Infection in Organ-Transplant Recipients

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A PRIMARY goal in organ transplantation is the prevention or effective treatment of infection, the most common life-threatening complication of long-term immunosuppressive therapy. The challenges involved in achieving this goal are several: a broad range of potential sources of infection ranging from latent viruses to pathogens of both community and hospital origin; immunosuppression-induced impairment of the inflammatory response, which attenuates the signs and symptoms of invasive infection; and the adverse effects of the antimicrobial drugs used for prophylaxis and therapy, which result both from the duration of therapy required and from interactions with the immunosuppressive drugs cyclosporine and tacrolimus. Our aim is to delineate the principles guiding infectious-disease practice in transplantation, emphasizing the prevention and early recognition of infection and the avoidance of common drug-related toxic effects.

Risk of Infection in Transplant Recipients

The risk of infection in transplant recipients is determined primarily by two factors: the intensity of exposure to potential pathogens (epidemiologic exposure) and the combined effect of all of the factors that contribute to a patient’s susceptibility to infection (the net state of immunosuppression). For example, the occurrence of infection in a patient whose immune status is thought to be nearly normal is evidence that an excessive environmental exposure has occurred or that the level of immune suppression is greater than was thought. Even minimal environmental exposure to organisms of low native virulence can cause invasive infection in a patient with a maximal level of immunosuppression.

Epidemiologic Exposure

Epidemiologic exposure occurs in the community and the hospital. In the community, patients may have recent or remote contact with potential pathogens. Short-term community exposure includes exposure to respiratory viruses and to such food-borne pathogens as salmonella, Listeria monocytogenes, and Campylobacter jejuni. Community exposure also includes recent and remote exposure to such organisms as those causing the geographically restricted systemic mycoses (Blastomyces dermatitidis, Coccioidoides immitis, and Histoplasma capsulatum), Mycobacterium tuberculosis, and Strongyloides stercoralis

Immunosuppression amplifies the effects of these infections, increasing the risk of tissue invasion, dissemination, and superinfection.

In the case of the systemic mycoses and tuberculosis, three patterns of disease are observed: progressive primary infection, reactivation infection, and re-infection. Systemic dissemination is common with all three. These infections may present with fever of unknown origin, progressive pneumonitis, or metastatic infection to such sites as the liver, mucocutaneous surfaces, bones and joints, genitourinary tract, and central nervous system.

Within the hospital, excessive environmental exposure may be domiciliary or nondomiciliary. Domiciliary exposure occurs on the hospital unit where the patient is housed, as a result of contamination of the air or potable water with pathogens such as aspergillus, legionella, or gram-negative bacilli such as Pseudomonas aeruginosa. In recent years, domiciliary outbreaks of infection by vancomycin-resistant Enterococcus faecium, methicillin-resistant Staphylococcus aureus, and Clostridium difficile have occurred through person-to-person spread on the hands of personnel or on contaminated equipment within the patient’s room. The hallmark of a domiciliary outbreak is the clustering of infections in time and space.

Nondomiciliary exposure occurs within the hospital when the patient is exposed to contaminated air during travel to or from clinical procedures such as surgery or radiologic imaging. Outbreaks due to nondomiciliary exposure are probably more common than domiciliary outbreaks but are generally more difficult to detect, because of the absence of clustering of cases. The best clue to the presence of...
such a problem is the occurrence of an opportunistic infection in a transplant recipient when the patient’s net state of immunosuppression would not be considered great enough to allow such an infection to occur without an unusually intense exposure.

**The Net State of Immunosuppression**

The net state of immunosuppression is the result of a complex interaction among multiple factors (Table 1), the most important of which are the nature of the immunosuppressive therapy (dose, duration, and temporal sequence of individual agents), the presence or absence of infection with immunomodulating viruses (notably cytomegalovirus [CMV], but also Epstein–Barr virus [EBV], hepatitis B and C viruses [HBV and HCV], and human immunodeficiency virus [HIV]), and the residua of technical complications of the transplantation procedure (e.g., devitalized or injured tissues, undrained fluid collections, and the need for indwelling foreign bodies). The sum of these factors constitutes the patient’s net state of immunosuppression.

**Timetable for Infection After Transplantation**

The immunosuppressive programs used in all forms of solid-organ transplantation are quite similar, with either cyclosporine or tacrolimus being the cornerstone of maintenance antirejection therapy. As a result, there are similar patterns of infection in all forms of organ transplantation and a consistent timetable for when different infections occur after transplantation (Fig. 1). This timetable is most easily organized into three segments: the first month, one to six months, and more than six months after transplantation. The clinician may use this timetable as a tool for developing a differential diagnosis in transplant recipients who present with infectious diseases, a tool for detecting excessive environmental exposure to pathogens that cause deviations from the timetable, and a guide to the design of cost-effective, targeted preventive strategies.

**Infection in the First Month After Transplantation**

Three types of infection occur in the first month after transplantation. Rarely, active infection is conveyed with the allograft. Although unusual cases of disseminated toxoplasmosis or herpes simplex infection have resulted from the transplantation of organs from donors with active systemic infections, the primary concern in evaluating a prospective donor is the possibility of bacteremia or fungemia. Such infections in either donor or recipient commonly seed the allograft, especially at the vascular suture lines, leading to the formation of a mycotic aneurysm and, possibly, catastrophic rupture. Untreated infection in the recipient can have a major impact after transplantation. In particular, transplantation of an organ into a patient with pneumonia or lung injury from pulmonary aspiration or infarction almost guarantees superinfection with nosocomial gram-negative bacilli, fungi, or both. Cultures obtained from the donor and recipient at the time of transplantation are used to guide perioperative antimicrobial therapy. A basic tenet is that all infections should be eliminated before transplantation.

More than 90 percent of the infections occurring in the first month are the same nosocomial bacterial or candidal infections of the surgical wound, lungs, urinary tract, or vascular-access devices that occur in surgical patients who are not in a state of immunosuppression. The key factors in determining the incidence of such infections are the nature of the operation and the technical skill with which the surgery and postoperative care are accomplished. As with any patient, the risk of postoperative infection increases with the duration of vascular access and use of drainage catheters, the duration of intubation, the presence of indwelling stents and other foreign bodies, and the presence of devitalized tissue or fluid collections. Antimicrobial prophylaxis can only delay the occurrence of infection in such circumstances unless technical or anatomical problems are corrected in conjunction with antimicrobial therapy.

Notable by their absence in the first month after transplantation are such opportunistic pathogens as *Pneumocystis carinii* and *Nocardia asteroides*. The occurrence of infections with these pathogens during this month suggests the presence of an important nosocomial hazard, increased susceptibility resulting from immunosuppression before transplantation, or preexisting infection of the donor or recipient. Although the amounts of immunosuppressive drugs administered are greatest during this period, the

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**Table 1. Factors Affecting the Net State of Immunosuppression in Transplant Recipients.**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunosuppressive therapy: dose, duration, and temporal sequence</td>
<td></td>
</tr>
<tr>
<td>Underlying immune deficiency: autoimmune disease, functional immune deficits</td>
<td></td>
</tr>
<tr>
<td>Integrity of the mucocutaneous barrier: catheters, epithelial surfaces</td>
<td></td>
</tr>
<tr>
<td>Devitalized tissue, fluid collections</td>
<td></td>
</tr>
<tr>
<td>Neutropenia, lymphopenia</td>
<td></td>
</tr>
<tr>
<td>Metabolic conditions</td>
<td>Uremia, Malnutrition, Diabetes</td>
</tr>
<tr>
<td>Alcoholism with cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Infection with immunomodulating viruses</td>
<td>Cytomegalovirus, Epstein–Barr virus, Hepatitis B and C viruses</td>
</tr>
<tr>
<td>Human immunodeficiency virus</td>
<td></td>
</tr>
</tbody>
</table>

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*The New England Journal of Medicine*
main determinant of the net state of immunosuppression is the level of sustained immunosuppression rather than the short-term effects of a particular immunosuppressive regimen.\textsuperscript{1,10}

Infection One to Six Months after Transplantation

After the first month, the nature of infectious diseases in transplant recipients changes. In addition to residual effects of earlier events, new types of infection appear. The immunomodulating viruses (particularly CMV, but also EBV, other human herpesviruses, HBV, HCV, and HIV, if present) begin to exert clinically significant effects. The combination of sustained immunosuppression and viral infection makes possible opportunistic infections due to \textit{Pneumocystis carinii}, aspergillus, and \textit{L. monocytogenes} in the absence of an excessive epidemiologic hazard.

Infection More Than Six Months after Transplantation

Six months after transplantation, patients can be divided into three categories in terms of their infectious-disease problems.

- More than 80 percent of patients have a good result from transplantation and are maintained on minimal long-term immunosuppressive therapy with good allograft function. Their infectious-disease problems are similar to those of the general community and are primarily respiratory. Opportunistic infection is unusual unless a particularly intense environmental exposure has occurred (e.g., the occurrence of nocardiosis or aspergillosis after digging in the garden).
- Approximately 10 percent of patients have chronic or progressive infection with HBV, HCV, CMV, EBV, or (probably) papillomavirus. Such viral infection may cause injury to the infected organ.
in the case of the hepatitis viruses and the retina in the case of CMV) or contribute to cancer (e.g., hepatocellular carcinoma following HBV or HCV infection, lymphoma due to EBV, and squamous-cell cancer due to papillomavirus) (Fig. 2).1,16-21

In 5 to 10 percent of transplant recipients, recurrent or chronic rejection develops, resulting in greater exposure to immunosuppressive agents, which often results in chronic viral infections. These patients are the most likely candidates for opportunistic pathogens, which often results in chronic viral infections. These patients are the most likely candidates for opportunistic infection, including infections with *Pneumocystis carinii*, *L. monocytogenes*, *N. asteroides*, *Cryptococcus neoformans*, and aspergillus.1,6,7,10 Lifelong prophylaxis with trimethoprim–sulfamethoxazole, careful attention to environmental exposure, and consideration of antifungal prophylaxis are needed for these patients.

**EVALUATION OF THE DONOR AND RECIPIENT BEFORE TRANSPLANTATION**

Pretransplantation screening is designed to prevent serious post-transplantation infection, either by excluding a donor or by defining the need for specific antimicrobial therapy after transplantation. Testing of the donor for HBV, HCV, and HIV is of particular importance.22-25 The efficiency of transmission of HBV or HIV from an infected donor approaches 100 percent if the donor is positive for hepatitis B surface antigen (HBsAg) or for HIV. Testing for HIV may be supplemented by the exclusion of some donors on the basis of high-risk behavior. Testing for the presence of HBsAg is effective in preventing the transmission of HBV at the time of transplantation. Recently, preliminary data suggested that some liver donors who had antibodies to hepatitis B core antigen and were seronegative for HBsAg transmitted HBV to liver-transplant recipients. Such donors are thought to pose little risk of transmitting HBV infection through organs other than the liver; HBV vaccine is recommended before transplantation for the recipients. In HBV-infected patients undergoing liver transplantation, hyperimmune globulin is useful in protecting the allograft from the consequences of recurrent infection.

Although there is general agreement that organs from donors with active HBV or HIV infection
should not be used, there is controversy regarding donors who are seropositive for antibodies to hepatitis C virus (anti-HCV). The risk of transmitting HCV with an extrahepatic allograft from a donor who is positive for anti-HCV is approximately 50 percent, with the risk approaching 100 percent if the donor’s blood contains HCV RNA by the polymerase-chain-reaction assay. In the United States approximately 5 percent of cadaveric donors are positive for anti-HCV. Given the extreme shortage of donor organs, controversy has developed over the use of organs from donors positive for anti-HCV. Current data suggest that HCV infection does not have a major effect on the survival of the patient in the first five years after transplantation, but the long-term effects are not yet clear.

Our approach has been to transplant organs from anti-HCV–positive donors only into critically ill patients awaiting heart, liver, or lung allografts, older patients with a limited expected life span, or patients awaiting renal transplantation who have been unable to find a suitable donor because of prior sensitization to major-histocompatibility-complex (MHC) antigens, for whom a particular matched donor represents a unique opportunity. Organs from donors positive for anti-HCV are not used for younger patients. Donors and recipients are evaluated serologically for other latent infections that can be transmitted with the allograft: CMV, EBV, Toxoplasma gondii, and syphilis are the most important.

Before transplantation the recipient undergoes tuberculin skin testing and serologic testing for histoplasma, coccidioides, strongyloides, and trypanosoma when specifically indicated. These tests are often less informative when performed after transplantation. Patients who are seronegative for varicella–zoster virus are at risk for life-threatening primary infection. Seronegative patients should be immunized against varicella before transplantation and, unless a persistent vaccine response is demonstrated, should receive varicella immune globulin and antiviral prophylaxis in case of varicella–zoster virus exposure after transplantation.

The care of tuberculin-positive transplant recipients is influenced by the increased risk of active tuberculosis during immunosuppression, by the potential for clinically significant hepatotoxicity from isoniazid and rifampin, and by alterations in the metabolism of cyclosporine and tacrolimus caused by antituberculous agents. The worldwide incidence of post-transplantation tuberculosis is approximately 0.8 percent; a positive skin test without additional risk factors is rarely associated with reactivation. However, both reactivation disease and primary infection occur at a higher rate in developing regions. The use of antituberculous agents is further complicated by a 10 to 15 percent incidence of chronic liver dysfunction in transplant recipients, due primarily to hepatitis C. Important risk factors for reactivation include nonwhite race, a history of active tuberculosis, the presence of a marked abnormality on the chest radiograph, exposure to a person with a confirmed case of tuberculosis, skin-test conversion, and the presence of other immunosuppressive processes (e.g., protein–calorie malnutrition).

The optimal treatment of tuberculin-positive patients after transplantation remains controversial. If the patient is reliable and close clinical follow-up with chest radiography twice a year is possible, no therapy is prescribed after transplantation for tuberculin-positive patients who have no additional risk factors. For those with one or more risk factors, including residence in regions of endemic disease or rejection necessitating higher levels of maintenance immune suppression, 9 to 12 months of isoniazid is prescribed, usually beginning after the immunosuppressive program has been stabilized.

**PRINCIPLES OF ANTIMICROBIAL THERAPY IN TRANSPLANT RECIPIENTS**

**Strategies for Antimicrobial Therapy**

There are three ways to use antimicrobial therapy in transplant recipients. Therapeutic use is the treatment of established clinical infection. Prophylactic use is the administration of antimicrobial agents to an entire population of patients in order to prevent a form of infection that is important enough to justify such an intervention. Preemptive use is the administration of therapy to a subgroup of patients defined by clinical or epidemiologic characteristics or by the results of a laboratory test that predicts a high rate of clinically significant disease. Because of the emphasis on the prevention of infection, particular attention is paid to prophylactic and preemptive strategies. In all patients, exogenous immune suppression must be reduced as much as possible to optimize both the prevention and the treatment of infection.

**Prophylaxis**

By far the most effective prophylactic therapy in transplant recipients is the use of trimethoprim–sulfamethoxazole for the first 4 to 12 months after transplantation (one single-strength tablet containing 80 mg of trimethoprim and 400 mg of sulfamethoxazole daily) in all patients who tolerate this combination agent. At most centers the incidence of Pneumocystis carinii pneumonia in patients who do not receive prophylaxis is 10 to 12 percent. The routine use of trimethoprim–sulfamethoxazole has effectively eliminated these infections, as well as reduced the risk of infection with many common respiratory pathogens, such as L. monocytogenes, N. asteroides, and T. gondii. In renal-transplant recipients, trimethoprim–sulfamethoxazole decreases the incidence of urinary tract infection in the first six months from...
30 to 60 percent to less than 5 percent.\textsuperscript{1,6,32} The dose and duration of prophylaxis must be individualized.

In organ-transplant recipients receiving prophylaxis with low-dose trimethoprim–sulfamethoxazole, the incidence of toxoplasmosis is low, as in patients with the acquired immunodeficiency syndrome receiving such prophylaxis. The group of patients at highest risk for active and disseminated toxoplasmosis consists of cardiac-transplant recipients who are seronegative for \textit{T. gondii} and receive an allograft from a seropositive donor.\textsuperscript{6,11,34,36} Symptomatic primary toxoplasmosis (transmitted by the donor organ) in heart-transplant recipients generally presents as myocarditis or cardiomyopathy (often with arrhythmia or heart failure), but occasionally as encephalitis or chorioretinitis. In these patients the risk of symptomatic disease is high (50 to 75 percent), and specific antitoxoplasmosis treatments that also provide protection against \textit{Pneu. carinii} (e.g., pyrimethamine and a sulfonamide) are usually substituted for trimethoprim–sulfamethoxazole for the first six months after transplantation.\textsuperscript{1,32,34,36}

**Preemptive Therapy**

Preemptive therapy takes two forms. The first links the administration of antimicrobial therapy to a clinical event or characteristic in an asymptomatic person; for example, administration of low-dose ganciclovir to patients seropositive for CMV who are receiving antilymphocyte-antibody therapy for rejection. The second approach entails the routine use of highly specific microbiologic assays to monitor patients thought to be at risk for a clinical disease before they become symptomatic. Such assays might detect respiratory colonization by aspergillus (which is followed by invasive disease in approximately 65 percent of transplant recipients) or CMV viremia and form the basis of appropriate preemptive therapy.

**Drug Toxicity in Transplant Recipients**

Drug toxicity in transplant recipients is more often due to drug interactions than to the adverse effects of single agents.\textsuperscript{37,38} Drugs that alter the metabolism of cyclosporine and tacrolimus tend to be inducers, inhibitors, or substrates of the hepatic CYP3A (cytochrome P-450-III A) enzyme system. Two CYP3A enzymes (CYP3A4 and CYP3A5) are responsible for most of the metabolism of cyclosporine. The CYP3A system (and CYP1A) are also responsible for tacrolimus metabolism, resulting in a drug-interaction profile similar to that of cyclosporine.

Three common types of drug interactions with antimicrobial agents occur in transplant recipients.

Up-regulation of the metabolism of cyclosporine or tacrolimus results in lower blood levels for a given dose of the immunosuppressive agent and an increased risk of rejection. Such drugs as rifampin, isoniazid, and nafcillin commonly have this effect.

Down-regulation of the metabolism of cyclosporine or tacrolimus results in higher blood levels for a given dose of the immunosuppressive agent and the possibility of nephrotoxicity, excessive immunosuppression, and an increased risk of life-threatening infection. Two classes of antimicrobial agents commonly have this effect: macrolides (erythromycin, clarithromycin, and azithromycin) and theazole antifungal agents (ketoconazole, itraconazole, and fluconazole).\textsuperscript{37,39}

Nephrotoxicity of two types may result from the interaction of therapeutic blood levels of the immunosuppressive agents with antimicrobial agents.\textsuperscript{37,40} First, certain antimicrobial agents, such as fluoroquinolones and trimethoprim–sulfamethoxazole, are well tolerated at low doses but produce cyclosporine- or tacrolimus-associated nephrotoxicity at higher doses.\textsuperscript{37,38} For example, in transplant recipients treated with cyclosporine or tacrolimus, ofloxacin, a fluoroquinolone, is well tolerated at doses of 200 to 400 mg a day, but not at higher doses. Trimethoprim–sulfamethoxazole is well tolerated at doses of up to one double-strength tablet a day, but not at doses needed to treat established pneumocystis pneumonia. Second, some antimicrobials, such as amphotericin and the aminoglycosides, can cause nephrotoxicity even at the first dose, and the incidence of nephrotoxicity increases with each succeeding dose.

In an attempt to avoid these interactions and toxic effects of antibiotic agents, \(\beta\)-lactam antibiotics, low-dose fluoroquinolones, and moderate doses of fluconazole have become the cornerstones of antimicrobial therapy in transplant recipients. Furthermore, the clinician must be prepared to adjust the immunosuppressive regimen both when antimicrobial therapy is begun and after it is completed. The importance of effective prophylaxis is clear, given the toxic effects associated with the treatment of infection.

**INFECTIONS OF PARTICULAR IMPORTANCE IN TRANSPLANT RECIPIENTS**

**CMV**

The most important pathogen affecting transplant recipients is CMV, which causes both direct effects, including tissue injury and clinical disease, and a variety of indirect effects diagrammed in Figure 2 and listed in Table 2.\textsuperscript{31,42} As a herpesvirus, CMV has two properties that determine its role in transplantation: latency and cell association. Once infected (the laboratory marker of infection is seropositivity), the patient harbors the virus for life. Activation from latency is induced by many of the factors present in transplant recipients: therapy with antilymphocyte antibodies and cytotoxic drugs, allogeneic reactions,
The direct effects of acute CMV infection in transplant recipients usually include otherwise unexplained fever with constitutional symptoms and laboratory abnormalities, including leukopenia, thrombocytopenia, mild atypical lymphocytosis, and mild hepatitis. The myriad indirect effects of CMV in transplant recipients are explained by the following observations. The virus replicates in a wide variety of cell types, including epithelial cells, endothelial cells, lymphocytes, mononuclear cells, and a variety of parenchymal cells. CMV activates cellular DNA, messenger RNA, and protein synthesis, resulting in the production of Fc receptors, intercellular adhesion molecules, viral proteins, and other proteins.

The impact of these CMV-induced effects on the organ transplant itself is potentially great. The transplanted organ appears to be more susceptible to the direct effects of CMV infection than are the native organs. Allograft infection may allow CMV to persist for several months, and the allograft may continue to be infected for years. The exact nature of the interaction between the dysfunctions of CMV and CMV infection is controversial in the absence of specific pathological changes or direct evidence of CMV infection.

Serologic tests are of great importance in defining the clinical risk from CMV at the time of transplantation. Seronegative recipients of organs from seropositive donors have a greater than 50 percent risk of symptomatic disease. However, serologic tests (whether serum antibody titers or measurements of IgM antibodies) have little diagnostic value thereafter. The diagnosis of disease due to CMV is accomplished by demonstrating viremia or tissue invasion. Currently, the best approaches to the diagnosis of CMV disease are either tests for antigenemia or quantitative polymerase-chain-reaction assays using blood samples (both of which give accurate information in a timely fashion) or the demonstration of virus by biopsy of infected tissues.

### Table 2. Effects of Cytomegalovirus in Transplant Recipients

<table>
<thead>
<tr>
<th>Effect</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct effects (acute)</td>
<td>Asymptomatic viral shedding, seroconversion, or both</td>
</tr>
<tr>
<td>Acute viral syndromes: febrile or mononucleosis-like illness</td>
<td>Fever and myalgia</td>
</tr>
<tr>
<td>Leukopenia or thrombocytopenia</td>
<td>Pneumonitis: nonproductive cough (pulmonary interstitial infiltrates)</td>
</tr>
<tr>
<td>Infection of allograft: hepatitis, pneumonitis, nephritis, myocarditis, or pancreatitis</td>
<td>Pneumonitis: nonproductive cough (pulmonary interstitial infiltrates)</td>
</tr>
<tr>
<td>Infection of native tissues (retina, gastrointestinal tract, pancreas) or encephalitis</td>
<td>Pneumonitis: nonproductive cough (pulmonary interstitial infiltrates)</td>
</tr>
</tbody>
</table>

*The role of cytomegalovirus in causing this effect remains controversial.*

and systemic infection and inflammation. Thus, systemic inflammation accompanied by the release of tumor necrosis factor and other proinflammatory cytokines stimulates a variety of intracellular messengers (e.g., the nuclear transcription factor NF-κB), which initiate activation of CMV from latency and resulting viral replication (Fig. 2). CMV is highly cell-associated, with the key host defense being MHC-linked, virus-specific cytotoxic T lymphocytes. Different forms of immunosuppression used in organ transplantation affect different aspects of viral infection; antilymphocyte antibodies and cytotoxic drugs enhance viral activation from latency, whereas cyclosporine, tacrolimus, and corticosteroids promote the persistence and spread of virus by suppressing the host’s antiviral immune responses.

Serologic tests are of great importance in defining the clinical risk from CMV at the time of transplantation. Seronegative recipients of organs from seropositive donors have a greater than 50 percent risk of symptomatic disease. However, serologic tests (whether serum antibody titers or measurements of IgM antibodies) have little diagnostic value thereafter. The diagnosis of disease due to CMV is accomplished by demonstrating viremia or tissue invasion. Currently, the best approaches to the diagnosis of CMV disease are either tests for antigenemia or quantitative polymerase-chain-reaction assays using blood samples (both of which give accurate information in a timely fashion) or the demonstration of virus by biopsy of infected tissues.
planted by a factor of 7 to 10. This observation is consistent with the effect of CMV-associated cytokines, growth factors, and immune suppression.

Treatment of clinical CMV disease usually requires administration of intravenous ganciclovir for two to four weeks; clearance of viremia should be documented before intravenous therapy is stopped. Such proof of cure is necessary to prevent relapse (the incidence of which is 50 to 75 percent in patients with primary infection and 10 to 20 percent in seropositive patients) and to limit the development of resistance to ganciclovir. Some centers add anticytomegalovirus hyperimmune globulin to the treatment of severe or relapsing disease, whereas others follow the intravenous course with two to three months of oral therapy. Low serum levels of ganciclovir, such as those achieved with oral therapy, may be associated with the development of ganciclovir resistance in the presence of high levels of replicating virus. Ganciclovir-resistant CMV may be treated with foscarnet, despite its inherent toxicity, or with combinations of antiviral agents.

The prevention of CMV infection is of great importance. Although there is no consensus about the optimal regimen for prophylaxis against CMV, three points are worth emphasizing. First, the intensity of prophylaxis must be proportional to the intensity of immunosuppression and to the risk of viral reactivation (e.g., when intravenous ganciclovir is given during antilymphocyte-antibody therapy). Second, prophylaxis must be initiated before reactivation of the virus. Third, to prevent relapses after premature termination of prophylaxis, effective antiviral prophylaxis with negative surveillance studies must be maintained for at least three months.

EBV and Post-Transplantation Lymphoproliferative Disease

Active replication of EBV is present in 20 to 30 percent of transplant recipients who are receiving immunosuppressive drugs for maintenance therapy, and in more than 80 percent of those receiving antilymphocyte-antibody therapy. Although a mononucleosis-like syndrome (usually heterophile-negative in this patient population) similar to that produced by CMV has been identified in some patients, the critical effect of EBV is its role in the pathogenesis of post-transplantation lymphoproliferative disease. This disorder is usually a B-cell lymphoproliferative process ranging in severity from a benign polyclonal process that wanes when immunosuppressive therapy is decreased (often in pediatric recipients) to a highly malignant monoclonal lymphoma that is resistant to all forms of treatment. Post-transplantation lymphoproliferative disease is often extranodal in presentation, with invasion of the brain, bone marrow, allograft, gastrointestinal tract, and liver not uncommon. Both antilymphocyte antibodies and cyclosporine or tacrolimus contribute to the pathogenesis of post-transplantation lymphoproliferative disease by causing the reactivation of latent EBV infection and, most likely, the loss of immune surveillance against EBV-immortalized B cells. Other risk factors for post-transplantation lymphoproliferative disease include primary EBV infection, a high level of viral replication in the oropharynx, and preceding CMV disease. Other than the reducing or stopping of all immunosuppressive therapies, optimal treatment of these patients remains to be defined.

Fever and Pneumonitis

Pulmonary infection is the most common form of tissue-invasive infection observed in transplant recipients. The important principle in treating these patients is that there is a reasonable chance of full rehabilitation if microbiologic cure is achieved. Early diagnosis and specific therapy are the cornerstones of cure. Therefore, invasive diagnostic techniques are justifiable in transplant recipients, and the rule is to be aggressive in pursuing early diagnosis and specific therapy.

The depressed inflammatory response of immunosuppressed transplant recipients may greatly modify or delay the appearance of pulmonary lesions on the radiograph. The presentation and evolution of the findings on chest radiography provide important clues to both the differential diagnosis of pulmonary infection in transplant recipients and the appropriate diagnostic workup (Table 3). Computed tomography (CT) of the chest has revolutionized the evaluation of immunocompromised patients. CT is particularly useful when the chest radiograph is negative or when the radiographic findings are subtle or nonspecific. It is also essential to the definition of the extent of the disease process and the selection of the optimal invasive technique to achieve microbiologic diagnosis — for example, needle aspiration for focal pleural-based lesions and transbronchial or thoracoscopic biopsy for diffuse parenchymal disease. Particularly with opportunistic fungal or nocardial infections, precise knowledge of the extent of the infection at diagnosis and the response of all sites to therapy will lead to the best therapeutic outcome. Therapy should be continued until infection has been eliminated at all sites. Atypical CT findings may suggest the presence of dual or sequential infection of the lungs, a situation that is common in transplant recipients.

Central Nervous System Infection

Central nervous system infection in transplant recipients has four distinct patterns. Acute meningitis is usually caused by L. monocytogenes. Subacute or chronic meningitis is usually caused by Crypt. neo-
**Table 3. Differential Diagnosis of Fever and Pulmonary Infiltrates in Organ-Transplant Recipients According to the Abnormality on Chest Roentgenography and Rate of Progression of the Illness.**

<table>
<thead>
<tr>
<th>Radiographic Abnormality</th>
<th>Cause</th>
<th>Subacute or Chronic Illness†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consolidation</td>
<td>Bacteria (including legionella)</td>
<td>Fungi, N. asteroides, tuberculosis</td>
</tr>
<tr>
<td></td>
<td>Thromboembolism</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td></td>
<td>Hemorrhage</td>
<td>Viruses, drug reactions, radiation, Pneumocystis carinii</td>
</tr>
<tr>
<td></td>
<td>Pulmonary edema</td>
<td>N. asteroides, tuberculosis, fungi, tuberculosis</td>
</tr>
<tr>
<td>Peribronchovascular abnormality</td>
<td>Pulmonary edema</td>
<td>Viruses, Pneumocystis carinii, radiation, drug reactions (occasionally</td>
</tr>
<tr>
<td></td>
<td>Leukocytosis reaction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bacteria</td>
<td>N. asteroides, tumor, fungi, tuberculosis</td>
</tr>
<tr>
<td>Nodular infiltrate‡</td>
<td>Bacteria (including legionella)</td>
<td>Fungi, N. asteroides</td>
</tr>
<tr>
<td></td>
<td>Pulmonary edema</td>
<td>Tuberculosis, Pneumocystis carinii</td>
</tr>
</tbody>
</table>

*Adapted from Rubin and Green.†

†An acute illness is defined as one that develops and requires medical attention in less than 24 hours. A subacute or chronic illness develops over a period of several days to weeks.

‡A nodular infiltrate is defined as one or more focal defects more than 1 cm² in area on chest radiography with well-defined borders, surrounded by acedent lung. Multiple tiny nodules of smaller size are seen in a wide variety of disorders (e.g., cytomegalovirus or varicella–zoster virus infection) and are not included here.

formans, although systemic infection with M. tuberculosis, L. monocytogenes, H. capsulatum, N. asteroides, S. stercoralis, or Coccioidiomycosis, or EBV–associated post-transplantation lymphoproliferative disease, can cause an identical clinical syndrome (fever and headache–evolving over several weeks, sometimes associated with an altered state of consciousness). Focal brain infection, presenting with seizures or focal neurologic abnormalities, may be caused by L. monocytogenes, T. gondii, or N. asteroides, and occasionally by EBV–associated post-transplantation lymphoproliferative disease, but it is most commonly the result of metastatic aspergillus infection. Finally, progressive dementia, with or without focal abnormalities or seizures, may be related to progressive multifocal leukoencephalopathy due to the papova-virus known as the JC virus; to infections with other viruses, including herpes simplex virus, CMV, and EBV; and occasionally to demyelination or other toxic effects of cyclosporine or tacrolimus. Together, L. monocytogenes, Cryptococcus neoformans, and Aspergillus fumigatus account for most of the central nervous system infections in transplant recipients.

The presentation of central nervous system infection in transplant recipients can be very different from that in normal patients. In particular, the anti-inflammatory effects of immunosuppressive therapy may obscure signs of meningeal inflammation associated with meningitis; changes in the level of consciousness may be subtle. The most reliable constellation of symptoms that suggests central nervous system infection includes unexplained fever and headache, which necessitates a complete and urgent neurologic evaluation by CT of the head and lumbar puncture.

**CONCLUSIONS AND FUTURE DIRECTIONS**

Infection and rejection, the two primary barriers to successful organ transplantation, are inextricably linked. The optimal treatment of the transplant recipient has two components: an immunosuppressive regimen to prevent and treat graft rejection, and an antimicrobial strategy that is closely tied to the specifics of the immunosuppressive program in the individual patient. As new immunosuppressive programs are defined, new antimicrobial programs will be necessary. To increase the safety of organ transplantation further, we need improved diagnostic tests to detect infection early and to monitor immune function, as well as new therapies to overcome antimicrobial resistance.

**REFERENCES**