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From the classic concepts to modern practice

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Abstract

Transplant infectious disease is a field in evolution. For most allograft recipients, immunosuppressive therapies are more potent and have reduced the incidence of acute allograft rejection. At the same time, these therapies have increased susceptibility to many opportunistic infections and virally-mediated malignancies. Immunological tolerance has been achieved in only small numbers of patients who avoid drug toxicities and infection for as long as tolerance persists. The traditional timeline of post-transplant infections remains useful in the development of a differential diagnosis for patients with infectious syndromes. However, patterns of infection in the post-transplant period have changed over the past decade. Recipients are derived from a broader range of socioeconomic and geographical backgrounds. Infections are diagnosed more often, with improved microbiological assays (e.g. nucleic acid testing, NAT) used routinely in the diagnosis and management of common infections and increasingly in the screening of organ donors. Patterns of opportunistic infection have been altered by the increased identification of organisms demonstrating antimicrobial resistance and by the broader use of strategies to prevent viral, bacterial and fungal (including *Pneumocystis*) infections. Newer techniques are being applied (e.g. HLA-linked tetramer binding, intracellular cytokine staining) to assess pathogen-specific immunity. These are being integrated into clinical practice to assess individual susceptibility to specific infections. Infection, inflammation and the human microbiome are recognized as playing a central role in shaping innate and adaptive immune responses, graft rejection and autoimmunity. The full impact of infection on transplantation is only beginning to be appreciated.

Keywords: organ transplantation, donor-derived infection, viral infection, immunosuppressive therapies, microbiome, nucleic acid test, opportunistic infections, prophylaxis, solid organ transplantation, tolerance

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Hot Topics

- Consider alterations in the timeline for infection with institution-specific strategies for immunosuppression and prophylaxis.
- Evaluate the cost-effectiveness of newer immunosuppressive regimens and laboratory assays.
- In resource-limited regions, which forms of immunosuppression and prophylaxis are cost-effective?
- The impacts of changes in the human microbiome, vaccination and antimicrobial therapies on graft survival are poorly understood. Consider interactions of specific pathogens with the innate and adaptive immune systems on graft function.

General Principles: the Risk of Infection after Transplantation

The diagnosis of infection is more difficult in transplant recipients than in immunologically normal hosts due to the effects of immunosuppression, which obscures the signs and symptoms of infection both acutely (inflammation) and chronically (cellular infiltration) [1–3]. Clinical presentations are

often complicated by non-infectious causes of fever (e.g. graft rejection). Drug toxicities and drug interactions (e.g. azole anti-fungal agents with calcineurin inhibitors) are common. Multiple simultaneous processes are often present (e.g. graft rejection and infection). As a result, specific microbiological and immunological diagnoses are needed to optimize therapy; invasive diagnostic procedures are often needed to achieve timely diagnoses.

One of the general principles of transplant infectious disease is that the *prevention of invasive disease, whether resulting from new exposure or by the activation of existing, latent infection, is easier than the treatment of established disease*. True toxicity of prophylaxis with low-dose antivirals, antifungals or daily trimethoprim-sulphamethoxazole (TMP-SMZ) is uncommon, although commonly misdiagnosed [1]. Toxicity of the treatment of such infections is common and may be life-threatening or cause permanent graft injury. In the absence of assays that allow individualization of immunosuppression after transplantation, prophylactic strategies are based on an assessment of the anticipated risk of infection based on experience (e.g. about 15% incidence of *Pneumocystis* pneumonia in immunosuppressed hosts without prophylaxis) or based on the ability to stratify risk based on serological or microbiological testing, epidemiological history, and the perceived intensity of immunosuppression. Thus, organ recipients who are colonized with VRE or *Aspergillus* or who receive seropositive organs for cytomegalovirus (CMV) or Epstein-Barr virus (EBV) require different prophylaxis and/or monitoring at different phases of the transplant continuum than those who lack such exposures. *The risk of infection is a continuous function of the interplay between these factors.*

Epidemiological exposures

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

Donor-derived infections. Infection is commonly transmitted with donor organs in the form of latent viral infections of the graft (e.g. CMV and EBV), infection or unrecognized colonization of the lungs, unknown bacteraemia or urinary tract infections, or surgical contamination at procurement or preservation. Infected organ donors have been found to transmit bacteria and fungi carrying resistance to routine surgical antimicrobial prophylaxis [4]. In the past few years, unexpected clusters of donor-derived infections in transplant recipients have been recognized, including those due to West Nile virus, lymphocytic choriomeningitis virus (LCMV), rabies, HIV, hepatitis B and hepatitis C viruses, herpes simplex virus, tuberculosis, endemic fungi and Chagas' disease [4–8]. Controversy persists regarding the use of organs from donors with undefined clinical syndromes (e.g. 'altered mental state' or fever), which have had a disproportionate role in the transmission of unusual pathogens associated with central nervous system infection or bacteraemia. This effect is amplified by the shortage of donor organs and the limited time-frame in which microbiological screening must be performed. These observations illustrate the need for new approaches to microbiological screening of donors.

Active or latent infections in transplant recipients should be eradicated or controlled to the greatest degree possible prior to transplantation as these will be exacerbated by immunosuppression [8]. Common recipient-derived pathogens include *M. tuberculosis*, some parasites (*Strongyloides stercoralis* and *T. cruzi)*, viral infections (herpes simplex virus (HSV) or varicella zoster virus (VZV, shingles)), endemic fungi (*Histoplasma capsulatum*, *Coccidioidioides immitis* and *Paracoccidioides braziliensis*), hepatitis B or C or, more recently, HIV. Although previously contraindicated, successful organ transplantation has been achieved in HIV-infected patients treated with highly active antiretroviral therapy (HAART), and in some cases with HIV-infected organ donors [9,10]. Employment, hobbies, travel, pets or marijuana use (*Aspergillus* species) may suggest clinically important exposures.

Net state of immunosuppression

The concept of the 'net state of immunosuppression' comprises all factors that may contribute to the risk of infection (Table 1) [1–3]. The impacts of preexisting disease processes are often underestimated. Renal failure and dialysis are associated with poor responses to bacterial infections and colonization with hospital-acquired flora [11]. Cirrhosis and portal hypertension reduce acute inflammatory responses (specific antibody formation, chemotaxis) and predispose to infection caused by *Cryptococcus* and *Aspergillus* species [12,13]. Lung failure may be associated with bacterial and fungal colonization and poor microbial clearance. These infectious hazards must be added to the post-transplant effects of immunosuppressive therapy (Table 2). The effects of some of

TABLE 1. The 'net state of immune deficiency'

Preexisting immune deficits
Critical illness
Malnutrition
Organ dysfunction (uraemia, cirrhosis, COPD/cystic fibrosis, heart failure)
Diabetes
Colonization with antimicrobial-resistant pathogens, hospitalization
Immunosuppressive therapies (current and past)
Acquired immune deficiencies (e.g. hypogammaglobulinaemia)
Prior therapies (chemotherapy, antimicrobials)
Mucocutaneous barrier integrity (catheters, lines, drains)
Fluid collections (blood, lymph, urine, bile, pus)
Neutropenia, lymphopenia
Viral co-infection (e.g. CMV, EBV, HCV, HBV, HIV)