310 Risk Factors and Approaches to Infections in Transplant Recipients

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Successful clinical organ transplantation dates from 1954, when the immunologic barrier to transplantation was ingeniously circumvented in a few patients with kidney failure by using organs from donors who were identical twins with the patients.[1] Subsequently, transplantation of organs from genetically different individuals was attempted with lymphoid irradiation to suppress the recipient's immune response to the allograft, but these efforts met with only occasional success. In the early 1960s, immunosuppressive regimens employing azathioprine and corticosteroids were introduced. These provided more effective control of allograft rejection that not only was sustainable but could be adjusted according to an individual patient's circumstances. This development catapulted kidney transplantation beyond the experimental stage, and both living-related and cadaveric renal transplantation became part of regular clinical practice. Attempts at heart and liver transplantation proved more challenging, and these clinical efforts remained limited to a few dedicated programs for more than a decade. The next major watershed in the development of transplantation was the introduction of cyclosporine in the early 1980s. This development ushered in a marked expansion of heart and liver transplantation, promoted further growth of renal transplantation, and made lung transplantation possible. Currently, more than 28,000 solid organ transplantations are performed yearly in the United States, and most patients retain the grafts and survive many years after transplantation.[2] As a result, patients with various types of transplants are now routinely encountered in general practice.

Except for issues related to the function and rejection of the transplanted organ, infections are the most important problem after transplantation. The clinical manifestations of infection are variable and depend on the infecting pathogen, the prior immune status of the host, the type of transplantation, the time after transplantation, and the level of pharmacologic immunosuppression. With this complexity in mind, it is useful to address some general principles that may aid in the diagnosis, management, and understanding of infections after transplantation.

The occurrence of infection requires a susceptible host and an available pathogen. Transplant recipients are not equally susceptible to all pathogens. For instance, most enteroviruses do not appear to infect transplant recipients with greater frequency or severity than they do normal hosts. A transplant recipient also may be quite susceptible to a given pathogen but may have a low risk of infection because of lack of exposure. For example, tuberculosis is rarely encountered at most transplantation centers in developed countries, but it can be a major problem in transplant recipients in parts of the world and in clinical settings in which infection cannot be avoided.[3] Likewise, transplant recipients with no past exposure to cytomegalovirus (CMV) who receive organs from CMV-seronegative donors are at low risk for CMV infection, whatever their level of immunosuppression. In clinical practice, the clinician can and should use this sort of information to assess each patient's individual susceptibility to important pathogens.

Infections are most frequent and most varied during the first 6 months after transplantation.[4] During this period, patients have all the risk factors for infection (Table 310-1): They may still be affected—either directly or indirectly—by their underlying disease; because they have undergone major surgery and been in the intensive care unit, they are at risk for wound and other nosocomial infections; and because they have received large doses of immunosuppressive drugs, the allograft may be malfunctioning as a result of rejection or other factors. This early period also covers the time of highest risk for infection by opportunistic microorganisms such as CMV and *Nocardia*, *Aspergillus*, *Pneumocystis*, or *Toxoplasma* organisms. These pathogens received much attention in the early literature on transplantation-related infections; more recently, their clinical impact has been diminished by the widespread use of antimicrobial prophylactic regimens early after transplantation.[5] These regimens have virtually eliminated some infectious complications, such as *Pneumocystis* pneumonia, and have provided substantial but still imperfect control of others, such as CMV disease. With time—usually about 6 to 9 months after transplantation—the risk of infection tends to decrease. The level of vigilance may therefore be reduced, except for individual patients whose risk has remained high because of continued requirement for high doses of immunosuppression.

Host Factors of Infection

Underlying chronic diseases of the transplant recipient may persist or even worsen after transplantation (see Table 310-1). The basic disease that led to transplantation may be cured by the procedure, but on occasion, it is not. Patients undergoing transplantation because of fulminant hepatitis B virus (HBV) infection usually clear the virus, but chronic infection with HBV or hepatitis C virus (HCV) persists in most patients after transplantation.[6] The end-organ effect of diabetes mellitus on blood vessels and nerves continues to be a major problem in diabetic patients with renal transplants and predisposes such patients to the development of infections of soft tissue and the urinary tract.[7] Single-lung transplant recipients are at risk for infection in their native lung as a result of structural problems caused by the underlying pulmonary disease.[8] Other preexisting medical conditions such as gallbladder disease or diverticulosis may be clinically quiescent before transplantation and first become manifest in the post-transplantation period, when their detection and management is complicated by chronic immunosuppressive therapy.

Along with the patient's underlying condition, medications, particularly antibiotics and immunosuppressive agents, have an effect on the type and severity of infections in the early post-transplantation period. For example, liver transplant recipients who receive antibiotics or corticosteroids before transplantation may be more likely to develop systemic *Candida* infections after transplantation.[9] Lung transplantation candidates who have received corticosteroids and other immunosuppressive medications to treat pulmonary fibrosis may reactivate asymptomatic CMV infection before they receive the transplant and may be at higher risk for disease caused by CMV after transplantation.[10]

Effect of Type of Transplantation

The type of transplantation is an important determinant of the type of infections occurring after transplantation. Sites of major surgery are vulnerable to bacterial and fungal infection. The transplanted organ has to survive outside the body and then must reestablish an adequate vascular supply to regain its functional integrity. Allograft reactions of

TABLE 310-1 Factors That Contribute to Infection after Transplantation

Category	*Examples and Comments*
Pretransplantation Host Factors	
Underlying medical conditions and chronic infections	Conditions that persist or recur (hepatitis B virus, hepatitis C virus, diabetes mellitus)
	Conditions that exacerbate (chronic bronchitis, gallbladder disease)
Lack of specific immunity	Conducive to important primary infections (e.g., cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, toxoplasmosis)
Prior colonization	Nosocomial gram-negative bacilli, *Candida* organisms, staphylococci, vancomycin-resistant enterococci
Prior latent or cryptic infection	Reactivation produces clinical infection (tuberculosis, cytomegalovirus, herpes simplex virus, varicella-zoster virus, *Trypanosoma cruzi* and possibly *Pneumocystis*)
Prior medications	Immunosuppressive agents and antibiotics influence post-transplantation 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
Infective immunosuppression	Primary cytomegalovirus infection and chronic hepatitis C virus infection are associated with more bacterial and fungal infection
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 allograft infection

the host-versus-graft or graft-versus-host type may occur (see Table 310-1). These reactions are known to reduce resistance to infection by viruses and to contribute to the graft's being a *locus minoris resistentiae.*[11] Data collected in the 1980s showed that the most common site of infection in recipients of solid organ transplants was the site of transplantation.[12-15] Recipients of bone marrow transplant do not have surgical sites, but they are unique because, in addition to depressed T-cell immunity common to other types of transplantation, leukopenia and depressed humoral immunity occur. This leads to a heightened vulnerability to many varieties of infection.

The contribution of surgical factors to infection is best illustrated by hepatic transplantation.[15,16] With this type of surgery, the function of the biliary and vascular anastomoses in the porta hepatis is most vulnerable. For example, 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.[15] There is also a striking correlation between the total hours that liver recipients spend in the operating room and the mean number of episodes of infection per patient (Fig. 310-1).[15] The duration of these operations is undoubtedly a reflection of many individual risk factors, including surgical stress, loss of blood and body fluids, direct tissue damage, and the various metabolic derangements that may occur during a prolonged operation. By the mid-1990s, improvements in anesthesia and surgical technique led to a decrease in the average length of liver transplantation surgery to 6 to 7 hours, but longer operations were still associated with a higher risk for fungal infection.[16] Lymphoceles resulting from interruption of lymphatic drainage after kidney transplantation may become superinfected with bacteria. In transplantation of the lung, peritracheal or peribronchial infection may follow breakdown of the airway anastomosis. Anastomotic infections may also predispose to infections of the transplanted lung, either directly or secondarily to obstruction after placement of a bronchial stent.[8]

The susceptibility of the grafted organ to invasion by CMV and other viruses is a striking example of the vulnerability of allografts to infection. Data collected in Pittsburgh in the 1980s on the frequency of CMV infection and disease in different groups of transplant recipients showed that the frequency of CMV pneumonia was 4 to 16 times higher in heart-lung transplant recipients than in patients with other types of transplants.[12-15] The vulnerability of the transplanted lung to infection extends to other viruses. Lung recipients also are susceptible to severe infections with adenovirus and paramyxoviruses, such as respiratory syncytial virus.[17] The reason the transplanted lung is so vulnerable to viral infections has not been elucidated. It may be related to the presence in the allograft of a cytokine milieu favorable to viral replication or to the inability of cytotoxic $CD8^+$ T cells to effectively kill cells with differing human leukocyte antigen (HLA) types. The transplanted liver is also more susceptible than a native liver to viral infections, including CMV, HBV, HCV, herpes simplex virus (HSV), and possibly adenovirus.[6,18,19]

Immunosuppression

Of all the factors contributing to the occurrence of infections in transplant recipients, the most obvious and probably the most consequential is iatrogenic immunosuppression. The effects of immunosuppressive agents have become more apparent as surgical techniques have improved and surgical infections have declined. Despite significant broadening availability of immunosuppressive agents after the introduction of cyclosporine in 1983, tacrolimus in 1994, mycophenolate mofetil in 1995, and rapamycin in 1999, the ideal suppressive regimen that prevents rejection but preserves antimicrobial immunity remains elusive.

The major immunosuppressive agents may be divided into several categories. Corticosteroids broadly inhibit immune responses, including innate inflammatory responses, cellular immunity, and, to a lesser extent, antibody formation.[20] Although corticosteroids are inadequate

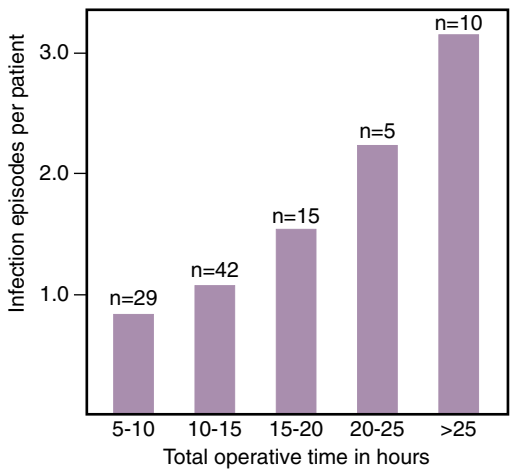

Figure 310-1 Frequency of severe infections in relation to time spent in liver transplant surgery. *(Data from reference 2.)*

as single agents to sustain graft survival, they have remained a part of most immunosuppressive regimens. High doses of prednisone and hyperglycemia were found to be significant factors in the frequency of infections and deaths from infection in kidney transplant recipients.[21] In an effort to free patients from the undesirable side effects of corticosteroid therapy, more transplantation centers have been prescribing early steroid withdrawal and steroid avoidance regimens, particularly in recipients of abdominal organ transplants.[22] In a meta-analysis of randomized trials in which steroid-free regimens were compared with steroid-based immunosuppression regimens in liver transplant recipients, no difference in overall risk of infection was revealed. However, the analysis revealed that steroid avoidance might reduce the risk of CMV infection and HCV recurrence.[23]

The introduction of cytotoxic drugs, such as methotrexate, cyclophosphamide, and azathioprine, was a major advance in immunosuppression that made transplantation across HLA barriers feasible. All the 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 disturbances. Azathioprine was once the mainstay of immunosuppression for transplanted organs, but its use has declined sharply since the introduction of cyclosporine and other more potent immunosuppressive medications.[22]

Cyclosporine was approved in 1983. It is an unusual cyclic peptide, consisting of 11 amino acids, whose main action is to inhibit the normal production of cytokines when $CD4^+$ T cells are exposed to foreign antigens.[24] The primary cytokine inhibited is interleukin-2. Suppressor cells and B cells are relatively spared. 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 very low rates of clinical infection, which is suggestive of the importance of corticosteroids and other cofactors for infection in transplant recipients (see Table 310-1). Most studies, whether randomized or historically controlled, have demonstrated that the introduction of cyclosporine led to lower rates of infection in transplant recipients.[15,25,26]

Hofflin and colleagues compared the rates of infectious morbidity and mortality between cohorts of heart transplant recipients receiving immunosuppressive regimens based on either azathioprine or cyclosporine.[26] Patients receiving cyclosporine had lower rates of infection (71% vs. 89%) and a lower infectious mortality rate (11% vs. 39%). The rates of infection have not been compared in liver recipients receiving azathioprine- versus cyclosporine-based regimens. However, most early deaths in liver transplant recipients are linked to infection, and the substantial decline in mortality rates among liver transplant recipients that occurred after cyclosporine was introduced implies an associated reduction in infectious mortality.[12,13,15]

Tacrolimus was approved in 1994. It is a macrolide produced by *Streptomyces tsukubaensis.* Despite some differences in the pathway of action, its mode of action is strikingly similar to that of cyclosporine in that it inhibits production of interleukin-2 and other cytokines by $CD4^+$ T cells.[27] It is about 10 to 100 times more potent than cyclosporine. Randomized trials have demonstrated that tacrolimus-based immunosuppression results in lower rates of acute rejection and graft loss than does cyclosporine-based therapy, particularly in kidney and liver transplant recipients. However, tacrolimus is linked to higher rates of neurologic and gastrointestinal symptoms and with development of diabetes mellitus.[28,29] Use of tacrolimus as primary immunosuppressive therapy has not been shown convincingly to either increase or decrease the risk of infection.[30]

Mycophenolate mofetil was approved in 1995 for renal transplant recipients and in 1997 for heart transplant recipients. It is a cytotoxic drug with an antiproliferative effect on T and B lymphocytes. It is not intended to replace cyclosporine or tacrolimus as primary immunosuppressive therapy; rather, it is meant to replace azathioprine in triple-drug regimens.[31] A blinded, randomized, three-arm study in renal transplant recipients revealed superiority of mycophenolate mofetil over azathioprine; biopsy-proven rejection occurred in 38% of azathioprine recipients, in comparison with 19.8% and 17.5% in the two mycophenolate mofetil conditions.[32] In this study, the numbers of patients developing infections were similar across the three groups. The main side effects of mycophenolate mofetil are marrow depression and diarrhea. The use of mycophenolate mofetil may also increase the risk of CMV disease.[31]

Rapamycin (also known as sirolimus) was released in 1999. Rapamycin interferes with cell cycle proliferation and blocks intracellular signaling mechanisms initiated by cytokines by inhibiting a regulatory kinase, mammalian target of rapamycin (mTOR).[31] Everolimus is another mTOR inhibitor that has been used in transplant recipients, but it is not yet approved in the United States. Unlike cyclosporine and tacrolimus, mTOR inhibitors have no direct nephrotoxicity. They frequently cause hyperlipidemia and occasionally cause myelosuppression. They also have been linked to delayed wound healing, oral ulcerations, and a rare drug-induced interstitial pneumonitis. Some data suggest that rapamycin use is associated with reduced rates of post-transplantation malignancy and CMV disease.[33,34]

Table 310-2 is a list of commercially available polyclonal and monoclonal antibody preparations used for immunosuppression in transplant recipients. These antibodies are used either to treat rejection refractory to corticosteroids or as "induction therapy."[22] Induction therapy, administered in the immediate post-transplantation period, is aimed at providing a high early level of immunosuppression while avoiding nephrotoxicity from calcineurin inhibitors. Each antibody has its own individual adverse effects and provides a variable, but usually long, duration of immunosuppression.[31,35-41] Mason and colleagues demonstrated a significant increase in infection rates during the first 3 months after use of polyclonal antithymocyte globulin for treatment of rejection of the heart.[38]

Many reports have also testified to the enhancing role of antithymocyte globulin and monoclonal OKT3 antibodies on CMV disease and post-transplantation lymphoproliferative disease in transplant recipients.[35,39-41] Antithymocyte globulins are raised in rabbits or horses by immunization with human thymocytes. Because they are foreign proteins, they may cause a serum sickness in the transplant recipient that typically begins about 10 days after administration. OKT3 is a

TABLE 310-2 Antibody Preparations Used to Prevent or Treat Rejection

Agent	*Adverse Effects*[31,35-41]
Polyclonal Antibodies	
Antithymocyte globulins* • 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 CMV, PTLD
Monoclonal Antibodies	
Anti-CD25 (IL-2 receptor) antibodies† • Basiliximab (Simulect) • Daclizumab (Zenapax)	Hypersensitivity reactions, infection risk not significantly increased
Anti-CD20 antibody‡ • Rituximab (Rituxan)	Infusion reactions, HBV reactivation
Anti-CD52 antibody§ • Alemtuzumab (Campath)	Infusion reactions, increased risk of CMV, *Pneumocystis jirovecii* pneumonia, invasive fungal infections, immunosuppression effects that can last up to 12 months
Anti-CD3 antibody‖ • Muromonab-CD3 (Orthoclone OKT3)	Aseptic meningitis, cytokine release syndrome, pulmonary edema, increased risk of CMV, PTLD

*Used for induction and rejection.
†Used for induction, not used for rejection.
‡Used primarily for humoral rejection, blood type (ABO) mismatch, and recipients with a positive crossmatch (off-label use).
§Used for induction and rejection (off-label use).
‖Used for rejection, not used frequently for induction.
CMV, cytomegalovirus; HBV, hepatitis B virus; PTLD, post-transplantation lymphoproliferative disease.

monoclonal mouse antibody directed against the CD3 receptor on T cells. OKT3 does not cause serum sickness, because immunosuppression can be achieved with milligram quantities of the drug. However, OKT3 antibodies can stimulate cytokine release from T cells and lead to pulmonary edema and a sepsis-like syndrome during the first 2 to 3 days of administration. Another poorly understood, but well-documented adverse effect of OKT3 is aseptic meningitis.

Alemtuzumab is an anti-CD52 monoclonal antibody and is currently approved for the treatment of B-cell chronic lymphocytic leukemia. It is increasingly being used in transplant recipients for either induction therapy or treatment for acute rejection unresponsive to corticosteroids. 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 cells, and $CD19^+$ B cells. This effect may last 12 months or longer after administration.[36] In contrast to agents that affect only T cells, its use has not been associated with an increased rate of post-transplantation lymphoproliferative disease, probably because its action against B cells suppresses Epstein-Barr virus (EBV) infection. The infectious risk of alemtuzumab is reported to be significantly higher when it is used as salvage treatment for acute rejection than when it is used as induction therapy.[42]

Infecting Microbial Agents

The most important pathogens infecting transplant recipients are listed in Table 310-3. There are two types of endogenous organisms. One type represents endogenous flora that colonize the mucous membranes of the gastrointestinal tract, including the oropharynx, the nares, and the skin adjacent to the oral and anal orifices. These are among the most important potential pathogens and are represented by the common gram-negative and gram-positive bacteria listed in Table 310-3. These organisms produce local infections by contaminating adjacent wound sites, or they may infect systemically by invading blood vessels or lymphatic vessels. They may be transmitted from one site to another in the same patient by a surgical procedure or on contaminated instruments and hands. They can also be transmitted from organ donors to recipients.

Candida spp. are a normal component of gastrointestinal tract flora and represent the most frequent and consequential fungal pathogens.[9] Superficial mucosal infections with *Candida* spp., such as thrush and *Candida* vaginitis, may be seen in all types of transplantation. Candidemia and visceral *Candida* infections are common after liver and pancreatic transplantation and occur occasionally in recipients of other types of transplants in an intensive care setting. Although *Candida albicans* remains the most commonly encountered species, some large transplantation centers are reporting increasing rates of invasive candidiasis with non-*albicans* species such as *Candida glabrata* and *Candida tropicalis*.[43]

Other colonizing organisms that received attention in the 1990s include antibiotic-resistant gram-positive cocci, such as vancomycin-resistant enterococci (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA). VRE has become a particular problem in liver transplant recipients, who have many risk factors for colonization, such as the prolonged use of broad-spectrum antibiotics.[44] One large liver transplantation center documented that nearly 15% of liver transplant recipients and candidates had rectal colonization with VRE, and this colonization was independently associated with an increased risk of VRE infection and death.[45] There is no current consensus on whether transplant recipients or candidates should be actively screened for MRSA or VRE colonization.

Another type of endogenous organism is found in latent tissue infection. Such infections are generally not detectable at the time of transplantation, but the microbial agents may reactivate and proliferate when the patient becomes immunosuppressed. The existence of this type of flora is best demonstrated by herpesviruses, *Toxoplasma* organisms, and the tubercle bacillus. Their latency may be detected indirectly by serologic or immunologic tests. The situation is less clear in the case of *Pneumocystis jirovecii*, but the remarkable frequency of *Pneumocystis*

TABLE 310-3 Common Microbial Agents Causing Infection after Transplantation

Bacteria	
Gram-negative bacteria • Enteric bacteria (*Escherichia coli,* other Enterobacteriaceae) • *Pseudomonas* • *Acinetobacter* • *Serratia* • *Bacteroides* and other anaerobes	This group of organisms can cause superficial wound infections or infections of the blood and deeper tissues of the urinary tract, lung, thorax, and abdomen. Despite a succession of highly effective antibiotics, these remain among the most frequent causes of bacterial infection.
• *Legionella*	Nosocomial from water supply.
Gram-positive aerobes	
• *Staphylococcus aureus* • *Staphylococcus epidermidis*	Infections with *S. epidermidis* and methicillin-resistant *S. aureus* have increased in frequency
• *Streptococcus* spp.	
• *Enterococcus* spp.	Vancomycin-resistant enterococci are major pathogens in liver transplant recipients
• *Pneumococcus* spp.	
• *Listeria monocytogenes*	*Listeria* organisms are an occasional cause of severe meningitis
• *Nocardia* spp.	
Gram-negative coccobacilli • *Haemophilus influenzae* • *Moraxella* spp.	Infection often seen with underlying lung disease
Fungi	
Candida spp.	*Candida* spp. are the most common endogenous fungi; deep *Candida* infection is a particular problem after liver transplantation
Aspergillus spp.	
Cryptococcus spp.	
Agents of mucormycosis	
Histoplasma capsulatum	Encountered primarily in endemic areas
Coccidioides spp.	Encountered primarily in the southwestern United States
Pneumocystis jirovecii	Probably latent in humans
Viruses	
Herpesvirus group • Herpes simplex (HSV) • Cytomegalovirus (CMV) • Varicella-zoster virus • Epstein-Barr virus (EBV) • Human herpesvirus-6 and -7	Herpesvirus infection is common after transplantation because many subjects are latently infected with one or more species that reactivate. Donor transmission is an important source of CMV and EBV
• Human herpesvirus-8	Highly associated with Kaposi's sarcoma
Human immunodeficiency virus type 1 (HIV-1)	Increasing numbers of organs are being transplanted in HIV-positive individuals with well-controlled infection
Adenovirus	Pediatric, only occasional in adults
Rotavirus	Primarily pediatric
Respiratory syncytial virus	During community outbreaks
Influenza A and B viruses	
Parainfluenza viruses	
West Nile virus	Donor transmission documented
Hepatitis B virus	
Hepatitis C virus	
Polyomavirus	BK virus causes nephropathy in kidney transplant recipients. JC virus causes progressive leukoencephalopathy.
Papillomavirus	
Parvovirus	Severe hypoproliferative anemia
Mycoplasmas	
Mycoplasma hominis	Can cause wound infection after transplantation, as well as other types of systemic infection, including arthritis, meningitis, and peritonitis
***Ehrlichia* Organisms**	
Ehrlichia chafeensis	Endemic areas
Ehrlichia ewingii	
Anaplasma phagocytophilum	
Protozoa and Parasites	
Toxoplasma gondii	Usually a primary infection in solid organ transplantation
Trypanosoma cruzi	May be reactivated in a previously infected recipient or be acquired from donor
Strongyloides stercoralis	Prior infection may intensify during immunosuppression

pneumonia in patients with the acquired immunodeficiency syndrome (AIDS) suggests that latent infection by this organism is common, if not ubiquitous.

A number of organisms are transmitted through the air from the physical environment, particularly fungi such as *Aspergillus, Coccidioides, Histoplasma,* and *Cryptococcus. Aspergillus,* cryptococcal, and nocardial infections are seen in all geographic regions, but post-transplantation coccidioidomycosis is a problem uniquely of certain endemic regions, such as the arid deserts of the southwestern United States, and most reported cases of histoplasmosis after transplantation have also occurred in endemic areas.[46,47]

The most frequent source of infectious agents in the patient's environment is still other human beings. In the postoperative period, nosocomial transmission of respiratory viruses and common gram-positive and gram-negative organisms occurs through contaminated hands of hospital personnel or through inanimate objects such as respiratory equipment, endoscopes, intravascular lines, and urinary catheters that have been handled by such personnel. This equipment may at times amplify the agent if organisms are permitted to grow in reservoirs such as water baths and humidifiers.

Some bacteria listed in Table 310-3 probably have exogenous sources, but these are often undefined. *Pseudomonas* organisms may come from environmental water sources or raw vegetables. *Listeria* may arise from contaminated food sources, but a source is rarely identified in the sporadic cases of meningitis that are seen in populations of transplant recipients.[48] The *Legionella* organisms, including *Legionella pneumophila* and *Legionella micdadei,* are well-described causes of pneumonia in transplant recipients.[49] Hot-water reservoirs have been demonstrated to be a common source of nosocomial legionellosis. Identification and treatment of these contaminated water sources is an important infection control practice in hospitals with endemic *Legionella* infection.[49,50]

Transfused blood products and donated organs have been documented sources of infection in transplant recipients.[51,52] Although transmission of some agents such as HCV and CMV has declined as a result of improved blood-banking practices, the reports of transmission of West Nile virus, rabies virus, and arenaviruses by transplanted organs have highlighted the threat of receiving blood and organs from other individuals.[53-56] It has also created a difficult and currently unresolved challenge to organ procurement agencies to develop laboratory tests that can prove a potential donor is free of these uncommon infections.[53] Another emerging agent is human herpesvirus-8. Donor transmission of this virus has not been recognized in the United States, but it has been demonstrated in Europe and shown to lead to clinical cases of Kaposi's sarcoma.[57] The major agents transmitted by allografts are listed in Table 310-4. Of these pathogens, CMV is most frequently transmitted by organs. It would be desirable to use only CMV-seronegative donors to transplant organs into CMV-seronegative transplant recipients.[11] However, such selection is not the usual practice because of the short supply of donor organs, the varying rate of morbidity from CMV infection after transplantation, and the availability of effective antiviral treatment. In order to prevent blood-borne transmission, CMV-seronegative transplant recipients are given blood transfusions from CMV-seronegative blood donors, or filters are used to deplete the blood of white blood cells, the component in the blood that carries the latent virus.

Toxoplasma organisms have been transmitted by seropositive heart donors, but transmission by other organs is rare.[58] HSV infections have occasionally been transmitted from kidney donors to HSV-seronegative recipients, and it is likely that EBV-seropositive donors are a major source of primary EBV infection in seronegative recipients.[59,60] The risk of HCV transmission is high (≈50%) when the donor is serologically positive for HCV, even in nonliver transplant recipients.[61] Organs from HCV-seropositive donors, however, are sometimes used in recipients who are severely ill or already seropositive for the virus. The risk of transmission of HBV is greatest if the organ donor has clear evidence of active infection, usually indicated by either a positive surface antigen (HBsAg) or core immunoglobulin M antibody (HBcIgM). The risk associated with receiving a graft from a donor who is seropositive for immunoglobulin G antibody to core antigen (HBcIgG) but seronegative for HBsAG and HBcIgM is less clear; however, it can be predicted partially on the basis of the organ that is transplanted and the immune status of the recipient. Approximately half of all liver transplant recipients eventually acquire HBV infection from an HBcIgG-positive donor, whereas the transmission rate is low (≤3%) for nonliver transplant recipients.[61] Preexisting immunity to HBV in the recipient, either by vaccination or by previous infection, appears to reduce but not totally eliminate the risk of transmission. Donors, whose only marker of HBV infection is a positive surface antibody (HBsAB), are considered to represent a low risk for transmission. Donor transmission of HBV has been successfully managed in recipients by treatment with lamivudine and hepatitis B immune globulin.[62]

Human immunodeficiency virus type 1 (HIV-1) is efficiently transmitted through donor organs, tissues, and blood products.[61,63] There is a consensus that organs from donors seropositive for HIV-1 should not be transplanted. The Centers for Disease Control and Prevention has developed guidelines mandating that organ procurement personnel obtain a history of any risk factors for HIV-1 infection that could signal the possibility of transmission of HIV-1 despite negative results of antibody tests. The mandate includes the responsibility of sharing any relevant information with the intended recipient and family.[64] In 2007, four organ recipients acquired HIV-1 and HCV from a donor who was seronegative for both viruses.[64] Cases like these have sparked interest in utilizing nucleic acid testing to identify infected donors during early infection when viremia is present, but antibodies have not yet developed. Such methods could potentially reduce the window period for detecting acute donor infections to 1 to 2 weeks.[65]

TABLE 310-4 Major Infective Agents Transmitted by Donated Tissues, Blood, and Blood Products

Type of Tissue	*Infective Agent*
Kidney, heart, liver, lung, bone marrow	Cytomegalovirus[11,41,52]
Heart, kidney	Toxoplasmosis[58]
Heart	*Trypanosoma cruzi*[54]
Kidney, liver	Herpes simplex virus[59]
Kidney	Human herpesvirus-8[57]
Kidney, heart, liver	HIV-1, hepatitis B virus, hepatitis C virus, West Nile virus[61]
Kidney, liver, lung	Lymphocytic choriomeningitis virus, Old World arenavirus[55,56]
Kidney, liver, cornea	Rabies[54]
Blood*	Cytomegalovirus, Epstein-Barr virus, HIV-1, hepatitis B virus, hepatitis A virus, delta hepatitis virus, hepatitis C virus, human T-cell lymphotropic virus 1[51]
	West Nile virus[55]
Leukocytes	Cytomegalovirus, HIV-1[51]

*On rare occasions, *T. cruzi* malaria, babesiosis, and syphilis have been transmitted by blood transfusion.[51]

HIV, human immunodeficiency virus.

Evaluation before Transplantation

Evaluation of the patient for infectious risks before transplantation has proved extremely valuable, and all transplantation centers have some formal screening mechanisms.[66] The first goal of such screening should be to detect the presence of any active infection in the candidate that might amplify and become a major problem after transplantation. Examples are a history of chronic bronchitis and the presence of active dental infection. Most patients with cystic fibrosis who undergo lung transplantation have pulmonary infections with resistant organisms such as *Pseudomonas aeruginosa* and MRSA. The perioperative antibi-

otic prophylaxis for these patients is usually targeted to cover the most recent isolates from the sputum.[8]

The second step in a pretransplantation evaluation is to document a history of exposure. The patient should be questioned about occupational exposures and hobbies, and a brief history of travel and residence should be obtained to explore possible exposure to tropical illnesses or endemic mycoses. This history should include past documentation of tuberculosis, previous tuberculin skin test results, and any exposure that might have placed the patient at risk of acquiring tuberculosis, such as extended travel in developing countries or incarceration in a prison. Third, a battery of tests to screen for infectious disease should be performed, as outlined in Table 310-5. The results establish the presence of chronic viral pathogens (HIV-1, HCV, HBV) and help assess susceptibility to reactivation or new infection by key transplant pathogens such as the herpesviruses and *Toxoplasma gondii.* Tuberculin skin testing should be performed for all patients unless they have had a definitely positive test result in the past. Coccidioidomycosis complement fixation antibody tests are also recommended for individuals with residence or significant exposure over the preceding 2 years in known endemic areas. Patients with residence outside the United States may require specialized testing for *Trypanosoma cruzi,* malaria, luminal parasites such as strongyloides, or human herpesvirus-8.[54]

The most useful tests before transplantation are the herpesvirus serologic profiles, because they predict whether the patient is at risk for reactivation or primary infection with these viruses. An example is knowledge of a patient's varicella serologic status: Few patients are seronegative, but these few are at high risk of potentially fatal varicella infection after transplantation. Knowledge of risk status allows for intensive counseling and immunization of these patients.[67] Seropositive patients, in contrast, can be told that they are at no risk from exposure to chickenpox or shingles and require no intervention after exposure. CMV antibody testing before transplantation provides the best way to stratify risk for CMV disease after transplantation. Many transplantation centers modify their management of high-risk CMV-seronegative patients who have seropositive donors by instituting closer follow-up or giving more aggressive antiviral prophylaxis.

The incidence of active tuberculosis is 30 to 50 times higher in transplant recipients than in the general population.[3] The risk of hepatotoxicity from isoniazid prophylaxis appears to be low in transplant recipients without preexisting liver disease.[68] We believe that most patients with positive tuberculin skin tests should be treated with isoniazid, but assessment of risks and benefits in individual patients is also important, and the optimal timing of prophylaxis should be considered. For instance, in liver transplant candidates with decompensated liver disease, isoniazid prophylaxis might be delayed until after liver transplantation, when the risk for tuberculosis is higher and the patient is more clinically stable.

HIV-positive patients with end-stage organ disease were previously denied access to organ transplantation: Because of the immunosuppression required for transplantation, HIV progression often accelerated. Now that highly active antiretroviral therapy can provide very effective virological suppression of HIV, more transplantation centers are offering organ transplantation to HIV-positive patients with well-controlled infection. Such transplantations, however, may be complicated by difficult drug interactions between the transplant immunosuppression regimen and antiretroviral therapy. So far, studies of kidney transplantation in selected HIV-infected patients show early term (1- to 3-year) survival of patients and grafts that are comparable to outcomes in renal recipients without HIV infection.[69,70] Surprisingly high rates of acute cellular rejection have been seen in HIV-positive renal recipients in some studies. This has been variously attributed to drug interactions between immunosuppressive agents and antiretroviral drugs or dysregulation of the immune system caused by HIV infection.[69] HIV-infected liver recipients may have worse survival than liver recipients without HIV infection, particularly if they are coinfected with HCV.[71] HIV-positive transplant recipients may be particularly susceptible to the immunosuppressive effect of anti-T cell antibodies, In one study of 11 HIV-positive renal recipients who received thymoglobulin, $CD4^+$ T cell counts remained below 200 cells/μL for an average of 342 days after drug administration, despite adequate suppression of HIV.[72]

TABLE 310-5 Routine Laboratory Studies before and after Transplantation

*Before Transplantation**	*After Transplantation*
Cytomegalovirus immunoglobulin G (IgG) antibody	Viral load monitoring for cytomegalovirus
Epstein-Barr virus IgG antibody	Antibody studies (as clinically indicated)
Herpes simplex (types 1 and 2) antibody	
Varicella-zoster IgG antibody	
Toxoplasma IgG antibody (heart transplant recipients)	
Hepatitis B screen†	
Hepatitis C enzyme immunoassay‡	
Human immunodeficiency virus antibody	
Tuberculin skin test	
Stool for ova and parasites§	

*For serologic studies, it is most important to collect serum before transplantation. Studies may then be done as clinically indicated.

†Should include at least surface antigen, core antibody, and surface antibody.

‡Second- or third-generation test. Liver candidates and patients with laboratory or clinical evidence of liver disease should also undergo a polymerase chain reaction assay for hepatitis C.

§Primarily useful for former or current residents of tropical and subtropical regions. The incidence of strongyloidiasis after transplantation has fallen dramatically since the mid-1980s.

IgG, immunoglobulin G.

Monitoring for Infection

Routine surveillance for bacterial infection is of limited benefit in most recipients of solid organ transplants. One possible exception might be the routine surveillance of respiratory secretions of lung recipients who are intubated in the intensive care unit. These patients are at risk for both pneumonia and transplant rejection, and it may be easier to assess changes in pulmonary status when serial sputum results are available. Surveillance for fungi is also a common practice after lung transplantation, because of the high risk for infection with *Aspergillus* and other molds.[8,73]

Many transplantation programs monitor for CMV infection in patients during the first 3 to 6 months after transplantation. Viral load assays such as blood antigenemia or quantitative polymerase chain reaction (PCR) testing for CMV have replaced conventional and shell vial cultures as the virus tests of choice. These tests are more rapid and sensitive than cultures. They provide quantitative information on viral load that is correlated with the development of symptomatic infection.[74] Routine virologic testing for CMV has enabled a preemptive approach to antiviral treatment and successfully prevented progression to overt CMV disease both in patients with stem cell transplants and in those with solid organ transplants.[74-76] Monitoring of the viral load by quantitative PCR has also been studied for other viral infections in transplant recipients. Some studies have correlated the presence of high viral loads of EBV in blood samples from transplant recipients with the later development of EBV-related lymphoproliferative disease.[77] The viral loads of HBV and HCV have predictive power for the course of these infections after transplantation, and their measurement is essential for monitoring the response to treatment.[62,78] According to preliminary evidence, quantitative PCR screening of renal transplant recipients for infection with BK virus (a polyomavirus) and the use of these results to adjust levels of immunosuppression may be an effective way to reduce the incidence of polyomavirus nephropathy.[79]

Prophylactic Measures

Prophylactic regimens are frequently used to prevent infection in transplant recipients. Immunization is potentially the most cost-effective way to prevent infection. Although trials large enough to demonstrate clinical effectiveness of vaccines have not been performed with transplant populations, numerous smaller studies of antibody responses have been conducted. The response of renal recipients to booster doses of tetanus and diphtheria toxoids appears to be adequate, although reduced in comparison with the response in immunocompetent persons.[80] Transplant recipients also respond to pneumococcal vaccine but have lower peak antibody titers and a less durable response than do healthy controls.[81] The seroconversion rates of transplant recipients to influenza vaccine are generally inferior to those of control populations.[82]

There is an understandable reluctance to use live vaccines in transplant recipients. Measles and varicella vaccines have been used safely in small groups of transplant recipients with seroconversion rates of 73% and 65%, respectively,[83] but more studies need to be done before live vaccines can be recommended for general use after transplantation. We advocate that transplant candidates update their immunizations and receive vaccines—including pneumococcal, influenza, and HBV vaccines—that are recommended for patients in the general population who have chronic diseases. Transplant candidates should also be offered varicella immunization if they are seronegative for this virus, and liver transplant candidates should receive immunization for hepatitis A if they lack immunity. After transplantation, patients should finish any incomplete immunization series before transplantation and continue to receive other established inactivated vaccines on schedule.[84] In practice, we often postpone immunization when the patient is heavily immunosuppressed (e.g., during the first 3 months after solid organ transplantation) because the response is likely to be poor in this setting. Concerns in the transplant community that vaccines may cause rejection have not been substantiated.[84]

Antimicrobial agents commonly used for prophylaxis are listed in Table 310-6. Transplant surgeons routinely administer perioperative intravenous antibiotics to prevent intraoperative sepsis and wound infections. The type of antibiotics used varies greatly, and the optimal durations have not been established by studies or consensus. Oral antibiotics to prevent infection are also widely used. The most commonly used prophylactic antimicrobial agent is trimethoprim-sulfamethoxazole (TMP-SMX). TMP-SMX provides superior prophylaxis against *P. jirovecii* pneumonia in all populations that have been studied. It has now become part of standard care at transplantation centers. Dosages as low as two to three double-strength tablets (160/800 mg per tablet) a week are effective. Daily dosing of TMP-SMX in the first few months after transplantation also reduces urinary tract and other bacterial infections in renal transplant recipients.[85] In one study, patients taking TMP-SMX had 25% higher serum creatinine levels than patients not taking TMP-SMX, but this was fully reversible on discontinuation of the TMP-SMX. It is claimed, but not proved, that TMP-SMX prophylaxis also decreases the rate of infections caused by some serious opportunistic pathogens, including *Legionella, Nocardia,* and *Listeria.*

Prophylactic quinolones are used at some stem cell transplantation centers. They have been shown to reliably decrease the rate of fever and gram-negative bacteremias during the neutropenic phase of chemotherapy.[86] No effect on mortality has been demonstrated. Antiviral prophylaxis is desirable in transplant recipients because of the clinical importance of herpesvirus infections. Acyclovir is effective in preventing HSV infection in the early post-transplantation period. It is indicated in HSV-seropositive liver and lung transplant recipients because they have a risk of visceral disease caused by HSV in the transplanted organ.[8,18,67] Acyclovir is also commonly used to prevent mucocutaneous HSV infection in other solid organ recipients. Although acyclovir has marginal therapeutic activity against CMV, controlled studies have revealed that it does provide some protection against CMV disease when given prophylactically in high doses.[87] Ganciclovir has been favored by many clinicians as the prophylactic antiviral agent of choice because it has greater intrinsic activity than acyclovir against CMV, while remaining active against HSV. When given to marrow recipients for 100 days after neutrophil engraftment, intravenous ganciclovir reduced CMV disease in the first 6 months by 72%, but its use was associated with excess neutropenia and increased bacterial infections.[88] Merigan and co-workers studied the use of intravenous ganciclovir prophylaxis for 4 weeks after heart transplantation and demonstrated a significant reduction in CMV disease in CMV-seropositive heart recipients.[89] The regimen was not effective in CMV-seronegative recipients who received organs from seropositive donors, By extending prophylaxis with intravenous ganciclovir prophylaxis to 100 days after transplantation in liver recipients, Winston and colleagues were able to achieve impressive reductions in CMV disease in all CMV serogroups.[90]

Large placebo-controlled trials of CMV prophylaxis with oral regimens have also demonstrated positive results. In a randomized trial in which oral ganciclovir (1 g three times daily) for 12 weeks was compared with placebo in liver transplant recipients, CMV disease was significantly reduced (from 17% to 4%) in the treatment group.[91] The cases of CMV disease in the patients taking oral ganciclovir consisted only of CMV syndromes and mild CMV hepatitis. Valacyclovir, a prodrug of acyclovir that yields serum levels of acyclovir similar to those achieved with intravenous dosing, was compared with placebo in 616 renal recipients.[92] The frequency of CMV disease among those taking valacyclovir was reduced from 5% to 1% in CMV-seropositive patients and from 39% to 14% in CMV-seronegative recipients with seropositive donors. Only 1% of patients developed CMV disease while taking valacyclovir.

Valganciclovir is an oral prodrug of ganciclovir that has 60% bioavailability and provides drug exposure similar to that provided by intravenous infusions. In one randomized trial, valganciclovir was compared with oral ganciclovir for CMV prophylaxis in 371 CMV-seronegative recipients of solid organ transplants who had CMV-seropositive donors; CMV disease occurred at equivalent rates in both

TABLE 310-6 Antimicrobial Prophylactic Regimens in Transplantation

Pathogen	*Prophylactic Agents*
Protozoa	
Toxoplasmosis	TMP-SMX Pyrimethamine
Virus	
Herpes simplex	Acyclovir*
Cytomegalovirus	Ganciclovir† Acyclovir Immunoglobulin Foscarnet‡
Influenza	Oseltamivir
Fungus	
Candida	Fluconazole Nystatin Clotrimazole
Aspergillus	Itraconazole Voriconazole Posaconazole Liposomal amphotericin B
Pneumocystis	TMP-SMX Dapsone Inhaled pentamidine
Bacteria	
Wound infection	Variable
Urinary tract infection	TMP-SMX
Neutropenic infection	Quinolones
Tuberculosis	Isoniazid
Pneumococcus	Penicillin (stem cell transplants)

*Includes oral and intravenous acyclovir and valacyclovir.
†Includes oral and intravenous ganciclovir and valganciclovir.
‡Used mostly in bone marrow recipients who have low blood cell counts.
TMP-SMX, trimethoprim-sulfamethoxazole.

groups during the first post-transplantation year. Almost all cases of CMV disease in the trial occurred more than 100 days after transplantation, after the prophylactic regimens were stopped.[93]

To prevent CMV disease, an alternative to CMV prophylaxis is to monitor patients with viral load testing for some months after transplantation and administer preemptive antiviral treatment when the viral load reaches a predetermined threshold. Potential advantages of preemptive therapy are lesser toxic effects and lower costs for antiviral drugs. Also, most cases of CMV disease being managed by preemptive therapy occur early after transplantation, when patients are still being closely monitored at the transplantation center.[94] Available data suggest that prophylaxis and preemptive therapy provide similar control of CMV disease.[88,94-96] There is some evidence, however, that long-term graft function may be superior when prophylaxis is employed.[87,92,95] Whether prophylaxis or preemptive therapy is the best approach has not been fully elucidated. Preemptive therapy is more widely used than prophylaxis in stem cell transplantation because of the concern for marrow toxicity in this population.[75,88] In solid organ transplantation, prophylaxis appears to have more advocates, but the evidence is still too unclear to force a consensus on which strategy is best.

Immune control is another available modality in CMV prophylaxis. Intravenous immune globulin has been widely studied for the prophylaxis of CMV disease after stem cell transplantation. The results of these studies have been mixed, and this approach is no longer strongly advocated for CMV control in this population. Although the results of studies of immune globulin prophylaxis for CMV in solid organ transplantation are also mixed, a systematic review of 11 randomized trials concluded that the use of immune globulin prophylaxis led to a reduction in both CMV disease and mortality.[97] None of the cited trials included prophylactic use of ganciclovir in its intravenous or oral formulations in either the treatment or control population. Thus, it remains unclear whether immune globulin adds any additional benefits beyond that achieved with modern antiviral approaches to CMV management.

The decision on how to manage CMV infection in transplant recipients is complex and is best made after careful consideration of the efficacy, side effects, and cost of the regimens under consideration, as well as the transplant type and the estimated risk of severe CMV disease in the intended recipient. Balancing and weighing these factors inevitably brings the values and philosophy of the treating physicians into play.

Transplant recipients are at risk for thrush and other forms of mucocutaneous candidiasis, but these are effectively prevented by treatment with oral nystatin or clotrimazole troches. Oral systemic azoles are also effective and should be preferred in intubated patients because topical preparations cannot reliably be delivered to the pharynx and esophagus. Prophylaxis can usually be discontinued when prednisone doses drop to 20 mg/day or less, but it may need to be restarted during treatment of rejection with high-dose steroids or intercurrent antibiotic use. Prophylaxis for systemic fungal infection is now being used in many centers for patients at high risk, such as stem cell, liver, and lung recipients. Intravenous and oral azoles have been the most widely used prophylactic agents. Controlled trials of antifungal prophylaxis in solid organ transplantation have largely been confined to studies in liver recipients. Fluconazole has been established as an effective agent; its use in liver recipients has produced a 75% reduction in invasive fungal infections but no improvement in mortality rates.[98] Limited data suggest that itraconazole and liposomal amphotericin may have similar efficacy, but both these drugs have more side effects than does fluconazole. *Candida* spp. are the major fungal pathogen in liver transplant recipients.[8,9,15] Lung recipients, in contrast, suffer from a high rate of infection with *Aspergillus* and other molds, and this has prompted lung transplantation centers to administer antifungal prophylaxis with agents active against molds, such as oral itraconazole and inhaled amphotericin, despite the lack of controlled antifungal trials in this patient group.[73]

In the early 1990s, large randomized studies in bone marrow recipients established fluconazole (400 mg/day) as a safe and effective drug for fungal prophylaxis.[99] Fluconazole's lack of activity against molds, however, is a definite shortcoming in allogeneic stem cell transplantation, because invasive mold infections are highly lethal in these patients and affect 10% or more of the population. A number of newer antifungal agents have been studied in large, controlled trials in stem cell transplant recipients, but a clear choice for a new prophylactic antifungal standard has not yet emerged. Because of their intrinsic activity, tolerability, oral availability, and the rigor and size of the supporting studies, voriconazole and posaconazole currently seem the most attractive candidates.[100] Both agents appear to reduce the incidence of invasive aspergillosis, but neither drug has been shown to reduce overall mortality rates.[101,102] With both, issues with variable serum levels arise: With posaconazole, absorption is limited and unpredictable; with voriconazole, metabolism varies. Pharmacokinetic monitoring may be needed to achieve optimal results with these compounds.[100]

Another form of prophylaxis that has been proposed is pyrimethamine (25 mg/day, together with folinic acid, 5 to 10 mg/day, for 6 weeks) for heart recipients who are seronegative for *Toxoplasma* and receive an organ from a *Toxoplasma*-seropositive donor.[103] However, the widespread use of TMP-SMX for *Pneumocystis* prophylaxis appears to provide excellent protection against *Toxoplasma* infection, and it is unclear whether the addition of pyrimethamine provides any further benefit.[104] Some stem cell transplantation centers also administer long-term oral penicillin prophylaxis to allogeneic transplant recipients because of the significant occurrence of severe pneumococcal infection late after transplantation.

Liver transplantation involves the breach of a potentially colonized upper gastrointestinal tract. Some groups have advocated decontamination of the gut as a method of decreasing bacterial and fungal sepsis in this population. Selective decontamination is usually accomplished with the oral administration of nonabsorbable antibiotics such as polymyxin E, gentamicin, and nystatin in the perioperative period.[105] The merits of gut decontamination remain uncertain, despite available clinical trials.

Prevention of Exposure to Infection

One way of decreasing infectious episodes in transplant recipients would be to prevent exposure to potential pathogens. Most transplantation centers have developed policies that are designed to reduce the chance of patients' encountering microbial pathogens. The recommendations usually target infections that are known to be important in transplant recipients and are based on the best current understanding of transmission and pathogenesis. Table 310-7 lists some recommendations found in recent publications.[66,106] The list gives some general guidelines and is not meant to be exhaustive. These recommendations also do not account for differences in susceptibility among patients. For instance, the risk for aspergillosis is not uniform among transplant recipients and is a concern mostly after allogeneic stem cell and lung transplantation or in patients who are receiving high doses of corticosteroids. Similarly, lung transplant recipients are known to have greater difficulty with respiratory viral infections than are kidney, heart, or liver recipients.[17] Clinicians can and should modify their recommendations on the basis of this differential susceptibility to infection, reserving the strictest recommendations for the patients at highest risk. Some pathogens such as *Mycobacterium tuberculosis* or *Coccidioides immitis* are relatively virulent, even in immunocompetent hosts, and it is probably not prudent for any transplant recipient, even one who is healthy and on low doses of immunosuppressive drugs, to work as a prison guard or participate in an archeological excavation outside of Tucson, Arizona.

Approach to Fever in the Transplant Recipient

Although immunosuppressive drugs can blunt the febrile response to infection, most transplant recipients with clinical infections have temperature elevations; often this is the first indication that something is awry. Patients should be told to monitor their temperature if they feel

TABLE 310-7 Prevention of Exposure to Pathogens

Type of Exposure	*Intervention*
Hospital Exposures	
Nosocomial bacteria	Use standard precautions, particularly hand washing before and after patient exposures
Respiratory viruses	Restrict access to visitors and staff with colds If contact cannot be restricted, use masks and gloves
Airborne molds	Remove patients from areas of construction, or erect barriers around construction Use masks for patient transport through high-risk areas Use HEPA-filtered air (only for stem cell transplant recipients)
Legionella infection	If nosocomial legionellosis is present, test water supply and decontaminate it, if possible Supply bottled water for oral use, and prevent exposure to aerosolized water, as in showers
Outpatient Exposures	
Enteric pathogens	Cook meat thoroughly, wash fresh fruit and vegetables, wash hands after cooking, avoid certain soft cheeses (e.g., brie, feta) Advise patient to avoid the following: • Drinking water from lakes, streams, and untested wells • Contact with human and animal feces • Unpasteurized milk and juices, raw eggs, and products made with raw eggs
Respiratory viruses	Advise patient to avoid small children or crowded public places or to wash hands after contact Immunize patient and family members against influenza yearly Provide pharmacologic prophylaxis for influenza (in selected patients)
Varicella	Advise varicella-zoster virus–seronegative patient to avoid contact with patients who have shingles or chickenpox
Zoonoses	Advise patient of the following: • To avoid changing litter boxes, cleaning bird cages, or cleaning aquaria • To wear gloves if such cleaning is unavoidable • To avoid jobs that involve frequent animal contact
Airborne molds	Advise patient to avoid closed spaces with high risks of fungal exposure (barns, silos, chicken coops, attics, caves) or high-risk activities (e.g., archeological excavation, especially in southwestern United States)
Legionella infection	Advise patient to avoid water aerosols (whirlpools and commercial displays) and hospital or other institutional tap water that is not tested or treated
Sexually transmitted diseases	Advise patient to use safe sexual practices
Exotic and tropical infections	Advise patient to confer with infectious disease specialist before international travel outside of North America and western Europe

HEPA, high-efficiency particulate air (filter).

ill and to call their physician if the temperature is elevated. For a febrile patient, the physician's first task is to identify possible sites and sources of infection and assess the severity of illness. Patients with typical upper respiratory tract infections and low-grade fevers (less than 38.0°C) can generally be observed clinically. If the patient has a temperature higher than 38.0°C and the cause is not apparent, a medical evaluation should be undertaken. If the patient has symptoms suggestive of a serious localized infection, the patient should be evaluated even in the absence of demonstrable fever.

The most important parts of this workup are a thorough history and a careful physical examination. A chest radiograph should be obtained to establish whether there is evidence for infection in the lungs. Patients with acute pulmonary infiltrates or with persistent fevers higher than 38.5°C usually need to be hospitalized for further workup. Most patients who cannot go about their normal daily activities should probably be evaluated in the hospital, unless the cause of their dysfunction is apparent and can be managed at home. Initial evaluation should include blood and urine cultures, examination of respiratory secretions (if pneumonia is suspected), white blood cell count and differential, liver function tests, and microscopic examination of the urine. Viral screening tests should be ordered if the patient is still in the high-risk early post-transplantation period (1 to 4 months) or has recently been treated for rejection or if the clinical findings are strongly suggestive of CMV disease. Delayed manifestations of CMV disease are not uncommon in CMV-seronegative patients with seropositive donor transplants who have received antiviral prophylaxis. The manifestations usually occur about 4 to 8 weeks after the antiviral prophylaxis is discontinued.[93] Antibiotics can often be withheld from patients who appear well and in whom no source of infection has been identified in the preliminary workup. A lumbar puncture need not be a routine part of the initial workup of febrile transplant recipients, but a sample of spinal fluid should be obtained from patients with headache or other neurologic complaints.

In a patient with a clear site of infection, evaluation should focus on quickly obtaining adequate samples for culture and smears from that site. Persistent fever (≥7 days) without positive culture findings or an apparent site of infection is a diagnostic and therapeutic problem.

Relatively few clinical entities appear to account for the majority of these fevers of unknown origin (FUOs), the most frequent of which are viral syndromes caused by CMV or occasionally by EBV. Human herpesvirus-6 has also emerged as an occasional cause of FUO in the early post-transplantation period.[107] Other infections that may manifest in this manner are parvovirus infection, systemic toxoplasmosis, and smoldering *Pneumocystis* infection manifesting with a normal-appearing chest radiograph. Deep tissue abscesses generally occur in or near the anatomic site of a recent operation. Disseminated candidiasis usually occurs early after transplantation in patients who are neutropenic or have stayed in the intensive care unit. These patients almost always have received broad-spectrum antibiotics and have central intravenous catheters. The risk for invasive candidiasis is highest in liver recipients; moderate in pancreas, lung, and heart-lung recipients; and low in kidney and heart recipients. Disseminated coccidioidomycosis and histoplasmosis may cause FUO; most of these cases occur in patients who reside in or have recently traveled to endemic areas. Tuberculosis, although uncommon, should always be considered a potential cause of FUO, especially if there is a history of exposure or of extensive residence or travel in developing countries. Whenever an unusual clinical syndrome is associated with fever in the early post-transplant period, clinicians should always consider the possibility of transmission of an unusual infection by the donor organ. Although donor-transmitted infections are uncommon, it may be helpful to look at the medical records of the donor and investigate whether other recipients of organs from the same donor are also ill. Clinicians should keep an open mind to potential causes because new agents are constantly being implicated in donor transmission.[53-56]

Not all fevers are caused by infections. Two important causes of noninfectious fevers in transplant recipients are drug reactions (especially reactions to anti–T-cell antibodies) and transplant rejection. Rejection is most likely to cause fever when it is severe and occurs early after transplantation. Fever caused by transplant rejection is most common in lung recipients, less common in kidney and liver recipients, and rare in heart recipients. Other noninfectious causes of fever are venous or arterial thrombosis, organ ischemia resulting from infarction or inadequate preservation, lymphoproliferative tumors, and hemolytic reactions.

Finally, it must also be conceded that infections in transplant recipients may occur without any fever. Fever sometimes appears to be suppressed by the use of high-dose corticosteroids; at other times, severe organ failure (heart, liver, or kidney) appears to be implicated. Some infections, such as progressive multifocal leukoencephalopathy, polyomavirus infections, or giardiasis, never cause fever, and others frequently do not. *Pneumocystis* pneumonia may manifest with only cough and dyspnea. Fungal infections, particularly focal fungal infections confined to the lung, are frequently afebrile. Even cryptococcal meningitis may manifest with only chronic headache and subtle neurologic symptoms. A good caveat for the physician is always to consider infection a possible cause of any new symptom or sign.

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