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313 Infections in Solid-Organ Transplant Recipients

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SHORT VIEW SUMMARY

Epidemiology

- Infections in organ transplant recipients typically represent opportunistic infections, reactivation of latent organisms, and complications related to surgery, health care–associated infections, or both. Infections may also be donor derived.
- Advances in medical practices and preventive strategies have modified the risks and timeline of many infections in the current era.

Types of Infections

- Bacterial infections are the most frequently occurring infections. Bacteremia occurs in 5% to 25% of transplant recipients.
- Fungal infections occur in 0.7% to 23% of patients. A majority of these are due to *Candida* or *Aspergillus* spp., with *Cryptococcus,* endemic mycoses, and other non-*Aspergillus* molds accounting for most of the others.
- Cytomegalovirus (CMV) is a major viral infection. In the era of routine antiviral prophylaxis, CMV disease typically occurs in the late post-transplant period. Other herpes viruses (herpes simplex virus, varicella-zoster virus, Epstein-Barr virus, human herpesvirus 6) are also seen with greater frequency and severity in transplant patients.
- Influenza and other respiratory viruses are a major cause of morbidity and mortality, especially in lung transplant recipients.
- BK virus nephropathy has emerged as an important cause of allograft dysfunction and loss in kidney transplant patients.

Management

- As a general principle, serologic assays, although valuable in the assessment of past exposure, are not reliable for the diagnosis of acute infections.
- Quantitative molecular assays have proved to be valuable tools for diagnosis, guiding preemptive therapy, and monitoring response to treatment for several viral pathogens (CMV, BK virus).
- Prophylaxis against *Pneumocystis* and *Toxoplasma* (heart transplant recipients) is considered standard. Preventive approaches are also routinely used for CMV, BK virus, fungal infections, and herpes simplex virus in selected transplant patients, based on risk factors.
- Evaluation should take into consideration the time elapsed since transplant, exposures, receipt of prior antimicrobial prophylactic agents, graft function, and the overall immunosuppressive state of the transplant recipient.

Advances in surgical techniques and immunosuppressive regimens have been pivotal factors 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 quasi-experimental procedure to an established and accepted modality of treatment for a variety of end-organ diseases. Table 313-1 depicts the most recent data on graft and patient survival released by the United Network for Organ Sharing (UNOS).[1] The best results are for living-related kidney transplantation; approximately 99% of the recipients are alive and 96% have a functioning allograft 1 year after transplantation. The greatest progress may have been in liver transplantation, in which the 1-year survival rate before the use of cyclosporine was only 32% compared with the current survival rate of 89%. The survival rates for lung, heart-lung, and intestinal transplant recipients have lagged behind the other groups, but these procedures were only introduced in the 1980s, and experience has been gained slowly because of the limited number of operations performed. Currently, fewer than 150 intestinal transplants are performed annually in the United States; however, 1-year patient survival rates at high-volume experienced centers currently approach 90%.

Improvements in graft and patient survival have been paralleled by a decline in mortality from infections (Fig. 313-1). The most recent 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 transplants (see Fig. 313-1). Nevertheless, infections still account for 13% to 16% of the deaths in kidney and heart transplant recipients and up to 21% in lung transplant recipients (Table 313-2). In liver transplant recipients, approximately 50% of the mortality within the first post-transplant year was infection associated.[2]

Although calcineurin inhibitors have been 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.[3] These concerns have spawned a growing interest in new regimens that enhance immunologic tolerance (e.g., interleukin-2 [IL-2] receptor inhibitors [basiliximab] and T cell–depleting antibodies [alemtuzumab or thymoglobulin]). T cell–depleting agents increase the risk of cytomegalovirus (CMV) infection. Use of these agents as antirejection but not induction therapy also confers a higher risk of fungal infections.

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. Thus, infections in transplant recipients must be evaluated in the context of time since transplant. Evolving medical practices and preventive strategies have modified the risk and timeline of many infections as discussed later.

Infections during the First 30 Days

Infections during this period are primarily surgical or technical complications related to transplantation or are health care associated. Bacterial infections, including those due to antimicrobial-resistant pathogens, are by far the most frequently occurring infections; vascular-catheter infections, health care–associated pneumonia, *Clostridium difficile* colitis, and surgical-site infections are the most common types. In the absence of antifungal prophylaxis, candidiasis and aspergillosis typically occur in the first month after transplantation. Except for the reactivation of herpes simplex virus (HSV), viral infections are not commonly encountered very early after transplant. Certain donor-transmitted infections (discussed later) may also manifest during this period.

Infections between 30 and 180 Days

Although nosocomial infections continue to pose a threat in patients requiring prolonged hospitalization, surgical infections decline in importance after 1 month and typical opportunistic infections associated with the immunosuppressed state emerge. These include *Pneumocystis jirovecii,* fungi, *Toxoplasma gondii, Nocardia,* and most

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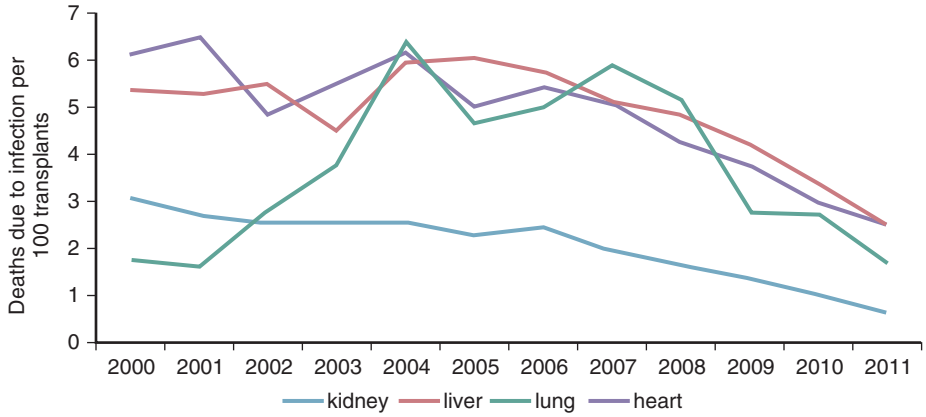

FIGURE 313-1 Deaths due to infections in organ transplant recipients since 2000 stratified by type of transplant. Primary and secondary causes of death are combined in the figure. *(Data from Organ Procurement and Transplantation Network database as of November 9, 2012.)*

TABLE 313-1 Overall Graft and Patient Survival Rates by Organ Transplant

TYPE OF TRANSPLANT	NUMBER OF TRANSPLANTS	GRAFT SURVIVAL (%) (1 YEAR)	PATIENT SURVIVAL (%) (1 YEAR)
Kidney (living donor)	5770	96.5	98.7
Kidney (deceased donor)	11,043	91.4	95.9
Kidney-pancreas	795	86.2/93.2*	96.6
Heart	2322	88.4	88.9
Liver (deceased donor)	6392	85.5	89.3
Intestine	129	74.8	78.4
Lung	1822	80.0	82.3
Heart-lung	27	89.8	90.3

*In the kidney-pancreas recipients, pancreas and kidney graft survival rates are 86.2% and 93.2%, respectively.
Modified from the 2009 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 2007. *Rockville, MD: Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation; 2009.*

TABLE 313-2 Leading Causes of Death in Organ Transplant Recipients 10 Years after Transplantation

	PERCENTAGE OF DEATHS DUE TO:				
TYPE OF TRANSPLANT	Vascular Events*	Infection	Malignancy	Graft Failure	Other
Kidney	22.4	15.4	8	—	—
Liver	12.5	15.5	11.8	—	11.3†
Heart	20	13	7.4	16.7	9.3†
Lung	9.4	21.4	—	20.5	18.4†

*These include cardiovascular and cerebrovascular events.
†Other causes of death are multiorgan failure in liver and heart transplant recipients and pulmonary diseases (acute respiratory distress syndrome, bronchiolitis obliterans, embolism, and pulmonary hypertension) in lung transplant recipients.
Data from Organ Procurement and Transplantation Network database as of November 9, 2012.

importantly, CMV. Historically, CMV infection and disease have occurred between 4 and 6 weeks after transplant. However, in the era of routine use of antiviral prophylaxis (typically given for 3 to 6 months after transplant), 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 after transplant. Notably, in lung transplant recipients *Aspergillus* infections now occur after 12 months; the median time to onset after transplant was 357 days in one report[4] and 33 ± 19.6 months in another.[5] Widespread use of mold-active antifungal prophylaxis and chronic rejection or its treatment, or both, likely account for these trends.

Infections Occurring 6 Months or Later

Infections more than 6 months after transplantation have been 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 3.5/1000 transplant-days in the first 6 months to 0.4/1000 transplant-days in the late period, the etiology of infections and infection-related mortality was similar in the two periods.[6] 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).[6]

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, with warts (verruca vulgaris) the most frequent infection. Also, some lymphomas and lymphoproliferative syndromes related to Epstein-Barr virus (EBV) occur after 1 year. Finally, although the risk for classic opportunistic infections declines, it never disappears completely. Infections due to mycoses such as cryptococcosis or histoplasmosis often manifest late and without an apparent inciting event or change in immunosuppression.

TABLE 313-3 Frequency, Types of Infections, and Sources of Infections Occurring in the First Year after Transplantation

TYPE OF TRANSPLANT	INFECTION EPISODES PER PATIENT	BACTEREMIA (%)	CMV DISEASE* (%)	FUNGAL INFECTIONS (%)	MOST COMMON SOURCE
Kidney	0.98	5-10	8	0.7	Urinary tract
Heart	1.36	8-11	25	8	Lung
Heart-lung	3.19	8-25	39	23	Lung
Liver	1.86	10-23	29	16	Abdomen and biliary tract

*Numbers reflect CMV disease rates in the absence of routine antiviral prophylaxis.
CMV, cytomegalovirus.
Data from references 14 and 44-49.

TYPES OF TRANSPLANTS AND CHARACTERISTICS OF INFECTIONS

Table 313-3 presents the type, severity, and characteristic sites of infections in kidney, heart, heart-lung, and liver transplant recipients observed during the first year after 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. The liver transplant group has almost twice the rate of bacteremia of the renal group. Invasive fungal infections are frequent in liver and heart-lung or lung recipients, intermediate in heart recipients, and rare in renal recipients. Table 313-3 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 will have been diagnosed with upper or lower urinary tract infection.[7] Many infections are uncomplicated cystitis, but graft pyelonephritis occurred in 13% of 1387 renal recipients over a 13-year period.[8] 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 urinary tract infection after 6 months was associated with worse long-term graft function and survival.[7] Abnormalities such as ureteral reflux, strictures at the ureterovesical junction, or neurogenic bladder should be sought in patients with recurrent infections. Administration of an extended course of antibiotics (≥4 weeks) and consideration of secondary antibiotic prophylaxis is reasonable in patients who have severe graft pyelonephritis or recurrent infections. Asymptomatic bacteriuria is common in kidney transplant recipients, and there are insufficient data for or against routine screening and treatment in this setting.

The clinician should also be alert to the occurrence of uncommon urinary pathogens. For example, urinary tract tuberculosis may arise from a focus in the native kidney. *Mycoplasma hominis* may cause a breakdown of the ureterovesical anastomosis with subsequent graft loss. Histoplasmosis may involve the transplanted kidney and cause renal failure. Adenovirus may cause hemorrhagic cystitis or nephritis, or both. BK virus is an important cause of renal allograft infection and is not typically associated with 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 opportunistic infections such as fungi, *Nocardia,* and *Pneumocystis.* More recently, these opportunistic agents have come under better control, and conventional bacterial pathogens have become relatively more common in transplant populations. Wound infections are infrequent (4% to 5%) but may be a serious problem, particularly if they involve the perinephric space. Body mass index greater than or equal to 30 kg/m^2, urinary leak, reoperation through the transplant incision, mycophenolate mofetil use, and diabetes are risk factors for infection.

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. Some suffer from chronic viral infections such as hepatitis C virus (HCV).

TABLE 313-4 Microbial Causes of Pneumonia in Transplant Recipients

Early Pneumonia (≤30 Days)
Common Causes
Gram-negative bacilli
Staphylococcus aureus
Aspiration
Less Common Causes
Aspergillus
Herpes simplex virus
Legionella
Toxoplasma gondii
Late Pneumonia (>30 Days)
Common Causes
Pneumococcus
Hemophilus influenzae
Influenza
No cause identified
Less Common Causes
Pneumocystis
Nocardia
Legionella
Aspergillus
Gram-negative bacilli
Staphylococcus aureus
Aspiration
Cytomegalovirus
Varicella zoster virus
Paramyxoviruses
Tuberculosis
Coccidioidomycosis
Histoplasmosis
Cryptococcus
Respiratory viruses*

*These include parainfluenza, respiratory syncytial virus, metapneumovirus, coronavirus, rhinovirus, and adenovirus.

Heart Transplant Recipients

The most common infections after heart transplantation are bacterial pneumonias, urinary infections, herpes virus infections, and invasive fungal infections. Pneumonia in heart transplant recipients is mostly caused by common pathogenic bacteria (Table 313-4). Although the incidence of pneumonia is highest during the first few months after transplantation, bacterial pneumonias occur sporadically in the late post-transplantation period, after the patient has recovered from the immediate effects of surgery. In a survey of 620 heart transplant

recipients at Stanford University, infections were the most common cause of death.[9]

Mediastinitis and sternal wound infections are postoperative complications unique to heart and heart-lung transplant recipients and occur in approximately 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 are thought to 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 pretransplant LVAD infection is associated with a higher rate of peri–heart transplant complications, long-term outcomes appear to be reasonable and LVAD infection is not considered a contraindication to heart transplant.[10]

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 seronegative patients and approximately 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.[9]

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) 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.

Heart recipients frequently suffer trauma to the tricuspid valve and right ventricular endocardium from repeated endomyocardial biopsies, a common post-transplantation practice. Heart transplant patients with cardiac valvulopathy are at high risk for adverse outcomes from endocarditis, and prophylaxis with dental procedures is considered to be appropriate in this group.[11] Most cases occur during the first year after transplantation and may be caused by unusual organisms such as *Aspergillus* or *Legionella* species.

Lung and Heart-Lung Transplant Recipients

Lung and heart-lung transplant recipients have infectious problems largely similar to those of heart transplant recipients, but the infections are more frequent and severe. 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's 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., cystic fibrosis, non–cystic fibrosis bronchiectasis) and are therefore at high risk for postoperative infection at the time of transplant surgery. Antimicrobial treatment directed against pretransplant colonizing bacteria is typically given for several weeks after transplant. Pretransplant colonization with certain *Burkholderia* spp. (*Burkholderia cenocepacia* in particular) has been associated with severe infection and decreased survival after transplant, and thus many transplant centers consider pretransplant *B. cenocepacia* colonization or infection to be a contraindication to lung transplantation.

Heart-lung and lung transplant recipients develop invasive pulmonary aspergillosis more frequently than patients with other types of organ transplants.[12] Risk factors have included pretransplant colonization, single lung transplant, and augmented immunosuppression for allograft rejection. 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. The airway lesions of this disease can be directly visualized during bronchoscopy. This form of aspergillosis has a better prognosis than aspergillosis invading the lung parenchyma. The predisposition of lung recipients to invasive aspergillosis has led many lung transplant centers to routinely use various targeted antifungal preventive strategies. Oral azoles and inhaled amphotericin are the most widely used agents.

In the late post-transplant period, up to two thirds of patients eventually develop obliterative bronchiolitis. This process is the main pathologic manifestation of chronic rejection of the lung. It 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 infection, as has been documented for CMV, HSV, paramyxoviruses, and adenovirus infections. Accordingly, lung transplant centers often utilize aggressive regimens for prevention of herpesvirus infections and include diagnostic tests for respiratory viruses in the workup of patients who present with acute chest infections. Community-acquired respiratory virus infections (influenza, parainfluenza, respiratory syncytial virus [RSV], metapneumovirus, coronavirus, rhinovirus, and adenovirus) are a significant cause of morbidity and have been associated with both short-term and long-term impairment of allograft infection. Other than for influenza, there are no therapies proven to improve outcomes for these other respiratory viruses.

Pulmonary nontuberculous mycobacterial infections are relatively common in lung transplant recipients and may arise from pretransplant colonizing strains or exogenous acquisition. *Mycobacterium abscessus* has been associated with severe infection after transplant, and some centers exclude patients with pretransplant *M. abscessus* infection (colonization) or disease.[13] Pretransplant colonization with other nontuberculous mycobacteria does not appear to be as closely associated with decreased survival or severe post-transplant infection, or both.

Prospective donors for lung transplantation are intubated in intensive care units. 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 intensive care unit, including methicillin-resistant *Staphylococcus aureus* and enteric gram-negative bacilli. 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.

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 as a secondary cause (see Table 313-2). Bacterial infections occur in 59% to 68% of the patients after liver transplantation. About half of these infections occur within 2 weeks after transplant. The most important sites of infection are the abdomen and biliary tract, surgical wound, lungs, and bloodstream, with or without associated catheter infection.

Liver transplant recipients have a high rate of fungal infections. The incidence has ranged from 15% to 42%, with a case-fatality rate of 25% to 82%.[14,15] 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.[16]

Candida is the predominant pathogen, causing 62% to 88% of the invasive fungal infections in this population, although it has declined in relative importance compared with *Aspergillus,* other molds, and *Cryptococcus.* Almost 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* species 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.

Invasive aspergillosis occurs in 1% to 8% of liver transplant recipients. Major risk factors for invasive aspergillosis in liver transplantation include retransplantation, fulminant hepatic failure as an indication for transplantation, renal dysfunction and hemodialysis, and poor allograft function.[12] Most *Aspergillus* infections now occur more than 90 days after transplantation, a possible consequence of improved early management and delayed occurrence of risk factors such as CMV infection. Liver transplant recipients are uniquely predisposed to disseminated aspergillosis.

Abdominal Infections in Liver Transplant Recipients

Transplantation of the liver differs from other transplant 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. Abdominal infections after liver transplantation are often related to technical aspects and complications of the operation. For example, anastomosis of the biliary duct to a Roux-en-Y loop of jejunum is associated with more intra-abdominal infections, especially invasive fungal infections, than is primary anastomosis of the donor's to the recipient's common bile duct.

Most *liver abscesses* in the transplanted liver are related to surgical problems such as biliary stricture and hepatic artery thrombosis. The organisms responsible are gram-negative enteric bacilli, enterococci, and anaerobes. The diagnosis is made by ultrasonography or computed tomography. Treatment with drainage and intravenous 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 stricture. 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 make a firm diagnosis of cholangitis because many patients do not manifest the classic Charcot's triad of fever, abdominal pain, and jaundice. The clinical presentation may resemble 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 T-tube cholangiography and endoscopic retrograde cholangiopancreatography may be followed by cholangitis and, occasionally, by bacteremia. Therefore, a single dose of a prophylactic antibiotic is recommended.

Peritonitis can accompany other intra-abdominal 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 occasionally 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. 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 directed against the responsible pathogens.

Pancreas Transplant Recipients

About 1300 pancreas transplant operations are performed in the United States annually, or approximately 1 for every 10 renal 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 urinary tract infection. However, intra-abdominal 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 because the gut harbors not only a large burden of lymphoid tissue but also cells that are the least well tolerated of any organ. Consequently, small bowel transplantation recipients are particularly susceptible to graft-versus-host disease and the managing the risk of rejection, infection, and graft-versus-host disease has proven challenging. Small bowel transplantation is often combined with a liver graft due to concurrent existence of intestinal failure-associated liver disease. Notably, 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 intestine failure–associated liver dysfunction.

More than 90% of the small bowel transplantation recipients develop significant infections, and the rates of infection are higher than in other transplant groups. Intra-abdominal pyogenic infections and bloodstream infections predominate, but the transplanted intestine,

like the lung allograft, is 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 post-transplantation period (i.e., >6 months after operation). The incidence of EBV-associated lymphoproliferative disorders approaches 10% at 5 years, and the tumors often involve the gut.

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 a surgical site infection in a transplant recipient. 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 after transplant.

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 or unusual skin lesion with a biopsy.

Infections of the Urinary Tract

Urinary tract infections are discussed earlier (see "Kidney Transplant Recipients").

Infections of the Bloodstream

Bacteremia occurs in 5% to 10% of the kidney and heart transplant recipients with higher rates (10% to 25%) in liver and lung transplant recipients (see Table 313-2). Besides catheter-related infections, pneumonia in heart and heart-lung transplant recipients, urinary tract infections and perinephric sources in renal transplant recipients, abdominal and biliary infections in liver transplant recipients, and surgical site and urinary tract infections in pancreatic transplant recipients are the most commonly identifiable sources of bacteremia. Predominant gram-negative bacteria are *Escherischia coli, Klebsiella* spp., and other Enterobacteriaceae, including extended-spectrum β-lactamase producing organisms, *Acinetobacter baumannii,* and *Pseudomonas 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 25.7/1000 person-years from 2 to 12 months after transplant.[17] Kidney recipients are more likely to develop gram-negative bacteremia 12 months after transplantation.[17]

Bacteremia due to *S. aureus* occurs with estimated rates of 15% to 38% in various organ transplant recipients.[18] The rates of methicillin-resistant *S. aureus* 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, probably due to the large size of the incision or colonization during candidacy.[18] The unadjusted 28-day all-cause mortality after gram-negative bloodstream infections in transplant recipients was 4.9%.[17] 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 it includes ascertaining the source of the bacteremia and likely pathogen. Common sites that produce bacterial bloodstream infections are the lung, urinary tract, abdomen (including the biliary tract), intravenous catheters, and soft tissues. The inability to discern a source is not rare, especially in liver transplant recipients; up to 21% of the bacteremias in liver transplant recipients have had no documented source, but most of these probably originated in the abdomen. The trend of increasing antimicrobial resistance among gram-negative bloodstream isolates may affect local decisions regarding empirical antibiotic therapy of transplant patients who present with possible bloodstream infections.

Infections of the Chest

The usual microbial causes of pneumonia in the transplant recipient are listed in Table 313-4. They are subdivided according to whether the pneumonia occurs during the first month after transplantation or later and whether the cause is common or less common. The key to the management of pulmonary infections in transplant recipients is rapid identification of the responsible pathogen and initiation of specific therapy. Patients with a brief duration of symptoms (3 days) who have a focal chest infiltrate and are producing sputum with neutrophils on Gram stain are likely to have a routine bacterial pneumonia.

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 and who have a nonproductive cough or diffuse infiltrates or nodular lesions on chest imaging are more likely to have an unusual or opportunistic pathogen, and consideration should be given to timely use of invasive diagnostic procedures, including bronchoscopy, to establish the diagnosis. Nodular infiltrates have a broad range of infectious etiologies (Table 313-5), and certain clinical and radiographic features may be helpful in discerning a specific etiology.[19] Invasive workup is also indicated for patients who are deteriorating rapidly or appear to have a conventional pneumonia but are not responding to treatment.

The frequency of *Legionella* infection varies widely, depending on its endemicity in the hospital and the sensitivity of diagnostic methods. The radiographic presentation is variable and may include focal infiltrates, nodular pleural-based lesions, lung abscess, and pleural or pericardial effusion. Legionellosis in transplant patients should be treated with a quinolone antibiotic or azithromycin. Infections caused by *Aspergillus, Nocardia,* or endemic mycoses may be relatively common in some regions. Community-acquired respiratory viruses such as

TABLE 313-5 Etiology of Pulmonary Nodules in Organ Transplant Recipients

Infectious
Bacterial
Nocardia
Mycobacteria
Legionella
Staphylococcus aureus (septic emboli)
Fungal
Aspergillus
Cryptococcus
Mucormycosis
Endemic fungi (histoplasmosis and coccidioidomycosis)
Other non-*Aspergillus* molds
Viral
Cytomegalovirus
Noninfectious
Malignancies
Post-transplantation lymphoproliferative disorder and other lymphomas
Carcinomas (typically lung neoplasms and hepatocellular carcinoma)
Nonmalignant Lesions
Rounded atelectasis

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;77:50-58.*

influenza, parainfluenza, RSV, metapneumovirus, coronavirus, rhinovirus, or adenovirus may cause pneumonia in transplant recipients. *Mycobacterium tuberculosis* is a major pulmonary pathogen, particularly in geographic areas where tuberculosis is endemic.

Abdominal and Gastrointestinal Infections

Intra-abdominal 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 transplant 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 susceptible to *Salmonella* infection, but infections caused by *Shigella or Campylobacter* do not appear to be increased in frequency. *C. difficile* colitis 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.[20] Toxic megacolon may develop in 5% to 12%, and recurrent colitis in approximately 22% of organ transplant recipients who have *C. difficile* colitis. *Helicobacter* infection has been associated with a low-grade gastric lymphoma called MALToma 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 be uncommon. Universal pretransplantation screening for *Strongyloides* is probably not cost-effective, but vigilance for this infection should be maintained for patients from endemic areas.

Hepatitis

The most important causes of hepatitis in transplant recipients are hepatitis B virus (HBV), HCV, and CMV. Less frequently, hepatitis in these patients may be caused by HSV, VZV, adenovirus, and human herpesvirus 6. Liver transplant candidates with chronic HBV infection routinely reinfect their allografts. In the 1980s, 5-year survival rate after transplantation for such patients was approximately 50%.[21] 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 in 12% to 20% of patients with HBV recurrence is fibrosing cholestatic hepatitis, characterized by marked cholestasis and hypoprothrombinemia, but only modest increases in serum transaminases. 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.

In the past, many transplant centers considered chronic hepatitis B infection to be a contraindication to liver transplantation. In the current era, the outcome for patients at risk for recurrent HBV infection after liver transplantation has been greatly improved by the availability of agents able to prevent or treat recurrence and the development of quantitative molecular assays to measure the hepatitis B viral load in the blood. The most effective approach to prevent recurrent HBV is the use of post-transplant combination therapy with antiviral agents and HBIG in addition to pretransplant antiviral therapy. Monotherapy with lamivudine is not recommended because of the reappearance of HBsAg after liver transplantation in 32% to 50% of the patients. Newer antiviral agents including adefovir dipivoxil, tenofovir, and entecavir have also been available for lamivudine-resistant HBV. Regardless of the agents used, HBV viral loads should be monitored after transplantation to detect breakthrough infection before clinical consequences develop. Antiviral therapy for HBV should be modified on persistent elevation of the viral load (>3 log copies/mL).[21]

Transplant candidates who have chronic HBV and those who are in the inactive HBsAg carrier state should initiate antiviral therapy for HBV that should be continued after transplantation. Reduction of HBV DNA to undetectable levels or at the minimum to less than 2×10^4 IU/mL before transplantation reduces the rates of post-transplant recurrence. Interferon therapy is not recommended in patients with decompensated cirrhosis because it may worsen the liver disease and is poorly tolerated.

The presence of chronic HBV infection also adversely influences long-term outcomes after kidney transplantation.[22] This is due in part to a higher rate of death from underlying cirrhosis and hepatocellular carcinoma in the HBV-infected patients.[22] This finding underscores the importance of carefully evaluating hepatitis serology and liver function in patients presenting as candidates for transplantation of organs other than the liver. All HBV uninfected liver and nonhepatic transplant candidates should receive HBV vaccine pretransplant as early as possible in the course of their illness, although the response to vaccine might be suboptimal due to underlying disease.

HCV infection occurs in all transplant groups, but the prevalence is highest among liver and kidney transplant recipients. A small number (4% to 7%) of HCV-infected transplant recipients (of all organ types) develop 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 depends to some extent on the organ transplanted. Liver transplant candidates who have HCV viremia before transplantation almost always reinfect their liver grafts after transplantation, and 46% to 97% develop hepatitis during the first 2 to 3 years after transplantation. Ongoing HCV infection leads 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 have shown that long-term outcomes (>5 years) after liver transplantation for HCV are similar to those after liver transplantation for other indications.[23] 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 have also shown that chronic HCV infection has an adverse impact on survival, but this effect is not clearly discernible until the second decade after transplantation. Excess deaths are due to not only the direct effects of liver disease but also a higher rate of sepsis.

Several factors have been shown to predict the progression of liver disease due to HCV after transplantation. In liver transplant recipients, these include the degree of immunosuppression, the 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 is associated with increased mortality and more severe histologic recurrence of HCV.

Antiviral treatment of recurrent HCV infection after liver transplantation is under active investigation. Interferon monotherapy produces end-of-treatment responses in only 12% to 36% of liver recipients with HCV infection, but very few patients have sustained responses 6 months later.[24] The use of combination therapy with long-acting pegylated interferons and ribavirin has led to sustained virologic response rates of 26% to 50%.[24] Based on these data, pegylated interferon with or without ribavirin has been the treatment of choice for histopathologically documented hepatitis C recurrence, but there are differences of opinion on optimal timing and selection of patients for treatment. In actual practice, interferon and ribavirin have side effects that make them difficult to administer to liver transplant recipients, so only a small proportion of the patients are actually able to benefit from their use. Currently, treatment is generally used only in patients with histologically significant disease (grade 3 or 4 inflammation, grade 2 to 4 fibrosis) rather than preemptively in all infected patients. With the development of several new classes of both direct-acting antivirals (protease inhibitors, RNA polymerase inhibitors, NS5A inhibitors) and host-targeted agents (cyclophilin inhibitors) that inhibit HCV replication, the indications for initiating therapy are likely to broaden and the efficacy of newer regimens is anticipated to be substantially improved compared with current pegylated interferon/ribavirin regimens.

TABLE 313-6 Selected Pathogens of the Central Nervous System in Organ Transplant Recipients

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

However, important drug interactions with current immunosuppressants will be a major challenge with the use of these agents in transplant patients. Early promising results of newer antiviral therapies will likely revolutionize or substantially alter the treatment of HCV infection in both orthotopic liver transplant candidates and recipients.

Hepatitis E virus (HEV) is composed of 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 organ transplant recipients.[25] Available evidence suggests that the most important mechanism is primary acquisition after transplant rather than donor-transmitted infection or reactivation of prior pretransplant infection. Currently, there are no proven effective preventive or therapeutic options for HEV infection, although small series reported a benefit of ribavirin with or without interferon.

Infections of the Central Nervous System

Central nervous system (CNS) infections in transplant patients require prompt diagnosis and early, appropriate therapy. Table 313-6 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.

Listeria 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 has been effective for prevention and may explain why listeriosis is observed less frequently in the current era.

Aspergillosis is an important cause of CNS infection in immunocompromised patients. The most common portal of entry is the lung; invasive sinus infection also occurs but is less common. Patients with aspergillosis typically have risk factors such as renal dysfunction or are requiring augmented immunosuppression. The type of transplant is also important: lung and liver transplant recipients are more susceptible than other transplant patients. *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 *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 post-transplantation 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.[26] Lumbar puncture should be performed in any patient with cryptococcosis, even in the absence of CNS signs. 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 patients with CNS cryptococcosis have CNS lesions due to *Cryptococcus* on neuroimaging.[26] New lesions developing after initiation of antifungal therapy may represent immune reconstitution syndrome, 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 solid-organ transplant recipients with cryptococcosis is approximately 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.

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 solid-organ transplantation 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 after transplant appears to be the 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 (50 to 75 mg/day) and sulfadiazine (4 to 6 g/day). Folinic acid (5 to 15 mg/day) is usually added to the regimen to prevent marrow suppression.

Nocardiosis may cause single or multiple brain abscesses or, less commonly, meningitis. The primary portal of infection is pulmonary with metastatic spread to bone, skin, and CNS. *Nocardia* brain abscesses may benefit from stereotactic biopsy and surgical drainage in addition to long-term (9- to 12-month) 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.

JC virus–associated progressive multifocal leukoencephalopathy and West Nile Virus are important causes of CNS infection and are discussed separately as follows.

SPECIFIC PROBLEM OF VIRAL INFECTIONS

This section covers most issues related to viral infections in transplant recipients. Hepatitis viruses were discussed earlier. The approach to antiviral prophylaxis and the pretransplantation evaluation of candidates and donors are discussed elsewhere in this book (see Chapter 311).

Human Herpesvirus 6

Human herpesvirus 6 (HHV-6) infection in transplant recipients is considered to be due to endogenous reactivation of the latent virus. Rarely, primary infections may be transmitted by the donor. 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 post-transplant period. Most patients with HHV-6 infection are asymptomatic, but it may manifest in a few as a febrile syndrome with leucopenia or rarely meningoencephalitis.

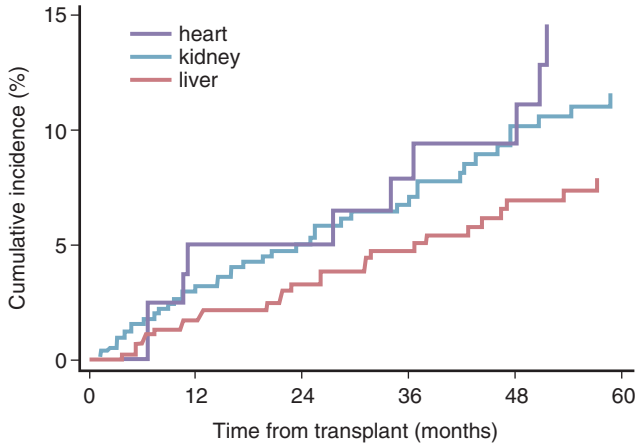

FIGURE 313-2 Cumulative incidence of herpes zoster after transplant in transplant recipients from 1996-2007 by organ type (*n* = 1077). Cumulative incidence curves were censored for patients lost to follow-up; death and retransplantation were considered competing risks. *(From Pergam SA, Forsberg CW, Boeckh MA, et al. Herpes zoster incidence in a multicenter cohort of solid organ transplant recipients.* Transpl Infect Dis. *2011;13:15-23.)*

Routine use of antiviral prophylaxis or preemptive therapy for HHV-6, however, is not currently recommended.

Herpes Simplex Virus and Varicella-Zoster Virus

HSV reactivates after transplantation in approximately 60% of recipients in the absence of antiviral prophylaxis. About half of these persons develop symptomatic oral or genital lesions. Genital herpes may become clinically evident for the first time after transplantation and can be distressing for the patient. Reactivation of HSV usually occurs during the first 1 to 2 weeks after transplantation. Visceral infection caused by HSV has been reported; most cases have been HSV hepatitis after liver transplantation or HSV pneumonia after lung transplantation. A rare event is primary HSV infection occurring early after transplantation; the donor organ may be the source. These primary HSV infections may produce a severe septic syndrome with hypotension and disseminated intravascular coagulation.

Most cases of reactivated HSV infection are easily diagnosed and respond well to antiviral therapy. Use of antiviral prophylaxis in seropositive patients prevents HSV infection; it is a reasonable approach and is preferred in patients who are at risk for visceral HSV infection, such as lung or liver transplant recipients. Low-dose acyclovir (400 mg twice daily) for the first 3 to 4 weeks after transplantation is usually sufficient.

Herpes zoster is reported in 7% to 18% of patients. Figure 313-2 depicts the cumulative incidence of herpes zoster in a cohort of transplant recipients from 1996-2007 by organ type.[27] Induction therapy with T-cell antibodies has been a predictor for the development of herpes zoster. Antiviral therapy is indicated because healing is often slow and transplant recipients occasionally develop neurologic complications or disseminated infection. Oral therapy with acyclovir, valacyclovir, or famciclovir suffices for dermatomal zoster. If the patient has ophthalmic zoster or there is evidence of dissemination, intravenous acyclovir is used initially. Primary VZV infection (chickenpox) in a transplant patient also usually requires admission to the hospital and treatment with intravenous acyclovir, although some pediatric heart transplant recipients on low doses of immunosuppression have been successfully treated for with oral valacyclovir. Obtaining serology results for VZV before transplantation identifies patients at risk for primary infection so that they can be vaccinated and counseled to avoid (and report) exposures. Varicella-seronegative transplant recipients who are exposed may benefit from the use of varicella-zoster immune globulin when given up to 10 days after exposure. However, it should be administered as soon as possible.

Cytomegalovirus

In the absence of preventive therapy, CMV infection (evidence of culturable virus or viral proteins or nucleic acid) occurs in 36% to 100% and symptomatic disease in 11% to 72% of organ transplant recipients. Primary infections occurring in seronegative recipients with a seropositive donor are more likely to be symptomatic. The proportion of infected patients who become symptomatic is also a function of the intensity of immunosuppression. The absolute viral load and change in viral load are the most important determinants of symptomatic infection (i.e., CMV disease) (see Chapter 140).[28]

The most common type of CMV disease is a mononucleosis syndrome characterized by fever with few or no focal symptoms. Abnormalities may be found on liver function tests, although jaundice rarely occurs. Tissue-invasive disease may manifest as pneumonitis, gastrointestinal disease, or hepatitis. In this era when prolonged antiviral prophylaxis is routinely used, CMV disease in organ transplant recipients is often a late manifestation, and approximately 30% of these cases have tissue-invasive disease.[29] Interstitial pneumonia is the most serious complication of CMV infection and is present in most fatal cases. Fever, dyspnea, hypoxemia, and diffuse infiltrates on chest radiographs are typical findings, but bronchoalveolar lavage (BAL) or lung biopsy is required for diagnosis. CMV pneumonia may coexist with other pathogens in the lung, particularly *Pneumocystis*.

One of the more troublesome manifestations of CMV disease is ulcerations in the gastrointestinal tract. These ulcerations are often multiple. They may be found anywhere from the esophagus to the rectum. Severe complications such as bleeding or perforation occur in some patients. CMV disease should be considered in the differential diagnosis of transplant recipients who have fever and acute or subacute abdominal symptoms, especially if transplantation occurred within the past 4 to 6 months or there was a recent intensification of immunosuppression. Definite diagnosis depends on endoscopy, and CMV may involve inaccessible parts of the bowel.

CMV hepatitis occurs in up to 17% of liver transplant recipients and is more common with primary than reactivation infection. The pathologic finding is microabscesses scattered around the liver lobule. CMV inclusion bodies may be easy to find or scant. The disease is typically mild and may be an incidental finding in asymptomatic patients undergoing liver biopsy to evaluate elevation of their liver enzymes.

Intravenous ganciclovir has been the preferred agent for treatment of severe symptomatic CMV disease in transplant recipients. However, oral valganciclovir is a reasonable alternative in carefully selected non–severely ill patients, thereby simplifying therapy.[30] In patients with CMV disease and viremia, therapy is typically continued until resolution of CMV viremia because the risk of relapse is lower in patients who do not have detectable CMV DNA after ganciclovir therapy.[31] Although ganciclovir is proved to be effective, its administration requires parenteral access. A large, randomized, multicenter trial (the VICTOR study) demonstrated that oral valganciclovir is safe and has long-term outcomes noninferior to those of intravenous ganciclovir for the treatment of CMV disease in non–severely ill organ transplant patients.[30] Foscarnet and cidofovir are also active against CMV but are used infrequently in solid-organ recipients because of their side effects, and they are generally used only in patients with ganciclovir-resistant CMV. Ganciclovir-resistant CMV has emerged as an important complication of transplant and has been associated with donor seropositive/recipient seronegative status, potent immunosuppression, and prolonged and incompletely suppressive antiviral drug exposure. The diagnosis is suspected in transplant recipients without a clinical or virologic response, or both, to full-dose ganciclovir therapy and can be confirmed with genotypic resistance testing directly from clinical specimens (e.g., blood and BAL). Mutations in specific regions of UL97 confer resistance to ganciclovir, whereas mutations in the UL54 region can confer resistance to ganciclovir, cidofovir, or foscarnet, either alone or in various combinations. An algorithm for the management of suspected ganciclovir-resistant CMV in transplant recipients has been published.[32]

The greatest advance in regard to CMV infection in transplantation in recent years has been the development of accurate and reproducible quantitative methods, including an international laboratory standard,

to assess viral load and the implementation of effective prophylactic and preemptive regimens to prevent disease caused by CMV. These topics are discussed in Chapter 311.

Respiratory Viral Infections

Respiratory viral infections received little mention in early reports of infections after organ transplantation but are now recognized to be important pathogens. The recent availability of PCR techniques to detect viruses is playing an important role in helping to diagnose these infections. Adenoviruses are a more common problem after pediatric than adult transplantation. They may cause asymptomatic infection, but they also can cause diffuse pneumonia, necrotizing hepatitis, and hemorrhagic cystitis. Antiviral agents such as ribavirin and cidofovir have been used to treat adenovirus infection, but their effectiveness remains uncertain.

Respiratory viruses, including RSV and parainfluenza, metapneumovirus, coronavirus, and rhinovirus, are an important cause of upper and lower tract infection in organ transplant recipients. The availability of highly sensitive molecular diagnostic tests has significantly improved the ability to make a definitive diagnosis and suggests that transplant patients may have prolonged shedding of these viruses. The seasonality varies according to the specific virus. Therapeutic options are limited, but ribavirin appears to be active in vitro against RSV; however, conclusive proof of efficacy is lacking. The aerosolized preparation has been used to treat RSV lung infection in stem cell and lung transplant populations. The overall impact of respiratory viruses appears to be significantly greater in lung compared with other organ transplant recipients.

Influenza has been documented frequently in transplant patients in recent studies, particularly among lung transplant recipients. Influenza is associated with substantial morbidity and mortality in organ transplant patients, and early therapy is associated with better clinical outcomes.[33] Immunocompromised persons, including transplant recipients, appear to have an increased risk for the development of resistance to neuraminidase inhibitors. Transplant patients and their household contacts should be given yearly immunizations with inactivated influenza vaccine, although immune responses appear to be diminished compared with nonimmunosuppressed persons. Consideration should also be given to providing antiviral prophylaxis to high-risk patients during outbreaks of influenza.

Polyomavirus Infections and Nephropathy

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.[34] For more than 2 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 nephropathy in 2% to 8% of renal transplant recipients, which frequently leads to graft failure.[35] In almost all cases, the responsible polyomavirus has been BK virus. JC virus and SV40 have been detected in a few patients, but their pathogenic role is less well established.

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 only rarely develop BK virus nephropathy, indicating that factors other than immunosuppression that are unique to the renal allograft are important. 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.[34]

BK virus primarily infects renal tubular cells producing intranuclear "ground-glass" inclusions accompanied by an interstitial nephritis (Fig. 313-3). Polyomaviruses may be detected in the urine by a variety of techniques, including culture, cytology, electron microscopy, and PCR; however, it is 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.[35] 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.).[34]

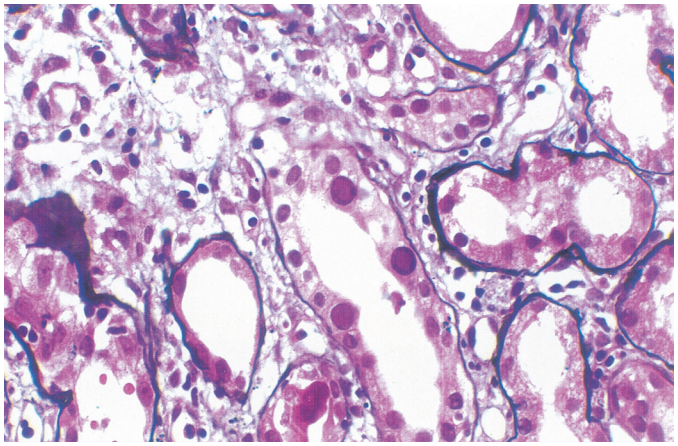

FIGURE 313-3 Characteristic histologic appearance of BK nephropathy in the kidney. The tubular cells have smudgy, basophilic intranuclear inclusions, and there is a pleomorphic cellular infiltrate of lymphocytes, plasma cells, and occasional neutrophils in the interstitium (Jones silver stain; ×400). *(Courtesy Agnes B. Fogo, MD.)*

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. With the advent of quantitative PCR assays, the primary approach is to prevent progression to BK virus nephropathy by using preemptive reduction in immunosuppression guided by viral load assays, typically from blood. Once histologically evident disease has developed, reduction in immunosuppression may improve or stabilize renal function, but nearly one third to one half 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.[34]

Progressive multifocal leukoencephalopathy (PML) occurs in patients with impairment of T-cell immunity and is caused by JC virus. Unlike the situation in acquired immunodeficiency syndrome, in which PML occurs in 4% to 5% of patients with low CD4 counts, PML is rare after transplantation. Patients develop profound neurologic deficits that can include various motor, sensory, visual, or cognitive findings occurring over a subacute course of weeks to months. A brain biopsy is required for a definitive diagnosis, but the diagnosis is strongly suggested by the finding of characteristic white matter changes on magnetic resonance imaging (MRI) and JC virus DNA by PCR in the CSF. There are no proven therapies for PML, but some reports have documented stabilization or improvement with reduction or withdrawal of immunosuppression (where feasible), but the overall prognosis is dismal, with mortality in the vast majority of patients within 6 to 12 months of diagnosis.

Other more recently described polyomaviruses include KI, WU, and Merkel cell–associated polyomavirus. The incidence, risk factors, clinical associations, and outcomes remain to be fully elucidated.

Human Herpesvirus 8 (Kaposi Sarcoma Herpes Virus)

Unlike other herpes viruses, human herpesvirus 8 (HHV-8) infection is not ubiquitous and is geographically restricted. The highest seroprevalence for HHV-8 is found in central and southern Africa, the Middle East, and European countries bordering the Mediterranean.

HHV-8 infection has been strongly linked to Kaposi sarcoma after transplantation, and most cases occur in patients who are seropositive before transplantation, indicating reactivated infection. Current estimates are that about 15% of HHV-8 seropositive patients develop Kaposi sarcoma during the first 3 years after transplantation, although more recent studies suggest that the risk of clinical disease may be lower.[36] Transmission of HHV-8 by transplanted allograft with subsequent development of Kaposi sarcoma has also been documented.[36] Most transplant recipients with Kaposi sarcoma present with mucocutaneous lesions; gastrointestinal lesions are seen in about 50% of patients, and lung or lymph node involvement occurs in approximately 20%.

Up to one half of transplant patients with Kaposi sarcoma experience regression of their tumors on reduction of immunosuppression. Switching from a calcineurin inhibitor to sirolimus has been associated with tumor regression. Patients who do not respond to a change in immunosuppression require chemotherapy. Mortality ranges from 10% to 60% depending on the extent of visceral involvement.

Lymphoproliferative Disease and Epstein-Barr Virus Infection

Primary EBV infection occurs in about three fourths of seronegative pediatric or adult transplant recipients. Reactivation infection, defined by viremia by PCR, is detected in up to one third of seropositive transplant recipients. Most infections occur within the first 4 months after transplantation. The most important disease associated with EBV infection in transplant recipients is post-transplantation lymphoproliferative disorder (PTLD). Most patients with PTLD (80% to 90%) have evidence of EBV infection by serologic rises or by measurement of EBV viral load in saliva or peripheral blood. The risk for PTLD is 10- to 76-fold higher in transplant recipients who are EBV seronegative before transplantation than in patients who are seropositive.[37] The other major risk factor for PTLD is the use of high doses of immunosuppression, especially polyclonal or monoclonal antibody formulations directed against T cells.[37] The detection of high viral loads of EBV in the blood by PCR has been associated with a high risk for PTLD in some studies, but the predictive power of this finding needs to be validated in larger, prospective studies.[37]

PTLD is variable in its presentation. It may resemble infectious mononucleosis without evidence of tissue involvement except in tonsils and peripheral lymph nodes. Another manifestation is a diffuse polymorphous B-cell infiltration in visceral organs. This type may be preceded by a mononucleosis-like episode that either evolves directly into the tissue infiltrative process or is temporally separated from it. The third clinical presentation is the appearance of localized extranodal lymphomas in the gastrointestinal tract, thorax, or other parts of the body, including the brain. These are mostly B-cell lymphomas and usually contain EBV genome detectable by nucleic acid hybridization or EBV-specific antigens detectable by immunohistochemistry. The tumors may be either monoclonal or oligoclonal, as determined by immunoglobulin G (IgG) light-chain phenotype or immunoglobulin gene rearrangement studies, and are typically of host rather than donor origin.

Antiviral agents such as acyclovir and ganciclovir inhibit the lytic phase of EBV infection and virion production, but not the replication of cells latently infected with EBV.[37] There is no definite evidence that the use of antiviral medications provides any benefit in treating or preventing PTLD, but theoretical considerations and data from some retrospective studies suggest that post-transplantation antiviral prophylaxis may decrease the overall incidence of PTLD.[37] Reduction or elimination of immunosuppression may lead to regression of PTLD in about one half of cases. Regression is more likely with tumors that appear during the first year after transplantation and with those that are polymorphous in appearance or contain tumor cells that are polyclonal by laboratory studies. Treatment of PTLD by infusion of monoclonal antibodies directed against surface antigens of B cells is a theoretically attractive approach and has achieved initial remissions in about two thirds of patients with PTLD.[37] Tumors with more malignant phenotypes require chemotherapy. The infusion of human leukocyte antigen (HLA)-compatible, EBV-specific cytotoxic T lymphocytes (CTLs) has been found to be an effective treatment in cases of PTLD occurring in marrow recipients.[37] Autologous EBV-specific CTLs have also been expanded in vitro from solid-organ transplant recipients with PTLD, but clinical experience using these cells for therapy is limited.[38] Significant technical advances have been made and ongoing clinical trials are underway to assess the feasibility and efficacy of adoptive therapy for prevention and treatment of PTLD in solid-organ transplant recipients.

West Nile Virus

Although most patients infected with this mosquito-borne RNA virus remain asymptomatic, clinical disease may manifest as abrupt onset of headache, malaise, gastrointestinal disturbances, generalized adenopathy, retroorbital pain, and, rarely, rash. The risk of West Nile virus (WNV) neuroinvasive disease may be as high as 40%.[39] It may manifest as encephalitis, meningitis, or poliomyelitis-like illness with acute flaccid paralysis. CSF typically reveals neutrophilic pleocytosis, occasionally with Mollaret-like cells. The diagnosis relies on serologic and PCR testing of the serum, CSF, or both. Detection of CSF WNV IgM is considered diagnostic of neuroinvasive disease; CSF PCR is less sensitive (50% to 70%) than CSF IgM antibody for diagnosis. The viremia is often transient and may not be useful for the diagnosis of acute infection. Supportive therapy remains the mainstay of management. Anecdotal reports have described the efficacy of WNV-specific immunoglobulin (IVIG) with high titers of WNV antibodies; however, this remains experimental.

Human Immunodeficiency Virus

Many centers now perform organ transplantation in carefully selected HIV-infected persons (suppressed HIV load, CD4 count ≥200 cells/mcL). Outcomes of kidney transplantation are generally comparable with non–HIV-infected recipients, although those for liver transplantation appear to be inferior and are related to HCV or HBV coinfection.[40] Experience with other organ transplants is limited. Interactions between immunosuppressive and HIV drugs complicate management and might be responsible for the relatively high rates of rejection seen in HIV-positive kidney transplant recipients. Acceleration of HIV infection or increased rates of opportunistic infections have not been reported as major problems in HIV-positive transplant recipients. Recently, renal transplantation between HIV-positive donors and recipients has been reported in some high incidence areas such as South Africa.[40a] Additionally, the legal barrier to the use of HIV-positive donors has been removed in the United States.[40b]

Donor-Derived Infections

An estimated 1% of the transplants are complicated by donor-derived infections (DDIs), and this rate is expected to increase largely as a result of improved recognition and reporting of these events. Although infrequent, DDIs are associated with substantial morbidity and mortality; deaths occurred in 40% of the recipients with documented transmissions.[41] Viral infections account for nearly one third of all confirmed DDIs. Transmission of certain viruses (e.g., CMV, EBV, HCV, and HBV) is expected to occur predictably. However, the risk can be mitigated by use of appropriate prophylactic measures in the recipient with minimal impact on post-transplant outcomes. Unexpected DDIs (e.g., lymphocytic choriomeningitis virus, rabies, WNV, HIV) have been documented with devastating sequelae. These infections have occurred when the disease was not suspected or recognized in the donor at the time of death.

Bacteremia in the donor, contamination during organ procurement, or donor respiratory tract colonization (in lung transplantation) may result in transmission of bacterial infections. *M. tuberculosis* disease or untreated latent infection may be transmitted with the allograft. Donor-derived tuberculosis is often unrecognized, particularly in areas of low prevalence. Indeed, tuberculosis is one of the more common bacterial causes of DDIs in the United States.[42] Recipients of an allograft from donors with inadequate treatment or incomplete or unreliable history of prior active or latent tuberculosis should receive chemoprophylaxis after transplantation.

Candidiasis is the most common donor-transmitted mycosis. Most cases are due to contamination of preservation fluid and occur in kidney transplant recipients. Donors with cryptococcosis, including

those with unrecognized cryptococcal meningoencephalitis, may transmit this yeast with the allograft. Active histoplasmosis or undiagnosed and presumably asymptomatic infection in the donor that had not resolved by the time of death can result in donor-derived histoplasmosis. Potential donors from an endemic area with either active or occult infection can also transmit coccidioidomycosis. In general, donors with undiagnosed meningoencephalitis are not suitable for donation because transmission of not only fungal pathogens but other diseases, including prion infections and *Balamuthia,* may occur (Table 313-7). Rare instances of aspergillosis and other filamentous fungi, including agents of mucormycosis, have also been transmitted from infected donors. More recently, these fungi have emerged as a serious complication of transplant tourism (the practice of traveling abroad to commercially acquire an organ) and have been associated with graft loss or death in 76% of the cases.[43]

Heart transplant donors and recipients should be serotested for toxoplasmosis. Given the paucity of cysts in noncardiac tissue, screening of non–heart donors for toxoplasmosis is not routinely performed. Donor screening for Chagas' disease should be performed in those who have lived or traveled in an endemic area.

TABLE 313-7 Infections with the Potential for Transmission from the Donor to the Recipient

Viruses
Viral hepatitis (B, C, and E)
Herpes viruses (cytomegalovirus, Epstein-Barr virus, herpes simplex virus)
Human immunodeficiency virus
Human T lymphocytic virus-I/II
West Nile virus
Lymphocytic choriomeningitis virus
Rabies
Creutzfeldt-Jakob disease
JC virus infection (progressive multifocal leukoencephalopathy)
Bacteria
Bacteremia
Bacterial meningitis *(Neisseria meningitidis, Streptococcus pneumoniae)*
Bacterial pneumonia or donor colonization (lung transplants)
Tuberculosis
Fungi
Candidiasis
Cryptococcosis
Endemic mycosis (histoplasmosis, coccidioidomycosis)
Filamentous fungi (aspergillosis, mucormycosis, scedosporiosis)
Other Agents
Toxoplasma gondii
Trypanosoma cruzi (Chagas' disease)
Leishmania spp.
Strongyloides stercoralis
Balamuthia mandrillaris
Naegleria fowleri
Treponema pallidum (syphilis)
Meningoencephalitis of unknown cause

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