CORE CURRICULUM IN NEPHROLOGY

Infectious Disease Following Kidney Transplant: Core Curriculum 2010

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INTRODUCTION

Despite increasingly refined preventive methods, infections remain a major source of morbidity after kidney transplant. Currently, donor screening processes for infection are under review at a national level, and modified recommendations are likely to emerge within the next 2 years. Recent trends in posttransplant management include widespread use of monitoring with quantitative molecular diagnostic assays for cytomegalovirus (CMV), BK polyomavirus (BKV), and sometimes Epstein-Barr virus (EBV) to prevent full-blown viral infections. However, increasingly resistant bacterial strains have arisen, particularly in health care–associated infections; this may complicate even outpatient therapy for urinary tract infection (UTI). Thorough knowledge of the timetable of infection after transplant and the most important infections that are likely to occur is essential for any nephrologist, regardless of whether practicing at a transplant center. Judicious management of immunosuppression can help decrease infection risk. Finally, strategies for decreasing environmental infectious exposures can help a kidney transplant recipient remain healthier in the long term.

More detailed information for all these topics can be found in the guidelines for the prevention and management of infections after solid-organ transplant of the American Society of Transplantation (AST) and guidelines of other societies. The first edition of the AST infectious disease guidelines was published in 2004, and the second edition, including many updates, was published in December 2009.

DONOR AND RECIPIENT SCREENING FOR INFECTION

Types of Pathogens Transmitted by Transplant

- A wide variety of viral, bacterial, fungal, and parasitic pathogens may be transmitted from the donor to the transplant recipient
  - Many, but not all, of these will be detected on traditional serologic screening
  - High-profile viral transmissions in the news in the past several years have included West Nile virus, rabies, lymphocytic choriomeningitis virus (LCM), seronegative human immunodeficiency virus (HIV), and hepatitis C virus (HCV); the first 3 of these frequently have fatal consequences
- Donor screening is undergoing national review by the Disease Transmission Advisory Committee (DTAC) of the United Network for Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN), and additional recommendations for screening may emerge in the near future

Serology Panel for Donors and Recipients

- Classically has included antibody testing for CMV, EBV, HIV, hepatitis B virus (HBV), HCV, human T-cell leukemia/lymphoma virus (HTLV-I/II), herpes simplex virus type 1 and 2 (HSV-1 and HSV-2), and varicella-zoster virus (VZV) and serologic test for syphilis (rapid plasma reagin [RPR]), toxoplasmosis, and sometimes other pathogens (Box 1)
- Other serologic tests may be added at certain centers depending on regionally important infections
  - Chagas disease in Central and South American programs and some areas of the Southwest United States
  - *Strongyloides* species serologic testing is important throughout the tropics; *Strongyloides* immunoglobulin G (IgG)-positive transplant candidates should be treated with ivermectin before transplant

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Box 1. Frequently Used Serologic Tests for Screening of Donors and Recipients Before Transplant

Tests commonly obtained in both donor and recipient
- Human immunodeficiency virus (HIV) antibody (commonly HIV-1 and HIV-2)
- Human T-cell lymphotropic virus (HTLV)-I/II antibody
- HSV (herpes simplex) immunoglobulin G (IgG) antibody (at some centers)
- Cytomegalovirus (CMV) IgG antibody
- Hepatitis C virus (HCV) antibody
- Hepatitis B virus (HBV) surface antigen (HBsAg)
- Hepatitis B core antibody (anti-HBcAg IgM and IgG)
- Hepatitis B surface antibody (anti-HBsAg) at some centers
- Rapid plasma reagin (RPR)
- Toxoplasma antibody (especially in heart recipients)
- Epstein-Barr virus (EBV) antibody panel[a]
- Varicella-zoster virus (VZV) antibody[a]

Other screening measures for infectious diseases
- PPD skin testing (all candidates, preferably with anergy panel)
- *Strongyloides* serologic test, consider use of stool ova and parasites for candidates from endemic areas
- Coccidioides serologic test (for candidates from endemic areas)
- *Trypanosoma cruzi* serologic test (for donors and recipients from endemic areas)

Possible future recommendations for screening
- West Nile virus (note recent recommendation for NAT of live donors)
- HHV-8 (Kaposi sarcoma herpesvirus)
- HHV-6 (in pediatric transplantation)[a]

Abbreviation: NAT, nucleic acid amplification testing.
[a]Particularly important in pediatric transplant candidates who are much more likely to be seronegative.
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to avoid disseminated strongyloidiasis post-transplant, which is a highly fatal complication
  - Coccidioidomycosis is an endemic infection in the Southwest United States, and some centers in that area screen recipients pretransplant and administer long-term antifungal prophylaxis accordingly
  - Histoplasmosis is endemic in the Midwest United States, but screening recommendations have yet to emerge

- Recommended actions based on donor serologic test results (Table 1)
  - Disqualification of donor: HIV positivity, hepatitis B surface antigen (HBsAg) positivity indicating active HBV infection (such donors sometimes are used in hyperendemic areas), and often HTLV-I positivity
  - Other serologic tests may indicate that the donor may be used preferentially for certain subgroups of patients
    - HCV-positive donors are used for HCV-positive recipients at many centers
    - Recent data by Bucci et al suggest that use of HCV-seropositive donors is associated with increased risk of death and new-onset diabetes compared with the use of HCV-seronegative donors; however, use of donor HCV-seropositive kidneys is still associated with better survival than remaining on the waiting list
  - Still other serologic tests help determine post-transplant prophylaxis
    - CMV donor-positive recipient-seronegative (D+/R−) patients may require more extensive prophylaxis for CMV
    - Hepatitis B core-positive donors (HBsAg negative, but positive for antibody to hepatitis B core antigen present a low, but real, risk (~1 in 30-40) of transmission of HBV to nonhepatic organ recipients; this risk can be minimized by effectively vaccinating the recipient before transplant or administering prophylaxis, including hepatitis B immune globulin and/or lamivudine

Increasing Trend Toward Molecular Testing for Donors

- Because of the seronegative HIV and HCV transmissions mentioned, the adequacy of antibody screening tests for these viruses and HBV have been under review
- Molecular testing for HIV, HCV, and HBV increasingly is performed at some organ procurement organizations, most commonly NAT (nucleic acid amplification testing)

Table 1. Interventions Related to Donor Screening Results

Serologic Finding	Action
Antibody to HIV	Exclude from organ donation
Antibody to HTLV I/II	Generally exclude from organ donation (may be used in life-threatening situations, with informed consent)
Antibody to HCV	If used, usually reserve organ for recipient with antibody to HCV or severely ill recipient
Antibody to CMV	Use information to determine prophylaxis (in conjunction with recipient serologic test results)
Antibody to EBV	Consider PCR monitoring if donor seropositive and recipient seronegative
HBsAg+ or IgM against HBcAg	Exclude from organ donation (possible use in life-threatening situations with intensive prophylaxis)
Antibody to HBsAg	Generally safe for organ donation
IgG against HBcAg	High-risk for transmission if liver used for donation, but used at some centers with intensive prophylaxis; nonhepatic organs carry a small risk of transmission of HBV and are used for vaccinated recipients or with prophylaxis
Rapid plasma reagin positive	Not a contraindication to donation; recipient should receive benzathine penicillin
Antibody to *Toxoplasma* species	Not a contraindication to donation; sulfa-allergic seronegative heart transplant recipients with a seropositive donor should receive pyrimethamine prophylaxis

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HBcAg, hepatitis B core antigen; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTLV, human T-cell leukemia/lymphoma virus; IgM, immunoglobulin M; PCR, polymerase chain reaction.

Adapted from the *American Journal of Transplantation* (Chung RT, Feng S, Delmonico FL. Approach to the management of allograft recipients following the detection of hepatitis B virus in the prospective organ donor. *Am J Transplant.* 2001;1:185-191) with permission of Wiley-Blackwell.

  - The purpose of NAT is to detect early viral infections in the "window" period before the development of specific antibodies to that virus
  - Challenges in NAT include the occurrence of false-positive results and the logistics of performing testing in the deceased donor time frame
  - Whether to perform NAT for all donors or a specific subset (eg, Centers for Disease Control and Prevention [CDC]-defined high-risk behavior) is under debate

History of Donor and Recipient

- The history can provide valuable clues that extend beyond serologic tests
  - Donor history obtained from the referring medical center and family may include such information as intravenous (IV) drug use, sexual promiscuity, previous incarceration, animal or bat bites, tuberculosis (TB) exposure, international origin or travel, and other potential exposures to be considered by the center transplanting the organ
  - In addition, culture data from the donor at the donor's hospital should be reviewed carefully; some cultures, eg, donor blood cultures, may not be finalized until after transplant and may require subsequent prophylactic antibiotic therapy in the recipient
- Donors with evidence of unexplained meningitis and/or encephalitis should not be used because of the risk of West Nile virus, rabies, LCM, etc
  - Donors with culture-proven bacterial meningitis may be used with appropriate antibiotic therapy in the recipient
  - Cerebrospinal fluid (CSF) pleocytosis with negative culture results should not be assumed to represent "partially treated bacterial meningitis"
- Recipients' occupations and hobbies may provide clues to post-transplant risk; for example, transplant candidates who are gardeners, landscapers, farmers, construction workers, or marijuana smokers have a higher risk of fungal colonization of the sinuses and airways than the general population and may have a higher risk of invasive fungal infection after transplant

Management of Partially Treated or Latent Infection in the Recipient

- Infections such as dialysis catheter–associated bacteremias, peritoneal dialysis (PD) catheter–associated infections, pneumonias, and complicated UTIs should be fully treated before transplant
- Patients with polycystic kidney disease who present with recurrent fevers should be assessed for occult infection in their native kidneys
- A purified protein derivative (PPD) skin test and/or TB interferon γ release assay (IGRA) should be performed to screen for latent TB infection
  - At many centers, isoniazid (INH) prophylaxis is initiated for a total of 9-12 months for transplant candidates who have a positive test result for latent TB infection, but have not received previous prophylaxis
  - Liver function tests should be performed at least monthly in patients on INH prophylaxis therapy
  - Although practice varies among centers, it is desirable to complete, for example, at least 2 months of INH treatment before transplant, whereas the course can be completed posttransplant
  - This is important because of the severity of reactivated TB after transplant and the high rate of disseminated infection, transplant loss, and mortality should overt TB infection occur

Pretransplant Immunizations in the Recipient

- The pretransplant screen is an excellent time to survey and update the patient's immunization status because vaccines generally work better before transplant and live vaccines are not administered after transplant
- Pediatric candidates should complete standard vaccine series to the extent possible before transplant
- Adult candidates should receive the following nonlive vaccines
  - Yearly injected influenza vaccine (both seasonal and H1N1 influenza)
  - Pneumococcal polysaccharide vaccine (PPV-23) if not given within 5 years
  - Hepatitis A and HBV vaccine series if seronegative
  - Td (tetanus-diphtheria vaccine) or Tdap (tetanus-diphtheria-acellular pertussis vaccine) if no tetanus vaccine given within the last 10 years
- Enhanced-potency (dialysis formulation) or additional booster doses of HBV vaccine may be used, particularly if the candidate fails to become positive for antibodies to HBsAg
- Varicella vaccine should be given to the candidate before transplant if seronegative for VZV (and if transplant is not anticipated within the next 3-4 weeks because VZV vaccine is live)
  - Primary varicella acquired after transplant can be extremely severe
  - Data from a large French pediatric study support the use of pretransplant VZV vaccination in decreasing the risk of primary varicella and also zoster reactivation post-transplant
  - The zoster vaccine can be administered to transplant candidates aged > 60 years only if they are not on immunosuppressive therapy and transplant is not anticipated within 3-4 weeks
    - The value of pretransplant zoster vaccine in preventing post-transplant zoster reactivation (shingles) is not yet known
- Human papillomavirus (HPV) vaccine is not live and should be administered to female transplant candidates aged 9-26 years if they have not yet been vaccinated
  - If the patient already has HPV, the vaccine may help prevent acquisition of additional strains of HPV
  - Some clinicians have proposed that HPV vaccine also may be useful in older females and in males because of the morbidity of HPV-associated carcinogenesis, but more data are needed

SUGGESTED READING

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POSTTRANSPLANT COMPLICATIONS: GENERAL CONSIDERATIONS

Intensified Immunosuppression and Risk of Infections

- The "net state of immunosuppression" is one of the determinants of infection risk after transplant
- When acute rejection is treated using high-dose steroids or particularly when steroid-resistant rejection is treated using antilymphocyte therapies, such as thymoglobulin or the monoclonal anti-CD52 antibody alemtuzumab, risk of infections increases for the next several months; this is particularly true for CMV, BKV, and EBV infection; however, bacterial, fungal, and parasitic infections also may occur
- Administration of ganciclovir derivatives during and for 2-3 months after antilymphocyte therapy for rejection can decrease the risk of CMV and EBV reactivation; resumption of CMV and/or EBV DNA monitoring can help detect such reactivation early
- The risk of bacterial and fungal infections after intensified immunosuppression is managed best by careful observation, minimization of environmental exposures, and early evaluation and treatment if symptoms occur

Molecular and Antigen-Based Diagnostic Testing

- Molecular diagnostic testing is useful in the posttransplant period and in some pretransplant screening situations
  - Most tests of this nature provide a quantitative viral load measured using one of a variety of sensitive methods, such as polymerase chain reaction (PCR), giving an opportunity for regular monitoring and pre-emptive antiviral therapy
- This strategy is used most often for early detection and treatment of CMV and BKV infection, but also may be used for EBV and, in some cases, other pathogens
- The magnitude of the viral load can dictate the aggressiveness of therapy, and the rapidity of its decrease can help determine the duration of therapy and need for secondary prophylaxis after completion of therapy
- The magnitude of the viral load in the case of CMV also can be a predictor of risk of ganciclovir resistance
- Molecular testing can be more helpful than IgG and IgM serologic tests for the diagnosis of active infection (eg, parvovirus, for which most adults are IgG positive and an IgM response may not be mounted; blood PCR and/or bone marrow examination may be the best way to make the diagnosis)
- Antibodies to the following fungal pathogens often are less useful for the diagnosis of active infection than antigen testing:
  - Cryptococcal antigen in blood or CSF
  - *Aspergillus galactomannan* antigen in blood or bronchoalveolar lavage (BAL) fluid
  - *Histoplasma* species urinary antigen testing

General Approach to Treatment Strategies

- If a specific pathogen is identified, antimicrobial therapy should be tailored to this pathogen; antimicrobial susceptibilities should be obtained for all bacterial isolates if possible because antimicrobial resistance is increasingly common
- In a critically ill patient, initial therapy should be broad spectrum, but can be narrowed down within 48-72 hours depending on the initial culture results and clinical course
- Agents such as aminoglycosides, amphotericin B, and other nephrotoxins should be avoided if other equally effective alternative agents are available

  - Exceptions may occur in the setting of multidrug-resistant bacteria, such as carbapenem-resistant *Klebsiella pneumoniae*, for example, which may be susceptible to only IV colistin

- Drug levels should be measured when these are available (vancomycin, aminoglycosides, flucytosine, voriconazole, and leflunomide) and doses should be adjusted appropriately
- If possible to decrease immunosuppression during an acute infection, this often will help resolve this infection
  - Examples include a decrease in mycophenolate mofetil (MMF) or steroid dose or targeting a lower level of tacrolimus or cyclosporine
- For some patients with recurrent infections, longer term decreases in immunosuppression may be considered to prevent recurrences if such a decrease can be accomplished without precipitating rejection
- In a transplant recipient who is neutropenic and has fever or other signs or symptoms of infection, filgrastim (granulocyte colony-stimulating factor [G-CSF]) should be administered to increase the neutrophil count; several studies have shown no increased risk of rejection from filgrastim
- In a leukopenic transplant recipient with signs or symptoms of infection, consideration should be given to decreasing or temporarily discontinuing other medications that can cause leukopenia (eg, azathioprine, MMF, and valganciclovir)
  - Administration of filgrastim may be necessary for some patients to remain on ganciclovir derivative therapy long enough to clear an episode of CMV viremia (discussed later)
- A separate section in this article is dedicated to drug interactions between antimicrobial agents and immunosuppressive agents

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➢ Turgeon N, Fishman JA, Basgoz N, et al. Effect of oral acyclovir or ganciclovir therapy after preemptive intravenous ganciclovir therapy to prevent cytomegalovirus disease in cytomegalovirus seropositive kidney and liver transplant recipients receiving antilymphocyte therapy. *Transplantation*. 1998;66:1780-1786.

POSTTRANSPLANT COMPLICATIONS: THE FIRST 6 MONTHS

The Paradigm of 3 Time Periods

- Originally articulated by Robert Rubin > 2 decades ago, this paradigm (shown in Fig 1) remains valid with some modifications today
- Briefly, the first month posttransplant includes largely postsurgical infectious complications
- The second period (months 2-6) involves the opportunistic infections traditionally associated with transplant, such as CMV infection
- In the third period (>6 months), patients are in 3 risk groups
  - The first group has done well with transplant function; immunosuppressive doses are tapered and risk of opportunistic infections is low

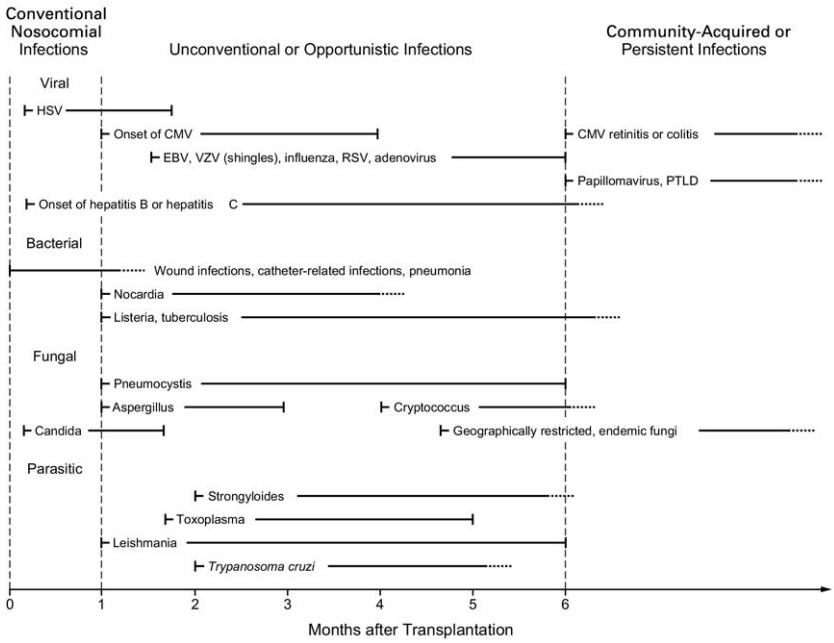

Figure 1. Timeline of usual appearance of infections after kidney transplant. Solid lines indicate the most common period for the onset of infection; dashed lines denote periods of ongoing, but lesser, risk. Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HSV, herpes simplex virus; PTLD, post-transplant lymphoproliferative disease; RSV, respiratory syncytial virus; VZV, varicella-zoster virus. Reprinted from the *New England Journal of Medicine* (Fishman JA, Rubin RH. Infection in organ-transplant recipients. *N Engl J Med.* 1998;338(24):1741-1751) with permission of Massachusetts Medical Society.

- The second group has had considerable rejection and/or intensive immunosuppression and transplant dysfunction; this group remains susceptible to the opportunistic infections seen in the second period
- The third group is subject to late progressive viral reactivations, such as BKV, late CMV, HBV and HCV, and HPV

Postoperative Complications and Health Care–Associated Infections

- During the first month, although immunosuppressive medications are given at high doses, opportunistic infections, such as CMV and *Pneumocystis jiroveci* (formerly *carinii*) pneumonia (PCP), generally are not seen yet
- HSV reactivation (oral, esophageal, and perineal) may occur and antiviral prophylaxis usually is given (in the form of acyclovir or its derivatives if the donor and recipient are both CMV seronegative)
- Oral candidiasis is common and prophylaxis with nystatin or clotrimazole usually is given; urinary tract candidiasis also is common and some centers give systemic prophylaxis, eg, fluconazole
- The most common infections during this period are postsurgical: urinary tract, wound or surgical site, IV catheter related, and pulmonary
- Multidrug-resistant bacteria including strains of *Acinetobacter*, *Klebsiella*, and *Pseudomonas*, as well as methicillin-resistant *Staphylococcus epidermidis* and VRE (vancomycin-resistant enterococcus) are increasingly problematic, especially in patients with long posttransplant intensive care unit (ICU) stays
- Technical complications, such as hematomas, urinary leaks, and lymphoceles, can provide the backdrop for the development of infected fluid collections

Cytomegalovirus

Clinical Presentation and Risk Factors

- CMV may occur through donor-derived transmission, reactivation of latent infection in a seropositive recipient, or less commonly from transfusions or community acquisition in a seronegative recipient
- Approximately two-thirds to three-quarters of adults are seropositive for CMV; children are more likely to be CMV seronegative at the time of transplant
- The highest risk group is the D+/R– serosubgroup

  - In these patients, CMV frequently is transmitted with the donor organ, but the recipient does not have antecedent immunity
  - These patients are more at risk of developing high viral loads, tissue-invasive disease, recurrences, and ganciclovir resistance than other serosubgroups
- CMV-seropositive recipients also can develop symptomatic CMV disease, particularly in the setting of recent rejection or intensification of immunosuppression
- CMV can cause
  - Asymptomatic viremia (usually low-level CMV DNA in blood)
  - Flulike symptoms known as "CMV syndrome" (usually moderately increased viral load)
  - Tissue-invasive disease (in which biopsy specimens show CMV inclusions in the affected organ, including pneumonitis, hepatitis, gastritis, colitis, esophagitis, etc)
- In contrast to patients with AIDS, CMV retinitis is uncommon in transplant recipients and, if it occurs, is often late in the course after several CMV recurrences
- CMV D−/R− patients should receive only CMV-free blood transfusions

Preventive Strategies

- Prophylactic therapy refers to administration of antiviral therapy (valganciclovir, ganciclovir, or valacyclovir) to all individuals at risk of CMV
- Pre-emptive therapy refers to selective administration of antiviral therapy to only those who develop evidence of CMV viremia on a sensitive early detection test (CMV PCR, antigenemia, etc)
- The value of prophylaxis has been validated in numerous studies and meta-analyses, not only for preventing direct CMV complications, but also indirect effects of CMV, such as risk of other opportunistic infections and, in some studies, acute rejection
- Proponents of pre-emptive therapy cite the value of less cost and toxicity, less resistance, and more opportunity to develop CMV-specific immunity
- Some centers use a combination of both strategies: prophylaxis because of its demonstrated benefits and pre-emptive monitoring to detect and treat "late CMV" after prophylaxis before it becomes overt

Therapy

- Therapy for established CMV viremia traditionally was with IV ganciclovir, but this can be cumbersome, particularly in patients with multiple recurrences
- The VICTOR (A Study of Valganciclovir po Compared to Ganciclovir IV in Patients With CMV Disease Who Are Solid Organ Transplant Recipients) study established the validity of treating many patients with oral valganciclovir; however, severely ill patients or those unable to tolerate oral medications should still be treated with IV ganciclovir
- Duration of therapy traditionally was 2-3 weeks for uncomplicated viremia and 4-6 weeks for tissue-invasive disease
  - The VICTOR study showed that a substantial subset of patients do not clear viremia by 3 weeks
  - Continuation of therapy until CMV blood viral load is undetectable is important
- For ganciclovir-resistant CMV, treatment with foscarnet, combination ganciclovir-foscarnet, or cidofovir may be initiated
  - Leflunomide, a rheumatoid arthritis drug with anti-CMV and BKV activity, has been used in some patients with refractory CMV syndromes
  - Maribavir, an investigational drug, is promising, but not currently available for compassionate use

EBV/Posttransplant Lymphoproliferative Disorder

- Approximately 90% of adults, but fewer children, are seropositive for EBV
- EBV D+/R− status leads to high risk of the recipient developing primary EBV infection; in addition, EBV may reactivate in EBV+ patients, particularly if receiving intensified immunosuppression, eg, antilym-

phocyte therapy for steroid-refractory rejection
- If EBV replication is unchecked, a lymphoproliferative process may ensue that initially is polyclonal but may progress to a monoclonal B-cell lymphoma
- Treatment for posttransplant lymphoproliferative disorder (PTLD) and/or high EBV viral loads includes a decrease in immunosuppression and sometimes rituximab and/or combination chemotherapy after the development of lymphoma
  - Rituximab has greatly improved the prognosis for PTLD
- EBV DNA quantitative PCR monitoring may be useful in detecting increases in EBV level early in patients at highest risk

Other Herpesviruses

- As mentioned, HSV can reactivate in the early posttransplant period, causing oral, esophageal, or perineal ulcerations
- VZV can reactivate and cause localized zoster or, in a highly immunosuppressed patient, disseminated zoster including hepatitis, meningoencephalitis, and/or pneumonitis
- HHV-6 and 7 are the viruses that cause roseola in infants
  - These can reactivate after transplant, often earlier than CMV, and cause cytopenia, fever, pneumonitis, hepatitis, and/or meningoencephalitis
  - The test of choice is PCR because $> 90\%$ of adults are seropositive

Early Reactivation of Hepatitis Viruses

- In patients with antecedent HBV or HCV before kidney transplant, reactivation of these viruses can occur under the influence of transplant immunosuppression
  - This reactivation can occur during the second period or sometimes years later
  - Careful pretransplant screening by a hepatologist and ongoing management is important
- In patients who acquire HBV or HCV from the donor, development of active disease may be clinically overt and rapid or may be more indolent
  - Cirrhosis occurs eventually in some, but not all, patients
  - Antibody seroconversion may not occur, and patients at risk of donor-derived transmission should be followed up with HCV RNA or HBV DNA assays
- With the advent of newer treatments for HBV, transplant of an HBsAg+ patient is safer now than in past eras; careful pretransplant screening by a hepatologist is important
- All pretransplant candidates should be effectively vaccinated against HBV if at all possible; there is no vaccine for HCV

Parvovirus B19

- Parvovirus B19 is the cause of a mild childhood infection, "fifth disease," with a low-grade fever and "slapped-cheek" rash in a healthy child
- When transplant recipients acquire parvovirus infection, the major manifestation is anemia, which may be severe
- Blood PCR for parvovirus and/or bone marrow biopsy are the best ways to make this diagnosis; many adults are seropositive for parvovirus IgG
- Treatment of active parvovirus infection is with IV immunoglobulin (IVIG)

Community-Acquired Respiratory Viruses

- Influenza (including novel H1N1), parainfluenza, respiratory syncytial virus (RSV), and adenovirus can cause both upper and lower respiratory tract infection
- Patients with lower respiratory tract infection may develop hypoxemia leading to ICU transfer and intubation, with diffuse bilateral infiltrates on chest x-ray; secondary bacterial pneumonias are common
- Antiviral therapy for influenza has included oseltamivir, zanamivir, amantadine, and rimantadine; however, widespread resistance has complicated treatment in recent years
- Inhaled ribavirin therapy may be used for severe RSV infection, although it is not used universally

- No specific antiviral therapy is available for parainfluenza virus
- Adenovirus infection has been treated with cidofovir in case series, but cidofovir is nephrotoxic
- Yearly influenza vaccination with the injected (nonlive) vaccine is important, although it may produce suboptimal antibody levels in transplant recipients
  - Novel H1N1 injected vaccine, if available, also is recommended for all transplant recipients
  - Guidance from the Transplantation Society and AST concerning novel H1N1 influenza can be found in the suggested readings
- Family members and health care workers should be vaccinated for both seasonal influenza and novel H1N1
  - If injected vaccine is available, it is preferred, but if only the live attenuated nasal vaccine is available, it can and should be administered to family members and health care workers (see Section Xf of the aforementioned guidance)
  - Health care workers who have fevers, chills, myalgias, or symptoms of respiratory infection should refrain from caring for transplant patients or should wear a mask and minimize contact if absolutely necessary that they provide this care
- Influenza postexposure prophylaxis should follow current CDC recommendations because the landscape of antiviral resistance is rapidly changing (see suggested readings)
- Infection control precautions should be observed according to the CDC's 2007 Guidelines for Isolation (see suggested readings)

Pulmonary Infections

Pneumocystis *Pneumonia*

- PCP remains a risk
  - Particularly significant within the first 6 months, but also longer-term for patients who have received intensive immunosuppression
  - PCP causes debilitation and long-term pulmonary dysfunction and is best avoided altogether
- The traditional prophylaxis, trimethoprim-sulfamethoxazole (TMP/SMX), also provides prophylactic activity against *Toxoplasma*, *Nocardia*, and *Listeria* species and a variety of respiratory and urinary tract pathogens, although resistance to TMP/SMX in urinary tract pathogens is becoming widespread
- Sulfa-allergic patients can receive aerosolized pentamidine monthly or take oral dapsone or atovaquone for PCP prophylaxis

Pneumococcal Pneumonia, Legionellosis, Nocardiosis

- Kidney transplant recipients are at higher risk of both community-acquired pathogens and more unusual pulmonary pathogens than the general population
- Pneumococcal pneumonia and other invasive pneumococcal infections are a threat to kidney recipients
  - Pneumococcal vaccine should be administered if not given within 5 years
  - Although more effective when given pretransplant, the vaccine can be administered safely to post-transplant patients
- Legionellosis may cause severe rapidly progressive multilobar pneumonias in immunocompromised patients
  - Hospital water supplies, including shower heads, may be the source, and infection control committees must investigate any outbreaks thoroughly
  - Some diagnostics, such as the *Legionella* urinary antigen, often detect only *Legionella pneumophila*; thus, clinicians should be alert to the possibility of other *Legionella* species
- Nocardiosis can cause cavitary nodular lesions with associated infiltrate
  - *Nocardia* species are found in the outdoor environment, and patients with extensive outdoor exposures, as well as those not receiving sulfa-based prophylaxis, may be at higher risk

- Chronic nonresolving pneumonias in which sputum cultures and empirical therapy have been unrevealing should prompt consideration of bronchoscopy and BAL cultures, particularly when nodular infiltrates are present that may suggest fungal, mycobacterial, or nocardial infection

Clostridium difficile-Associated Diarrhea

- Since 2005, an epidemic strain of *Clostridium difficile*–associated diarrhea (CDAD) has appeared in many hospitals that appears to be more transmissible and more highly associated with severe disease than previous strains
- Patients frequently present with copious diarrhea $\geq$ 10 times daily, but occasionally have only mild diarrhea
- Leukocytosis, fever, abdominal distention and pain, and ileus are adverse prognostic factors; in the setting of abdominal distention, kidneys, ureter, bladder (KUB) radiograph may show a dilated colon and may lead to colectomy to prevent rupture
- Treatment of CDAD traditionally involved a decrease in other antibiotics and treatment with oral metronidazole or oral vancomycin
  - For severe disease, oral vancomycin may be more effective, but also is more costly
  - IV metronidazole may be needed when ileus is present because IV vancomycin does not penetrate the intestinal lumen
  - Adjunctive therapy with vancomycin enemas, *Lactobacillus* species, and IVIG has been advocated by some clinicians for refractory cases
- Recurrences are common because *C difficile* is a spore-forming bacterium
  - Antibiotic therapy kills only replicating bacteria
  - Some clinicians advocate longer tapering courses of oral vancomycin and/or lengthy courses of *Lactobacillus* to prevent recurrences
  - Preliminary evidence indicates that *Lactobacillus* is safe in this population and may help prevent recurrences

Urinary Tract Infections

- UTIs are common in kidney transplant recipients; although these may be uncomplicated bladder infections, rapid progression to involve the transplant (transplant pyelonephritis) is common and may be accompanied by bacteremia, high fevers, and overt sepsis
- Recurrent infections may occur with either the same organism or multiple different organisms; the presence of foreign bodies, such as stents, in the urinary tract may provide a nidus for persistence
- Traditionally, quinolones, such as ciprofloxacin, were used widely for UTI therapy, but antimicrobial susceptibility patterns are changing with alarming rapidity
  - Increasingly, Gram-negative organisms such as *Escherichia coli*, *Klebsiella* species, *Pseudomonas* species, and others may be resistant to quinolones, as well as TMP/SMX, amoxicillin-clavulanate, and cephalexin
  - Oral options may be limited or nonexistent, and courses of home IV therapy are becoming more common, even for less symptomatic UTIs

Foodborne Infections

- Kidney transplant recipients potentially can develop severe disease from foodborne pathogens
  - *Listeria* species can cause bacteremia and meningitis and may be transmitted by nonpasteurized dairy foods, such as soft cheeses, and also turkey franks, hot dogs, deli meats, and a variety of other foods
  - Salmonellosis in a transplant recipient is more likely to be bacteremic and involve metastatic seeding of organs outside the gastrointestinal tract
  - Hepatitis A may be fulminant
- Reinforcement of food precautions (discussed later) is important

Fungal Infections

Candidiasis

- Candidiasis of the oropharynx and urinary tract is very common shortly after transplant
- Occasionally, candidal peritransplant abscesses may occur, but these are more common in liver and pancreas transplant recipients

- Fluconazole resistance is increasing, particularly with *Candida glabrata*, and may require other agents, such as echinocandins

Histoplasmosis, Coccidioidomycosis, Cryptococcosis

- Geographically endemic mycoses, such as histoplasmosis (Midwest) and coccidioidomycosis (Southwest United States), may reactivate after transplant, sometimes years later
  - Old calcified granulomata and hilar lymph nodes may give clues to the presence of latent infections of this type (or mycobacterial)
  - For histoplasmosis, the urinary antigen test is more useful than an antibody panel for detection of reactivation posttransplant; however, tissue culture and histopathologic examination are central to diagnosis
- Cryptococcosis is associated with birds and bird droppings, including pigeons and pet birds
  - Cryptococcosis can cause meningitis, nodular pulmonary infiltrates, and occasionally skin and soft-tissue infection
  - Serum or CSF cryptococcal antigen is a useful diagnostic test

Aspergillosis and Other Mold Infections

- Aspergillosis traditionally was the most common and most feared of mold infections, frequently occurring in the lungs and sinuses, but progressing to orbits, brain, and widespread dissemination in some cases
- Gardening, farming, marijuana smoking, and other outdoor and plant exposures are risk factors, as well as posttransplant neutropenia and intensive immunosuppression
- Hospital or domiciliary construction exposures may be the source of mold infections
- In recent years, emergence of non-*Aspergillus* mold infections, such as *Scedosporium/Pseudallescheria* species, has been noted; some of these emerging fungal infections are less sensitive to traditional antifungals
- Standard amphotericin therapy is used infrequently in this population because of nephrotoxicity; liposomal formulations of amphotericin are less nephrotoxic but not non-nephrotoxic and require an indwelling IV catheter
- Newer antifungals, such as voriconazole and posaconazole, are highly active against many fungal pathogens, but are costly and have potential side effects, as well as interaction with calcineurin inhibitors (CNIs); the value of combination therapy is being explored (eg, a newer azole plus an echinocandin for invasive aspergillosis)

TB and Nontuberculous Mycobacteria

- TB remains a threat in many countries worldwide in which transplant is performed
  - The tuberculin skin test is incompletely predictive of risk
  - IGRA may be helpful when patients have received BCG vaccination
- Reactivation of TB posttransplant carries a high risk of extrapulmonary disease and dissemination
  - Even if the patient recovers, there is a significant risk of rejection because of the interaction between rifampin and CNIs
  - Some centers have used rifampin-free regimens
- Nontuberculous mycobacteria, particularly *Mycobacterium avium* (MAI) and rapid-growers (*Mycobacterium fortuitum, Mycobacterium chelonae,* and *Mycobacterium abscessus*), may cause chronic cavitary pulmonary nodular infections; the rapid growers also may cause surgical site infections, particularly in the Southeast United States

Parasitic Infections

- *Strongyloides* is a parasite that can persist for decades in the intestinal system because of an autoinfection cycle
  - Under the influence of immunosuppression, *Strongyloides* hyperinfection and disseminated infection can occur, with Gram-negative bacteremias, pneumonitis, and meningitis caused by the migration of parasites carrying Gram-negative bacteremia with them

- This complication is highly fatal, and it is best to detect and eradicate *Strongyloides* species pretransplant when possible

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POSTTRANSPLANT COMPLICATIONS: LONG TERM

BK Polyomavirus

- BKV is a member of the polyomavirus family, along with JC virus and simian virus 40 (SV40); it has a predilection for cells of the urinary tract
- BKV causes an asymptomatic chronically progressive interstitial nephritis in the transplant, ultimately resulting in transplant dysfunction and fibrosis; ureteral stenosis may occur
  - Less commonly, JC virus can cause similar findings
- Biopsy specimens from transplants affected by BKV allograft nephropathy (BKVAN) may show characteristic cellular changes or look more like rejection
  - BKV in situ hybridization can help confirm the diagnosis, but false negative results may occur
- Transplant loss caused by BKVAN occurred in as many as 4%-8% of all recipients until the advent of screening programs, which have significantly decreased transplant loss through early detection
- Screening can be with BKV DNA on blood or urine or urine decoy cells (cytology)
- When BKV is detected at greater than a threshold (eg, 10,000 copies/mL in blood), immunosuppression is decreased as a first step; the development of BKV-specific cellular immunity appears to be crucial to control of this infection
- Many patients are able to clear initial BKV viremia with a decrease in immunosuppression, but for those with continued high or increasing viral loads, treatment with leflunomide, cidofovir, IVIG, ciprofloxacin, or combinations thereof may be initiated
- BKV therapy may take a long time to work, but unless transplant dysfunction is already extensive, clinicians should not give up and should continue to modify treatment in an attempt to decrease viral load and protect the function of the allograft

Hepatitis Viruses: Late Progressive Disease

- As mentioned, HBV or HCV, either preexisting in the recipient or acquired at the time of transplant, may gradually progress to cirrhosis in the late posttransplant period
- However, patients $>$ 20 years from transplant with functioning transplants may have

detectable HBV and HCV viral loads without evidence of liver dysfunction

Late CMV

- Late CMV may occur shortly after discontinuation of prophylaxis or, more rarely, years after transplant
- Some centers have added pre-emptive monitoring after prophylaxis to detect late CMV and treat it rapidly
- Retinitis is more common in late presentations than in those who develop CMV in the first few months posttransplant
- Secondary prophylaxis with suppressive courses of valganciclovir may help prevent recurrences

Human Papillomavirus

- HPV high-risk types are associated with cervical and anal neoplasia, as well as skin cancers
- Adherence to screening Papanicolaiou smears and skin examinations is important
- The value of pretransplant HPV vaccination in preventing these posttransplant complications is being investigated

Hypogammaglobulinemia

- Posttransplant hypogammaglobulinemia can occur from 6 months to $>$ 20 years posttransplant and may confer increased risk of a variety of infections
- A decrease in B-cell–active immunosuppression (particularly azathioprine or MMF) and/or IVIG administration may help decrease infection risk

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DRUG INTERACTIONS BETWEEN ANTIMICROBIALS AND IMMUNOSUPPRESSIVE AGENTS

A summary of drug-drug interactions between antimicrobial and immunosuppressive agents is provided in Table 2.

Agents That Affect CNI and Sirolimus Levels

- Agents causing increased CNI/sirolimus (SRL) levels
  - Azole antifungal agents (ketoconazole, fluconazole, itraconazole, voriconazole, and posaconazole) are active at the cytochrome P450 site and increase CNI and SRL levels
    - These agents can be used; however, when one of these agents is started, the transplant team should be informed and should monitor levels closely, with or without a pre-emptive decrease in CNI or SRL doses
    - Conversely, when the medication is stopped, CNI and SRL levels will decrease and appropriate adjustments should be made
  - Macrolide antibiotics (particularly erythromycin and clarithromycin) increase CNI and SRL levels
    - Azithromycin is the preferred agent because its interaction with these agents is minimal and generally does not require dose readjustment

Agents That Decrease CNI and SRL Levels

- Rifampin dramatically decreases these drug levels and can lead to rejection because of difficulty maintaining therapeutic levels
- Rifampin is best avoided unless needed for combination treatment of life-threatening staphylococcal infection or active TB (for the latter, rifampin-sparing regimens have been described)

Table 2. Drug-Drug Interactions Between Antimicrobial and Immunosuppressive Agents[g]

Anti-infective Drug	Immunosuppressant[a]	Interaction	Severity or Toxicity[b]	Weight[c]
Fluoroquinolones				
Ofloxacin	CsA	Increases CsA	2	B
Ciprofloxacin	CsA	Increases CsA	3	B
Levofloxacin	CsA	None		A
Gatifloxacin[d]	CsA, Tac, SRL	None		B
Moxifloxacin[d]	CsA, Tac, SRL	None		B
Macrolides				
Erythromycin[e]	CsA, Tac, SRL	Increases CsA, Tac, SRL	1	A
Clarithromycin[e]	CsA, Tac	Increases CsA, Tac	1	A
Azithromycin[f]	CsA	Possible increase CsA	3	C
Dirithromycin	CsA	Possible increase CsA	3	C
Aminoglycosides				
Gentamicin[e]	CsA, Tac	Nephrotoxicity	1	B
Tobramycin[e]	CsA, Tac	Nephrotoxicity	1	B
Amikacin[e]	CsA, Tac	Nephrotoxicity	1	B
Sulfonamides[f]	CsA	Decreases CsA; increases nephrotoxicity	2	B
Other antibacterial				
Nafcillin	CsA	Decreases CsA; increases nephrotoxicity	2	C
Rifampin[eh]	CsA, Tac, everolimus	Decreases CsA, Tac, everolimus	1	A
Quinupristin/dalfopristin[i]	CsA	Increases CsA	2	B
Linezolid	Azathioprine	Bone marrow suppression	2	C
Chloramphenicol[j]	CsA, Tac	Increases CsA, Tac	2	B
Prophylactic drugs				
TMP/SMZ[g]	CsA	Increased nephrotoxicity	2	A
Atovaquone	Azathioprine	Bone marrow suppression	2	B
Atovaquone	CsA	None		A
Dapsone	Tac	Increases Tac	3	C
Antifungal agents				
Amphotericin B[e]	CsA, Tac	Nephrotoxicity	1	A
Liposomal amphotericin[e]	CsA, Tac	Nephrotoxicity	1	A
Caspofungin[k]	CsA	CsA increases caspofungin hepatotoxicity	3	C
	Tac	Decreased tacrolimus	2	C

(Continued)

Table 2 (Cont'd). Drug-Drug Interactions Between Antimicrobial and Immunosuppressive Agents[g]

Anti-infective Drug	Immunosuppressant[a]	Interaction	Severity or Toxicity[b]	Weight[c]
Ketoconazole[el]	CsA, Tac, SRL	Increased CsA, Tac, SRL[k]	1	A
Itraconazole	CsA, Tac, SRL	Increased CsA, Tac, SRL	2	A
Voriconazole[em]	CsA, Tac, SRL	Increased CsA, Tac, SRL[l]	1	A

Note: Drugs with minimal or no interactions include penicillins, beta lactams, tetracyclines, isoniazid, ethambutol, and pyrazinamide. Unusual situations or minimal data: the antimalarial drugs chloroquine, mefloquine, and quinidine may inhibit Tac metabolism. Tac levels should be monitored during treatment or prophylaxis with chloroquine or mefloquine before travel to malaria endemic regions. Antiretroviral drugs are not included here.

Abbreviations: AUC, area under the curve; CsA, cyclosporine A; CYP3A4, cytochrome P-450 enzyme 3A4; SRL, sirolimus; Tac, tacrolimus; TMP/SMZ, trimethoprim-sulfamethoxazole.

[a]Fewer data are available for interactions of anti-infectives with Tac, SRL, or everolimus compared with CsA. However, all 3 drugs are metabolized by CYP3A4, and when studies have been performed, agents that have significant effects on the metabolism of CsA by CYP3A4 show similar or greater effects on Tac and SRL.

[b]Severity graded: 1 = severe interaction; use alternative drug if possible, otherwise monitor levels of immunosuppressant or potential toxic effects and modify dose accordingly; 2 = moderate interaction, requires monitoring levels or potential toxicity and may require modification of immunosuppressant dosing; and 3 = minor interaction or does not have major toxicity.

[c]Weight of evidence: A = very good evidence, such as clinical trial, pharmacokinetic studies in volunteers or patients, many well-documented case reports, or biochemical evidence confirming interaction; B = good evidence such as several well-documented case reports; and C = anecdotal experience, 1 or 2 case reports.

[d]No patient data reported. Manufacturer's data indicate no interaction with CYP3A4 or other enzymes involved in the metabolism of CsA, Tac, or SRL. Together with clinical data showing no interaction with warfarin, results indicate there should be no significant interaction with these immunosuppressants.

[e]Drugs with significant interactions or toxicities.

[f]Single report. Manufacturer's in vitro studies indicate no interaction between azithromycin and CYP3A4 or related enzymes.

[g]Magnitude of effect appears to differ between family members and is dependent on sulfa dose. Most severe reported for sulfadimidine, less so for sulfisoxazole and others. Monitoring levels of both sulfa and immunosuppressant, particularly with high-dose sulfa therapy, such as that used for *Pneumocystis jiroveci* and *Nocardia* species, is appropriate. Low doses used for prophylactic regimens usually not problematic.

[h]Likely applies to rifabutin and rifapentine. Magnitude of effect may be less for rifabutin. Effect seen with rifampin in 2 days, usually maximal at 1 week. Typically requires substantial increase (≥2-fold) in CsA dose to maintain same levels.

[i]Pharmacokinetic data from manufacturer for 24 healthy individuals show a 63% increase in AUC, 30% increase in time to maximum concentration, 77% increase in half-life, and 34% decrease in CsA clearance.

[j]Transient decrease followed by 50% increase in CsA levels. Tac levels increased rapidly to 200% of baseline by day 5-6 of chloramphenicol therapy.

[k]Manufacturer's data and Sable CA, Nguyen BY, Chodakewitz JA, DiNubile MJ. Safety and tolerability of caspofungin acetate in the treatment of fungal infections. *Transplant Infect Dis.* 2002;4:25-30; increased aspartate and alanine aminotransferase levels to 2-3 times upper limit of normal in volunteers receiving caspofungin and CsA. No effect on CsA levels, increase of 35% in caspofungin levels. Dose reduction recommended for patients with moderate hepatic insufficiency. Modest decrease in AUC and time to maximum concentration of Tac in healthy individuals.

[l]Manufacturer of SRL states that the combination of ketoconazole and SRL is contraindicated in all cases. Combination resulted in >10-fold increase in AUC of SRL.

[m]Voriconazole substantially increases CsA, Tac, and SRL levels. CsA dose should be decreased by half. Tac dose should be decreased by two-thirds. The manufacturer of voriconazole states that concomitant use of SRL and voriconazole is contraindicated.

Adapted from the *American Journal of Transplantation* (Guidelines for the prevention and management of infectious complications of solid organ transplantation. *Am J Transplant* 2004;(suppl 10):1-166) with permission of Wiley-Blackwell.

Agents That Show Synergistic Nephrotoxicity in Patients on CNI Therapy

- Amphotericin, foscarnet, aminoglycosides (gentamicin, tobramycin, and amikacin), and sometimes quinolones and high-dose TMP/SMX can cause enhanced renal dysfunction in patients receiving cyclosporine and tacrolimus
- When possible, alternatives to nephrotoxic agents should be sought, prehydration should be used (especially with foscarnet), and duration of treatment should be held to a minimum if possible

SUGGESTED READING

➢ Guidelines for the prevention and management of infectious complications of solid organ transplantation. *Am J Transplant.* 2009;9(suppl 4):S1-S281.

➢ Kapturczak MH, Meier-Kriesche HU, Kaplan B. Pharmacology of calcineurin antagonists. *Transplant Proc.* 2004;36(2 suppl):25S-32S.

STRATEGIES FOR SAFER LIVING

The AST infectious disease guidelines (updated second edition pending) contain a section with strategies for safer living, which covers food and water precautions, pets and animal contact, occupational and recreational hazards, precautions for West Nile virus and other insect vector-borne infections, ill contacts, and travel issues. The reader is encouraged to consult these guidelines for further details. For patients planning international travel, a visit to a travel clinic familiar with the needs of transplant recipients at least several months before the planned trip is essential.

SUGGESTED READING

➢ Guidelines for the prevention and management of infectious complications of solid organ transplantation. *Am J Transplant.* 2009;9(suppl 4):S1-S281.

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CONCLUSION

A preventative approach, as well as detailed knowledge of the timetable of infections after transplant, can greatly improve the outlook of a transplant recipient from the standpoint of infection risk. Newer recommendations are likely to emerge in the near future from a comprehensive ongoing re-examination of donor screening policies. Challenges in the management of post-transplant patients include the emergence of antimicrobial resistance, imperfections of current diagnostic assays, and the relative paucity of randomized trials of treatment (except for CMV).

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