

## REVIEW ARTICLE

## MEDICAL PROGRESS

## Infection in Solid-Organ Transplant Recipients

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**I**NCREASINGLY POTENT IMMUNOSUPPRESSIVE AGENTS HAVE DRAMATICALLY reduced the incidence of rejection of transplanted organs while increasing patients' susceptibility to opportunistic infections and cancer.<sup>1,2</sup> At the same time, patterns of opportunistic infections after transplantation have been altered by routine antimicrobial prophylaxis for *Pneumocystis carinii* (also called *P. jirovecii*) and cytomegalovirus. These patterns have also been altered by the emergence of new clinical syndromes (e.g., polyomavirus type BK nephropathy) and by infections due to organisms with antimicrobial resistance. New quantitative molecular and antigen-based microbiologic assays detect previously unrecognized transplantation-associated pathogens such as lymphocytic choriomeningitis virus. These assays are used in the management of common infections such as those due to cytomegalovirus and Epstein-Barr virus (EBV). In this article, I review general concepts in the management of transplantation-associated infections and discuss recent advances and challenges.

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## GENERAL CONCEPTS

It is more difficult to recognize infection in transplant recipients than it is in persons with normal immune function, since signs and symptoms of infection are often diminished. In addition, noninfectious causes of fever, such as allograft rejection, may develop in transplant recipients. Antimicrobial therapy frequently has toxic effects that may involve interactions with immunosuppressive agents. The spectrum of potential pathogens is broad, and infection often progresses rapidly. Early and specific microbiologic diagnosis is essential for guiding treatment and minimizing nonessential drug therapy. Invasive diagnostic procedures are often required for accurate and timely diagnosis.

## RISK OF INFECTION

The risk of infection after transplantation changes over time, particularly with modifications in immunosuppression. Unfortunately, no assays accurately measure a patient's risk of infection. Currently, therefore, the clinician assesses a recipient's risk of infection while considering the risk of allograft rejection, the intensity of immunosuppression, and other factors that may contribute to his or her susceptibility to infection. Prophylactic strategies are based on the patient's known or likely exposures to infection according to the results of serologic testing and epidemiologic history. The risk of infection in the transplant recipient is a continuous function of the interplay between these factors.

## EPIDEMIOLOGIC EXPOSURES

Epidemiologic exposures can be divided into four overlapping categories: donor-derived infections, recipient-derived infections, nosocomial infections, and community infections.

*Donor-Derived Infections and Screening*

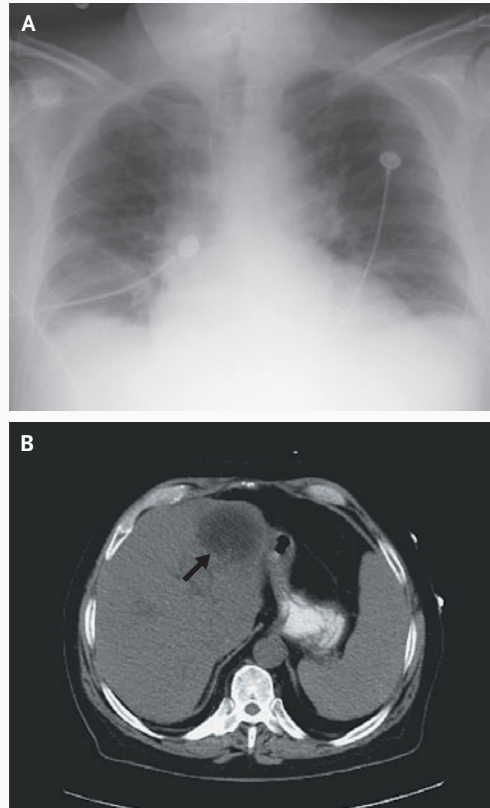
Transplanted organs facilitate the transmission of infections from organ donors. Mandatory reporting of transplantation-associated infections has increased awareness of this problem. Most often, these infections (e.g., cytomegalovirus infection, tuberculosis, and *Trypanosoma cruzi* infection) are latent in transplanted tissues. Transmission may also be due to active donor infection such as viremia or bacteremia that was undiscovered at the time of organ procurement (Fig. 1A).<sup>3</sup>

Organ donors also may become infected with nosocomial organisms that are resistant to routine surgical antimicrobial prophylaxis, and they may transmit these organisms (e.g., vancomycin-resistant enterococcus and azole-resistant candida species) to recipients.<sup>4-6</sup>

Clusters of infections derived from deceased donors have been described, including transplantation-associated West Nile virus infection, lymphocytic choriomeningitis virus infection, rabies, human immunodeficiency virus (HIV) infection, and Chagas' disease.<sup>3,7-10</sup> In recent outbreaks of West Nile virus infection, lymphocytic choriomeningitis virus infection, and rabies, signs of infectious encephalitis in organs from deceased donors were masked by unrelated acute neurologic events and thus were not recognized.

Nonspecific signs such as altered mental status or abnormal results of liver-function tests may be the sole basis on which to investigate potential donor-related infections. In the normal host, infections due to West Nile virus or lymphocytic choriomeningitis virus are generally self-limited. However, in organ-transplant recipients with these infections, rapid progression, permanent neurologic damage, and death are more common because of the broad immunologic deficits that are present after transplantation.

The screening of transplant donors for infection is limited by the available technology and by the short period during which organs from deceased donors can be used. At present, the routine evaluation of donors for infectious disease generally relies on antibody detection with the use of serologic tests for common infections (Fig. 2). Since seroconversion may not occur during acute infections and the sensitivity of these tests is not 100%, some active infections remain undetected. Some organs that contain unidentified pathogens will inevitably be implanted. Improved donor screening will require the use of more sensitive (e.g., molecular) and rapid assays by organ-pro-



**Figure 1. Effect of Donor-Derived Infection or Graft Injury on the Risk of Infection after Transplantation.**

Panel A is a chest radiograph showing pneumonia resulting from donor-derived herpes simplex virus infection. Fever and pneumonia developed in a kidney-transplant recipient 3 days after a technically successful transplantation, and the patient had abnormal results on liver-function tests. Blood and sputum contained herpes simplex virus. This virus was also detected in donor serum by means of a polymerase-chain-reaction assay. Recipients of the liver, heart, and other kidney from the same donor were symptomatic and were treated successfully with antiviral therapy. Panel B is a computed tomographic scan showing a liver abscess at the site of an ischemic graft injury. The patient had persistently and mildly abnormal liver-function tests (elevated alkaline phosphatase and total bilirubin levels) after undergoing technically successful orthotopic liver transplantation with early graft ischemia. Three years later, fever and chills developed, and a heterogeneous 6-cm abscess (arrow) with intrahepatic biliary ductal dilatation was detected. Therapy included percutaneous drainage and administration of antimicrobial agents for organisms including vancomycin-resistant *Enterococcus faecalis* and *Candida glabrata*.

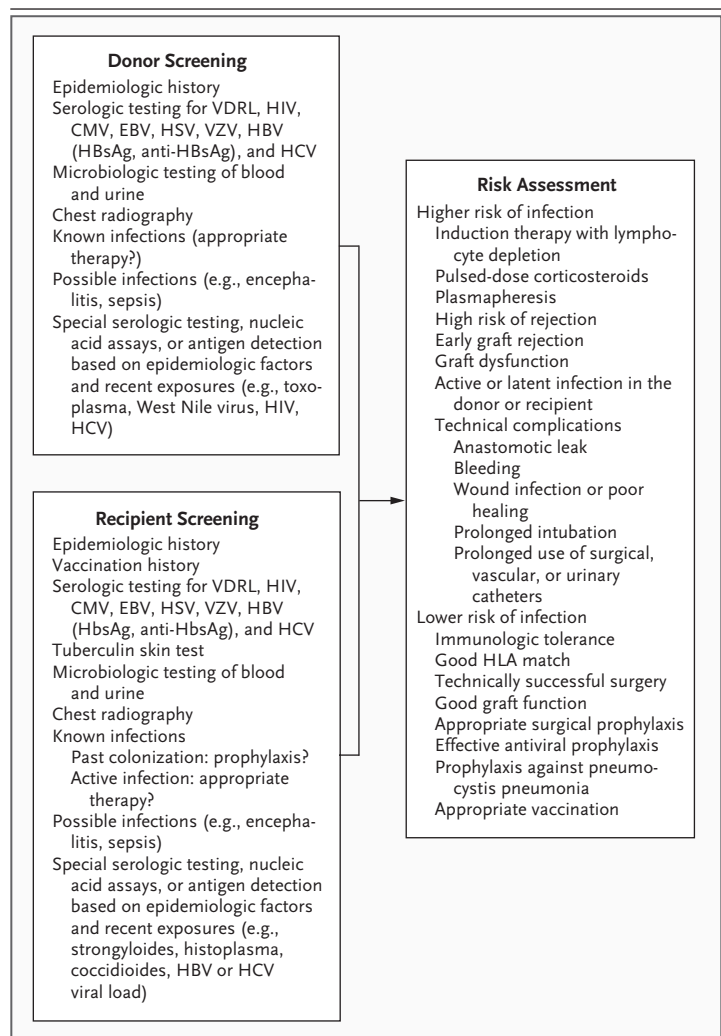
curement organizations. Augmented screening is recommended on a regional basis for endemic or epidemic infections such as West Nile virus infection, Chagas' disease, and strongyloidiasis.<sup>11</sup>

Some documented infections, such as sepsis and HIV infection, preclude organ donation. Organs from donors with specified known infections may be considered for specific recipients — provided there is appropriate informed consent — based on the urgency of the need for transplantation and the availability of effective antimicrobial therapies. For example, some livers from donors who were seropositive for Chagas' disease have been used successfully with benznidazole prophylaxis in regions where the disease is endemic.<sup>12</sup> Similarly, although organs from donors infected with the hepatitis B virus (HBV) and who had test results that were positive for antibodies against hepatitis B core antigen and negative for antibodies against hepatitis B surface antigen were rejected in the past, they are currently used for some recipients who have been vaccinated or who were previously infected, provided there is treatment with specific antiserum and anti-HBV antiviral agents.<sup>13-18</sup> The use of organs infected with the hepatitis C virus (HCV) remains controversial and is generally reserved for HCV-infected recipients.

Transplantation of organs from deceased donors who had fever or viral syndromes is controversial, and the uncertainty highlights the need for improved microbiologic screening tools. In cases in which the need for transplantation is relatively less urgent, it is reasonable to avoid the use of organs from donors with unexplained fever, rash, encephalitis, or untreated infectious syndromes.

#### Recipient-Derived Infections and Detection

Active infection in transplant recipients should be eradicated before transplantation, since immunosuppression will exacerbate the infectious process. Individualized epidemiologic histories can guide preventive strategies.<sup>11</sup> Common recipient-derived pathogens include *Mycobacterium tuberculosis*, certain parasites (e.g., *Strongyloides stercoralis* and *T. cruzi*), viruses (e.g., cytomegalovirus, EBV, herpes simplex virus, varicella-zoster virus [which causes shingles], HBV, HCV, and HIV), and endemic fungi (e.g., *Histoplasma capsulatum*, *Coccidioides immitis*, and *Paracoccidioides brasiliensis*).<sup>19-29</sup> Activities such as travel, raising pigeons (which is associated with *Cryptococcus neoformans* infection), or marijuana use (which is associated with infection with aspergillus species) increase the risk of infection. Infections that can be treated or controlled do not preclude transplantation.



**Figure 2. Assessment of the Risk of Infection at the Time of Transplantation.**

The risk of infection transmitted from the organ donor or activated in the recipient can be assessed at the time of transplantation. Donor and recipient screening are based on the epidemiologic history and serologic testing. The use of sensitive molecular and protein-based assays may enhance the safety of organ transplantation while expanding the use of potentially infected grafts. The transplant recipient's risk is a function of the technical outcome, epidemiologic factors, and the intensity of immunosuppression. VDRL denotes Venereal Disease Research Laboratory test, HIV human immunodeficiency virus, CMV cytomegalovirus, EBV Epstein-Barr virus, HSV herpes simplex virus, VZV varicella-zoster virus, HBV hepatitis B virus, HBsAg hepatitis B surface antigen, anti-HBsAg antibodies against hepatitis B surface antigen, and HCV hepatitis C virus.

Temporally distant *S. stercoralis* infection may reemerge, often in the first year after transplantation, as a hyperinfestation syndrome consisting of hemorrhagic enterocolitis, pneumonia, and gram-negative bacteremia or meningitis.<sup>24,25</sup> Empirical treatment with ivermectin before trans-

plantation prevents such infection in strongyloides-seropositive recipients. The importance of donor-derived or recipient-derived exposures to endemic fungi such as *H. capsulatum* or tuberculosis is shown by the increased rate of activation of these infections among transplant recipients; this rate is 50 times higher among transplant recipients than it is among the general population, notably in endemic regions.<sup>11</sup>

The course of HCV infection after liver transplantation remains discouraging. Since effective antiviral therapies are lacking, recipients are uniformly reinfected by HCV, with outcomes determined by the viral strain, the presence or absence of previous immunity, and the response to antiviral therapy.<sup>30-34</sup>

Successful transplantation has been achieved in HIV-infected patients treated with highly active antiretroviral therapy.<sup>26-28</sup> In such recipients, the toxic effects of drugs and interactions between calcineurin inhibitors and antiretroviral agents require careful monitoring. Liver-transplant recipients with HIV and HCV coinfection may have an accelerated course of recurrent HCV infection.

#### Nosocomial Infections and Antimicrobial Resistance

Patients waiting for transplantation may become colonized with nosocomial, antimicrobial-resistant organisms, including methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococcus, fluconazole-resistant candida species, *Clostridium difficile*, and antimicrobial-resistant gram-negative bacteria or aspergillus species.<sup>35-43</sup> After transplantation, these pathogens may cause pneumonia or may infect hematomas, ascitic fluid, wounds, and catheters.

#### Community Infections

Exposures that are relatively benign in a normal host may lead to major infection after transplantation. Common microorganisms include those noted above, pathogens in soil such as aspergillus or nocardia species, *C. neoformans* in birds, and respiratory viruses with subsequent bacterial or fungal superinfection.

#### NET STATE OF IMMUNOSUPPRESSION AND MONITORING OF IMMUNE FUNCTION

The net state of immunosuppression refers to all factors that contribute to the patient's risk of infection (Fig. 3). The main determinants of risk are the dose, duration, and sequence of immunosup-

#### Figure 3 (facing page). Dynamic Assessment of the Risk of Infection after Transplantation.

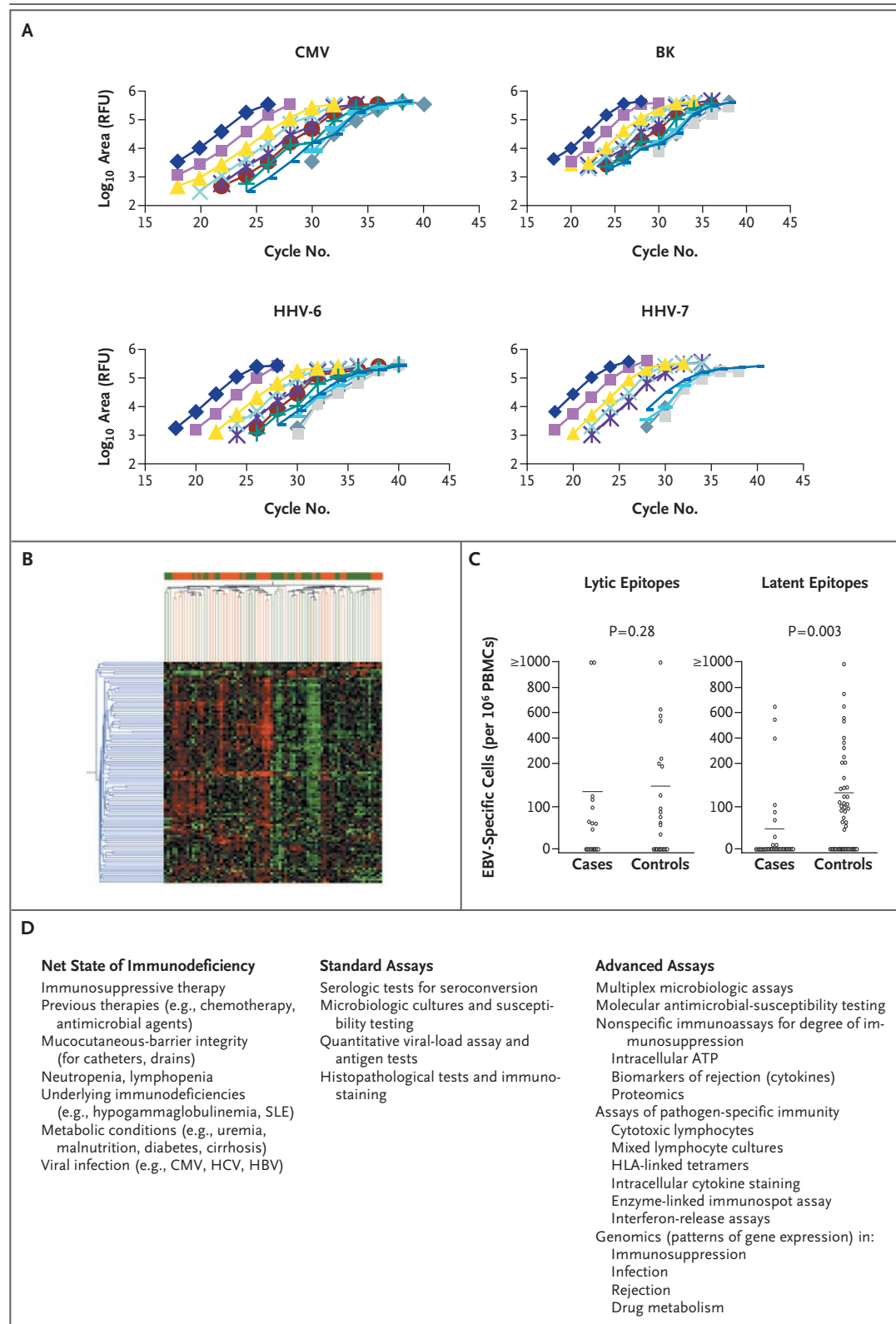
The risk of infection is a function of the net state of immunodeficiency. The presence of specific, common infections can be detected by means of quantitative assays measuring nucleic acids or proteins derived from potential pathogens. Multiple simultaneous quantitative (multiplex) assays can be performed diagnostically in a single sample with the use of polymerase chain reaction. Each line represents a single patient's sample (Panel A). The presence of specific infections can be assessed with the use of genomic arrays measuring the up-regulation or down-regulation of host genes during infection (Panel B, courtesy of Shaf Keshavjee, M.D., University of Toronto). Lytic and latent epitopes are viral antigens presented in either the lytic or latent phase of Epstein-Barr virus (EBV) infection. The transplant recipient's cellular immune response to specific pathogens such as EBV can be determined by measurements of cellular activation by pathogen-specific antigens (Panel C, courtesy of Christian Brander, Massachusetts General Hospital). The factors contributing to the degree of immunologic impairment and standard assays that assess the patient's risk of infection will be supplemented in the future by new quantitative measures of allograft- and pathogen-specific immune function and the risk of infection (Panel D). RFU denotes relative fluorescence units, CMV cytomegalovirus, BK polyomavirus type BK, HHV-6 human herpesvirus 6, HHV-7 human herpesvirus 7, PBMCs peripheral-blood mononuclear cells, SLE systemic lupus erythematosus, HCV hepatitis C virus, and HBV hepatitis B virus.

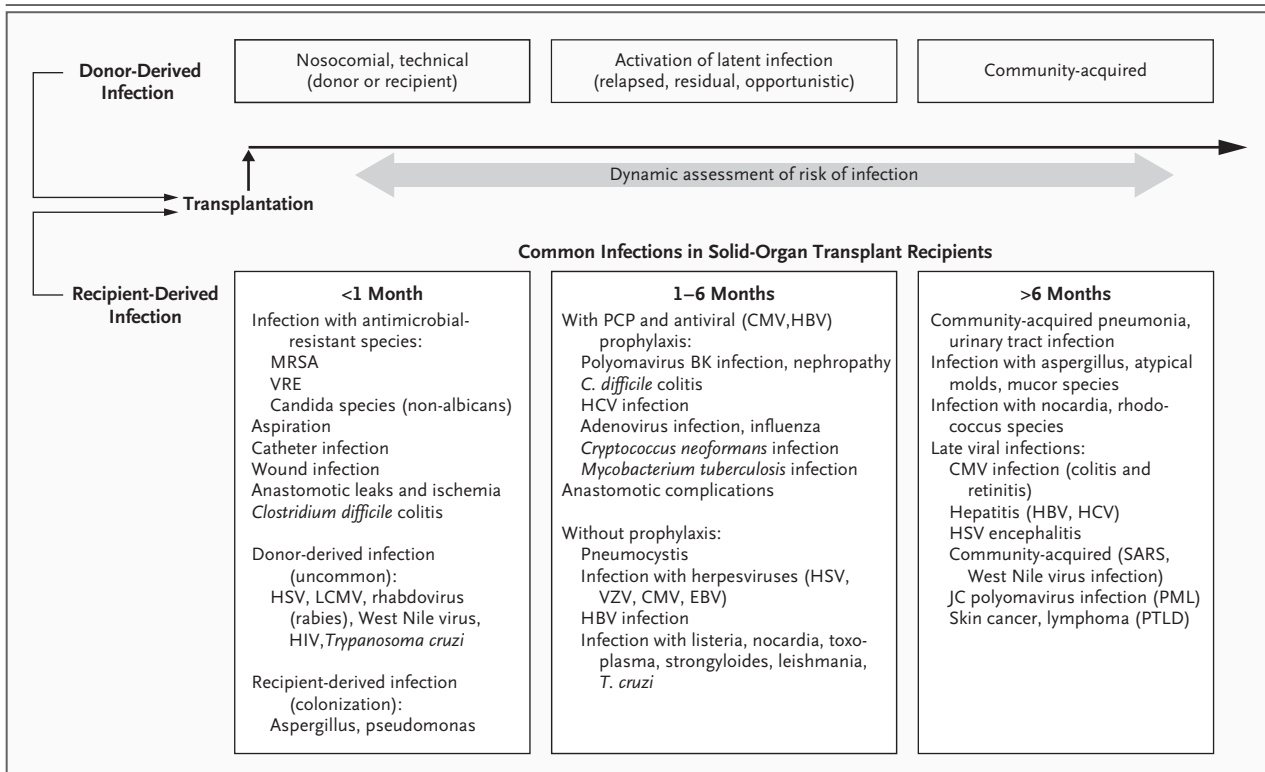
pressive therapies. Drug levels are used to guide immunotherapy. This approach often results in toxic effects from drugs (e.g., renal injury from calcineurin inhibitors) and infection or graft rejection. These relatively crude measures of immunosuppression may eventually be supplanted by assays that allow individualization (minimization) of immunosuppression. Some nonspecific and pathogen-specific measures of cell-mediated immune function are available.<sup>44</sup> Unique patterns of gene and protein expression have been observed with specific infections and with graft rejection. In the future, new assays based on these patterns may guide the use of immunosuppression to prevent rejection and infection or to provide care for patients with active infection (Fig. 3).

#### PREVENTION OF INFECTION

Antimicrobial prophylaxis has dramatically altered the incidence and severity of post-transplantation infections (Fig. 4). Three general preventive strategies are used: vaccination, universal prophylaxis,







**Figure 4. Changing Timeline of Infection after Organ Transplantation.**

Infections occur in a generally predictable pattern after solid-organ transplantation. The development of infection is delayed by prophylaxis and accelerated by intensified immunosuppression, drug toxic effects that may cause leukopenia, or immunomodulatory viral infections such as infection with cytomegalovirus (CMV), hepatitis C virus (HCV), or Epstein–Barr virus (EBV). At the time of transplantation, a patient's short-term and long-term risk of infection can be stratified according to donor and recipient screening, the technical outcome of surgery, and the intensity of immunosuppression required to prevent graft rejection. Subsequently, an ongoing assessment of the risk of infection is used to adjust both prophylaxis and immunosuppressive therapy. MRSA denotes methicillin-resistant *Staphylococcus aureus*, VRE vancomycin-resistant *Enterococcus faecalis*, HSV herpes simplex virus, LCMV lymphocytic choriomeningitis virus, HIV human immunodeficiency virus, PCP *Pneumocystis carinii* pneumonia, HBV hepatitis B virus, VZV varicella–zoster virus, SARS severe acute respiratory syndrome, PML progressive multifocal leukoencephalopathy, and PTLD post-transplantation lymphoproliferative disorder. Modified from Fishman and Rubin<sup>1</sup> and Rubin et al.<sup>45</sup>

and preemptive therapy.<sup>46</sup> The need for immunization against measles, mumps, rubella, diphtheria, pertussis, tetanus, HBV infection, poliomyelitis, varicella, influenza, and pneumococcal pneumonia should be evaluated before transplantation.<sup>47</sup> Vaccination is generally less effective during immunosuppression.<sup>11</sup> Pneumococcal vaccine is recommended every 3 to 5 years, and influenza vaccine is recommended annually. Other vaccines are appropriate for patients who travel to regions where certain illnesses are endemic. Live vaccines are generally contraindicated after transplantation, since they may cause disseminated infection in immunocompromised hosts. The immunologic protection provided by vaccines may be limited in extent or duration.<sup>48,49</sup>

Promoting lifestyle changes after transplantation may help limit exposures to some potential pathogens. Attention to hand washing should be observed after food preparation, gardening, and contact with feces or secretions. Transplant recipients should avoid close contact with people who have respiratory illnesses, and they should avoid environments such as construction sites, which have known pathogens. Dietary advice might include avoidance of well water and lake water (which may contain cryptosporidium or giardia species), undercooked meats, unwashed fruits and vegetables, and unpasteurized dairy products (which may contain *Escherichia coli* or *Listeria monocytogenes*).

Routine surgical prophylaxis varies, depending

on the organ transplanted and local epidemiologic factors. For liver transplantation, antimicrobial agents that provide coverage for skin flora, biliary enterococcus species, anaerobes, and Enterobacteriaceae are routinely prescribed. For lung transplantation, prophylaxis is aimed at gram-negative bacteria, molds, and geographic fungi (e.g., histoplasma). Prophylaxis may be adjusted according to known colonization patterns with pseudomonas, methicillin-resistant *S. aureus*, vancomycin-resistant enterococcus, or fungi.

Antifungal prophylaxis is based on both risk and epidemiologic factors. Most invasive fungal infections in transplant recipients are due to non-albicans candida and aspergillus species. The greatest risks associated with early fungal infections include aspergillus at the tracheal anastomosis after lung transplantation and candida species after pancreas or liver transplantation. Invasive fungal infections are most common in liver recipients requiring admission to the intensive care unit, surgical re-exploration or retransplantation, or transfusion of large amounts of blood products and in liver recipients with metabolic dysfunction (involving the liver allograft, kidney, or diabetes), respiratory failure, cytomegalovirus infection, or HCV infection. The risk is increased after broad-spectrum antimicrobial therapy.<sup>50-56</sup> Prophylaxis should be considered in such high-risk hosts.

Most transplantation centers use trimethoprim-sulfamethoxazole prophylaxis for as little as 3 months or for as long as a lifetime to prevent pneumocystis pneumonia as well as infections with *Toxoplasma gondii*, *Isospora belli*, *Cyclospora cayentanensis*, many nocardia and listeria species, and common urinary, respiratory, and gastrointestinal pathogens. Low-dose trimethoprim-sulfamethoxazole is well tolerated and should be used unless there is evidence that the patient has an allergy or interstitial nephritis. Alternative agents for prophylaxis against pneumocystis include dapsone, atovaquone, and pentamidine, but they are less effective than trimethoprim-sulfamethoxazole and lack the breadth of protection.<sup>57</sup>

The prevention of post-transplantation cytomegalovirus and other herpesvirus infections and the availability of oral antiviral agents have revolutionized post-transplantation care.<sup>58</sup> Two preventive strategies have emerged. With universal prophylaxis, antimicrobial therapy is provided to all at-risk patients for a defined period. In con-

trast, with preemptive therapy, sensitive quantitative assays (e.g., molecular assays and antigen detection) are used to monitor patients at predefined intervals in order to detect infection before symptoms arise. Depending on the potential pathogen and institutional protocols, a positive assay triggers the initiation of antimicrobial therapy, a reduction in the intensity of immunosuppression, intensified monitoring, or all of these steps. Preemptive therapy incurs extra costs for monitoring and coordination of outpatient care, but it avoids the costs and toxic effects of prophylactic antiviral therapy.

The crude risk of specific infections has traditionally been defined by means of serologic testing; the risk is lower in a seropositive host or higher in a seronegative recipient of an organ from a seropositive donor. A variety of newer techniques (e.g., HLA-linked tetramer binding and intracellular cytokine staining) measure pathogen-specific immunity and provide insight into the risk of specific infections and the ability of the host to clear invasive disease (Fig. 3).<sup>59</sup>

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#### CHANGING THE PATTERN OF INFECTION

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Early in the evolution of solid-organ transplantation, there was a limited number of available immunosuppressive agents, and antirejection protocols (i.e., use of corticosteroids, calcineurin inhibitors, and azathioprine) were relatively standardized. As a result, the timeline for the development of common post-transplantation infections was relatively predictable.<sup>1,45</sup> Changes in immunosuppressive regimens, routine prophylaxis, and improved graft survival have altered the original pattern (Fig. 4). Corticosteroid-sparing regimens and antipneumocystis prophylaxis have made pneumocystis pneumonia less common. Herpesvirus infections are uncommon while patients are receiving antiviral prophylaxis. Newer immunosuppressive approaches, including the use of sirolimus, mycophenylate mofetil, T-cell and B-cell depletion, and costimulatory blockade, have largely replaced high-dose corticosteroids and azathioprine.

With changes in typical immunosuppression, new patterns of infection have emerged. Sirolimus-based regimens have been associated with idiosyncratic noninfectious pneumonitis, which is easily confused with pneumocystis pneumonia or

viral pneumonia.<sup>60</sup> T-lymphocyte-depleting antibodies commonly used for initial or induction therapy are associated with increased viral activation — notably, activation of cytomegalovirus, EBV, and HIV.<sup>28,61,62</sup> Cellular depletion after induction therapy often persists beyond the period of antimicrobial prophylaxis, resulting in late infections with viruses such as cytomegalovirus and JC polyomavirus as well as fungal infections and malignant conditions after transplantation. Infections that occur after the usual period or that are unusually severe suggest excessive immunosuppression or exposure. The timeline for a given patient is reset with each episode of rejection or intensification of immunosuppression (e.g., with bolus corticosteroids), with an increased risk of opportunistic infections.

#### EARLY POST-TRANSPLANTATION PERIOD

Opportunistic infections are generally absent during the first month after transplantation, since the full effect of immunosuppression is not yet present. Infections such as viremia and candidemia in this period are generally donor-derived or recipient-derived, or they are associated with technical complications of surgery (Fig. 1B). Therapy must be guided by antimicrobial-susceptibility data, making microbiologic analysis of aspirates or biopsy specimens essential. *C. difficile* colitis is common in this setting. Early graft injuries (e.g., ischemia of bile ducts or pulmonary reperfusion injury) may later become foci for liver or lung abscesses (Fig. 1B). Unexplained early signs of infection, such as hepatitis, pneumonitis, encephalitis, rash, and leukopenia, may be donor-derived.

#### INTERMEDIATE POST-TRANSPLANTATION PERIOD

Viral pathogens and allograft rejection are responsible for the majority of febrile episodes that occur during the period from 1 to 6 months after transplantation. Trimethoprim-sulfamethoxazole prophylaxis generally prevents most urinary tract infections and opportunistic infections such as pneumocystis pneumonia, *L. monocytogenes* infection, *T. gondii* infection, and infection with sulfasusceptible nocardia species. Infection due to endemic fungi, aspergillus, cryptococcus, *T. cruzi*, or strongyloides may occur. Herpesvirus infections are uncommon with antiviral prophylaxis. However, other viral pathogens, including polyomavirus BK, adenovirus, and recurrent HCV, have emerged. Given the array of potential pathogens,

in the future, multiplex quantitative assays will be used to monitor acute infections (Fig. 3).

#### LATE POST-TRANSPLANTATION PERIOD

The risk of infection diminishes 6 months after transplantation, since immunosuppressive therapy is usually tapered in recipients who have satisfactory allograft function. However, transplant recipients have a persistently increased risk of infection due to community-acquired pathogens (Fig. 4). In some patients, chronic viral infections may cause allograft injury (e.g., cirrhosis from HCV infection in liver-transplant recipients, bronchiolitis obliterans in lung-transplant recipients, accelerated vasculopathy in heart-transplant recipients with cytomegalovirus infection) or a malignant condition such as post-transplantation lymphoproliferative disorder (PTLD) or skin or anogenital cancers (Fig. 1). Recurrent infection may develop in some patients despite minimization of their immunosuppression. These patients are at increased risk for opportunistic infection with listeria or nocardia species, invasive fungal pathogens such as zygomycetes and dematiaceous molds, and unusual organisms (e.g., rhodococcus species). Minimal signs of infection merit careful evaluation in such high-risk patients; they may benefit from lifetime trimethoprim-sulfamethoxazole or antifungal prophylaxis. Such long-term prophylaxis carries some risk of the development of microbial resistance to the prophylactic agents and possible future drug interactions.

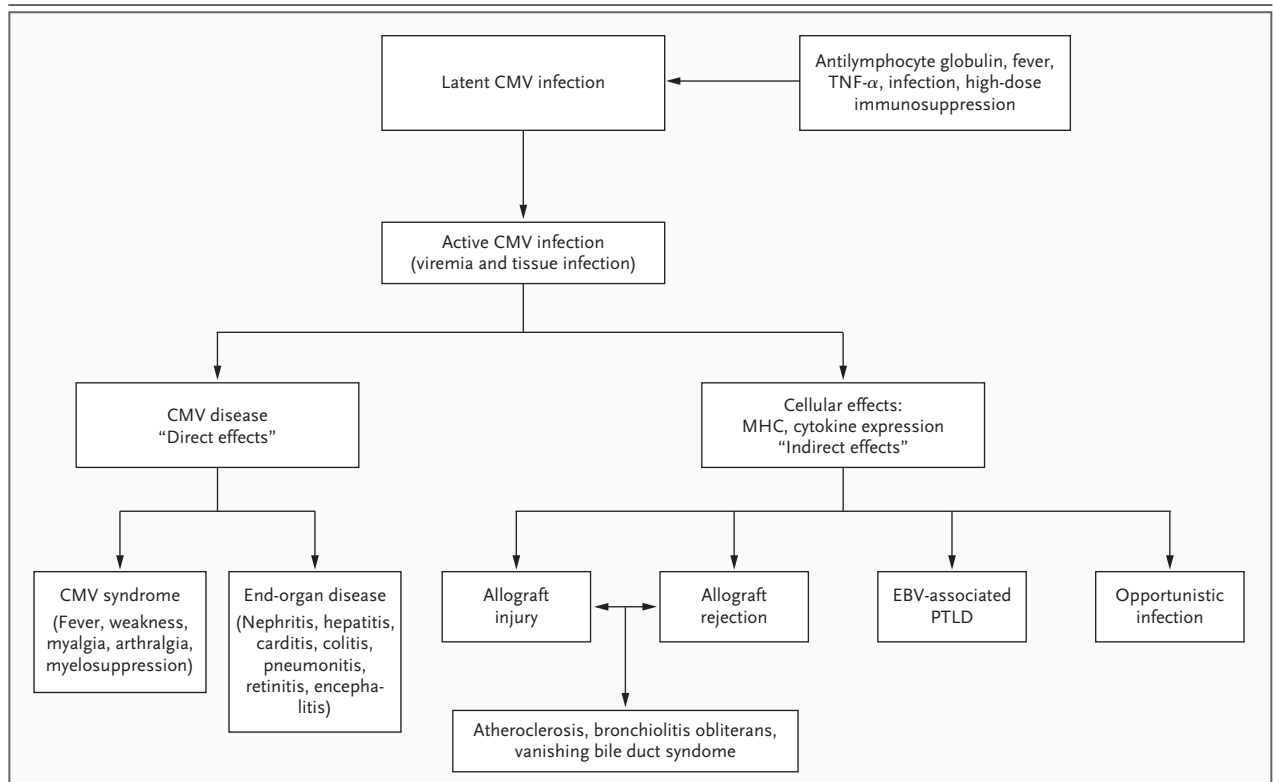
#### COMMON INFECTIONS IN TRANSPLANTATION

Early and specific microbiologic diagnosis is essential in the immunocompromised host, often necessitating invasive diagnostic techniques. Reduction in the intensity of immunosuppression may be useful until the acute process is controlled, although this approach risks allograft rejection. Reversal of immune deficits such as neutropenia or hypogammaglobulinemia may be achieved by the administration of colony-stimulating factors or intravenous immune globulin. Viral coinfection must be recognized and treated.

#### CYTOMEGALOVIRUS INFECTION

Cytomegalovirus infection may cause both invasive disease, or “direct effects,” and a variety of secondary immune phenomena (Fig. 5) in trans-





**Figure 5. Cytomegalovirus Infection.**

Cytomegalovirus (CMV) causes both invasive disease ("direct effects") and immunologic phenomena ("indirect effects"), including graft rejection and a predisposition to opportunistic infections. CMV may be activated by febrile illness (through the release of tumor necrosis factor  $\alpha$  [TNF- $\alpha$ ]), by depletion of antilymphocyte antibodies, or during treatment for graft rejection. MHC denotes major histocompatibility complex, EBV Epstein-Barr virus, and PTLD post-transplantation lymphoproliferative disorder.

plant recipients.<sup>1,63,64</sup> Invasive disease generally occurs during the first year after completion of prophylaxis and is manifested most often as fever and neutropenia; some patients have lymphadenopathy, hepatitis, thrombocytopenia, pneumonitis, gastrointestinal invasion (with diffuse colitis, gastritis, ulcers, and bleeding), pancreatitis, chorioretinitis (which is often late), or meningoencephalitis (which is uncommon). Cytomegalovirus infection is also associated with an overall increase in the risk of additional infections, including infections with other viruses and EBV-associated PTLD. In addition, cytomegalovirus infection may contribute to vasculopathy in heart-allograft recipients and to the bronchiolitis obliterans syndrome in lung-allograft recipients.

#### Epidemiology

Primary infection, reactivation, or viral superinfection with cytomegalovirus may develop in transplant recipients. Serologic assays are useful in de-

termining a patient's risk of infection, but they are generally of little use in the diagnosis of acute infections. Seropositivity is also associated with the presence of cellular immunity.<sup>65</sup> Primary infection, the most severe form of disease, occurs when seronegative recipients who have not previously received immunologic therapy receive allografts from latently infected, seropositive donors (i.e., D+/R-combinations). Without antiviral prophylaxis, most newly infected patients have asymptomatic viremia, although invasive disease develops in a subgroup of patients. Seroconversion in seronegative transplant recipients who have received allografts from seropositive donors generally occurs during the first year after transplantation; however, 25% of recipients do not undergo seroconversion and may benefit from prolonged prophylaxis.<sup>66</sup>

#### Prevention

Both universal antiviral prophylaxis and pre-emptive antiviral therapy reduce the risk of invasive

cytomegalovirus infection.<sup>67-69</sup> Universal antiviral prophylaxis also helps to prevent other viral infections such as herpes simplex virus, varicella-zoster virus, EBV, and human herpesvirus 6 (HHV-6) and human herpesvirus 7 (HHV-7) infections. Universal antiviral prophylaxis also reduces the risk of fungal infections such as pneumocystis, candida, and aspergillus, complications of viral infections such as HHV-6, HHV-7, accelerated HCV and PTLD, and bacterial infections (Fig. 4).<sup>54,70-73</sup> In addition, prevention of cytomegalovirus infection may reduce episodes of both early and late acute rejection in renal-transplant recipients, cardiac vasculopathy in heart-transplant recipients, and the bronchiolitis obliterans syndrome in lung-transplant recipients (Fig. 5).<sup>74-79</sup> The relationship between acute rejection and cytomegalovirus disease has not been shown in all studies.<sup>80</sup>

Although optimal regimens remain undefined, most centers provide anticytomegalovirus prophylaxis for the first 3 to 6 months after transplantation, using valacyclovir, high-dose acyclovir, ganciclovir, valganciclovir, or, less commonly, cytomegalovirus hyperimmune globulins.<sup>1,81</sup> Several situations require special consideration. First, the use of induction therapy with depleting anti-lymphocyte antibodies for seropositive donors or seropositive recipients increases the risk of cytomegalovirus reactivation and generally merits extended prophylaxis followed by monitoring for active infection. Second, although recipients of heart and lung transplants who are seropositive or who receive transplants from seropositive donors generally receive prophylaxis for at least 6 to 12 months, some may benefit from longer courses of antiviral prophylaxis if they lack evidence of protective immunity (i.e., if they have not undergone seroconversion), if they have persistent viral secretion (e.g., in sputum), or if they require a greater intensity of sustained immunosuppression. However, patients receiving longer courses of ganciclovir or valganciclovir may incur marrow suppression from these agents. Some patients treated for active cytomegalovirus infection may have a relapse without an additional period of prophylaxis after treatment.

Ganciclovir resistance in patients with cytomegalovirus infection is uncommon, but when present, it is most often due to mutations in the cytomegalovirus *UL97* gene (a viral protein kinase that phosphorylates the drug) or the *UL54* gene (cytomegalovirus DNA polymerase). Such resis-

tance may present as slowly responsive or relapsing infection, most commonly in patients who were seronegative for cytomegalovirus at the time of transplantation and received allografts from seropositive donors, in patients who receive inadequate or prolonged doses of oral ganciclovir or valganciclovir, especially during active infection, or in patients who undergo intensified immunosuppression. Recipients of lung transplants are also at relatively high risk for resistance to ganciclovir. Ganciclovir resistance has been observed with both universal and preemptive approaches.<sup>82-84</sup>

#### *Diagnosis and Therapy*

Quantitative diagnostic assays for cytomegalovirus are essential for management of infection. These include molecular assays (polymerase-chain-reaction [PCR] and other amplification assays) and antigen-detection (pp65 antigenemia) assays. In patients with neurologic manifestations of cytomegalovirus infection (including chorioretinitis) and gastrointestinal disease (colitis and gastritis, often with ulceration), blood-based cytomegalovirus assays may be negative. Thus, invasive procedures such as colonoscopy with biopsy or lumbar puncture may be necessary. Invasive disease and the cytomegalovirus syndrome (which is manifested as fever and leukopenia) warrant therapy, generally with intravenous ganciclovir. Results of studies of oral valganciclovir therapy for cytomegalovirus disease are encouraging.<sup>85,86</sup> Intravenous ganciclovir is currently preferred for the initiation of therapy for gastrointestinal disease. Documentation of cure in patients with gastrointestinal cytomegalovirus infection includes negative results of microbiologic assays and healing of ulcers and colitis on endoscopic evaluation. Relapse, which is common with inadequate therapy, carries the risk of the emergence of resistance to antiviral agents.

#### **EPSTEIN-BARR VIRUS AND POST-TRANSPLANTATION LYMPHOPROLIFERATIVE DISORDER**

PTLD, a heterogeneous group of lymphoproliferative disorders, occurs in 3 to 10% of adults who are solid-organ transplant recipients; it is associated with a reported mortality of 40 to 60%.<sup>87-89</sup> PTLD accounts for more than half of post-transplantation malignant conditions in pediatric solid-organ-transplant recipients. It varies from a benign polyclonal, B-cell, infectious mononucle-

osis-like syndrome to malignant, monoclonal lymphoma.<sup>90-92</sup> Risk factors for PTLD include primary EBV infection after transplantation in seronegative recipients of allografts from seropositive donors, allograft rejection, exposure to antilymphocyte antiserum, and cytomegalovirus coinfection. PTLD occurring in the first year after transplantation is usually CD20+ and B cell in origin. In contrast, later disease may be EBV-negative and T cell, natural killer cell, or null cell in origin, generally with a worse prognosis.

The role of EBV in non-B-cell PTLD is less clear. The clinical presentation of EBV-associated PTLD varies (Table 1). PTLD is generally extranodal, often with mass lesions in proximity to the transplanted organ. Both B-cell and T-cell PTLD may infiltrate allografts and may be confused with allograft rejection or other viral processes. Occasionally, patients with PTLD have evidence of remitting-relapsing EBV infection, which reflects an interplay between antiviral immunity and immunosuppression.

Quantitative EBV viral-load testing, flow cytometry, analysis of immunoglobulin gene rearrangements, and histologic analysis with staining for EBV-derived RNA are helpful in guiding the diagnosis and management of PTLD.<sup>93,94</sup> In the polyclonal form, particularly in children, a reduction in immunosuppression may lead to regression of the PTLD but poses the risk of allograft rejection. The progression of disease requires alternative approaches that may include the administration of chemotherapy, irradiation (for central nervous system disease), and treatment with anti-CD20 antibodies. Adoptive immunotherapy (T-cell transfer) is under investigation as a treatment strategy for PTLD. Further data are needed to define a possible protective role of sirolimus against PTLD.<sup>93</sup>

#### POLYOMAVIRUSES BK AND JC

Polyomaviruses have been identified in transplant recipients in association with nephropathy (e.g., polyomavirus BK-associated nephropathy) and ureteral obstruction, and the JC virus has been associated with progressive multifocal leukoencephalopathy.<sup>95-99</sup> No effective antiviral therapy exists for polyomaviruses. Detection of BK virus nucleic acids in blood and urine has been useful for assessing responses to therapy in patients with polyomavirus-associated nephropathy. Therapy requires a reduction in immunosuppression. Experimental therapies include cidofovir, an inhibitor of

**Table 1. Clinical Presentations of Post-Transplantation Lymphoproliferative Disorder Associated with Epstein-Barr Virus.**

Unexplained fever (fever of unknown origin)
Mononucleosis-like syndrome (fever, malaise, pharyngitis, tonsillitis)
Gastrointestinal bleeding, obstruction, or perforation
Abdominal-mass lesions
Infiltrative disease of the allograft
Hepatocellular or pancreatic dysfunction
Central nervous system disease

viral DNA synthesis that has considerable nephrotoxicity; leflunomide, an immunosuppressive agent with antiviral properties against BK virus and cytomegalovirus; and intravenous immune globulin. None of these agents have been shown to have efficacy in the treatment of polyomaviruses or have been subjected to rigorous controlled trials. In patients with renal failure due to polyomavirus-associated nephropathy, successful retransplantation has been achieved after reversal of immunosuppression for a sufficient time to allow the emergence of antiviral immunity.<sup>98,99</sup>

#### CENTRAL NERVOUS SYSTEM INFECTION

Central nervous system infection in transplant recipients is a medical emergency. The broad spectrum of causative organisms includes listeria, herpes simplex virus, JC virus, and *C. neoformans*. Empirical therapy must be initiated while the results of imaging studies (preferably magnetic resonance imaging), lumbar puncture (including studies such as PCR for detection of herpes simplex virus and cryptococcal antigen), blood cultures, and other cultures are pending. Included in the differential diagnosis are noninfectious causes such as toxic effects of calcineurin inhibitors and lymphoma.

#### PNEUMONITIS AND PNEUMOCYSTIS INFECTION

Pneumocystis pneumonia remains common in the absence of specific prophylaxis.<sup>56,100</sup> Pneumocystis pneumonia should be considered in patients in whom marked hypoxemia, dyspnea, and cough develop in spite of a paucity of physical or radiologic findings. No radiographic patterns are pathognomonic in the immunocompromised host. Computed tomographic imaging is useful to define the extent of disease and to direct invasive techniques for microbiologic sampling. Noninfectious processes may contribute to the pathogenesis of pneumonitis; these processes include the toxic

effects of sirolimus, which may be obscured by coinfection.<sup>60</sup>

## CONCLUSIONS

The study of infectious diseases associated with transplantation focuses on the prevention of infection in transplant recipients. The interaction of infection and immunosuppression is the central concern. The induction of immunologic tolerance so that exogenous immunosuppression is avoided in transplant recipients, might, if successful, reduce the risk of infection after transplantation. However, two caveats would remain. First, exposures to infections subsequent to the development of tolerance might abrogate tolerance and induce allograft rejection.<sup>101,102</sup> Second, the induction of tolerance to an allograft might induce immunologic unre-

sponsiveness to latent organisms in that organ.

Techniques currently under development, such as more sensitive microbiologic assays, immunoassays, and genomic and proteomic markers, may provide the potential for individualized immunosuppression and prophylactic strategies (Fig. 3).<sup>103,104</sup> Such assays may ultimately permit a more dynamic assessment of the immune status of transplant recipients over time, allowing titration of immunosuppression and reducing deaths from infection and malignant conditions.<sup>105</sup>

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