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## Donor-Derived Infectious Complications and Disease Transmission

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### 1. Introduction

Organ transplantation is now the treatment of choice for many end-stage diseases. However, the gap between organ demand and donor availability has progressively widened, and the severe shortage of organs for transplantation has resulted in the increasing use of expanded donor criteria, allowing the inclusion of older donors as well as donors with mild disease. Thus, organ donation may involve the risk of the transmittal of unwanted host factors, such as infections and malignancies. Infectious microbes and unexpected diseases that are present in an organ donor have the potential to be transmitted to the transplant recipient. Although the transmission of donor-derived infectious diseases was reported to occur in less than 1% of all donations from deceased donors, significant morbidity and mortality can occur following such disease transmissions. Infectious diseases remain a major complication in solid organ transplantation, and the study of donor-derived infections is an evolving field. Despite recent improvements in the microbiological screening of donors and detailed reviews of potential donors' medical records, persistent clusters of donor-derived infections in transplant recipients remain. Bacterial, viral, fungal, parasitic, and other rare infections can be transmitted through organs and tissue allografts. However, the transmission of microorganisms from allografts is not likely to cause infectious complications in every transplant recipient. The risk of infection is mostly related to the recipient's net state of immunosuppression. The balance between the recipient's state of immunosuppression and epidemiological exposures contribute to the risk of infection (Fishman, 2007; Fishman & Rubin, 1998). Immunosuppression not only increases the risk of tissue invasion, dissemination, and superinfection, but also blunts the typical inflammatory responses that alert clinicians to the presence of infection after exposure. As a result, the recognition of infection is more difficult in transplant recipients than in individuals with normal immunities. The presentations of infections are often complicated by noninfectious events, such as allograft rejection. Specifically, 40% of infections in liver transplant recipients were not associated with fever (Chang et al., 1998). Thus, intervention treatments of infections may be delayed. The goals of patient care after organ transplantation are to prevent the transmission of donor-derived infections, to recognize the presence of infections in solid-organ transplant recipients, and to intervene early when such infections occur. In addition, malignancies that are transmitted from the donor due to direct transmission of

tumors or to tumors arising in cells of donor origin can also occur in organ transplantation. For example, melanoma, which is one of the most frequently reported and lethal donor-derived malignancies, has a high transmission rate. Therefore, potential organ donors should be carefully screened for histories of malignancies.

## 2. Potential infections of the donor

Potential infections acquired from a donor can be classified into two categories: infections that already existed in the patient prior to becoming a potential donor and nosocomial exposures of the donor after hospitalization. Preexisting infections may be present in either living or deceased donors, and the majority of such infections are viral. Some of these infections, which might be detected by donor and recipient screening, involve infection from a seropositive donor to a seronegative recipient, including the transmission of cytomegalovirus (CMV), Epstein-Barr virus (EBV), or toxoplasmosis, while others are unexpected despite routine donor screening. Unexpected clusters of donor-derived viral infections in transplant recipients have occurred, including rabies, West Nile virus (WNV), Human immunodeficiency virus (HIV), herpes simplex virus, hepatitis B virus (HBV), and hepatitis C virus (HCV) (Morris et al., 2010). Nosocomial donor infections are most commonly related to bacterial pathogens. These infections are usually caused by the same nosocomial pathogens that infect other patients with similar lengths of stay in the intensive care unit. Wu and colleagues have shown that several factors, including a longer stay in an intensive care unit, previous cardiopulmonary cerebral resuscitation, and the use of inotropic agents, contribute to the risk of infection of a potential donor (Wu et al., 2008). Additionally, infected donors may also transmit microorganisms that are resistant to formal antimicrobial treatments. The use of organs from deceased donors with potential infections is controversial, and there is a need for improved microbiological screening tools and therapies.

Opportunistic infections are generally uncommon in the first 1–4 weeks after transplantation because the impact of immunosuppression depends on prolonged exposure to suppressive therapies. Unexplained early infections in this period are generally donor-derived or associated with surgery-related complications. Thus, a thorough investigation of infectious diseases in a potential donor is mandatory. The implementation of a preventive strategy of universal prophylaxis that provides antimicrobial therapy to all at-risk potential donors may alter the incidence and severity of organism transmission as well as post-transplant infections. However, routine antimicrobial prophylaxis should be adjusted based on the organ transplanted, individual exposures, and hospital epidemiology. Prophylaxis can also be adjusted according to known colonization patterns. All active infections in the donor should be eradicated or controlled prior to transplantation, as these may be transmitted and reactivated in the transplant recipient, which may lead to significant morbidity and mortality.

## 3. Screening of the risks of infections of organ donors

Benjamin Franklin said that an ounce of prevention is worth a pound of cure. The pretransplantation screening of potential organ donors is essential for the prevention of disease transmission, as well as the success of solid organ transplantation. Pretransplantation infectious disease screenings of potential donors are helpful in: (1) identifying conditions

that may disqualify the donor, (2) identifying and treating active infections prior to transplantation, (3) identifying the risk of infection and determining strategies for preventing and mitigating infection after transplantation, and (4) implementing preventive interventions, such as updating the recipient’s vaccination status. Although there is general consensus on the major infections for which screening should be performed, there is some variation in the types of screening used in different transplantation centers. A number of publications have discussed guidelines for the pretransplant screening of organ donors (Avery, 2004; Delmonico & Snyderman, 1998; Fischer & Avery, 2009). Some documented infections preclude organ donation under specific infectious conditions, including uncontrolled sepsis, HIV or human T-cell lymphotropic virus (HTLV) infection, rabies, WNV infection, and lymphocytic choriomeningitis virus (LCMV) infection. Therefore, organ donors should be screened for the risk of infection on the basis of organ-procurement standards. The screening should include the donor’s medical history as well as laboratory serologic testing.

3.1 Screening the donor’s medical/behavioral history

A thorough medical history and physical examination are the first steps in donor screening. An accurate medical and social history, as well as the donor’s recent and remote exposures, is important in the assessment of donor eligibility. This initial evaluation may address current or active infections prior to organ procurement. Each potential donor should be screened for medical conditions that may affect the function of the donated organ, for the presence of transmissible disease or malignancies that are treated or untreated, or for any other known condition that may be transmitted by the donor organ that may reasonably affect the recipient. This history should also be used to identify whether the potential donor has factors associated with an increased risk of transmission of infection, including the blood-borne pathogens HIV, HBV, and HCV. The data that should be collected when assessing donor eligibility are summarized in Table 1.

Medical history
Previous infection
Vaccinations
Occupational exposures
Travel history
History of transfusions with blood or blood products
Any contact with people with human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or other transmissible diseases
Tattooing, ear or body piercing
Use of illicit drugs
Sexual behavior
Incarceration
Contact with animals, including pets, bats, stray dogs, or rodents
Physical examination

Table 1. Suggested data to be collected for determining eligibility prior to organ donation

However, due to the limited pool of donors, it has become increasingly important to consider marginal donors, including those with infections at the time of donation. The decision to use organs from an infected donor reflects the urgency of transplantation for the recipient and the availability of alternative organs.

### 3.1.1 Exclusion of high-risk donors

The transmission of HIV through liver transplantation has been reported sporadically (Ahn & Cohen, 2008; Samuel et al., 1988). The Centers for Disease Control and Prevention of the United States (US) has issued guidelines for the classification of donors possessing a high risk for HIV infection (CDC, 1994). Potential donors who meet any of the criteria listed below should be excluded from the donation of organs or tissues and may be considered only if the risk to the recipient of not performing the transplant is deemed greater than the risk of HIV transmission and disease. In such a circumstance, it is recommended to inform the recipient and discuss the possibility of HIV transmission.

#### Behavior/history exclusionary criteria

1. Men who have had sex with another man in the preceding 5 years.
2. Persons who report nonmedical intravenous, intramuscular, or subcutaneous injection of drugs in the preceding 5 years.
3. Persons with hemophilia or related clotting disorders who have received human-derived clotting factor concentrates.
4. Men and women who have engaged in sex in exchange for money or drugs in the preceding 5 years.
5. Persons who have had sex in the preceding 12 months with any person described in items 1-4 above or with a person known or suspected to have HIV infection.
6. Persons who have been exposed in the preceding 12 months to known or suspected HIV-infected blood through percutaneous inoculation or through contact with an open wound, non-intact skin, or mucous membrane.
7. Inmates of correctional systems. (This exclusion is to address issues such as difficulties with informed consent and the increased prevalence of HIV in this population.)

#### Specific exclusionary criteria for pediatric donors

- Children meeting any of the exclusionary criteria listed above for adults should not be accepted as donors.
- Children born to mothers with HIV infections or mothers who meet the behavioral or laboratory exclusionary criteria for adult donors (regardless of their HIV status) should not be accepted as donors unless HIV infection can be definitely excluded in the child as follows:
  - Children greater than 18 months of age who are born to mothers with, or at risk for, HIV infection, who have not been breast fed within the last 12 months, and whose HIV antibody tests, physical examination, and review of medical records do not indicate evidence of HIV infection can be accepted as donors.
  - However, children less than or equal to 18 months of age who are born to mothers with, or at risk for, HIV infection should not be accepted as donors regardless of their HIV test results.

3.2 Laboratory screening tests

In the US, all laboratory testing of donors must be performed in an appropriately accredited laboratory utilizing nationally licensed, approved, or cleared serological screening tests. Laboratory screening of potential donors is generally performed for HIV, HBV, HCV, and syphilis. The serological tests most frequently used for donor screening are listed in Table 2.

Human immunodeficiency virus (HIV) antibody
Hepatitis B (HBV) serologic tests:
HBV surface antigen (HBsAg)
HBV core antibody (HBcAb IgM and IgG)
HBV surface antibody (HBsAb)
Hepatitis C (HCV) antibody
Venereal Disease Research Laboratory (VDRL) test or Rapid Plasma Reagin (RPR)
Cytomegalovirus (CMV) antibody IgM and IgG
Epstein-Barr virus (EBV) antibody panel
Herpes simplex virus antibody
Varicella-Zoster virus antibody
Human T cell lymphotropic virus (HTLV-I/II) antibody (for donors originating from high-incidence areas)
Toxoplasma antibody (optional, not routinely performed for noncardiac donors)
Blood and urine cultures

Table 2. Common screening tests for potential organ donors

Serology for HTLV-I/II is routinely performed in the US, but in Europe and other areas, this assay is restricted to donors living in, or originating from, high-incidence areas. However, the risk of infection may be difficult to assess, especially if HTLV has been transmitted vertically or sexually. Toxoplasmosis is a major concern, particularly in heart transplantation, but it is rarely transmitted to liver recipients (Mayes et al., 1995). Thus, toxoplasmosis screening is not routinely performed for noncardiac donors. Donor screening for toxoplasmosis is also not advocated based on the small amount of information gained and the high rate of false-positive results. In addition, a seropositive result for toxoplasma does not contraindicate organ donation, but does provide information that determines appropriate prophylaxis and treatment options following transplantation.

3.2.1 Donors with identified infections

The use of organs from deceased donors who had fevers or viral infections remains controversial, indicating the need for improved microbiological screening tests. However, the urgent demand for organs has led to the use of organs from donors with identified infections for specific recipients based on the urgency of the need for transplantation and the availability of antimicrobial therapies. Ideally, all active bacterial or fungal infections in the donor should be treated and resolved prior to transplantation. Currently, no recommendations are available regarding the optimal duration of therapy before transplantation or the interval required between resolution of the infection and transplantation. It may not be possible to document clearance of the infection in an emergent situation of life-saving transplantation. Common infections in donors that have



been treated adequately should not preclude the use of organs, and decisions must be flexible and individualized to the recipient.

Additionally, livers from donors with HBV infection (HBcAb- or HBsAg-positive) may be used in recipients who have previously been infected or are in life-threatening situations, with appropriate treatment with specific anti-HBV antiviral agents (Seehofer & Berg, 2005; Trautwein, 2004). Similarly, the use of HCV-infected organs is generally reserved for HCV-infected recipients or for selected HCV-negative recipients (Ghobrial et al., 2001; Vargas et al., 1999; Velidedeoglu et al., 2002). Suggested organ donation strategies that are based on donor screening data are summarized in Table 3 (Grossi & Fishman, 2009).

Serologic finding	Action
Antibody to human immunodeficiency virus (HIV)	Exclude from organ donation
Antibody to human T-cell lymphotropic virus (HTLV) I/II	Generally exclude from organ donation (may be used in life-threatening situations with informed consent)
Antibody to hepatitis C virus (HCV)	If used, organs are usually reserved for recipients with antibodies to HCV or severely ill recipients
Antibody to cytomegalovirus (CMV)	Use information to determine prophylaxis (in conjunction with recipient serology)
Antibody to Epstein-Barr virus (EBV)	Consider PCR monitoring if donor is seropositive and recipient is seronegative
Hepatitis B virus (HBV) surface antigen (HBsAg) + or HBV core antibody (HBcAb IgM) +	Exclude from organ donation (possible use in life-threatening situations with intensive prophylaxis)
HBV surface antibody (HBsAb) +	Generally safe for organ donation
HBV core antibody (HBcAb) IgG +	High-risk for transmission if liver is 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 (RPR) +	Not a contraindication to donation. Recipient should receive benzathine penicillin
Antibody to Toxoplasma	Not a contraindication to donation. Sulfa-allergic, seronegative heart transplant recipients with a seropositive donor should receive pyrimethamine prophylaxis

Table 3. Suggested strategies based on donor screening results

3.3 Additional considerations for donor screening

Despite the use of highly sensitive assays and the development of new policies, the transmission of infections to organ transplant recipients remains uncommon. However, it does occur with sufficient frequency to suggest that the current approaches to donor screening are inadequate. Many potential exposures are too nonspecific to allow appropriate decision-making regarding the risk of transmission.

### 3.3.1 Hemodilution of donor blood samples

All blood samples obtained and used for screening tests must be assessed for hemodilution, which is defined as the dilution of plasma that is sufficient to affect the results of communicable disease testing. Blood samples from a deceased organ donor who underwent blood loss and transfusion of blood products or infusion of colloids and crystalloids are likely to be hemodiluted, which might lead to false-negative test results. The Food and Drug Administration (FDA) of the US has published regulations to test specimens from donors who have undergone transfusion or infusion (FDA, 2007). Test results from donors who have suffered blood loss that was sufficient to require fluid replacement, certain volumes of transfusion, and/or infusions should be interpreted with caution. The donor might be ineligible unless a pretransfusion sample was available for testing or an appropriate algorithm was used to determine if plasma dilution is sufficient to affect test results.

### 3.3.2 The window period

The window period is the time between initial infection and when a test can reliably detect that infection, and the poor sensitivity of antibody-based tests within this period increases the risk of infection transmission through organ transplantation. As seroconversion may not occur during an acute infection, some active infections remain undetectable. For example, the period from initial HIV exposure to the development of HIV antibodies is approximately 22 days, but it can be up to 3–6 months. On average, it takes 2–8 weeks from the time of possible exposure for the development of detectable levels of HIV antibodies, leading to accurate test results. Therefore, the donor may be seronegative while potentially infected. However, recent improvements in the sensitivity of virus-detection assays using nucleic acid testing (NAT) have resulted in a significant shortening of the window period (Busch et al., 2005; Fiebig et al., 2003). The use of NAT may also detect viral replication in HBV core antigen (HBcAg)-positive donors who are HBV surface antigen (HBsAg)-negative, in addition to reducing the window period of HBV infection (Biswas et al., 2003; Kleinman & Busch, 2006). The window period of HCV infection can be reduced by the use of NAT as well (Kolk et al., 2002; Schreiber et al., 1996), suggesting the routine use of NAT in the screening of potential organ donors for HIV, HBV, and HCV.

### 3.3.3 Living donors versus deceased donors

The screening of living and deceased donors is largely different based on the period during which the evaluation is performed. The screening of a prospective living donor is conducted at the transplantation center, and the time between screening and transplantation is variable. The screening of living donors should include a thorough medical and behavioral history, physical examination, laboratory serological tests, radiographic imaging studies, and tests for any untreated underlying infectious diseases as needed. Repeat screening tests should be considered in the presence of newly developing clinical symptoms and signs in living donors between the time of initial screening and transplantation.

In contrast, the period for deceased donor screening is very short, typically on the order of hours. The laboratories associated with organ procurement organizations (OPOs) should operate on a 24-hour basis in order to generate the information needed to determine donor eligibility (Delmonico & Snyderman, 1998; Schaffner, 2001). Because of time constraints,



serologic tests are often limited to routinely available and rapid methods. In addition, the quality of testing may not be identical in each OPO, and some infections that require more sensitive testing may be difficult to detect at an early stage. Therefore, a detailed medical history of the potential deceased donor is required to identify potential infections that might not be reflected in serologic tests. If a deceased donor with a potential infection risk is to be used, the recipient should be informed of the risk of infection transmission. In the future, the development of more sensitive and rapid molecular serologic tests may allow immediate detection of viral infections, such as HBV, HCV, and HIV.

4. Transmission of specific pathogens

A variety of pathogens, including bacteria, fungi, parasites, and viruses, may be transmitted through organ transplantation (Table 4) (Gottesdiener, 1989; Ison et al., 2009).

<i>Bacteria</i>	<i>Mycobacteria</i>
Staphylococcus aureus	Mycobacterium tuberculosis
Klebsiella species	Nontuberculous mycobacteria
Bacteroides fragilis	
Pseudomonas aeruginosa	<i>Parasites/Protozoa</i>
Escherichia coli	Toxoplasma gondii
Salmonella species	Strongyloides stercoralis
Yersinia enterocolitica	Plasmodium species
Treponema pallidum	Trypanosoma cruzi
Brucella species	
Bartonella species	<i>Viruses</i>
Enterobacter species	Cytomegalovirus
Acinetobacter species	Epstein-Barr virus
	Herpes simplex virus
<i>Fungi</i>	Varicella-zoster virus
Aspergillus species	Human herpesvirus-6, 7, 8
Candida species	Hepatitis B, C
Histoplasma capsulatum	Human immunodeficiency virus
Cryptococcus neoformans	Human T cell lymphotropic virus (HTLV)
Coccidioides immitis	Parvovirus B19
Scedosporium apiospermum	Rabies
Prototheca species	Lymphocytic choriomeningitis virus (LCMV)
	BK virus
	West Nile virus

Table 4. Pathogens that are transmitted with solid organ transplantation

4.1 Bacteria

Bacteria are the most common cause of infections in liver transplant recipients, with a reported incidence of 35–70%. Numerous factors may be associated with recipient infection, and bacterial transmission from the donor is one of the possible sources. Deceased donors may harbor known or unsuspected bacterial infections, which should be rapidly evaluated

by review of medical records, temperature charts, radiography, and cultures when available. It is desirable to obtain blood cultures prior to transplantation since occult donor bacteremia may occur. If an illness might have involved bacteremia, a thorough investigation should be performed to make sure that the target organ has not been infected. Previous studies, conducted on a small scale, have documented severely compromised initial allograft function when organs from infected donors were used for desperate recipients (Bull et al., 1995; Nery et al., 1997). Therefore, transplantation programs have been reluctant to use organs from donors known to have active bacterial infections. Occasionally, however, a bacterial or fungal blood culture taken before organ recovery is reported as positive only after life-saving organs have been transplanted into a needy recipient. A retrospective review of bacteremic donors has found no evidence that transmitting bacterial infection results in poorer outcomes after organ transplantation (Freeman et al., 1999). Moreover, organs have been successfully transplanted from donors with bacterial meningitis with no evidence of infectious complications in the recipients, who were given appropriate antimicrobial therapy (Lopez-Navidad et al., 1997; Satoi et al., 2001). Therefore, potential donors with positive blood cultures should not be totally excluded as possible donors. This may increase organ availability and help improve the organ shortage.

#### 4.1.1 Syphilis

Syphilis is a sexually transmitted infection with a worldwide incidence that is caused by the spirochete *Treponema pallidum*. Although the transmission of syphilis by means other than sexual routes is infrequent, it can be transmitted through blood transfusion and organ transplantation. Serologic testing of potential organ donors for syphilis is recommended, but evidence of syphilis infection is not considered a contraindication to organ donation if appropriate prophylactic antibiotics, such as benzathine penicillin, are administered to the recipient (Caballero et al., 1998; Ko et al., 1998). Therefore, current guidance suggests that organ transplantation from a donor with serologic evidence of a syphilis infection is safe as long as there is appropriate treatment of recipients in the posttransplantation phase. Recommended regimens of 2–3 doses weekly of 2.4 million units of intramuscular benzathine penicillin or an equivalent early syphilis therapeutic regimen should be given as soon as possible after transplantation for appropriate prophylaxis and treatment of early syphilis acquired from transplantation.

#### 4.2 Fungi

Any known active and invasive fungal infection in the potential donor is a contraindication to transplantation. However, endemic mycoses may be present in dormant forms and transmitted to recipients by organ transplantation. For example, histoplasmosis that was transmitted by transplantation has been described, but most cases appeared to involve the reactivation of a past infection in the recipient (Limaye et al., 2000). Nonetheless, radiographic signs of suspected previous histoplasmosis have not been considered a contraindication to donation, and a consensus regarding recommendations for donor screening for endemic mycoses has not emerged yet.

##### 4.2.1 *Candida* species

The incidence of fungal infections in liver transplant recipients is higher than in recipients of other types of solid organ transplants. The reasons for this high rate of fungal infection are

not completely understood, but specific risk factors, including retransplantation, prolonged or repeat surgeries, high transfusion requirements, renal failure, fungal colonization, and predisposition to fungal infections in liver transplant recipients, have been identified (Castaldo et al., 1991; Collins et al., 1994). The incidence of invasive fungal infections following liver transplantation ranges between 14% and 42%, and these infections are associated with high overall mortality rates (Briegel et al., 1995; Paya, 2002). Most fungal infections generally occur within the first 3 months following liver transplantation and are viewed as classic nosocomial infections instead of donor-derived transmissions. Infections due to *Candida* species are the most common invasive fungal infections among solid organ transplant recipients, accounting for over half of all fungal infections. However, the occurrence of invasive candidiasis, especially among liver and small bowel transplant recipients, is often substantially higher.

The diagnosis of invasive candidiasis is dependent on the recovery of the organism from a sterile body site, such as the bloodstream, intraabdominal fluid, pleural fluid, or abscess material. Unfortunately, cultures, especially blood cultures, are not sensitive enough to identify patients with invasive candidiasis. Even with newer blood culture techniques, the overall sensitivity of blood cultures for identifying *Candida* species is estimated to be 70% (Berenguer et al., 1993). Thus, the development of nonculture-based diagnostic methodologies is especially important. Presently, the 1-3, beta-d-glucan assay is probably the most reliable, with a sensitivity and specificity of 70% and 87%, respectively, among patients who have proven invasive candidiasis (Obayashi et al., 2008; Ostrosky-Zeichner et al., 2005). The treatment of invasive candidiasis in organ transplant recipients, which is similar to treatment in most other patients, is based on updated clinical practice guidelines for the management of candidiasis (Pappas et al., 2009).

#### 4.2.2 *Aspergillus* species

Aspergillosis accounts for 1–9.2% of invasive fungal infections in liver transplant recipients (Brown et al., 1996; Gavalda et al., 2005; Kusne et al., 1992). It is similar to other fungal infections in that aspergillosis is likely to be a nosocomial infection after transplantation and not due to donor-derived transmission. A number of well-characterized risk factors have been shown to portend a high risk of invasive aspergillosis following liver transplantation, of which retransplantation and renal failure are among the most significant (Fortun et al., 2002; Gavalda et al., 2005; Singh et al., 2001). Historically, invasive aspergillosis in liver transplant recipients has predominantly occurred in the early posttransplant period. The mortality rate of liver transplant recipients with invasive aspergillosis has ranged from 83–88% (Denning, 1996; Singh et al., 1997; Singh et al., 2006), highlighting the need for aggressive diagnostic evaluation and treatment. A substantial delay in establishing an early diagnosis remains a major impediment to the successful treatment of invasive aspergillosis. Cultures of respiratory tract secretions are less sensitive, and fungus may only be detected in clinical samples from the late stages of the disease. However, a positive culture of *Aspergillus* from respiratory tract samples does not always indicate invasive disease, and the significance of a positive culture from an airway sample also varies with the type of organ transplant.

The utility of the galactomannan test for the early diagnosis of invasive aspergillosis has been assessed in solid organ transplant recipients. However, false-positive galactomannan

tests have been documented in up to 13% of liver transplant recipients (Kwak et al., 2004), but the sensitivity of the assay for the diagnosis of invasive aspergillosis may be improved by testing bronchoalveolar lavage (Husain et al., 2007). The diagnosis of invasive aspergillosis using the 1-3, beta-d-glucan assay has not been fully defined, but one study has shown that the test was useful for the diagnosis of invasive aspergillosis in living-donor liver transplant recipients (Kawagishi et al., 2006).

Currently, prophylaxis against invasive aspergillosis is not routinely recommended in all solid organ transplant recipients. A more rational approach is to provide antifungal prophylaxis to high-risk liver transplant recipients (Singh & Husain, 2009). The treatment of invasive aspergillosis in liver transplant recipients remains generally the same as in other patients. Prompt initiation of antifungal therapy is crucial for achieving optimal outcomes in recipients with invasive aspergillosis. Because of their lower potential of nephrotoxicity, lipid formulations of amphotericin B have been the mainstay for the treatment of invasive aspergillosis in solid organ transplantation since the early 1990s. The availability of newer triazole agents and echinocandins that have potent anti-*Aspergillus* activity and better tolerability profiles have led to an expanded arsenal of antifungal agents for the treatment of invasive aspergillosis. Voriconazole is now regarded as the drug of choice for the primary treatment of invasive aspergillosis in all hosts, including solid organ transplant recipients, based on the clinical guidelines of the Infectious Diseases Society of America (IDSA) for the treatment of invasive aspergillosis (Walsh et al., 2008). For the primary treatment of invasive pulmonary aspergillosis, intravenous or oral voriconazole is recommended for most patients, while the parenteral formulation is recommended for seriously ill patients. In patients developing toxicity to or with contraindications against voriconazole, liposomal amphotericin B is considered an alternative primary therapy according to the IDSA guidelines, but higher doses are not recommended. Amphotericin B lipid complex, itraconazole, caspofungin, posaconazole, or micafungin are other rational choices for alternative therapies for invasive aspergillosis (Walsh et al., 2008).

Currently, caspofungin, which is the only echinocandin approved by the FDA for the treatment of invasive aspergillosis, has been used successfully as a single agent or in combination with other drugs for salvage therapy in invasive aspergillosis (Carby et al., 2004; Forestier et al., 2005). However, the efficacy of combination antifungal therapy for invasive aspergillosis has not been fully defined. Thus, the routine administration of a combination regimen for primary therapy is not recommended. In the context of salvage therapy, an additional antifungal agent may be added to existing therapy, or combination antifungal drugs from different classes other than those in the initial regimen may be used (Walsh et al., 2008).

#### **4.2.3 *Cryptococcus* species**

Cryptococcosis, which is the third most common invasive fungal infection, accounts for approximately 8% of the invasive fungal infections in solid organ transplant recipients. The overall incidence of cryptococcal disease in solid organ transplant recipients ranges from 0.3–5% (Singh & Forrest, 2009). As in most other hosts, cryptococcal disease in solid organ transplant recipients is considered a reactivation of a quiescent infection. However, rare cases of transmission from donor organ and tissue grafts have also been reported (Beyt & Waltman, 1978; Kanj et al., 1996; Ooi et al., 1971). Approximately 53–72% of solid organ

transplant recipients with cryptococcosis develop disseminated disease or central nervous system (CNS) involvement. Among solid organ transplant recipients, liver transplant recipients had a 6-fold higher risk for developing disseminated disease than recipients of other types of transplants. The overall mortality of solid organ transplant recipients with cryptococcosis in the current era is 14%, but it may be higher in those with CNS involvement (Singh et al., 2007).

All patients with suspected cryptococcosis should undergo complete evaluations, including lumbar punctures, blood and urine cultures, chest X-rays, or bronchoalveolar lavages with biopsies when necessary, in order to determine the extent of the disease, as this will dictate management. Distinguishing between disseminated disease and localized pulmonary and asymptomatic disease is necessary prior to initiating therapy. In patients with neurologic and disseminated disease or severe pulmonary disease, the recommended treatment includes induction therapy with an amphotericin B product and flucytosine, followed by consolidation with fluconazole, and, finally, maintenance with fluconazole (200–400 mg/day) for 6–12 months in order to complete the regimen. The recommended treatment for focal or incidentally detected pulmonary disease in otherwise asymptomatic patients is fluconazole (400 mg/day) for 6–12 months (Dromer et al., 2008; Saag et al., 2000). Currently, the use of extended-spectrum azoles, such as voriconazole, itraconazole, and posaconazole, have not shown any extra benefits over fluconazole (Singh & Forrest, 2009).

### 4.3 Mycobacteria

*Mycobacterium tuberculosis* (TB) is a serious opportunistic infection that may affect transplant recipients. The prevalence of active TB among solid organ transplant recipients is estimated to be 1.2–6.4% in most countries, and it has been reported to be up to 15% in highly endemic areas. The mortality rate in these populations is close to 30% (Munoz et al., 2005). The incidence of active TB in adult liver transplant recipients has been reported to be 0.47–2.3% (Munoz et al., 2005; Torre-Cisneros et al., 2009). The most frequent mode of acquisition is thought to be reactivation of dormant disease; however, transmission with an allograft has been documented to occur in liver transplant recipients (Aguado et al., 2009; Kiuchi et al., 1997). Because of this risk, all potential living donors should be given a thorough history, documenting TB risk factors, exposures, and infections, and undergo a tuberculin skin test (TST) or interferon- $\gamma$  release assay. If either test is positive, additional testing and a symptom review should be performed in order to rule out active infection. Prospective living donors with active TB should not be considered for transplantation, and those with latent TB infection should be given treatment (with isoniazid for 9 months or rifampin for 4 months) prior to transplantation. However, one study demonstrated no benefit to treating prospective living donors with latent TB infections prior to transplantation (Hernandez-Hernandez et al., 2006). The optimal length of therapy prior to liver donations remains unclear, and a shorter course of therapy might be feasible with the caveat that the recipients will be treated after liver transplantation. In the case of deceased donors, it is not possible to perform TSTs, but a history of previously active TB and any associated treatment should be obtained from the donor's family or relatives. Organs from potential donors, whether living or deceased, with active TB or a high suspicion of active TB should not be used. Recipients of organs from donors with latent TB should consider preventive therapy with isoniazid for up to 9 months (Yehia & Blumberg, 2010).



The initiation of posttransplant preventive treatment should begin as soon as medically possible after the recipient is stabilized in order to prevent the development of reactivated diseases. Once therapy is started, transplant recipients should be routinely monitored for drug-related hepatotoxicity. A suggested approach is to monitor liver enzymes at 2-week intervals for 6 weeks and then monthly. If significant hepatotoxicity is observed, alternative regimens, such as ethambutol plus either levofloxacin or moxifloxacin, could be considered for high-risk individuals (Aguado et al., 2009). If no alternative treatment is possible, then careful clinical follow-up with prompt diagnostic attention to pulmonary symptoms is likely the best strategy.

The standard treatment recommendation for active TB in the general population is to administer a 4-drug regimen of isoniazid, rifampin, pyrazinamide, and ethambutol for a 2-month intensive phase, followed by a continuation phase of 4–7 months (Blumberg et al., 2003). Other agents used in the treatment of TB are aminoglycosides and fluoroquinolones, which are primarily used in cases of multidrug resistance or intolerance of first-line medications. Treatment of active TB in liver transplant recipients should consider the known risks of drug-related hepatotoxicity and drug-drug interactions between antituberculosis medications and immunosuppressive agents. These considerations also have an impact on the suggested length of treatment. The ideal length of TB therapy in liver transplant recipients remains controversial, and it is affected by the extent of the disease, choice of regimen, response to therapy, and resistance profile of the organism.

#### 4.4 Protozoa/parasites

Parasitic diseases may affect transplant recipients as a result of natural infection, recrudescence of a previous latent infection in the recipient, or transmission by organ transplantation. For the most part, only those organisms that can complete their life cycle within the human host lead to more severe infections in an immunocompromised host. The incidence of parasitic infection is expected to increase in solid organ transplant recipients due to the universal expansion of transplantation programs, and the increase in the numbers of donors or recipients who are originally from endemic areas but are currently spreading throughout the world.

##### 4.4.1 *Toxoplasma gondii*

*Toxoplasma gondii* infection in transplant recipients can be caused by a primary infection transmitted by an allograft. Although recipients of heart transplantation have the highest incidence of this disease among solid organ transplant recipients, toxoplasmosis has been described in liver transplant recipients as well. Transplant recipients with active toxoplasmosis may present with brain abscess, chorioretinitis, pneumonitis, or disseminated disease. The diagnosis of toxoplasmosis requires the identification of tachyzoites in biopsy samples or clear seroconversion. The presence of multiple ring-enhancing lesions in a CNS imaging study, especially with the coexistence of anti-toxoplasma IgG antibodies, is suggestive of CNS toxoplasmosis and is sufficient to start presumptive treatment for CNS toxoplasmosis. Optimal treatment after solid organ transplantation has not been well-defined. The recommendations of treatment for active toxoplasmosis generally includes a prolonged course (4–6 weeks or longer) of pyrimethamine and sulfadiazine with folinic

acid, followed by suppressive therapy, or trimethoprim-sulfamethoxazole treatment, followed by suppressive therapy (Kotton & Lattes, 2009).

#### 4.4.2 *Trypanosoma cruzi*

Chagas disease, caused by the flagellate protozoan parasite *Trypanosoma cruzi*, has been transmitted by unscreened blood transfusion, from infected mother to fetus, by laboratory accidents, or even by organ transplantation (de Faria & Alves, 1993; Vazquez et al., 1993). Routine screening for *Trypanosoma cruzi* prior to transplantation is not yet mandatory. In countries where the disease is endemic, transplant teams do accept organs from infected donors provided no better donor is available in a reasonable life-saving situation and with informed consent. Diagnosis can be achieved by direct parasitological tests, including the examination of whole blood preparations, by a concentration method (Strout test) (Strout, 1962) in the acute phase, and by serological tests in the intermediate and chronic stages. Two drugs, nifurtimox and benznidazole, are available for treatment. Parasitic cure is achieved in 60–100% of acute cases when either drug is administered for 30–60 days (Bern et al., 2007).

#### 4.4.3 *Strongyloides stercoralis*

*Strongyloides stercoralis* is endemic in tropical and subtropical regions. Strongyloidiasis, which has mainly been described in kidney transplant recipients, has been considered in most cases to be caused by reactivation of a latent infection (Hoy et al., 1981). More recently, a few cases have been documented in pancreatic and intestine transplant recipients and were attributed to transmission from the donated organs (Ben-Youssef et al., 2005; Patel et al., 2008). The clinical disease may present with pulmonary involvement, sepsis, meningitis with multiple gram-negative rods, and acute and severe abdominal disease, including ileus and intestinal obstruction, and gastrointestinal hemorrhage. These symptoms are caused by the damage inflicted by larvae that penetrate through the intestinal wall. A definitive diagnosis is based on the identification of larvae in clinical specimens, mainly in stool and duodenal aspirate. All recipients with confirmed diagnoses should be treated with ivermectin or albendazole. Thiabendazole is another agent that has been extensively used clinically, but it is probably the least satisfactory of all available drugs because of its high relapse rates and toxicities (Liu & Weller, 1993). Strongyloidiasis can be a devastating disease in transplant recipients despite therapy. The mortality rate approaches 50–70% in recipients with hyperinfection syndrome and disseminated infection (Patel et al., 2008).

#### 4.5 Viruses

Solid organ transplant recipients are uniquely predisposed to develop severe clinical illnesses related to a variety of common and opportunistic viruses. Transplant recipients may acquire viral infections from the donor (donor-derived transmission), from reactivation of endogenous latent infection, or from the community. Herpes viruses, most notably CMV and EBV, are the most common opportunistic viral pathogens that cause infection after solid organ transplantation. HBV and HCV are unique challenges, particularly among liver transplant recipients. Infection by polyoma BK virus is an important cause of allograft dysfunction in kidney transplant recipients, but viremia is relatively uncommon in liver transplant recipients. Other less common viral infections, including adenoviruses,

parvovirus B19, and WNV, may affect liver transplant recipients as well. Treatment of virus infections with proven effective antiviral drug therapies should be weighed against the potential reduction of immunosuppression. For viruses without proven effective therapies, reduction in the degree of immunosuppression remains the sole effective strategy for management. Therefore, the prevention of viral infections is of the utmost importance, and this may be accomplished by pretransplant screening of the donor and recipient to determine prophylactic and preventive strategies to be utilized after transplantation or posttransplant vaccinations and effective antiviral treatments.

#### 4.5.1 Cytomegalovirus

*Cytomegalovirus* (CMV) infections, which have been recognized in every human population, are widely distributed in the general population with seroprevalence ranging from 30–97% (Humar & Snyderman, 2009; Paya, 2001). The patterns of CMV acquisition vary greatly based on geographic and socioeconomic backgrounds of each population, and seroprevalence increases generally with age. Importantly, CMV infection is a major cause of morbidity in patients receiving solid organ transplants. CMV disease usually occurs 1–4 months after liver transplantation, and those recipients who are seronegative for CMV and receive an allograft from a seropositive donor are at highest risk. Other risk factors for CMV disease include the recipient's overall state of immunosuppression (e.g., type of drug, dose, timing, duration) and various host factors (e.g., age, comorbidity, neutropenia). The risk of CMV disease also varies with the type of transplant. This may be due to the degree of immunosuppression or the viral load present in the transplanted allograft. The lowest risk of disease occurs when both donor and recipient are seronegative for CMV. Thus, pretransplant CMV screening of donors and recipients should be performed to allow for risk stratification.

The diagnosis of CMV infection and disease has evolved considerably. Historically, the histological detection of owl's eye inclusion bodies has been used for the diagnosis of CMV disease. However, this method is limited by its invasive approach and insensitivity for detecting CMV organ involvement. For years, culture-based methods, such as shell-vial centrifugation detection or culture of the organism from clinical specimens, were used for CMV diagnosis. However, tissue culture can take weeks and the shell-vial centrifugation assay is insensitive compared with molecular assays. Newer methods for diagnosing CMV disease include detection of the pp65 antigen and a molecular diagnostic test; both methods are performed on serum and are rapid, with reasonable sensitivity and specificity. The pp65 antigen assay is a semiquantitative fluorescent assay that is based on the detection of infected cells in peripheral blood. This assay has a far higher sensitivity and specificity than culture-based methods (Mazzulli et al., 1999). Molecular diagnostic tests, which may detect CMV deoxyribonucleic acid (DNA), can be qualitative or quantitative. Quantitative measurements of CMV DNA levels have become popular at many transplantation centers. The viral loads measured are associated with the severity of CMV infection (Humar et al., 1999). Generally, both the pp65 antigen assay and quantitative CMV viral load testing can be utilized in preemptive protocols for the diagnosis of CMV infection, as well as to guide the management of CMV disease (Caliendo et al., 2000; Emery et al., 2000).

Currently, two strategies commonly used for CMV prevention include universal prophylaxis and preemptive therapy. Universal prophylaxis involves providing antiviral

therapy to all at-risk patients beginning in the early posttransplant period for a defined duration of 3–6 months. Drugs that have been considered for universal prophylaxis include ganciclovir, valganciclovir, acyclovir, valacyclovir, and immunoglobulin preparations (Gane et al., 1997; Paya et al., 2004; Snyderman et al., 1993). Valganciclovir, which is a valine ester prodrug of ganciclovir, has improved bioavailability over the oral form ganciclovir. In preemptive therapy, patients are monitored for early evidence of CMV replication at regular intervals (often weekly). Patients with early replication are then treated with antiviral therapy in order to prevent symptomatic disease. Each approach has advantages and disadvantages that must be considered in the context of the patient and the allograft. The major concern with CMV prophylaxis continues to be late-onset CMV disease, which is defined as disease occurring sometime after discontinuation of antiviral prophylaxis. In contrast, preemptive therapy has the potential advantage of targeting therapy to patients at highest risk and thereby decreasing drug costs and toxicity.

No consensus exists regarding the optimal treatment of CMV disease. However, intravenous ganciclovir has been used successfully in numerous therapeutic trials to treat solid organ transplant recipients with CMV disease and has been considered the mainstay for therapy. The basic principle governing CMV treatment is the clearance of viremia. Therefore, patients with evidence of CMV viremia should be maintained on therapy until viremia has dropped below the negative threshold level for a given test. This helps prevent relapse and the development of resistance to ganciclovir. The incidence of ganciclovir-resistant CMV remains generally low in most cases after solid organ transplant. In a prospective multicenter study, the overall rate of resistance was 1.9% in those who received oral ganciclovir versus 0% among those receiving valganciclovir (Boivin et al., 2004). However, resistance should be suspected if the patient develops CMV disease after prolonged courses of antiviral prophylaxis or the viral load fails to respond to standard ganciclovir treatment. Genetic resistance testing may be very helpful in managing resistant CMV. Therapeutic options for resistant CMV include reduction or discontinuance of immunosuppression and increasing the dosage of intravenous ganciclovir or switching to foscarnet alone or foscarnet in combination with low dose ganciclovir. Other unproven or untested therapeutic options, including cidofovir, compassionate release maribavir, leflunomide, and artesunate, may be considered for refractory cases (Humar & Snyderman, 2009).

#### 4.5.2 Epstein-Barr virus

EBV is also a herpes virus, and humans are the only known hosts of EBV. This virus has a worldwide distribution with seropositive rates of 90% among adults, and its transmission depends on the socioeconomic background of the population. In most nonindustrialized communities, the vast majority of individuals are EBV-seropositive before the age of 5 years. However, in the more developed affluent countries, seropositivity can be delayed until the fourth decade of life (Allen, 2005). Although EBV infection may be acquired from the community, donor-derived transmission from an EBV-seropositive donor organ is an important source of infection among solid organ transplant recipients. EBV is associated with the majority of cases of posttransplantation lymphoproliferative disorder (PTLD), which is recognized as one of the most devastating complications of organ transplantation. The development of PTLD after solid organ transplantation usually occurs in the first year after transplantation. Prolonged or extensive immunosuppression and transplantation from an EBV-seropositive donor into a seronegative recipient are the two major risk factors for



the development of PTLD after solid organ transplantation. CMV infection, which may contribute to the net state of immunosuppression, is known to be another risk factor for the development of PTLD after transplantation. The incidence of PTLD also varies with the type of organ transplantation; the risk for the development of PTLD is highest after small bowel transplantation (up to 32%), followed by moderate risk (3–12%) following lung, heart, and liver transplantation, and relatively low risk (1–2%) for kidney transplantation (Gottschalk et al., 2005). The reasons for these differences are not completely understood, but the recipient's net state of immunosuppression and the amount of lymphoid tissue present in the transplanted allografts may be important.

PTLD may present with a diverse spectrum of nonspecific clinical symptoms and signs that involve other organs, including the CNS, bone marrow, kidneys, lungs, small intestine, and spleen. Because early diagnosis and treatment may result in better outcome, there is great interest in developing tests to predict the development of PTLD. Several investigations have indicated that monitoring EBV viral load and analysis of EBV-specific cytotoxic T lymphocyte responses may be helpful in assessing the risk of PTLD development in recipients (Qu et al., 2000; Rose et al., 2001; Smets et al., 2002). However, tissue biopsies with histological classifications remain the current mainstay of PTLD diagnosis.

The treatment of PTLD remains controversial because of the lack of a unifying consensus dictating the specific treatment approaches that should be undertaken for all categories of patients. The general approach to therapy involves a stepwise strategy that starts with the reduction of immunosuppression; subsequent therapies depend on the clinical situation and should be based largely on the clinical response and histopathological characteristics of the disease. Additional therapies currently used in clinical practice include antiviral agents, intravenous immune globulin, cytokine and anticytokine therapies, surgery or radiation, anti-B cell antibodies, and T cell-based cellular immunotherapies (Allen & Preiksaitis, 2009; Gottschalk et al., 2005). However, the efficacy of individual therapies is difficult to assess because they are often combined. Additional future research is needed to address several unresolved issues and to enhance the diagnosis, prevention, and treatment of PTLD.

#### **4.5.3 Hepatitis B virus**

The transmission of HBV by organ transplantation is hazardous to allograft recipients. The acquisition of HBV infection has been associated with rapidly progressive liver disease, leading to high rates of liver failure and mortality. Therefore, all prospective donors and recipients should be tested for HBV prior to liver transplantation. Although the response to vaccination in patients with end-stage organ disease may be suboptimal, it is prudent to vaccinate all seronegative transplant candidates with HBV vaccine. Donor screening usually includes, at least, HBsAg and HBV core antibody (HBcAb) assays, and it is most useful to test for IgG and IgM in the HBcAb assay. HBsAg or HBcAb-IgM positivity usually indicates active HBV infection, and HBsAg-negative and HBcAb-IgM-positive individuals may represent infection in the window period. A HBsAg-negative and HBcAb-IgG-positive result may represent either a false-positive test or persistent HBV infection (Lok et al., 1988). Isolated HBsAb positivity, which usually indicates prior vaccination or resolved infection, is not generally considered a risk for HBV transmission. Historically, prospective organ donors with either HBsAg or HBcAb positivity were not utilized because of the significant risk of HBV transmission to a liver transplant recipient. However, it has now become more



common to transplant livers from HBcAb+ or HBsAg-positive donors with intensive posttransplantation prophylaxis (Dodson et al., 1999; Wachs et al., 1995).

The relative risk of HBV transmission and posttransplantation management based on the serologic test results of the donor is summarized in Table 5. A donor who is positive for HBsAg poses the greatest risk of HBV transmission after transplantation. The risk of HBV infection may be reduced in recipients who are positive for anti-HB antibodies; however, infection has been well documented after transplantation from a donor positive for HBsAg, irrespective of the recipient's immunization status. Therefore, all recipients receiving transplanted organs from HBsAg-positive donors should be prophylactically treated with hepatitis B immunoglobulin (HBIG) and antiviral therapy. The major drawback of HBIG therapy is the cost, and, therefore, diverse strategies of HBIG administration, in terms of dosage and duration, exist in different transplantation centers. However, frequent monitoring of liver function, HBsAg, anti-HB antibodies, and HBV DNA in the allograft recipient, as well as the maintenance of adequate anti-HB antibody levels, is recommended.

Antibodies against the HBcAg are only present after HBV infection, and they cannot be the result of previous HBV vaccination. Therefore, organs from any donor testing positive for anti-HBc antibodies can transmit HBV to allograft recipients. A positive result for anti-HBc antibodies should be further defined by determining whether the antibodies are of the IgM or the IgG class in order to identify donors with either recent HBV exposure or current HBV infection. If the anti-HBc antibody is of the IgM class, indicating a recent or ongoing acute HBV infection, then recipients should be treated in a manner analogous to allograft recipients from an HBsAg-positive donor. If the anti-HBc antibody is of the IgG class, then there is high risk of HBV transmission with liver transplantation. The approach to liver transplantation from an anti-HBc IgG-positive donor should be as aggressive as that from an HBsAg-positive donor. Therefore, the same regimens of HBIG in combination with oral lamivudine are recommended. However, several centers have described the successful prevention of graft HBV using lamivudine therapy alone (Malkan et al., 2000; Mutimer et al., 2000). Additionally, HBsAg, anti-HB antibody levels, and HBV DNA should be closely monitored in recipients in order to detect active infection as well (Chung et al., 2001).

Donor HBV serology	Risk of HBV transmission	Post-transplantation Prophylaxis
HBsAg +	High	HBIG and lamivudine
Anti-HBc IgM +, HBsAg -, Anti-HBs +/-	High	HBIG and lamivudine
Anti-HBc IgG +, HBsAg -, Anti-HBs +/-	High	HBIG and lamivudine or lamivudine alone
HBsAg -, Anti-HBc -, Anti-HBs +/-	Rare	Not recommended

HBsAg, hepatitis B Surface antigen; Anti-HBc, antibody of hepatitis B core antigen; Anti-HBs, antibody of hepatitis B surface antigen; HBIG, hepatitis B immunoglobulin.

Table 5. Relative risk of HBV transmission and suggested post-transplantation management of liver transplant recipients according to donor serologic status

The lowest risk of HBV transmission occurs when the donor is negative for both HBsAg and anti-HBc antibodies, a situation that is considered evidence of no active infection. However, in rare cases, HBV transmission to liver allograft recipients has been reported, even when the donors are negative for all markers of HBV, including HBsAg, anti-HBc antibodies, and anti-HB antibodies (Chazouilleres et al., 1994)

#### 4.5.4 Hepatitis C virus

Prospective organ donors with HCV infection have traditionally posed a dilemma because of the high risk of transmission of HCV through organ transplantation. A donor positive for HCV RNA, indicating active viral replication, has a much higher risk of transmission (Pereira et al., 1992). The risks of transmission from HCV RNA-negative and HCV antibody-positive donors have not yet been fully defined. However, all recipients of organs from HCV-infected donors are indeed at risk of becoming HCV infected after liver transplantation. In recent years, the use of organs from HCV-seropositive donors for life-saving transplantations in HCV-seronegative recipients has been studied, with acceptable results. There are no increases in the 1- and 5-year mortality and morbidity rates associated with liver transplantation from HCV-positive versus HCV-negative donors (Rosengard et al., 2002).

The greatest concern of HCV infection after liver transplantation is that at least 25% of recipients progress to cirrhosis within 5 years, with a 42% annual risk of decompensation once cirrhosis has developed (Berenguer, 2002). The treatment of HCV in liver transplant recipients is complicated further by poor sustained viral response (SVR) rates and reports of progressive fibrosis with hepatic decompensation despite SVR. Combination therapy for HCV after liver transplantation is currently recommended, and the most widely used is pegylated-interferon (Peg-IFN) plus ribavirin. Treatment of HCV with Peg-IFN plus ribavirin after liver transplantation is generally only successful in achieving SVR in 20–45% of recipients and is associated with high rates (30–50%) of discontinuation due to intolerability (Ponziani et al., 2011; Wang et al., 2006). The inability to reach target RBV doses due to the high prevalence of renal insufficiency in recipients is a major limiting factor in achieving an acceptable SVR rate (Chalasani et al., 2005; Gane et al., 1998).

In contrast to HBV, there is no HCV vaccine to prevent transmission. A general concept in managing liver transplant recipients at risk for HCV infection or recurrence is to avoid precipitating factors, such as acute rejection, the use of older or extended criteria donors, and CMV infection. Additionally, slow tapering of all immunosuppressive agents and avoiding over- or under-immunosuppression is theoretically more likely to lead to a lower incidence of HCV recurrence and acute rejection.

#### 4.5.5 Human immunodeficiency virus (HIV)

HIV-seropositive donors have traditionally not been utilized in transplantation, due to the known risk of transmission to the recipient. However, despite routine screening, transmission of HIV, which can be an uncommon complication of organ transplantation, is a public health concern. Specifically, if the donor is in the window period after infection but prior to development of anti-HIV antibodies, the recipient is at risk of HIV infection (Ahn & Cohen, 2008).

The CDC guidelines address donor screening, testing, and exclusion for prevention of HIV transmission through organ transplantation. The guidelines note that prospective donors may be considered if “the risk to the recipient of not performing the transplant is deemed to be greater than the risk of HIV transmission and disease.” In this circumstance, informed consent is deemed essential. Posttransplant testing of all recipients of high-risk donors for HIV is suggested but not mandated. The treatment of recipients infected by donor-derived HIV transmission is similar to that of HIV-seropositive individuals who have undergone liver transplantation after HIV infection has been confirmed. To maintain virological control of HIV infection, it is recommended to regularly and quantitatively measure HIV RNA and CD4-positive T-cell counts. If patients have persistent HIV viremia, a phenotypic HIV drug resistance assay should be carried out to determine alternative treatment options (Blumberg & Stock, 2009).

#### 4.5.6 Other unusual viruses

Respiratory viruses, including influenza, respiratory syncytial virus, parainfluenza virus, rhinovirus, human metapneumovirus, coronavirus, bocavirus, and polyomaviruses, have been identified as causes of significant morbidity and mortality among transplant recipients. All of these viruses cause a range of diseases, from mild congestion and rhinorrhea, to more severe tracheobronchitis, bronchiolitis, and pneumonia. Transplant recipients are at a higher risk of infectious complications than are immunocompetent hosts, and they often present with mild or atypical symptoms. Although respiratory viruses are increasingly recognized in transplant recipients, there is still much to be learned about their impact. Prospective studies are needed to define the optimal timing, duration, and treatment regimen of each of the viruses.

*Parvovirus B19*, which is a nonenveloped single-stranded DNA virus, is a common human pathogen that causes erythema infectiosum in children. The virus is primarily spread person-to-person by infected respiratory droplets, but transmission through organ transplantation has been reported as well (Yango et al., 2002). Parvovirus B19 infection can be either symptomatic or asymptomatic, depending on the age and immunologic status of the host. In immunocompromised hosts, this infection can cause persistent anemia and occasionally pancytopenia. Therefore, parvovirus B19 infection should be specifically suspected in solid organ transplant recipients with otherwise unexplained anemia. Currently, there is no antiviral drug available for the treatment of parvovirus infection, but intravenous immunoglobulin has been shown to be beneficial in transplant recipients with parvovirus B19 infection (Eid et al., 2006).

*Adenovirus* is an important viral infection in pediatric liver transplantation. The clinical presentations of infected patients range from self-limited fever, gastroenteritis, or cystitis, to devastating illness with necrotizing hepatitis or pneumonia. Symptomatic infections frequently occur early after transplantation, indicating the possibility of donor transmission (Ison, 2006). The diagnoses of adenovirus can be performed through antigen detection, culture, molecular diagnosis, or histopathology. Unfortunately, there is no definitive treatment for adenoviral infection at this time. The most important component of therapeutic strategy is supportive care along with a reduction of the degree of immunosuppression (Ison & Green, 2009).

*Human T-lymphotropic virus (HTLV-I/II)*, which is endemic in certain areas including the Caribbean and Japan, is often asymptomatic. Infection with HTLV-I can progress to HTLV-I-associated myelopathy/tropical spastic paraparesis or adult T-cell leukemia/lymphoma after years or decades. Serology for HTLV-I/II is routinely performed in the US but not in other areas. In Europe and other areas, this assay is restricted to donors living in, or originating from, high-incidence areas. HTLV-I-seropositive donors are often not utilized and are only considered in life-threatening situations with appropriate informed consent. However, the use of HTLV-I-seropositive donors should be conducted with caution because the donor-derived transmission of HTLV-I with rapid development of myelopathy in recipients has been reported (Toro et al., 2003).

*West Nile virus (WNV)*, a flavivirus that can cause meningoencephalitis has recently appeared in the United States. WNV transmission through blood transfusions and solid organ transplantation has been reported as well (Iwamoto et al., 2003). Organ recipients receiving immunosuppressive drugs may be at high risk for severe disease after WNV infection. The US Health Resources and Service Administration has issued a guidance statement regarding donors and WNV, which recommends testing all prospective live donors with nucleic acid amplification tests (NAAT) prior to transplant and suggests avoiding the use of organs from donors with any form of unexplained or confirmed WNV encephalitis.

*Lymphocytic choriomeningitis virus (LCMV)*, a rodent-associated arenavirus, has been reported with donor-derived transmission to organ recipients leading to fatal infection (Fischer et al., 2006). LCMV infection in humans with normal immune systems usually causes either asymptomatic or mild, self-limited illnesses. Aseptic meningitis can occur in some patients, but the infection is rarely fatal. However, LCMV can cause serious infection in persons with impaired immune systems.

*Rabies*, a rhabdovirus, is another potentially fatal donor-derived infection (Srinivasan et al., 2005). The virus spreads inward from nerve endings in muscle or skin to the CNS and then disseminates outward to other organs. The majority of infected individuals develop the furious or encephalitic form of the disease, while others develop the paralytic or dumb form, mimicking Guillain-Barre syndrome. The disease is highly lethal, leading to very few survivors following infection (Willoughby et al., 2005). Therefore, clinicians are encouraged to avoid donors who pose even a small risk of rabies infection.

## 5. Transmission of malignancy

Malignancy after transplantation can develop in three different ways: (1) de novo occurrence, (2) recurrence of malignancy, and (3) donor-related malignancy that can be due to either direct transmission of tumors or tumors arising in cells of donor origin. Despite all efforts to secure a safe organ for transplantation, there continues to be some risk of donor-derived malignancy that can be transmitted to recipients (Ison et al., 2009). Such risks may specifically be overlooked in the emergent donation process. Therefore, the risk of unintended transmission of tumors from donors to recipients must be placed in perspective. Few reports on transmitted cancers have been published, and the risk has never been reliably quantified. One study quantified the risk using a population-based cancer registry, and they estimated a 1.3% risk of having a donor with an undetected malignancy and a 0.2%



risk of cancer transmission (Birkeland & Storm, 2002). These risks are small compared with the benefits of organ transplantation.

Melanoma is one of the most frequently reported and lethal donor-derived malignancies with a high transmission rate (Strauss & Thomas, 2010). The transmission of melanoma might be related to the biological characteristics of melanoma, including tumor dormancy, late recurrence, circulating tumor cells, and the destiny of micrometastases. Melanoma cell dormancy explains the late recurrence that can occur long after the initial treatment of melanoma. The high incidence of circulating tumor cells should be considered in the context of melanoma transmission, even in organ donors with early melanoma who present apparently disease-free following removal of a primary melanoma up to several decades previously. This scenario suggests that melanoma cells can remain dormant at distant sites for decades and possibly forever in immunocompetent patients and reactivate only after transplantation into an immunosuppressed recipient. Therefore, prospective organ donors should be carefully screened for a history of melanoma. The current recommendation for the treatment of donor-related melanoma in renal transplant recipients includes withdrawal or discontinuation of immunosuppression leading to graft rejection, followed by explantation of the allograft after rejection (Penn, 1996). However, this approach is certainly not feasible for liver transplant recipients because of the lack of alternative organ support.

Additionally, prospective organ donors with a past history of several malignancies, including choriocarcinoma, lung cancer, and advanced-stage breast or renal cancer, should be avoided, despite curative resections. Donors with an extended disease-free interval after curative breast, colon, or renal surgery may be used after a detailed review of pathology reports. The use of organs from donors with small, localized, low-grade renal cell carcinoma is acceptable, as demonstrated by the fact that kidneys with such locally excised tumors have been transplanted without evidence of malignancy transmission. Moreover, organs from donors with in situ cancers can be considered with minimal hesitation and with the recipient's informed consent. Donors with cerebral malignancies rarely transmit these tumors to recipients. The risk of malignancy transmission utilizing organs from donors with benign or low-grade astrocytoma (grade I and II) is extremely low. In contrast, the use of organs from donors with high-grade astrocytoma (grade III-IV) tumors, malignant tumors with ventriculocystic shunts, or histories of extensive cranial surgery that disrupts the blood-brain barrier, is associated with a higher donor malignancy transmission rate (Buell et al., 2003).

Once a donor-transmitted malignancy is suspected, confirmation is essential in order to determine treatment approach. Confirmation can be made by the comparison of donor and recipient tumor histology, fluorescence in-situ hybridization (FISH), which has been utilized to identify the donor origin of tumor cells in sex-mismatched transplant recipients, or PCR-based amplification of highly polymorphic regions in the DNA. Recent reports have relied upon FISH and PCR analysis to confirm tumor origins (Gandhi & Strong, 2007). The fact that tumors in transplant recipients arise from foreign DNA can be exploited. However, there is currently no consensus in the guidelines for the management of recipients with donor-transmitted malignancies. In some cases, the reduction or cessation of immunosuppression might lead to rejection of the donor-derived tumor, which is perceived as a foreign antigen by the recovering immune system of the recipients, similar to the rejection of a transplanted organ by a nonimmunosuppressed recipient. However, a



majority of the recipients also require a traditional approach to treating the malignancy, including specific antineoplastic chemotherapy, radiotherapy, or surgery.

## 6. Conclusion

Donor-derived disease transmission remains a rarely recognized complication of solid organ transplantation, although the reported number of potential donor-derived infections and malignancies has increased every year. This increase is most likely the result of the improved recognition and the development of a formalized reporting process. The true incidence rates are not well known but will be clarified over time through enhanced reporting systems and the improved evaluation of suspicious cases. Since there is substantial morbidity and mortality among affected recipients, a better understanding of the risk of disease transmission is important in order to better inform patients and to provide advice on how to minimize transmissions in the future.

Additionally, thorough pretransplantation screening of the donor and recipient for potential diseases is essential to the success of transplantation as well as to determine prophylactic and preventive strategies to be utilized after transplantation. Future advances will likely include more rapid diagnostic testing to refine the assessment of the risks of transmission posed by a particular donor. Moreover, clinicians should be constantly aware of the possibility of the donor-derived transmission of diseases. Earlier identification of transmission events may decrease morbidity and mortality rates through earlier intervention.

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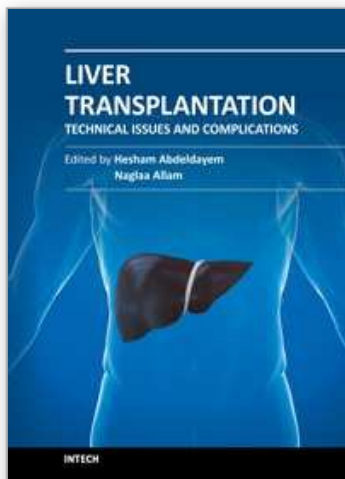
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This book covers a wide spectrum of topics including, but not limited to, the technical issues in living and deceased donor liver transplant procedures, cell and experimental liver transplantation, and the complications of liver transplantation. Some of the very important topics, such as the arterial reconstruction in living donor liver transplantation, biliary complications, and the post-transplant-lymphoproliferative disorders (PTLD), have been covered in more than one chapter.

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