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308 Infections in Solid-Organ Transplant Recipients

Nina Singh, Ghady Haidar, and Ajit P. Limaye

Advances in surgical techniques and immunosuppressive regimens have had a pivotal role in optimizing outcomes after transplantation. The introduction of cyclosporine in the 1980s and tacrolimus a decade later heralded the era of modern immunosuppression, and transplantation advanced from being a quasiexperimental procedure to an established and accepted modality of treatment for a wide range of end-organ diseases. Table 308.1 depicts the most recent data on graft and patient survival reported by the United Network for Organ Sharing (UNOS).[1] The best results are for living-related kidney transplantation; ≈99% of the recipients are alive, and 96% have functioning allograft 1 year after transplantation. The most significant progress may have been in liver transplantation, in which the 1-year survival rate before the use of cyclosporine was only 32% compared with 89% at present. Outcomes after lung transplantation continue to be limited by the development of chronic lung allograft dysfunction with 1-, 5-, and 10-year survival rates of 80%, 50%, and 20%, respectively in the current era.[1] Fewer than 150 intestinal transplantations are performed annually in the United States; however, 1-year patient survival rates at high-volume experienced centers approach 90%.

Improvements in graft and patient survival have been paralleled by decline in the number of deaths associated with infections (Fig. 308.1). Current data from the Organ Procurement and Transplant Network show that infection-related mortality within the past decade has continued to decline in all types of organ transplantations (see Fig. 308.1). Nevertheless, infections still account for ≈24% of the first-year deaths in kidney and heart transplant recipients and up to 34% in lung transplant recipients (Table 308.2). In liver transplant recipients approximately 32% of the mortality within the first posttransplantation year was infection associated.[2] Infections contribute to 10% to 13% of the deaths after 10 years in kidney, liver, and heart recipients and 25% in lung recipients (Table 308.3).

The clinical manifestations of infection are variable and depend on the infecting pathogen, prior immune status of the host, the type of transplantation, time elapsed since transplantation, and the intensity of pharmacologic immunosuppression (Table 308.4). With this complexity in mind, it is useful to address some general principles that may facilitate the approach to diagnosis, management, and understanding of infections after transplantation.

FUNDAMENTALS OF IMMUNOSUPPRESSIVE THERAPY

Among factors contributing to the occurrence of infections in transplant recipients, an obvious and probably the most consequential is iatrogenic immunosuppression. The effects of immunosuppressive agents have become more apparent as surgical techniques have improved, and antimicrobial prophylaxis has come to be used more widely. The goal is to optimize immunosuppressive regimen such that it prevents rejection but preserves antimicrobial immunity and minimizes long-term metabolic complications and the risk of malignancy.

Corticosteroids

Although inadequate as sole agents to sustain graft survival, corticosteroids remain a key component of most immunosuppressive regimens. Corticosteroids broadly inhibit immune responses, including innate inflammatory responses, phagocytic function, cellular immunity, and, to a lesser extent, antibody formation. In an effort to obviate undesirable side effects of corticosteroid therapy, more transplantation centers practice early withdrawal and use steroid-free regimens. Meta-analyses of trials of corticosteroid-free regimens in kidney and liver transplant recipients have not shown beneficial effect of corticosteroid reduction on overall infectious risk, but analysis of specific infectious outcomes in liver transplantation suggested that corticosteroid avoidance might reduce the risk for cytomegalovirus (CMV) infection and hepatitis C virus (HCV) recurrence.[2,3]

Antimetabolite Agents

The introduction of cytotoxic drugs, such as azathioprine, was a major advance in immunosuppression that made transplantation across human leukocyte antigen (HLA) barriers feasible. All cytotoxic drugs interfere with DNA synthesis, thereby suppressing the bone marrow and reducing peripheral blood cell counts. In addition to marrow suppression, azathioprine may cause pancreatitis, a reversible hepatitis, rash, and gastrointestinal (GI) disturbances. As such, use of azathioprine has decreased in the current era.

Mycophenolate mofetil, approved in 1995, is a cytotoxic drug with an antiproliferative effect on T and B lymphocytes and has replaced azathioprine in triple-drug regimens, comprising a calcineurin inhibitor agent and corticosteroids. Its use has been associated with lower rates of biopsy-proven rejection compared with azathioprine, with similar risk of infections. The main side effects of mycophenolate mofetil are myelosuppression and diarrhea.

Calcineurin Inhibitor Agents

The calcineurin inhibitor agent cyclosporine is a cyclic peptide derived from *Tolypocladium inflatum* and was approved for clinical use in 1983. It inhibits the production of cytokines, primarily interleukin-2 (IL-2), and consequently the generation of effector T cells or $CD4^+$ T cells (Fig. 308.2). Concentrations of the drug as low as 100 ng/mL effectively inhibit mixed lymphocyte reactions. Patients treated with cyclosporine alone for various autoimmune diseases show low rates of clinical infection, which demonstrates the importance of corticosteroids and other cofactors for infection in transplant recipients. Tacrolimus, approved in 1994, is a macrolide produced by *Streptomyces tsukubaensis*. Despite some differences, its mode of action is similar to that of cyclosporine in that it inhibits production of IL-2 and $CD4^+$ T cells. However, it is 10 to 100 times more potent than cyclosporine. Although a major component of the immunosuppressive effects of cyclosporine and tacrolimus is accounted for by the antagonism of calcineurin activity, tacrolimus also inhibits steps distal to calcineurin activation in the T-cell activation cascade.[4] As such, tacrolimus has the ability to reverse steroid-resistant allograft rejection, whereas cyclosporine is ineffective for the treatment of rejection. Clinical trials have demonstrated that tacrolimus-based immunosuppression results in lower rates of acute rejection and graft loss than cyclosporine-based therapy, particularly in kidney and liver transplant recipients, with no convincing evidence that it enhances the risk for infection.

Major adverse effects of calcineurin inhibitor agents are nephrotoxicity, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, neurotoxicity, hypertension, and diabetic mellitus. In comparison with cyclosporine, tacrolimus is associated with less hypertension but higher rates of diabetes mellitus and neurotoxicity.

Mammalian Target of Rapamycin Inhibitors

Rapamycin, also known as sirolimus, was released in 1999. It is a macrolide antibiotic derived from *Streptomyces hygroscopicus*. Rapamycin

interferes with cell-cycle proliferation and blocks intracellular signaling mechanisms by inhibiting a regulatory kinase—mammalian target of rapamycin (mTOR) (see Fig. 308.2). Unlike cyclosporine and tacrolimus, mTOR inhibitors have no direct nephrotoxicity. They frequently cause hyperlipidemia and occasionally cause myelosuppression. They have also been linked to delayed wound healing, oral ulcerations, and a rare drug-induced interstitial pneumonitis that can mimic *Pneumocystis* pneumonia. Some data suggest that rapamycin use is associated with reduced rates of posttransplantation malignancy and CMV disease. Everolimus is a hydroxyethyl derivative of rapamycin that differs from sirolimus in its pharmacokinetics, but it has a similar side-effect profile and infectious risk.

TABLE 308.1 Overall Graft and Patient Survival Rates by Organ Transplanted

TYPE OF TRANSPLANT	NO. OF TRANSPLANTS	GRAFT SURVIVAL (%) (1 YR)	PATIENT SURVIVAL (%) (1 YR)
Kidney (living donor)	4348	98.8	99.1
Kidney (deceased donor)	13969	96.8	96.6
Kidney pancreas	798	98.7/91.6[a]	97.4
Heart	2573	91.7	92.0
Liver (living donor)	359	90.1	94.4
Liver (deceased donor)	6768	90.1	92.0
Intestine	141	78.0	83.7
Lung	1826	88.8	89.7
Heart-lung	15	73.3	73.3

[a]Graft survival for kidney was 98.7 and for pancreas was 91.6%, respectively.
Data depict 1-year survival for year 2015 transplants. Modified from US Organ Procurement and Transplantation Network data as of June 30, 2017. Washington, DC: US Department of Health and Human Services; 2017.

Biologic Agents

Although calcineurin inhibitors have remained the mainstay of immunosuppression for more than 3 decades, long-term outcomes remain suboptimal largely due to renal dysfunction and metabolic complications from cumulative exposure to these agents. For example, chronic renal dysfunction develops in 7% to 21% of the organ transplant recipients and increases the risk of death by approximately fourfold. These concerns have spawned a growing interest in new regimens that enhance early immunologic tolerance, for instance, IL-2 receptor inhibitors (basiliximab) and T-cell–depleting antibodies (alemtuzumab or Thymoglobulin). These agents have delayed and reduced the incidence of acute rejection, but it is unclear if they have any impact on long-term outcomes. They have no role as maintenance immunosuppressants.

The biologic agents used for immunosuppression in transplant recipients are shown in Table 308.5. These include polyclonal or monoclonal antibody preparations that are used either to treat refractory rejection or as induction therapy that is administered in the immediate

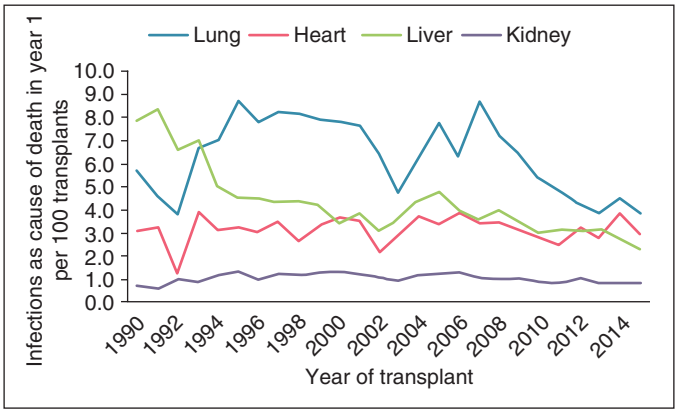

FIG. 308.1 Infections as cause of death in year 1 per 100 transplants.

TABLE 308.2 Infections Are Leading Causes of Death in Organ Transplant Recipients in the First Year After Transplantation

	PERCENTAGE OF DEATHS DUE TO SPECIFIED CAUSES IN THE FIRST POSTTRANSPLANT YEAR				
TYPE OF TRANSPLANT	VASCULAR EVENTS	INFECTION	MALIGNANCY	GRAFT FAILURE	OTHER
Kidney	26.4	24.4	3.1	0.7	1.6
Liver	16.7	32.3	5.1	12.2	10.6
Heart	18.2	23.4	2.1	26.2	11.3
Lung	14.0	34.2	3.3	16.1	5.22

TABLE 308.3 Infections Remain an Important Contributor to Morbidity in Organ Transplant Recipients 10 Years After Transplantation

	PERCENTAGE OF DEATHS IN ORGAN RECIPIENTS SURVIVING AT LEAST 10 YEARS				
TYPE OF TRANSPLANT	VASCULAR EVENTS[a]	INFECTION	MALIGNANCY	GRAFT FAILURE	OTHER[b]
Kidney	18.7	11.3	9.3	1.0	1.3
Liver	13.0	13.0	10.0	6.8	7.2
Heart	20.8	10.0	16.7	5.9	6.7
Lung	8.7	25.2	14.6	19.3	16.3

[a]Vascular events include cardiovascular and cerebrovascular events.
[b]Other includes multiorgan failure in liver, kidney, and heart recipients, and respiratory complications in lung transplant recipients (respiratory failure, bronchiolitis obliterans, pulmonary hypertension, pulmonary embolism).
Data modified from the US Organ Procurement and Transplantation Network database as of June 30, 2017. Washington, DC: US Department of Health and Human Services; 2017.

TABLE 308.4 Factors That Contribute to Infection After Transplantation

VARIABLE	EXAMPLES AND COMMENTS
Pretransplantation Host Factors	
Underlying medical conditions and chronic infections	Conditions that persist or recur (diabetes mellitus, malignancy) Conditions that exacerbate (chronic bronchitis, gallbladder disease)
Lack of specific immunity	Conducive to important primary infections (e.g., cytomegalovirus [CMV], Epstein-Barr virus [EBV], varicella-zoster virus [VZV], toxoplasmosis)
Prior colonization	Nosocomial gram-negative bacilli, *Candida* and *Aspergillus* organisms, staphylococci, vancomycin-resistant enterococci,
Prior latent infections	Reactivation produces clinical infection (tuberculosis, CMV, herpes simplex virus, VZV, cryptococcosis, *Trypanosoma cruzi*)
Prior medications	Immunosuppressive agents and antibiotics influence posttransplantation susceptibility to infection.
Transplantation Factors	
Type of organ transplanted	Site of transplantation and allograft are most common sites of infection. Allograft may transmit infection or be more susceptible to infection as a result of ischemic injury or allograft reactions.
Trauma of surgery	Surgical stress, duration of surgery
Immunosuppression	
Immunosuppressive agents	Corticosteroids, azathioprine and other cytotoxic agents, cyclosporine, tacrolimus, rapamycin, polyclonal and monoclonal antilymphocyte serums
Immunosuppressive viruses	CMV, EBV, human herpesvirus 6, and chronic hepatitis C virus infection associated with higher risk of bacterial and fungal infections
Allograft Reactions	
Graft-versus-host reaction	Affects all areas of immunity and is a major factor in bacterial, viral, and fungal infection in stem cell transplantation
Host-versus-graft reaction	Possible cofactor in infections affecting the allograft

TABLE 308.5 Biologic Preparations Used to Prevent or Treat Rejection

AGENT	ADVERSE EFFECTS
Polyclonal Antibodies	
Antithymocyte globulins[a] Anti–human thymocyte immune globulin (rabbit) (Thymoglobulin) Lymphocyte immune globulin, antithymocyte (equine) (ATGAM)	Serum sickness, thrombocytopenia, lymphopenia (can last up to 2–3 years with Thymoglobulin), increased risk of cytomegalovirus and posttransplantation lymphoproliferative disease
Monoclonal Antibodies	
Anti-CD25 (interleukin-2 receptor) antibodies[b] Basiliximab (Simulect)	Hypersensitivity reactions, infection risk not significantly increased
Anti-CD20 antibody[c] Rituximab (Rituxan)	Infusion reactions, hepatitis B virus reactivation
Anti-CD52 antibody[d] Alemtuzumab (Campath)	Infusion reactions, increased risk of cytomegalovirus, *Pneumocystis jirovecii* pneumonia, invasive fungal infections, immunosuppression that can last up to 12 mo
Other Agents	
Anti–B7 fusion protein (costimulation ligand)[e] Belatacept (Nulojix)	Increased rate of Epstein-Barr virus–associated posttransplantation lymphoproliferative disease

[a]Used for induction and rejection treatment.
[b]Used for induction but not to treat rejection.
[c]Used primarily to treat humoral rejection, blood type (ABO) mismatch, and recipients with a positive crossmatch (off-label use).
[d]Used for induction and rejection treatment (off-label use).
[e]Used for maintenance immunosuppression.

posttransplantation period and aims to provide a high early level of immunosuppression while avoiding nephrotoxicity from calcineurin inhibitors. These agents can generally be divided into T-cell nondepleting and depleting drugs. The first such agent, a murine monoclonal antibody (Muromunab-CD3 [OKT3]), was associated with an unfavorable toxicity profile, including cytokine-release syndrome (fever, rigors, hypotension, or rarely, severe pulmonary edema and respiratory distress) and a substantial risk of opportunistic infections. This agent was withdrawn from the market in 2010.

Basilixmab is a nondepleting agent approved by the US Food and Drug Administration (FDA) for prophylaxis of rejection in kidney transplantation. An anti-CD25 monoclonal antibody, it binds to the IL-2 receptor and prevents activation of T cells by circulating IL-2. It is relatively well tolerated and is not associated with cytopenias or serum sickness. However, it cannot be used for the treatment of acute rejection as it causes no T-cell depletion.

Antithymocyte globulins, such as Thymoglobulin, are polyclonal antibodies prepared in rabbits or horses by immunization with human thymocytes. As such, they are foreign proteins that may cause serum sickness that typically begins about 10 days after administration. They result in profound immunosuppression due to T-cell depletion, which lasts for 3 to 6 months. Antithymocyte globulin increases the risk of CMV disease and posttransplantation lymphoproliferative disease (PTLD).

Alemtuzumab is a monoclonal antibody that is approved for the treatment of B-cell chronic lymphocytic leukemia. This agent targets a cell surface molecule (CD52) common to many immune cells and causes significant reduction in $CD4^+$ and $CD8^+$ T cells, natural killer (NK) cells, and $CD19^+$ B cells. This effect may last 12 months or longer after administration. It is increasingly used with transplant recipients for either induction therapy or for the treatment of acute rejection unresponsive to corticosteroids. Receipt of alemtuzumab for induction therapy confers a higher risk of CMV viremia and more severe and disseminated fungal infections. In contrast to agents that affect only T cells, its use has not been associated with an increased rate of PTLD, probably because its action against B cells that suppresses Epstein-Barr virus (EBV). The infectious risk of alemtuzumab is significantly higher when used as salvage treatment for acute rejection than when used as induction therapy.

Rituximab is another chimeric mouse/human monoclonal antibody that targets the CD20 antigen expressed on B lymphocytes. Rituximab is approved to treat a variety of B-cell malignancies and autoimmune diseases. In organ transplantation it has been primarily used to treat antibody-mediated rejection. Rituximab also does not appear to increase the general risk for infections but has been associated with reactivation of HBV infection and progressive multifocal leukoencephalopathy.[5] Patients receiving therapy with rituximab may also mount poor antibody responses to immunization.

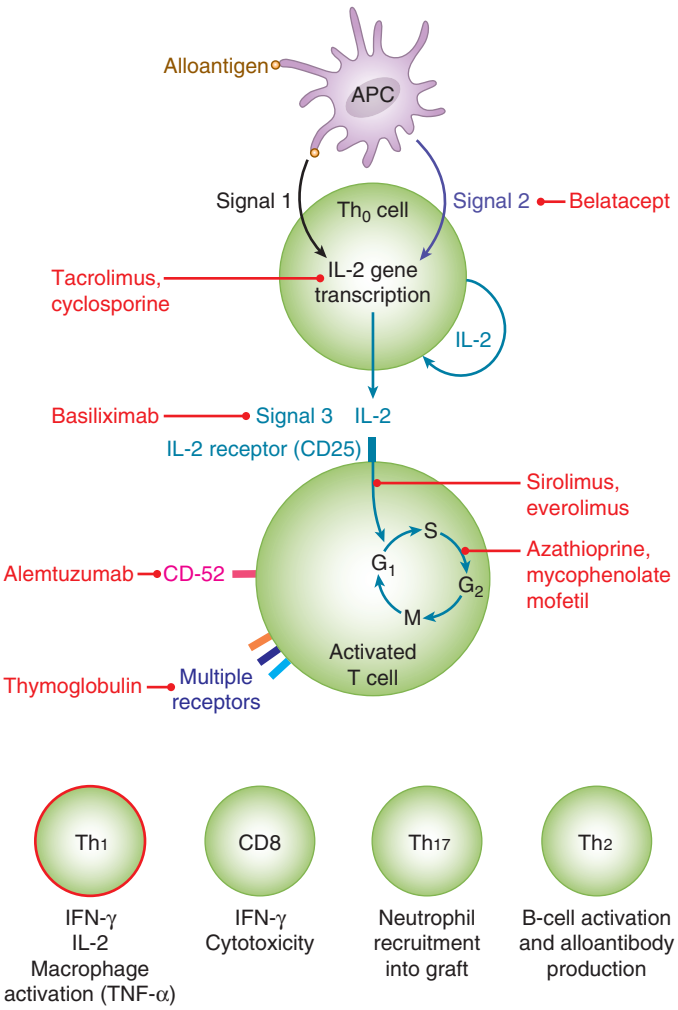

FIG. 308.2 Cyclosporine inhibits the production of cytokines, primarily interleukin-2, and consequently the generation of effector T cells or $CD4^+$ T cells. Rapamycin interferes with cell-cycle proliferation and blocks intracellular signaling mechanisms by inhibiting a regulatory kinase, mammalian target of rapamycin. *APC,* Antigen-presenting cell; G_1, G_2, cell-cycle "gap" phases with growth; *IFN-γ,* interferon-γ; *IL-2,* interleukin-2; *M,* cell-cycle mitotic phase; *S,* cell-cycle DNA replication phase; *TNF,* tumor necrosis factor.

Belatacept is a novel fusion protein that avidly attaches to receptors on antigen-presenting dendritic cells. It selectively inhibits costimulation signaling, thereby interfering with effective T-cell activation. Belatacept requires intravenous (IV) administration on a defined schedule that tapers off to every-4-weeks infusions by 2 to 3 months after transplantation.[6] It is approved as an antirejection agent in kidney recipients, based on trials that showed significantly better creatinine clearance and similar graft survival when it replaced cyclosporine.[7] The overall infectious risk of belatacept does not appear to be greater than cyclosporine-based immunosuppression. However, development of progressive multifocal leukoencephalopathy and PTLD, particularly involving the central nervous system (CNS) has been documented. For this reason, belatacept use is contraindicated in EBV-seronegative recipients.

PRETRANSPLANT EVALUATION FOR INFECTIONS

Evaluation of the patient for active and latent infection will allow optimization of pretransplantation and posttransplantation management. The UNOS has issued a list of required infectious disease screening tests for all transplantation candidates.[8] The initial transplantation evaluation should consist of a thorough history and physical examination, with a particular emphasis on demographics, country of origin, occupation, travel history, and exposure history, including exposure to animals. Current medications should be reviewed, specifically immunosuppressants such as corticosteroids, which may predispose the patient to opportunistic infections before transplantation. All relevant microbiology and hospital medical records should be examined for evidence of latent or active infection and colonization with drug-resistant bacteria. The pretransplantation setting is also an important opportunity to update the potential recipient's immunization as vaccinations are more effective when given before immunosuppression (discussed later in the immunizations section).

Pretransplantation serologic screening is pivotal in mitigating the risk of infection posttransplantation, as outlined in Table 308.5. Knowledge of the recipient's herpesvirus serostatus, especially that of CMV, is used in conjunction with the donor's CMV serostatus to risk stratify the recipient and determine the optimal posttransplantation preventive strategy.[9–11] Persons who are EBV mismatched (EBV-seropositive donor/EBV-seronegative recipient [D^+/R^-]) are at an increased risk of PTLD and are more closely monitored for EBV. Routine pretransplantation evaluation should also include testing for human immunodeficiency virus (HIV), latent tuberculosis (TB), *Toxoplasma gondii* (particularly in heart transplant candidates), hepatitis A and B (for which vaccination should be offered, if seronegative), hepatitis C, and syphilis.

Transplant Candidates Colonized With Multidrug-Resistant Bacteria

Other than patients with cystic fibrosis (CF), the natural history of transplant candidates colonized with multidrug-resistant (MDR) organisms, particularly MDR gram-negative bacteria, has not been fully described. A few observational studies have demonstrated that pre–liver transplant rectal colonization with extended-spectrum β-lactamase-producing or carbapenem-resistant Enterobacteriaceae is a risk factor for posttransplant colonization and infection.[11a,11b] However, while mortality rates approached 50% for persons with posttransplant CRE infection, pretransplant CRE colonization was not a risk factor for death.

Selective Testing for Specific Infections in Transplant Candidates

Additional testing for human T-cell lymphotropic virus 1 (HTLV-1), *Trypanosoma cruzi,* malaria, *Strongyloides stercoralis*, *Brucella,* or human herpesvirus 8 (HHV-8)[12] may be required in patients with residence or extended travel in regions where these infections are prevalent. *Strongyloides stercoralis* is also endemic within the southeastern United States, where screening should be considered.[13] Serologic screening for *Leishmania* before transplantation may be considered for candidates with a history of potential exposure to this protozoan parasite in tropical or subtropical regions and in the Mediterranean countries, although conclusive data are lacking. Screening for *Coccidioides* antibodies should be routinely performed in recipients from areas of endemicity of this fungus. HTLV-1 is endemic to Southeast Asia, the Pacific Islands, Western Africa, parts of South America, and the Caribbean. The effect of immunosuppression on the natural history of HTLV-1 is not well defined, and routine HTLV-1 serologic testing of donors is no longer routinely used because of concerns about specificity. Transplant candidates seropositive for HTLV-1 can be considered for transplantation but should be informed about potentially increased risk of developing acute T-cell leukemia and HTLV-1–associated myelopathy/tropical spastic paraparesis (Table 308.6).[14]

TIME OF OCCURRENCE OF INFECTIONS AFTER TRANSPLANTATION

The frequency, types of infections, and specific pathogens encountered after transplantation generally follow a predictable time to onset. However, evolving medical practices and preventive strategies have led to modifications in the risk and timeline of several infections, as discussed later. Nevertheless, infections in transplant recipients must be evaluated in the context of time elapsed since transplant.

TABLE 308.6 Antimicrobial Drug Interactions With Immunosuppressive Agents and Suggestions for Dosage Adjustment

ANTIMICROBIALS		EFFECT ON CYP3A4	IMMUNOSUPPRESSANT LEVEL		DOSAGE ADJUSTMENT[a]	
			CALCINEURIN INHIBITOR	mTOR INHIBITOR	CALCINEURIN INHIBITOR	mTOR INHIBITOR
Azoles	Fluconazole	Moderate-strong inhibitor at doses > 400 mg	↑↑↑	↑↑	Reduce FK and CsA by ⅓–½	Monitor levels/ reduce doses
	Voriconazole	Strong inhibitor	↑↑	↑↑	Reduce FK by ⅔, CsA by 1/2	Technically "contraindicated," but usually reduce mTOR dose
	Posaconazole	Strong inhibitor	↑↑	↑↑	Reduce FK by ⅔, CsA by ¼	
	Isavuconazole	Weak inhibitor	↑	↑	Monitor levels; currently no preemptive adjustment recommended	
Rifamycins (CYP3A4 induction: rifampin > rifapentine > rifabutin)	Rifampin	Strong inducer	↓↓↓	↓↓↓	Avoid rifampin	
	Rifabutin	Moderate inducer	↓↓	↓↓	Increase calcineurin inhibitor /mTOR dose by 50%; frequent monitoring	
Macrolides	Azithromycin	—	—	—	None	
	Clarithromycin	Moderate to strong inhibitor	↑↑	↑↑	Reduce calcineurin-inhibitor mTOR dose by ½	
ARV (ritonavir/cobicistat)		Strong inhibitors	↑↑↑	↑↑↑	Major interaction; calcineurin inhibitors have been dosed once weekly/q2 weeks. In the current era, switch to ART to avoid boosted agents (e.g., use integrase inhibitors)	
Nafcillin (not oxacillin)		Weak inducer	↓	↓	Monitor levels; no empiric adjustment	

[a]Dose adjustments per prescribing information; actual practices may vary.
ART, Antiretroviral therapy; *CsA,* cyclosporine A; *CYP3A4,* cytochrome P3A4; *FK,* tacrolimus; *mTOR,* mammalian target of rapamycin.

TABLE 308.7 Typical Timeline for the Onset of Infections After Transplantation

	MAJOR PREDISPOSING FACTORS		
	DAY 0–30	DAY 30–180	DAY 180 AND BEYOND
Pathogens	Surgical complications, nosocomial infections, pretransplant colonizers, donor-derived infections; low opportunistic infection risk	Effects of iatrogenic immunosuppression, high risk of opportunistic pathogens, residual postsurgical sequelae	Community acquired pathogens; risk of opportunistic pathogens lifelong and determined by overall state of immunosuppression such as treatment of rejection, intensity of maintenance regimen
Bacteria	Gram-negative and gram-positive bacteria (including multidrug-resistant strains), *Clostridioides difficile*, pretransplant colonizers (e.g., *Burkholderia cepacia*)	*Nocardia*, tuberculosis and nontuberculous mycobacteria, nosocomial gram-negative/ gram-positive bacteria,	*Streptococci*, *Legionella, Listeria*; nosocomial bacteria if hospitalized; risk of opportunistic bacteria never resolves
Fungi	*Candida* spp.; *Aspergillus* uncommon, except for patients with cystic fibrosis	Molds (*Aspergillus*, mucormycosis), *Candida* and *Pneumocystis* less common in the current era	*Cryptococcus* and endemic mycoses; ongoing risk for invasive mold disease; *Pneumocystis* and toxoplasmosis if off prophylaxis
Viruses	Respiratory viruses; herpesviruses uncommon in the current era of routine antiviral prophylaxis	Herpesviruses (cytomegalovirus [CMV]) if off prophylaxis; BK virus, respiratory viruses	Reactivation of chronic viral infections (herpes zoster, CMV), Epstein-Barr virus (posttransplantation lymphoproliferative disorder), respiratory viruses, norovirus, JC virus
Other	Donor-derived bacteria/fungi, unrecognized donor-derived viruses, opportunistic fungi such as *Cryptococcus* and endemic mycoses	Wide geographic and institutional variability; should be evaluated in the context of the prophylactic regimen and endemic pathogens (leishmaniasis, Chagas disease, gastrointestinal parasites)	Timeline is "reset" and opportunistic infection risk increases markedly with the treatment of rejection, particularly with T-cell–depleting agents (alemtuzumab, Thymoglobulin)

Infections in First 30 Days

Infections during this period are primarily surgical or technical complications related to transplantation or are health care–associated (Table 308.7). Bacterial infections, including those due to antimicrobial resistant pathogens, are by far the most frequently occurring infections; vascular-catheter infections, health care–associated pneumonia, *Clostridioides difficile* (formerly *Clostridium difficile*) colitis, and surgical site infections being most common. Invasive fungal infections are uncommon in the first month, except for invasive candidiasis, which generally manifests as candidemia or surgical site infections. In the absence of mold-active prophylaxis, invasive aspergillosis can occur in lung transplant recipients with prior mold colonization. Viral infections such as herpes simplex virus (HSV) and HHV-6 may be encountered very early posttransplantation. Certain donor-transmitted infections (discussed later) may also manifest during this period.

Infections Between 30 to 180 Days

Although nosocomial infections continue to pose a threat in patients requiring prolonged hospitalization, rates of surgical infections typically decline after 1 month, and opportunistic infections associated with immunosuppression emerge. These include *Pneumocystis jirovecii,* fungi, *T. gondii, Nocardia,* and most important, cytomegalovirus (CMV).

Historically, CMV infection and disease have occurred between 4 and 6 weeks posttransplantation. However, in the era of routine use of antiviral prophylaxis, typically given for 3 to 6 moths posttransplantation, most CMV disease now occurs later, after antiviral prophylaxis has been discontinued ("late-onset" CMV disease). *Pneumocystis* pneumonia and, to a large extent toxoplasmosis, are seen infrequently today because of the effectiveness of trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis. Invasive aspergillosis has long been regarded as an early-occurring infection. However, most cases now occur between 1 and 6 months posttransplantation. Notably, in lung transplant recipients *Aspergillus* infections occur after 12 months; the median time to onset posttransplantation was 357 days in one report[15] and 33 ± 19.6 months in another.[16] Widespread use of mold-active antifungal prophylaxis and chronic rejection and/or its treatment likely account for these trends.

Infections Occurring 6 Months or Later

Infections more than 6 months after transplantation are mostly community acquired and similar to those seen in the general population. However, contemporary data from the Spanish consortium for the study of infections in transplant recipients show that although the rate of infections declined from 3.5 per 1000 transplant-days in the first 6 months to 0.4 per 1000 transplant-days in the late period, the etiology of infections and infection-related mortality was similar in the two periods.[17] Patients with chronic graft dysfunction and graft-related reoperations are at higher risk for late infections. Heart, kidney, and liver transplant recipients have lower rates (≈0.3/1000 transplant-days), whereas pancreas and lung transplant recipients have the highest incidence rates of late infections (0.76 and 1.4/1000 transplant-days, respectively).[17]

Other late manifestations may represent reactivated or chronic viral infections. Herpes zoster may occur at any time after transplantation. A number of tumors related to viral infection may also occur late, the most frequent being cutaneous malignancies. Also, some lymphomas and lymphoproliferative syndromes related to EBV occur after 1 year. Infections due to mycoses, such as cryptococcosis or histoplasmosis, often manifest late and without an apparent inciting event or change in immunosuppression. Finally, although the risk for classic opportunistic infections declines, it never disappears completely. In this regard, treatment of rejection, particularly with T-cell–depleting agents resets the timeline and renders the patient susceptible to opportunistic pathogens noted earlier, the risk of which declines in the late posttransplantation period (see Table 308.7).

UNIQUE CHARACTERISTICS OF INFECTIONS IN DIFFERENT TYPES OF TRANSPLANTS

Table 308.8 presents the type, severity, and typical sites of infections in kidney, heart, heart-lung, and liver transplant recipients observed during the first year after transplantation. In addition, certain risks are unique for specific types of transplantation. Kidney transplant recipients have the lowest number of episodes of infection per patient, whereas liver and heart transplant recipients have intermediate rates. Heart-lung or lung recipients, by contrast, have more than three times the number of infections. Liver transplant recipients have almost twice the rate of bacteremia of the renal group.[18–24] Invasive fungal infections are frequent in liver and heart-lung or lung recipients, intermediate in heart recipients, and rare in renal recipients. Table 308.3 also shows that the most common sites of infection are closely related to the site of surgery.

Kidney Transplant Recipients

Most infections, including bacteremia in these patients, arise from the urinary tract. By 3 years after transplantation, more than half of all renal recipients would have been diagnosed with upper or lower urinary tract infection (UTI).[25] Although most infections were uncomplicated cystitis, graft pyelonephritis occurred in 13% of 1387 renal recipients over a 13-year period.[26] In this study, pyelonephritis occurring in the first 3 months was associated with reduced graft survival, but later infections were not. However, a larger, multivariate analysis of more than 28,000 kidney recipients in the Medicare database showed that UTIs after 6 months were associated with worse long-term graft function and survival.[25] Abnormalities such as ureteral reflux, strictures at the ureterovesical junction, or neurogenic bladder should be sought in patients with recurrent infections. Administering an extended course of antibiotics (≥4 weeks) and consideration of secondary antibiotic prophylaxis are reasonable in patients who have noncorrectable urologic abnormalities and severe graft pyelonephritis or recurrent infections. Although asymptomatic bacteriuria is common in kidney transplant recipients, a randomized, controlled trial in kidney transplant recipients showed no benefit of routine screening and treatment for asymptomatic bacteriuria.[27]

The clinician also should be alert to the occurrence of uncommon urinary pathogens. For example, urinary tract TB may arise from a focus in the native kidney. *Mycoplasma hominis* may cause a breakdown of the ureterovesical anastomosis with subsequent graft loss. Presence of struvite stones, encrusted cystitis, alkaline urine, and apparent sterile pyuria is suggestive of *Corynebacterium urealyticum*. This bacterium may be overlooked in routine cultures in standard media as it requires incubation for more than 48 to 72 hours or requires special media for isolation. Histoplasmosis may involve the transplanted kidney and cause renal failure. Adenovirus may cause hemorrhagic cystitis and/or nephritis. BK virus is an important cause of renal allograft infection and is not typically associated with systemic clinical signs or symptoms.

Historically, pneumonia occurred in 25% to 30% of kidney transplant recipients and was the most common infectious cause of death. In the past, transplantation-associated pneumonia was often due to CMV and pathogens such as fungi, *Nocardia*, and *Pneumocystis*. Currently, however, these opportunistic agents have come under better control, and conventional bacterial pathogens have become far more common in transplant populations. Wound infections are infrequent (4%–5%) but may be a serious problem, particularly if they involve the perinephric space. Body mass index ≥30 kg/m^2, urinary leak, reoperation through the transplant incision, mycophenolate mofetil use, and diabetes mellitus are risk factors for infection.[17] Some renal transplant recipients continue to have frequent problems with infection even after the first 6 months. These patients have often received excessive immunosuppression or have chronic dysfunction of the allograft or other major organs.

Heart Transplant Recipients

The most common infections after heart transplantation are bacterial pneumonias, urinary infections, herpesvirus infections, and invasive fungal infections. Pneumonia in heart transplant recipients is mostly

TABLE 308.8 Frequency, Type of Infections, and Sources of Infections Occurring in the First Year After Transplantation

TYPE OF TRANSPLANT	INFECTION EPISODES PER PATIENT	BACTEREMIA (%)	FUNGAL INFECTIONS (%)	MOST COMMON SOURCE OF INFECTION
Kidney	0.98	5–10	0.7	Urinary tract
Heart	1.36	8–11	8	Lung
Heart-lung	3.19	8–25	23	Lung
Liver	1.86	10–23	16	Abdomen and biliary tract

Data summarized from references 18–24.

TABLE 308.9 Microbial Causes of Pneumonia in Transplant Recipients

EARLY PNEUMONIA (≤30 DAYS)	LATE PNEUMONIA (>30 DAYS)
Common Causes	
Gram-negative bacilli	*Pneumococcus*
Staphylococcus aureus	*Haemophilus influenzae*
Aspiration	Influenza virus
	No cause identified
Less Common Causes	
Aspergillus	*Pneumocystis*
Herpes simplex virus	*Cryptococcus*
Legionella	*Nocardia*
Toxoplasma gondii	Cytomegalovirus
	Legionella
	Varicella-zoster virus
	Mucormycosis
	Paramyxoviruses
	Mycobacteria
	Histoplasmosis
	Coccidioidomycosis
	Respiratory viruses[a]

[a]These include influenza virus, parainfluenza virus, respiratory syncytial virus, metapneumovirus, coronavirus, rhinovirus, or adenovirus.

caused by common pathogenic bacteria (Table 308.9). Although the incidence of pneumonia is highest during the first few months after transplantation, bacterial pneumonias occur sporadically in the late posttransplantation period, after the patient has recovered from the immediate effects of surgery. Heart transplant recipients requiring renal replacement therapy and thoracic reoperation are at an increased risk for invasive pulmonary aspergillosis and should receive voriconazole prophylaxis.[28]

Mediastinitis and sternal wound infections are postoperative complications unique to heart and heart-lung transplant recipients and occur in ≈2.5% of patients. The pathogens seen are similar to those observed in other patients undergoing cardiothoracic surgery, with staphylococci predominating. One must also be alert to the possibility of unusual pathogens. Mediastinitis and sternal wound infections in heart recipients have been caused by *M. hominis, Legionella, Aspergillus*, Mucormycetes, and *Nocardia.* Factors that predispose to mediastinitis in this population are repeat operations for hemorrhage, use of antirejection therapy, and diabetes mellitus. Surgical drainage is a crucial component of treatment of mediastinitis in the transplant patient.

Left ventricular assist devices (LVADs) are now widely used as a bridge to transplantation. Infections of these devices are common and fall into distinct types: driveline infections, which are often limited to the exit site; deep infections in the pocket surrounding the device; and internal infection of the device, which is often associated with bloodstream infection. Management of these infections is challenging; however, in many cases the infection can be controlled well enough to permit transplantation. Available experience suggests that the use of antimicrobial therapy before, during, and after transplantation is associated with fewer relapses than short-course therapy. Although pretransplantation LVAD infection is associated with a higher rate of periheart transplantation complications, long-term outcomes appear to be reasonable, and LVAD infection is not considered a contraindication to heart transplantation.[29]

A number of other infections occur more commonly in heart recipients than in patients receiving other types of transplants. These include toxoplasmosis, nocardiosis, and Chagas disease. *Toxoplasma*-seronegative heart recipients are at risk for toxoplasmosis because the infection can be acquired from organisms encysted in the heart muscle of *Toxoplasma*-seropositive donors. Clinical toxoplasmosis usually occurs a few weeks to a few months after transplantation and is manifested by necrotizing pneumonitis, myocarditis, and encephalitis. Before the use of preventive therapy, the rates of toxoplasmosis were 60% to 80% in donor *Toxoplasma*-seropositive/recipient *Toxoplasma*-seronegative patients and ≈5% to 10% in *Toxoplasma*-seropositive recipients. Clinical toxoplasmosis is now uncommon in heart recipients, likely because of the use of TMP-SMX for *Pneumocystis* prophylaxis.[30] In heart transplant recipients who are *Toxoplasma* mismatches but are intolerant of TMP-SMX, the prophylactic regimen must cover both *Toxoplasma* and *Pneumocystis*.

In endemic regions such as Latin America, symptomatic reactivation of *Trypanosoma cruzi* may be seen in immunocompromised patients, including transplant recipients. About one-fourth of patients who undergo heart transplantation for cardiomyopathy caused by chronic *T. cruzi* infection have relapses of acute Chagas disease, with clinical manifestations of fever, myocarditis, and skin lesions. The disease can usually be controlled with chemotherapy. Detection of parasitemia by microscopy or polymerase chain reaction (PCR) assay in blood samples is useful to monitor for reactivation and guide chemotherapy after transplantation.

Nocardia infections have also been more frequently reported in heart and lung transplant recipients than in recipients of kidney or liver transplants, but the biologic reason for this increased rate of nocardiosis is unknown. The doses of TMP-SMX used for *Pneumocystis* prophylaxis might not provide reliable protection against *Nocardia* infection. However, resistance to TMP-SMX remains uncommon, even among breakthrough *Nocardia* infections.

Heart transplant recipients frequently incur trauma to the tricuspid valve and right ventricular endocardium from repeated endomyocardial biopsies, a common posttransplantation practice. Patients with cardiac valvulopathy are at high risk for adverse outcomes from endocarditis, and prophylaxis with dental procedures is appropriate in this group.[31]

Lung and Heart-Lung Transplant Recipients

The heightened vulnerability of the transplanted lung to infection is multifactorial. In addition to mechanical factors related to decreased mucociliary clearance, diminished lymphatic drainage, and ablation of the cough reflex appear to play an important, if poorly understood, role. The types of infections seen in lung transplant recipients are similar to those in heart-lung recipients, although the overall survival rate is better. Heart-lung transplantation is now usually reserved for patients who have Eisenmenger syndrome and whose cardiac abnormalities cannot be surgically repaired. Single- and double-lung procedures leave the donor heart available for another patient with end-stage heart disease. A unique aspect of single-lung transplantation is the occurrence of infections in the native lung that may be predisposed to infection because of defects of ventilation or perfusion caused by the underlying lung disease.

Lung and heart-lung transplant recipients experience a high rate of bacterial lung infections, especially during the first few weeks after transplantation. These patients also have higher rates of mediastinitis, invasive fungal infections, and CMV pneumonia than heart recipients. Some patients undergoing lung transplantation are chronically colonized with multidrug-resistant bacteria (e.g., CF, non-CF bronchiectasis) and are therefore at high risk for postoperative infection at the time of transplant surgery. Multidrug-resistant gram-negative bacteria in patients with CF, such as *Stenotrophomonas maltophilia* and *Pseudomonas aeruginosa,* do not preclude transplantation; instead, the posttransplant prophylactic regimen must target these organisms.[32]

Pretransplant *Burkholderia cepacia* complex infections in patients with CF pose a unique challenge. *Burkholderia multivorans* infections do not portend poor outcomes, in contrast with *Burkholderia cenocepacia*.[33] For this reason, patients with CF who are known to be colonized with *B. cenocepacia* are often denied listing for lung transplantation at many centers. However, selected persons with *B. cenocepacia* can undergo lung transplantation at referral centers with experience in managing these infections, which often includes prolonged posttransplant antibiotics. Patients and their families should be counseled about the risk of poor outcomes. Lung transplant candidates with CF may also be colonized with molds, such as *Scedosporium* complex and *Lomentospora (Scedosporium) prolificans,* and voriconazole is commonly used as prophylaxis in patients with fungal colonization. However, institutional practices on routine screening and management vary widely.

In the late posttransplant period, up to two-thirds of patients eventually develop chronic lung allograft dysfunction (CLAD), thought to

represent chronic allograft rejection, and manifests as two major phenotypes: bronchiolitis obliterans syndrome or a more recently described restrictive allograft syndrome.[34] CLAD has been associated with recurrent pulmonary infections and is one of the major causes of death in lung transplant patients. The lung allograft is also particularly susceptible to viral infections, as has been documented for CMV, HSV, and community-acquired respiratory virus infections (influenza virus, parainfluenza [PIV], respiratory syncytial virus [RSV], metapneumovirus (MPV), coronavirus, rhinovirus, and adenovirus) that are a significant cause of morbidity and have been associated with both short-term and long-term impairment of allograft infection.

Pulmonary nontuberculous mycobacterial infections are relatively common in lung transplant recipients and may arise from pretransplant colonizing strains or exogenous acquisition. *Mycobacterium abscessus* warrants special mention, as it can lead to devastating consequences posttransplantation, including aggressive and destructive surgical site infections and disseminated disease and mortality.[32,35] Because of drug resistance and poor treatment response, pretransplantation colonization or disease is considered by some centers to be a contraindication to lung transplantation.[35,36] However, some centers have reported acceptable outcomes in patients with pretransplantation *M. abscessus* disease, with the understanding that posttransplantation complications can be expected and should be managed with aggressive and prolonged therapy.[37,38] Every effort should be made to control the infection before transplantation, and antibiotics should generally be continued in the posttransplantation setting.

Acute development of hyperammonemia after lung transplantation is a rare but an often fatal complication after lung transplantation, the etiology of which is poorly understood but includes unmasking of urea cycle disorders, effects of immunosuppressive agents, or infections with urea-splitting organisms, such as *Mycoplasma* or *Ureaplasma*.[39] A multimodal treatment approach is required, which may include renal replacement therapy, bowel decontamination, amino-acid supplementation, nitrogen scavenger therapy for urea-splitting organisms, and antibacterial therapy (quinolones, tetracyclines, or macrolides) for microbiologically proven cases.[39]

Prospective donors for lung transplantation are intubated in intensive care units (ICUs). Therefore the airways of these donors are often colonized with microorganisms, and occult parenchymal infection may be present. Before implantation of the lungs, it is customary to obtain cultures and Gram stains of the donor airways to guide antibiotic therapy in the recipient. Initial antibiotic prophylaxis should be aimed at common nosocomial pathogens encountered in the ICU, including methicillin-resistant *S. aureus* (MRSA) and enteric and nosocomial gram-negative bacilli; the regimen can be narrowed to target the donor's pathogens. Another problem unique to lung transplantation has been dehiscence of the airway anastomosis. This occurs during the first few weeks after transplantation. It is frequently associated with bacterial or fungal infection at the anastomotic site. The incidence of this complication appears to be declining.

Invasive Aspergillosis After Lung Transplantation

Heart-lung and lung transplant recipients develop invasive pulmonary aspergillosis more frequently than patients with other types of organ transplants. Risk factors for invasive aspergillosis in addition to renal dysfunction are relative ischemia at the anastomotic site, receipt of a single-lung transplant, hypogammaglobulinemia, CMV infection, precolonization and/or postcolonization of the airways with *Aspergillus,* and augmented immunosuppression for allograft rejection.[40] A unique form of aspergillosis involving the airway mucosa or bronchial anastomotic sites, called tracheobronchial aspergillosis, is observed almost exclusively in lung and heart-lung recipients (Fig. 308.3). The airway lesions of this disease can be directly visualized during bronchoscopy.[41]

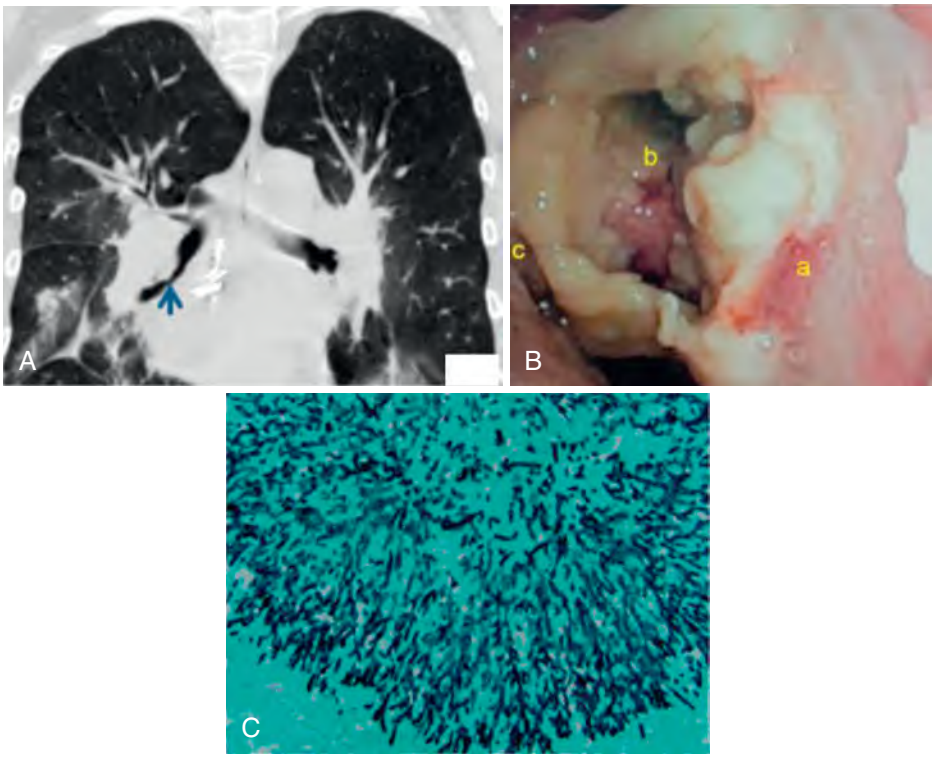

FIG. 308.3 A unique form of aspergillosis involving the airway mucosa or bronchial anastomotic sites, called tracheobronchial aspergillosis, is observed almost exclusively in lung and heart-lung recipients. (A) Coronal view showing an endobronchial lesion partially obstructing the bronchus intermedius *(blue arrow)*. (B) Bronchoscopy of the left allograft bronchus showing showed irregular lesions comprised of yellowish pseudomembranes mixed with necrotic debris that completely occluded the entrance into the left upper lobe and lingula. Note the presence of ulcerative lesions (e.g., "a" with shallow erythematous base, "b" with deep ulcer and bleeding crater, and "c" with necrotic ulcer), which are characteristic features of ulcerative bronchitis. (C) Histopathology and Grocott-Gomori methenamine silver stain of biopsy specimen of the lesions in B demonstrating numerous fungal forms consistent with *Aspergillus* species. *(A and B from Haidar G, Crespo M, Maximous S, et al. Invasive Tracheobronchial* Aspergillosis *in a Lung Transplant Recipient Receiving Belatacept as Salvage Maintenance Immunosuppression: A Case Report.* Transplant Proc. *2016;48:275–278.)*

This form of aspergillosis has a better prognosis than aspergillosis invading the lung parenchyma and is commonly treated with systemic and local (i.e., nebulized) antifungal therapy combined with surgical débridement, as feasible.

Continuous exposure of the organ to the environment and post-transplantation *Aspergillus* colonization poses a risk for subsequent invasive disease in lung transplant recipients. As such, many lung transplantation centers routinely use antifungal preventive strategies. Direct administration by means of inhalation of the polyene agents (amphotericin B formulations) allows deposition of the drug directly into the distal bronchial tree, thereby obviating the systemic side effects and drug interactions. Inhaled amphotericin B deoxycholate and the lipid formulations (lipid complex and liposomal) are both generally well tolerated; however, aerosolized lipid formulations are associated with fewer side effects.[40] A potential limitation of aerosolized amphotericin B is the fact that deposition in single-lung transplant recipients occurs preferentially in the allograft, with erratic distribution in the native lung, which could be a potential source of infection.[42] In addition, aerosolized amphotericin B may not prevent systemic fungal infections because candidemia has been reported in lung transplant recipients with such an approach. Finally, long-term use of these agents has also been associated with the emergence of *Aspergillus* spp., such as *A. flavus, A. terreus,* and *A. alliaceus,* with reduced susceptibility to amphotericin.[43]

Triazoles, including itraconazole and voriconazole, have led to a decrease in the incidence of invasive aspergillosis in lung transplant recipients. The potential for hepatotoxicity is a concern, particularly with voriconazole.[44] Association of prolonged voriconazole use with skin cancers and periostitis can be treatment-limiting toxicities in lung transplant recipients. Sparse data exists for posaconazole prophylaxis in lung transplant recipients. The risk of hepatotoxicity may be lower with this drug; however, achieving therapeutic levels in the perioperative period is challenging, particularly with the suspension formulation. Although serum posaconazole concentrations correlated with levels within the bronchoalveolar fluid in lung transplant recipients, steady-state levels were rarely reached in the newly transplanted lungs.[45] Extended-released and IV formulations of posaconazole were approved in 2013 and 2014, respectively, and have been shown to have much more favorable pharmacokinetics parameters, although data on their use in lung transplant prophylaxis are limited. Thus the role of posaconazole as primary prophylaxis in the perioperative period is uncertain. There are no data on the use of isavuconazole for prophylaxis after lung transplantation. Immunosuppressant levels should be monitored and dosages adjusted accordingly in patients receiving azole antifungal agents (Table 308.10).

Therapeutic drug monitoring, although not necessary for fluconazole, should be performed for azole antifungal agents in transplant recipients if the use of these agents is anticipated for at least a week (see Table 308.6). Adequate plasma trough levels for the triazole antifungal agents have correlated with successful outcomes, both when used as prophylaxis and treatment of invasive fungal infections after transplantation. In addition, monitoring trough plasma levels avoids overexposure for example, voriconazole concentrations >5.5 mg/L are thought by some to predispose to visual and neurologic adverse events in transplant recipients.

TABLE 308.10 Etiologies of Nodular Pulmonary Infiltrates in Transplant Recipients

ETIOLOGY	
INFECTIOUS	**NONINFECTIOUS**
Bacterial	**Malignancies**
Nocardia	PTLD and other lymphomas
Mycobacteria	Carcinomas (typically lung neoplasms and hepatocellular carcinoma)
Legionella	**Nonmalignant Lesions**
Staphylococcus aureus (septic emboli)	Rounded atelectasis
Fungal	
Aspergillus	
Cryptococcus	
Mucormycosis	
Endemic fungi (histoplasmosis and coccidioidomycosis)	
Other non-*Aspergillus* molds	
Viral	
Cytomegalovirus	

PTLD, Posttransplantation lymphoproliferative disease.
Data from Copp DH, Godwin JD, Kirby KA, et al. Clinical and radiologic factors associated with pulmonary nodule etiology in organ transplant recipients. Am J Transplant. *2006;6:2759–2764; and Paterson DL, Singh N, Gayowski T, et al. Pulmonary nodules in liver transplant recipients.* Medicine. *1998;77:50–78.*

Liver Transplant Recipients

Liver transplant recipients have higher rates of infection than renal or heart transplant recipients, and most deaths are associated with infection, either as a primary or a secondary cause (see Table 308.2). Bacterial infections occur in 59% to 68% of the patients after liver transplantation, and ≈50% of these infections occur within 2 weeks after transplantation. The most important sites of infection are the abdomen and biliary tract, the surgical wound, the lungs, and the bloodstream, with or without associated catheter infection.

Abdominal Infections After Liver Transplantation

Transplantation of the liver differs from other transplantation operations in the length and difficulty of the surgery and the frequency of bleeding. In addition, many liver transplant recipients have poor nutrition and severe metabolic difficulties. Surgical site infections account for most infections in the early period after liver transplantation, and in general, short-course prophylactic antibiotic regimens targeting skin and intestinal flora are favored, with national guidelines recommending perioperative administration of piperacillin-tazobactam or ampicillin plus cefotaxime for 24 hours or less.[46,47] Decisions about the optimal prophylactic regimen become more complicated in individuals colonized with drug-resistant bacteria, particularly vancomycin-resistant *Enterococcus* (VRE). In a study, 32% of patients colonized with VRE before liver transplantation received tigecycline prophylaxis to target their VRE.[46] Compared with VRE-colonized patients who received ampicillin-sulbactam prophylaxis, there was no difference in the frequency of microbiologically confirmed deep surgical site infections, including those caused by VRE. As such, perioperative prophylaxis based on history of VRE colonization or infection may not be routinely necessary.[48]

The Achilles heel of liver transplantation surgery is the function of the biliary and vascular anastomoses. In consequence, most abscesses in the transplanted liver result either from liver ischemia caused by hepatic artery thrombosis or from obstruction to bile flow from biliary strictures.[18] The organisms responsible are gram-negative enteric bacilli, enterococci, and anaerobes. The diagnosis is made by ultrasonography or computed tomography (CT). Treatment with drainage and IV antibiotics is usually successful, provided the source is biliary infection and any structural abnormalities can be corrected. If hepatic artery thrombosis is the predisposing factor, the infectious symptoms can usually be controlled with antibiotics, but retransplantation may be necessary.

Cholangitis after liver transplantation also results from technical problems. The most common predisposing problem is biliary strictures. Patients with strictures may have periodic bouts of cholangitis. Some patients improve after dilatation procedures or stent placement, but in others operative repair is necessary. It may not be easy to establish a firm diagnosis of cholangitis because many patients do not manifest the classic Charcot triad of fever, abdominal pain, and jaundice. The clinical presentation may mimic allograft rejection. The diagnosis is more reliable if bacteremia is present or if a liver biopsy indicates pericholangitis. Empirical treatment for cholangitis should include antibiotics to cover gram-negative enteric bacilli, enterococci, and anaerobes. Procedures such as liver biopsy, T-tube cholangiography, or endoscopic retrograde cholangiopancreatography may be followed by cholangitis and occasionally by bacteremia.

Peritonitis can accompany other intraabdominal infections and frequently complicates biliary leaks or disruption of an abdominal viscus. Bile peritonitis may occur after extraction of a T-tube. It is often well tolerated and may resolve by itself, but on occasion the leak persists and the chemical peritonitis becomes secondarily infected. The most common organisms involved in peritonitis are enterococci and aerobic

enteric gram-negative rods, but staphylococcal and candidal infections are not infrequent. Treatment of established peritonitis requires antibiotic therapy, together with drainage of associated abscesses and repair of technical problems such as biliary leaks.

Abdominal abscesses are usually found in patients who have had frequent or lengthy abdominal operations.[18] Nearly one-third of the abdominal abscesses are associated with bacteremia. The location is frequently subhepatic, but splenic, pericolic, and pelvic abscesses are also seen. Most patients with abscesses have undergone an abdominal operation within the preceding 30 days. Although common enteric organisms cause most abscesses, staphylococci and *Candida* are also seen. Imaging studies usually define the location of the abscess. As with any other abscesses, the appropriate treatment is a combination of drainage and antibiotics.

Fungal Infections After Liver Transplantation

Liver transplant recipients have a high rate of fungal infections, ranging from 15% to 42% with case-fatality rate of 25% to 82%.[49] Risk factors for invasive fungal infections include renal dysfunction, fulminant hepatic failure, longer operative time, retransplantation, hepatic iron overload, and colonization with *Candida* at the time of transplantation.[50] In the era of Model for End-stage Liver Disease (MELD) scores as the basis for prioritizing liver transplantation, a MELD score ≥30 is the most influential factor for invasive fungal infections, with fungal infections occurring in 24% to 28% of these patients.[51]

Candida is the predominant fungal pathogen, causing 62% to 88% of the invasive fungal infections in this population. Others include *Aspergillus, Cryptococcus,* and molds as agents of mucormycosis. Nearly one-third of candidal infections in liver transplant recipients are caused by non-*albicans* species. Fluconazole prophylaxis was found to be a risk factor for the emergence of non-*albicans Candida* spp. as pathogens in liver transplant recipients. Invasive candidiasis contributes significantly to mortality after liver transplantation. In a case-controlled study, liver transplant recipients with invasive candidiasis had a 36% mortality rate, compared with 2% in the control patients. Unfortunately, infections due to *Candida* can be difficult to diagnose, and the β-D-glucan assay has limited accuracy in diagnosis invasive candidiasis in liver transplant recipients.[52]

Invasive aspergillosis occurs in 1% to 8% of liver transplant recipients with unique predisposition to disseminated aspergillosis. Historically, outcomes in transplant recipients with invasive aspergillosis have been notably poor. with mortality rates ranging from 65% to 92%.[49] However, judicious use of immunosuppression, early recognition, and overall advances in management have led to steady improvement in outcomes, with the currently reported mortality rate of ≈22% in liver transplant recipients with invasive aspergillosis. Well-defined risk factors exist for invasive aspergillosis in most patients. These include retransplantation, fulminant hepatic failure as an indication for transplantation, renal dysfunction and requirement of any form of renal replacement therapy, and poor allograft function.[53] Most disease now occurs more than 90 days after transplantation, a possible consequence of improved early management and delayed occurrence of risk factors, such as CMV infection.

Antifungal prophylaxis targeted toward high-risk patients is a rational approach toward the prevention of invasive fungal infections. Practice guidelines recommend fluconazole for these patients.[54] Potential limitations of fluconazole, however, include lack of activity against *Aspergillus*, emergence of fluconazole-resistant *Candida* spp. as pathogens, and metabolic interactions with the immunosuppressive agents. Routine use of use of triazoles is limited by the risk of hepatotoxicity and erratic pharmacokinetics profile in the posttransplantation period. The echinocandins have activity for both *Aspergillus* and *Candida* spp. and low likelihood for drug interactions. Echinocandin-resistant *Candida* infections have been documented, albeit less frequently. Prophylaxis with these agents may be beneficial in patients who are at high risk for invasive *Aspergillus* or have received fluconazole before transplantation.[55] Both micafungin and anidulafungin are well tolerated in liver transplant recipients. It is reasonable to continue prophylaxis for 14 to 21 days or until the risk factor, such as requirement for renal replacement therapy, abates.

Pancreas Transplant Recipients

About 1300 pancreas transplant operations are performed in the United States annually, or approximately 1 for every 10 kidney transplantations.[1] Current patient and graft survival rates are similar to those for kidney transplantation alone, but infection-related morbidity is higher. Some studies have shown more wound complications and CMV disease among the patients receiving combined kidney-pancreas than kidney transplantation alone.

The postoperative infection rate and the causative pathogens depend primarily on the technique used for drainage of exocrine secretions of the pancreas. In recent years the practice of draining these secretions into the small bowel (enteric drainage) has gained precedence over the previous practice of drainage into the bladder. Enteric drainage has been associated with lower rates of UTI. However, intraabdominal infections remain a significant complication of enteric drainage procedures, and aerobic and anaerobic enteric bacteria predominate in abscesses associated with enteric drainage. The microorganisms in infections in which the viscus has not been opened are usually from the skin flora. *Candida*, however, is a common pathogen in all types of surgical site infections, including those that use bladder drainage.

Small Bowel Transplant Recipients

Small bowel transplantation is the preferred therapy for intestinal failure and total parenteral nutrition-related complications. Small bowel transplantation is unique as the gut not only harbors a large burden of lymphoid tissue, but these cells are the least tolerogenic of any organ. In consequence, small bowel transplant recipients are particularly susceptible to graft-versus-host disease (GVHD), and managing the risk of rejection, infection, and GVHD has proven challenging. Small bowel transplantation is often combined with a liver graft due concurrent existence of intestinal failure–associated liver disease. Of note, inclusion of liver graft with intestinal graft may be immunologically protective. However, isolated intestinal transplantation is becoming increasingly more frequent, likely due to improved management of intestinal failure–associated liver dysfunction. Despite improvements in post-transplantation management, outcomes continue to be worse than those of other organ transplants.

Greater than 90% of the small bowel transplant recipients develop significant infections, and the rates of infection are higher than in other transplant groups. Intraabdominal pyogenic infections and bloodstream infections predominate, but the transplanted intestine, like the lung allograft, is very susceptible to CMV infection, including a tendency to relapse after successful antiviral treatment. Multivisceral transplant recipients and patients undergoing colonic segment transplantation with small bowel transplantation are more likely to develop infections. The susceptibility of small bowel transplant recipients to infections continues in the late posttransplantation period, that is, more than 6 months after operation. The incidence of EBV-associated lymphoproliferative disorders approaches 10% at 5 years, and the tumors often involve the gut.

SPECIFIC SITES AND TYPES OF INFECTION

Infections of the Skin and Surgical Site

Infections of the skin are common after transplantation but are rarely life threatening. All organ transplant recipients are at risk for wound infections. The most common bacterial pathogen is *S. aureus*, but infections with enterococci, gram-negative bacteria, *Candida,* and *M. hominis* may also be seen. Rarely, mucormycosis can cause surgical site infection in transplant recipients. Subcutaneous infections caused by *Alternaria, Exophiala*, and other darkly pigmented or dematiaceous fungi are encountered occasionally. Biopsy with fungal culture is required for a specific diagnosis. Cellulitis or necrotizing infections can also be due to cryptococcosis. Unlike stem cell transplant recipients, organ transplant recipients rarely develop fusariosis.

The most common cutaneous viral infections are those caused by HSV and varicella-zoster virus (VZV). Warts are a common problem, particularly more than 5 years posttransplantation.

The skin is also a target organ for many systemic infections, and bacterial, fungal, nocardial, mycobacterial, and CMV infections may

include skin manifestations. *Mycobacterium chelonae* causes nodular lesions, often on the extremities. As a rule, one should aggressively investigate any new and/or unusual skin lesion with a biopsy.

Infections of the Urinary Tract

UTIs are one of the most common causes of fever in kidney transplantation, especially in the first 6 months after transplantation.[56] Patients with retained urinary stents are at a higher risk, resulting in a general recommendation to remove these stents within 4 weeks. These patients may not manifest "classic" features of UTIs or pyelonephritis, as normal hosts would. In addition, both allograft pyelonephritis and rejection can present with fevers, tenderness over the graft, and acute kidney injury. Allograft pyelonephritis, especially in the first 3 months, has been linked to long-term kidney graft dysfunction but does not affect graft survival at 5 years.[57]

In patients with signs of severe infection, the choice of empirical antibiotics should take into account the history of resistant organisms as well as local epidemiologic data. Oral step-down regimens are reasonable, as long as the patient is improving. Imaging with renal ultrasound or noncontrast CT scanning should be considered to assess for complications, such as obstruction and abscesses. It is also important to consider infections caused by unusual pathogens, such as *M. hominis*, *M. tuberculosis,* or BK virus. However, BK virus may cause allograft infection but not usually fever or systemic manifestations.

Infections of the Bloodstream

Bacteremia occurs in 5% to 10% of kidney and heart transplant recipients, with higher rates (10%–25%) in liver and lung transplant recipients (see Table 308.8). Besides catheter-related infections, pneumonia in heart and heart-lung transplant recipients, UTIs and perinephric sources in renal transplant recipients, abdominal and biliary infections in liver transplant recipients, and surgical site and UTIs in pancreatic transplant recipients are the most commonly identifiable sources of bacteremia. Predominant gram-negative bacteria are *Escherichia coli, Klebsiella* spp., and others, including extended-spectrum β-lactamase–producing and carbapenem-resistant organisms, *Acinetobacter baumanii,* and *P. aeruginosa*. The highest incidence of gram-negative bloodstream infections has been observed within the first month after transplantation (210.3/1000 person-years), with a sharp decline to 25.7 per 1000 person-years from 2 to 12 months posttransplantation.[58] Kidney recipients are more likely to develop gram-negative bacteremia 12 months after transplantation.[58]

In kidney transplant recipients the source of bacteremia is usually the urinary tract, due to disruption of the urinary tract during surgery, the lack of a valve between the bladder and transplanted ureter, and the presence of an indwelling stent in the early posttransplantation period. Bloodstream infections are common after liver transplantation due to the immunosuppression of pretransplant cirrhosis and the prolonged operation time. Risk factors after liver transplantation include diabetes mellitus, urinary and vascular catheterization, posttransplantation renal replacement therapy, massive blood loss and transfusions, reoperation, and bile duct complications.[59,60] In a study of 704 liver transplant recipients over a 10-year period, 39.4% of bloodstream infections occurred in the immediate postoperative period (<10 days).[61] The most frequent pathogens were Enterobacteriaceae (41%), *Staphylococcus aureus* (19.8%), enterococci (13.1%), *P. aeruginosa* (8.8%), and *Candida* (7.1%). Bloodstream infections occurring early after transplantation were associated with increased 1-year mortality.

In lung transplant recipients with CF the colonizing bacteria are important causes of bloodstream infections, in particular *B. cepacia*, which can lead to the cepacia syndrome, with progressive necrotizing pneumonia, persistent bacteremia, and death.[62] Bloodstream infections in heart, pancreas, and intestinal transplant recipients also occur and have been linked to intravascular catheters, abdominal leaks, and UTIs.

Bacteremia due to *S. aureus* occurs with estimated rates of 15% to 38% in various organ transplant recipients.[63] The rates of MRSA have increased over time. Among organ transplant recipients, lung recipients have the highest incidence and attack rate. Most common sources are vascular catheters, pneumonia, or wound infections. Nearly one-half of all *S. aureus* bacteremias occur within 90 days of transplantation; early-onset bacteremias are more likely to occur after liver transplantation, likely due to the large size of the incision or colonization during candidacy.[63] The unadjusted 28-day all-cause mortality after gram-negative bloodstream infections in transplant recipients was 4.9%.[58] Kidney recipients had lower mortality than liver transplant recipients.

The basic approach to bacteremia is the same whether or not the patient has undergone transplantation and includes ascertaining the source of the bacteremia and likely pathogen. The inability to discern a source is relatively common, especially in liver transplant recipients; up to 21% of the bacteremias in these patients may have had no documented source, but most of these probably originated in the abdomen. The trend toward increasing antimicrobial resistance among gram-negative bloodstream isolates has an impact on local decisions regarding empirical antibiotic therapy of transplant patients who present with possible bloodstream infections.

Pulmonary Infections

The usual microbial causes of pneumonia in the transplant recipient are listed in Table 308.9. Pneumonia accounts for up to 80% of infections in solid-organ transplant (SOT) recipients and can occur at any time in the posttransplantation period.[64] The etiology varies by transplant type and time of onset after transplant, with nosocomial pathogens predominating in the early posttransplantation period and opportunistic and community-acquired pathogens occurring later. Guidelines for the treatment of community-acquired and health care–associated pneumonia have been published elsewhere.[65,66] Knowledge of pretransplant colonizers, particularly for lung transplant recipients with CF; pretransplantation serologies, for example CMV, recent exposures; hospitalizations; and prior antimicrobial courses should be part of the evaluation. Community-acquired respiratory viruses, such as influenza virus, PIV, RSV, MPV, coronavirus, rhinovirus, or adenovirus, may cause pneumonia in transplant recipients.

Opportunistic causes of pneumonia can occur at any time after the first month, although the net state of immunosuppression determines the ongoing risk of opportunistic pathogens. For instance, transplant recipients with stable doses of immunosuppression many years after transplantation would be considered at low risk for pulmonary infections due opportunistic pathogens, whereas those whose immunosuppression has been augmented for the treatment of rejection would be considered at higher risk. In the latter group a thorough evaluation for fungal infections (endemic mycoses in cases of compatible epidemiology, invasive mold disease, cryptococcosis), nocardiosis, mycobacterial, *P. jirovecii, Rhodococcus equii*, and other pathogens should be undertaken. In cases where opportunistic infections are suspected, the appearance of the radiographic abnormalities may assist in informing both diagnostic and therapeutic decisions, with the caveat that there is substantial overlap between different entities. Nodular infiltrates have a broad range of infectious etiologies (see Table 308.10), and certain clinical and radiographic features may be helpful in discerning a specific etiology.[67] In one study, for example, pulmonary nodules were found to have diverse etiologies and were infectious in 56% of patients (bacterial, 22%; fungal, 33%; viral, 2%) and noninfectious in 44% (PTLD, 25%; carcinoma, 18%).[67]

Acute rejection in lung transplant recipients can mimic pulmonary infections.[68] Thus early bronchoscopy, with appropriate microbiologic testing and culture and nonculture diagnostics of the blood, are crucial in establishing the diagnosis when the patient fails to respond to presumably appropriate antimicrobial therapy or when the suspicion for opportunistic pathogens is high. Whether empirical therapy directed against opportunistic pathogens is warranted should be considered on a case-by-case basis; indeed, it is often difficult to rationalize or justify a regimen that will treat all possible etiologies, underscoring the importance of a thorough microbiologic investigation.

Empirical therapy to cover common typical and atypical bacterial pathogens can be initiated while culture results are awaited. Patients who have an illness lasting longer than 7 days, who have a nonproductive cough, or who have diffuse infiltrates or nodular lesions on chest imaging are more likely to have an unusual or opportunistic pathogen and should undergo invasive diagnostic procedures, including bronchoscopy, in a timely manner to establish the diagnosis.

Tuberculosis

M. tuberculosis is a major pulmonary pathogen, particularly in geographic areas where TB is endemic. The frequency of TB in transplant recipients ranges from 1.2% to 15%, with higher rates in endemic areas.[69] Most cases of posttransplantation TB are due to reactivation of latent infection in low endemicity areas. Prior exposure to *M. tuberculosis* (positive tuberculin skin test [TST], positive interferon-γ [IFN-γ] release assay [IGRA], and/or residual TB lesions in pretransplantation chest imaging), dialysis, and T-cell–depleting antilymphocyte antibodies confer a higher risk for TB. IL-2 receptor antibodies (basiliximab), on the other hand, do not appear to increase this risk. Although most transplant recipients develop TB in the first year after transplantation, up to one-third of the patients, particularly kidney transplant recipients may develop TB later in the posttransplant period.[69] Extrapulmonary or disseminated forms of disease are more frequent in the first 6 months after transplantation.

Diagnostic Considerations

Although the diagnostic yield of TST is low, it remains the initial step in the detection of latent infection. IGRAs are whole-blood tests that can also aid in the diagnosis of *M. tuberculosis* infection. QuantiFERON-TB (QFT) Gold In-Tube test (Qiagen, Summit, NJ) and T-SPOT (Oxford Immunotec, Marlborough, MA) are approved by the FDA. The data on the performance of QFT Gold Plus, a new generation of QFT assay are limited.

QFT Gold In-Tube test is technically easier to perform; however, T-SPOT had greater sensitivity and specificity in immunosuppressed patients.[70] In kidney transplant recipients, QFT Gold In-Tube test had higher positivity than TST for determining the risk of latent infection and development of TB.[70] Neither TST nor IGRAs, however, differentiate between tuberculous infection and disease. In addition, in patients with T-cell anergy due to end-stage organ failures, IGRAs may be falsely negative, which is usually signified by a poor mitogen response in the control tube.

Management of Tuberculosis

All transplant candidates should undergo TST testing, even if they have been vaccinated against *Mycobacterium bovis* (bacillus Calmette-Guérin [BCG]). Many centers have shifted to IGRA testing instead. Patients previously treated for latent infection or for active disease need not undergo TST or IGRA. Chest radiography should be performed to evaluate for old healed TB. Upon exclusion of active TB, treatment for latent infection can be initiated while awaiting transplantation and, if necessary, continued for an appropriate duration after the transplant. Treatment for latent infection should be used in transplant candidates awaiting transplantation or transplant recipients who have any one of the following risks: (1) TST with an induration ≥5 mm and/or a positive IGRA; (2) clinical or radiographic evidence of untreated TB, that is, apical scaring, calcification in the lungs or lymph nodes, pleural thickening; or (3) history of contact with a patient with active TB.[69] Patients who have previously received adequate treatment for latent infection or active TB need not be treated again.

Treatment of Latent Tuberculosis

Isoniazid (300 mg/daily) supplemented with pyridoxine (vitamin B_6) for 9 months is the treatment of choice for latent TB. All patients receiving isoniazid should be routinely monitored for hepatotoxicity. Management of latent TB in liver transplant recipients can be challenging, given potential the risk of hepatotoxicity. A systematic review and meta-analysis of individual patient data, however, documented minimal isoniazid-related hepatotoxicity and significant reduction in TB reactivation in liver transplant recipients.[71] In patients with severe, decompensated liver disease, it is reasonable to defer latent TB infection therapy until after transplantation. Thus, although generally well tolerated even among pre–liver transplant patients, alternatives to isoniazid may be needed when hepatic dysfunction ensues.[72] Rifampin for 4 months carries a lower risk for liver injury than isoniazid but is a potent inducer of the cytochrome P450, accelerates the metabolism of immunosuppressive agents, and may lead to rejection and allograft loss (see Table 308.6). It is advisable to use regimens that include rifamycins before transplantation, given their significant drug interactions with the immunosuppressive drugs. A recently approved regimen of isoniazid-rifapentine once weekly for 12 weeks significantly shortens treatment duration but does not avoid isoniazid adverse effects or rifamycin-related effects on drug metabolism.[73] Rifabutin, a rifamycin, is a less potent cytochrome inducer than rifampin and has been used for the treatment of latent TB in the transplant setting.[72] Limited data exists with the use of quinolones treatment of latent TB. Levofloxacin use in one report was associated with a high incidence of tenosynovitis.[74]

Treatment of Active Tuberculosis

Treatment of TB in transplant recipients is similar to that in the general population with the following caveats. Rifampin is associated with a profound interaction with the immunosuppressive agents that poses a risk of graft rejection and warrants careful monitoring of the levels of these drugs. The dose of calcineurin inhibitors should be increased, and levels should be closely monitored (see Table 308.6). Even with careful monitoring, concurrent use of rifampin incurs substantial risk of rejection, graft loss, and overall higher mortality. Rifabutin may be considered instead of rifampin. Treatment should be continued for 12 to 18 months of for rifamycin-sparing regimens. It is noteworthy that, as in HIV-infected patients, transplant recipients upon initiation of treatment can develop immune reconstitution syndrome (IRS) that mimics worsening or progression of disease and may manifest as fever, lymphadenopathy, or worsening respiratory symptoms.[75] Awareness of this entity can obviate unnecessary changes in treatment.

Pulmonary Infections Due to Endemic Mycoses

Coccidioidomycosis

Coccidioides immitis and *Coccidioides posadasii* are the etiologic agents of coccidioidomycosis. These dimorphic fungi are normal residents of selected desert soils of the lower Sonoran Life Zone and are present only in the Western Hemisphere. The areas of highest endemicity in the United States include the southwestern Arizona, the San Joaquin Valley of California, and West Texas. Coccidioidomycosis is also found in southern Nevada, New Mexico, Utah, and coastal southern California. Outside of the United States, this fungus is found in high concentrations in northern Mexico, with limited endemicity in Central and South America.

Coccidioidomycosis is acquired by inhalation of arthroconidia that undergo morphologic transformation into spherules in the terminal bronchioles, resulting in a primary pulmonary infection. Coccidioidomycosis occurs in 1.5% to 8.7 % of the transplant recipients in endemic areas.[76] Infections typically occur in the first year after transplantation. Delayed onset of coccidioidomycosis may occur in patients who receive antifungal prophylaxis in the early posttransplantation period. Pneumonia is the most common manifestation. However, extrapulmonary dissemination resulting in meningitis, osteomyelitis, fungemia, and skin lesions may occur in up to 75% of the transplant recipients, and mortality rates range from 50% to 63%.

In patients with pretransplant history of coccidioidomycosis or asymptomatic seropositivity, targeted prophylaxis with fluconazole is recommended, typically for a prolonged duration (6–12 months or longer).[76] More recently, fluconazole prophylaxis for 1 year for all recipients in endemic regions has been shown to be superior to targeted prophylaxis.[77] For patients already receiving itraconazole, voriconazole, or posaconazole for *Aspergillus* prophylaxis, no additional fluconazole is required. Although caspofungin has modest in vitro anticoccidioidal activity, the clinical efficacy of this agent for treatment or prophylaxis of coccidioidomycosis is not established. Therefore transplant recipients whose antifungal prophylaxis comprises an echinocandin should receive additional prophylaxis with an azole.

Fluconazole and itraconazole are the antifungal agents of choice for the treatment of coccidioidomycosis.[78] For patients with rapidly progressive or severe infection, a lipid formulation of amphotericin B is recommended, followed by secondary prophylaxis with fluconazole or another azole to avoid relapse.[78] Although there are no standard recommendations for the duration of total treatment, a patient

should be treated until the infection is quiescent based on clinical, serologic, and radiographic follow-up, and this may take months or years to achieve. For coccidioidal meningitis, lifelong treatment is recommended.

Histoplasmosis

Histoplasma capsulatum is a dimorphic fungus that resides in the soil of certain regions of North, Central and South America, Africa, and Asia. Up to 75% of individuals residing in certain areas of the Ohio and Mississippi River Valley of the United States may have been infected with *H. capsulatum*. However, most are asymptomatic. In the absence of outbreaks in the community, histoplasmosis has occurred in 0.1% to 0.5% of transplant recipients.[79] Histoplasmosis is acquired by inhaling microconidia or hyphal fragments of the mold phase of the organism. It is widely postulated that histoplasmosis in transplant recipients represents reactivation of latent infection; however, the supportive evidence is weak at best.[80] Pulmonary disease is the most common manifestation; common findings include fever, weight loss, hepatomegaly, splenomegaly, lymphadenopathy, cutaneous or subcutaneous lesions, and mucosal lesions in the mouth or GI tract. CNS involvement occurs in about 5% to 10% of cases.

Liposomal amphotericin B is recommended for patients with moderately severe or severe manifestations of histoplasmosis, with transition to itraconazole after a 1- to 2-week induction phase, except in patients with CNS involvement, in whom 5 to 6 weeks of liposomal amphotericin B is recommended.[80] Itraconazole should be continued for at least 1 year with periodic monitoring of *Histoplasma* antigen. Fluconazole is less effective and is not recommended unless itraconazole is contraindicated or not tolerated. Voriconazole and posaconazole are active in vitro against *H. capsulatum*; however, the yeasts are resistant to the echinocandins.

Routine screening for histoplasmosis before transplantation is not recommended, given that the incidence even in endemic areas is below 0.5%. Assuming a sensitivity of 98% and specificity of 98% for the screening test, the positive predictive value would be 20%. As such, only one in five individuals treated for a positive result could benefit, although four would be subjected to the adverse effects and drug interactions associated with itraconazole.[80] However, patients who have recovered from active histoplasmosis, with or without treatment, during the 2 years before the initiation of immunosuppression may be considered for itraconazole prophylaxis.[81]

Abdominal and Gastrointestinal Infections

Intraabdominal infections in liver transplant recipients have already been discussed. These infections also occur with an increased frequency among recipients of pancreas and small bowel transplants. They are less common after transplantation operations that do not involve the abdomen. When they do occur, they are usually related to preexisting medical conditions, such as biliary stones or diverticulosis.

Studies in developing countries show that transplant recipients are very susceptible to *Salmonella* infection, but infections caused by *Shigella or Campylobacter* do not appear to be increased in frequency. *C. difficile* has emerged as one of the most common causes of diarrhea in transplant recipients who are heavily treated with antibiotics. *C. difficile* colitis developed in 6% of the transplant recipients, with 73% of the cases occurring within the first 30 days.[82] Toxic megacolon may develop in 5% to 12% and recurrent colitis in approximately 22% of organ transplant recipients who have *C. difficile* colitis. *Helicobacter pylori* infection has been associated with a low-grade gastric lymphoma called mucosa-associated lymphoid tissue lymphoma in a small number of transplant recipients. Most of these tumors have regressed after reduction of immunosuppression and use of antibiotics to treat the *Helicobacter* infection. Hyperinfection and disseminated infection with *Strongyloides* were substantial problems in the past but appear to have virtually disappeared. Universal pretransplantation screening for *Strongyloides* is probably not cost-effective, but vigilance for this infection should be maintained for patients from endemic areas. Screening patients with residence in or extensive travel to endemic areas is reasonable.

Diarrhea

Diarrhea in transplant recipients can be self-limited, mimicking the course of viral and bacterial causes of diarrhea in the general population. Polypharmacy and the immunosuppressive regimen, particularly mycophenolate, can also lead to diarrhea in these patients.[83] *C. difficile* infection is a more frequently encountered problem in transplant recipients than other hospitalized populations.[84] Norovirus infection has only recently been identified as a cause of protracted diarrhea in transplant recipients and may be associated with severe wasting, debilitation, and sometimes mortality.[11,85] Patients with protracted diarrhea should have their stool tested for norovirus, as that can obviate the need for invasive procedures. CMV, mycobacteria, *Cryptosporidium, Giardia,* microsporidia, and other pathogens can also cause diarrheal syndromes; an endoscopic evaluation should be considered in cases of refractory diarrhea with no known cause.

Central Nervous System Infections

CNS infections in transplant patients require prompt diagnosis and early appropriate therapy. Table 308.11 lists the most important agents. Absent notably from the list are pyogenic bacteria and HSV, which are otherwise common pathogens in transplant patients at sites outside the CNS. The highest risk for opportunistic CNS infection is from 1 to 6 months after transplantation; an exception is cryptococcal meningitis, which is often a "late" event. CNS infections should always be suspected in febrile transplant recipients with headache, altered mental status, seizures, focal neurologic deficit, or a combination of these manifestations. CNS imaging (via CT scan or magnetic resonance imaging [MRI]) should generally be undertaken in these patients, to identify any focal lesions that may point toward brain abscesses due to bacteria, molds (*Aspergillus,* agents of mucormycosis, and *Scedosporium*), *Nocardia*, and toxoplasmosis. Neurologic opportunistic infections that do not manifest as focal lesions include CMV, HSV, VZV, JC virus (JCV), HHV-6, and *Listeria monocytogenes*.[64] Lumbar puncture should be performed as indicated. It is important to remember that altered mental status in the transplant setting can also result from malignancies (such as PTLD) and vascular, toxic, or metabolic etiologies, including side effects of immunosuppressive agents.[86]

L. monocytogenes typically causes bacteremia, meningitis, and at times cerebritis in transplant recipients. The Gram stain of the cerebrospinal fluid (CSF) is negative in more than half of the cases. Usually, the diagnosis is made by culturing the organism from CSF or blood. All patients with *Listeria* bacteremia should undergo lumbar puncture, even in the absence of CNS signs, because the mortality rate is much higher when CNS disease is present. Infection responds well to antibiotic therapy, but relapses may occur. Routine use of TMP-SMX for prophylaxis has been effective for prevention and may explain why listeriosis is observed less frequently in the current era.

TABLE 308.11 Key Pathogens of the Central Nervous System in Transplant Recipients

Bacteria
Listeria monocytogenes
Nocardia spp.
Viruses
Varicella-zoster virus
Polyomavirus (JC virus)
Human herpesvirus 6
West Nile virus
Zika virus
Fungi
Cryptococcus neoformans
Dematiaceous fungi
Aspergillus spp.
Agents of mucormycosis
Other Pathogens
Toxoplasma gondii

Aspergillosis is an important cause of CNS infection in immunocompromised patients. The most common portal of entry is the lung; invasive sinus infection with continuous spread also occurs but is less common. Patients with aspergillosis typically have risk factors such as renal dysfunction or require augmented immunosuppression. *Aspergillus* is an angiotropic mold, and hematogenous spread to the brain can occur early in the course of the infection. CNS imaging reveals single or multiple enhancing lesions with predilection for the gray-white junction, and galactomannan can be detected in blood or CSF is most patients.

Other fungi that may cause parenchymal brain infections in transplant recipients include the agents of mucormycosis (Mucorales) and dematiaceous fungi, such as *Cladophialophora*. The overall mortality rate is high in patients with CNS infection caused by Mucorales or dematiaceous fungi, and therapy with a combination of antifungal medication and surgical resection is generally recommended.

Cryptococcal meningitis usually occurs in the late posttransplantation period and has a subacute course. Pulmonary disease caused by *Cryptococcus* coexists in about 40%, and fungemia is present in 33% to 35% of the cases.[87] Lumbar puncture should be performed in any patient with a positive serum cryptococcal antigen or blood culture, even in the absence of CNS manifestations, given that documentation of CNS disease has an impact on treatment recommendations. The spinal fluid usually has fewer than 500 white blood cells/mL, with lymphocytic predominance and a positive cryptococcal antigen test. India ink preparations reveal positive findings in 40% to 50% of patients. Serum cryptococcal antigen is positive in 88% to 98% of transplant recipients with CNS cryptococcosis.

Up to 33% of the patients with CNS cryptococcosis have CNS lesions due to *Cryptococcus* on neuroimaging.[87] New lesions developing after initiation of antifungal therapy may represent IRS, an inflammatory tissue response that results from improvement in cellular immunity after reduction or cessation of immunosuppression and reversal of *Cryptococcus*-associated immunosuppression. Overall mortality in SOT recipients with cryptococcosis remains ≈15% to 20%. Receipt of calcineurin inhibitors is associated with a lower mortality rate that may be attributable in part to the synergistic interactions of calcineurin inhibitors with antifungal azoles. In transplant recipients with cryptococcosis, discontinuation of calcineurin inhibitors was the only modification of immunosuppression that influenced the development of IRS. Patients in whom the calcineurin inhibitor was discontinued had a fivefold higher risk of IRS.[88] Neither discontinuation nor reduction of other immunosuppressive agents, such as antimetabolites or corticosteroids, affected this risk. Because calcineurin inhibitors also have synergistic interactions with antifungal agents, continuation at reduced dosages, as opposed to stopping these agents, appears rational in minimizing the risk of IRS.

Although active opportunistic infections generally preclude transplantation, emerging data suggest that transplantation after recent cryptococcal disease in persons with cirrhosis may not be a categoric exclusion and may be cautiously undertaken in liver transplant candidates who are otherwise deemed clinically stable.[89]

T. gondii is a protozoan that can cause a nonspecific encephalopathy, diffuse meningoencephalitis, or progressive single or multiple brain lesions. *Toxoplasma* infection has been reported in all types of SOT but has most often been described in cardiac transplantation because the organism can become encysted in cardiac muscle after primary infection. Recipient seronegative status with primary infection posttransplantation appears to be most likely mechanism. The donor heart can then become a source of infection for a nonimmune cardiac recipient. Serology should be performed on cardiac donors and recipients to identify patients at risk for disease transmitted by the allograft. The fatality rate is high, and often the diagnosis is not established until autopsy. The treatment of choice is pyrimethamine and sulfadiazine with the addition of folinic acid to the regimen to prevent marrow suppression.

Nocardia spp. may cause single or multiple brain abscesses or, less commonly, meningitis. The primary portal of infection is pulmonary with potential for spread to bone, skin, and CNS. *Nocardia* brain abscesses may benefit from stereotactic biopsy and surgical drainage in addition to long-term (9–12 months) antimicrobial therapy. Sulfonamides are the mainstay of treatment because they penetrate the CNS well, and most isolates are susceptible. Combination therapy is typically used for disseminated disease. Agents such as amikacin, imipenem, and cefotaxime have shown good activity, with more rapid killing than sulfonamides.

JCV is an important cause of CNS infection and is discussed separately later.

SPECIFIC PROBLEMS OF VIRAL INFECTIONS

This section covers most issues related to viral infections in transplant recipients (Tables 308.12 and 308.13). Hepatitis viruses were discussed earlier. The approach to antiviral prophylaxis and the

TABLE 308.12 Routine Laboratory Tests Recommended Before Transplantation

Cytomegalovirus IgG antibody
Epstein-Barr virus IgG antibody
Herpes simplex (types 1 and 2) antibody
Varicella-zoster IgG antibody
Toxoplasma IgG antibody (heart transplant recipients)
Hepatitis B screen[a]
Hepatitis C enzyme immunoassay[b]
Human immunodeficiency virus antibody
Tuberculin skin test or interferon gamma release assay for tuberculosis
Stool for ova and parasites; *Strongyloides* antibody[c]
Trypanosoma cruzi antibody[d]
Syphilis screening (EIA or RPR)

[a]Should include surface antigen, core antibody, and surface antibody.
[b]Liver candidates and patients with laboratory or clinical evidence of liver disease should also undergo a polymerase chain reaction assay for hepatitis C.
[c]Primarily useful for patients at risk for strongyloidiasis, such as former or current residents of tropical and subtropical regions.
[d]For residents of endemic areas in Central and South America.
EIA, Enzyme immunoassay; *IgG,* immunoglobulin G; *RPR,* rapid plasma reagin.

TABLE 308.13 Infections With the Potential for Donor Transmission (See Chapter 304)

Viruses

Viral hepatitis (B, C, and E)
Herpes viruses (cytomegalovirus, Epstein-Barr virus, herpes simplex virus)
Human immunodeficiency virus
Human T-lymphotropic virus I/II
West Nile virus
Lymphocytic choriomeningitis virus
Rabies
Creutzfeldt-Jakob disease
JC virus infection (progressive multifocal leukoencephalopathy)
Dengue
Arenaviruses

Bacteria

Bacteremia
Bacterial meningitis (*Neisseria meningitidis, Streptococcus pneumoniae*)
Bacterial pneumonia or donor colonization (lung transplants)
Tuberculosis and nontuberculous mycobacteria
Borrelia burgdorferi

Fungi

Candidiasis
Cryptococcosis
Aspergillosis
Endemic mycosis (histoplasmosis, coccidioidomycosis)
Agents of mucormycosis

Other Agents

Toxoplasmosis
Trypanosoma cruzi (Chagas disease)
Leishmaniasis
Strongyloides stercoralis
Balamuthia mandrillaris
Naegleria fowleri
Treponema pallidum (syphilis)
Babesia
Malaria
Schistosomiasis

pretransplantation evaluation of candidates and donors are discussed elsewhere in this book.

Cytomegalovirus

Despite progress in treatment and prevention, CMV remains one of the most important infections in the setting of organ transplantation, resulting in substantial morbidity and mortality. A DNA herpesvirus, CMV establishes latency in cells of the myeloid (but not lymphoid) lineage after primary infection,[90] and seroprevalence rates range from 30% to 97%.[91] Both innate and adaptive immunity are required to control CMV, although the role of the innate immune system is incompletely understood.[92] CMV is a ligand for Toll-like receptor 2 (TLR2), and TLR2 polymorphisms (Arg753Gln) have been associated with an increased risk of CMV reactivation, prolonged replication, and disease after liver transplantation.[93] Control of CMV ultimately depends on multiple immune mechanisms, including the NK cells of early-acting innate immunity and the $CD4^+$ (T-helper or Th), and $CD8^+$ (cytotoxic) T cells.[94] NK cells are the first line of defense against CMV, but their activity is transient, and the cellular arm of the adaptive immune response is ultimately required to limit viremia. CMV-specific neutralizing antibodies appear 2 to 4 weeks after primary infection,[92] but clinical observations imply that humoral immunity plays only a part in the control of CMV.[95] Indeed, antibodies do not terminate CMV infection but, rather, limit dissemination of reactivated latent virus.[96] Thus, although donor and recipient CMV serostatus is used to stratify the risk of CMV infection after transplantation, posttransplantation seroconversion has limited ability to predict CMV immunity or risk of disease.[97]

Risk Factors

Patients at highest risk for CMV infection are seronegative recipients of seropositive organs (D^+/R^-). These patients do not have a preexisting pool of CMV-specific $CD8^+$ memory T cells or antibody and thus have up to a 92% incidence of viremia and 50% to 65% rate of symptomatic infection by 90 days posttransplantation without prophylaxis.[91,98] Seropositive recipients (R^+) are at an intermediate risk of CMV infection, with approximately 40% to 60% developing viremia without prophylaxis.[91] There is a nuanced difference in the CMV risk between the D^+/R^+ and D^-/R^+ groups. In the former, viremia may represent either donor-derived infection or recipient-derived reactivation of latent virus, a distinction that is not possible to make without viral sequencing. Seronegative recipients of seronegative organs (D^-R^-) are at low risk of transplant-related infection, although they can acquire primary CMV infection from blood products or other mechanisms.

The use of lymphocyte-depleting antilymphocyte antibodies (e.g., Thymoglobulin and alemtuzumab) is also associated with CMV disease, particularly when used as antirejection as opposed to induction therapy.[91,99] Absolute viral load and viral kinetics appear to be important determinants of CMV disease.[100,101] In part due to the higher burden of transplanted lymphoid tissue, lung and small bowel transplant recipients are at a higher risk of CMV compared with other organ transplant recipients. Coinfection with other herpesviruses (HHV-6 and HHV-7) appear to enhance, whereas immunosuppressive regimens that include mTOR inhibitors (sirolimus, everolimus) reduce the risk of CMV.[102,103]

Clinical Manifestations

CMV may present as (1) CMV infection or viremia that implies CMV replication, irrespective of attributable symptoms, and (2) CMV disease, which is symptomatic CMV infection.[91] In the absence of preventive therapy, CMV infection occurs in 36% to 100% and symptomatic disease in 11% to 72% of transplant recipients. Primary infections occurring in seronegative recipients with a seropositive donor are more likely to be symptomatic.

The most common type of CMV disease is mononucleosis-like viral syndrome with fevers, malaise, and cytopenias. Abnormalities may be found on liver function tests, although jaundice rarely occurs. Tissue-invasive disease may manifest as pneumonitis, GI disease, or hepatitis. In this era, when prolonged antiviral prophylaxis is routinely used, CMV disease in organ transplant recipients often is a late manifestation, and ≈30% of these cases have tissue-invasive disease.[104] Interstitial pneumonia is the most serious complication of CMV infection and is present in most fatal cases. CMV pneumonia may coexist with other pathogens in the lung, particularly *Pneumocystis*.

GI CMV disease typically manifests as ulcerations in the GI tract that may be found anywhere from the esophagus to the rectum. Severe complications, such as bleeding or perforation, occur in some patients. Patients with tissue-invasive disease in the absence of viremia are referred to as having compartmentalized disease, and this presentation is often seen with GI CMV disease. CMV hepatitis occurs in up to 17% of liver transplant recipients and is more common with primary than with reactivation infection. The pathologic finding is microabscesses scattered around the liver lobule. CMV inclusion bodies may be readily seen or scant.

Laboratory Diagnosis and Immune Monitoring

The greatest advance in regard to CMV in transplantation in recent years has been the development of accurate and reproducible quantitative molecular methods, including an international laboratory standard, to assess viral load. Most laboratories performing quantitative nucleic acid testing (NAT) for CMV are now using PCR-based assays that offer good precision and accuracy, have broad dynamic range, and relatively shorter turnaround time than conventional PCR assays.

There is growing interest in the use of CMV-specific immune assays to facilitate clinical decision making regarding antiviral therapy for the management of CMV. Instead of broadly applying a "one size fits all" strategy, knowledge of an individual patient's anti-CMV immune responses could conceivably allow more optimal risk stratification. It is hoped that this would result in more efficacious, individualized strategies to prevent and treat CMV by customizing the duration of prophylaxis, postprophylaxis monitoring, preemptive therapy, and treatment of CMV viremia.[105,106] Transplant recipients with CMV viremia and who lacked CMV-specific $CD8^+$ T-cell responses failed to control CMV despite prolonged antiviral therapy. In contrast, all but one patient with detectable CMV-specific $CD8^+$ T-cell responses had suppressed viremia after the discontinuation of therapy.[107] Although these results are promising, CMV-specific immune assays are not FDA approved in the United States, and other data show that relying on a single immunologic marker may not capture the full nuance of anti-CMV immunity.[108] Thus at present it is unclear whether to incorporate these assays into clinical practice.

Prevention

There are generally two strategies for the prevention of CMV: (1) prophylaxis, whereby "at-risk" patients are given antivirals (typically valganciclovir) for a defined period (usually 3–6 months), and (2) preemptive therapy, whereby SOT recipients are monitored and treated for evidence of early-stage CMV viremia in an attempt to prevent progression to CMV disease.[91] Although each of the strategies has been studied individually and been shown to be effective for the prevention of CMV (compared with either placebo or no-prevention strategy), there is paucity of direct comparative studies. As such, the benefit of one strategy over the other has long been debated. Because the totality of evidence supporting the use of preemptive therapy is more limited than for prophylaxis,[91,109] prophylaxis with valganciclovir has emerged as the dominant strategy for the prevention of CMV in D^+/R^- transplant patients. However, prophylaxis is associated with adverse drug reactions such as cytopenias, which can be compounded by the concurrent use of mycophenolate mofetil, azathioprine, and prophylactic TMP-SMX. In addition, some patients are given longer durations of prophylaxis that might be necessary, and others go on to develop late-onset CMV disease once prophylaxis is completed. Indeed, 30% to 40% percent of D^+/R^- patients will develop late-onset CMV disease upon discontinuation of prophylaxis[110] that is associated with higher mortality, bacterial and fungal superinfections, and graft loss.[111] Viral monitoring after completion of prophylaxis appears to have limited efficacy for the prevention of late-onset CMV disease.[112] Prolonged prophylaxis (up to 12 months) is frequently used in lung recipients, particularly in the D^+/R^- group.[113] Antiviral prophylaxis is appropriate in patients receiving lymphocyte-depleting agents for rejection, although preemptive monitoring may also be acceptable.[91]

A recent randomized controlled trial has shown that preemptive therapy significantly reduced CMV disease compared to prophylaxis in high-risk D^+/R^- liver transplant recipients.[113a] Based on these data, the 2019 American Society of Transplantation CMV guidelines now recommend preemptive therapy for CMV prevention in these patients.[113b]

Challenges with preemptive therapy are logistic coordination for screening and promptly acting upon the results.[91] In addition, the optimal viral load thresholds to guide the initial of antiviral therapy, the duration of therapy, and laboratory monitoring are not known. Some patients with low-level viremia will have spontaneous clearance,[92] whereas concerns have been expressed about the possibility of failure of this strategy among CMV D^+/R^- lung transplant recipients who may experience rapid replication of CMV.[91,114] However, in contrast to prophylaxis, CMV disease has been documented in only 2.6% of patients receiving preemptive therapy in the current era and occurs largely within 100 days of transplantation.[104] Possible biologic basis for the relative lack of late-onset CMV disease with the preemptive approach is that by allowing controlled CMV replication to occur before an antiviral agent is administered, the patient's immune system is primed, resulting in enhancement of CMV-specific humoral and cellular immune responses that are critical for long-term control of the virus.[115] In contrast, viral replication is almost completely suppressed with the use of antiviral prophylaxis,[116] which might prevent development of CMV-specific immune responses.

Other strategies for CMV prevention exist but limited evidence exists to support their routine use. CMV immunoglobulin and intravenous immune globulin (IVIG) have been used for prophylaxis, but this is an uncommon practice in the valganciclovir era.[117–120] There is considerable interest in a CMV vaccine, but clinical trials have shown mixed results.[121] A CMV glycoprotein-B vaccine resulted in increased anti-CMV antibody titers and reduced CMV viremia,[122] whereas the DNA-based vaccine ASP0113 failed to show any difference in CMV viremia in D^+/R^- kidney transplant recipients when given after transplant.[123] Additional studies on CMV vaccines, including consideration of pretransplantation administration, are needed in high-risk transplant candidates and recipients.

Treatment

IV ganciclovir or its oral derivative valganciclovir are the mainstay for the treatment of CMV disease. The duration of treatment is typically at least 2 weeks, with documentation of clearance of viremia and resolution of signs and symptoms of CMV.[91] The need for secondary prophylaxis or posttreatment monitoring is not standard and can be considered based on the specific clinical situation,[91] although in a study of kidney and liver transplant recipients, secondary CMV prophylaxis did not provide additional benefit after the treatment of CMV disease.[124]

Ganciclovir-resistant CMV poses a unique challenge. Ganciclovir requires phosphorylation by a viral kinase encoded by the *UL97* gene (unique long, open reading frame 97), followed by additional phosphorylation steps by cellular kinases.[125] It then inhibits the viral DNA polymerase, encoded by the *UL54* gene. Mutations in both *UL97* and *UL54* can arise, conferring ganciclovir resistance. Risk factors for resistance include prolonged low-dose oral prophylaxis, D^+/R^- serostatus, profound immunosuppression, lung transplantation, initial high-grade viremia, and suboptimal drug dosing during the treatment of CMV, which is often done in the setting of cytopenias.[91,126] Although some *UL97* mutations can respond to dose-escalation of ganciclovir, mutations conferring high-level resistance do not, necessitating the use of foscarnet and cidofovir, both of which are profoundly nephrotoxic.[127] Neither foscarnet nor cidofovir require phosphorylation via the viral kinase and are thus unaffected by *UL97* mutations. They both inhibit the viral DNA polymerase, and resistance to all three drugs can be conferred by viruses with certain *UL54* or dual *UL97-UL54* mutations.

Patients with drug-resistant CMV have poor outcomes, as do those with "refractory CMV" who have been ongoing CMV viremia and disease while receiving ganciclovir, despite no objective evidence of resistance on CMV genotyping.[127] Reduction of immunosuppression or a switch to an mTOR-inhibitor–based regimen, may be considered on an individual basis in case of severe disease.[91] The use of CMV-specific immunoglobulin for the treatment of resistant/refractory CMV is of unproven efficacy but is often used.[128] Unlike hematopoietic cell transplant recipients, adoptive immunotherapy for the treatment of ganciclovir-resistant CMV is rarely used in organ transplantation due in part to lack of availability, the hypothetical risk of precipitating graft rejection, and concerns that efficacy of the transfused T cells may be reduced in presence of calcineurin inhibitors and corticosteroids. However, autologous CMV-specific T cells from a CMV D^+/R^- lung allograft recipient with ganciclovir-resistant CMV disease resulted in long-term reconstitution of protective antiviral immunity, CMV infection, disease-free survival, and no allograft rejection.[129]

Given the dismal outcomes and toxicities of available therapies, efforts are underway for new, safer drugs for the treatment of resistant CMV. Maribavir is a direct inhibitor of the UL97 viral kinase and is an alternative to foscarnet and cidofovir. Although it failed to prevent CMV infections in high-risk liver transplant recipients, this was attributed in part to the low dose used (100 mg twice daily).[130] In a phase II trial, however, that used optimal dosages, it was effective for the treatment of CMV disease resistant or refractory to standard therapy among hematopoietic cell and organ transplant recipients, with no major toxicities observed.[131] Brincidofovir (formerly CMX001) is a lipid-conjugated oral prodrug of cidofovir with no nephrotoxicity and broad antiherpesvirus activity.[91] Although it was effective against CMV in a phase I study of high-risk hematopoietic cell transplant recipients,[132] a larger phase III trial was discontinued because of associated high rates of GI toxicity. An IV formulation is being developed with the goals of reducing toxicity. Letermovir (AIC246) is a novel nonnucleoside CMV inhibitor that targets the viral terminase complex.[133] Its advantages include good oral bioavailability and lack of significant toxicity. Based on promising results in a placebo-controlled trial in HSCT recipients,[134] this agent has been FDA approved for the prevention of CMV in HSCT recipients. Limited clinical experience exists with letermovir use in the SOT setting, and resistance may develop earlier than with valganciclovir and foscarnet. A clinical trial of letermovir prophylaxis among CMV D^+/R^- kidney transplant recipients is underway. Letermovir has no activity against HSV and VZV so prophylaxis against those viruses, when used, must be continued during letermovir prophylaxis.

Epstein-Barr Virus and Posttransplantation Lymphoproliferative Disorder

EBV is a ubiquitous gammaherpesvirus that infects human B lymphocytes and epithelial cells, with seroprevalence rates of ≈50% among children age 5 years and 90% to 5% among adults.[135–137] In immunocompetent individuals, EBV results in subclinical infection during infancy and infectious mononucleosis in adolescence.[138] In organ transplant recipients, EBV infection can be transmitted from the graft or represent reactivation of latent infection. It can result in PTLD, which encompasses a spectrum of diseases ranging from lymphoid proliferation to overt lymphomas.[135]

Immunobiology

The life cycle of EBV is characterized by an early productive replicative phase after primary infection in which mature infectious virions are produced, leading to cell death (the lytic cycle), and a nonproductive phase in which the virus is incorporated into and replicates with the host DNA, with lifelong persistence of the viral genome in B cells in a latent state. These cells are kept in check by NK cells and EBV-specific cytotoxic T cells (CTLs). Posttransplantation immunosuppression has the potential to allow proliferation of EBV latently infected B cells to go unchecked.[138–140] Although abnormal B cells in SOT recipients are usually of recipient origin, these cells in HSCT recipients are typically of donor origin.

Risk Factors

Patients with a D^+/R^- serostatus are considered at the highest risk for PTLD.[135] Due to the lower rates of seropositivity in children, PTLD is more common in pediatric compared with adult organ transplant recipients, occurring at rates of about 20% and 1%, respectively. The increased risk of PTLD in recipients of lymphoid-rich organs, such as intestines and lungs, compared with kidneys, hearts, and livers, is due to the amount of infected donor B cells coming over with the graft, as

well as the overall net state of immunosuppression.[139] Other risk factors include the use of T-cell depleting antibodies, CMV infection, younger age in children, older age in adults, and HLA polymorphisms.[139] The costimulation blocker belatacept is associated with PTLD in EBV D^+/R^- recipients, predominantly involving the CNS. There is a black box warning against its use in this setting.[141]

Clinical Manifestations and Diagnosis

Primary EBV infection in organ transplant recipients can present with a variety of manifestations, including a nonspecific viral syndrome.[139] EBV-related PTLD has a bimodal pattern of onset. It typically presents early after transplantation, with most cases occurring in the first year, although late cases (5–7 years) have been reported in the aging organ transplant population. A small subset of PTLD is EBV negative and occurs later (>5 years posttransplantation). The virus has a predilection to involve the allograft but may also involve any organ, including CNS disease. EBV viral load quantitative NAT of the blood has potential for diagnosis.[139] However, although it is understood that higher viral loads correlate with disease, the optimal thresholds that should prompt diagnostics/therapeutic interventions are unknown. In addition, unlike CMV, the role of preemptive therapy with periodic viral load monitoring of high-risk patients is less well defined. Regardless, patients with high-level or escalating viremia, particularly those with D^+/R^- serostatus, should undergo computed or positron emission tomography of the neck, chest, abdomen, and pelvis and core needle or excisional biopsy of lesions. Tissue should be stained for EBER ("EBV-encoded small nuclear RNA," a marker for EBV-infected cells), and flow cytometry of lymphocytes should be performed.[139] However, some patients with EBV-driven PTLD may not have viremia if the PTLD is restricted to the graft itself or to the GI tract.[139] Thus PTLD should be considered in organ transplant recipients presenting with an unexplained febrile illness, particularly during the first year after transplantation or after augmentation of immunosuppression for rejection. Bone marrow biopsies, lumbar punctures, and other tests can be considered based on the clinical scenario.

The importance of histology for the diagnosis of PTLD cannot be overstated. PTLD manifests as polymorphic and monomorphic forms, with the latter generally associated with a worse prognosis. Histologic manifestations include monomorphic B-cell neoplasms, such as diffuse large B-cell and Burkitt lymphomas; classic Hodgkin lymphoma-type PTLD; and polymorphic forms.[135] T-cell neoplasms and EBV-associated smooth muscle tumors are rare. EBV-related hemophagocytosis has been described in the posttransplantation setting, often with devastating consequences.[142]

Prevention and Treatment

The role of antiviral drugs in the management of PTLD is controversial. Acyclovir and ganciclovir have no activity against latent virus, which is the predominant form of the virus in PTLD. Expression of Z EBV replication activator (ZEBRA) in PTLD suggests that few virions may enter the lytic cycle,[143] and based on the consideration that antivirals could potentially eliminate these virions, antiviral drugs are frequently used. However, PTLD occurs in patients receiving valganciclovir for other reasons, such as CMV prophylaxis, and EBV viral loads can rise despite the receipt of these antivirals, given that they have no activity against latently infected or EBV-transformed B cells.[144] Results of EBV vaccine studies have been disappointing,[145] and data supporting the routine use of IFN-γ, adoptive T-cell transfer, or prophylactic immunoglobulin are sparse.[146,147] A pilot study investigated the role of anti-CD20 monoclonal antibody rituximab used before transplantation for the prevention of EBV in kidney transplant recipients.[148] Among 17 EBV D^+/R^- kidney transplant candidates, the 5 who underwent living donation were treated with a single dose of rituximab 4 weeks before transplantation. None of these 5 patients developed EBV viremia, compared with 58% of those who received kidneys from deceased donors and thus did not receive rituximab. Only 1 patient developed PTLD (nonrituximab group). This strategy warrants further investigation in prospective controlled trials.

A preemptive approach whereby immunosuppression is reduced in the face of rising viremia has been associated with a lower risk of PTLD.[149] This strategy is based on the hypothesis that recovery of the host's immune system will allow the development of CTL against EBV with subsequent control of EBV-driven B-cell proliferation.[139] Rituximab has also been used as preemptive therapy in at-risk patients with escalating viremia,[150] but additional experience is needed. Adoptive immunotherapy, although successfully used in treating established EBV infections after HSCT, is an uncommon practice in organ transplantation. B-cell and T-cell malignancies should be managed using conventional chemotherapy.

Herpes Simplex Virus

Herpes simplex viruses (HSVs) 1 and 2 are ubiquitous HHVs that cause orolabial, genital herpes, and/or perianal herpes.[151] Most adults are seropositive for HSV,[152] and the majority of cases of posttransplantation HSV represent reactivation of latent virus, although rare cases of donor-transmitted infection have been reported. In the absence of antiviral prophylaxis, 35% to 75% of HSV-seropositive transplant recipients will develop clinically apparent HSV disease.[153–156] A unique manifestation of HSV occurring early after transplantation is fulminant hepatitis, hypotension, and disseminated intravascular coagulation with fatal outcomes in ≈two-thirds of cases.[157] However, the use of antiviral prophylaxis in the current era has greatly reduced the incidence of HSV.[158] Patients receiving CMV prophylaxis have lower rates of HSV reactivation, whereas those who are CMV seronegative should receive acyclovir, valacyclovir, or famciclovir for HSV-specific prophylaxis for at least 4 weeks after transplantation, as the majority of severe HSV disease occurs within the first month posttransplantation.[153] Antivirals may need to be resumed after augmentation of immunosuppression for rejection.

Mucocutaneous manifestations of HSV in transplant recipients are similar to those of the general population, with painful erythematous papules that progress to characteristic fluid-filled vesicles. These can be treated with oral acyclovir, valacyclovir, or famciclovir until all lesions are healed. The diagnosis can typically be made clinically, although direct-fluorescent antibody (DFA) testing, PCR, culture, histopathology with immunohistochemistry, and Tzank smear of lesions can be used, especially in atypical cases.[151] In transplant recipients these mucocutaneous lesions are capable of spreading into the respiratory and GI tracts by direct extension, resulting in HSV esophagitis and pneumonia. Viremic dissemination can occur. Patients with visceral disease, such as fulminant hepatitis, disseminated disease, or HSV encephalitis should be treated with high-dose acyclovir (10 mg/kg every 8 hours, adjusted for renal dysfunction). An obstructive nephropathy due to deposition of acyclovir crystals in the renal tubules may occur in dehydrated patients or if the infusion is given too rapidly. It should be noted that HSV encephalitis is a rare entity and does not occur with increased frequency in the organ transplant population; PCR of the CSF is the preferred method for diagnosis.[159]

As with ganciclovir-resistant CMV, the treatment of acyclovir resistance is challenging. Resistance rates in the immunocompromised host range from 3.6% to 6.3% and should be considered in patients with recurrent or refractory mucocutaneous disease despite appropriately dosed antivirals. Because acyclovir requires phosphorylation by a viral thymidine kinase (TK) for activity, the most common resistance mechanism is reduction or absence of HSV TK. Systemic foscarnet and cidofovir and topical treatments (cidofovir, trifluridine, and imiquimod), which do not rely on viral TK for activity, have been used in this setting.[151,160]

Varicella-Zoster Virus

VZV is spread through direct contact with skin lesions or through airborne spread from respiratory droplets.[161] Primary infection results in acute varicella or chickenpox. In the past, greater than 90% of adults in the United States were reported to have acquired chickenpox during childhood, although, in the current era children are administered a live vaccine. After primary infection, VZV remains latent for life in cranial nerves and dorsal root ganglia and can reactivate decades later as herpes zoster (shingles).[162]

Herpes zoster is reported in 7% to 18% of patients. Fig. 308.4 depicts the cumulative incidence of herpes zoster in a cohort of transplant

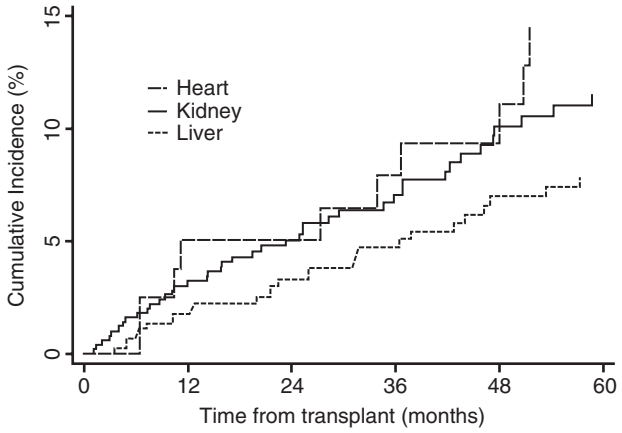

FIG. 308.4 Cumulative incidence of herpes zoster in a cohort of transplant recipients from 1996–2007 by organ type.

recipients from 1996–2007 by organ type. Induction therapy with T-cell antibodies has been a predictor for the development of herpes zoster. The majority of individuals, even those with no history of varicella, will be seropositive.[163] Regardless, all patients should undergo serologic testing to document prior exposure to VZV during their pretransplantation evaluation process. Many patients who are VZV seropositive are already receiving primary prophylaxis for CMV or HSV. In those who are both CMV and HSV seronegative but VZV seropositive, it is reasonable to administer short-term prophylactic antivirals.[161] A recent study showed that, unlike the case with HSV, the use of a preemptive approach for CMV was not associated with an increased risk of VZV infections.[158]

VZV-seronegative transplant patients are at risk for acute varicella, which can lead to extensive cutaneous involvement and visceral dissemination, including pneumonia, hepatitis, encephalitis, and disseminated intravascular coagulopathy.[164] Herpes zoster, which usually manifests as a painful vesicular dermatomal rash, may present atypically in SOT recipients, with multidermatomal rashes, multiorgan involvement, invasive complications, and even without a rash (so-called "zoster sine herpete"), highlighting the need for appropriate diagnostic testing, such as DFA of scrapings of skin lesions, PCR, and culture.[161,165,166] Herpes zoster ophthalmicus (trigeminal ganglion), Ramsay Hunt syndrome (geniculate ganglion), and VZV encephalitis have all been described in SOT.

Immunocompromised patients with primary varicella should be treated with IV acyclovir,[161] followed by a switch to an oral equivalent. Localized uncomplicated dermatomal zoster can be treated with oral antivirals for 7 days or until lesions are crusted. More severe manifestations of herpes zoster are treated with IV acyclovir, including VZV encephalitis, herpes zoster ophthalmicus, and Ramsay Hunt syndrome.

VZV seronegative patients who are exposed to persons with primary varicella or herpes zoster should receive secondary prophylaxis with varicella zoster immunoglobulin (VariZIG [SAOL Therapeutics, Roswell, GA], which was FDA approved in 2012) or, if VariZIG is not available, acyclovir or nonspecific IVIG within 10 days of exposure. They should be placed in isolation between days 10 and 21 postexposure (the incubation period of VZV), or 28 days if VariZIG is given.[161] All immunocompromised patients with any form of VZV infection, including those with localized dermatomal zoster, should be placed on airborne and contact precautions until all lesions have crusted.[167] Patients with localized lesions should be instructed to cover them.

Vaccination of household contacts is an important part of preventing VZV infections in SOT recipients.[161] In addition, transplantation patients should be isolated from vaccinated contacts who develop varicella-like rash because vaccine-associated rashes can result in transmission.[168] Because the VZV vaccine is a live-attenuated vaccine, it is generally contraindicated in organ transplant recipients and should be given pretransplantation in patients who meet criteria.[167] A study of a recombinant VZV vaccine in HSCT recipients[169] documented that the vaccine was immunogenic in patients who were ineligible for live-attenuated VZV vaccine.[170] In 2017 the recombinant VZV vaccine (Shingrix) was approved for use in persons older than 50 years.[171] Although administration of this vaccine to organ transplant recipients will likely be safe, there are no data on its use in these patients.

Human Herpesviruses 6 and 7

These viruses cause roseola in infants. Previously felt to be two variants of the same virus, HHV-6A and HHV-6B was recognized as two distinct viruses in 2012.[172] HHV-6B has been implicated in most primary infections in children and reactivation events after transplantation, whereas HHV-6A predominates in the lymph nodes of HIV-infected adults.[173–175] HHV-6 replication has been associated with CMV disease, aggressive hepatitis C recurrence in liver transplant recipients, other opportunistic infections (particularly invasive mycoses), acute rejection, and decreased graft survival.[176,177] Compared with HHV-6, less is known about the clinical characteristics of HHV-7 infection.[175] Specific testing for HHV-7 is mainly performed for research purposes as there have not been any clear clinical syndromes associated with HHV-7 infection in SOT.

HHV-6 infects multiple cell lines and establishes latent infection in mononuclear cells; it has also been found in normal brain tissue and CSF. In less than 1% of humans HHV-6 is chromosomally integrated and is inherited through the germline.[176] Because greater than 95% of humans are infected, disease usually represents reactivation of latent virus. However, it is possible for HHV-6 to be transmitted horizontally by donated chromosomally integrated HHV-6–positive organs.[178] Reactivation occurs relatively early, generally within the first 2 to 4 weeks after SOT.[175,179] Because ganciclovir has anti–HHV-6 activity, reported reactivation rates vary and depend on whether patients were administered CMV prophylaxis.[176]

Overall, 22% to 55% of the transplant recipients, particularly those who are not receiving antiviral prophylaxis for CMV, may develop HHV-6 infection, typically in the early posttransplantation period. Most patients with HHV-6 infection are asymptomatic, but a few may manifest as a febrile syndrome with leukopenia or rarely meningoencephalitis. Most infections due to HHV-6 are asymptomatic, and overt disease occurs in less than 1% of SOT recipients.[180] Symptoms include fever, rash, a nonspecific viral syndrome similar to CMV, hepatitis, gastroduodenitis and colitis, myelosuppression, and pneumonia and rarely meningoencephalitis. However, given the ubiquitous nature of HHV-6, detection of virus in blood and tissue does not prove disease, and these symptoms can only be attributed to HHV-6 after the exclusion of other more likely etiologies.[175]

When evaluating patients with possible HHV-6 disease, it is also important to consider the potential detection of chromosomally integrated HHV-6 in blood samples, characterized by persistent high-level HHV-6 viremia (more than a million copies/mL); this may be misinterpreted as substantial active infection, leading to unnecessary treatment.[181,182] In these cases fluorescent in situ hybridization with a specific HHV-6 probe performed on metaphase chromosome preparations from peripheral blood will demonstrate integrated HHV-6.[181] HHV-6 encephalitis presents with fever and confusion, sometimes with a rash; brain imaging shows signal intensities in the medial temporal lobes. In this setting, detection of HHV-6 in the CSF is required for diagnosis, although high levels of HHV-6 DNA can also be detected in the CSF in individuals with chromosomal integration. Testing hair follicles and nails for HHV-6 can be done to evaluate for chromosomal integration in these individuals.[183]

There are no specific FDA-approved antiviral drugs for the treatment of HHV-6 infection. Ganciclovir, cidofovir, and foscarnet have all shown efficacy against HHV-6 in vitro. HHV-7 appears to be resistant to ganciclovir.[184] Both HHV-6 and HHV-7 are resistant to acyclovir and penciclovir.[184] Routine use of antiviral prophylaxis or preemptive therapy for HHV-6, however, is not currently recommended.

Human Herpesvirus 8 (Kaposi Sarcoma Herpesvirus)

Unlike most herpesviruses, human infection with HHV-8 is not ubiquitous, and rates vastly differ by geographic region.[185] Seroprevalence is estimated to be between 0% to 5% in North America, northern Europe, and Asia; between 5% to 20% in the Mediterranean and Middle East; and greater than 50% in parts of Africa.[186] The incidence of active HHV-8

infection after SOT therefore mirrors its geographic distribution. After primary infection, HHV-8 exhibits a latent phase interrupted by lytic (viremic) reactivations.[187] HHV-8 is primarily transmitted via saliva or sexual routes but has also been transmitted via blood products. It can also be donor derived; residence in an HHV-8 endemic area and the receipt of an organ from a donor residing in an endemic region confers an increased risk for posttransplantation HHV-8–related disease.[12] Clinically apparent disease usually manifests a median of 30 months after transplantation (range, 3–124 months).[185] Even though ganciclovir is active in vitro, no association was found between the use of CMV prophylaxis and the development of HHV-8 infection.[12]

HHV-8 infects B cells, macrophages, endothelial cells ("spindle cells" of Kaposi sarcoma [KS] lesions), and epithelial cells.[188] It is the causative agent of KS, primary effusion lymphoma, and multicentric Castleman disease.[175] KS manifests as progressive, violaceous multifocal mucocutaneous lesions with potential dissemination to visceral organs, including the transplanted allograft. HHV-8 has been reported to cause nonneoplastic processes, such as fever, pancytopenia, and bone marrow failure; the hemophagocytic syndrome; and clonal gammopathy after transplantation. In addition, during its lytic phase, HHV-8 produces high levels of proinflammatory cytokines and chemokines, such as IL-6 and IL-10. This milieu can lead to potentially fatal organ damage, which has been seen in a newly described entity called Kaposi sarcoma herpesvirus-associated inflammatory cytokine syndrome (KICS), first reported in HIV but also seen in organ transplantation.[187]

A multidisciplinary approach is recommended when treating patients with HHV-8, with involvement of oncology, infectious disease, and dermatology specialists. Antivirals are of unproven efficacy, although ganciclovir, foscarnet, and cidofovir all have in vitro activity. However, the cornerstone of therapy should be reduction of immunosuppression. Switching from a calcineurin inhibitor to an mTOR inhibitor may be considered due to their antitumor responses.[189] Patients whose lesions do not regress with this approach may require intralesional chemotherapy, radiation therapy, surgery, or systemic chemotherapy, based on the extent of the disease. In a recent report a combined liver-kidney transplant recipient with severe KICS achieved remission after treatment with a variety of agents, including cidofovir, foscarnet, mTOR inhibitors, rituximab, corticosteroids, IVIG, and etoposide.[187]

Serologic screening of donors and recipients is not routinely performed due to the uncertainty of whether knowledge of these results would have any clinical implications or change management. In a recent multicenter prospective study from Italy, SOT donors and recipients underwent serologic testing for HHV-8 and were found to have seroprevalence rates of 4% and 18%, respectively.[12] After transplantation, 25% (3/12) of HHV-8 D^+/R^- recipients developed a primary infection, one of whom succumbed to a lethal nonmalignant HHV-8–related illness. Only 2.1% (2/93) of HHV-8 R^+ patients had viral replication, and only one developed KS. Although these numbers are small, pretransplantation HHV-8 risk stratification in high-prevalence areas appears to be reasonable, although additional data are required to define its role and the role of routine posttransplantation monitoring for HHV-8 viremia.[12]

Human Immunodeficiency Virus

The current era has seen reductions in acquired immunodeficiency syndrome (AIDS)-related deaths, and a near-normal life expectancy is expected for most patients who achieve a normal CD4 count and viral load suppression on antiretroviral therapy (ART).[190] Therefore about half of all deaths in people on ART in Europe and North America are caused not by AIDS and its associated opportunistic infections but, rather, by non–AIDS-defining cancers, cardiovascular and respiratory diseases, and end-stage liver and kidney failure. Organ transplantation of HIV-infected individuals has thus been steadily gaining traction since the late 1990s.[191,192]

Several studies have demonstrated acceptable short-term survival and no increased risk of HIV-related complications in kidney and liver transplant recipients,[191,193] despite the use of Thymoglobulin induction. Limited data with cardiac, lung, and pancreatic transplantation also seem to be promising.[194–196] A notable exception is liver transplant recipients with HCV coinfection, who in the pre–direct-acting antiviral (DAA) era experienced aggressive HCV recurrence, graft loss, sepsis, and death.[197–199] A surprising observation is that HIV-infected transplant recipients have a threefold higher risk of acute rejection,[191] thought to be related to interactions between protease inhibitors and calcineurin inhibitors, and immune dysregulation. However, the advent of integrase strand transfer inhibitors (which do not interact with the cytochrome P3A4 system) as part of the ART backbone has made dosing posttransplantation immunosuppression much less cumbersome and is anticipated to mitigate significant drug interactions seen with protease inhibitor–based regimens with the immunosuppressive agents.

Human Immunodeficiency Virus Screening

All transplantation candidates should undergo HIV testing, and persons with HIV should only be listed if they are virally suppressed on ART, with CD4 counts of ≥200 cells/μL.[200] Exceptions can be made for patients with liver cirrhosis, who may not be able to tolerate ART pretransplantation due to liver failure and in whom the CD4 count threshold is ≥100 cells/μL (due to splenic sequestration).[200]

Human Immunodeficiency Virus–to–Human Immunodeficiency Virus Transplantation

Growing disparity between the number of patients wait-listed for organ transplantation and organs available disproportionately affects persons with HIV,[190] and it has been estimated using HIV-infected deceased donors would expand the donor pool by an additional 360 to 600 donors annually in the United States.[201,202] HIV-to-HIV kidney and, to a lesser extent, liver transplants have already been performed in South Africa, Switzerland, and the United Kingdom.[203–205] In the South African trial, HIV-to-HIV deceased donor kidney transplantations were performed on 27 patients, all of whom were virally suppressed on first-line ART, with a median CD4 count of 288 cells/mm^3.[203] One-, 3-, and 5-year graft and patient survival rates were similar to those of HIV-negative transplant recipients at the same institution during the same time period, and there were no cases of AIDS-defining opportunistic infections despite the use of Thymoglobulin. In the United States the use of HIV-infected donors was made illegal in 1988, but in 2013 President Barack Obama introduced the HIV Organ Policy Equity (HOPE) Act, which aimed at legalizing HIV-to-HIV organ transplantation.[190] Currently, HIV-to-HIV kidney and liver transplantations are being performed in the United States but under clinical trial protocols only.[206–208] As data from these trials emerge, they are expected to shed light on the safety of HIV-to-HIV organ transplantation compared with the use of HIV-negative donors, on the natural history of superinfection with donor-derived virus (including resistant viruses), and on the implications of this practice on HIV viral reservoirs and cure. If the results of these trials are promising, HIV-to-HIV organ transplantation might ultimately be performed outside the research setting.

RNA Respiratory Viruses

Respiratory viral infections received little mention in early reports of infections after organ transplantation but are now recognized to be important pathogens. Influenza continues to cause significant morbidity and mortality in transplant recipients. RSV, PIV, MPV, coronavirus, and rhinovirus are an important cause of upper and lower tract infection in organ transplant recipients. The overall impact of respiratory viruses appears to be significantly greater in lung compared with other organ transplant recipients.

Recent guidelines on diagnosis and management have been published elsewhere.[209] All transplant recipients and candidates, as well as their household contacts, should receive the influenza vaccine.[210] Although its efficacy is not absolute, a recent study in nontransplant recipients showed that influenza vaccination during the 2013–14 influenza season attenuated adverse outcome among adults who were hospitalized with laboratory-confirmed influenza.[211] There is currently no effective treatment for RSV, PIV, human MPV (hMPV), rhinovirus, or coronavirus.[209] Ribavirin, IVIG, and steroids have all been studied for the treatment of RSV, PIV, and hMPV, with mixed results. Aerosolized ribavirin is expensive, teratogenic, and requires special precautions for administration and is therefore used less commonly than oral ribavirin. Observational studies showed no significant differences in 6-month

outcomes between those treated with either oral or inhaled ribavirin therapy for RSV infection after lung transplantation.[212] Palivizumab is an anti-RSV monoclonal antibody that is indicated for RSV prevention in children but has not been studied in transplant recipients. Initial studies using experimental agents, such as ALN-RSV01 for the treatment of RSV in lung transplant recipients and of DAS181 for the treatment of PIV in immunocompromised hosts, have been completed; however,[213,214] the status of definitive studies is uncertain at present. Trials evaluating the efficacy of RSV-specific antiviral agents and vaccines are underway.

Polyomaviruses

BK virus and JCV are the two most important polyomaviruses. Polyomavirus infection of the urinary tract was first described in a renal transplant recipient almost 40 years ago, and subsequent studies have shown that polyomaviruses can be detected in up to 60% of renal transplant patients.[215] For more than two decades after the discovery of these viruses, they were occasionally associated with transient renal dysfunction or ureteral stenosis. Since the late 1990s, polyomaviruses (BK virus specifically) have emerged as important causes of nephritis/nephropathy in 1% to 8% of renal transplant recipients and leads to progressive graft dysfunction/graft failure in 10% to 50% of the cases.[216] In almost all cases the responsible polyomavirus has been BK virus. JCV and SV40 may also be associated with nephropathy, but their clinical course is less severe.

It is not known why BK nephropathy has emerged only recently. The usual explanation is the introduction of new, potent immunosuppressive medications. However, other nonrenal transplant patients receiving similar immunosuppression rarely develop BK virus nephropathy, indicating that factors other than immunosuppression that are unique to the renal allograft are relevant. BK virus infection can develop either via primary infection (community- or donor-transmitted) or reactivated infection, particularly because the majority of adults are seropositive. Allograft rejection (and resulting treatment) may be an important predisposing factor. Patients with polyomavirus nephropathy typically do not have fever or other symptoms of infection and present with only a rising serum creatinine.[215]

BK virus primarily infects renal tubular cells producing intranuclear "ground-glass" inclusions accompanied by an interstitial nephritis (Fig. 308.5). Polyomaviruses may be detected in the urine by a variety of techniques, including culture, cytology, electron microscopy, and PCR; however, they are limited by low specificity for nephropathy. The specificity of PCR diagnosis can be enhanced by quantitation of BK virus in blood, with higher viral loads having greater specificity for nephropathy.[216] Although noninvasive assays play an important role, biopsy remains useful for definitive diagnosis, staging of disease (with implications for prognosis), and for identifying concomitant processes (rejection, etc.).[215] Natural history studies in kidney transplant recipients have shown a predictable pattern of progression of BK virus infection: initial detection of BK virus in urine, then in blood, then progression to BK virus nephropathy, typically over the course of months.

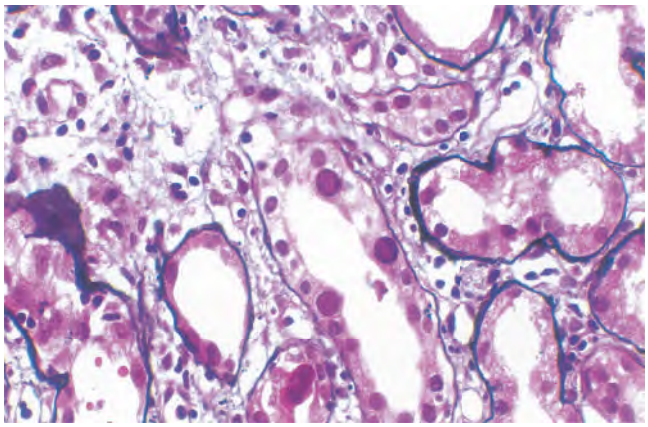

FIG. 308.5 BK virus primarily infects renal tubular cells producing intranuclear "ground-glass" inclusions accompanied by an interstitial nephritis.

Progressive multifocal leukoencephalopathy (PML) occurs in patients with impairment of T-cell immunity and is caused by JCV. Unlike the situation in AIDS, in which PML occurs in 4% to 5% of patients with very low CD4 counts, PML is rare after transplantation. Recent case reports and case series in organ transplant recipients have shown that a spectrum of disease due to JCV exists, including JCV granule cell neuronopathy, JCV encephalopathy, and JCV meningitis.[217] A brain biopsy is required for a definitive diagnosis, but the diagnosis is strongly suggested by the finding of characteristic white matter changes on MRI and detection of JCV DNA by PCR in the CSF.

A novel polyomavirus called human polyomavirus 7 (HPyV7) was recently described.[221] It caused pruritic, brown papules in transplant recipients, who also had HPyV7 viremia. Diagnosis was initially delayed due to cross reactivity with JC and BK proteins but was eventually made using PCR. These findings support the use of molecular biologic technologies in the search for infectious causes of idiopathic diseases having a suspected viral etiology.

BK virus to date has no effective therapy except for reduction in immunosuppression.[218] Once histologically evident disease has developed, reduction in immunosuppression may improve or stabilize renal function, but 10% to 0% of the patients still progress to kidney failure. Antiviral agents such as cidofovir and leflunomide, fluoroquinolones, or IVIG have been reported to be useful therapies in anecdotal reports, but definitive evidence that these agents are effective is lacking.[215] Although universally fatal with no known treatment, a lung transplant recipient with JCV encephalopathy had stabilization of her cognitive deficits with reduction of immunosuppression and initiation of mirtazapine, which is thought to exert anti-JCV activity by blocking its entry.[217] Other studies have shown a role of reduction in immunosuppression.[219] Although intriguing, the use of mirtazapine and other potential anti-JCV agents remains experimental, and immune reconstitution remains the cornerstone of therapy. In patients with non–life-sustaining organ transplants (i.e., kidney transplant recipients), complete cessation of immunosuppression should be strongly considered; this should be done slowly, to avoid precipitating severe acute graft rejection and PML-IRIS, which can be dramatic. A clinical trial of adoptive T-cell immunotherapy for PML is underway.[220]

Adenovirus

Adenovirus causes a wide spectrum of disease in transplant recipients, from asymptomatic replication to hematuria in kidney transplant recipients, to a severe disseminated form with multiorgan failure.[221] Unfortunately, the only available drug with in vitro activity is cidofovir, which can lead to unacceptable nephrotoxicity. Brincidofovir is a lipid-linked conjugate of cidofovir that has oral bioavailability and lacks nephrotoxicity. A randomized placebo-controlled phase II trial that evaluated brincidofovir for the prevention of adenovirus disease in pediatric and adult allogeneic HSCT recipients with asymptomatic viremia appears promising. [222] There is currently an expanded access protocol to provide brincidofovir for the treatment of serious adenovirus infection and disease.[223] Adoptive immunotherapy has been used in HSCT recipients, but data in organ transplant recipients are lacking.

Parvovirus B19

Parvovirus B19 is a small, nonenveloped, ubiquitous virus that is readily transmitted among children and susceptible adults through the respiratory route. Many persons are infected during childhood, and seropositivity rates among adults are ≈60%.[224] Once infected with parvovirus B19, immunocompetent individuals are considered immune. However, reinfection or reactivation can occur, presumably in context of immunosuppression.[225] Transplant recipients are infected via droplet inhalation, blood-products transfusion, and allograft tissue.[225] Nosocomial outbreaks in transplantation units have been reported. Parvovirus B19 infection can occur years after transplantation. However, ≈two-thirds of the transplant recipients with parvovirus B19 infection present within the first 3 months after transplantation.[225] The low rate of infection among transplant recipients does not support routine determination of parvovirus B19 serostatus in transplant recipients or donors. When infection

is suspected or confirmed in hospitalized transplant recipients, standard and droplet precautions should be implemented to avoid nosocomial transmission.

Hypoproliferative anemia is a consistent manifestation; however, leukopenia and thrombocytopenia can also occur.[226] Fever is present in ≈25% of the patients. Arthralgia and, less commonly, rash may occur. Approximately 10% of the patients may develop tissue-invasive disease, such as hepatitis, myocarditis, pneumonitis, collapsing glomerulopathy, encephalitis, or vasculitis.[225]

Parvovirus B19 serology is not reliable due to inadequate or delayed humoral response to infection. Molecular assays are the preferred diagnostic tools. Parvovirus B19 DNA can be detected in specimens such as blood, bone marrow, and tissue from infected organs. The detection of parvovirus B19 DNA in transplant recipients should be interpreted, however, with caution as it can be detected in the serum and tissue samples even from asymptomatic individuals long after the initial infection. However, the detection of viral DNA in transplant recipients in presence of clinical findings is suggestive of active infection. The examination of bone marrow and immune histochemical staining or in situ hybridization could be helpful in establishing the diagnosis; typical bone marrow findings include hypercellularity, presence of giant pronormoblasts, and absence of late normoblasts.

Specific antiviral agents to treat parvovirus B19 infection are not available. IVIG is frequently used in symptomatic patients; however, spontaneous resolution of the infection without receiving IVIG can occur. Despite therapy, up to 30% of the transplant recipients may experience relapse.[225] Such cases can be successfully treated with additional courses of IVIG.[225]

Zika Virus

Zika virus is a mosquito-borne flavivirus that emerged in the Americas on Easter Island, Chile in 2014 and in northeast Brazil in 2015, and it causes Guillain-Barré syndrome and congenital microcephaly.[227] Its spread throughout South America in 2015 led to an aggressive public health response and the establishment of a national surveillance system and laboratory testing.[228] Reports of sexual and blood transmission have intensified apprehension about infection spread.[229] In a small case series in transplant recipients, Zika virus infection occurred with abnormal graft function, thrombocytopenia, and bacterial superinfection.[230] Although negative testing of individual blood donations provides some reassurance of safety, little is known about the persistence of Zika virus in organs and tissues.[231] Cases of corneal transplantation from Zika-infected donors have been reported, with no untoward events in the recipient.[232] Recent guidance statements about the management of potential Zika-positive donors have been published.[229] It is reasonable to accept donors who have been to areas with Zika transmission after discussing the risks and benefits with the recipient. However, until additional data are available, organs from donors residing in a Zika-endemic region, who had symptoms suggestive of Zika virus infection, should not be used unless symptoms can be attributed to another etiology that does not preclude transplantation. Because up to 80% of infections can be asymptomatic and adequate serology for the virus is still in development, making definitive recommendations for asymptomatic living donors residing in Zika-affected areas is challenging. Potential living donors should be counseled on measures to avoid mosquito bites and only practice protected sex until donation.

Norovirus

Norovirus is one of the most common causes of enteritis worldwide, resulting in acute-onset and short-lived diarrhea in the immunocompetent host. Norovirus infection has only recently been identified as a cause of protracted diarrhea in transplant recipients that can last for months and may be associated with severe wasting, debilitation, and sometimes mortality. In addition, due to lack of awareness among clinicians, norovirus testing may not be sent, resulting in unnecessary invasive procedures, such as colonoscopies. In a recent study 16% (31/193) of transplant recipients who presented with diarrhea tested positive for norovirus by PCR.[85] Other common features included nausea/vomiting (58%), abdominal pain (52%), and wasting (35%). Acute kidney injury occurred in 23% and persisted in 21% after 6 months. Median duration of diarrheal symptoms was 4 months (range, <1–20), and 11 of 31 (35.4%) patients had relapses after improvement. Wasting, incompatible kidney transplant status, the receipt of Thymoglobulin for induction, and plasmapheresis were associated with longer diarrhea durations. There is no proven treatment for norovirus, although nitazoxanide, reduction in immunosuppression, and IV or enteral immunoglobulin have all been given. Prospective studies are needed to define the optimal therapeutic intervention, if any, for this virus.

Hepatitis Viruses

Hepatitis A Virus

Hepatitis A virus (HAV) is largely transmitted person-to-person by the fecal-oral route or consumption of contaminated food or water. Disease is usually self-limited but can be fulminant, especially with increasing age or underlying liver disease. All liver transplant candidates and nonliver organ transplant candidates with chronic liver disease or other known risk factors for HAV should be tested for anti-HAV immunoglobulin G and vaccinated if seronegative, preferably before transplantation. Those who are also hepatitis B nonimmune should receive the combined HAV/HBV vaccine. Last, patients with fulminant hepatic failure due to acute HAV should be assessed for liver transplantation.[233]

Hepatitis B Virus

With the introduction of routine childhood vaccination programs in many countries, the incidence of HBV has been decreasing globally. However, HBV infection remains an important etiology of acute and chronic liver disease requiring liver transplantation. The prevalence of chronic HBV infection is also higher in patients with end-stage renal disease than in the general population. It is estimated that approximately 2% to 9% of organ donors in the United States are anti-HBc^+ and can potentially transmit HBV to recipients, with the risk being determined by host (presence of viremia, type of organ transplanted) and recipient factors (HBV serostatus, intensity/type of immunosuppression). Immunosuppression is a major risk factor for progression of HBV infection, and all organ transplant candidates should be routinely assessed for HBV infection and vaccinated if susceptible.

Liver Transplant Candidates and Recipients

Historically, in the absence of specific preventive strategies, liver transplant candidates with chronic HBV infection routinely reinfected their allografts, leading to poor outcomes due to recurrent HBV infection. Reinfection rates after transplantation have been lower and outcomes better in patients with fulminant hepatitis B infection and in those with hepatitis D coinfection, but these represent only a minority of the patients with HBV infection. A unique and particularly aggressive syndrome of recurrent HBV infection observed in 12% to 20% of liver transplant recipients with HBV recurrence is fibrosing cholestatic hepatitis, characterized by marked cholestasis and hypoprothrombinemia but only modest increases in serum aminotransferases. Fibrosing cholestatic hepatitis is more likely to occur in patients with pretransplant HBV replication and results in rapid death in almost all cases. A paucity of inflammatory response in this syndrome suggests that the virus may be directly cytopathic. The incidence of this complication has decreased with more effective strategies to prevent HBV reinfection of the liver allograft.

In the current era the outcome for patients at risk for recurrent HBV infection after liver transplantation has been greatly improved by the use of preventive strategies and the development of quantitative molecular assays to measure the hepatitis B viral load in the blood. Historically, before the availability of antiviral agents for hepatitis B surface antigen–positive ($HBsAg^+$) patients undergoing liver transplantation, HBV hyperimmune globulin (HBIG) was used intraoperatively and postoperatively to prevent reinfection of the allograft but was limited by logistic considerations (need for IV therapy) and substantial cost. With the development of effective and generally well-tolerated antiviral agents for HBV, there has been a shift from lifelong HBIG alone to combination therapy with an initial period of HBIG followed by indefinite antiviral therapy. Among antiviral agents, monotherapy with lamivudine is generally not recommended because of the reappearance of HBsAg

after liver transplantation in 32% to 50% of patients after several years, related to emergence of resistance. Newer antiviral agents, including tenofovir formulations and entecavir, appear to be more potent and have higher barriers to resistance than lamivudine. HBV viral loads are routinely monitored after transplantation to detect breakthrough infection before clinical consequences develop.

Transplantation candidates who have chronic active HBV infection and those who are inactive HBsAg carriers should initiate antiviral therapy for HBV at the time of transplantation and have therapy continued after transplantation. Reduction of HBV DNA to low or undetectable levels before transplantation reduces the rates of post-transplantation recurrence. IFN therapy is no longer routinely used because of its relatively lower efficacy and tolerability compared with antiviral agents.

Livers from anti-HBc$^+$ liver donors are routinely used for transplantation at many centers after appropriate counseling and consent of intended recipients. The approximate estimated risk for HBV transmission from an anti-HBc$^+$ donor is significantly influenced by recipient HBV serostatus: 4% (naturally immune, anti-HBc$^+$/anti-HBs$^+$), 14% (isolated anti-HBc$^+$), 15% (vaccine immune, anti-HBs$^+$), and 58% (nonimmune with all HBV markers negative).[234] Posttransplantation preventive strategies in the recipient are tailored accordingly, with monitoring for HBV infection.

Nonliver Organ Transplant Candidates and Recipients

The presence of chronic HBV infection also adversely influences long-term outcomes after kidney transplantation, but there are fewer studies in other nonliver, nonkidney organ transplant populations.[235] Cirrhosis and hepatocellular carcinoma contribute to the higher death rate in kidney transplant recipients with pretransplantation chronic HBV infection.[235] This finding underscores the importance of carefully evaluating hepatitis serology and liver function in patients presenting as candidates for transplantation. All HBV-uninfected candidates should receive HBV vaccine pretransplantation as early as possible in the course of their illness, although the response to vaccine might be suboptimal due to underlying disease. Because immune suppression posttransplantation significantly increases the risk for HBV progression, all HBsAg$^+$ patients are generally recommended to initiate (or continue) antiviral therapy at the time of and after transplantation, including those who might not have met criteria for initiation of HBV therapy before transplantation.

The overall risk of HBV acquisition from an HBV anti-HBc$^+$ (HBsAg$^-$ donor for a nonliver organ is generally estimated to be low [up to 5%]) and is lower in recipients with prior vaccine (anti-HBs$^+$) or natural (anti-HBc$^+$) immunity, and from donors without HBV viremia. The use of organs from such donors is considered acceptable, after appropriate counseling and consent and with appropriate posttransplantation monitoring, according to current guidelines.[233,234]

Hepatitis C Virus

There has been a substantial evolution in the approach to HCV infection in organ transplantation with the advent of several highly effective and generally well-tolerated antiviral regimens. Historically, HCV infection has been prevalent in all transplant groups but highest among liver and kidney transplant recipients. A small number (4%–7%) of HCV-infected transplant recipients (of all organ types) developed progressive fatal cholestatic liver disease during the first year after transplantation. These cases are marked by a high viral load, and liver biopsies show severe hepatocyte dropout with minimal parenchymal inflammation. The long-term outcome of other HCV-infected patients depended to some extent on the organ transplanted. Liver transplant candidates who had HCV viremia before transplantation nearly universally reinfected their liver grafts after transplantation, and 46% to 97% developed clinically significant hepatitis during the first 2 to 3 years after transplantation. Ongoing HCV infection led to graft cirrhosis in up to 30% of patients by 5 years after transplantation. Findings from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) liver transplantation database showed that long-term outcomes (>5 years) after liver transplantation for HCV were similar to those after liver transplantation for other indications.[236] However, a retrospective analysis of more than 10,000 liver recipients in the UNOS database showed that medium-term survival of HCV-infected patients was inferior to that of uninfected patients. Longitudinal studies in kidney transplant populations showed that chronic HCV infection had an adverse impact on survival, but this effect was not clearly discernible until the second decade after transplantation. Excess deaths were due not only to the direct effects of liver disease but also to a higher rate of sepsis.

Several factors were shown to predict the progression of liver disease due to HCV after transplantation. In liver transplant recipients these include the degree of immunosuppression, use of antirejection therapy, high viral loads before or early after transplantation, older donor age, CMV infection, and, in some studies, infection with HCV type 1b. Although the choice of a calcineurin inhibitor and use of mycophenolate mofetil have not been conclusively shown to have an effect on HCV recurrence rates, higher cumulative exposure to corticosteroids was associated with increased mortality and more severe histologic recurrence of HCV.

Historically, the use of combination therapy with long-acting pegylated IFNs and ribavirin led to sustained virologic response rates of 26% to 50% but was associated with significant toxicities, and there was controversy regarding indications for treatment.[237] With the availability of several new classes of potent antiviral agents with pangenotypic activity (protease inhibitors, RNA polymerase inhibitors, NS5A inhibitors), the indications for initiating therapy are evolving rapidly, and the majority of HCV-infected patients are now recommended to be treated.[238] Preliminary studies have shown efficacy rates greater than 90% (comparable to nontransplantation) with various treatment regimens in the posttransplantation setting.[238] However, important drug interactions, certain toxicities, dosing of some regimens in patients with renal dysfunction, risk for HBV reactivation in coinfected patients, and high cost are challenges with the new regimens. The availability of generally safe and effective HCV regimens has raised important issues with regard to the optimal timing of therapy for HCV-infected transplantation candidates. For example, deferral of HCV treatment until after transplantation might allow receipt of an organ from an HCV-infected donor, with subsequent treatment of recipient/donor HCV after transplantation, thereby potentially decreasing wait-time on the transplant list. This approach has to carefully consider the increased complexity of the medical regimen posttransplantation, risk for drug interactions and toxicities, and the anticipated wait-times for an individual patient. Another approach made feasible with newer HCV therapies is the transplantation of an organ from an HCV viremic donor into an HCV noninfected recipient, with early initiation of therapy in the recipient posttransplantation. Initial pilot studies have shown the feasibility and preliminary efficacy of this approach that could expand the pool of donors to include HCV-viremic donors.[239]

HIV and HCV-coinfected liver transplant recipients warrant special mention. Based on data from the pre-DAA era, HIV/HCV-coinfected patients experience more aggressive recurrence of HCV, rejection, sepsis, graft loss, and death compared with those with HIV or HCV monoinfection.[198] Fibrosing cholestatic hepatitis also disproportionately affects HIV/HCV-coinfected liver transplant recipients. These poor outcomes have been linked to low body mass index, the need for combined liver and kidney transplant, and the use of older and HCV-seropositive donors. Potential solutions should include early referral for transplantation, optimization of peritransplantation management, improving immunosuppression to mitigate the risk of rejection, and most important, early initiation of DAAs for HCV infection, although the optimal timing (before or after transplantation) remains to be determined.

Hepatitis E Virus

Hepatitis E virus (HEV) comprises multiple genotypes and is endemic in many regions of the world. The virus is a small, nonenveloped RNA virus that is transmitted by the fecal-oral route and was previously thought to cause only an acute hepatitis. However, progression to chronic hepatitis may occur in up to 50% of organ transplant recipients.[240] Available evidence suggests that the most important mechanism is primary infection posttransplantation rather than donor-transmitted infection or reactivation of pretransplantation infection. Diagnosis is