INTRODUCTION

Solid organ transplantation is a therapeutic option for many human diseases. Liver, kidney, heart, and lung transplantation have become standard therapy for selected end-stage diseases; pancreas (including islet cell) and small bowel transplantation are also being evaluated in this regard. The quality of life and survival rates following organ transplantation have greatly improved due to advances in surgical technique, immunosuppressive therapy, and medical management. However, complications such as infection and allograft rejection, which are related by immunosuppressive therapy, remain major causes of morbidity and mortality following solid organ transplantation. The level of immunosuppression in any given patient is determined by several factors. First, the dose, duration, and temporal sequence in which immunosuppressive medications are administered must be considered (582). Recently, a number of new immunosuppressive agents have been introduced and marketed (Table 1). Most of these agents depress cell-mediated immunity; however, blunted antibody responses and leukopenia may also be a result of the use of these agents. The resultant depressed cell-mediated immunity leads to increased...
TABLE 1. Immunosuppressive agents used in solid organ transplantation

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of action</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>Down-modulates lymphocyte and macrophage function; impedes other aspects of inflammatory response</td>
<td>Major cause of bone loss posttransplantation; effective pan T-cell and macrophage inhibition</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Inhibits cell proliferation, interfering with DNA synthesis</td>
<td>Associated with leukopenia</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Blocks T-cell activation targeting calcineurin, inhibits cytokine production (IL-2, IFN-γ, etc.)</td>
<td>Elevated levels associated with fluconazole, itraconazole, and ketoconazole use; nephro- and neurotoxicity</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Depletes T cells; impairs T-cell function via down-regulation of T-cell receptor-CD3 complex</td>
<td>Seldom used except as a substitute for other immunosuppressive agents</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Decreases antigen-driven lymphocyte proliferation</td>
<td>Unknown effect on opportunistic infections</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>Inhibits IMP dehydrogenase, selectively suppressing proliferation of T and B lymphocytes</td>
<td>As for cyclophosphamide</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Blocks proliferation of cycling cells</td>
<td>Adverse effects include fever, chills, and other cytokine-related (TNF-α) side effects</td>
</tr>
<tr>
<td>OKT3 monoclonal antibody</td>
<td>Depletes T cells; impairs T-cell function</td>
<td></td>
</tr>
<tr>
<td>Antilymphocyte globulin</td>
<td>Depletes lymphocytes</td>
<td></td>
</tr>
<tr>
<td>Antithymocyte globulin</td>
<td>Depletes T cells; inhibits T-cell activation</td>
<td></td>
</tr>
<tr>
<td>Total lymphoid irradiation</td>
<td>Inhibits development of primary antigen-specific response</td>
<td></td>
</tr>
</tbody>
</table>

a IL-2, interleukin-2; IFN-γ, gamma interferon; TNF-α, tumor necrosis factor alpha.

susceptibility to intracellular pathogens (e.g., Toxoplasma gondii) and the herpesviruses, similar to the situation in human immunodeficiency virus (HIV)-infected patients. However, in contrast to this group of patients, organ transplant recipients are most intensely immunosuppressed early in the posttransplantation period and become progressively less immunosuppressed as immunosuppressive therapy is gradually withdrawn over time. Second, the presence of metabolic abnormalities, such as protein malnutrition, uremia, and hyperglycemia, and the presence of damage to mucocutaneous barriers and foreign bodies that interrupt these barriers, such as intravenous lines, endotracheal tubes, urinary catheters, and chest and biliary tubes, are important factors (582). Third, the presence of immunomodulating viruses, such as cytomegalovirus (CMV) and HIV contribute to the net level of immunosuppression (582).

The optimal approach to infection in the solid organ transplant recipient is prevention; failing this, its prompt and aggressive diagnosis and therapy are essential. The sources of infectious agents posttransplantation include endogenous organisms, the allograft itself, and the environment. An important principle to consider when evaluating solid-organ transplant recipients (and other immunocompromised hosts) for infection is that the usual inflammatory response to an infectious organism may be attenuated due to immunosuppressive therapy and that therefore the signs and symptoms of infections may be blunted and diagnostic techniques may be compromised. Because of this, aggressive and often invasive investigations of seemingly minor findings may be warranted. This is important because solid-organ transplant recipients have the potential to live a normal life for many years, assuming that their allograft function remains satisfactory and that they do not suffer from serious infections.

In this article, we present a review of infections in the solid-organ transplant recipient, beginning with a discussion of pretransplantation infectious diseases evaluation and an overview of the timing of infection posttransplantation and then focusing on individual types of infection.
TABLE 2. Pretransplantation infections diseases evaluation

<table>
<thead>
<tr>
<th>History</th>
<th>Antibiotic allergies: probable or documented</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imunosuppressive therapy: type and duration (current or past)</td>
<td>Past medical history: infectious diseases</td>
</tr>
<tr>
<td>Oral: dental caries, sinusitis, pharyngitis, HSV infection</td>
<td>Cardiovascular: valvular heart disease, heart murmur (need for endocarditis prophylaxis)</td>
</tr>
<tr>
<td>Respiratory: pneumonia, tuberculosis</td>
<td>Gastrointestinal: diverticulitis, diarrheal disease, hepatitis A, B, or C, intestinal parasitic infection</td>
</tr>
<tr>
<td>Genitourinary: urinary tract infections, prostatitis, vaginitis, genital herpes, genital warts, syphilis, gonorrhea, pelvic inflammatory disease, chlamydial infection</td>
<td></td>
</tr>
<tr>
<td>Cutaneous: skin and nail infections, varicella, and zoster</td>
<td>Osteoarticular: osteomyelitis, prosthetic joint(s)</td>
</tr>
<tr>
<td>Childhood illnesses: chicken pox, measles, rubella</td>
<td>Immunization vaccines several months prior to transplantation (219).</td>
</tr>
<tr>
<td>Other: mononucleosis, other infectious diseases not included above</td>
<td>Exposure history</td>
</tr>
<tr>
<td>Travel history: prior residence in or travel to areas associated with the geographically restricted endemic mycoses and/or parasitic disease, especially S. stercoralis, malaria, etc.</td>
<td></td>
</tr>
<tr>
<td>Tuberculosis: exposure, prior tuberculous skin testing, chest X-ray abnormality</td>
<td></td>
</tr>
<tr>
<td>Risk factors for blood-borne pathogen infection (including HIV)</td>
<td>Vaccinations</td>
</tr>
<tr>
<td>Animal and pet exposure (including vaccination status of pets):</td>
<td>Tetanus-diphtheria (update)</td>
</tr>
<tr>
<td>Brucella exposure</td>
<td>Influenza</td>
</tr>
<tr>
<td>Occupational exposure: farming, animal husbandry, gardening</td>
<td>Pneumococcus</td>
</tr>
<tr>
<td>Drinking-water source</td>
<td>Hepatitis B</td>
</tr>
<tr>
<td>Exposure to young children</td>
<td>H. influenzae type b (pediatric patients)</td>
</tr>
<tr>
<td>Dietary habits: consumption of raw meat, unpasteurized milk products, and seafood</td>
<td></td>
</tr>
</tbody>
</table>

Physical examination

<table>
<thead>
<tr>
<th>Infectious-diseases testing</th>
<th>Serologic studies of the donor should includ tests for HIV-1 and HIV-2, HTLV-1, syphilis, hepatitis B virus (HBV), hepatitis C virus (HCV), CMV, T. gondii, and Epstein-Barr virus (EBV).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculin skin test and limited anergy panel</td>
<td>All potential organ donors are also evaluated for any latent or active infections that may preclude the use of the allograft. Serologic studies of the donor should include tests for HIV-1 and HIV-2, HTLV-1, syphilis, hepatitis B virus (HBV), hepatitis C virus (HCV), CMV, T. gondii, and Epstein-Barr virus (EBV).</td>
</tr>
<tr>
<td>Chest and sinus X rays</td>
<td>All allografts from donors who are seropositive for HIV-1 or HIV-2 should not be used for transplantation. The use of allografts from donors seropositive for HBV and/or HCV is controversial and is discussed in a later section. Donor sero-positivity for CMV, T. gondii, and EBV is not a contraindication to the use of the allograft but provides important information vis-à-vis the risk of reactivation of these agents in the recipient(s) posttransplantation (see later sections). Other donor-transmitted infectious agents, such as Treponema pallidum and H. capsulatum, should be considered on a case-by-case basis.</td>
</tr>
<tr>
<td>Urine analysis and culture for bacteria</td>
<td></td>
</tr>
<tr>
<td>Stool culture and examination for ova and parasites</td>
<td></td>
</tr>
<tr>
<td>Serologic tests: CMV, VZV, EBV, HSV, T. gondii, syphilis, HBV, HCV, HIV (geographically restricted endemic mycoses if history of exposure present [see text])</td>
<td></td>
</tr>
</tbody>
</table>

Vaccinations

<table>
<thead>
<tr>
<th>Vaccinations</th>
<th>Vaccine several months prior to transplantation; however, studies are required to document the safety of this approach (219).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetanus-diphtheria (update)</td>
<td>A recent study has demonstrated the safety of the varicella vaccine in pediatric renal transplant recipients, and strong consideration should be given to immunization of transplant candidates with no history of chicken pox (795). Immunization with live vaccines should be done as early as possible prior to transplantation. All transplantation recipients should receive influenza vaccinations yearly. The pneumococcal vaccine should be administered every 5 to 6 years, although the immune response to these vaccines may be impaired in transplantation recipients (246, 402, 432, 732).</td>
</tr>
<tr>
<td>Influenza</td>
<td></td>
</tr>
<tr>
<td>Pneumococcus</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td></td>
</tr>
<tr>
<td>H. influenzae type b (pediatric patients)</td>
<td></td>
</tr>
<tr>
<td>Inactivated polio vaccine</td>
<td></td>
</tr>
</tbody>
</table>

Avoidance of Epidemiological Exposures Posttransplantation

Following transplantation, patients are again counseled regarding measures aimed at reducing infection. Patients who are not immune to varicella-zoster virus (VZV) are counseled to avoid exposure to persons with chicken pox or shingles; if such an exposure does occur, a physician should be contacted immediately to administer varicella-zoster immune globulin. All fresh fruits and vegetables should be washed. All meat and seafood should be thoroughly cooked. The source of the patient's drinking water should be reviewed. Patients with cats should avoid changing litter boxes, if possible (if the litter box cannot be avoided, gloves should be worn and the litter box should be changed daily). Gloves should be worn to clean fish aquaria. A mask should be worn when cleaning bird cages if this activity is unavoidable. Patients should avoid contact with people who have colds, influenza, tuberculosis, and other contagious infections. The household environment should be kept clean, and patients should not engage in activities such as cleaning out dusty attics. Towels should not be shared with others unless they are washed between uses. Any plans for travel outside of the United States, Canada, or western Europe should be discussed with the patient's physician prior to departure. All persons living in the same quarters should receive a yearly influenza vaccine, and inactivated rather than oral polio vaccine should be administered to those requiring polio vaccination, because the vaccine strain can be transmitted to household contacts (24).

DONOR-RELATED TRANSMISSION OF INFECTIOUS AGENTS

All potential organ donors are also evaluated for any latent or active infections that may preclude the use of the allograft. Serologic studies of the donor should include tests for HIV-1 and HIV-2, HTLV-1, syphilis, hepatitis B virus (HBV), hepatitis C virus (HCV), CMV, T. gondii, and Epstein-Barr virus (EBV).

Allografts from donors who are seropositive for HIV-1 or HIV-2 should not be used for transplantation. The use of allografts from donors seropositive for HBV and/or HCV is controversial and is discussed in a later section. Donor sero-positivity for CMV, T. gondii, and EBV is not a contraindication to the use of the allograft but provides important information vis-à-vis the risk of reactivation of these agents in the recipient(s) posttransplantation (see later sections). Other donor-transmitted infectious agents, such as Treponema pallidum and H. capsulatum, should be considered on a case-by-case basis.

TIMING OF INFECTIONS POSTTRANSPLANTATION

There are three time frames, influenced by surgical factors, the level of immunosuppression, and environmental exposures, during which infections of specific types most frequently occur posttransplantation. These include the first month; the second through the sixth months, and the late posttransplant period (beyond the sixth month).

Most infections during the first month posttransplantation are related to surgical complications. These include bacterial and candidal wound infections, pneumonia, urinary tract infection, line sepsis, and infections of biliary, chest, and other drainage catheters; these are similar to infections occurring in general surgical patients. In general, any episode of unexplained fever or bacteremia occurring in the early posttransplantation period should be suspected as being caused by technical or anatomical problems related to the allograft. A thorough understanding of the technical aspects of transplantation is essential when caring for patients with infectious disease syndromes posttransplantation. For example, the biliary
anastomoses most commonly present in liver transplantation recipients include the choledochocholangioplasty and the Roux-en-Y choledochojejunostomy. The former is preferred because it maintains the native sphincter of Oddi. The latter is used in situations where there are abnormalities of the extrahepatic biliary system, such as in patients with primary sclerosing cholangitis, in patients undergoing retransplantation, and in patients with previous bile duct surgeries, but it predisposes to reflux of enteric organisms into the biliary system with a resultant higher risk of infection (503).

In the first month posttransplantation, renal and pancreas transplant recipients are at risk for perigraft hematomas, lymphoceles, and urinary leaks. Liver transplant recipients are at risk for portal vein thrombosis, hepatic vein occlusion, hepatic artery thrombosis, and biliary stricture formation and leaks. Heart transplant recipients are at risk for mediastinitis and infection at the aortic suture line, with resultant mycotic aneurysm, and lung transplantation recipients are at risk for disruption of the bronchial anastomosis.

The only common viral infection during the first month posttransplantation is reactivated herpes simplex virus (HSV) infection in individuals seropositive for this virus prior to transplantation. The prophylactic use of acyclovir during this period has, however, significantly reduced its incidence. Notably, pathogens classically associated with intense cell-mediated immunosuppression are rarely seen during this period.

The period from the second to sixth months posttransplantation is the time during which infections “classically” associated with transplantation manifest. Opportunistic pathogens such as CMV, Pneumocystis carinii, Aspergillus spp., Nocardia spp., T. gondii, and Listeria monocytogenes manifest during this period. These are discussed more thoroughly in the sections that follow.

In addition, during the early and middle periods, reactivation disease syndromes are occasionally encountered due to organisms present in the recipient prior to transplantation. The introduction of high-dose immunosuppression may result in clinical illness due to reactivation of Mycobacterium tuberculosis, an occult focus of bacterial infection, viral hepatitis, H. capsulatum, or C. immitis. Chronic or latent infection of the donor which involves the allograft, such as HIV, HBV, HCV, or fungal or mycobacterial infection, may be transmitted to the immunosuppressed recipient and become clinically apparent during the early and middle periods.

From 6 months posttransplantation onward, most transplantation recipients do relatively well, suffering from the same infections seen in the general community. These include influenza virus infection, urinary tract infection, and pneumococcal pneumonia. The only opportunistic viral infection commonly seen during this period is reactivated VZV infection manifesting as herpes zoster. Rarely, CMV retinitis occurs. Two situations predispose patients to other infection in this late posttransplantation period. First, patients who have had frequent episodes of acute rejection requiring augmented immunosuppressive therapy or those with chronic rejection who are maintained at a higher baseline level of immunosuppression remain at risk for the opportunistic agents more classically seen in the second to sixth months posttransplantation (C. neoformans, CMV, P. carinii, L. monocytogenes, and Nocardia spp.). Second, patients with chronic infections, such as HIV, HBV, and HCV infections, may suffer from morbidity associated with these agents.

In transplantation recipients undergoing retransplantation, the aforementioned timetable may be altered, with infections characteristic of any given period occurring simultaneously and, in general, with an increased severity of infection.

### TABLE 3. Incidence of infectious diseases in solid-organ transplant recipients

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>Incidence of infection (%)&lt;sup&gt;a&lt;/sup&gt; in patients receiving:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Liver</td>
</tr>
<tr>
<td><strong>Bacterial</strong></td>
<td></td>
</tr>
<tr>
<td>Bacterial</td>
<td>33–68</td>
</tr>
<tr>
<td>CMV</td>
<td>22–29</td>
</tr>
<tr>
<td>HSV</td>
<td>3–44</td>
</tr>
<tr>
<td>VZV</td>
<td>5–10</td>
</tr>
<tr>
<td>Candida spp.</td>
<td>1–26</td>
</tr>
<tr>
<td>Mycelial fungi</td>
<td>2–4</td>
</tr>
<tr>
<td>P. carinii</td>
<td>4–11</td>
</tr>
</tbody>
</table>

<sup>a</sup> Data are from large studies in a variety of transplantation centers (31, 38, 119, 133, 203, 213, 217, 218, 242, 251, 299, 301, 317, 369, 376, 379, 412, 414, 434, 464, 509, 514, 519, 529, 585, 637, 714, 736, 748, 754, 775).

#### BACTERIAL INFECTIONS

The types of bacterial infections observed following solid-organ transplantation are divided as follows: (i) those related to the transplantation operation or to its technical complications; (ii) those related to prolonged hospitalization (i.e., nosocomial infections); (iii) those related to the immunosuppressive treatment (e.g., L. monocytogenes meningitis); and (iv) those occurring months after the operation, when the immunosuppressed patient has resumed normal life (e.g., community-acquired pneumonia) (513).

#### Common Bacterial Infections

Bacterial infections occur in 33 to 68% of liver transplant recipients, 21 to 30% of heart transplant recipients, 35% of pancreas transplant recipients, 47% of kidney transplant recipients, and 54% of lung transplant recipients, although the severity of infection varies among these populations (38, 75, 133, 217, 218, 242, 512, 414, 450, 509, 514, 519, 736) (Table 3).

In liver transplant recipients, bacterial infections of the liver, biliary tract, peritoneal cavity, bloodstream, and surgical wound are most common. Most such infections occur within the first 2 months following transplantation (414, 519). Many of these infections are related to technical problems with the liver graft, such as bile leaks or biliary obstruction. Bacterial liver abscesses are sometimes associated with biliary strictures but more often are related to ischemia of the allograft from thrombosis of the hepatic artery. Computed tomography, ultrasonography, cholangiography, and angiography are required to evaluate anatomical abnormalities (168). The flora for these infections typically involves enterococci, anaerobes, gram-negative enteric rods, and staphylococci. Recently, infections with vancomycin-resistant enterococci have been seen in many liver transplant centers, and there has even been a report of bacteremia due to vancomycin-dependent Enterococcus faecium in a recipient of small-bowel and liver transplants (241). Risk factors for bacterial infections in liver transplant recipients include CMV infection, acute rejection, prolonged hospitalization, increased operative transfusion requirement, prolonged duration of surgery, rejection, reoperation, elevated creatinine levels, retransplantation, and elevated bilirubin levels; pretransplantation antibacterial agents may have a protective effect (133, 218, 427, 519, 736). In liver transplant recipients, the presence of a Roux-en-Y choledochojejunostomy increases the risk of sepsis overall, infectious complications related to liver biopsy, and enterococcal and pseudomonas bacteremia (83,
Selective bowel decontamination is used to prevent colonization of the oral cavity and gastrointestinal tract by aerobic gram-negative bacilli and fungi while sparing the anaerobic gut flora (675), thus preserving the antagonistic activity related to the anaerobic gut flora (colonization resistance) (724). Selective bowel decontamination has little effect on the anaerobic and gram-positive aerobic bacterial flora. A preponderance of gram-positive infections, including infections caused by unusual organisms such as Lactobacillus spp., has been noted after liver transplantation when selective bowel decontamination is used (503, 514). Several studies of selective bowel decontamination in liver transplantation recipients have been performed. Several nonrandomized trials have suggested that the use of a selective bowel decontamination regimen can reduce bacterial infections (229, 549, 578, 580, 767–770). Randomized, controlled trials have recently shown that selective bowel decontamination significantly reduces gram-negative infections in liver transplantation recipients (28, 646).

The most common type of infection in the lung transplant recipient is pulmonary (82). Pulmonary infections are more common in lung transplant recipients than in other organ recipients for several reasons (509). Transplanting lungs from donor to recipient by current techniques results in denervation of the lungs and airways, thus abolishing the cough reflex distal to the tracheal or bronchial anastomosis. In addition, mucociliary clearance is impaired. Rejection leads to airway inflammation, encouraging colonization and infection. Infection may be acquired from the donor lungs or from autocontamination from the native lung in single-lung recipients. The anastomosis is particularly vulnerable to local pathogen colonization, as the suture material present may initiate a local immune response (368). In one study, pulmonary infections occurred in 38% of lung transplant recipients in the first 2 weeks following transplantation; the most common bacterial organisms were Klebsiella pneumoniae, Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus, and Enterobacter cloacae (152). Lung transplant recipients are also at risk for mediastinitis owing to small leaks from the airway anastomosis, although this complication is now infrequently seen due to improvements in surgical technique (380). Lung and heart-lung transplant recipients with underlying cystic fibrosis have been shown to be at no greater risk of infections than those without cystic fibrosis in some studies (151, 203). However, other studies indicate that B. cepacia, an organism frequently present in these patients, may contribute to early mortality following lung transplantation for cystic fibrosis (553). In addition, foci of infection in the sinuses may lead to sinusitis following transplantation for cystic fibrosis (369).

Risk factors for bacterial pneumonia following single-lung transplantation include underlying primary or secondary pulmonary hypertension and the presence of airway complications of stenosis or dehiscence (308). In some but not all studies, lung transplant recipients receiving cyclosporine have been shown to have a higher incidence of bacterial pneumonia than those receiving tacrolimus (249, 345). The incidence of bacterial pneumonia in lung transplant recipients may be reduced dramatically by the use of antimicrobial agents tailored to the results of cultures and stains for bacteria (and fungi) from the airways of the donor and recipient at the time of transplantation (500).

Pulmonary infections are also the predominant infections seen in heart transplant recipients (673). Other types of bacterial infections seen in heart transplant recipients include wound infections, of which midline sternotomy infection can be particularly devastating; bacteremia, which most commonly results from vascular catheter infection; and urinary tract infection (748). Endocarditis has been rarely reported and has been postulated to be related to valvular lesions procured by the biopsy bioptome being colonized by circulating bacteria (251).

Renal transplant recipients have a 28 to greater than 90% incidence of urinary tract infections occurring after hospital discharge (790). Multiple factors, including renal insufficiency, nutritional inadequacies, decreased amounts of urine flowing across the uroepithelium, opportunities for sepsis from dialysis accesses, underlying diabetes mellitus, and/or polycystic kidney disease, contribute to this increased incidence (790). Furthermore, the contamination rate for cadaveric kidneys at the time of transplantation may be as high as 25% (790). Patients who receive a simultaneous pancreas transplant with bladder drainage have the added risk of enzymatic digestion of the protective glycosaminoglycan layer overlying the urothelium (790). In addition, the change in urinary pH due to pancreatic exocrine secretions and underlying glycosuria in diabetic patients favor bacterial urinary tract infection in combined kidney-pancreas transplant recipients (412). Pathogens causing urinary tract infections in renal transplant recipients include enterococci, staphylococci, and P. aeruginosa, in addition to the usual enteric gram-negative bacteria (790). Corynebacterium urealyticum, a urea splitter, may lead to the development of struvite stones (790). Wound infections may also be seen in renal transplant recipients. A prolonged period of hemodialysis before transplantation and prolonged bladder catheterization are risk factors for urinary tract infection, while high creatinine levels in plasma and prolonged bladder catheterization are risk factors for wound infection (386). Because urinary tract infections in transplant patients may be asymptomatic and occur in the absence of pyuria, a high index of suspicion and routine surveillance with urine cultures is needed to detect them (790).

Prophylaxis with trimethoprim-sulfamethoxazole reduces the incidence of bacterial infection of the urinary tract and bacteria following renal transplantation (208, 419). One prospective, randomized, double-blind trial with 132 renal transplant recipients compared placebo with trimethoprim-sulfamethoxazole daily given as follows: 160 or 320 mg of trimethoprim and 800 or 1,600 mg of sulfamethoxazole daily when hospitalized followed by 160 mg of trimethoprim and 800 mg of sulfamethoxazole after discharge for an average of 8.9 months (419). Patients randomized to receive trimethoprim-sulfamethoxazole experienced fewer hospital days with fever (3.3 versus 7.7%; P < 0.001) and fewer bacterial infections during the transplant hospitalization after removal of a urinary catheter (0.76 versus 1.88 per 100 days; P < 0.005) and following discharge from the hospital (0.08 versus 0.30 per 100 days; P < 0.001) than did patients receiving placebo. During the transplant hospitalization, 320/1,600 mg daily was highly effective for prophylaxis whereas 160/800 mg daily gave unexpectedly low levels in blood and was effective only for prevention of urinary tract infection after catheter removal. Prophylaxis was most effective for prevention of infections of the urinary tract (24 infections versus 54 in patients receiving placebo; P < 0.005) and bloodstream (1 versus 9; P < 0.01) (208). The authors recommended trimethoprim-sulfamethoxazole prophylaxis for at least 1 year after transplantation for all nonallogenic renal transplant patients (419). Another prospective, randomized trial of no prophylaxis versus 160 mg of trimethoprim and 800 mg of sulfamethoxazole daily for 4 months in renal transplant recipients demonstrated a decrease in urin-
nary tract infections from 38 to 8% (P < 0.05) (708). Controversy exists regarding the exact dosing, timing, and duration of trimethoprim-sulfamethoxazole prophylaxis for urinary tract infection in renal transplant recipients (527). Recurrent urinary tract infections should be investigated by ultrasound of the native and transplanted kidneys and/or computed tomography and nuclear medicine scanning as indicated (790).

The most common bacterial infections in pancreas transplant recipients are wound and intra-abdominal infections (412). In one study of 34 adult pancreas transplant recipients, there were six surgical wound infections and one of each of the following: intraperitoneal abscess, peripancreatic abscess, pelvic abscess, severe cellulitis, peritonitis, and perirectal abscess. Gram-positive organisms caused the majority of these infections, followed by gram-negative rods and anaerobes (412).

Human small bowel transplant recipients are at risk for intra-abdominal and wound infections. In a study of nine patients undergoing small bowel transplantation, there were five episodes of bacteremia, and it was suggested that bacteremia may occur as a result of translocation of bacteria and may be an early indicator of allograft rejection (566). In the same study, there was one wound infection. Enterococcus spp. were the most frequently isolated organisms, followed by S. aureus and E. cloacae (566).

**Legionella spp.**

Legionella infection in solid-organ transplant recipients can be nosocomial or community acquired and can be seen at any time posttransplantation but most commonly within several weeks of transplantation and frequently coinciding with episodes of rejection (12). Legionella pneumophila is the most common species, but L. micdadei, L. bozemanii, and L. dumoffii have been reported as pathogens in transplant recipients (160, 318, 333, 718). Legionella infection in solid organ transplant recipients typically causes pneumonia with symptoms of fever, chills, headache, diarrhea, chest pain, malaise, dyspnea, and cough and pulmonary infiltrates seen on chest X ray (329, 771). Pulmonary abscess and cavitation may occur (43, 771). These infections are not easily distinguished from other bacterial pneumonias except by bacteriologic studies. Cases of hepatic allograft involvement, peritonitis in a kidney transplant recipient, and pericardial effusion in a heart transplant recipient have been reported (20, 706, 718). The mortality in transplant recipients with Legionella infections is high. To what extent this results from the virulence of the organism rather than delayed diagnosis is uncertain. Prompt request of diagnostic tests for Legionella spp., including direct fluorescent-antibody testing and culture of sputum or bronchoalveolar lavage specimens, and possibly urinary antigen testing, in any patient in whom this is suspected is mandatory (12). Serologic testing is of limited usefulness because of the need to obtain acute- and convalescent-phase titers and because seroconversion is not specific for Legionella infection (160, 565) and because the humoral response may be absent in transplant recipients (518).

Empiric treatment for Legionella spp. is often appropriate pending the results of diagnostic studies. Erythromycin is the classic agent used for treatment and may be used with rifampin (12). If the Legionella pneumonia is nosocomial, a search should be made for sources of Legionella in the environment, especially in the hot-water supply and ventilation systems (545). Transmission has been linked to drinking water, contaminated respirators, nebulizers, water heaters, room humidifiers, and aerosolization of water from cooling towers and evaporative coolers (12). In renal transplant recipients, corticosteroid dosage and number of hemodialysis days are risk factors for legionellosis (398). Trimethoprim-sulfamethoxazole, used as P. carinii prophylaxis, may prevent legionellosis (see later section) (398). Prophylaxis with erythromycin has also been suggested to prevent Legionella pneumonia in outbreak situations (328).

**Nocardia spp.**

Nocardial infections have been reported to occur primarily in renal and heart transplant recipients, fewer than 4% of whom develop this type of infection (774). Nocardial infection is most commonly caused by Nocardia asteroides but may be caused by other species including N. transvalensis, N. brasiliensis, N. nova, N. otitidis caviarium, and N. farrinica (16, 445, 459, 476, 562, 774). The most common presentation is pulmonary and includes fever and cough, with pulmonary infiltrates, pleural effusion, cavitation lesions, or nodules visualized on the chest X ray (27, 277, 526, 550). Nocardial brain abscess, meningitis, and ventriculitis may also be seen (270, 271, 541). Cutaneous lesions may occur in isolation or as a manifestation of disseminated disease (205, 562). Unusual presentations include septic arthritis, myocarditis, adrenalitis, involvement of the renal allograft, epididymoorchitis, cutaneous lesions, and mediastinitis (the last of these is found especially after cardiac transplantation) (300, 558, 562, 588, 699, 764). Risk factors for nocardiosis include allograft rejection, high-dose prednisone, azathioprine- as opposed to cyclosporine-based immunosuppression, and granulocytopenia (16, 774).

Gram and modified acid-fast stains and cultures of sputum or bronchoalveolar lavage fluid are useful for the diagnosis of pulmonary nocardial infection (27). All transplant patients with nocardiosis should be evaluated for central nervous system disease (16). Sulfonamides, either alone or in combination with trimethoprim, are the treatment of choice for nocardiosis (16). Alternatives include minocycline, ciprofloxacin, chloramphenicol, erythromycin, amikacin, ampicillin, amoxycillin-clavulanate, ciprofloxacin, imipenem, ceftriaxone, cefuroxime, and cefotaxime. Antibiotic susceptibility testing should be performed (although standards for susceptibility testing are currently unavailable) (205). Antimicrobial therapy should be continued for a prolonged period after cure because of the tendency for relapse, but the optimal duration of therapy is unknown (16). Trimethoprim-sulfamethoxazole, used as for P. carinii prophylaxis, may prevent nocardiosis.

**Salmonella spp.**

In the United States, the annual incidence of nontyphoid Salmonella infection in the renal transplant population is 20 times that in the normal adult population; the incidence is even higher in patients in tropical regions (156). The occurrence of infection is strongly associated with antirejection therapy (312). The most common presentation is febrile illness with bacteremia (156). Other reported presentations include urinary tract infection such as pyelonephritis, orchitis, prostatitis, and perinephric abscess; gastroenteritis; focal manifestations including abscesses of the soft tissues, sacral and perianal areas, and teeth; septic arthritis; pulmonary infection including pneumonia, lung abscess, pleural effusion, and septic pulmonary emboli; vascular infection including infections of saccular aneurysms, vascular grafts, and arteriovenous fistula; pseudocystic aneurysm in the arterial stump of the transplanted kidney and septic axillary phlebitis; infected intravenous injection sites; sinusitis; meningitis; cholecystitis; lymphocele infection; localized fluid in the abdomen; and peritonitis (51, 59, 156, 428, 597, 645). Recurrence of nontyphoidal salmonellosis is com-
mon (312). Those with recurrent infection should be investigated for evidence of latent infection (156). The optimal therapy for *Salmonella* infection in transplantation recipients is not known (312). Surgery is indicated in those with infection of a vascular prosthesis or focal suppuration (156).

**Listeria monocytogenes**

Transplant recipients are at greatest risk for infection caused by *L. monocytogenes* during the first 2 months following transplantation, but listerial infection may occur at any time following transplantation (302, 663). Rejection and its management may increase the risk of listeriosis (23, 663). Listeriosis may be transmitted via contaminated food and is most common from the months of July to October (663). Two-thirds of infected transplant patients have infections involving the central nervous system including meningitis, meningoencephalitis, and encephalitis, and one-third have primary bacteremia (484, 663). Patients with meningitis present with headache, fever, signs of meningeal irritation, depressed level of consciousness, seizures, and/or focal neurological deficits (663). *L. monocytogenes* may also cause pneumonia, endophthalmitis, rectal abscess, and myocarditis (the last is reported in heart transplant recipients) (8, 669, 663, 664). The portal of entry for *L. monocytogenes* is the gastrointestinal tract, and patients may report cramps and diarrhea as the initial manifestations of their infection (582). A fatality rate of 8%, associated primarily with meningitis, has been associated with listerial infection in renal transplant recipients (609).

In patients with central nervous system involvement, cerebrospinal fluid examination often but not always reveals a predominance of polymorphonuclear leukocytes, a low concentration of glucose, and a negative Gram stain (663). Importantly, *L. monocytogenes* may be confused with diptheroides in Gram-stained smears of pus or sputum (663). Intravenous ampicillin and gentamicin are recommended for treatment (663). Trimethoprim-sulfamethoxazole is also effective and when used as prophylaxis for *P. carinii* may additionally prevent listeriosis (23).

**Other Bacterial Infections**

Other unusual bacterial infections have been reported in transplant recipients. For example, *Mycoplasma hominis* infection of perihepatic hematomas has been reported in a liver transplant recipient (327). *Mycoplasma hominis* and *Ureaplasma urealyticum* have been reported as causes of mediastinitis following heart-lung transplantation (71). A case of *Rhodococcus equi* pulmonary infection in a heart transplant recipient has been described (621).

**VIRAL INFECTIONS**

**Cytomegalovirus**

CMV infection occurs in the majority of solid-organ transplant recipients (166), primarily in the first 3 months posttransplantation, when immunosuppression is most intense. CMV infection occurs in 44 to 85% of kidney, heart, and liver transplant recipients. Symptomatic CMV disease occurs in 8, 29, 23, 50, 22, and 39% of kidney, liver, heart, pancreas/kidney-pancreas, human small bowel, and heart-lung transplantation recipients, respectively, (299, 413, 566). CMV may be transmitted to transplant recipients via infected donor organs or cellular blood products, the former being the primary source of CMV infection after solid-organ transplantation (677). Three major patterns of CMV transmission are observed in solid-organ transplantation recipients. Primary infection develops when a CMV-seronegative individual receives cells latently infected with the virus from a seropositive donor followed by viral reactivation. Secondary infection or reactivation infection develops when endogenous latent virus is reactivated in a CMV-seropositive individual posttransplantation. Superinfection or reinfection occurs when a seropositive recipient receives latently infected cells from a seropositive donor and the virus that reactivates posttransplantation is of donor origin (110).

Following primary infection with CMV, long-term cellular and humoral immunity usually develop but CMV remains latent or persistent within the host. Viral persistence is controlled in the immunocompetent host by an intact cellular immune system. Immunosuppression administered following transplantation may lead to uncontrolled viral replication and consequently to symptomatic CMV infection. A patient without prior immunity to CMV pretransplantation who receives an organ with latent or persistent virus (primary infection) is at higher risk of uncontrolled replication than a patient who had prior immunity to CMV pretransplantation (secondary infection or reinfection). Likewise, the higher the degree of immunosuppression, the higher the risk of uncontrolled viral replication. In addition, many of the immunosuppressive compounds administered to transplant recipients, such as prednisone and OKT3 monoclonal antibodies, may directly reactivate CMV from latency into a persistent replicative state. For these reasons, certain patient characteristics place transplant recipients at risk for CMV infection. These include CMV immunity of the donor and the recipient (the seronegative recipient of an organ from a seropositive donor is at highest risk), the use of antilymphocyte preparations (e.g., OKT3 monoclonal antibodies), and fulminant hepatitis at the time of transplantation (in liver transplant recipients) (66, 352, 727). It has been proposed that immunosuppression with tacrolimus may be associated with a lower incidence of CMV disease than cyclosporine, but this remains to be proved (640). Large studies are under way to evaluate the impact of newer immunosuppressive agents such as mycophenolic acid or rapamycin.

In the immunosuppressed solid-organ transplant recipient, CMV has three major effects. (i) causes infectious diseases syndromes (see below); (ii) has been implicated in causing increased immunosuppression, which may explain the frequent association of CMV with other opportunistic infections, such as fungal and *Pneumocystis* infections (576); and (iii) has been associated with allograft rejection in the form of early-onset allograft rejection in renal transplant recipients (207) and chronic allograft rejection (allograft atherosclerosis) in cardiac transplant recipients (in some but not all studies) (235, 346, 625). In liver transplant recipients, the vanishing bile duct syndrome has been associated with CMV in some but not all studies (18, 19, 313, 429, 489, 520, 789). CMV infection therefore has a potential impact on both patient and graft outcome.

CMV infection in solid-organ transplant recipients exhibits a wide range of clinical manifestations, from asymptomatic infection to severe, lethal, CMV disease (632). Most cases of CMV disease following transplantation are of mild to moderate severity and are rarely fatal in the current decade. Manifestations of mild to moderate disease include fever and malaise without additional signs or symptoms. Leukopenia with or without thrombocytopenia may be present. Myalgias, arthralgias, and at times frank arthritis may occur. But CMV mononucleosis syndrome seen in immunocompetent hosts is rarely seen in transplant recipients. The majority of viremic episodes accompany clinical symptoms. Viremia, as documented by surveillance cultures, can be the sole indication of CMV infection.
in the absence of clinical symptoms. However, asymptomatic CMV infection as documented by surveillance cultures may impact the posttransplantation course indirectly by being associated with other (e.g., bacterial) infections (517, 519).

Organ involvement by CMV correlates with the organ transplanted as follows: hepatitis occurs most frequently in liver transplant recipients, pancreatitis occurs most frequently in pancreas transplant recipients, and pneumonitis occurs most frequently in lung and heart-lung transplant recipients. In addition, myocarditis, although rare, typically presents in heart transplant recipients (253). Whether the predispersion of CMV to cause disease in the allograft is secondary to increased surveillance of the transplanted graft remains unknown. Other sites of involvement of CMV include the gastrointestinal tract, gallbladder, pancreas, epididymis, biliary tract, retina, skin, endometrium, and central nervous system (394, 438, 497, 510, 521, 540, 603, 665, 679). In renal transplant recipients, systemic CMV is associated with a glomerulopathy characterized by enlargement or necrosis of endothelial cells and accumulation of mononuclear cells and fibrillar material in glomerular capillaries (569); and in liver transplants, it is associated with nonspecific hepatitis (516). Whether these histologic abnormalities in which CMV cannot be detected in that organ are due to indirect mechanisms (e.g., immune system mediated) or to other viruses associated with CMV (e.g., human herpesvirus 6) remains unknown.

CMV hepatitis typically manifests as elevated concentrations of γ-glutamyltransferase and alkaline phosphatase, peaking 2 to 4 days later than aminotransferase levels, with only minimally increased bilirubin levels (516). CMV pneumonitis results in fever, dyspnea, and cough with findings of hypoxemia and pulmonary infiltrates (332). Radiographic appearances include bilateral interstitial, unilateral lobar, and nodular infiltrates. As suggested above, recipients of lung allografts are particularly prone to CMV pneumonitis, which may be severe in this population. CMV can affect any segment of the gastrointestinal tract, including the esophagus, stomach, and small and large intestines. Symptoms include dysphagia, odynophagia, nausea, vomiting, delayed gastric emptying, abdominal pain, gastrointestinal hemorrhage, and diarrhea (660, 728). Endoscopic findings include erythema and diffuse, shallow erosions or localized ulcerations; however, endoscopic findings are not specific, and so biopsy is essential (690). Intestinal perforation may ensue. CMV inclusion bodies or positive CMV cultures may be found from tissue obtained at endoscopy in the absence of endoscopic findings; the significance and relevance of this are unclear (660). A high index of suspicion for CMV colitis should be maintained in any transplant recipient who presents with lower gastrointestinal bleeding in the first 4 months following transplantation. CMV retinitis is distinctive in that it usually presents more than 6 months posttransplantation. Patients may be asymptomatic or may experience blurring of vision, scotomata, or decreased visual acuity. The diagnosis is made funduscopically.

The diagnosis of CMV infection in tissue has traditionally been based on the recognition of cytomegatlic inclusion bodies (439). CMV may also be detected in tissue specimens by immunohistochemistry or DNA hybridization techniques. Tube cell culture and shell vial culture techniques are used to detect replicating CMV in body fluids and tissue, with the former having the disadvantage of taking 7 to 14 days of incubation for CMV to exhibit a cytopathic effect. The rapid shell vial culture technique can, however, detect the presence of CMV after 16 h of incubation (629). Importantly, akin to bacterial blood cultures, multiple viral blood cultures may be necessary to detect CMV by the shell vial assay (505). Detection of CMV antigenemia in blood leukocytes of transplant recipients is at least as sensitive as and more rapid than the shell vial technique and provides an early marker of active CMV infection (184, 719, 722). PCR techniques can detect CMV DNA in peripheral blood leukocytes (149), serum (508), plasma (657), and other clinical specimens and can detect CMV RNA in peripheral blood leukocytes (507). The clinical usefulness of these techniques is in the process of being evaluated. The serologic diagnosis of CMV infection is suboptimal compared to the above techniques; many patients with positive CMV cultures do not show concomitant evidence of seroconversion (518, 647). Serologic testing is, however, recommended for the pretransplantation evaluation of transplant donors and recipients.

Effective currently available antiviral agents for the treatment of CMV include ganciclovir and foscarnet. Ganciclovir has excellent activity against all members of the herpes family of viruses. Intravenous ganciclovir has been successfully used in uncontrolled, nonrandomized therapeutic trials to treat solid-organ transplant recipients with CMV disease (85, 102, 123, 135, 145, 146, 172, 185, 256, 257, 278, 311, 321, 335, 344, 382, 418, 425, 446, 483, 491, 515, 575, 579, 594, 649, 650, 668, 669, 676, 678, 752, 776). One caveat is that treatment of CMV may not reduce disease if the pathogenesis of the disease is immune system mediated (561). Oral ganciclovir has recently been approved for use as maintenance therapy to prevent the relapse of CMV retinitis in HIV-infected patients. The absorption of ganciclovir following oral administration is low, and its role in the treatment of CMV infection and disease following solid-organ transplantation is under study. Oral ganciclovir may be useful as maintenance therapy in patients treated with intravenous ganciclovir with identified risk factors for relapse; however, this also remains to be proven.

Side effects of ganciclovir in solid-organ transplant patients are less frequent than in HIV-infected patients or in bone marrow transplant recipients; they include leukopenia, thrombocytopenia, anemia, cosinophilia, bone marrow hypoplasia, hemolysis, nausea, infusion site reactions, diarrhea, renal toxicity, seizures, mental status changes, fever, rash, and abnormal liver function tests (85, 141, 193, 603, 626). Hematologic and renal function should be monitored while the patient is on ganciclovir. Renal toxicity may occur when ganciclovir is used in conjunction with other nephrotoxic agents such as amphotericin B, azathioprine, and cyclosporine and when it is used in children. The long-term safety of ganciclovir in adult and especially in pediatric transplant recipients remains to be established (143).

The possibility of viral resistance should be considered in patients with poor clinical response or persistent viral excretion during ganciclovir therapy. Mutations in viral thymidine kinase and/or DNA polymerase genes appear to mediate resistance (193).Fortunately, a recent study has shown that ganciclovir prophylaxis in solid-organ transplant recipients does not select ganciclovir-resistant isolates of CMV (60), although the widespread and prolonged use of ganciclovir, especially now that an oral preparation is available, may trigger the emergence of resistant strains.

CMV disease in transplant recipients is typically treated with 2 to 3 weeks of intravenous ganciclovir. CMV retinitis requires a longer course of therapy. Unlike the treatment of CMV in patients with HIV infection, long-term maintenance is seldom required in recipients of solid organs. In a study of bone marrow transplant recipients, a negative result of a PCR assay in either blood or urine at the conclusion of antiviral therapy seemed to be a better marker for effective antiviral treatment than did clinical improvement or negative blood cultures (177). A similar approach might indicate that ganciclovir therapy...
should be continued or discontinued in solid-organ transplant recipients. Quantitative antigenemia and CD8+ bright T lymphocytes in peripheral blood are other potential markers indicating the appropriate times to stop antiviral therapy (720). Recurrent tissue-invasive CMV disease has been reported to occur in 25% of solid-organ transplant patients in whom an initial episode of tissue-invasive CMV disease occurs. Recurrent CMV disease appears to respond to ganciclovir as well as does initial CMV disease (602).

There is less experience with the use of foscarnet for the treatment of severe CMV infection in solid-organ transplant recipients (39, 357, 406, 572). Until more data are available, foscarnet should be reserved for patients who are intolerant of ganciclovir or who have failed to respond to ganciclovir therapy. Its main side effects are nephrotoxicity, anemia, hyperphosphatemia, hypophosphatemia, hypercalcemia, hypocalcemia, nausea, vomiting, and seizures. Although high concentrations of acyclovir inhibit CMV in vitro, clinical trials have demonstrated no benefit in the treatment of CMV infection (735).

CMV hyperimmune globulin has been found by some investigators to be ineffective in the treatment of CMV disease in solid-organ transplant recipients (86) and by others to possibly be an effective therapeutic agent (388, 555). Although the combination of CMV immune globulin and ganciclovir has proved efficacious in the treatment of CMV disease in some studies (135), the expense of immune globulin needs to be considered. Combination therapy may be useful in specific subsets of patients, for example, those with severe CMV pneumonia. Overall, intravenous ganciclovir remains the drug of choice for the treatment of CMV disease in solid-organ transplant recipients.

Methods of preventing CMV infection include (i) selection of allografts from CMV-seronegative donors for CMV-seronegative recipients; (ii) use of CMV-seronegative, filtered, or leukocyte-poor blood products; (iii) active immunization with a vaccine; (iv) passive immunization with immune globulins; (v) prophylaxis with antiviral agents such as interferons, acyclovir, ganciclovir, or foscarnet; and (vi) preemptive therapy.

Knowledge of the CMV serostatus of the donor and recipient pretransplantation will predict which patients will develop CMV disease. Although the patient at highest risk for developing CMV infection is the seronegative recipient of a sero-negative allograft, protective matching of seronegative donors and seronegative recipients is not currently advocated due to the scarcity of donor organs (685). The use of CMV-seronegative, filtered, or leukocyte-poor blood products reduces CMV transmission (69, 452, 551, 604), and these should be used, at least in seronegative recipients.

In theory, one of the simplest interventions for the prevention of CMV disease after transplantation would be immunization of seronegative recipients with a vaccine given once in anticipation of future viral challenge. A live attenuated CMV vaccine, which uses the Towne strain of virus, is both safe and immunogenic; however, there is no significant decrease in the incidence of CMV disease in renal transplant recipients receiving this vaccine, although there is a decrease in the severity of CMV disease in the donor seropositive/recipient-seronegative (D+/R−) subgroup (32, 33, 74, 220, 424, 532, 534, 535). New interest in developing a vaccine subunit product has emerged over the last few years (533). A subunit vaccine containing recombinant glycoprotein B being developed by several biotechnology companies is undergoing clinical trials (81).

Immune globulin preparations, including unscreened (unsective) and hyperimmune globulin preparations, have been studied as agents for CMV prophylaxis. The efficacy of the prophylactic administration of immune globulin preparations in solid-organ transplant recipients is controversial. Several studies have been performed but are not homogeneous in study design, CMV antibody titers, dosage, timing of administration, duration of treatment, or preparation used, thus making comparison difficult (29, 34, 41, 44, 113, 121, 162, 174, 194, 200, 227, 228, 231, 245, 254, 282, 337, 340, 347, 401, 448, 449, 481, 499, 543, 590, 592, 651–653, 670, 671, 680, 681, 697, 705, 757, 761, 796). In randomized controlled trials, immune globulins have been reported to be effective in preventing CMV disease in renal transplant recipients (unscreened immune globulin and hyperimmune globulin) (192, 245, 653) and in liver transplant recipients (hyperimmune globulin) (590, 651, 652). A recent meta-analysis of the use of immune globulin to prevent symptomatic CMV disease in solid-organ transplant recipients showed a beneficial effect (common odds ratio, 0.59 [95% confidence interval, 0.39 to 0.86]) of immune globulin compared to no prophylaxis (221). Recent reports have demonstrated contamination of some immune globulin preparations with HCV (54). Given the cost of immune globulin prophylaxis (typically several thousand dollars per patient) a formal comparison between antiviral agent and immune globulin prophylaxis needs to be done to determine the most effective and least expensive regimen. One such study suggested that immune globulin and ganciclovir both reduce symptomatic CMV infection but that the latter is less costly (119).

Among the first antiviral agents to be used in the prevention of CMV infection and disease following solid-organ transplantation, specifically following renal transplantation, were the interferons. Studies with human and fibroblast leukocyte interferon showed mixed effects (109, 296, 756). Studies with recombinant interferon demonstrated an unacceptably high rate of steroid-resistant allograft rejection and allograft loss (366, 371, 755). Although further prophylactic investigations have not been extensively pursued, a recent study with human lymphoblastoid interferons demonstrated a delay in CMV excretion and a decrease in CMV reactivation in the D+/R+ subgroup without an increased incidence of allograft rejection or allograft loss (411). In view of the association with rejection and the less than optimal prophylactic effects of interferons overall, their use in solid organ transplant recipients remains to be thoroughly evaluated.

Despite possessing little in vitro activity against CMV at clinically achievable levels, acyclovir has, in the past, been the only available oral agent, and many investigators have studied acyclovir for CMV prophylaxis following solid-organ transplantation. Overall, its role in this capacity is unclear. Unfortunately, the majority of studies have evaluated acyclovir in combination with ganciclovir or immune globulins and/or have not included control groups receiving placebo (29, 40, 179, 181, 182, 356, 396, 417, 458, 591, 681, 730, 782). One prospective, randomized, placebo-controlled study, however, has shown acyclovir to be effective in preventing CMV infection and disease following renal transplantation, and one prospective, randomized study has shown intravenous followed by oral acyclovir to be effective in preventing secondary CMV infection and disease following liver transplantation (31, 591). However, many other studies do not show the same effect, and a further study from the same institution that demonstrated the efficacy of prophylactic oral acyclovir in renal transplant recipients reported, as part of a study of rejection prophylaxis regimens, no difference in the incidence of CMV disease in D+/R− patients (a subgroup that was particularly benefited in the original study) receiving acyclovir prophylaxis compared to those receiving no prophylaxis (29, 211, 420, 426, 782). Given the conflicting results of several studies, oral acyclovir prophylaxis for CMV cannot be recommended outside of investiga-
tional settings, with the exception of its use in renal transplant recipients. Most renal transplant programs view oral acyclovir prophylaxis as the “gold standard” in terms of CMV prevention.

The role of ganciclovir in the prophylaxis of CMV infection and disease following solid-organ transplantation remains to be clearly established (30, 114, 169–171, 210, 387, 426, 447, 474, 499, 538, 574). As with acyclovir, most studies of ganciclovir prophylaxis are difficult to interpret because they lack control groups receiving placebo and instead compare ganciclovir to acyclovir or different preparations of immune globulins, agents which are themselves of controversial efficacy in the prevention of CMV infection and disease following solid-organ transplantation.

Still, the therapeutic efficacy of ganciclovir makes it a most attractive prophylactic agent for CMV infection and disease following solid-organ transplantation have been performed. A randomized, prospective, double-blind, placebo-controlled trial of ganciclovir for 28 days following heart transplantation has shown a reduced incidence of CMV illness in the seropositive-recipient group and delayed incidence of CMV shedding (447). A randomized study done with D+/R− renal transplant recipients, which compared ganciclovir given for 14 days (from days 14 to 28 posttransplantation) to no prophylaxis has, however, shown no change in the incidence of CMV infection or disease (although a delayed onset of CMV infection and reduced severity of CMV disease were demonstrated) (574). The failure to show changes in the incidence of CMV infection or disease may be related to the delay in initiation of prophylaxis in this study. A randomized study of lung transplant recipients has shown that a regimen of ganciclovir, beginning 1 week after lung transplantation and continued until day 90, is more effective than a 3-week course of ganciclovir beginning after transplantation followed by high-dose orally administered acyclovir in terms of reducing CMV infection. Ganciclovir given over this length of time delayed the onset of CMV infection (169). The expense and potential side effects related to the need for long-term intravenous administration and access are disadvantages. A randomized study showed decreased CMV infection and disease and delayed onset of CMV infection and disease in liver transplant recipients receiving 2 weeks of ganciclovir followed by high-dose acyclovir compared to those receiving only oral acyclovir following transplantation (426). A recent study showed that ganciclovir administered for 100 days after liver transplantation decreased the incidence of CMV disease (777). Other randomized trials with liver transplant recipients show conflicting results (114, 474). In addition, several nonrandomized trials of ganciclovir prophylaxis of CMV infection and disease following solid-organ transplantation have been performed (30, 170, 210, 280, 387, 433, 499, 682); many but not all of these studies have shown a beneficial effect of ganciclovir prophylaxis on CMV disease.

Overall, although not uniformly shown to be beneficial, ganciclovir is the only antiviral agent currently available which has been shown to have some degree of efficacy in the prophylaxis of CMV infection in the majority of solid-organ transplant recipients. Although this is not standard practice in all transplantation programs, on the basis of published randomized trials a 2-week course of ganciclovir should be considered for CMV prophylaxis in certain solid-organ transplant recipients; a 4-week course is recommended for CMV-seropositive recipients of heart allografts. Ganciclovir alone is not effective, how-

ever, in solid-organ transplant populations at highest risk for CMV disease, such as lung transplant recipients, and donor CMV-seropositive/recipient CMV-seronegative individuals unless it is administered for a prolonged period (90 days). The studies to date have used intravenous ganciclovir, which is not ideal because of the ongoing need for intravenous access and the costs engendered. Therefore, other strategies, such as oral ganciclovir and combinations of single or several antiviral agents with or without CMV hyperimmune globulin and preemptive therapy, should be considered for these patients. In addition, newer drugs are under investigation for CMV prophylaxis.

Preemptive therapy of CMV infection involves the administration of antiviral agents to a subgroup of patients prior to the appearance of disease. This is dependent on a laboratory marker or patient characteristic which identifies a subgroup of individuals at high risk for disease at a time when antimicrobial intervention would be maximally effective in aborting the disease process (584). Compared with a prophylactic approach of administering antiviral agents to all patients, only patients at risk of developing symptomatic CMV infection would receive specific antiviral therapy. Therefore, fewer patients would receive an antiviral agent, and probably for a shorter period, leading to advantages in terms of cost, emergence of resistant viral strains, and medication side effects.

Candidate laboratory tests for this therapeutic mode include PCR to detect CMV DNA or CMV RNA, antigenemia tests, and viral culture, among others. A recent study of liver transplant recipients demonstrated that a 7-day course of ganciclovir given when CMV was identified by surveillance cultures provided effective prophylaxis against CMV disease (641). Quantitation of PCR-amplified CMV has been successfully used to predict the development of CMV pneumonitis in lung and heart-lung transplant patients (93) and has been suggested as a marker for preemptive therapy. We have shown that PCR can detect CMV DNA in the sera of liver transplant recipients prior to the onset of symptomatic CMV infection and is a potential marker for preemptive therapy (508). Other methods of surveillance, including alternative molecular biological methods and antigenemia assays, are also being studied in this mode (520). With any of these methodologies, a commitment to careful surveillance and follow-up, which may prove to be quite costly, is critical.

Identifying patient characteristics that place transplant recipients at risk for CMV infection is another facet of preemptive therapy. This requires the active investigation of risk factors for CMV infection following solid-organ transplantation. Such risk factors include the use of OKT3 monoclonal antibody and the presence fulminant hepatitis at the time of transplantation (in liver transplant recipients) (291, 539). Studies done in kidney, liver, and kidney-pancreas transplant recipients, using either no controls or historical controls, suggest that ganciclovir may be effective in preventing CMV disease in patients receiving antilymphocyte therapy (OKT3, antilymphocyte globulin, or antilymphocyte globulin) for allograft rejection or induction therapy (66, 305, 415, 546, 654, 727). A recent randomized study performed with CMV-seropositive renal transplant recipients showed that ganciclovir is effective in reducing the occurrence of CMV disease in patients receiving antilymphocyte therapy (290). Two randomized studies performed with kidney transplant recipients who are receiving antilymphocyte therapy have shown that hyperimmune globulin reduces the severity of symptomatic primary and secondary CMV infection (448, 671). However, one study evaluating acyclovir and immune globulin in liver transplant recipients receiving OKT3 showed no beneficial effect (680). Overall, the
use of an effective anti-CMV agent such as ganciclovir at the
time of antilymphocyte therapy seems warranted. A similar
approach, based on other risk factors, requires further study
but may also be beneficial. Preemptive therapy is a promising
approach, whether based on early detection of CMV or tar-
getting of patients with risk factors for CMV, both of which
need further development and optimization.

**Herpes Simplex Virus**

HSV most commonly causes reactivation infection but may
cause primary infection, transmitted by person-to-person con-
tact or via the allograft (164, 224, 376, 502). HSV antibodies
are found in three-quarters of adult solid-organ transplant
recipients (637). Following primary infection, the virus remains
latent in the sensory nerve ganglia (37). HSV reactivation
results in oral or genital mucocutaneous lesions, usually during
the first month posttransplantation (501, 637), in about one-
third of adult transplant recipients (262, 376, 637, 712) and 8% of
pediatric transplant recipients (595) (due to their lower
prevalence of latent HSV infection) (15, 76). Reactivation or
primary HSV infection occasionally causes pneumonitis, tra-
cheobronchitis (332), esophagitis, hepatitis, or disseminated
infection. The use of OKT3 monoclonal antibodies has been
associated with an increased frequency of HSV reactivation
(637).

Most orolabial infections are mild, although severe ulcer-
ation and discomfort, which may be complicated by bacterial
superinfection or esophageal involvement, are noted in some
patients. Anogenital infection usually presents as large areas of
ulceration and may or may not have the typical vesicular ap-
pearance of HSV infection in the nonimmunocompromised
host. Less commonly, zosteriform lesions on the buttocks,
chancr-like genital lesions, or oral nodules and plaques can
result (87).

HSV can cause pneumonia, which is associated with a mor-
tality rate of up to 75% despite treatment with acyclovir, in
solid-organ transplant recipients (9, 144). This usually occurs
as a secondary pneumonia in intubated patients with severe
pneumonia caused by other agents (166). The virus is reactiv-
ated in the oropharynx, the mucosa is traumatized by the
endotracheal tube, and the virus is presumably spread via
the endotracheal tube to the lower respiratory tract. Certain
ca-
vats must be noted. HSV isolated from sputum or other respi-
atory secretions does not definitively imply HSV pneumonitis,
and bronchoalveolar lavage with cytologic testing and culture is
required if lung biopsy is not feasible. Also, even if HSV is
believed to be causing pneumonitis, another pathogen should
be sought, as HSV is often a secondary pathogen.

HSV esophagitis causes dysphagia, and mimics candidial
esophagitis clinically, radiographically, and macroscopically.
Esophagitis may complicate orolabial infection, particularly if
the mucosa has been traumatized by endotracheal intubation
or nasogastric tubes (582). These procedures should be
avoided in transplant patients who have active labial or in-
traoral infection. HSV is also a cause of diffuse or focal hepa-
titis in solid-organ transplant recipients, usually during the
first 2 months posttransplantation (25, 262, 425, 692). It is
characterized by a rapidly progressive course accompanied by
hypotension, disseminated intravascular coagulation, meta-
bolic acidosis, gastrointestinal bleeding, and associated bacte-
remia (377). HSV may additionally cause chronic viral hepata-
titis following liver transplantation (607). Disseminated HSV
disease has rarely been reported following solid-organ trans-
plantation (425). Uncommonly, disseminated cutaneous infec-
tion with HSV may occur at sites of previous skin injury such
as burns and eczema (eczema herpeticum) (582). Herpes en-
cephalitis as seen in the nonimmunocompromised host is rarely
seen in the solid-organ transplant recipient.

The diagnosis may be made by performing a direct immu-
nofluorescence test, Tzanck test, or culture of tissue and/or
body fluids (10). Typing of isolates may be performed by a
variety of techniques (421). Serologic techniques are helpful in
the diagnosis of primary infections when a positive immuno-
globulin M (IgM) titer or a fourfold or greater rise in IgG titer is
observed between acute- and convalescent-phase sera and in
the determination of the pretransplantation serologic status of
solid-organ transplant recipients.

Treatment of HSV infection with acyclovir has been shown to
be effective (76, 376). Side effects of acyclovir include local
inflammation or phlebitis after intravenous infusion, renal tox-
icity due to precipitation and crystallization of the drug in the
renal tubules (predominantly when the intravenous form is
used), confusion, delirium, lethargy, tremors, seizures, nausea,
light-headedness, diaphoresis, and rash. Mucocutaneous HSV
infection in solid-organ transplant recipients should be treated
with oral acyclovir at 200 mg five times daily if the infection has
a benign course or with intravenous acyclovir at 5 mg/kg every
8 h in more serious cases (343). Disseminated or deep HSV
infection should always be treated with intravenous acyclovir
(284). The dose should be adjusted in patients with renal fail-
ure. Low-dose acyclovir (200 mg orally three or four times
daily) appears to prevent HSV hepatitis in liver and kidney
transplant recipients (248, 377, 529, 619) and is, in our expe-
rience and that of others (95, 262, 648), a good prophylactic
regimen for HSV infection. Although more toxic than acyclo-
vir, ganciclovir and foscarinet are also effective against HSV.
Newer agents, some recently marketed (e.g., famciclovir), are
under evaluation and will probably increase the number of
anti-HSV drugs that will be of benefit in solid-organ transplan-
tation.

A concern with respect to chronic acyclovir use is the devel-
opment of resistant mutants of HSV. Acyclovir resistance may
arise from mutations in the genes for thymidine kinase or DNA
polymerase (453). Acyclovir-resistant isolates have been asso-
ciated with progressive and severe disease in immunocom-
promised patients, particularly those with AIDS, and it is possible
that resistance will become a problem for transplant recipients
in years ahead (187), although this has not occurred to date
(61).

**Varicella-Zoster Virus**

VZV causes two distinct clinical diseases following trans-
plantation. Ninety percent of adult solid-organ transplant re-
cipients are VZV seropositive pretransplantation, and thus
VZV reactivation in this group will cause herpes zoster. The
remaining 10% are VZV seronegative and are thus at risk for
primary infection (304).

Localized dermatomal reactivation results in herpes zoster and
typically occurs after the first 6 months posttransplantation in
5 to 13% of patients (166, 262, 376, 637). Localized derma-
tomal zoster may involve two or more adjoining dermatomes,
and there may be a few sites of cutaneous dissemination at
distant sites. Additionally, a syndrome of unilateral pain with-
out skin eruption associated with rises in specific antibody to
VZV has been described in transplant patients (409).

Primary VZV infection occurs following exposure of a VZV-
seronegative transplant recipient to VZV. The virus is trans-
mitted by contact with an infected individual, presumably via
the respiratory route. It is unclear if VZV can be transmitted
by the allograft itself. Primary VZV in the solid-organ trans-
Monoclonal polymorphic B-cell vaccines are used safely in other severely immunosuppressed pediatric renal transplant recipients (795). In addition, live recent study has demonstrated the safety of this vaccine in the use of live vaccines in solid-organ transplant recipients, a VZV has recently been approved. Despite concerns regarding though this has not been formally studied. A vaccine against VZV has recently been approved. Despite concerns regarding the use of live vaccines in solid-organ transplant recipients, a recent study has demonstrated the safety of this vaccine in pediatric renal transplant recipients (795). In addition, live vaccines are used safely in other severely immunosuppressed patients such as patients with AIDS. Such vaccines should preferably be administered several months prior to transplantation. Varicella vaccination prior to solid-organ transplantation should reduce morbidity in seronegative pediatric recipients and provide considerable cost savings (354).

It is important to keep in mind that although most infections in transplant recipients are not contagious, contact with a patient who has VZV infection, be it zoster or chicken pox, is a risk for all seronegative contacts, including healthy staff working in transplant centers (787).

### Epstein-Barr Virus

EBV infection in transplantation recipients may cause mild symptoms such as malaise, fever, headache, and sore throat but may also be associated with posttransplantation lymphoproliferative disease (PTLD), which is a significant cause of morbidity and mortality in transplant recipients (Table 4) (238, 276, 305, 726). The term PTLD acknowledges the fact that these lesions are heterogeneous and may not meet the diagnostic criteria for lymphoma. The spectrum of PTLD ranges from polyclonal to monoclonal (24). Monoclonal lesions may or may not contain detectable chromosomal abnormalities. The incidence of PTLD varies with the organ transplanted; rates of 1% for renal, 1.8 to 4.5% for cardiac, 2.1 to 2.2% for liver, 10% for lung, 11% for kidney-pancreas, 4.5 to 9.4% for heart-lung, and 14% for small bowel transplant recipients have been reported (215, 238, 475, 557, 743, 765). The process is often multicentric and may involve the central nervous system, eyes, gastrointestinal tract (with bleeding and perforation), liver, spleen, lymph nodes, lungs, allograft, oropharynx, and other organs (2, 103, 178, 183, 190, 258, 334, 407, 472, 475, 496, 556, 559, 616, 644). Clinical presentations are varied and include a mononucleosis-like syndrome with fever, adenopathy, tonsillitis and sore throat, fever (including “fever of unknown origin”), abdominal pain, anorexia, jaundice, bowel perforation, gastrointestinal bleeding, renal dysfunction, hepatic allograft dysfunction, pneumonia, pulmonary infiltrates, and weight loss (76, 250, 475, 696). An association of EBV with squamous cell carcinoma, sarcoma, carcinoma of the colon and stomach, T-cell lymphoma, Hodgkin’s disease, and smooth muscle tumors in solid-organ transplantation recipients has been noted (325, 372, 393, 691, 701, 772).

The pathogenesis of PTLD involves EBV replication, often stimulated by OKT3 or antithymocyte globulin, followed by

### Table 4. Treatment of EBV-related conditions in solid organ transplant recipients

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical findings</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated posttransplantation infectious mononucleosis</td>
<td>Fever, pharyngitis, cervical adenopathy, +/- splenomegaly</td>
<td>Acyclovir</td>
<td>Good</td>
</tr>
<tr>
<td>Benign polyclonal polymorphic B-cell hyperplasia</td>
<td>Fever, pharyngitis, cervical adenopathy</td>
<td>Acyclovir, ganciclovir, +/- immunsuppression</td>
<td>Good</td>
</tr>
<tr>
<td>Early malignant transformation in polyclonal polymorphic B-cell lymphoma</td>
<td>Fever, +/- pharyngitis, adenopathy</td>
<td>Acyclovir, ganciclovir, down immunsuppression IFN-α, gamma globulin, anti-B-cell monoclonal antibodies</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Monoclonal polymorphic B-cell lymphoma</td>
<td>Solid tumor masses in allograft, soft tissue, brain, gastrointestinal tract, lung, liver</td>
<td>Down immunsuppression, chemotherapy, radiation therapy, resection</td>
<td>Poor</td>
</tr>
</tbody>
</table>

a Adapted from reference 274 with permission of the publisher.

b IFN, interferon.
cyclosporine-induced inhibition of virus-specific cytotoxic T lymphocytes that normally control the expression of EBV-infected, transformed B cells (24). PTLD has been shown to be of donor origin in some cases (17, 564). Risk factors for PTLD include EBV seronegativity prior to transplantation, OKT3 therapy for rejection, receipt of tacrolimus rather than cyclosporine for immunosuppression, and CMV seromismatch (128, 693, 742, 743). Up to 87% of renal transplant recipients have oropharyngeal excretion of EBV posttransplantation (104, 107). Increased levels of circulating EBV-infected lymphocytes and decreased EBV nuclear antigen antibody responses have been associated with the development of PTLD in solid-organ transplant recipients in some but not all studies (129, 570). In hepatic allograft recipients, the finding by in situ hybridization of occasional cells infected with EBV in posttransplant liver biopsy specimens does not predict progression to lymphoproliferative disease (314).

Treatment of EBV-related PTLD is outlined in Table 4 (274). High-level EBV oropharyngeal shedding, found in primary infection, is inhibited by acyclovir and ganciclovir, suggesting that antiviral therapy may be useful early, when levels of viral replication are low (24, 142, 542). Unfortunately, once PTLD is established, the treatment has been disappointing, with the exception of drastically reducing the level of immunosuppression, which appears to have a beneficial effect in localized or polyclonal as well as multifocal or monoclonal PTLD (42, 275, 530). Disease localized to the transplanted organ or lymph nodes can be reversed with reduced immunosuppression and antiviral therapy; extranodal, multifocal, and brain disease typically require chemotherapy and/or radiation therapy and are associated with a high mortality rate (743). Anti-B-cell antibodies have recently been proposed as a therapeutic option (389). The use of certain antiviral agents for CMV prophylaxis may reduce the incidence of lymphoproliferative disease both because of the possible activity of these agents against EBV and because of the association of CMV with EBV, but this remains to be proven (306). In any case, more information and uniformity is needed to better manage EBV-related syndromes in transplant recipients.

**Hepatitis Viruses**

HBV is a DNA virus of the hepadnavirus family. Fulminant hepatitis and cirrhosis caused by HBV are important indications for liver transplantation. Unfortunately, recurrent HBV occurs in 80 to 90% of patients following liver transplantation and results in significant morbidity and a 50 to 60% mortality rate. In contrast, primary HBV, acquired from the donor liver or by blood product transfusion, is typically mild (140). Of note is the finding that HBV cirrhosis of the liver allograft is uncommon in patients transplanted for fulminant HBV infection but can occur, and HBV recurrence is rare in patients with concomitant hepatitis D virus infection (Table 5) (147, 598). Recurrent HBV typically begins with the silent appearance of HBsAg 2 to 6 months posttransplantation, followed by evidence of hepatocellular injury. The spectrum of liver injury ranges from self-limited or mild persistent hepatitis to aggressive chronic hepatitis and fulminant liver failure (140). Immunologically well-matched patients have a higher predisposition for the development of progressive hepatocellular injury mediated by immune destruction of infected hepatocytes than do totally mismatched patients, whereas totally mismatched patients may be at risk for direct cytopathic injury to hepatocytes from uncontrolled replication of HBV. An unusual pattern of fibrosing cholestatic hepatitis has also been described in a small subset of patients with recurrent HBV infection following liver transplantation (150).

The safety and efficacy of renal, heart, heart-lung, small bowel, and pancreas transplantation in HBsAg-positive patients are controversial. Increased mortality from liver disease or sepsis has been found in some but not all studies of renal transplantation recipients (140). Increased mortality, if it occurs, is seen 10 years or more following renal transplantation. The acquisition of HBV soon after renal transplantation, however, appears to carry a graver prognosis of early death from liver failure (140). Virtually all renal transplant patients with severe chronic active hepatitis and 50 to 60% of those with mild chronic active hepatitis on liver biopsy progress to cirrhosis following transplantation (140).

The diagnosis of HBV infection is made by serologic testing. Preoperative HBV DNA levels predict the risk of recurrent disease. Because of this, attempts have been made to reduce the vaccine load prior to transplantation. Interferon therapy has been studied in this regard, and although it may be beneficial in some patients, others experience exacerbation of disease activity that can be complicated by spontaneous bacterial peritonitis, variceal hemorrhage, or death. Furthermore, although it is possible to reduce HBV DNA levels in serum prior to transplantation, recurrent infection can still occur. Newer, more powerful antiviral agents may be more effective than interferon in this regard, especially agents such as Lamivudine (140). In liver transplantation recipients with HBV infection, the administration of 10,000 U of HBV immune globulin during the anhepatic phase followed by daily administration for 6 days and then intermittently to maintain anti-HBs antibody titers at levels greater than 100 IU (some suggest greater than 500 IU) results in survival rates comparable to those seen in patients undergoing transplantation for other conditions (140, 355). All transplantation recipients who are not immune to HBV should receive the HBV vaccine prior to transplantation, because the vaccine failure rate posttransplantation is high (737). Allografts from donors who are positive for HBsAg should not be utilized. There is controversy about whether allografts from donors who are hepatitis B core antibody positive should be used.

HCV is a small, single-stranded RNA virus. It is a common cause of chronic liver disease and an important indication for liver transplantation. It may also be transmitted with any type of allograft used in solid-organ transplantation or via blood product transfusion (524). Currently, both sources are screened for antibody to HCV; it is estimated that the risk of posttransfusion hepatitis is approximately 3 per 10,000 U transfused (158). Many renal transplantation recipients are infected with this virus prior to transplantation. Organs from donors with HCV antibody who are PCR positive are most likely to transmit HCV infection. Organs from donors who are HCV antibody positive and PCR negative are much less likely to

<table>
<thead>
<tr>
<th>Initial liver disease</th>
<th>No. of patients</th>
<th>No. (%) of HBsAg positive patients after liver transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic HBV with cirrhosis</td>
<td>32</td>
<td>19 (60)</td>
</tr>
<tr>
<td>HBV DNA positive</td>
<td>14</td>
<td>13 (93)</td>
</tr>
<tr>
<td>HBV DNA negative</td>
<td>18</td>
<td>6 (33)</td>
</tr>
<tr>
<td>Fulminant hepatitis B</td>
<td>11</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hepatitis B and D cirrhosis</td>
<td>36</td>
<td>5 (14)</td>
</tr>
</tbody>
</table>

* Adapted from reference 598 with permission of the publisher.
transmit infection but cannot be regarded as completely safe (698). Some workers have advocated restriction of HCV antibody-positive donors to life-saving transplants, such as heart, lung and liver; others have advocated that HCV antibody-positive organs be transplanted only into HCV antibody-positive recipients (468, 523, 698).

HCV is a major cause of chronic hepatitis following renal transplantation; however, as yet there has not been a demonstrable effect of HCV on actuarial patient or graft survival (222, 581, 698). Renal transplant recipients who are HCV antibody positive at the time of transplantation have a higher prevalence of abnormal liver enzymes in follow-up than do those who are HCV antibody negative. In liver transplant recipients, pretransplant HCV infection is associated with a high incidence of recurrence and is the major etiological agent of posttransplantation hepatitis (50, 92). Recurrent HCV infection following liver transplantation for HCV-induced cirrhosis may be associated with accelerated rates of graft damage, especially in patients with HCV-1b (195, 214). Nonetheless, liver transplantation in patients with HCV infection has a good medium-term prognosis (196, 431).

Diagnosis is made by detection of HCV-RNA by reverse transcriptase PCR and other assays; serologic testing is a poor marker of HCV infection in transplant recipients (422). Different HCV strains or subtypes, characterized by genotyping, are linked with the severity of disease and responsiveness to interferon therapy (698). For patients with hepatitis thought to be caused by HCV, liver biopsy is important to confirm the diagnosis histologically and to delineate the severity of disease. HCV viral particle levels increase with antilymphocyte therapy (799).

Two therapeutic options, interferon and ribavirin, have been evaluated in solid-organ transplant recipients in a preliminary fashion. A concern with the use of interferon is its association with allograft rejection when used to treat CMV (see above). Nonetheless, preliminary results in liver and kidney transplant recipients treated with interferon show a biochemical response rate, albeit lower than that seen in immunocompetent patients (698, 788). Similarly, preliminary results in liver transplant recipients treated with ribavirin are encouraging, but more studies are needed (137).

Human Immunodeficiency Virus

HIV may be transmitted by solid-organ transplantation (374, 615). Since 1985, organ donors have been tested for HIV antibody, reducing substantially the transmission of HIV by this route. HIV itself does not appear to adversely affect the outcome for the transplanted organ (186). In fact, solid-organ transplant recipients with HIV infection may require lower levels of immunosuppressive therapy than do those without HIV infection to maintain allograft function (225). New HIV infection may also occur in previously stable transplant recipients (403). Patients with secondary HIV infections do better than those with primary infections. The mean time from transplantation to the development of AIDS is 32 months in patients with primary infection and 17 months in those with secondary infection (186). However, the natural history of all these patients, particularly those with secondary infection, demonstrates that some HIV-positive recipients may do well and may survive for prolonged periods despite opportunistic infections and the superimposed immunosuppression (68, 165). Shorty after transplantation, HIV-infected patients may develop prolonged unexplained fevers associated with splenomegaly, lymphadenopathy, abnormal liver function tests, leukopenia, lymphopenia, thrombocytopenia, and/or anemia (186). The AIDS-defining conditions seen in transplant recipients are similar to those seen in nontransplant recipients (186).

Despite routine testing of donors of blood and organs for antibodies to HIV, transmission of HIV to recipients of transplanted organs may still occur, even though this event is rare; one episode involved a donor who initially tested negative by enzyme immunoassay but who had received 56 units of blood and blood products, and another episode involved the procurement of organs prior to the donor’s seroconversion (70, 568, 633). Careful investigation of donors for factors placing them at risk for infection with HIV should be an integral part of pretransplantation screening (186).

Papovaviruses

Solid-organ transplant recipients are at high risk of developing anal human papillomavirus infection and neoplasia (490). There is a 4- to 14-fold increase in the incidence and prevalence of human papillomavirus-associated high-grade intraepithelial and invasive squamous tumors of the cervix in women with renal allografts (490). Although a role for papilomavirus in the maintenance of cutaneous squamous cell carcinoma has been suggested, one study did not support this proposal (176). Papillomavirus is found in the urine of 0.5% of renal transplant patients and is associated with papillomatous lesions including urethral papillomatosis (391).

Progressive multifocal leukoencephalopathy, a slowly progressive central nervous system infection caused by JC virus, has been found rarely in renal transplant recipients (440, 567). BK virus was first isolated from the urine of a renal transplant recipient with a ureteral stricture and since then has been linked to this complication in other reports (582).

Other Viruses

Several other viruses cause notable disease states in solid-organ transplant recipients. Reactivation of the latent human herpesvirus 6 carrier state in solid-organ transplant recipients has been suggested (791). In addition, as with any herpesvirus, primary infection may occur. Studies are under way to optimize the diagnostic techniques and determine clinical relevance of this virus in solid-organ transplant recipients. Parvovirus B19 has been described as causing severe pneumonia after heart transplantation, as well as profound aplastic anemia and fulminant hepatic failure following liver transplantation (330, 385). Adenovirus infection occurred in 7 to 19% of pediatric liver transplant patients in one study (595, 798). Presentations included fever with adenovirus cultured from the throat, fever with nodular pulmonary infiltrates concomitant with a primary CMV infection, disseminated disease, interstitial pneumonia, cough, corzya, pharyngitis, conjunctivitis, and progressive hepatitis leading to graft loss requiring retransplantation (595, 798). Adenovirus has also been reported to cause hemorrhagic cystitis in solid-organ transplant recipients (56). It has been proposed that adenovirus may be transmitted with the allograft (56). In vitro susceptibility to ganciclovir has been demonstrated for several adenovirus serotypes (56).

Yearly influenza vaccination is recommended, although some suggest that the efficacy of conventional influenza vaccination is questionable in solid-organ transplant recipients (583). Amantadine or rimantadine may be useful for prophylaxis following exposure to influenza A virus and for treatment of established influenza A infection (24).
Fungal Infections

Overview

The incidence of systemic fungal infection varies with the type of organ transplanted, occurring in 5 to 17% of heart, 14 to 22% of heart-lung, 2 to 42% of liver, and 2 to 14% of kidney transplant recipients (72, 82, 97, 99, 111, 112, 117, 132, 167, 213, 237, 301, 317, 328, 376, 464, 512, 514, 611, 709, 739). The differences in attack rates among recipients of various transplanted organs are largely due to technical issues related to the transplantation procedure and the tendency to administer more immunosuppressive therapy to recipients of organs other than kidneys (i.e., patients who have no alternative life support system, such as dialysis, if their allografts fail) (289). In lung transplant recipients, the incidence of fungal infections has been greater in patients receiving tacrolimus than in those receiving cyclosporine in some but not in all studies (249, 345).

Risk factors for fungal infections in transplant recipients include the use of large doses of corticosteroids, multiple or recent rejection episodes, hyperglycemia, poor transplant function, leukopenia, and older age (27, 309). Risk factors for invasive fungal infections following liver transplantation include urgent transplantation, preoperative steroids and antibiotics, reintubation, RISK score, high intraoperative transfusion requirement, method of biliary reconstruction, steroid dose, creatinine level, length of transplant operation, retransplantation, antibiotic therapy, vascular complications, CMV infection, bacterial infection, posttransplantation hemorrhage with reoperation, the vanishing bile duct syndrome, choledochojunostomy, abdominal or thoracic reoperation, and the use of OKT3 monoclonal antibody (38, 98, 117, 264, 739). Candida spp., Aspergillus spp., C. neoformans, P. carinii, the zygomycetes, and the geographically restricted endemic mycoses constitute the major fungal pathogens in solid-organ transplant recipients. The mortality of fungal infections in solid-organ transplant recipients varies from 27 to 77%, despite having a relatively lower incidence than bacterial or viral infections. Difficulty in establishing an early diagnosis, lack of effective therapy in certain situations, difficult management of certain antifungal drugs due to toxicity and/or interaction with immunosuppressive drugs, and limited data on effective antifungal prophylactic regimens in solid-organ transplantation represent major problems in the management of fungal infections in this population.

The clinical presentations of fungal infections in solid-organ transplant recipients are nonspecific and often overlap with other infectious and noninfectious processes. In any fungal infection diagnosed in a solid-organ transplant recipient, a careful search should be made for metastatic infection, especially involving the skin and the skeletal and central nervous systems. Since the diagnosis of a large number of episodes of severe fungal infection is established only postmortem, the clinician must maintain a high index of suspicion for this type of infection. An aggressive diagnostic approach, including extensive cultures, radiologic imaging, and biopsy of pathologic lesions for histopathologic examination, staining for microorganisms, and culture, needs to be taken.

Candida spp.

Among candidal species, Candida albicans is most frequently implicated; however, C. krusei, C. glabrata, C. zeylanoides, and C. tropicalis have also been reported as pathogens. Most fungal infections caused by Candida spp. occur in the first 2 months following solid-organ transplantation. Portals of entry include the gastrointestinal tract and urinary and intravascular catheters. Transmission of Candida spp. with renal allografts has been suggested (444).

Cell-mediated immunity, compromised by immunosuppressive therapy, plays a major role, together with the macrophage and neutrophil function, in the defense against candidal infections. In addition, conditions that lead to increased candidal colonization, such as antibiotic use, diabetes mellitus, the presence of indwelling bladder or intravenous catheters, and gut mucosal disruption by surgical transplantation procedures, play a major role in the pathogenesis of Candida infection in solid-organ transplantation. Most cases of candidiasis originate from endogenous sources (although nosocomial transmission can occur), and thus decreasing the degree of colonization is of potential benefit in solid-organ recipients. The use of a selective bowel decontamination regimen may reduce the incidence of serious candidal infections in liver transplant recipients (767). Heart-lung recipients have a high incidence of candidal colonization of their tracheal and bronchial secretions (probably originating from the donor trachea), and the donor duodenal segment is frequently colonized with Candida spp., thus being a possible infection source for pancreas recipients. Colonization of the recipient’s gastrointestinal tract is a potential source of intra-abdominal or disseminated infection in patients whose organ transplantation surgery requires disruption of gut mucosa (orthotopic liver and pancreas transplantation recipients).

Specific risk factors for deep candidal infections in liver transplant recipients include male liver donors, retransplantation, long initial transplantation time, high number of erythrocyte units transfused posttransplantationally, alcoholic liver disease, and posttransplantation bacterial infection (710).

Pancreas transplant recipients are highly susceptible to candidal infection for multiple reasons including the drainage of pancreatic exocrine secretions into the bladder, creating a nonacidic environment favoring candidal colonization; the presence of indwelling bladder catheters; and underlying diabetes mellitus (288). Similarly, in renal transplant recipients, the urinary tract is the most common site of infections, especially those caused by Candida spp., and underlying diabetes mellitus, present in some renal transplant recipients, is associated with defective killing of C. albicans.

Serious candidal infections following solid-organ transplant can present in a myriad of ways including catheter-related sepsis, intra-abdominal abscesses (most commonly in patients having undergone abdominal surgery, such as liver and pancreas transplant recipients), pulmonary infection, urinary tract infection (including cystitis, pyelonephritis, urethral obstruction, and parenchymal fungus balls), arthritis, esophagitis (which may be of the severe necrotizing variety associated with esophageal perforation), endocarditis, aortitis, invasive cutaneous and subcutaneous infection, brain abscess, and mediasinitis (5, 7, 36, 53, 65, 119, 131, 198, 212, 324, 336, 479, 482, 487, 495, 536, 563, 631, 656, 700, 747). Catheter-related sepsis due to Candida spp. and, rarely, other fungi is a common presentation of fungal infection in solid-organ transplant recipients and, as in other populations, is associated with prolonged hospitalization, especially in intensive care units, with central venous catheters in place. Candidal infection in heart and heart-lung transplant recipients may be a cause of sudden death either due to rupture of the aortic anastomosis secondary to mycotic aneurysms or due to mediastinal abscesses secondary to dehiscence of an airway anastomosis (161).

Surveillance cultures are routinely obtained in some solid-organ transplant programs; however, their predictive value, especially as pertains to fungal infection, remains unknown. Heart-lung, pancreas, and liver transplant recipients are often
colonized with Candida spp., and even though most patients who develop a deep candidal infection are known to have been previously colonized, a large number of colonized patients do not develop the infection. In a study performed with liver transplant recipients, colonization with C. albicans in three or more sites did not appear to correlate with deep fungal infection; surveillance cultures were positive in 8 of the 11 patients who developed deep candidal infection but also in 8 of 16 patients without infection—a sensitivity of 78% but a specificity of only 50% (709). However, in a separate study of liver transplant recipients, fungal colonization was a highly significant predictor for early but not late infections (117). More extensive studies are required to establish the role of surveillance cultures in managing solid-organ transplant recipients.

The diagnosis of candidal infection in solid-organ transplantation is made by obtaining fungal stains and cultures of appropriate specimens. Fine-needle aspiration cytology may be useful in the diagnosis of fungal pyelonephritis in renal transplant recipients (498).

Cryptococcus neoformans

Infections caused by C. neoformans can occur any time following solid-organ transplantation (613). Cryptococcal infection occurs in 2.5 to 3.6% of renal transplant recipients (361, 624, 750). C. neoformans is found in soil, especially soil containing bird droppings; infection is acquired by inhalation. C. neoformans has a polysaccharide capsule which has antiphagocytic properties. Cell-mediated immunity, compromised by immunosuppressive therapy, plays a major role, together with the macrophage and neutrophil function, in the defense against cryptococcal infection.

Cryptococcal infection following solid-organ transplantation may present with a subacute or occasionally more acute meningitis, pneumonia, pleural infection, cutaneous lesions, fever alone, and, rarely, other unusual forms such as retinitis, arthritis, pyelonephritis, or “fever of unknown origin” (3, 120, 233, 266, 286, 363, 395, 455, 525, 613, 643, 751). Symptoms of central nervous system involvement include headache, memory loss, disorientation, confusion, dyscalculia, dysphasia, muscle weakness, unsteadiness, tremor, urinary incontinence, and behavioral and emotional disturbances; there may be focal neurologic signs or seizures (613). Cutaneous involvement may be in the form of ulcers, aceneform papules or papules, subcutaneous swellings or tumors, ecchymoses, granulomata, gammats, abscesses, vesicles, palpable purpura or papules, necrotizing vasculitis, or cellulitis (14, 331, 436, 628). Cutaneous involvement usually indicates systemic disease (14). In men, foci of cryptococcal infection within the prostate gland may be a source of hematogenous dissemination (536). The development of coma, usually in association with delayed diagnosis and therapy, resulting in overwhelming infection and increased host debilitation, and the presence of severe concurrent infection which further reduces the host defense to C. neoformans contribute to death (361). The direct mortality due to C. neoformans is 36% (361). Interestingly, cyclosporine may have a protective effect against infection with C. neoformans (596).

The cryptococcal antigen test, performed on serum and cerebrospinal fluid (and occasionally pleural fluid), provides a sensitive and rapid means of diagnosis. A cerebrospinal fluid examination should be performed in any solid-organ transplant recipient with unexplained fevers, as well as in any such patient with C. neoformans isolated from any site (175). Cerebrospinal fluid may show a lymphocytic pleocytosis, hypoglycorrachia, and an elevated protein level (289). Culture and fungal stains, including calcofluor white, India ink, and methamine silver stains, are also helpful in the diagnosis. The cryptococcal antigen test is also useful for monitoring the response to therapy (721). Importantly, cryptococcuria, when demonstrated, is almost always indicative of systemic infection; C. neoformans is rarely a contaminant or nonpathogenic colonizer of the urinary tract (175).

Mycelial Fungi (Excluding Zygomycetes)

The Aspergillus spp. most frequently implicated in causing disease in solid-organ transplant recipients include A. fumigatus, A. flavus, A. niger, and A. terreus. In addition, an expanding list of unusual organisms including Pseudallescheria boydii, Scopulariopsis brevipes, Chaetomium globosum, Trichosporon beigeli, Sporothrix schenckii, Dactylaria constricta, Scedosporium prolificans, Trichoderma viride, Phialophora verrucosa, and Cladosporium trichoides, and Conidiobolus coronatus have been reported as causes of serious fungal infections in solid-organ transplant recipients (6, 10, 13, 48, 101, 199, 260, 326, 350, 353, 420, 454, 471, 480, 504, 511, 723, 741, 744, 760, 778, 783). Concomitant Aspergillosis and Nocardia infection has been reported (96, 459).

Invasive aspergillosis occurred in 2% of kidney transplant recipients at the University of Minnesota over an 8-year span and in 1.5% of liver transplant recipients at the University of Pittsburgh over a 10-year period (379, 714, 754). In a study performed in Paris, France, 4.5% of heart transplant recipients seen over a 9-year period developed invasive aspergillosis (259). Lung transplant recipients are at highest risk for pulmonary mold infections; at Stanford University, 15% of all lung transplant recipients developed invasive aspergillosis (368).

Alveolar macrophages normally kill inhaled aspergillal conidia, while functioning neutrophils eliminate residual mycelia (762). Neutrophil and macrophage dysfunction present in solid-organ transplant recipients treated with steroids favor the development of aspergillosis (762). Once tissue infection develops, invasion of blood vessels is the rule, accounting for the three cardinal features of invasive aspergillosis in organ transplant recipients: tissue infarction, hemorrhage, and dissemination with metastatic seeding (289). Most fungal infections caused by Aspergillus spp. occur in the first 3 months following solid-organ transplantation (379, 430). A finding common to all types of solid-organ transplant patients is the overall fatal outcome of disseminated aspergilial infection, reaching nearly 100% mortality, despite amphotericin B use. Isolated pulmonary disease due to Aspergillus spp. has a better prognosis than disseminated disease (435). Rare survival of patients with central nervous system disease has also been reported (216).

The portal of entry for Aspergillus spp. is usually the respiratory tract (lungs and paranasal sinuses). Rarely, dissemination from a primary skin lesion or contiguous spread from a previously sustained skin lesion to bone may occur (155, 384, 392). Aspergillus spp. may also invade the gastrointestinal tract or, rarely, gain entry through an intravenous catheter. It has been proposed that certain isolates of A. fumigatus are more pathogenic than others (695).

In patients with aspergillosis, pulmonary symptoms, including nonproductive cough, pleuritic chest pain, dyspnea, and low-grade fever, predominate (762). Chest radiographic findings include nodular opacities, interstitial infiltrates, cavitory lung disease, or a pulmonary embolus-type pattern; the chest x-ray may also be normal (259, 277). From the lungs, Aspergillus spp. may disseminate to almost any organ, including the brain, liver, spleen, kidneys, heart, pericardium, blood vessels, thyroid, gastrointestinal tract, bones, and joints (125, 189, 316,
342, 349, 470, 655). Clinical manifestations of central nervous system aspergillosis include alteration of mental status, diffuse central nervous system depression, seizures, evolving cerebrovascular accidents, and headache (713, 754). The cerebrospinal fluid is almost always sterile (754). Aspergillus spp. may cause peritonitis in renal transplant recipients on continuous ambulatory peritoneal dialysis and in liver transplant recipients and may cause intra-abdominal abscesses in liver transplant recipients (52, 173, 601). Endophthalmitis may occur, usually in conjunction with endocarditis (232, 473, 758). Among other unusual presentations of aspergillal infections in solid-organ transplant recipients are tracheobronchitis, with infection limited to the anastomotic site and large airways in heart-lung and lung transplant recipients, primary cutaneous involvement, wound infection (including mediastinitis with ruptured pseudoaneurysm in heart transplant recipients), and spinal epidural abscess (46, 90, 91, 315, 323, 368, 408, 531). Cases of aspergillal infection of the native lung after single-lung transplantation have been reported (105, 441).

Risk factors for invasive aspergillal disease include prolonged surgical time, laparotomies (excluding those done for transplantation), high creatinine level, neutropenia, CMV infection, and augmented immunosuppressive therapy, especially high-dose corticosteroid administration and OKT3 administration (259, 261, 379, 618). Tacrolimus has been associated with a decreased incidence of aspergillosis compared to cyclosporine (714). We have identified the following as additional risk factors for aspergillosis in liver transplant recipients: fulminant hepatitis, long pretransplantation prothrombin time and high bilirubin level, high intratransplantation transfusion requirement, posttransplantation bacterial infection, and the vanishing bile duct syndrome. Disseminated aspergillosis has been reported to complicate liver transplantation for fulminant hepatic failure refractory to corticosteroid therapy; a thorough evaluation for invasive fungal infection is mandatory prior to transplantation in such patients (77). Cases of invasive aspergillosis sometimes appear in clusters coincident with hospital construction and renovation (21, 58).

One should consider all pulmonary infections in transplant recipients to be possibly caused by mycelial fungi (64). Also, positive cultures for Aspergillus spp. in transplant recipients should never be ignored even though the isolation of Aspergillus spp. from respiratory and wound specimens does not always imply disease, as this fungus may be a colonizer or a laboratory contaminant. Repeated isolation of Aspergillus spp. from sputum is suggestive of invasive disease (379, 754), and the combination of a positive sputum culture and cavitary lung disease is highly suggestive of invasive disease (754). Conversely, sputum cultures are not always positive for Aspergillus spp. in patients with invasive aspergillosis (63, 754). Bronchoalveolar lavage permits isolation of the pathogen in 75 to 100% of patients (259). Infection is certain if fungal filaments are present; but the isolation of the fungus solely by culture is usually difficult to interpret, especially in the presence of other pathogens (259). In these cases and if these procedures are negative and aspergillosis is in the differential diagnosis, a transbronchial biopsy or an open lung biopsy should be performed. The diagnosis of extrapulmonary infection is more difficult. Any suspicious lesion (e.g., skeletal or cutaneous) should be biopsied (100). Patients with positive Aspergillus wound cultures should be investigated for local invasion and should not be assumed to be just colonized with the fungus (379).

Zygomycosis

Zygomycetes, including Rhizopus spp., Mucor spp., Absidia spp., and Cunninghamella bertholletiae, have been reported to cause infection in 1 to 9% of solid-organ transplants at a median time of 60 days after transplantation (638). Corticosteroids, underlying metabolic disturbance resulting in an acidoic state, such as that associated with diabetic ketoacidosis or pancreatic transplant recipients with a bicarbonate leak, and deferoxamine therapy are risk factors for zygomycosis (272, 289, 638, 684). In a review of 46 solid-organ transplant recipients with mucormycosis, 64% had diabetes mellitus (638). Infection occurs by inhalation, ingestion, or traumatic inoculation of fungal spores and may be nosocomial and spread by air-conditioning systems, particularly during construction (485, 638).

Zygomycetes are associated with rhinocerebral, pulmonary, gastrointestinal, cutaneous, and disseminated infections (including cardiac and hepatic infection), which have a 56% mortality rate (55, 94, 116, 201, 247, 265, 267, 272, 287, 338, 360, 375, 423, 464, 485, 528, 554, 608, 638, 684, 703, 773, 800). The rhinocerebral form is most common and usually presents as one of two subtypes: (i) a highly fatal rhino-orbital-cerebral form that involves the ophthalmic and internal carotid arteries or (ii) a less invasive rhinomaxillary form that involves the sphenopalatine and greater palatine arteries, resulting in thrombosis of the turbinates and necrosis of the palate (638). Pulmonary disease presents as nodular or cavitary lesions (638). Cutaneous and soft tissue infections in transplant recipients with zygomycosis present as wound infections, nodular lesions with necrotic ulceration, venous cannula site infections, necrotizing fasciitis, and sinus tract infections (follow ing renal biopsy) (166, 638). A rare form of zygomycosis is gastrointestinal; intestinal perforation may ensue (638). The diagnosis is made by early biopsy and histopathologic examination of the involved area(s) (638).

Endemic Dimorphic Fungi

Infections with the geographically restricted endemic mycoses (due to Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis, and Paracoccidioides brasiliensis) can occur any time following solid-organ transplantation. Infections with the geographically restricted endemic mycoses also present in a myriad of ways, and, at least for histoplasmosis and coccidioidomycosis, dissemination appears to be the rule (763). Histoplasmosis is endemic in the central United States, as well as in many other countries, and is acquired by inhalation of the infectious microconidia of H. capsulatum (797). The incidence of histoplasmosis in solid-organ transplant recipients is higher than that in the normal population and depends on the geographic exposure of the patients transplanted. Histoplasmosis occurred in 0.4% of renal transplant recipients in Minneapolis, Minn. (138). Primary and reactivation infection and transmission with the renal allografts have been postulated (138, 749, 781). Outbreaks of histoplasmosis have been reported in association with construction work within the hospital area (763). Transplant recipients found to be seropositive for H. capsulatum prior to transplantation should be evaluated for the presence of clinically detectable disease and considered candidates for prophylaxis (e.g., with itraconazole) following transplantation.

H. capsulatum infection in solid-organ transplantation recipients is usually disseminated and typically presents with nonspecific signs and symptoms. Fever is the most common presenting symptom (but may be absent), and night sweats, chills, cough, headache, arthritis, myalgias, and/or cutaneous, intes-
tinal, and oral mucosal lesions may be present (79, 138, 191, 571, 662, 763, 794). Cutaneous manifestations include papules, plaques, ulcers, purpuric lesions, abscesses, furunculoid and impetiginized areas, erysipelas-like eruptions associated with panniculitis, dermatitis, and diffuse exfoliative erythroderma (136, 191). Hepatosplenomegaly may be present (136, 763). The central nervous system can be involved (404, 763). Chest X rays may be normal or show hilar adenopathy, diffuse or miliary infiltrates, pleural effusion, and focal infiltrates (138, 763). The diagnosis may be made by serologic testing; urine antigen testing; histopathologic examination of bone marrow, respiratory secretions, and skin and other tissue biopsy specimens; and culture of respiratory secretions, blood, bone marrow, and other tissues (763).

Infection with *C. immitis* occurs in solid-organ transplant recipients who have resided in, currently reside in, or have traveled to the desert areas of the southwestern United States, northern Mexico, and areas of endemic infection in Latin America at any time during their life (622, 729). In one study, symptomatic coccidioidomycosis occurred in 7% of renal transplant recipients in Arizona during a 10-year period (115). In another study in Arizona, symptomatic coccidioidomycosis occurred in 4.5% of heart transplant recipients during a 6-year period (269). There has been one report of disseminated coccidioidomycosis in a liver transplant recipient (157), and we have seen a second case at our institution. Primary and reactivation infection occur, and although this infection can occur at any time after transplantation, it is most likely to occur in the first year posttransplantation (115). Disseminated infection is most common, followed by isolated pulmonary infection (115, 610). Nonproductive cough and fever are the most common complaints (115). Chest X-ray findings include nodular infiltrates, alveolar infiltrates, reticular interstitial disease, lobar infiltrates, miliary interstitial disease, hilar adenopathy, and, rarely, cavitory disease (792). Extrapulmonary sites of involvement include the spleen, urine, joints, liver, brain, thyroid, pancreas, blood, peritoneum, muscle, myocardium, and skin (115, 729). Lymphopenia is often present. Risk factors for dissemination include male sex and blood group B antigen (115). Coccidioidomycosis may depress cell-mediated immunity (339).

The diagnosis may be made by serologic testing (although this is not always positive), histopathologic examination of lung and other tissue biopsy specimens, or culture of respiratory secretions, blood, urine, bone marrow, joint fluid, and other tissues (115).

Before transplantation, levels of coccidioidal antibodies in serum should be measured in any patient with any endemic exposure to *C. immitis*, no matter how brief or how remote (268). Patients with a history of coccidioidomycosis prior to transplantation or reactive coccidioidal serologic tests before the time of transplantation may benefit from receiving an antifungal drug for some period after surgery (268, 269). Also, for these patients, periodic serologic surveillance and antifungal therapy should be considered during periods of increased immunosuppression such as during treatment of rejection episodes (268).

It is not clear that infections with *B. dermatitidis* and *P. brasiliensis* occur with increased frequency in solid-organ transplant recipients. Blastomycosis is endemic in the southern United States bordering the Mississippi and Ohio River valleys, the Upper Midwestern states, and the Canadian provinces adjacent to the Great Lakes and the Saint Lawrence River. Blastomycosis is an uncommon infection following transplantation and does not appear to have a predilection to occur at any special time in the posttransplantation period (623). The lung and skin are the most common sites of involvement in solid-organ transplant recipients (89, 157, 244, 295, 623). In one case, a renal transplant recipient was believed to have contracted blastomycosis from a contaminated needle in a veterinarian’s office (89). The diagnosis may be made by performing appropriate stains and cultures of respiratory secretions, skin, and other tissues. Based on our experience and that reported in the literature, it appears that transplantation recipients with blastomycosis have a high rate of relapse (623). There are rare reports of *P. brasiliensis* infection in solid-organ transplant recipients (686).

**Miscellaneous Fungal Infections**

In addition to *Aspergillus* spp. and the zygomycetes, *Phialophora gourgeroti*, *Alternaria* spp., *Paeclomyces* spp., *Pleurophoma pleurospora*, *Neocosmospora vasiforma*, *Fusarium oxysporum*, *Exophiala jeaneselmei*, *Exophiala pisciphila*, *Acremonium falciforme*, *Bipolaris* spp., and *Exserohilum rostratum* have been reported as causes of primary cutaneous infections after solid-organ transplantation; chromoblastomycosis has also been reported (4, 46, 47, 67, 159, 263, 281, 463, 635, 685, 687, 725, 734, 793). Solid-organ transplant recipients have also been shown to have an increased risk of superficial fungal infections including dermatophytosis and onychomycosis in some but not all studies (88, 111, 319, 410, 620, 630). *Hansenula anomala* has been reported as a cause of urinary tract infection in a renal transplant recipient (547).

**Treatment**

Treatment of deep fungal infections in solid-organ transplant recipients does not differ significantly from that in other types of immunocompromised hosts, although it carries certain special characteristics. Immunosuppression should be reduced as tolerated in patients whose graft is essential for survival. For some fungal infections (e.g., primary cutaneous, central nervous system, skeletal, and pulmonary aspergillosis), surgical extirpation or debridement remains an integral part of the management for both diagnostic and therapeutic purposes (100, 243, 316, 408, 754).

Intravenous amphotericin B has been the mainstay of treatment for deep fungal infections in solid-organ transplant recipients. Although effective in many cases, its use in solid-organ transplantation is associated with undesirable side effects. Aside from the bone marrow toxicity (which may aggravate or be confused with that caused by azathioprine or CMV infection), nephrotoxicity is a common side effect. Although this nephrotoxicity is reversible in other immunosuppressed patients following drug discontinuation or salt loading, solid-organ transplant patients requiring treatment with this drug may already have an impaired renal function. Solid-organ transplant recipients are treated with a variety of drugs (e.g., cyclosporine) which, by themselves or in association with amphotericin B, may potentiate renal toxicity. Interaction between cyclosporine and amphotericin B has been associated with acute renal failure, and amphotericin B may increase cyclosporine levels in plasma (348). Despite the difficulties with the use of amphotericin B, it should, in our opinion, still be regarded as the first-line agent for serious fungal infections in solid-organ transplant recipients, until more experience is gained with the antifungal agents discussed below. It is worth noting, however, that some organisms, such as *Pseudallescheria boydii*, are resistant to amphotericin B, emphasizing the need for identification of all fungal isolates in solid-organ transplant recipients.

Liposomal forms of amphotericin B appear to have fewer
side effects, including nephrotoxicity, at equivalent doses, thus allowing the administration of a much larger amount of drug. Although this type of preparation is effective in other patient populations, its safety profile in solid-organ transplantation and its expected efficacy in the treatment of severe fungal infections remain to be evaluated. Preliminary reports from other investigators and our own experience suggest that this type of preparation is clinically useful in some types of solid-organ transplant recipients, and it has been used to successfully treat a variety of candidal, aspergillal, and cryptococcal infections (341, 537, 552).

Although once again there are no data pertaining specifically to solid-organ transplant recipients, 5-fluorocytosine, if tolerated, should be combined with amphotericin B for the initial treatment of serious cryptococcal infection in organ transplant patients and should be followed by an azole (see below).

Due to the high frequency of nephrotoxicity with amphotericin B, the use of azole antifungal agents for treating fungal infections in transplant recipients is attractive. Ketoconazole, an oral broad-spectrum antifungal drug, has had little role in the treatment of fungal infections in solid-organ transplant recipients. Low efficacy against the commonly encountered pathogens, the production of liver dysfunction, its interaction with cyclosporine, and an erratic gastrointestinal absorption make its use difficult in this patient population (307, 348).

Fluconazole, owing to its pharmacokinetics, low incidence of side effects, and minimal interference with cyclosporine, is a potentially useful compound in solid-organ transplant recipients. Fluconazole is well absorbed, is available in both oral and intravenous preparations, and has good cerebrospinal fluid penetration. Its antifungal spectrum includes Candida albicans, Cryptococcus neoformans, and Coccidioides immitis, among others. However, it has poor in vitro activity against Aspergillus spp. Studies of immunocompromised patients show fluconazole to be an effective drug for the treatment of oral and esophageal candidiasis, cryptococcal meningitis, and deep-seated candidal infections (78, 122, 707). It may also be useful for therapy of candidemia. One important caveat in the treatment of Candida infection with fluconazole is that certain candidal species such as C. krusei and C. glabrata have a low susceptibility in vitro. Again, although fluconazole appears to play a role in the therapy of coccidioidomycosis, its role in solid-organ transplant patients with this infection has not been extensively studied. Following initial treatment of coccidioidomycosis with amphotericin B, chronic maintenance therapy with an oral azole such as fluconazole is required (269).

Itraconazole is another oral imidazole that is being increasingly used in solid-organ transplant populations. In preliminary nonrandomized clinical trials, itraconazole has efficacy in treating aspergillal infections in immunocompromised patients (189, 441, 733). Furthermore, its therapeutic range is broad and includes H. capsulatum, B. dermatitidis, C. immitis, and Candida spp., among others (234). Its interaction with cyclosporine, although present, is of a lesser degree than that observed with ketoconazole (189, 367). Its erratic absorption, especially in patients with low gastric acidity, make it mandatory that its concentrations in plasma be monitored. Overall, itraconazole appears to be relatively well tolerated, and its oral administration makes it an attractive agent for the prolonged treatment of fungal infections in this patient population.

Immunotherapy as a complementary approach to antifungal drug therapy needs further evaluation. Gamma interferon activates macrophage function in vitro, resulting in antifungal killing. Although potentially useful in the defense against fungal infection, its positive immunomodulatory role with subsequent increase in allograft rejection is of potential concern. Colony-stimulating factors (e.g., granulocyte-macrophage colony-stimulating factor) can boost monocyte and neutrophil turnover and function; their in vivo role in the defense against fungal infections in immunocompromised patients is under evaluation. Their use in solid-organ transplant recipients needs to be thoroughly studied, especially in the context of any association with allograft rejection. Likewise, the combination of antifungal drugs with immunoglobulin preparations or antifungal monoclonal antibodies may merit further study.

Prophylaxis

Prophylaxis of severe fungal infections should be a major priority in solid-organ transplant patients. Potential risk factors for the development of fungal infection need to be identified in each type of solid-organ transplantation. Patients with specific risk factors should be monitored carefully by the clinician. Close surveillance of patients’ idiosyncrasies merits attention; fungemia has been described in a patient who ingested brewer’s yeast, and cryptococcal infection has been found in a patient who ingested pigeon droppings for medicinal purposes. Methods that have been proposed to prevent fungal infections include selective bowel decontamination, early enteral feeding to prevent breakdown of the gastrointestinal mucosal barrier, and systemic and bowel antifungal prophylaxis.

Oral nonabsorbed antifungal agents have been studied as prophylactic agents for invasive fungal infections following solid-organ transplantation. Although some studies have suggested that topical antifungal agents might prevent invasive candidal infections following liver transplantation (229), other studies, have shown that invasive candidal infections occur despite nystatin prophylaxis. Clotrimazole troches appear to be of equal efficacy to nystatin (586). However, neither oral nystatin nor clotrimazole prevents mycelial fungal infection. Therefore, the use of topical antifungal agents is not sufficient to prevent invasive fungal infections. Selective bowel decontamination regimens are used, especially in abdominal transplantation recipients, in an attempt to eliminate gram-negative aerobic bacillus and yeast colonization of the gastrointestinal tract (667). Candidal carriage in the alimentary tract of liver transplantation recipients is high (378). Whether selective bowel decontamination reduces the incidence of invasive fungal infections has not been evaluated in a randomized, controlled fashion, but this may explain the relatively low incidence of invasive fungal infection, especially candidal infection, at our institution (767). Nevertheless, the protection provided by selective bowel decontamination, if present, is incomplete.

Systemic amphotericin B has been shown to have prophylactic efficacy against invasive fungal infections in liver transplantation recipients in some (460, 462) but not all (639) studies. It is not an optimal agent for this purpose, however, due to its toxicity and its intravenous formulation. In a placebo-controlled trial, a 5-day course of liposomal amphotericin B, 1 mg/kg/day, has been shown to prevent fungal infections in liver transplant recipients, with an overall incidence of invasive fungal infections of 0 of 40 (0%) in the liposomal amphotericin group versus 6 of 37 (16%) in the placebo group ($P < 0.01$) (711). Prophylactic aerosol and spray amphotericin formulations have also been shown to prevent invasive aspergillosis in a nonrandomized study (259). Fluconazole is an attractive prophylactic agent for liver and pancreas transplant recipients because of its oral formulation and anti-candidal activity. Its poor activity against mycelial fungi make it a less useful antifungal prophylactic agent in transplant recipients with a high risk of mycosis.
rate of aspergillus infection, such as lung transplant recipients. Itraconazole is theoretically more promising in this regard but has not, to date, been studied as a prophylactic agent for invasive fungal infections in transplantation recipients. Interestingly, studies in which prophylaxis with immunoglobulin is given in an attempt to reduce CMV infection in renal transplant recipients show a decrease in fungal infection (653). Whether this is due to a decrease of some forms of CMV infection (partially accomplished in these studies) or to a direct or indirect effect of immunoglobulin on fungal infection remains unknown. Prophylaxis studies with antiviral compounds which result in a decrease of CMV infections have not yet addressed the issue of a possible reduction (or augmentation) of other opportunistic organisms such as fungi. The use of preemptive therapy with amphotericin B or itraconazole in liver transplantation recipients with risk factors for invasive fungal infections is another approach that may reduce the incidence of fungal infections following liver transplantation. For example, some groups have adopted the policy of administering amphotericin B during OKT3 therapy for acute rejection in lung transplantation (627).

The use of protective isolation (laminar air flow and air filtration [HEPA filters]) provides environmental protection against aspergillosis, but due to cost issues, it cannot be recommended (259). Solid-organ transplant recipients should not be housed in the vicinity of renovation activities, and flowers and potted plants, which may be colonized with Aspergillus spp., should not be permitted in patient rooms.

**Pneumocystis carinii**

Among patients who are not receiving prophylactic therapy, *P. carinii* causes pneumonia in approximately 10% of heart, kidney, and liver transplant recipients in the first 6 months posttransplantation and in a higher proportion of lung and heart-lung transplant recipients (118, 255, 283, 370, 376, 461, 477, 514). The incidence of this infection appears to be higher in children than in adults (118).

*P. carinii* pneumonia in solid-organ transplant recipients typically has a subacute presentation, with fever, dyspnea, nonproductive cough, radiographic findings of interstitial infiltrates, and hypoxemia out of proportion to the physical and radiographic findings (252, 279). In addition, *P. carinii* may be found in asymptomatic transplant recipients (118, 255). *P. carinii* pneumonia is associated with an increased incidence of pneumothorax (252). Typical radiographic findings include diffuse interstitial or interstitial and alveolar infiltrates, but atypical findings may be seen as well (589). *P. carinii* is often isolated with CMV (279). Clusters of cases of *P. carinii* pneumonia have been reported, and a question of person-to-person transmission has been raised (35, 49, 108, 283, 297, 600).

The diagnosis is made by examining bronchoalveolar lavage fluid or a lung biopsy specimen by one of several techniques, including calcofluor white, methenamine silver, and Wright-Giemsa staining and monoclonal antibody techniques (283, 365, 606). In the case of lung biopsy specimens, histopathologic examination is also helpful. *P. carinii* pneumonia is treated with high-dose trimethoprim-sulfamethoxazole (15 to 20 mg/kg/day in divided doses) or intravenous pentamidine (4 mg/kg/day) for 14 to 21 days, with the former regimen being preferable. Adverse effects of trimethoprim-sulfamethoxazole include anorexia, nausea, vomiting, a transient rise in creatinine levels, and hyponatremia; adverse effects of pentamidine include renal dysfunction, bone marrow depression, hypoglycemia, hypocalcemia, liver dysfunction, and seizures (163).

Importantly, low-dose trimethoprim-sulfamethoxazole (e.g., one single-strength or one double-strength tablet every day) provides excellent prophylaxis for *P. carinii* pneumonia (180, 292, 370, 694) and, in our opinion, should be given to all solid-organ transplant recipients for at least 6 months posttransplantation (180, 493). Prophylaxis beyond 6 months posttransplantation is indicated for heart-lung and lung transplant recipients and for patients with ongoing risk factors for *P. carinii* pneumonia such as multiple episodes of rejection, treatment with OKT3 monoclonal antibodies, or persistent allograft dysfunction (283, 370, 442, 661). Importantly, prophylaxis should be reinstituted, if it has been discontinued, in patients receiving augmented immunosuppression. Alternatives to trimethoprim-sulfamethoxazole for prophylaxis include intravenous or aerosolized pentamidine, dapsone, and atovaquone (661). For single-lung allograft recipients who cannot tolerate trimethoprim-sulfamethoxazole, there is some controversy about the use of aerosolized pentamidine, which may be inadequately delivered to the remaining diseased and therefore poorly ventilated lung, which would therefore be at risk for *P. carinii* infection; one study, however, has shown that this regimen is effective in this patient population (477).

**MYCOBACTERIAL INFECTIONS**

*Mycobacterium tuberculosis*

Over the past several years, there has been an increase in the incidence of active tuberculosis, including drug-resistant tuberculosis, in the United States. *M. tuberculosis* infection occurs in approximately 1% of solid-organ transplant recipients in North America and Europe (236, 548, 672). Solid-organ transplant recipients are at increased risk for both primary and reactivation infection, and disseminated disease is more common in this population than in nonimmunocompromised populations. Rarely, *M. tuberculosis* is transmitted with the allograft (466). There is a 30% mortality rate associated with *M. tuberculosis* infection in transplant recipients (642).

*M. tuberculosis* infection does not conform to the timetable mentioned earlier in this review and may present at any time posttransplantation (400). Presentations include typical cavitary pulmonary disease, as well as intestinal, skeletal, cutaneous, disseminated, and central nervous system disease (1, 11, 22, 45, 127, 148, 293, 322, 381, 405, 492, 544, 548, 560, 573, 582, 659, 672). *M. tuberculosis* infection in transplantation recipients is usually accompanied by pyrexia (293, 548), although excessive sweating and weight loss are not common (548). *M. tuberculosis* is highly contagious, and all patients with pulmonary tuberculosis should be promptly isolated; there have been reported outbreaks of *M. tuberculosis* infection in transplant programs (689).

The diagnosis of tuberculosis differs little in the solid-organ transplantation population compared to other populations, with a few exceptions. *M. tuberculosis* infection should be suspected in any transplant patient with pulmonary infiltrates (642). Importantly, the tuberculin skin test is positive in only one-quarter to one-third of solid-organ transplantation recipients with tuberculosis (548, 642). Smears for acid-fast bacilli and mycobacterial culture should be performed on appropriate specimens (e.g., sputum) whenever this diagnosis is suspected. In cases of suspected pulmonary tuberculosis, early invasive techniques, such as bronchoscopy with bronchoalveolar lavage, transbronchial biopsy, and/or open lung biopsy, should be performed if routine sputum examination is unyielding. A high index of suspicion for metastatic or disseminated infection should be maintained, and aggressive and early diagnostic techniques (e.g., liver biopsy, lymph node biopsy, and blood
cultural infection (culture) should be performed to document the presence of these entities. Granuloma formation in biopsy specimens is highly suggestive of *M. tuberculosis* infection (672).

Transplant recipients with active tuberculosis should receive 12 months of therapy with at least two bactericidal drugs (isoniazid, rifampin, or pyrazinamide) to which the organism is susceptible, although a recent study has shown successful treatment of liver transplant recipients with 9 months of isoniazid, 6 months of rifampin, and 3 months of pyrazinamide therapy (236). At our institution, patients with active pulmonary tuberculosis have been identified in the pretransplantation screening process and have not been excluded as transplant candidates if therapy was instituted and sputum smears for acid-fast bacilli were negative at the time of organ availability. Continuation of antituberculous treatment posttransplantation has resulted in no major side effects and in radiologic and microbiologic cure. Antimycobacterial therapy has important toxicities and drug interactions in solid-organ transplantation recipients (486). Isoniazid, streptomycin, and ethambutol are excreted by the kidneys, and their doses must often be adjusted in renal transplant recipients. Rifampin and possibly isoniazid induce hepatic enzymes and increase the catabolism of corticosteroids and cyclosporine (383, 437). There are several reports of allograft rejection during rifampin therapy (84, 457, 488). Glucocorticoid doses should be increased and cyclosporine levels should be carefully monitored in patients taking rifampin (437, 704). Close monitoring of liver function tests, as well as liver biopsy for evaluation of elevated liver function tests in liver transplant recipients receiving isoniazid or rifampin are suggested (672).

As discussed above, a detailed history of tuberculosis exposure should be obtained for all transplant candidates and a tuberculin test should be performed prior to transplantation (593). Recommendations for isoniazid prophylaxis are, however, controversial (405, 548, 659). Although isoniazid prophylaxis is recommended by the American Lung Association for patients with positive tuberculin tests who are receiving immunosuppressive therapy, several groups have suggested that in the absence of other risk factors for tuberculosis, isoniazid prophylaxis be withheld due to the high risk of isoniazid hepatotoxicity (294, 672, 702). If possible, isoniazid prophylaxis should be administered for several months prior to surgery (400). In addition, tuberculin test-positive transplant recipients who have not previously been treated might benefit from isoniazid prophylaxis when they receive antilymphocyte preparations (672). Patients with other risk factors for active tuberculosis, such as recent tuberculin conversion, Asian, African, or Native American heritage, a history of inadequately treated tuberculosis, close contact with an untreated patient with *M. tuberculosis* infection, chest X-ray abnormalities, or other immunosuppressing conditions, should receive isoniazid prophylaxis for 6 to 12 months posttransplantation (548). Isoniazid prophylaxis should also be considered for recipients of allografts from donors with a history of tuberculosis or a positive tuberculin test (400).

**Nontuberculous Mycobacteria**

Nontuberculous mycobacteria are ubiquitous organisms and are capable of colonizing or infecting solid-organ transplant recipients. Nontuberculous mycobacteria reported as pathogens in solid-organ transplant recipients include *M. kansasii*, *M. avium-intracellulare*, *M. fortuitum*, *M. xenopi*, *M. haemophilum*, *M. marinum*, *M. chelonae*, *M. abscessus*, *M. gastri*, *M. scrofulaceum*, and *M. thermoresistibile*. These infections generally occur late in the post-transplant period (range 10 days to 269 months, mean 48 months) (1, 26, 62, 73, 124, 126, 130, 139, 204, 209, 223, 230, 239, 285, 293, 358, 359, 362, 400, 405, 450, 467, 469, 478, 486, 506, 522, 577, 587, 599, 634, 659, 688, 704, 715, 717, 740, 745, 746, 753, 779, 781).

Nontuberculous mycobacteria can cause acute disseminated disease, but they most commonly cause chronic infection manifesting as cutaneous lesions of the extremities, tenosynovitis, and joint infection. Less frequently, allograft, pulmonary, or intestinal involvement occurs. Fever is the exception rather than the rule, in contrast to tuberculous infections (126). Typical skin lesions begin as painful erythematous or violaceous subcutaneous nodules that may progress to form an abscess, and they often exude purulent or serious fluid and develop into cutaneous ulcers. The most commonly involved joints include the digits, wrists, elbows, ankles, and knees. Although most patients are remarkably tolerant of these infections and may have a symptomatic interval of 1 to 12 months before diagnosis, early diagnosis and therapy are needed before skin breakdown leads to significant superinfection, particularly if the site of infection involves joints (124).

Failure to respond to standard antimicrobial therapy should raise the question of infection with an unusual organism such as a nontuberculous mycobacterium. Aspiration or biopsy of lesions for histopathologic testing, staining for mycobacteria, and mycobacterial culture are essential for diagnosis. Transbronchial lung biopsy is useful in determining the significance of rapidly growing mycobacteria in sputum and in differentiating rejection from infection in heart-lung and lung transplant recipients (715). It is noteworthy that synovial fluid in patients with arthritis and synovitis is generally rich in polymorphonuclear leukocytes, and radiographs of the involved joints are frequently normal (126). Although granulomas may be seen in tissue biopsy specimens, this is not uniformly the case, and, instead, probably due to the immunosuppressed state, there may be a predominance of polymorphonuclear cells mimicking bacterial infection (209). Stains for acid-fast bacilli may be negative in the presence of positive cultures, which should always be performed.

Solid-organ transplant recipients are at risk for nontuberculous mycobacterial infections because of their depressed cell-mediated immunity and the effects of chronic corticosteroid administration on the skin; more specific risk factors are as yet poorly defined. In the cardiac transplant recipient, a history of open heart surgery and immunosuppressive therapy with cyclophosphamide as opposed to azathioprine appears to be associated with an increased risk of infection with nontuberculous mycobacteria (634). A possible association of nontuberculous mycobacterial infection with nocardiosis has not been substantiated (486, 634). In contrast to tuberculosis, person-to-person transmission of nontuberculous mycobacterial infections is not thought to occur, although the appearance of two cases of *M. haemophilum* infection in a renal dialysis unit raised a question of contamination or person-to-person spread (230). *M. chelonae* has been isolated from the water softener resin of a renal dialysis unit, which is a potential source of infection (26). A question of a bovine graft as a possible source of *M. kansasii* infection has been raised; this organism is found in milk and other dairy products (659). *M. marinum* is typically associated with exposure to aquatic environments, swimming pools, or fresh- or saltwater beaches; as mentioned above, solid-organ transplantation recipients should be warned of the hazards of infection from home aquariums.

Published reports do not define the optimal therapeutic regimen for these infections, which have included antimicrobial agents, surgical debridement, and/or the lessening of the immunosuppressive treatment. Surgical debridement is often
necessary for both diagnosis and treatment. In cases of solitary pulmonary nodules secondary to nontuberculous mycobacterial infections, it is unclear if additional therapy is required if the lesion has been completely removed.

The sporadic and infrequent incidence of infections caused by nontuberculous mycobacteria make it difficult to determine which drug regimens are optimal in treatment. Empiric treatment is indicated, based on the results of in vitro susceptibility testing. Clinical responses may, however, occur despite in vitro resistance (704). Previous authors have outlined possible therapeutic options for nontuberculous mycobacterial infection (780, 784). The cornerstone drugs include rifampin, rifabutin, isoniazid, ethambutol, and streptomycin. These drugs are frequently used in combinations such as rifampin, isoniazid, and ethambutol for *M. kansasii* and isoniazid, rifampin, and streptomycin for *M. xenopi*; however, for most of these organisms, there are no uniformly accepted regimens. Single-drug therapy with drugs such as clarithromycin may play a role in situations such as cutaneous *M. chelonae* infection (746). The outcome of nontuberculous mycobacterial infections in solid-organ transplantation recipients is generally favorable.

**PARASITIC INFECTIONS**

Parasitic infections in solid organ transplantation recipients are generally not associated with distinctive presentations, with the exception of *S. stercoralis* and *T. gondii*, which are discussed below. In addition, in patients with Trypanosoma cruzi-associated cardiomyopathy undergoing heart transplantation, a new acute phase of Chagas’ disease may be seen. This is characterized by fever, cutaneous lesions (with or without parasites), and myocarditis (with or without parasites) and is responsive to specific drug therapy (399, 674). Parasites have been demonstrated in the transplanted hearts of such patients, and thus the long-term viability of the allografts may be compromised. Overall, heart transplantation in patients with Chagas’ cardiomyopathy is controversial (57, 351, 674). Chagas’ disease may be transmitted by renal transplantation, and there have been two instances of central nervous system involvement in this setting (197, 397, 456).

**Toxoplasma gondii**

Toxoplasmosis following solid-organ transplantation is usually the result of reactivation of latent disease in the seropositive-donor heart because of the predilection of the parasite to invade muscle tissue, but it may occur in any type of solid-organ transplantation recipient (595, 658, 716). Over 50% of seronegative heart transplant recipients who receive organs from seropositive donors develop symptomatic primary infection in the absence of prophylaxis (202). In one study of *T. gondii*-seronegative recipients of allografts from *T. gondii*-seropositive donors, 57% of heart, 20% of liver, and <1% of kidney transplant recipients acquired primary *T. gondii* infection (658). In the same study, it was suggested that *T. gondii* was transmitted to a seronegative liver transplant recipient by blood or blood products (658). Clinical presentations include meningoencephalitis, brain abscess, pneumonia, myocarditis, pericarditis, hepatitis, and retinochorioiditis (451, 636). The onset of clinically significant infection has been reported to be between 1 day and 7 years after transplantation, although most cases occur within 2 months posttransplantation (134, 451).

The receipt of OKT3 monoclonal antibody may be a risk factor for developing disseminated primary *Toxoplasma* infection (325). The diagnosis is made with certainty only by histologic demonstration of trophozoites with surrounding inflammation in tissue. Biopsy specimens may be stained with Wright, Giemsa, or periodic acid-Schiff stains or with specific antibodies. Pulmonary organisms may be detected in bronchoalveolar lavage samples; diagnosis of cardiac disease typically requires multiple cardiac biopsy specimens (226, 738). Serologic testing is not very useful; however, a positive IgM titer or a fourfold rise in the IgG titer supports a diagnosis of toxoplasmosis. Elevations of antibody levels in CSF or vitreous fluid relative to those in peripheral blood also are indicative of infection. Antigen detection and PCR techniques are being developed and may be useful (202).

Toxoplasmosis is treated with (i) pyrimethamine with folinic acid and sulfadiazine or (ii) clindamycin and pyrimethamine with folinic acid (80). Toxoplasmosis is generally prevented by the same doses of trimethoprim-sulfamethoxazole used for *P. carinii* prophylaxis administered for at least 6 months post-transplantation (494). An alternative is pyrimethamine, 25 mg daily (785, 786). Randomized, controlled trials evaluating these two prophylactic regimens in solid-organ transplant recipients are unavailable.

**Strongyloides stercoralis**

*S. stercoralis* is the one helminth that deserves special mention as concerns transplant recipients. *S. stercoralis* can be maintained in the human intestinal tract for decades and can cause disseminated infection in transplantation recipients. Ninety million people are infected worldwide, including 400,000 in rural Puerto Rico and the southeastern United States, notably Louisiana, Tennessee, and Kentucky. Individuals harboring this helminth may be asymptomatic. There has been only one report suggesting the possibility of transmission of strongyloidiasis by solid-organ transplantation (310). In most cases, symptoms of strongyloidiasis develop in the first 6 months posttransplantation (154). In simple intestinal strongyloidiasis, rhabditiform larvae are isolated in the stool or duodenal secretions; symptoms include abdominal pain, diarrhea, abdominal distension, nausea, and vomiting (154). Adynamic ileus, small bowel obstruction, and/or gastrointestinal hemorrhage may also be seen (154). This organism has an autoinfective cycle whereby rhabditiform larvae transform to filariform (infectious) larvae in the gut and invade the intestinal mucosa (internal autoinfection) or perianal skin (external autoinfection). This may result in a hyperinfection syndrome characterized by an increase in worm burden without the accompanying spread of larvae outside the usual migration pattern (i.e., gastrointestinal tract, lungs); gastrointestinal and pulmonary symptoms including tachypnea, dyspnea, cough, and hemoptysis predominate (154, 759). Alveolar or interstitial infiltrates may be seen on chest X-ray (154). Disseminated strongyloidiasis is characterized by enterocolitis and widespread dissemination of larvae to extraintestinal organs (e.g., heart, lungs, central nervous system, and skin); larvae may entrain gram-negative bacilli, resulting in gram-negative bacteraemia and occasionally meningoencephalitis (153, 206, 298, 465, 617, 731, 766). Fever, rash, and headache may be noted (154). Disseminated infection has a mortality rate of 71% (154).

As noted in the discussion on the pretransplantation evaluation, patients who have travelled to or resided in an area of endemic infection should be examined for the presence of this parasite prior to transplantation. The diagnosis is made by examining stool specimens for rhabditiform larvae; several stool specimens should be examined, since the yield of a single stool examination is only about 27% (465). Other means of diagnosis include duodenal aspirate, urine, ascitic fluid, wound
and sputum examination, jejunal biopsy, culture, and serologic testing. Although eosinophilia is not universally found, if it is present it suggests the possibility of strongyloidiasis.

Thiabendazole and ivermectin are used to treat strongylo-
diasis (153, 614). Patients harboring this parasite prior to transplanta-
tion should receive 25 mg of thiabendazole/kg/day twice daily for 3 days prior to transplantation (390). Follow-up stool examinations should be performed. Consideration may additionally be given to administering preemptive thiabendazole therapy to all transplant candidates who have travelled to or resided in an area of endemic infection regardless of the results of stool examinations, which are insensitive, although this is controversial (154). Patients found to be infected with *S. stercoralis* following transplantation should be treated with a longer course of thiabendazole (5 to 14 days) (153, 465). Monthly suppression of *S. stercoralis* with thiabendazole may be required in patients who live in areas of endemic infection (153). Interestingly, cyclosporine has some activity against *S. stercoralis* and may eliminate the threat of disseminated infection in transplant recipients (605). To the best of our knowledge, there have been no reported cases of transplantation recipients with disseminated strongyloidiasis; the effects of tacrolimus against this organism are unknown. Personnel caring for transplantation plant recipients is essential to prevent and treat these some-

**CONCLUSIONS**

A detailed understanding of infections in solid-organ transplant recipients is essential to prevent and treat these sometimes devastating setbacks to an otherwise successful procedure. The epidemiology of infections in this population is changing because of the use of prophylactic regimens (e.g., *P. carinii* and nocardial infections are seen less frequently as a result of trimethoprim-sulfamethoxazole prophylaxis), vaccination, new immunosuppressive regimens (e.g., *S. stercoralis* infection appears not to occur in patients given cyclosporine), and careful control of infectious exposures. As transplantation practices evolve, we should remain aware that the epidemiology of infections in solid-organ transplant recipients may change further. For example, we are optimistic that a much-needed improved approach to CMV prophylaxis will evolve over the next few years, lessening the burden of this infection on transplantation recipients. The morbidity and mortality of CMV in solid-organ transplant recipients have been lowered in the last few years for multiple reasons. The same may apply to other opportunistic infections. New antifungal agents will hopefully reduce the high mortality rate of mycelfal fungal infections in solid-organ transplantation recipients; prophylaxis for these infections may also become a welcome reality. On the other hand, the introduction of new practices such as xenotransplantation has a high potential to change the epidemiology of posttransplantation infections and even to introduce novel infectious pathogens (106).

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