients with a negative TST, a second TST should be performed at about 2 weeks to look for a booster effect. An IGRA test can be performed after an initial negative TST in those at risk. In patients with evidence of LTBI by TST or IGRA, active TB should be ruled out before proceeding to transplant. Live donors should undergo a similar screening as recipients. TST and IGRAs may not be avail able on deceased donors; therefore, risk should be assessed based on a detailed history from the donor's family regarding previous active or latent TB and any treatment received and chest imaging.

All transplant recipients with LTBI should receive treatment. Con sideration should be given to time to transplantation, drug–drug inter actions with ongoing treatments, and potential toxicities. In patients in whom the transplant is unlikely to occur until at least 4–6 months, shorter courses are suggested (e.g., rifampin for 4 months or isoniazid plus rifapentine for 12 weeks). If the transplant is likely to occur sooner, isoniazid for 9 months is recommended. When possible, LTBI should be treated prior to transplantation; however, the transplant should not be delayed to complete treatment. For liver transplant candidates or HCT candidates receiving chemotherapy, treating prior to transplanta tion is challenging due to potential hepatoxicity or significant drug– drug interactions. In these patients, it may be safer to begin therapy after transplantation once liver function has normalized or the con ditioning regimen has been completed. SOT recipients who received an organ from an untreated donor with known LTBI should also be treated. If a living donor has LTBI, treatment of the donor should pri oritize their risk of progression to active TB following national guide lines for the treatment of LTBI. CHAPTER 148 Infections in Transplant Recipients Nontuberculous Mycobacteria Nontuberculous mycobacteria (NTM) are ubiquitous in the

environment, and some species are important opportunistic human pathogens. Transplant recipients are at increased risk of NTM infection. The lungs are the most common site of infection and the most frequently colonized organ. Disease due to NTM can be separated into pulmonary, disseminated, catheter- and cardiac implantable electronic device–associated infection, surgical site deep-seated infection, and skin and soft tissue (SST) infections. Lung followed by heart transplant recipients are at highest risk of post transplant NTM disease. Because structural lung disease increases the risk of colonization, allo-HCT recipients with cGVHD of the lungs are also at risk. Lung transplant candidates with cystic fibrosis or chronic obstructive pulmonary disease are at increased risk of being colonized or infected by NTMs, and pretransplant isolation of NTM is associated with increased risk of NTM disease after transplant. NTM disease is associated with increased mortality and CLAD. Most common infections are due to Mycobacterium abscessus and M. avium complex. Diagnosis of NTM disease from nonsterile sites, especially the respiratory tract, can be a challenge. Validation of criteria suggested for the routine diagnosis of pulmonary NTM in immunocompetent individuals is lacking in transplant recipients; however, these provide a useful framework for the diagnosis of pulmonary NTM in transplant recipients. In lung transplant recipients, the threshold for treatment of infection should be lower, given the high rate of infection, secondary dissemination, or development of CLAD. Treatment of NTM is com plex and often compromised due to drug–drug interaction and drug toxicities. Species-level identification is necessary to design a treat ment regimen. For detailed treatment strategies, the reader is referred

to Chap. 185 and American Thoracic Society/British Thoracic Society guidelines. The length of treatment should be guided by the specific clinical scenario; localized SST infections require shorter treatment durations, whereas pulmonary or disseminated NTMs require at least 1 year (frequently longer).

All patients with NTM infection pretransplant should start treat ment before transplantation. Routine screening for NTM infection in lung transplant candidates is recommended, and those found to be colonized or infected should be treated, ideally for at least 3 months prior to proceeding to transplant. Rapidly growing NTMs, especially M. abscessus, have been associated with a high risk of deep surgical site infection and with frequent bone involvement. Treatment regimens should be based on species identification and susceptibility testing when appropriate, as well as stabilization of disease before transplant and ability to tolerate the designed regimen. Therapeutic drug moni toring can help to reduce toxicity. Bilateral lung transplant is preferred in those already colonized or infected with NTMs prior to transplant. Despite these measures, the risk of posttransplant infection is high, and the patient should be counseled about this risk. Some PIDs that result in susceptibility to mycobacterial infection present with disseminated NTM or TB. Without successful replace ment of the deficient immune system via allo-HCT, these infections are difficult to treat. Management of these infections is challenging; aggressive antimicrobial treatment is required before, during, and early after transplant. Ideally, infection and associated inflammatory response should be partially controlled prior to transplantation, which usually requires at least 3 months of treatment before the starting con ditioning. Drug–drug interactions and drug toxicities in the peri- and posttransplant period are a challenge. In the first few months after engraftment, IRIS-like phenomena are common in patients being treated for active mycobacterial infection at the time of transplantation. PART 5 Infectious Diseases Definitive diagnosis of IRIS is a challenge, as there are no clear diagnostic criteria for this disease. Classically, there is worsening of symptoms or imaging at the site of prior infection that coincides with tapering of immune suppression. Adequate

management requires ongoing treatment of the underlying infection, and augmented immu nosuppression or anti-inflammatory therapy. Once symptoms are TABLE 148-3 Prophylactic Regimens Commonly Used to Decrease Risk of Infection in Transplant Recipients RISK FACTOR ORGANISM PROPHYLACTIC DRUG EXAMINATION(S)a Neutropenia, mucositis Candida Fluconazole Candida is part of the normal GI flora; everyone with disruption of the mucosal integrity is at risk Prolonged neutropenia, high-dose corticosteroids, enhanced immunosuppression Aspergillus and other molds Posaconazole Blood tests (GMN, β-d-glucan) are less sensitive if triazoles are being administered and are always negative in mucormycosis Travel to or residence in an area with known risk of endemic fungal infection Histoplasma, Blastomyces, Coccidioides, Talaromyces marneffei Triazoles considered in context of clinical and laboratory assessment Chronic hepatitis B HBV Entecavir HBV serology, HBV DNA Chronic hepatitis C HCV Prophylaxis not used; treat to achieve persistent virological response Latent herpesviruses HSV, VZV, significantly lower efficacy for CMV, EBV Acyclovir or valacyclovir Serologic tests for HSV, VZV, CMV, HHV-6, EBV, KSHV (HHV-8); PCR CMV Letermovir (more experience in HCT) or valganciclovir (active against HSV and VZV) Exposure (unknown reservoir) or colonization Pneumocystis jirovecii Trimethoprim-sulfamethoxazole (TMP-SMX) Second line: dapsone, pentamidine, atovaquone Parasites Toxoplasma gondii Strongyloides stercoralis TMP-SMX or atovaquone for toxoplasma Ivermectin for Strongyloides LTBI Mycobacterium tuberculosis Isoniazid or rifampin in patients with recent seroconversion, positive chest imaging, or recent known exposure and no previous treatment, once active TB is ruled out aSerologic examination, TST, and IGRAs may be less reliable after transplantation. Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; GI, gastrointestinal; GMN, galactomannan; HBV, hepatitis B virus; HCT, hematopoietic stem cell transplantation; HCV, hepatitis C virus; HHV, human herpesvirus; HSV, herpes simplex virus; IGRA, interferon γ release assay; KSHV, Kaposi’s sarcoma–associated herpesvirus; LTBI, latent TB infection; PCR, polymerase chain reaction; TB, tuberculosis; TST, tuberculin skin test; VZV, varicella-zoster virus.

controlled, tapering of immunosuppression should be done slowly, taking into consideration other potential toxicities of ongoing immu nosuppression and predisposition to other opportunistic infections. ■ ■NOCARDIOSIS Nocardia is an aerobic gram-positive bacillus found in the soil that infects predominantly immunocompromised people. It is more fre quently acquired by inhalation, although skin inoculation also occurs (typical with Nocardia braziliensis). The presentation varies from acute with fever, cough, and dyspnea, to subacute or chronic with night sweats and weight loss. Radiologic findings are commonly dense nod ules, sometimes with cavitation, but a variety of pulmonary infiltrates may be seen (Fig. 148-1). Dissemination to the CNS occurs in 25% of cases and is frequently asymptomatic. Brain MRI is recommended in all patients with Nocardia to rule out brain abscess. Antibiotic sus ceptibility can be predicted based on species identification, but this may take time. All Nocardia species are susceptible to linezolid, so this antibiotic may be administered empirically until identification and susceptibilities are obtained. Most isolates are also susceptible to TMP-SMX, amikacin, and imipenem or meropenem. Combination of two or more antibiotics and long duration of treatment (usually 6–12 months) is recommended by many experts, but comparative tri als are not available. PREVENTION OF INFECTIONS IN TRANSPLANT RECIPIENTS There are three different and complementary approaches to prevent infections after transplant: minimizing exposures (lifestyle modifica tions), immunizations, and chemoprophylaxis. Hand hygiene and avoiding sick contacts are some of the most impactful ways to avoid infection. Other suggested lifestyle modifications include recommen dations for food and water safety, specifically making sure the drinking water is safe, avoiding raw or poorly cooked eggs and meat, and peeling or carefully washing fruits and vegetables. Hobbies and pets are impor tant

components of healthy rehabilitation after transplant, but some specific recommendations can make these safer and reduce the risks of infection. Examples of these are to avoid landscaping, gardening, and Chest imaging, antigen testing, serology HCV serology, HCV RNA Serologic test for Toxoplasma and Strongyloides TST and/or IGRA; if indeterminate, clinical assessment of exposure and risk

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