Opportunistic Infections in Renal Allograft Recipients

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Despite the technical, immunologic, and immunosuppressive advances of the past three decades, infection remains a major barrier to success for the renal transplant patient. More than 80% of renal transplant recipients suffer at least one episode of infection in the first year posttransplant, and infection remains the leading cause of death at all points in the posttransplant course. The most challenging infections observed in these patients are those that are grouped under the term opportunistic infection. This term is used to describe infection due to microorganisms that are normally nonpathogenic or rarely pathogenic for humans or that cause infection of a type and/or severity rarely encountered in the normal host. The range of potential causes of opportunistic infection in the renal allograft recipient is broad and includes viruses such as the herpes group and papovaviruses; bacteria such as Listeria monocytogenes, Nocardia asteroides, and Legionella; a wide variety of fungal species, but most particularly Candida, Aspergillus, Cryptococcus neoformans, and the Mucoraceae; and such protozoans as Pneumocystis carinii, Strongyloides stercoralis, and Toxoplasma gondii. Despite the fact that their pathogenesis may be very different, these opportunistic infections share several characteristics that account for the difficulties in clinical management:

1. The incidence and severity of these infections is greatly influenced by the type and intensity of the immunosuppressive therapy being administered.

2. Clinical presentation is usually occult, with the extent of disease at the time of diagnosis often far out of proportion to the severity of the symptoms. This is because of two factors: the majority of the organisms causing such infections are relatively bland, exciting little in the way of inflammatory signs or symptoms; and, even more important, the immunosuppressive therapy being administered will limit the inflammatory response and thus tend to blunt the clinical manifestations of the disease process.

3. Success in therapy is directly proportional to the rapidity with which the diagnosis is made and specific treatment initiated. Given the insidious nature of the clinical presentation, the diagnostic acumen of the responsible physician is constantly being challenged to achieve this goal.

4. Therapy for most of these infections is rendered particularly difficult by the toxicity of most of the available therapies and the usual requirement for a prolonged course of therapy.

5. Opportunistic infection is better prevented than treated.

The risk of opportunistic infection in the renal transplant recipient is due to an interaction between two major factors; the net state of immunosuppression present and the epidemiologic exposures that the individual encounters. The net state of immunosuppression is determined by a complex array of events including: the nature, dose, and duration of the immunosuppressive therapy being administered; the presence or absence of granulocytopenia and technical factors that could compromise the primary mucocutaneous barrier to infection; such metabolic factors as uremia, hyperglycemia, and the state of nutrition; and finally, the immunomodulating...
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Effects of such viruses as cytomegalovirus (CMV), the hepatitis viruses, and the human immunodeficiency virus (HIV). Epidemiologic exposures of importance may occur in the community, but are most important within the hospital environment in which air contamination with such organisms as Aspergillus and Legionella are important causes of morbidity and mortality in this patient population. The interaction between the net state of immunosuppression and the epidemiologic factors is best defined by a timetable that delineates the different points in the posttransplant course when each infection is most likely to occur.1,2

TIMETABLE FOR INFECTION AFTER RENAL TRANSPLANTATION

In terms of risk for particular causes of infection, the posttransplant course can be divided into three distinct time periods: (1) the first month after the transplant, (2) 1 to 6 months posttransplant, and (3) more than 6 months posttransplant (Fig 1). This timetable can be used by the clinician for two purposes: the development of an etiologic differential diagnosis when a renal transplant patient presents with an infectious disease syndrome such as pneumonia or fever of obscure origin; and as an epidemiologic tool, since exceptions to this timetable almost invariably connote an excessive epidemiologic hazard with epidemic potential.1,2 For example, although CMV infection accounts for more than two thirds of the fevers in the middle time period, it is an unlikely cause of fever at other points in the posttransplant course.3,4 Although invasive aspergillosis may occur in the middle or late time periods, it is exceedingly rare in the first month posttransplant, with every such episode in our experience being correlated with an unusual hazard within the hospital environment.1,2 Because of the usefulness of such associations, it is useful to review the different forms of infection encountered during each of these time periods.

Infection in the First Month Posttransplant

The infectious disease problems observed in the first month after renal transplantation are of three types: (1) infection that was present in the allograft recipient prior to transplant and which continues, possibly exacerbated by immunosuppressive therapy; these include hepatitis, smouldering conventional bacterial infection, tuberculosis, strongyloidiasis, and the geographically restricted systemic mycoses (blastomycosis, coccidioidomycosis, and

Fig 1. Timetable for the occurrence of infection in the renal transplant patient. Exceptions to this timetable should initiate a search for an unusual hazard. HSV, herpes simplex virus; EBV, Epstein-Barr virus; VZV, varicella-zoster virus; CNS, central nervous system; UTI, urinary tract infection. Modified with permission.2
histoplasmosis); (2) infection transmitted via a contaminated allograft; and (3) the routine bacterial infections of the surgical wound, lungs, intravenous (IV) lines, and bladder catheters found in nonimmunosuppressed patients undergoing comparable types of surgery. It is this last category of infection that is the most important cause of infection in the first month posttransplant.

Noteworthy by their absence during this period are the classical opportunistic pathogens such as Aspergillus, *N. asteroides*, and *P. carinii*. Such infections rarely occur during the first month posttransplant under normal circumstances, even though the daily amounts of immunosuppressive therapy being administered during this period are the highest at any point in the posttransplant course. This observation underlines two important points: the duration of immunosuppression is a more important determinant of the net state of immunosuppression than the particular dose of drug being administered on a given day or over a few days; and the cost of excessive immunosuppressive therapy in terms of infection risk will be borne weeks after such therapy is administered rather than immediately.1,2

**Infection 1 to 6 Months Posttransplant**

There are two major classes of infection observed in this period, with the second in large part dependent on the effects of the first. The most important types of infection 1 to 6 months after renal transplantation are viral infections, particularly those due to the herpes group viruses, most particularly CMV, and the hepatitis viruses. At this point in the posttransplant course, the duration of immunosuppression has been sufficient to reactivate latent herpes group viruses and the incubation period of transplant-associated hepatitis infection has now been completed, so that overt viral infection is the rule. In addition, these viruses, particularly CMV, are themselves immunosuppressing. It is the subgroup of transplant patients with overt viral infection that is at highest risk of opportunistic infection during this time period.1,2 Thus, infection due to such opportunistic pathogens as *Pneumocystis carinii*, *Listeria monocytogenes*, and the fungi may occur during this period in this group of patients.

**Infection More Than 6 Months Posttransplant**

Renal transplant patients who continue to receive immunosuppressive therapy to keep their allografts functioning more than 6 months posttransplant can be divided into three categories in terms of types of infectious disease problems to which they are vulnerable: (1) those whose chronic viral infection, acquired earlier in the posttransplant course, progresses due to the chronic immunosuppressed state; prime examples are progressive chorioretinitis due to CMV, progressive liver disease due to either non-A, non-B hepatitis or hepatitis B, hepatocellular carcinoma due to hepatitis B, or EBV-associated lymphoproliferative disease; (2) patients free of chronic viral infection with good renal function who are receiving minimal immunosuppressive therapy, and whose infectious disease problems are similar to those in the general community; and (3) patients with chronic immunosuppression, who have chronic infection with the immunomodulating viruses, and who are at the greatest risk of life-threatening opportunistic infection with such pathogens as *P. carinii*, *C. neoformans*, *L. monocytogenes*, and *N. asteroides*.1,2

**OPPORTUNISTIC INFECTIONS OF PARTICULAR IMPORTANCE IN THE RENAL TRANSPLANT PATIENT**

**Viral Infection**

Viral infections are the most common category of infection affecting renal transplant patients. Although such agents as hepatitis B virus, the virus(es) causing non-A, non-B hep-
atitis, and HIV when present contribute to the net state of immunosuppression and thus indirectly play a role in the pathogenesis of opportunistic infection, they themselves do not fulfill the criteria for opportunistic infection. All the clinical manifestations of these infections in transplant patients can be observed in immunologically normal individuals. In contrast, the combination of a chronically immunosuppressed state and infection with viruses of the herpes group and papovaviruses results in clinical syndromes not observed in nonimmunosuppressed individuals, and thus produces true opportunistic infection.

The four major human herpesviruses (CMV, EPV, VZV, and HSV) share three characteristics that explain their great clinical impact on organ transplantation: latency (primary infection results in lifelong dormant infection capable of being reactivated by such factors as immunosuppression and allograft rejection at any time); cell association (spread of the virus occurs from cell to cell with direct contact between the cells being important, thus rendering neutralizing antibody ineffective and cell-mediated immunity predominant in controlling the infection); and oncogenicity (all the herpesviruses should be considered potentially oncogenic, particularly in the setting of chronic immunosuppressive therapy).

Cytomegalovirus is the most important infectious agent infecting transplant patients. Its clinical effects may be grouped into four categories: (1) a variety of clinical infectious disease syndromes produced directly by the virus, ranging from acute infections including prolonged fevers, pneumonia, hepatitis, and colitis, to chronically progressive chorioretinitis; (2) an immunosuppressed state produced by the virus that extends that caused by the immunosuppressive drugs and contributes significantly to the net immunosuppressed state of the transplant patient, thereby playing an important role in the pathogenesis of opportunistic superinfection due to P carinii, a variety of fungi, and L monocytogenes; (3) a form of allograft dysfunction that appears to be associated with CMV, and apparently has a different pathogenesis, histologic appearance, and clinical course than does classic allograft rejection; and (4) malignancy possibly produced or made possible by the virus.

The first two of these clinical effects of CMV are well established; the last two remain unproved hypotheses. Cytomegalovirus infection is strongly influenced by the type and intensity of immunosuppressive therapy, with the various antilymphocyte antibody preparations (both polyclonal and monoclonal) having the greatest CMV-promoting effects. Attempts to use hyperimmune anti-CMV globulin prophylactically and the antiviral drug ganciclovir (DHPG) therapeutically appear promising; however, clinical management of this condition remains difficult.

Epstein-Barr virus infection probably has many of the same clinical effects as CMV, but because of the ubiquity of CMV this hypothesis has been difficult to prove. It is clear that EBV plays an important role in the pathogenesis of B cell lymphoproliferative disease in this patient population. Immunologically normal individuals infected with this virus develop cytotoxic T lymphocytes specific for EBV-induced antigens on the surface of infected B lymphocytes. These serve as an important surveillance mechanism in preventing the outgrowth of virally induced, transformed cells thought to initiate the oncogenic process. In immunosuppressed patients, this surveillance mechanism is impaired, and the greatest impairment is associated with cyclosporine. The induced lymphoproliferative disease appears to evolve from a polyclonal state responsive to a decrease in immunosuppressive therapy and/or high-dose IV acyclovir therapy into a highly malignant monoclonal state that is relatively unresponsive to therapeutic interventions.

The most common form of VZV infection observed in renal transplant patients is localized dermatomal zoster, which occurs in
approximately 10% of transplant recipients. Since such infections rarely disseminate, this should not be construed as opportunistic infection. In contrast, individuals who are susceptible to primary infection with this virus are at high risk for a devastating, disseminated disease characterized by encephalitis, pneumonia, hepatic failure, pancreatitis, hemorrhagic rash, and disseminated intravascular coagulation. Thus, every transplant patient should be screened for antibody to VZV. Seronegative individuals, particularly children, should be monitored for exposures to this virus, with prompt administration of varicella zoster immune globulin (VZIG) in such circumstances. In our experience, VZIG is about 75% effective; therefore, close clinical follow-up after prophylaxis is mandatory, particularly since the globulin may attenuate the rash without affecting the lethal visceral dissemination. Thus, we have seen primary VZV infection after VZIG prophylaxis without a single skin lesion, which nevertheless caused florid pancreatitis and disseminated intravascular coagulation. High-dose IV acyclovir therapy can be life-saving if initiated early enough in the clinical course.1,14

Localized HSV infections both oral and anogenital, in the transplant patient are common and tend to be recurrent and more severe than in the normal host; the lesions may have an atypical morphology, ie, ulcerations are more prominent than vesicles. True disseminated infection is uncommon, although primary disseminated infection apparently conveyed with the allograft has been reported. Acyclovir therapy has been a major advance in the therapy of these infections.1,14

The human papovaviruses, BK and JC viruses, are found in many transplant patients, although their clinical significance in general is still unclear. However, JC virus has been shown to be the cause of the devastating opportunistic neurologic disease, progressive multifocal leukoencephalopathy. In addition, these agents should be regarded as potentially oncogenic. The closely related wart viruses (papillomaviruses) have been implicated in the pathogenesis of squamous cell carcinoma of the skin in this patient population.1

Bacterial Infection

The most important single bacterial cause of opportunistic infection in the renal transplant patient is L monocytogenes, a Gram-positive bacillus with a predilection for the CNS. The portal of entry for Listeria is the gastrointestinal tract, with the following clinical syndromes being observed: bacteremia, sometimes in the setting of a gastroenteritis syndrome; an acute-subacute meningitis (the most common clinical syndrome); meningoencephalitis; and cerebritis without concomitant meningitis. Therapy of choice consists of meningeal doses of penicillin or ampicillin plus gentamicin; high-dose trimethoprim-sulfamethoxazole (TMP-SMX) appears to be an effective treatment for penicillin-allergic individuals.1,15,16

N asteroides, although commonly grouped with fungal infection because of a common pathogenesis and clinical presentation, is an occasional cause of opportunistic bacterial infection in immunosuppressed patients. Typically, the patient presents with cough, fever, and nodular infiltrates abutting the pleura on chest x-ray. It is important to recognize, however, that this organism has a high propensity for invading pulmonary blood vessels and metastasizing to the skin, CNS, or other sites. Indeed, metastatic lesions, particularly of the skin, may be the first recognizable sign of disseminated nocardial infection. Prolonged (more than 4 months) therapy with sulfisoxazole or TMP-SMX is quite effective.17

Rapidly progressive pulmonary infection with Legionella pneumophila or Legionella micdadei has occurred in transplant patients, particularly during nosocomial epidemics. Indeed, in such hospital epidemics the attack rates and the severity of the infections will be significantly greater in these individuals than in nonimmunosuppressed patients. With early
diagnosis, effective therapy with high-dose, IV erythromycin can be quite effective.  

**Fungal Infection**

Fungal infection in the renal transplant patient is of two types: disseminated primary or reactivation infection with one of the geographically restricted systemic mycoses (histoplasmosis, coccidioidomycosis, blastomycosis, and paracoccidioidomycosis) and posttransplant infection with agents that rarely cause invasive infection in the normal host (Candida, Aspergillus, Cryptococcus neoformans, and the Mucoraceae). For the first category of pathogens there are a variety of clinical presentations that should lead to their consideration in individuals who have been in endemic areas: a subacute respiratory illness, with either focal or disseminated interstitial or miliary infiltrates on chest x-ray; a nonspecific systemic febrile illness; or an illness in which metastatic aspects of the infection predominate (eg, mucocutaneous manifestations in histoplasmosis and blastomycosis or CNS manifestations in coccidioidomycosis).  

A more common problem is the acquisition of fungal infection posttransplant. Two patterns are observed: primary infection, usually of the lungs but occasionally of the nasal sinuses, caused most commonly by Cryptococcus neoformans or Aspergillus; and sequential and concurrent secondary infection, either of the lungs or via infected IV lines, by Candida, Aspergillus, or Torulopsis glabra.  

**Protozoan Infection**

There are three major causes of protozoan infection in the renal transplant patient: P carinii, S stercoralis, and T gondii. All three fill the criteria of opportunistic infection in this patient population.  
P carinii not uncommonly produces a diffuse, interstitial pneumonia in renal transplant patients not receiving TMP-SMX prophylaxis. Experience at the Massachusetts General Hospital, the University of Minnesota, and the University of Wisconsin suggests that low-dose prophylaxis, ie, one single strength tablet at bedtime (which does not interact adversely with cyclosporine therapy) is quite effective in preventing pneumocystis pneumonia. The attack rate for this infection in patients not receiving prophylaxis is highest in two groups of individuals: patients with CMV infection 1 to 4 months posttransplant, and patients more than 6 months posttransplant who have chronic rejection, have received extensive immunosuppression, and have chronic viral infections. Both TMP-SMX and pentamidine are effective therapies for this infection.  

S stercoralis is unique among intestinal nematodes in two ways: because of its ability to perpetuate itself with an autoinfection cycle, it can persist in the gastrointestinal tract of individuals many years after exposure; and depressed cell-mediated immunity can permit tissue invasion and dissemination. The result can be two life-threatening infections in the transplant patient: a hyperinfection syndrome that represents an exaggeration of the normal life cycle of the parasite, with major impact on the gastrointestinal tract (a severe, ulcerating hemorrhagic enterocolitis) and/or lungs (hemorrhagic pneumonia); and a disseminated strongyloidiasis syndrome, in which the worms, often accompanied by Gram-negative bacteria from the gut, can invade the brain, the abdominal viscera, and other tissues. With this latter form of disease, the clinical presentation may be that of Gram-negative sepsis or meningitis that responds poorly to antibacterial therapy. Although patients with the fully developed syndrome can be treated with repeated courses of oral thiabendazole (with or without the addition of conventional antibacterials), it is far better to screen patients who have lived in areas with endemic strongyloidiasis. Routine stool ova and parasite examinations are inadequate for this purpose, with duodenal intubation and
purged stool specimens necessary for adequate screening.\textsuperscript{1,18}

\textit{T gondii} uncommonly may cause disseminated infection in the renal transplant patient with a particular impact on the CNS. Rarely, transmission of this infection with the allograft has occurred, although this is a much greater problem in cardiac transplant recipients. The treatment of choice for this condition is pyrimethamine plus a sulfonamide.\textsuperscript{1}

**SUMMARY**

The risk of opportunistic infection in the renal transplant patient is due to an interaction between two major factors: the epidemiologic exposures (particularly within the hospital environment) and the net state of immunosuppression. The net state of immunosuppression is determined by the nature, dose, and duration of the immunosuppressive therapy being administered; the presence or absence of granulocytopenia and technical factors that could compromise the primary mucocutaneous barriers to infection; such metabolic factors as uremia, hyperglycemia, and the state of nutrition; and, finally, the immunomodulating effects of such viruses as CMV, the hepatitis viruses, and HIV. The major types of opportunistic infection to which the renal transplant patient is susceptible are the following: the viruses of the herpes group and papovaviruses; bacteria such as \textit{L monocytogenes}, \textit{N asteroides}, and \textit{Legionella}; such fungi as \textit{Candida}, \textit{Aspergillus}, \textit{C neoformans}, and the Mucoraceae; and protozoans such as \textit{P carinii}, \textit{S stercoralis}, and \textit{T gondii}.

**REFERENCES**