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Organ Transplantation, Risks

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Donor-Derived Infections

Donor-derived viral infections represent a significant risk to recipients in the solid organ and hematopoietic stem cell transplantation (SOT and HSCT) setting. Viruses can be transmitted due to latent or active infection in the donor at the time of donation; rarely, donor infection is very acute and transmission occurs during the incubation period of infection, before symptoms or other evidence of infection can arise, for example, when the donor is transfused with infected blood near the time of death. Clinical consequences of infection in the transplant recipient depend on the virulence of the infecting pathogen, immune status of the recipient to the pathogen in question, and level of host immunosuppression, among other factors. Immunocompromised patients may have unusual presentations of infection, and even organisms of low virulence may cause high morbidity and mortality in these recipients.

Routine donor screening is in place for cytomegalovirus (CMV), Epstein–Barr virus (EBV), herpes simplex virus (HSV), varicella zoster virus (VZV), hepatitis B (HBV), hepatitis C (HCV), and human immunodeficiency virus (HIV), although positive donor testing does not preclude organ transplantation, with the exception of HIV. Transplantation of an organ from an infected donor is at the discretion of the transplant center and transplanting surgeon. The most commonly recognized transplant-transmitted pathogens are the herpesviruses (e.g., HSV, VZV, CMV, EBV, human herpes virus 8 (HHV-8)), hepatitis viruses (e.g., HBV, HCV), and retroviruses (e.g., human T-cell leukemia virus (HTLV)), although transmission of HIV is now unusual given current screening using nucleic acid testing (NAT). Most notable are infections that are either emerging in donor populations, or are otherwise unusual in causing illness in transplant patients. Many of these pathogens are zoonotic in nature. Some examples include West Nile virus (WNV), rabies, and lymphocytic choriomeningitis virus (LCMV) (Table 1).

WNV transplant-associated transmission was recognized during the first large epidemic seasonal activity in the US in 2002, when four organ recipients developed infection from a common donor (three complicated by neuroinvasive disease, the other by febrile illness), and was associated with a donor who contracted the infection from blood transfusion. The risk of infection through transfusion has been greatly reduced by blood donor screening initiated by NAT in 2003, although rarely, breakthrough infections can still occur. Subsequently, there has been an additional report of transplant transmission from a donor who likely acquired infection by mosquito in 2005; in that investigation, the donor was found to be IgM positive, indicating evidence of recent acquisition of infection, but viremia could not be detected by NAT. WNV infection has also been suspected to be transmitted through HSCT. Meningitis and encephalitis of unknown etiology in a patient recently post-transplant should cause clinicians to consider transplant transmission of WNV. Although WNV neuroinvasive disease occurs in less than 1% of WNV infections overall, transplant patients who acquire infections have an estimated 40-fold risk for developing neuroinvasive disease compared with the general population.

In 2004, four recipients of kidneys, a liver, and an arterial segment from a common organ donor died of encephalitis later diagnosed as rabies. Encephalitis developed in all four recipients within 30 days of transplantation and was associated with delirium, seizures, respiratory failure, and coma. Antibodies against rabies virus were present in three of the four recipients along with the donor, who had reportedly been bitten by a bat. This investigation also outlines the importance of careful accounting and management of tissue and organ-associated conduits in hospitals; during the investigation, the source of rabies infection in the arterial segment recipient was not clear.

Two separate occurrences of transplant transmission of LCMV have also been reported in 2003 and 2005. The transplant recipients had abdominal pain, altered mental

Table 1 Viral pathogens in transplantation recipients

Herpes simplex virus
Varicella zoster virus
Epstein–Barr virus
Cytomegalovirus
HHV-6
HHV-7
HHV-8/KSHV
Parvovirus B19
West Nile virus
Rabies
Hepatitis B and C virus
Papillomavirus
Polyomavirus BK/JC
Adenovirus, RSV, influenza, parainfluenza viruses
Lymphocytic choriomeningitis virus (LCMV)
Metapneumovirus
HIV
SARS-associated coronavirus

status, thrombocytopenia, elevated transaminases, coagulopathy, graft dysfunction, and either fever or leukocytosis within 3 weeks after transplantation. Seven of the eight recipients died. In both investigations, LCMV could not be detected in the organ donor, requiring further epidemiologic investigation to try to confirm the source. No source of LCMV infection was found in the 2003 cluster; in the 2005 cluster, the donor had had contact in her home with a pet hamster infected with a viral strain identical to the LCMV detected in the transplant recipients.

Transplant-transmitted infection is rare and might be difficult to recognize, but physicians should consider the possibility, particularly when unexplained neurologic complications occur. These investigations underscore the challenge in detecting and diagnosing infections that occur in recipients of organs or tissues from a common donor. The potential for disease transmission from donor source may not be considered in recipient evaluation. In these investigations, the ability to connect illnesses to a common organ donor was facilitated by the fact that multiple recipients were hospitalized at the same facility. As organ and tissue transplantation becomes more common, the potential risks of disease transmission may also increase.

Because of improved diagnostic assays, donor-transmitted infections are increasingly recognized, although often times, the impact of infection is not well understood. The advent of polymerase chain reaction (PCR) and other genetic material-based tests have allowed for detection of active viremia, in contrast to serologic tests, which reflect past acquisition of infection. This is important not only for recipient diagnosis, but also for recognition of donor infection retrospectively; donor diagnosis is only possible if appropriate specimens are stored postmortem.

Recognition of viral infection transmitted through transplantation is increasing, likely both due to increased recognition of unexpected symptoms consistent with transmission, and due to increasingly sophisticated diagnostic testing in both the recipient and the donor. Investigation of potential donor-transmitted infection requires rapid communication among physicians in transplant centers, organ procurement organizations, and public health authorities. An immediate system for tracking and disseminating pertinent patient data to evaluate donor-derived infection and associated adverse event outcomes is needed. Until such a system can be established, clinicians should report unexpected outcomes or unexplained illness in transplant recipients to their local organ and tissue procurement organizations.

Reactivation of Latent Infections

Given the frequency of latent viral infection, notably among herpesviruses, reactivation of latent infection provides a major source of infection after transplantation. The specific virus, the tissue infected, stimuli for activation, and the nature of the host immune response impact the nature of viral latency. Some viruses are metabolically inactive when latent, while others continue to replicate at low levels that may be determined by the effectiveness of the host's immune response. Multiple factors contribute to viral reactivation after transplantation, including graft rejection and therapy, immune suppression (especially reduction of T-cell mediated, cytotoxic immunity), inflammation, and tissue injury. Numerous cellular pathways are involved in the control of viral replication and are activated after transplantation, such as nuclear factor κB, IκB, and JAK-STAT (the Janus family of protein tyrosine kinases (JAKS) and signal transducers and activators of transcription (STAT) proteins). Antirejection therapy can also result in a significant release of pro-inflammatory cytokines which may increase viral replication. In general, reactivation of viruses, especially late after transplantation, should suggest new immune defects (e.g., cancer) or relative over-immunosuppression.

Latency and reactivation has been best studied in the herpesviruses, which establish lifelong, latent infection after primary infection. In general, latency is considered to be the absence of viral replication, with viral genomes present in the cell without replication or spread. Studies of other viruses, such as Friend virus in mice, suggest that protective antiviral immunity is an active process mediated by 'leaky' (low-level) viral replication. The existence of true latency, as opposed to low-level replication, remains controversial. Herpesviruses make 'latency' proteins that both control viral persistence within the target cell and influence other cellular processes. The latent state is characterized by low levels or the absence of detectable viral antigens, minimal transcription of productive or lytic cycle genes, and expression of the latency-associated viral transcripts. Viral latency may be occasionally interrupted, leading to reactivation and spread of infectious virus with or without recurrent disease. EBV establishes latency in B lymphocytes in association with expression of a limited set of viral genes. Immune control of HSV infection and replication occurs at the level of skin or mucosa during initial or recurrent infection and in the dorsal root ganglion, where latency and reactivation are controlled by immune mechanisms mediated by interferons, myeloid and plasmacytoid dendritic cells, CD4(+) and CD8(+) T cells, and other cytokines. Despite similarities, the molecular details and mechanisms of latency and reactivation vary considerably among the herpesviruses. Mechanisms responsible for maintenance of latency are unclear.

Reactivation of CMV has been extensively studied. CMV viral genomes can be found in CD14+ monocytes and CD34+ progenitor cells, although the primary reservoir for latent CMV and the mechanisms by which latency is maintained are unknown. Allogeneic immune responses

and fever (via tumor necrosis factor-α (TNF-α)) have been shown *in vitro* to increase both CMV promoter activity and viral replication. Immune suppression is not essential for the reactivation of latent CMV, but serves to perpetuate such infections once activated. Subclinical activation of CMV is common and increasing diagnosed by sensitive molecular assays.

For other viruses such as BK polyomavirus, specific types of tissue damage such as warm ischemia and reperfusion injury may precipitate viral activation; they have been linked to an inflammatory state in grafts (via activation of TNF-α, nuclear factor kappa B (NF-κB), neutrophil infiltration, and nitric oxide synthesis), tubular-cell injury, and enhanced expression of cell-surface molecules, all of which may contribute to viral activation. Thus, immune injury, inflammatory cytokines, and ischemia-reperfusion injury stimulate viral replication and change expression of virus-specific cell-surface receptors. The hosts' direct pathway antiviral cellular immune response within allografts is less effective due to mismatched major histocompatibility antigens between the organ donor and host with dependence on indirect pathways of antigen presentation. These factors may render the allograft more susceptible to viral infection.

Common reactivation infections after transplantation include CMV, HBV, HCV, HIV, HSV-1 and HSV-2, HPV, and VZV (as zoster). Other less clinically common viral infections related to reactivation include the polyoma viruses BK and JC, human herpes virus 6 (HHV-6), human herpes virus 7 (HHV-7), and HHV-8. Reactivation of one virus may lead to reactivation of others; multiple studies have shown that infection with HHV-6 and/or HHV-7 are risk factors for CMV disease and CMV infection may trigger HHV-6 and HHV-7 reactivation. While some reactivation infections routinely cause significant clinical disease, such as CMV, HSV, and VZV, others may cause more variable illness. HHV-6, for example, commonly reactivates with immunosuppression, especially after HSCT, often with clinically significant infection. By contrast, the role of both HHV-6 and HHV-7 in SOT recipients is less well defined; while reactivation is common, clinical disease is generally not evident.

New Infections

Based on epidemiologic exposures, new infections from the environment are commonly acquired after transplantation. The respiratory viruses are the most common new infections after transplantation, including RSV, influenza, parainfluenza, and adenovirus. New respiratory pathogens (metapneumovirus and SARS coronavirus) also cause major infections in immunocompromised hosts. Gastrointestinal viruses such as rotavirus or Norwalk virus are common and can cause significant diarrhea and dehydration; diarrheal syndromes may alter absorbance of calcineurin inhibitors (e.g., cyclosporine and tacrolimus), with unexpectedly elevated levels of tacrolimus. Nonimmune patients can acquire primary EBV, CMV, VZV, parvovirus B19, and other infections in the post-transplantation period. In the absence of previous immunity and with the attenuation of immunity due to the immunosuppressive regimen, new infections are often more severe and prolonged than in the general population. For example, parvovirus B19 infection is often more persistent and relapsing in transplantation patients, occasionally complicated by the unusual findings of hepatitis, myocarditis, pneumonitis, glomerulopathy, arthritis, or transplantation graft dysfunction.

'Direct Effects' and 'Indirect Effects' of Viral Infection

The effects of viral infection are conceptualized as 'direct' and 'indirect' (see **Table 2**). This classification serves to separate the tissue-invasive viral infection (cellular and tissue injury) from effects mediated by inflammatory responses (e.g., cytokines) or by alterations in host immune responses. Syndromes such as fever and neutropenia (e.g., with CMV infection) or invasive disease resulting in pneumonia, enteritis, meningitis, and encephalitis are considered direct effects. Indirect effects of viral infections are generally thought to be immunomodulatory responses to viral infections mediated by cytokines, chemokines, and/or growth factors. The impact of these effects is diverse and includes systemic immune suppres-

Table 2 Direct and indirect effects of CMV infection

Direct effects of CMV infection	*Indirect effects of CMV infection*
Fever and neutropenia syndrome (leukopenia, fever, myalgia, fatigue, thrombocytopenia, hepatitis, nephritis)	Increases risk of secondary infection by bacteria, fungi, and viruses
Myelosuppression	Increases risk of graft rejection
Pneumonia	Increases risk of PTLD
Gastrointestinal invasion with colitis, gastritis, ulcers, bleeding, or perforation	May increase risk of HHV-6 and HHV-7 infection
Hepatitis	
Pancreatitis	
Chorioretinitis	

sion predisposing to other opportunistic infections (notably with CMV or HCV infections). In addition, viral infection may alter the expression of cell-surface antigens (e.g., major histocompatibility antigens) provoking graft rejection and/or cause disregulated cellular proliferation (contributing to atherogenesis in cardiac allografts, obliterative bronchiolitis in lung transplantation, or to oncogenesis). Increased viral replication and persistence may contribute to allograft injury (fibrosis) or chronic rejection. Infection with one virus may stimulate replication of other viruses in a form of viral 'cross talk'. As was noted above, infection with HHV-6 and/or HHV-7 serve as risk factors for CMV disease and vice versa. The direct and indirect effects of HHV-6 reactivation can be significant: HHV-6 infection is associated with high levels of IL-6 and TNF-α, and in pediatric renal or bone marrow transplantation, HHV-6 reactivation is strongly associated with acute rejection. Co-infection with HCV and CMV predicts an accelerated course for hepatitis. Co-infection with CMV and EBV increases the risk for post-transplantation lymphoproliferative disorders (PTLD) by 12–20-fold. A more theoretical concern is that T-cell responses against viral infections are thought to produce cross-reacting immune responses against graft antigens, possibly via 'alternative recognition' within the T-cell receptor. This cross-reactivity is termed 'heterologous immunity' and may provoke abrogation of graft tolerance.

Virus Specific Syndromes

The HHV family has eight human members, all of which can cause significant disease in transplantation recipients. The risk of many of these infections is reduced by the use of valganciclovir or acyclovir after transplantation. HSV-1 and -2 (HHV-1 and -2) usually cause oral and genital ulceration, although it may occur in more unexpected areas as well. Recurrent disease can be problematic for some patients and warrants consideration of secondary prophylaxis with antiviral therapy. VZV (HHV-3) is common with an incidence of herpes zoster among 869 patients after SOT of 8.6% (liver 5.7%, renal 7.4%, lung 15.1%, and heart 16.8%), with a median time of onset 9.0 months, as reported by Razonable *et al.* in 2005. After allogeneic HSCT, in one study by Koc *et al.* 41 of 100 (41%) developed VZV reactivation a median of 227 days (range 45–346 days) post-transplantation. Both primary and disseminated VZV infection can be lethal in these populations. Nonimmune transplantation patients should be monitored carefully after exposure to clinical varicella and the use of antiviral therapy or varicella immunoglobulin for prophylaxis should be considered. EBV (HHV-4) can cause febrile systemic illness, lymphocytosis, leukopenia, hepatitis, and mediates post-transplantation lymphoproliferative disease (PTLD). PTLD constitutes a spectrum of disease, which is often responsive to reduced immunosuppression in previously immune hosts. EBV-seronegative individuals with primary infection after transplantation are at increased risk for EBV-mediated PTLD. The clinical presentation of CMV (HHV-5) can range from a 'CMV syndrome' including fever, malaise, leukopenia, to a 'flu-like' illness with myalgias and fatigue, to a more significant end-organ disease with pneumonitis, colitis, encephalitis, hepatitis, or chorioretinitis. CMV is the single most important pathogen in transplantation recipients due to direct and indirect effects (see above).

HHV-6 commonly reactivates after transplantation, especially after HSCT where it is associated with hepatitis, pneumonitis, CMV reactivation, bone marrow suppression, and encephalitis. HHV6 causes less symptomatic clinical infection after SOT, although the indirect effects of reactivation have not been studied. HHV-7 commonly reactivates after transplantation. The clinical symptoms caused by HHV-7 are uncertain, although neurological symptoms seem to be significant, especially in children. HHV-8 causes Kaposi's sarcoma and is seen in SOT recipients at a rate 500–1000 higher than the general population, with a prevalence of 0.5–5% depending on the patient's (and donor's) country of origin.

Hepatitis B and C are among the most common indications for liver transplantation, and can complicate other transplantations as well. Hepatitis C is currently the most common indication for liver transplantation, accounting for 40–45% of cases in recent times. Recurrent post-transplantation hepatitis C infection poses a conundrum between treating the hepatitis C and reducing immunosuppression without precipitating rejection. Given the risk of precipitating graft dysfunction, hepatitis C treatment with interferon and ribavirin is often deferred in extrahepatic transplant recipients. For hepatitis B, the goal is complete viral suppression before and after transplantation, using hepatitis B immunoglobulin as well as antiviral agents with lower-dose immunosuppression. At this time, it is unclear which antivirals and immunosuppressive regimens are optimal for this population. Liver transplantation for HBV with combination viral prophylaxis and hepatitis B immunoglobulin results in survival rates equivalent to other indications for liver transplantation.

Respiratory viruses are the most common community-acquired infections in transplantation recipients. Given the increased rates of pneumonia and bacterial and fungal superinfection, prevention (vaccination, avoidance of sick individuals) is essential. Diagnosis of respiratory viruses within a few hours via enzyme-linked immunosorbent assay (ELISA) or immunofluorescent staining is available in most medical centers. Viral cultures are time consuming and expensive. Respiratory syncytial virus and parainfluenza are the most common community-acquired respiratory viruses, followed by influenza and adenovirus.

Antiviral medications (rimantidine, amantidine, or oseltamivir) may prevent or reduce the severity of illness. The use of ribavirin or RSV immune globulin in adults to prevent RSV infection is unproven. Ribavirin is commonly used for documented RSV infections of the lower respiratory tract.

Metapneumovirus and severe acute respiratory syndrome-associated coronavirus (SARS-CoV) are emerging pathogens in transplantation patients. The clinical spectrum of disease from metapneumovirus ranges from symptomatic (even fatal) to asymptomatic cases. Some groups have suggested a possible correlation with graft rejection in lung transplant recipients. Diagnosis is often made using molecular assays; the full impact of this infection in transplantation is yet to be realized. SARS, caused by a zoonotic coronaviruses, is a highly contagious and rapidly progressive form of viral pneumonia, which spread from Asia to many parts of the world in early 2003. A number of transplantation patients were infected, some of whom died. The impact of SARS and resulting infection control issues was significant for both active organ transplantation (i.e., concerns about transmitting donor-derived infections) as well as routine follow-up care for transplantation patients, some of who deferred healthcare visits.

Gastrointestinal viruses such as rotavirus or Norwalk virus may cause significant diarrhea and dehydration. Enteroviral infections in the summer months in the northern hemispheres are common and can have a more complicated and prolonged course in renal transplantation recipients.

BK virus is associated with a range of clinical syndromes in immunocompromised hosts: viruria and viremia, ureteral ulceration and stenosis, and hemorrhagic cystitis. The majority of patients with BK virus infections are asymptomatic. Infection by JC polyomavirus has been observed in renal allograft recipients as both nephropathy (in association with BK virus or alone) and/or progressive multifocal encephalopathy (PML). JCV establishes renal latency but receptors are present in multiple tissues including the brain. Infection of the central nervous system generally presents with focal neurologic deficits or seizures and may progress to death following extensive demyelination.

Human papilloma virus (HPV) infections can cause significant disease in renal transplantation recipients, including oral, skin, genital, and rectal lesions ranging from warts and dysplasia to malignancy (especially squamous cell carcinoma). The recent arrival of a vaccine for genital HPV infections may help reduce these infections.

In transplantation recipients, parvovirus B19 infection can cause erythropoietin-resistant anemia, pancytopenia, myocarditis, or pneumonitis. Direct renal involvement with glomerulopathy and allograft dysfunction has been reported in renal transplantation recipients. Clinical and virologic responses to treatment with intravenous immunoglobulin are usually excellent.

Several zoonotic viruses have caused major illness and death in the transplantation setting, including WNV, rabies, and lymphocytic choriomeningitis virus (LCMV). All have been recently reported as donor-derived infections related to SOT, with clinically subtle infections in the donor and often deadly infections in the recipients. WNV is more morbid after SOT; the risk of meningoencephalitis in a SOT patient infected with WNV has been estimated to be 40%, compared with <1% in normal hosts. Donors in endemic areas should be screened for WNV, as the prevalence can be high. Aside from donor-derived infections, rabies and LCMV have not been reported.

Although HIV-infected patients are living longer and dying less often from complications related to acquired immunodeficiency syndrome (AIDS), they are experiencing significant morbidity and mortality related to end-stage liver and renal disease. Preliminary studies suggest that both patient and graft survival are similar in HIV-negative and HIV-positive kidney and liver transplantation recipients. However, HCV infection appears to be accelerated even in controlled HIV infection. Ongoing multicenter trials of transplantation in HIV infections are continuing. Drug interactions between the immunosuppressive regimen and antiretroviral drugs necessitate careful monitoring. The profound and long-lasting suppression of the CD4+ T-cell count in patients who receive thymoglobulin induction therapy has been associated with an increased risk of infections requiring hospitalization.

Diagnostic Assays

Rapid and sensitive molecular biology-based assays for many of the common viruses after transplantation have replaced, for the most part, serologic testing and *in vitro* cultures for the diagnosis of infection. Serologic assays are generally less sensitive in transplant patients, as humoral immune responses may be delayed or absent. In one series, 29% of patients with parvovirus B19 infection as shown by PCR assay had a negative IgM assay. Quantitative molecular tests allow the optimization and individualization of antiviral therapies for prevention and treatment of infection. This advance is most significant in the management of CMV, EBV, hepatitis B, and hepatitis C viruses, where quantitative assays (such as viral loads or antigenemia tests) guide antiviral therapy. Nonquantitative (i.e., qualitative) assays are less useful in management as they do not assess responses to therapy and cannot differentiate primary infection, from reactivation or reinfection. For example, chromosomal integration of latent HHV-6 DNA (which happens in 1–3% of immunocompetent subjects) leads to high levels of viral DNA, whether or not the infection is active; one group concludes that any diagnosis of HHV-6 encephalitis should not be made without first excluding chromosomal HHV-6 integration by measuring

DNA load in CSF, serum and/or whole blood. Latent infections due to EBV and CMV may be qualitatively positive by PCR, confirming the need for quantitative assays.

Blood tests may not always accurately reflect the level of end-organ diseases; thus, it may be useful to test specific affected tissues as well the blood. In this regard, histologic evaluation of tissues using pathogen-specific immunohistochemistry may augment systemic assays. Patients with CMV colitis, for example, may have negative molecular or antigenemia blood assays for CMV. In addition, patients may shed CMV in secretions without true infection, limiting the diagnostic capacity of a positive culture. BK polyomavirus may be detectable in the urine (either by cytology, looking for the classic decoy cells, or by PCR) before it is detectable in the blood, providing a window of opportunity for reducing immunosuppression possibly in advance of invasive disease. Adenovirus may be detectable in local infections, such as cystitis, with negative blood assays.

Therapy

The treatment of viral infections in the renal transplantation recipient includes: the reduction of immunosuppression, antiviral therapy, diagnosis and treatment of co-infections (such as CMV, EBV, HHV-6, or -7), and use of adjunctive therapies such as immunoglobulins or colony stimulating factors. The overall level of immunosuppression has a major impact on both the risk of reactivation of latent infection and the ability to clear such an infection. Reducing the immunosuppressive regimen during active viral infection can be a major contribution toward clearing infection, although it presents a risk of graft rejection. As protective cytotoxic immunity to viruses is generally T-cell (CD8+) mediated, an initial reduction of antimetabolites (if neutropenic) and calcineurin inhibitors merits consideration. In contrast, a reduction of the steroid dose during the acute phase of a febrile illness may cause acute adrenal insufficiency.

When available, antiviral therapies (such as acyclovir, ganciclovir, ribavirin, lamivudine, and oseltamivir) are often essential. The toxicity of some agents (such as cidofovir, foscarnet, and ribavirin) may complicate management, notably in the face of reduced renal function in patients receiving calcineurin inhibitors as part of the immunosuppressive regimen. The duration of therapy is often longer in transplant patients than in normal hosts, and often reflects the ability to reduce the overall level of immunosuppression, that is. less immunosuppression may result in a shorter treatment time. The increased information provided by molecular diagnostics may allow for more directed treatment regimens.

Antiviral therapy is often used for prophylaxis in the post-transplantation period, especially for individuals at risk for primary infection. In general, acyclovir and related agents are used to prevent HSV and VZV and ganciclovir or valganciclovir to prevent CMV as well as HSV and VZV. The relative advantages of universal prophylaxis (i.e., the use of antiviral medication in all susceptible patients for a period after transplantation) or monitoring with preemptive (early) therapy remain to be established. Meta-analyses suggest that universal prophylaxis with antiviral medications in SOT recipients reduces CMV disease and CMV-associated opportunistic infections, graft rejection, and mortality; their use is recommended for high risk individuals (CMV-positive recipients and in CMV-negative recipients of CMV-positive organs). Some studies indicate that universal prophylaxis and preemptive therapy are effective in reducing the incidence of CMV disease. In the HSCT setting, where the risks of bone marrow toxicity from valganciclovir are higher, many programs choose to use preemptive monitoring and therapy for CMV.

Various adjunctive therapies have been helpful in treating and preventing viral infections. Immunoglobulins (i.e., intravenous immune globulins (IVIG), CMV, and HBV hyper-immune globulins (both prepared from plasma preselected for high titer antibodies to CMV and HBV, respectively), as well as monoclonal antibodies such as those for RSV) have been helpful in preventing and treating viral infections, likely due to both direct and indirect immunomodulatory properties. A significant percent of patients have post-transplantation hypogammaglobulinemia, which has been linked to increased mortality and may benefit from globulin repletion. This may be most apparent in the setting of active infections, as well as prophylaxis. Immunostimulatory agents, such as interferon-alpha used to treat hepatitis C, can be helpful at treating the viral infection but may perturb the relationship between the graft and the host, precipitating rejection. Reversal of neutropenia can be done using colony stimulating factors such as G-CSF, which is generally well tolerated in sold organ transplantation patients.

Vaccination

Vaccines should be given to patients as early as possible in the course of organ failure and well in advance of transplantation to optimize immune responses. In general, a response to vaccination is more likely to occur when given pre-transplantation rather than after transplantation. Nonlive viral vaccines such as hepatitis B, hepatitis A, injectable influenza, rabies, HPV, injectable polio may be given both pre- and post-transplantation (see **Table 3** for classifications). Live viral vaccines such as attenuated influenza (delivered by nasal spray), measles, mumps, rubella, varicella (both Varivax, for protection against varicella in nonimmune subjects, as well as Zostavax, for protection against zoster), yellow fever, oral polio, and

Table 3 Viral vaccines, classified by type of vaccine

Virus	*Live attenuated*[a]	*Killed*	*Subunit/protein*
Measles	x		
Mumps	x		
Rubella	x		
Varicella-zoster (both for varicella and zoster)	x		
Yellow fever	x		
Smallpox	x		
Influenza	x (intranasal)	x (injectable)	x (injectable)
Japanese encephalitis	x	x	
Poliovirus	x (oral)	x (injectable)	
Hepatitis A virus		x	
Rabies virus		x	
Hepatitis B			x
Human papilloma virus			x

[a]Live-attenuated vaccines are generally contraindicated in immunocompromised hosts.

vaccinia (smallpox) should generally be avoided after SOT and in patients who are chronically immunosuppressed (such as those with GVHD); some may be given after HSCT. Consideration of future travel or trips home should also be considered in the pre-transplantation period. Vaccines for CMV, EBV, RSV, and other viral pathogens are under further investigation.

See also: Transmissible Spongiform Encephalopathies.

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Origin of Viruses

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Glossary

Archaea A domain of prokaryotic microorganisms whose informational mechanisms (DNA replication, transcription, and translation) are closely related to those of eukaryotes.

Homology Two biological structures are homologs if they originated from a common ancestral structure.