Prophylaxis Strategies for Solid-Organ Transplantation

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In addition to the net state of immunosuppression, the risk of infection after transplantation is largely determined by the transplant recipient's epidemiologic exposures. Potential sources of infection in the transplant recipient include the environment and the recipient's endogenous flora. This article presents aspects of prevention of infection after solid-organ transplantation such as avoidance of epidemiologic exposures, antibacterial prophylaxis, prophylaxis for tuberculin-positive transplant recipients, and prophylaxis against infections with *Pneumocystis carinii* and *Toxoplasma gondii*.

**AVOIDANCE OF EPIDEMIOLOGIC EXPOSURES AFTER TRANSPLANTATION**

Various measures can be taken to reduce high-risk epidemiologic exposures both in the hospital and in the community, and patients should be counseled in ways to reduce infection risk [4, 5]. For the most part, the recommendations that follow are based on clinical experience, available knowledge of the transmission of infectious agents, and the opinions of respected authorities [2, 4, 5] (A-III).

**Hospital exposures.**

A. Care must be taken to ensure that patients are not exposed to *Legionella*, from showers, toilet facilities, and contaminated air-conditioning systems, or to *Aspergillus* spores, from construction sites. Showers, toilets, and air-conditioning systems should be monitored and properly serviced. HEPA-filtered air-handling systems should be used when the air supply is potentially contaminated. Transplant recipients should be equipped with special masks when transported through high-risk areas within the hospital.

B. Reverse isolation and other protected environments that have been used in bone marrow transplantation do not appear to be useful in the prevention of infection in solid-organ transplant recipients.

C. Plants and flowers are potentially contaminated with gram-negative organisms and should not be allowed in patient rooms.

D. Staff should wash their hands before and after each patient interaction to prevent the spread of nosocomial pathogens.

**Community exposures.**

A. Transplant recipients who are not immune to varicella-zoster virus should avoid exposure to persons with chicken pox or shingles and anyone with a localized rash after vaccination. If such exposure occurs, recipients should immediately contact a physician to obtain varicella-zoster immunoglobulin.

B. Transplant recipients should avoid contact with...
children and adults who have respiratory virus infections and anyone with tuberculosis or another contagious disease.

C. Household members of transplant recipients should receive the influenza vaccine yearly. Family members requiring polio vaccination should receive the inactivated rather than the live (oral) polio vaccine because the vaccine strain can be transmitted to household contacts.

D. If the safety of drinking water is in question, the water should be boiled for 1 full minute before it is used.

E. All meat, chicken, eggs, and seafood should be thoroughly cooked to decrease exposure to *Salmonella* species, *Campylobacter*, *Escherichia coli*, and hepatitis A virus. All fruits and vegetables should be thoroughly washed. Unpasteurized milk, products made with unpasteurized milk, unpasteurized fruit juices, and sprouts should be avoided.

F. If cleaning up after pets is unavoidable, gloves should be worn (e.g., to change cat litter boxes and to clean fish aquaria), and masks should be worn when bird cages are cleaned. Changing cat litter boxes daily will eliminate the risk of toxoplasmosis because the oocysts do not have time to sporulate.

G. All individuals should practice safe sex and avoid IV drug use.

H. Plans to travel outside one’s country of residence, particularly to areas requiring malaria prophylaxis and vaccines, should be discussed with the transplant recipient’s physician a reasonable length of time before departure.

### ANTIBACTERIAL PROPHYLAXIS

Bacterial infections occur in 33%–68% of liver transplant recipients, 54% of lung transplant recipients, 47% of kidney transplant recipients, 35% of pancreas transplant recipients, and 21%–30% of heart transplant recipients, usually within 2 months after transplantation [2, 6, 7]. Bacterial infections most commonly involve surgical wounds, lungs, the urinary tract, or vascular-access devices and are similar to those that occur in surgical patients who are not immunosuppressed.

Perioperative antibacterial prophylaxis has been shown to be effective in preventing wound infections in kidney transplant recipients [8, 9]. Although there is a paucity of randomized clinical trials demonstrating the benefit of perioperative prophylaxis in patients undergoing transplantation of organs other than kidneys, it has become the standard of practice at most transplant centers.

### Transplant-Specific Problems

The technical complexity of solid-organ transplant surgery adds a unique dimension of risk for bacterial infections that is directly related to the nature of the surgery and the organ that is being transplanted.

The incidence of bacterial infections is particularly high in liver transplant recipients. Bacterial infections of the liver (intra- and extrahepatic abscesses), biliary tract (cholangitis), peritoneal cavity, surgical site, and bloodstream are most common [10–14]. Significant risk factors include prolonged duration of surgery, transfusion of large volumes of blood products, use of a choledochojejunostomy (Roux-en-Y) instead of a choledochostomy (duct-to-duct) for biliary anastomosis, repeat abdominal surgery, and cytomegalovirus infection [11, 12, 15–17]. Common bacterial pathogens include enterococci, staphylococci, aerobic gram-negative bacilli, and anaerobes [10–19]. Infections with vancomycin-resistant enterococci have become particularly problematic [18].

Selective bowel decontamination (SBD) is used in liver transplant recipients to prevent colonization of the oral cavity and gastrointestinal tract by aerobic gram-negative bacilli and fungi while sparing the anaerobic gut flora, thus preserving the antagonistic activity related to the latter (colonization resistance) [20–23]. The use of SBD has been shown to result in a reduction of bacterial infections in several nonrandomized trials [24–28] and in 2 randomized, controlled trials in liver transplant recipients [29, 30]. Various nonabsorbable oral and topical agents are used, but they have not been compared in large controlled trials; thus, there is no consensus on the advantages of the different regimens. Diminished efficacy of SBD has been noted when the antibiotic regimens are administered for <1 week before the surgery. Some centers have noted an increased incidence of infections with organisms not covered by SBD, including *Lactobacillus* species [31]. The impact of SBD on the rising incidence of infections with vancomycin-resistant enterococci and methicillin-resistant staphylococci has been noted at some liver transplant centers but has not been fully characterized.

Pulmonary infections are common in lung and heart-lung transplant recipients, because of impaired mucociliary clearance and abolition of the cough reflex distal to the tracheal or bronchial anastomosis [32–39]. The anastomosis is particularly vulnerable to colonization with pathogens including gram-negative bacilli (*Pseudomonas*) and staphylococci. In some centers, lung and heart-lung transplant recipients with cystic fibrosis (CF) were found to be at greater risk for life-threatening bacterial infections, particularly with multidrug-resistant organisms such as *Burkholderia cepacia*, whereas this was not the case at other centers [40–43]. To reduce the risk of infection in patients with CF, perioperative antibiotics are chosen on the basis of sputum culture results obtained preoperatively, and the antibiotics are administered for a longer period postoperatively (14 days). In addition, prophylactic sinus surgery or drainage and administration of intrasinus antibiotics has been suggested for patients with CF before or after transplantation, in an attempt to reduce the burden of bacteria and the incidence of posttransplant in-
feictions (see the article by Speich and van der Bij [44], in this issue, for further details) [45].

Pneumonia is the most common bacterial infection after heart transplantation [46–48]. Gram-negative pneumonia in the early posttransplant period is associated with a significant mortality rate. Direct transmission of pathogens from a donor with positive blood cultures may result in bacteremia, sepsis, and/or mediastinitis in the heart transplant recipient; transmission of gram-negative pathogens is particularly devastating. Because there is often an immediate need, the use of infected donor organs can be made safe with appropriate perioperative antibiotic therapy [49].

Kidney transplant recipients have a high incidence of urinary tract infections (UTIs). Because patients may be asymptomatic and without pyuria, surveillance cultures are often necessary to detect UTIs (see the article by Muñoz [50], in this issue, for further details) [51, 52].

Prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) has been shown to be effective for the prevention of UTIs and bacteremia after kidney transplantation in randomized clinical trials [53–55]. In addition, it is effective prophylaxis for P. carinii (see below) and also reduces the risk of infections with Listeria monocytogenes and Nocardia asteroides. TMP-SMX prophylaxis may also be useful in protection against T. gondii reactivation in heart transplant recipients (see below). Controversy exists regarding the exact timing, dose, and duration of TMP-SMX prophylaxis for UTIs in kidney transplant recipients. Ciprofloxacin has been found to be effective in the prevention of UTIs in kidney transplant recipients in ≥2 randomized trials and may thus be a useful alternative agent if TMP-SMX cannot be used [56, 57].

The most common bacterial infections in pancreas transplant recipients are wound and intra-abdominal infections [58]. Entecric bacteria are the most common pathogens.

Key factors in determining the incidence of bacterial infections in the postoperative period include the nature of the operation, the technical skill with which the surgery is performed, and the quality of the postoperative care. The risk of postoperative bacterial infections increases with the prolonged use of any catheters, stents, or other foreign bodies and the presence of devitalized tissue and fluid collections. Successful intervention includes the correction of technical and anatomic problems in conjunction with antimicrobial therapy.

**Recommendations.**

A. Perioperative antibacterial prophylaxis aimed at preventing wound infections should begin on an on-call basis in the operating room and should continue for <24 h and <3 days after transplantation, in kidney transplant and other solid-organ transplant recipients, respectively (A-II). Although perioperative prophylaxis in lung and heart-lung transplant recipients is sometimes continued until mediastinal drains and central lines are removed, administration of prophylactic antibiotics is not recommended beyond 7 days after surgery in patients who do not have CF (C-III).

The choice of an antibiotic regimen should be guided by the resident flora of the transplanted site, the prevalent bacterial flora known to cause wound infections, and the antibiotic susceptibility at a particular institution. Regimens should be individualized by the type of organ transplant, as needed. For example, kidney transplant patients are given cefazolin or ampicillin-sulbactam, to cover uropathogens and staphylococci; gram-negative coverage is added to treatment regimens for pancreas transplant recipients; and extended-spectrum cephalosporins are given to liver transplant recipients to cover gram-negative bacilli, enterococci, and staphylococci.

Lung and heart-lung transplant recipients with underlying CF should receive culture-directed antimicrobial prophylaxis, which should be continued for 14 days after transplantation or until purulent secretions are no longer seen in the airways at bronchoscopy (A-III). Routine sinus surgery is advocated by some centers (B-III).

Liver transplant recipients should also receive antibacterial prophylaxis immediately before and after each posttransplant cholangiogram, other biliary tract manipulation, or liver biopsy (A-III).

B. SBD may be recommended for liver transplant recipients and should start a minimum of 1 week before the surgery and continue for 1–3 weeks postoperatively (B-III). Efficacy is reduced if the regimen is started <1 week before surgery. Because of the difficulty in timing of the SBD, it is not used very often in cadaver transplantation but may be feasible in transplantation of organs from live donors. Numerous different regimens are used, but there is no general consensus regarding which approach is optimal. Randomized trials are needed to compare the numerous regimens with respect to efficacy, tolerability, and toxicity.

C. TMP-SMX prophylaxis with 1 single-strength TMP (80 mg)–SMX (400 mg) tablet daily for the first 6 months after transplantation is recommended to protect against UTIs, particularly in kidney transplant recipients (A-I). This regimen also protects against infection with P. carinii (A-I) (see below). There is an added advantage in that TMP-SMX prophylaxis also appears to reduce the incidence of infections with L. monocytogenes, N. asteroides, and T. gondii (see below).

Prophylaxis for >6 months is indicated for patients with ongoing risk factors for infection with P. carinii and T. gondii, including multiple episodes of rejection treated with OKT3 monoclonal antibodies, or for patients with persistent allograft dysfunction. Prophylaxis should be reinstituted in patients in whom it has been discontinued when they receive augmented immunosuppression (A-III). Anecdotal success has also been
Prophylaxis against UTIs.

Posttransplant Prophylaxis of Tuberculin-Positive Patients

Isoniazid (INH) prophylaxis of PPD-positive patients is best accomplished before transplantation, if possible. Although the American Lung Association recommends INH prophylaxis for patients who have positive PPD test results and receive immunosuppressive therapy, recommendations for INH administration after transplantation are controversial [2, 59–66]. INH prophylaxis was shown to prevent tuberculosis in a randomized trial involving kidney transplant recipients [67]. Posttransplant prophylaxis with INH is complicated by the potential for clinically significant hepatotoxicity, alterations in the metabolism of cyclosporine and tacrolimus, and the possibility of selecting out INH-resistant strains [68]. Furthermore, a positive skin test without additional risk factors is rarely associated with reactivation; the reported incidence of posttransplant tuberculosis is ∼0.6% in kidney transplant centers in the United States and between 3.5% and 11.8% in areas in which tuberculosis is endemic [61, 62, 64, 69]. Factors associated with a higher risk of reactivation include (1) residence in regions with high endemicity, (2) history of active tuberculosis or exposure to someone with active disease, (3) recent skin-test conversion, (4) abnormal chest radiograph, and (5) presence of excessive immunosuppression. Patients with any of these risks should be given 9–12 months of INH therapy after transplantation if possible. Although the use of augmented immunosuppression, recommendations for INH administration after transplantation are controversial [2, 59–66]. INH prophylaxis was shown to prevent tuberculosis in a randomized trial involving kidney transplant recipients [67]. Posttransplant prophylaxis with INH is complicated by the potential for clinically significant hepatotoxicity, alterations in the metabolism of cyclosporine and tacrolimus, and the possibility of selecting out INH-resistant strains [68]. Furthermore, a positive skin test without additional risk factors is rarely associated with reactivation; the reported incidence of posttransplant tuberculosis is ∼0.6% in kidney transplant centers in the United States and between 3.5% and 11.8% in areas in which tuberculosis is endemic [61, 62, 64, 69]. Factors associated with a higher risk of reactivation include (1) residence in regions with high endemicity, (2) history of active tuberculosis or exposure to someone with active disease, (3) recent skin-test conversion, (4) abnormal chest radiograph, and (5) presence of excessive immunosuppression. Patients with any of these risks should be given 9–12 months of INH after the immunosuppressive regimen has been stabilized.

INH prophylaxis may also be useful in previously untreated PPD-positive transplant recipients while they are receiving antilymphocytic therapies [59, 70]. INH prophylaxis should also be considered for recipients of allografts from donors with a history of tuberculosis or tuberculin reactivity without adequate prophylaxis [61].

Recommendations. Transplant recipients with positive PPD test results and a high risk of tuberculosis reactivation should be given 9–12 months of INH therapy after transplantation, beginning after the immunosuppressive regimen has been stabilized (B-I). Factors associated with a higher risk of reactivation include (1) residence in regions with high endemicity, (2) history of active tuberculosis or exposure to someone with active disease, (3) recent skin-test conversion, (4) abnormal chest radiograph, and (5) presence of excessive immunosuppression (e.g., rejection requiring higher levels of immunosuppressive, concomitant protein-calorie malnutrition).

INH prophylaxis should be considered for recipients of allografts from donors with a history of tuberculosis or tuberculin reactivity without adequate prophylaxis and for previously untreated PPD-positive transplant recipients while they are receiving antilymphocytic therapies (C-III).

PROPHYLAXIS AGAINST OTHER PATHOGENS

P. carinii

P. carinii pneumonia (PCP) has effectively been eliminated with the use of TMP-SMX prophylaxis. There is an ∼10%–12% incidence of PCP in solid-organ transplant recipients when TMP-SMX prophylaxis is not given [1–4, 71–73]. TMP-SMX prophylaxis also protects against UTIs [53–55], L. monocytogenes, N. asteroides, and T. gondii (see below).

Recommendations. TMP-SMX prophylaxis with 1 single-strength TMP (80 mg)–SMX (400 mg) tablet daily for the first 6 months after transplantation is recommended to protect against infection with P. carinii in all solid-organ transplant recipients (A-II).

Prophylaxis beyond 6 months is indicated for patients with ongoing risk factors for PCP, including multiple episodes of rejection treated with OKT3 monoclonal antibodies, or with persistent allograft dysfunction. Prophylaxis should be reinstalled in patients in whom it has been discontinued when they receive augmented immunosuppression. Anecdotal success has also been reported with the use of TMP-SMX three times weekly as prophylaxis, but controlled studies have not been performed.

T. gondii

More than 50% of heart transplant recipients who are seronegative for T. gondii and receive seropositive organs develop active, disseminated toxoplasmosis [1–3, 73–76]. Primary toxoplasmosis in these patients generally presents as myocarditis or cardiomyopathy and is associated with significant morbidity and mortality. OKT3 monoclonal antibody therapy may also be a risk factor for developing toxoplasmosis. There are numerous reports of a decrease in the incidence and severity of toxoplasmosis with the use of prophylactic pyrimethamine [1–4, 73, 77]. The addition of sulfadiazine (used in combination with pyrimethamine for treatment of toxoplasmosis) has not been studied for use in prophylaxis. The incidence of toxoplasmosis is also reported to be low in those patients receiving TMP-SMX prophylaxis, but there have been no randomized, controlled trials comparing pyrimethamine with TMP-SMX. The incidence of toxoplasmosis varies geographically, and areas of low incidence may not require anything more than the TMP-SMX prophylaxis that is given for PCP. Reactivation of latent toxoplasmosis in seropositive recipients is usually asymptomatic or associated with minimal morbidity.

Recommendations. Pyrimethamine (25 mg daily) plus folinic acid (15 mg t.i.d.) for 6 months after heart transplantation is recommended in seronegative recipients of seropositive or-
gans (A-II). TMP-SMX prophylaxis for PCP may also be effective in preventing toxoplasmosis (A-II), but controlled studies comparing this regimen to pyrimethamine have not been performed.

Surveillance for seroconversion is recommended in high-risk patients in high-incidence areas, and treatment with pyrimethamine-sulfadiazine plus folinic acid should be initiated upon seroconversion and continued for 6 weeks. Prophylaxis for >6 months is indicated for patients with ongoing risk factors for toxoplasma reactivation, including multiple episodes of rejection treated with OKT3 monoclonal antibodies, or for patients with persistent allograft dysfunction. Prophylaxis should be reinstituted in patients in whom it has been discontinued when they receive augmented immunosuppression.

References