Hematopoietic stem cell transplantation (HSCT) is a treatment for multiple medical conditions that result in bone marrow failure and as an antineoplastic adoptive immunotherapy for hematologic malignancies. HSCT is associated with profound compromises in host barriers and all arms of innate and acquired immunity. The degree of immune compromise varies by type of transplant and over time. Immune reconstitution occurs within several months after autologous HSCT but takes up to a year or longer after allogeneic HSCT. In those patients who develop chronic graft-versus-host disease, immune reconstitution may take years or may never completely develop. Over time, with strengthening immune reconstitution and control of graft-versus-host disease, the risk for infection dissipates.

Infection in Organ Transplantation: Risk Factors and Evolving Patterns of Infection

Jay A. Fishman and Nicolas C. Issa

The nature of infections after solid-organ transplantation has changed with increasingly potent immunosuppressive regimens, routine use of antimicrobial prophylaxis, and improved microbiologic diagnostic tools. New pathogens have been identified in this population including many with significant antimicrobial resistance. Intensification of immunosuppressive regimens, including the use of T- and B-lymphocyte depleting agents, presents an increased risk for infection and requires linkage to microbiologic monitoring and prophylaxis against opportunistic infections. The effect of these regimens is reflected in the increased recognition of viral and fungal infections beyond 1 year after transplantation. Donor-derived infections represent a challenge to organ transplantation in terms of microbiologic screening of donors and the need for communication among clinical centers, organ procurement organizations, and public health authorities. New approaches to microbiologic assessment of organ donors and recipients are needed. In the future, improved assays for microbiologic and immunologic monitoring will allow individualization of prophylactic strategies to reduce the risk of infection in this highly susceptible population.

Infectious Complications Associated with Immunomodulating Biologic Agents

Sophia Koo, Francisco M. Marty, and Lindsey R. Baden

The armamentarium of biologic therapies targeting specific elements of the immune system is rapidly expanding. This review describes the spectrum of infectious complications associated to date with each of the immunomodulating biologic therapies approved by the US Food and Drug Administration.
Infections in Pediatric Transplant Recipients: Not Just Small Adults

Marian G. Michaels and Michael Green

Transplantation increasingly is being used as treatment for children with end-stage organ diseases, hematopoietic rescue from therapy used to treat malignancies, and as cure for primary immune deficiencies. This article reviews some of the major concepts regarding infections that complicate pediatric transplantation, highlighting differences in epidemiology, evaluation, treatment and prevention for children compared with adult recipients.

Cytomegalovirus in Hematopoietic Stem Cell Transplant Recipients

Per Ljungman, Morgan Hakki, and Michael Boeckh

This article examines the clinical manifestations of and risk factors for cytomegalovirus (CMV). Prevention of CMV infection and disease are also explored. Antiviral resistance and management of CMV are examined.

Viral Impact on Long-term Kidney Graft Function

Ilkka Helanterä, Adrian Egli, Petri Koskinen, Irmeli Lautenschlager, and Hans H. Hirsch

Acute rejection episodes are an important risk factor for the functional deterioration of solid-organ transplants. With more intense immunosuppressive protocols, the rate of acute rejection episodes has significantly declined in the last decade, but long-term graft function and graft survival are challenged by increasing viral complications. In this article, recent data on the role of adenovirus, polyomavirus BK and JC, cytomegalovirus, human herpesvirus-6 and -7, and parvovirus B19 on the long-term outcome of kidney transplantation are reviewed. An update on the pathophysiology of smoldering viral replication, associated inflammatory damage, and the presumed indirect viral effects is provided, and the implications for diagnostic tests and antiviral intervention are discussed.

Herpes Viruses in Transplant Recipients: HSV, VZV, Human Herpes Viruses, and EBV

Kevin Shiley and Emily Blumberg

The herpes viruses are responsible for a wide range of diseases in patients following transplant, resulting from direct viral effects and indirect effects, including tumor promotion. Effective treatments and prophylaxis exist for the neurotropic herpes viruses HSV-1, HSV-2, varicella zoster virus, and possibly HHV-6. Antivirals seem to be less effective at prevention of the tumor-promoting effects of Epstein-Barr virus and HHV-8. Reduction in immunosuppression is the cornerstone to treatment of many diseases associated with herpes virus infections.

Respiratory Viral Infections in Transplant and Oncology Patients

Deepali Kumar and Atul Humar

Respiratory viral infections are a significant cause of morbidity and mortality in the immunocompromised host. In the last two decades, there has been significant advancement in the epidemiology and laboratory
diagnosis of respiratory viral infections. In addition, the clinical consequences of many respiratory viruses in the immunocompetent and immunocompromised host continue to be studied. Many therapeutics have also now become available, although their efficacy in transplant recipients remains uncertain. This article describes the current knowledge about respiratory viral infections as it relates to solid organ transplant, hematopoietic stem cell transplant, and oncology settings.

**Antiviral Drug Resistance: Mechanisms and Clinical Implications** 413

Lynne Strasfeld and Sunwen Chou

Antiviral drug resistance is an increasing concern in immunocompromised patient populations, where ongoing viral replication and prolonged drug exposure lead to the selection of resistant strains. Rapid diagnosis of resistance can be made by associating characteristic viral mutations with resistance to various drugs as determined by phenotypic assays. Management of drug resistance includes optimization of host factors and drug delivery, selection of alternative therapies based on knowledge of mechanisms of resistance, and the development of new antivirals. This article discusses drug resistance in herpesviruses and hepatitis B.

**Fungal Infections in Transplant and Oncology Patients** 439

Anna K. Person, Dimitrios P. Kontoyiannis, and Barbara D. Alexander

Recent shifts in the epidemiology of invasive fungal infections (IFIs) among transplant and oncology populations have led to new recommendations on treatment; however, they have also brought new controversies. New pharmacologic therapies are being studied and guidelines for management of several IFIs have been changed accordingly. More information is being discovered about unique genetic factors that put some transplant recipients at greater risk than others for fungal infection. The role of immunomodulation continues to be investigated, and the delicate balance of maintaining some immune integrity while assuring protection of the graft remains critical. For transplant and oncology patients, the diagnosis and management of IFIs remain challenging, and improving outcomes depends on continued progress in all of these arenas. This article highlights recent advances and important factors to consider when treating transplant and oncology patients with IFIs.

**Parasitic Infections in Solid Organ Transplant Recipients** 461

Patricia Muñoz, Maricela Valerio, Daniel Puga, and Emilio Bouza

Parasitic infections are an uncommon but potentially severe complication in solid organ transplant (SOT) recipients. An increase in donors who have emigrated from tropical areas and more transplant recipients traveling to endemic areas have led to a rise in parasitic infections reported among SOT recipients. Clinicians should include these infections in their differential diagnosis and promote adherence to preventive measures in SOT recipients.
## Contents

### Infections Transmitted by Transplantation
Michele I. Morris, Staci A. Fischer, and Michael G. Ison

Infections are frequently transmitted through solid-organ and, to a lesser extent, stem cell transplantation. There are 2 major types of donor-derived infections that are transmitted: those that would be expected secondary to donor and recipient screening (ie, transmission of cytomegalovirus, Epstein-Barr virus, or toxoplasmosis from a seropositive donor to a seronegative recipient) and those that are unexpected despite routine donor screening (ie, human immunodeficiency virus and hepatitis C virus transmitted from a seronegative donor). Expected transmissions occur frequently and screening and prophylaxis strategies are applied to at-risk individuals in nearly all transplant centers globally. Several high profile donor-derived infectious disease transmissions have been recognized; these reports have raised awareness of this rare complication of transplantation. Issues related to the epidemiology of, screening for, and management of proven or probable donor-derived infections are reviewed in this article.

### Immunotherapy and Vaccination After Transplant: The Present, the Future
Vincent C. Emery, Hermann Einsele, Sowsan Atabani, and Tanzina Haque

Vaccination and adoptive immunotherapy for herpes virus infections has become an attractive option for the control of a virus family that negatively affects transplantation. In the future, enhanced ability to select antigen-specific T cells without significant in vitro manipulation should provide new opportunities for refining and enhancing adoptive immunotherapeutic approaches. This article focuses on advances in the area of vaccinology for some of these infections and in the use of adoptive immunotherapy. At present, many of these approaches in transplant recipients have focused on infections such as human cytomegalovirus, but the opportunity to use these examples as proof of concept for other infections is discussed.

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