FOR PHYSICIANS, NURSES, AND PHARMACISTS

State of The Art Management of POSTTRANSPLANT SEQUELAE

Presented by:

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES OF
THE NATIONAL INSTITUTES OF HEALTH
U S DEPARTMENT OF HEALTH AND HUMAN SERVICES

Infectious Complications Posttransplantation

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This program is supported by an unrestricted educational grant from Wyeth.

Educational Objectives

At the conclusion of this program, participants will be able to:

- Discuss the immunosuppressive drugs used in transplantation and the risks and benefits of their use
- Define the net state of immunosuppression and identify contributing factors
- Outline the timetable of infection following renal transplantation
- Describe the infections that occur most commonly following renal transplantation
- Summarize risk factors for, effects of, and treatment options for these infections

Target Audience

Transplant surgeons, transplant nephrologists, transplant nurses, transplant coordinators, pharmacists, and other healthcare professionals who are involved in the treatment and management of renal transplant recipients

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Infectious Complications Posttransplantation

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Introduction

Since the first successful kidney transplantation in the 1950s,[1] and particularly since the introduction of potent and selective immunosuppression in the 1980s, a great deal of progress has been made in graft preservation and patient survival. Renal transplantation has been transformed from an interesting experiment into a practical means of rehabilitating patients with end-stage renal disease of a variety of etiologies. Between 1988 and 1996, the 1-year survival rate for living-donor grafts increased from 88.8% to 93.9%, and the rate for deceased-donor grafts increased from 75.7% to 87.7%. The projected half-life for living-donor grafts, censored to exclude patients who died with functioning grafts, grew by 112%, from 16.9 years to 35.9 years, and the half-life for deceased-donor grafts increased by 77%, from 11.0 years to 19.5 years.[2] This increasing success is largely a result of advances in several areas[3]:

- Tissue typing and donor-recipient matching, which minimizes rejection
- Careful donor evaluation, organ procurement, organ preservation, and recipient preparation
- Impeccable surgical technique
- Individualized immunosuppression that balances prevention and treatment of graft rejection with minimal risk of infection due to overly aggressive immunosuppression
- Use of antimicrobial prophylaxis or preemptive treatment to prevent infection and/or its sequelae

Despite the strides that have been made, transplant recipients remain vulnerable to several types of infection. This risk is determined largely by interaction between the net state of immunosuppression, technical/anatomic abnormalities that result in an ongoing need for external devices, environmental exposures to pathogens, and a disturbance in the patient's normal bacterial balance that opens the door to darwinian competition for nutrients and adherence to mucosal surfaces by opportunistic, potentially antimicrobial-resistant organisms.[3,4] This publication will describe the most common posttransplant infections, factors that contribute to their incidence, their potential impact, and available treatments.

Key Concepts

There are several concepts that are consistent themes in discussions of posttransplant infection and that can help guide evolving approaches to this ongoing issue.

The Whole Is Greater Than the Sum of Its Parts

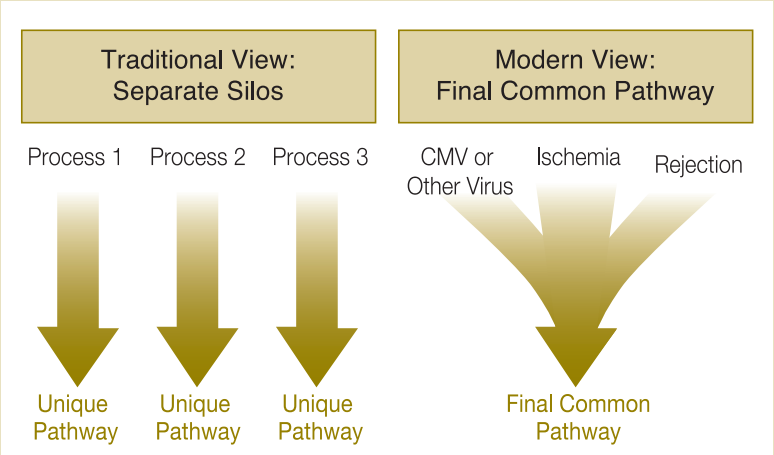
Not only must the clinician look at the whole picture for each patient, but it is also important to remember that each patient is a unique combination of influences, conditions, and susceptibilities. Nothing that happens to a transplant recipient happens in isolation, and each patient must be addressed in the context of all factors combined—ie, a gestalt—for optimal outcomes to be achieved.

The "Common Pathway" Hypothesis

This hypothesis illustrates the above concept, suggesting that a variety of processes may take a variety of paths to merge, finally, on one common pathway that results in the net effect of all factors influencing the patient's susceptibility to infection. For example, there has long been a "chicken-and-egg" question regarding rejection and infection, but it has become apparent that either can precede the other and can facilitate the other.[5] Infection, rejection, and even vaccination can all stimulate production of cytokines, chemokines, and growth factors that, in turn, create a receptive environment for both rejection and infection. This novel approach contrasts with the traditional view, the "silo" hypothesis, which postulates separate pathogenetic trails resulting in separate, unique pathologies. (Figure 1)

Figure 1

The Common Pathway vs the Silo Hypothesis



CMV = cytomegalovirus.

Figure courtesy of Robert H. Rubin, MD.

Timing Is Crucial

Timing affects the type of infection to which the patient is vulnerable and the impact the infection may have. In a normal host, symptoms increase steadily

in proportion to viral load; in the transplant recipient, however, symptoms may remain occult and then suddenly escalate at a point when there is very little available time left for effective antimicrobial treatment. (Figure 2) Therefore, constant monitoring of viral load and early diagnosis of infection are essential to initiating treatment before that point is reached. Different infections are prevalent at different intervals posttransplantation, but with any type of infection, the microbial burden increases with time; the later in this course therapy is begun, the longer and more intense it must be, increasing the chance of resistance to antimicrobial drugs and of transmission to other individuals.

Figure 2

Correlation of Symptoms and Microbial Load

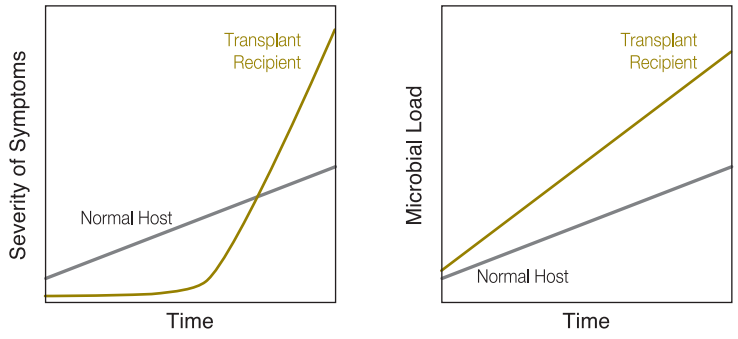


Figure courtesy of Robert H. Rubin, MD.

The Net State of Immunosuppression

This is determined by several combined factors, all of which must be considered together in any assessment of a patient's risk for infection. These factors are summarized below:[3,6]

- The nature of the immunosuppressive regimen: the dose, duration, and temporal sequence of drugs used in the regimen
- Neutropenia, largely drug related
- Acquired abnormalities such as damage to the mucocutaneous surfaces of the body and foreign objects (eg, catheters) that compromise the function of mucocutaneous barriers
- Metabolic abnormalities, such as protein-calorie malnutrition, including low serum albumin levels, which have been associated with increased mortality in both the transplant and the dialysis settings[7,8]; uremia, which may have effects such as depression in cell-mediated immunity and delayed response to inflammation; and hyperglycemia
- Viral infection: cytomegalovirus (CMV), Epstein-Barr virus (EBV), hepatitis B and C viruses (HBV, HCV), human herpesvirus-6 (HHV-6), and human immunodeficiency virus (HIV) are all immunomodulating viruses; 90% of infections, especially opportunistic infections (OIs), occur in the context of viral replication; indeed, fungal infection in the absence of viral replication should trigger a search for an environmental hazard
- Advanced age, which has been observed to increase infection risk while reducing rejection risk, suggesting that older transplant recipients may require lower doses of immunosuppressive drugs than do younger patients[9]
- Race: although African American transplant recipients are known to have poorer transplantation outcomes than do whites in terms of graft survival, they have been observed to have a lower risk of infectious complications; thus, in contrast to older patients, African Americans may need—and be able to tolerate—higher immunosuppressive doses than do white patients[10]

The Therapeutic Prescription

For the transplant recipient, the therapeutic prescription must create a balance between immunosuppression to reduce the risk of graft rejection and antimicrobial therapy to keep the immunosuppressed patient safe from infection. The first steps in the establishment of a therapeutic prescription are to ascertain any recent and remote exposures, identify any infections that are present, and eradicate those infections before transplantation.[3,6]

Immunosuppression In Renal Transplantation

Table 1 summarizes the major classes of immunosuppressive drugs used in transplantation.

Along with azathioprine, corticosteroids were the first drugs used in transplantation.[11] They actually are more anti-inflammatory than immunosuppressive, although they exert both effects. Their anti-inflammatory activity is caused by inhibition of proinflammatory-cytokine production, particularly interleukin-2 (IL-2), which results in

Table 1

Immunosuppressive Drugs Used in Transplantation[3,12,13]

Class	Example(s)	Activity	Common Side Effects
Corticosteroids	Prednisone, methylprednisolone	Inhibit inflammatory response and cytokine expression (and, thus, T-cell activation) via several mechanisms	Vulnerability to infection, blunted signs of infection, osteoporosis, diabetes, hyperlipidemia, hypertension
Antimetabolites	Azathioprine	Interfere with DNA synthesis	Vulnerability to infection, neutropenia
CNIs	Cyclosporine, tacrolimus	Inhibit calcineurin phosphatase and T-cell activation	Nephrotoxicity, hemolytic-uremic syndrome, vulnerability to herpes group virus infection (both), hyperlipidemia and hypertension (cyclosporine), diabetes (tacrolimus)
Purine synthesis inhibitors	Mycophenolate mofetil	Prevent proliferation of B and T cells	Cramping, diarrhea, neutropenia
TORIs	Sirolimus	Inhibit IL-2–driven T-cell proliferation	Hyperlipidemia, thrombocytopenia
Depleting antibodies	ATG (polyclonal), OKT3 (monoclonal)	Deplete T and/or B cells	Cytokine-release syndrome, allergic reactions, vulnerability to infection (both), cytopenia (polyclonal)

CNI = calcineurin inhibitor; TORI = target of rapamycin inhibitor; IL = interleukin; ATG = antithymocyte globulin; OKT3 = muromonab-CD3.

a decrease in the inflammatory response to noxious stimuli of any type. The immunosuppressive effects of corticosteroids result from the same cytokine suppression, leading to inhibition of T-cell activation and proliferation and, hence, of clonal expansion in response to antigenic stimulation.[3] There is a limit to the amount of corticosteroid a patient can take, because even in low doses these drugs can have serious adverse side effects, most prominently bone loss/fracture risk and increased vulnerability to infection.[12] Thus, efforts have been concentrated on substituting other drugs for corticosteroids to achieve the desired net state of immunosuppression with minimal risk.

Azathioprine was used initially as a supplemental drug in corticosteroid-sparing regimens, and it is still used today. Until the 1980s, the standard immunosuppressive protocol comprised corticosteroids plus azathioprine, a potent antirejection drug. Azathioprine inhibits microbe-specific T-cell responses, increasing the patient's susceptibility to infection of several types; in addition, it can cause considerable myelosuppression. It has become clear, however, that azathioprine metabolism is catalyzed by the enzyme thiopurine methyltransferase, which is genetically heterogeneous in humans. Therefore, both the marrow toxicity and the immunosuppressive efficacy of azathioprine are affected by the speed with which a particular patient metabolizes it, and this offers the opportunity for individualized dosing to achieve maximum benefit with minimal toxicity.[3,13]

The first calcineurin inhibitor (CNI), cyclosporine, was introduced in the early 1980s and dramatically improved renal graft survival, particularly those from deceased donors (from approximately 50% to more than 80% at 1 year) while reducing the need for corticosteroids.[11] Cyclosporine is a selective inhibitor of IL-2 (T-cell growth factor).[14] It exercises dose-related inhibition of microbe-specific T-cell cytotoxic activity, which is the main host defense against many infections, especially herpes group viruses.[6] Tacrolimus, also a CNI, has similar effects to those of cyclosporine but is up to 100 times more potent.[6,13]

Mycophenolate mofetil is a highly selective inhibitor of de novo purine synthesis. Its antirejection effects appear to be similar to but more potent than those of azathioprine, for which it is often substituted. Its primary adverse effects are gastrointestinal, which may be easier for patients to tolerate than are the myelosuppressive side effects of azathioprine.[3,6,13]

Sirolimus (rapamycin) is a target of rapamycin inhibitor that inhibits growth factor signaling for both immune and nonimmune cells. This antiproliferative effect may make sirolimus useful in the prevention and treatment of chronic allograft injury.[6] Interestingly, sirolimus has been observed to slow the growth of tumors, which may also give it utility in oncologic settings.[13,15]

Although sirolimus use has been accompanied by high incidences of aphthous ulcers and *Pneumocystis carinii* pneumonia (making temporary antipneumonia prophylaxis advisable), these adverse effects are transient and dose related and can be managed. In one study, patients who switched immunosuppressants indicated a preference for sirolimus over CNIs.[16] As clinical experience with sirolimus increases, target therapeutic windows are narrowing, and, thus, doses are lowering, reducing the incidence of adverse effects. The coadministration of sirolimus and a CNI in lower doses than those used in monotherapy with either drug may provide increased benefit with reduced adverse effects. There is a clear need, however, for evidence-based dosing guidelines,

especially because sirolimus is being used first line, as a switch drug in the effort to reduce CNI use, and in various combinations.[15,17]

Both polyclonal antibodies (eg, antithymocyte globulin [ATG]) and the more specific monoclonal antibodies (eg, OKT3) are potent T-lymphocyte–depleting agents that are extremely effective in reversing acute, corticosteroid-refractory rejection. These agents, however, stimulate the release of proinflammatory cytokines, such as tumor necrosis factor (TNF), thereby substantially increasing the net state of immunosuppression and causing reactivation of herpes group viruses, especially CMV and EBV. Efforts to develop more specific therapies yielded the monoclonal antibodies to the IL-2 receptor, daclizumab and basiliximab, which decrease the incidence of acute rejection but have the potential advantage of not triggering cytokine release.[3]

Posttransplant Infection

Timing

Observation has revealed a temporal pattern of posttransplant infection. As Figure 3 illustrates, transplant recipients are affected by different pathogens at different points in time.

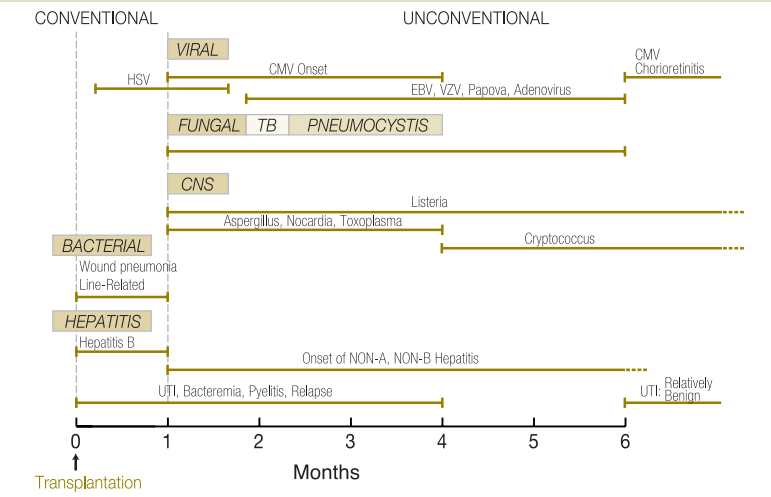
During the first month posttransplantation, despite the fact that the dosage of immunosuppressive drugs is higher than it will be in later periods, there is a notable absence of infection by opportunistic pathogens, suggesting that the duration of sustained immunosuppression is a more significant determinant of the net state of immunosuppression than is the daily dose of each drug. There are 3 types of infection seen during the first month: those that were present and not eradicated pretransplantation and that may be exacerbated by the immunosuppressive regimen posttransplantation, those that were conveyed to the recipient with the allograft, and those that would be expected in the general population undergoing similar surgery—bacterial and candidal infections of the surgical wound, urinary tract infection, vascular access infection, and pneumonia. The last group comprises more than 90% of the infections seen in the first month posttransplantation, and their incidence is largely associated with technical problems.[8,18]

The major infections seen during months 1 to 6 posttransplantation are the immunomodulating viruses, such as the herpes group viruses CMV, EBV, and HHV-6; HAV, HBV, and HCV; and HIV, which exert their primary direct effects during this period. Additionally, these infections combine with sustained immunosuppressive therapy to increase the patient's net state of immunosuppression and, thus, allow the development of OIs, even absent strong exposure.[3]

More than 6 months posttransplantation, patients essentially fall into one of 3 groups. About 80% have had good transplantation outcomes, are on low-dose maintenance immunosuppression, have no chronic viral infections and good renal function, and are primarily at risk for community-acquired infections, particularly with respiratory viruses. Approximately 10% have chronic viral infection, such as CMV, hepatitis, EBV, or papillomavirus, which can lead to damage of the infected organ or malignancy. The other 10% are those whose allografts are not functioning well, who have had recurrent episodes of rejection resulting in a need for greater exposure to immunosuppression and, thus, chronic viral infection, and are therefore at highest risk for life-threatening OIs. These last patients should be kept on antimicrobial prophylaxis indefinitely.[3,18]

Figure 3

Timetable of Posttransplant Infection[6]



HSV = herpes simplex virus; CMV = cytomegalovirus; EBV = Epstein-Barr virus; VZV = varicella-zoster virus; TB = tuberculosis; CNS = central nervous system; UTI = urinary tract infection.

Reprinted with permission from Rubin RH et al. *Transpl Infect Dis*. 1999;1:29-39.

Etiologies

Posttransplant infections can be classified into several categories according to their causes (Table 2). One category comprises infections associated with

perioperative technical complications, suggesting that the more skilled the care given to the patient, the lower the risk of this type of infection. Preservation of the integrity of the skin and mucous membranes is particularly important, as the skin is the first line of defense against iatrogenic damage. Thus, it is desirable to minimize the ongoing need for invasive devices such as vascular access or drainage catheters.[3] Another category, nosocomial exposures, can occur in the patient's hospital room (domiciliary), with contamination of the air or water in the immediate environment, or when patients are taken to central facilities in the hospital, such as the radiology suite (nondomiciliary), especially if, for instance, there has been recent construction work. The nondomiciliary environment is less controllable than is the patient's room; therefore, the importance of protecting patients as they are transported within the hospital is being stressed increasingly.[3,19]

Once discharged from the hospital, the patient is at risk for infection from various exposures within the community. The systemic mycoses and *Mycobacterium tuberculosis* have similar epidemiologic, pathogenic, and clinical mechanisms, with infection via the lungs, the strong possibility of reactivation of latent infection in addition to the acquisition of de novo infection, and an increased effect in immunosuppressed patients. *Strongyloides stercoralis* is the one helminth that can remain asymptomatic in the gastrointestinal tract for several decades after the patient leaves the area where the infection was acquired, and initiation of immunosuppressive therapy can cause hyperinfestation syndrome or dissemination of infection throughout the body. Respiratory infections are the most common community-acquired infections, and they are likely to have a more severe impact on immunosuppressed patients. Food- and water-borne infections are also a hazard. As with all posttransplant infections, prevention is easier and safer than is treatment. Therefore, screening, vaccination where applicable, good hygiene, and, most important, efforts to protect the patient from exposure should be used. Patients should be separated as much as is possible from individuals with infection and should be advised to avoid travel to places with poor sanitation and to avoid certain activities, such as gardening, that can increase their potential for exposure.[3]

In addition to the infections above, the incidence of new and emerging fungal infections is growing.[4] Finally, the viral infections of particular importance for transplant recipients include the herpes group, the hepatitis viruses, papillomavirus, and HIV.[3] These will be discussed in more detail below.

Table 2

Sources of Posttransplant Infections[3]

Technical Complications

- Transplantation of contaminated allograft
- Anastomotic leak or stenosis
- Wound hematoma
- Intravenous line contamination
- Iatrogenic skin damage
- Mismanagement of endotracheal tube (aspiration)
- Biliary, urinary, or drainage catheter

Nosocomial Hazard

- *Aspergillus* spp
- *Legionella* spp
- *Pseudomonas aeruginosa*, other gram-negative bacilli
- *Nocardia asteroides*

Community Exposures

- Geographically limited systemic mycoses
  - *Histoplasma capsulatum*
  - *Coccidioides immitis*
  - *Blastomyces dermatitidis*
- *Strongyloides stercoralis*
- OIs due to ubiquitous saprophytes in environment
  - *Cryptococcus neoformans*
  - *Aspergillus* spp
  - *Nocardia asteroides*
  - *Pneumocystis carinii*
- Circulating respiratory infections
  - *Mycobacterium tuberculosis*
  - Influenza
  - Adenoviruses
  - Parainfluenza
  - Respiratory syncytial virus
- Contaminated food or water
  - *Salmonella* spp
  - *Listeria monocytogenes*

Viral Infections

- Herpes group
- Hepatitis
- Papillomavirus
- Human immunodeficiency virus

Adapted with permission from Rubin RH. Infection in the organ transplant recipient. In: Rubin RH, Young LS, eds. *Clinical Approach to Infection in the Compromised Host*. 4th ed. New York, NY: Kluwer Academic/Plenum Publishers; 2002: chapter 17.

Antimicrobial Treatment

There are 3 methods of using antimicrobial treatment: prophylactic, in which antimicrobials are given to an entire patient population to prevent infection; preemptive, in which they are given to a subgroup of patients identified to be at high risk for infection before they become symptomatic but in whom a pathogen is detected; and therapeutic, in which antimicrobials are administered to eradicate established infection. An example of successful prophylaxis is the use of

low-dose trimethoprim-sulfamethoxazole. This has essentially eliminated the risk of *Pneumocystis* infection, which previously had an incidence of up to 15% in the first 6 months posttransplantation, although trimethoprim-sulfamethoxazole has myelosuppressive potential.[3,20]

Of importance to the use of antimicrobials in this setting is awareness of their potential impact on the metabolism of the CNIs. Both cyclosporine and tacrolimus are metabolized via the hepatic cytochrome P-450 (CYP450) enzymes. Drugs that inhibit CYP450 activity, such as the macrolide antibiotics (eg, erythromycin) and the azole antifungals (eg, fluconazole), may downregulate CNI metabolism, resulting in high blood levels of CNIs and a possibility of nephrotoxicity, excessive immunosuppression, and an increased risk of infection. Drugs that induce CYP450 activity, such as rifampin and nafcillin, may upregulate CNI metabolism, causing decreased bioavailability and an increased risk of rejection.[14,18,21]

Coadministration of certain antimicrobials with CNIs may result in synergistic nephrotoxicity. This may be dose related, in that high-dose antimicrobials, such as trimethoprim-sulfamethoxazole or the fluoroquinolones, may cause renal dysfunction in the presence of therapeutic CNI doses, whereas low doses of antimicrobials are well tolerated; it may be accelerated, wherein the nephrotoxicity that one might expect to see with coadministration of CNIs and drugs such as amphotericin B or aminoglycosides occurs much sooner than expected; or it can be idiosyncratic, occurring with the first dose. The possibility of such nephrotoxicity highlights the importance both of treating patients prophylactically to avoid the possible toxicities of later treatment and of monitoring blood levels vigilantly.[18,21]

Herpes Group Viruses

The herpes group viruses are the most important microbial pathogens among renal transplant recipients; included in this group are CMV, EBV, varicella-zoster virus, herpes simplex virus, and HHV-6, -7, and -8. They all share 3 characteristics[3]:

- Latency: Once an individual is infected, there is always latent intracellular virus that can be reactivated later, either spontaneously or in reaction to an exogenous stimulus such as immunosuppression.
- Cell association: These viruses are transmitted via direct cell-to-cell contact, as in transplantation. Once infected cells are in contact with susceptible cells, the host's humeral immunity is not very effective in eradicating the infected cells. A key host defense is major histocompatibility complex (MHC)-restricted, virus-specific cytotoxic T cells. The degree to which immunosuppression affects the cytotoxic T-cell response impacts the effect on the course of infection. In the presence of MHC disparity, the host may have increased difficulty in eliminating virus.[22]
- Potential oncogenicity: It is known that EBV is the primary etiologic factor for posttransplant lymphoproliferative disease (PTLD); in addition, however, the presence of CMV further increases the incidence of PTLD,[23,24] most likely because of the cytokines, chemokines, and growth factors that are upregulated in the presence of CMV. It is also well known that HHV-8 is responsible for Kaposi's sarcoma.[25,26]

Cytomegalovirus

CMV is the most important single pathogen that affects transplant recipients. It is important not only by itself but as a model for the possible effects of other viruses. Therefore, the largest portion of this discussion will address this virus. There are 3 patterns of CMV infection among transplant recipients: primary infection—CMV infection in a patient who was previously seronegative; reactivation, or recurrent infection—CMV disease in a patient who was CMV seropositive pretransplantation that is reactivated from latency; and superinfection, or reinfection—CMV disease in a previously infected patient that is distinct from the original strain.[3,27] The peak incidence of CMV disease among unprotected patients ranges between 1 and 6 months posttransplantation, but among patients receiving inadequate antiviral prophylaxis, it could occur later.[3]

CMV: Risk Factors, Pathogenesis, and Effects

CMV-seronegative recipients of organs from seropositive donors (D+/R-) are most at risk for CMV infection and disease. Studies have shown that up to 73% of D+/R- recipients develop primary CMV infection.[28,29] The nature of the immunosuppression used also influences CMV risk: The incidence is increased further by the use of thymoglobulin, ATG, or OKT3.[30-32] These drugs have the ability to reactivate latent infection, whereas the CNIs and corticosteroids cannot reactivate latent CMV but can amplify the effects of a small amount of virus to cause clinical disease—the "in vivo PCR [polymerase chain reaction]" effect.[5] Thus, the antimicrobial strategy is influenced by the type of immunosuppression the patient is receiving.

The close link between CMV and cytokines manifests in several ways. TNF is the key mediator in the pathogenesis of CMV infection. TNF combines with the TNF receptor on latently infected cells; this initiates a

downstream signaling pathway involving activation of protein kinase C and nuclear factor kappa B (NFκB); the activated p65/p50 NFκB heterodimer translocates into the nucleus and binds to the CMV immediate early enhancer region, initiating viral replication.[5,33,34] Endothelial cells, which have a key role in this process, are affected by cytokines and viral infection and can themselves produce cytokines. Infected cells produce IL-1, which activates destructive activity in surrounding cells.[35]

Additionally, it is understood that there is a bidirectional association between rejection and CMV infection. This phenomenon also may be explained by the fact that these 2 events produce the same array of cytokines—hence the observation that each may predict the occurrence of the other.[5,28,36] Similarly, levels of TNF and IL-1, which are pivotal mediators in the inflammatory response to infection that results in sepsis, have been found to be elevated further in patients with sepsis who have active CMV infection.[37] Thus, patients with latent CMV who experience any process that upregulates release of proinflammatory cytokines may develop symptoms of CMV disease—the "second-wave phenomenon" [Personal communication, R.H. Rubin, MD, March 2005].[38]

Table 3 lists the direct and indirect effects of CMV infection. The end-organ effects of CMV are seen much more often in transplanted organs than in native organs; thus, liver transplant recipients are more likely to have CMV hepatitis than are recipients of other organs, and recipients of lung transplants are more likely to have pneumonia.[3,18,39]

Table 3

Effects of CMV[3,86]

Direct Effects	Indirect Effects
Viral syndrome	Immune modulation
Fever	Increase in net state of immunosuppression
Most prolonged posttransplant fevers	Decrease in cell-mediated immunity
Weakness	Increase in OIs
Myalgia, arthralgia	Allograft injury, rejection
Anorexia	Oncogenicity
Cytopenias	Increase in incidence of EBV-associated PTLD
End-organ disease	
Hepatitis	
Gastrointestinal disease	
Pneumonitis	
Nephritis	
Chorioretinitis	

CMV = cytomegalovirus; OIs = opportunistic infections; EBV = Epstein-Barr virus; PTLD = posttransplant lymphoproliferative disease.

The indirect effects of CMV are not due to the viral infection itself but most likely to the cytokine response to viral replication. That they include allograft injury is borne out by the facts that patients without CMV experience less rejection than do those with CMV and that effective anti-CMV prophylaxis has been observed to reduce the rate of rejection, as it does the risk of OIs.[29,40]

Of major importance is that CMV infection increases the patient's net state of immunosuppression, rendering the patient highly vulnerable to OIs; evidence for this is similar to that for the association of CMV with allograft injury. First, most patients who develop posttransplant OIs do so shortly after infection with an immunomodulating virus such as CMV; second, effective prophylaxis minimizes a patient's risk for OIs.[18,40]

CMV: Treatment

Until recently, ganciclovir was the gold standard for CMV therapy; however, long-term administration of intravenous (IV) ganciclovir is not practical, safe, or cost-effective, and oral ganciclovir, like oral acyclovir, has low oral bioavailability and must be given in high doses.[29,41,42] The emergence of CMV strains that are resistant to antivirals, particularly to ganciclovir, is a growing problem. Resistance may develop in the presence of a high viral load, primary CMV infection (D+/R-), subclinical infection, intermittent antiviral therapy, or subtherapeutic doses of antiviral drugs, which can be common with drugs that have low bioavailability.[43-46]

The most promising recent development has been the introduction of valganciclovir, the valine ester of ganciclovir, which has oral bioavailability and efficacy equivalent to those of IV ganciclovir and similar or superior to those of oral ganciclovir. Valganciclovir can be used interchangeably with IV ganciclovir depending on individual patients' needs. Studies to date have found little or no ganciclovir resistance with valganciclovir use. Valganciclovir provides safe, effective oral therapy for both prevention and treatment of CMV disease, with a low daily pill burden, which may enhance patient adherence to therapy, further minimizing the risk of resistance.[40,41,47-51]

Foscarnet, although it has efficacy comparable to that of IV ganciclovir, is associated with significant nephrotoxicity and neurotoxicity and is not recommended as alternative monotherapy unless all other choices have been exhausted.[46,52] IV CMV immune globulin has been found most useful in combination with ganciclovir or acyclovir, although its cost may be prohibitive.[3,53,54]

Epstein-Barr Virus

Like CMV, EBV infects a large proportion of the population, most often without clinical manifestation. EBV replicates easily in the oropharyngeal epithelium and is commonly transmitted via saliva, although it can also be conveyed to a seronegative recipient in a seropositive transplanted organ. The recipient's B cells become infected while traveling through the oropharynx, with the typical result of lifelong latent infection and, consequently, transformation, immortalization, and proliferation of the B lymphocytes. The latent virus exists in a circular episomal form that is not susceptible to antiviral treatment, as is EBV in the lytic phase. In immunocompetent hosts, the proliferation of the infected B cells is curtailed by a cytotoxic T-cell response that accounts for the primary clinical manifestation seen in this population, infectious mononucleosis. In immunocompromised hosts, however, this response is impaired or absent, and lymphoproliferation occurs.[3,23,55-57]

Posttransplant Lymphoproliferative Disease

The incidence of PTLD among kidney transplant recipients ranges between 1% and 3%.[3] PTLD comprises several entities, which have been classified by the Society of Hematopathology and are described in Table 4. Factors that play significant roles in the pathogenesis of EBV-associated PTLD include primary infection, EBV load, the presence of HCV, the presence of CMV, and D/R CMV mismatch. Another factor is the patient's cytokine milieu, in that higher levels of certain cytokines and lower levels of others predict the development of PTLD. Although the patient's net state of immunosuppression is more of a risk factor than is any particular drug, patients receiving CNIs and/or OKT3 are at higher risk for PTLD than are those on other types of immunosuppression. The B-cell antiproliferative action of sirolimus, in contrast, suggests that use of this drug is not a risk factor for PTLD. In fact, patients with PTLD on CNIs who were switched to sirolimus in one study did not experience reactivation of the PTLD.[15,16,23,24,58,59]

Immune reconstitution is the preferred method of clearing PTLD; thus, the first step in treatment is reduction of the patient's immunosuppression as much as is feasible.[23,57,58,60] The role of antiviral prophylaxis or preemptive treatment is less clear. Although transformed cells do not respond to this therapy, antivirals may affect the continuing lytic infection that triggers the proliferation process. It has also been postulated that the impact of antiviral treatment on possible coinfection with CMV may explain their ability to reduce PTLD.[23,56,59]

Table 4

Types of PTLD[3,87,88]

Type	Features
Lymphoid hyperplasia	Common; usually polyclonal, often regresses with reduced immunosuppression
Polymorphic	Common (monoclonal); wide range of B-cell malfunction, destructive lesions; some response to reduction in immunosuppression
Lymphomatous or monomorphic	Monoclonal; mostly diffuse large B-cell lymphoma, but also Burkitt-like and mucosa-associated lymphoma; no response to reduction in immunosuppression
Other	Plasmacytoma, myeloma, T-cell–rich/Hodgkin's disease–like large B-cell lymphoma; chronically aggressive

PTLD = posttransplant lymphoproliferative disease.

Because PTLD is a B-cell–lymphoproliferative disease, cancer chemotherapy, such as a modified CHOP (cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone) regimen, is a potential therapy. Reports of its use in small groups of patients have been promising.[57,61] There have been several reports of PTLD remission achieved with anti–B-cell monoclonal antibodies among solid organ transplant recipients. This type of therapy, which may exert its effect by limiting EBV-infected B-cell proliferation, is also attractive because of its low toxicity.[23,57,58,62] Several experimental therapies show promise but require further study.

Human Herpesvirus-6

HHV-6 is a β-herpesvirus that is closely related to CMV and HHV-7. HHV-6 is a potent stimulus for release of proinflammatory cytokines, which may explain its immunomodulatory and myelosuppressive effects. HHV-6 has a number of clinical sequelae; direct effects include fever, mononucleosis, interstitial pneumonitis, and hepatitis. The most recognized direct effect besides myelosuppression is encephalitis, which has been documented in several reports.[3,26,63]

The interaction between CMV and HHV-6 has been one of ongoing curiosity. Coinfection with the 2 viruses is very common, and several studies have suggested that HHV-6 facilitates infection with CMV, as may HHV-7 as well. It is postulated that coinfection with HHV-6 and CMV promotes development of symptomatic CMV disease and that HHV-6 infection also increases the patient's susceptibility to other OIs.[26,63,64] The close association of HHV-6 and CMV is further supported by the observation that HHV-6 responds to treatment with antivirals such as ganciclovir, although it is less sensitive to acyclovir.[26,63]

Other Infections In Renal Transplantation

Hepatitis

The incidence of chronic liver disease among recipients of solid organ transplants has remained between 10% and 15% during the past 20 years. Although some of this incidence can be ascribed to the use of certain drugs, particularly immunosuppressants, the majority is due to infection with HBV and HCV.[3,8,65]

HBV Infection

The advent of more sensitive screening methods, better infection control, and a pretransplantation vaccine for patients without anti-HBV antibodies has considerably lowered the transmission of HBV from transfused blood or a transplanted organ, as well as the risk of disease posttransplantation due to HBV. When HBV infection is acquired during transplantation, it is associated with an increased incidence of fulminant hepatitis.[8,65,66]

A greater problem is seen for patients who harbor HBV pretransplantation. In 1988, Rao and Andersen reported on 57 renal transplant recipients followed for at least 10 years. In the second decade posttransplantation, 22 patients (39%) had evidence of liver dysfunction; of these, 15 (68%) had evidence of HBV infection. Of 14 patients who underwent biopsies, 7 (50%) had chronic persistent hepatitis, and 5 (36%) had chronic active hepatitis. Five (36%) of the 14 biopsied patients had cirrhosis, and 2 (29%) of the 7 deaths in the second decade were due to liver disease.[67] In another, larger study, both 10-year patient ($P<.001$) and graft ($P<.001$) survival were significantly lower among patients with either HBV or HCV infection, and the incidence of liver-related mortality significantly higher ($P<.01$), than in noninfected controls.[66]

A major advance in the management of HBV infection has been the introduction of lamivudine, a nucleoside analog that appears to be very safe and effective for managing HBV after renal transplantation. The drawback of lamivudine treatment is that resistance to the drug has been observed to occur in up to 46% of renal transplant recipients within 15 months posttransplantation. Proposed solutions to this problem include close monitoring to predict the emergence of drug-resistant HBV and the institution of combination therapy, which would allow the use of lower doses of each agent.[68-71]

HCV Infection

Most liver disease in kidney transplant recipients is due to HCV infection. Although HCV is not as virulent as is HBV, it is more common, with a prevalence 5 to 10 times greater in patients with end-stage renal disease than in the general population; its course is more indolent than that of HBV, and its effects often are not seen for a few years posttransplantation.[65,66,72] HCV appears to have a bidirectional relationship with CMV. Researchers have observed that both clinical and subclinical reactivation of CMV in transplant recipients were factors in HCV incidence. In addition, late-onset CMV disease has been observed in transplant recipients with recurrent HCV hepatitis but with no other CMV-precipitating factors.[39,73,74] In a recent study in 92 transplant recipients, coinfection with HCV and (clinical or subclinical) CMV was observed to increase the incidence of HCV-associated allograft failure and mortality.[39]

Although interferon-α and ribavirin have both shown modest efficacy as monotherapy for HCV, they have a synergistic antiviral effect when given in combination. Both drugs, however, have significant side effects. More recently, pegylated interferon has demonstrated efficacy superior to that of interferon-α, with a similar adverse-effect profile. Viramidine, a ribavirin prodrug, causes less life-threatening hemolysis than does ribavirin. A combination of this agent with pegylated interferon may eventually be the HCV treatment of choice for renal transplant recipients.[72,75,76]

Polyomavirus

Like CMV, the polyomaviruses BKV and JCV are highly prevalent in the general population; following initial infection, the viruses remain latent in the kidney, becoming reactivated under conditions of impaired immune function, including immunosuppression for organ transplantation. In one study, BKV infection was found in 22.2% of kidney transplant recipients, JCV in 10.9%, and both in 3.6%. The rates of primary and reactivated infection with BKV were similar, but there were significantly more primary JCV infections than there were reactivations.[77,78]

The prevalence of polyomavirus-induced nephropathy among renal transplant recipients is estimated to be between 1% and 8%, and the prognosis for both graft function and patient survival is poor.[77,79,80] Diagnosis presents a dilemma owing to the histologic resemblance between polyomavirus and acute rejection; this problem is particularly troubling because reduction in immunosuppression is currently the gold standard of therapy for polyomavirus nephropathy.

Other therapies under study include cidofovir, which has shown some promise in conjunction with lowered immunosuppression in small studies.[80]

Fungal Infections

Fungal infection, currently seen less frequently than is viral infection, was the primary posttransplant infection in the past. Recent advances, including reductions in the use of corticosteroids, improved surgical technique, and the development of effective treatments, have reduced the incidence of invasive fungal infection following solid organ transplantation. Although renal transplant recipients have the lowest rate of fungal infection of all solid organ transplant recipients, prolonged dialysis pretransplantation, diabetes, immunosuppression with tacrolimus, and rejection have been found to be risk factors for fungal infection among these patients. Suppression of gut flora by antibiotics, metabolic derangement favoring fungal growth (eg, use of corticosteroids), and interruption of host barriers (eg, with IV lines or catheters) also facilitate fungal invasion.[65,81,82] As with viral infection, the risk of fungal infection is largely dependent on the interaction between exposure and the net state of immunosuppression.[83]

Currently, there are 5 types of fungal infections of importance in the setting of renal transplantation.

Candida spp is the most common, accounting for 90% to 95% of all invasive fungal infections in renal transplant recipients and remaining limited to the genitourinary tract in most patients. Typical manifestations include infection related to vascular access and urinary tract infection. Deep wound infection may occur in patients with diabetes. Disseminated infection occurs in less than 5% of renal transplant recipients.[82,83]

Cryptococcus neoformans has been reported to occur in approximately 2.8% of renal transplant recipients, arising later in this population, perhaps because renal transplant recipients are less immunosuppressed than are recipients of other organs. This fungus has a pulmonary portal of entry; it is disseminated rapidly to the central nervous system, the skin, the bones, and soft tissue. Although this is not considered a geographically limited infection, it does appear to develop earlier among patients in the northeastern United States.[82-84]

Aspergillus spp is an angioinvasive fungus; in most patients, the lungs are the portal of entry, as with *C neoformans*. Once blood vessels are infected, tissue infarction, hemorrhage, and metastases often follow, and central nervous system effects are not uncommon. Additionally, pulmonary involvement is seen in up to 90% of solid organ transplant recipients with invasive aspergillosis.[82-84]

Endemic mycoses, primarily histoplasmosis, are geographically limited, occurring most frequently in the southwest and midwest United States. In endemic areas, most patients with histoplasmosis are thought to have primary infection, whereas reactivation is the most likely etiology in nonendemic areas. Most transplant recipients infected with histoplasmosis develop progressive, disseminated disease.[82,83]

As mentioned, a group of new and emergent fungal infections is growing and now constitutes more than 10% of opportunistic fungal infections. These include *Scedosporium*, *Mucor*, and *Fusarium*.[4]

The cornerstones of treatment for fungal infections have been amphotericin B and the azole antifungals. Problems exist, however, with both types of treatment. Amphotericin B is associated with severe nephrotoxicity. Additionally, the emerging fungal infections, as well as some of the more established ones, are resistant to treatment with conventional antimicrobial agents. Voriconazole, a newer, broad-spectrum antifungal, has been shown to be effective in treating fungal infections that are resistant to other drugs and is the current treatment of choice for these infections.[4,82,85] Interestingly, sirolimus immunosuppression may be useful in deterring posttransplant fungal infection, as this agent has been shown to have strong antifungal activity, particularly against *Candida* spp.[15]

Conclusion

Many advances have been made in the management of posttransplant infections, but further improvement is needed, and research is ongoing. As the efforts to control these conditions continue, it is important to keep in mind that infection risk comprises the interaction of multiple factors; each must be addressed on its own, but we must not lose sight of their effects on one another, as well as the effects of other factors, such as D/R matching, pretransplant serologic status, race, and age, all of which impact the incidence, treatment, and outcomes of posttransplant infections. The principles of the gestalt, the common pathway for pathogenesis, the timing of infections, and the net state of immunosuppression must all be considered.

With these principles in mind, a group of experts have developed evidence-based guidelines for prevention and treatment of infection in solid organ

transplant recipients. The recommendations in these guidelines are based on the rating system established by the Infectious Disease Society of America for both strength of recommendation and quality of evidence. It is hoped that these guidelines will provide direction for both current treatment practice and future research.

In the care of the renal transplant recipient, particular attention should be paid to the fungal and viral infections (especially the herpes group viruses) that can still wreak so much havoc in this setting; it is important to look for both direct and indirect effects of these infections and to consider them in light of the individual patient's risk factors and vulnerabilities. A therapeutic prescription should be planned for each patient that balances immunosuppression to prevent graft rejection with antimicrobial treatment to control infection. Perhaps the most important principle to remember is that infection is far better prevented than treated; patient outcomes will be optimal if the sequelae of posttransplant infection can be avoided completely.

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State-of-the-Art Management of Posttransplant Sequelae
Infectious Complications Posttransplantation

CME/CE Posttest and Evaluation

Release Date: July 2005 Expiration Date: July 31, 2006

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POSTTEST

Thomas R. is a 53-year-old white man who underwent kidney transplantation because of polycystic renal disease, receiving an organ from a living related donor. Thomas was seronegative for cytomegalovirus (CMV) pretransplantation, whereas his donor was CMV seropositive. Thirty days posttransplantation, Thomas received OKT3 for acute rejection refractory to prednisolone. His maintenance immunosuppression consists of cyclosporine, prednisone, and mycophenolate mofetil.

1. What increases Thomas's risk for CMV infection and disease? (Select one answer.)
   a. Donor/recipient pretransplant CMV serostatus
   b. Use of OKT3 for rejection
   c. Use of a calcineurin inhibitor (CNI) for immunosuppression
   d. a and b
   e. All of the above

2. You decide to monitor Thomas for CMV regularly. Which method combines superior sensitivity, specificity, timeliness, and adaptability? (Select one answer.)
   a. Tissue culture
   b. Shell vial culture
   c. p65 antigenemia assay
   d. Quantitative polymerase chain reaction
   e. They all have similar qualities.

3. Thomas develops asymptomatic CMV infection. Which statement is true regarding agents for preventing and treating CMV disease? (Select one answer.)
   a. Intravenous (IV) ganciclovir should not be used to initiate therapy for CMV disease.
   b. Valganciclovir has bioavailability equivalent to that of IV ganciclovir.
   c. Oral ganciclovir has bioavailability equivalent to that of IV ganciclovir.
   d. Foscarnet is the safest treatment for CMV.
   e. Valacyclovir is used for both prophylaxis and treatment of CMV disease.

4. The net state of immunosuppression results from a combination of factors in addition to immunosuppressive drugs, including:
   a. Metabolic factors
   b. Viral infection
   c. Age
   d. a and b
   e. All of the above

5. The CNIs have several side effects, the most significant of which to renal transplant recipients is/are:
   a. Nephrotoxicity
   b. Vulnerability to herpes group viruses
   c. Nausea
   d. a and b
   e. All of the above

6. The herpes group viruses are most likely to be seen _____ month(s) posttransplantation.
   a. 1
   b. 1 to 6
   c. >6
   d. >12

7. Antimicrobial treatment may be given:
   a. Prophylactically, to an entire patient population to prevent infection
   b. Preemptively, to a subgroup of patients at high risk
   c. Therapeutically, to treat established infection
   d. All of the above

8. CMV has a bidirectional relationship with:
   a. The patient's net state of immunosuppression
   b. Allograft rejection
   c. HCV
   d. All of the above
   e. None of the above

9. The first choice of treatment for posttransplant lymphoproliferative disease is:
   a. Reduced immunosuppression
   b. Cancer chemotherapy
   c. Antiviral drugs
   d. Anti–B-cell antibodies

10. The prevalence of polyomavirus nephropathy in renal transplant recipients is estimated to be between _____ and _____.
    a. 1%, 4%
    b. 1%, 8%
    c. 3%, 8%
    d. 3%, 12%
    e. 6%, 9%

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CME/CE Posttest and Evaluation (DL-05-105C)

Release Date: July 2005 Expiration Date: July 31, 2006

Posttest Answer Key (questions from page 13)

1. a b c d e	3. a b c d e	5. a b c d e	7. a b c d	9. a b c d
2. a b c d e	4. a b c d e	6. a b c d	8. a b c d e	10. a b c d e

PROGRAM EVALUATION

The University of Minnesota would appreciate your comments regarding the quality of the information presented.

1. Each of the following program's educational objectives were fully met:
   - Discuss the immunosuppressive drugs used in transplantation and the risks and benefits of their use
     ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree
   - Define the net state of immunosuppression and identify contributing factors
     ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree
   - Outline the timetable of infection following renal transplantation
     ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree
   - Describe the infections that occur most commonly following renal transplantation
     ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree
   - Summarize risk factors for, effects of, and treatment options for these infections
     ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree
2. The quality of the educational process (method of presentation and information provided) was satisfactory and appropriate.
   ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree
3. The educational activity has enhanced my professional effectiveness and improved my ability to treat/manage patients.
   ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree ❑ N/A
4. The educational activity has improved my ability to communicate with patients.
   ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree ❑ N/A
5. The information presented was free of promotional or commercial bias. ❑ Agree ❑ Disagree
6. What changes will you make in your practice as a result of participating in this program?

   _____

   _____
7. Comments/suggestions regarding *this* material:_____

   _____

   _____
8. Recommendations for *future* presentations:_____

   _____

   _____
9. What is the most important barrier to the optimal posttransplant management of patients receiving renal transplants? (Select one answer.)
   ❑ Patient adherence ❑ Infections
   ❑ Side effects of immunosuppressive agents ❑ Neoplasia
   ❑ Renal function ❑ Other
10. Approximately how many patients do you see per week?_____
11. Approximately what percentage of your patients are renal transplant recipients?

    _____

_____
Full Name

_____
Company/Affiliation

_____
Street Address

_____
City State ZIP Code

_____
Email Address Fax Number

Degree: ❑ MD ❑ RN ❑ Other _____
❑ DO ❑ PharmD

Job Title
- ❑ Transplant Surgeon
- ❑ Nephrologist
- ❑ Transplant Coordinator
- ❑ Transplant Pharmacist
- ❑ Transplant Case Manager
- ❑ Nurse
- ❑ Other _____

Practice Type
- ❑ Private
- ❑ Group
- ❑ Transplant Center
- ❑ Academic

Practice Location
- ❑ Urban
- ❑ Suburban
- ❑ Rural

I certify that I completed this CME/CE activity. The actual amount of time I spent in this activity was: _____hours _____minutes.

_____
Signature Date Completed

PHYSICIANS: Are you licensed in the United States? ❑ YES ❑ NO NURSES: State of license and number _____

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