49 Emerging and Rare Viral Infections in Transplantation

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Viral infections are common following solid organ and hematopoietic stem cell transplantation, as detailed in other chapters. While cytomegalovirus (CMV) remains the most prominent virus in transplantation, and the clinical manifestations and complications of infection with other herpesviruses (e.g., herpes simplex virus, Epstein–Barr virus, and human herpesviruses 6 and 8) are well described, improvements in diagnostic techniques have led to the recognition of a number of additional viruses with potential pathogenicity in the immunocompromised host. Outbreaks of emerging viruses, the resurgence of vaccine-preventable viral infections, and the identification of viruses which cause self-limited infection in immunocompetent children but significant disease in transplant recipients have highlighted the breadth of pathogens in this patient population. Some of these emerging and unusual viral pathogens are discussed in alphabetical order below.

49.1 Astrovirus

Astrovirus is a common cause of viral gastroenteritis throughout the world and has been a cause of outbreaks of diarrheal disease in schools, hospitals, nursing homes, and military bases [1–3]. Several recent reports have highlighted the impact of this RNA virus on immunocompromised hosts. In addition to its role in gastroenteritis in these patients, one astrovirus subgroup (VA1/HMO-C) has been reported to cause encephalitis in allogeneic hematopoietic stem cell transplant (HSCT) recipients and children with X-linked agammaglobulinemia [4, 5]. Molecular techniques including reverse-transcription polymerase chain reaction (RT-PCR), RNA sequencing, and next-generation sequencing have demonstrated the presence of this subgroup in the cerebrospinal fluid (CSF) and brain tissue of infected patients. Immunohistochemical staining on biopsy tissue has confirmed the presence of invasive infection. There are no known antiviral treatments available, and central nervous system (CNS) infection has been fatal in the cases reported to date. Additional study is needed to determine the prevalence of astrovirus infection in transplanted patients.

49.2 Bocavirus

Bocavirus is a human parvovirus that causes upper and lower respiratory tract infection, gastroenteritis, and encephalitis in children [6, 7]. Infection is most common in the late fall and winter, and most commonly presents with rhinorrhea, fever, cough, wheezing, or diarrhea. Thirty percent of children develop hypoxia, and a variety of radiographic findings have been reported, including peribronchial cuffing, lobar infiltrates, and pleural effusions. Nosocomial infection has occurred [8]. Bocavirus infection has been reported in the first few weeks following hematopoietic stem cell transplantation, presenting with fever, rhinorrhea, cough, diarrhea, and hypoxia [9]. Virus has been detected in high quantities in plasma, nasopharyngeal aspirates, and stool. Fecal shedding occurs for several weeks to months after clinical resolution of infection [10]. Severe and prolonged diarrhea has been described in liver transplant and hematopoietic stem cell recipients [11]. It has been suggested that bocavirus, like respiratory syncytial virus (RSV) and parainfluenza, may play a role in the development of bronchiolitis obliterans, a manifestation of chronic rejection in lung transplantation [12–14]. To date, there are no data on antiviral efficacy against bocavirus.

49.3 Chikungunya Virus

Chikungunya virus, a mosquito-borne alphavirus transmitted by *Aedes aegypti* and *Aedes albopictus*, is a tropical infection which has caused epidemic disease in India, Thailand, Malaysia, Madagascar, and Reunion Island [15, 16]. It is endemic in eastern, central, and southern Africa. In 2013, chikungunya was reported in St. Martin, with epidemic

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spread throughout the Caribbean, Central America, South America, and Florida, where infection spread locally via *A. aegypti* [17].

After an incubation period of 2–4 days, infection presents with high fever, headache, myalgias, and arthralgias, and can resemble dengue. Arthralgias are typically symmetric and involve large joints, particularly in the legs and arms. Frank arthritis may also occur in the interphalangeal joints, wrists, and ankles. Half of patients also develop a rash, which can be maculopapular, petechial, or bullous and is most commonly located on the trunk, with occasional involvement of the face, extremities, palms, and soles. Ocular pain has also been reported. Rarely, meningoencephalitis, myocarditis, or hepatitis can occur. Symptoms resolve in 7–10 days, although arthralgias and joint stiffness may persist for weeks to months after fever resolves. Severe manifestations of infection with fatal outcomes have been reported in patients with underlying diabetes, lung disease, or chronic neurologic conditions.

Laboratory findings include lymphopenia, thrombocytopenia, elevated transaminases, and hypocalcemia. Diagnosis may be made serologically or by RT-PCR. IgM antibodies develop as fever resolves, typically 1 week after symptom onset. There is currently no known effective antiviral therapy for chikungunya.

During a widespread outbreak of infection on Reunion Island in the Indian Ocean, organ and tissue donors were screened for the presence of chikungunya infection [18]. Corneal donors were found to have serologic and PCR evidence of infection in serum and corneal tissue. Transmission of infection with corneal transplantation is presumed to occur. There have been no reports of transmission of chikungunya in solid organ or stem cell transplantation to date although with reports of infection in Asia, Europe, and North America in travelers from endemic areas, the risk of transmission and the clinical course of infection in these patients require further study.

49.4 Coronavirus

In February 2003 a worldwide outbreak of severe respiratory infection occurred, infecting more than 8000 patients over several months in 29 countries, most severely affecting southern China, Hong Kong, and Canada, with well-described healthcare-associated outbreaks [19–26]. Eighty percent of those affected were previously healthy, with no comorbid conditions. The outbreak began in Guangdong Province, China, in November 2002 and with global travel spread rapidly to multiple continents. The infection of numerous health care workers and the rapidly fatal course of infection, even in healthy hosts, were remarkable. Named Severe Acute Respiratory Syndrome (SARS), this infection was quickly determined to be due to a new strain of coronavirus, a group of viruses known to cause human disease since the 1960s [27].

Patients initially noted high fever, myalgias, headache, and cough, and subsequently became dyspneic [19, 20, 25, 28]. A productive cough was seen in nearly one third of patients, while rash and lymphadenopathy were absent. Lymphopenia, thrombocytopenia, mild elevation of transaminases, prolonged prothrombin time with elevated D-dimers, elevated lactate dehydrogenase (LDH) and creatine kinase (CK), and hyponatremia were common lab findings [25]. Chest radiographs revealed focal airspace consolidation or ground glass opacities, initially without the interstitial infiltrates most characteristic of viral pneumonitis, with lower lung field predominance [22, 25]. Pleural effusions and mediastinal lymphadenopathy were generally absent. Histopathologic findings in lung biopsies and at autopsy included diffuse alveolar damage consistent with adult respiratory distress syndrome (ARDS), with significant alveolar edema, minimal inflammation, and no viral inclusions.

Treatment included corticosteroids and intravenous or oral ribavirin. Although published data are not yet available in humans, animal models suggest that monoclonal antibody to SARS coronavirus (SARS-CoV) is effective in decreasing viral replication and improving outcomes [26]. The overall case fatality rate during the SARS epidemic was nearly 10% [19]. A novel coronavirus was rapidly isolated and identified as the cause of SARS and sequenced, allowing for RT-PCR and serologic testing to be developed [29, 30].

During the SARS outbreak in Toronto, a liver transplant recipient was fatally infected while visiting a medical center for an outpatient clinic visit nearly 10 years posttransplant [31]. Disseminated infection was described in a lung transplant recipient in whom virus was detected in lungs, bowel, lymph nodes, liver, kidney, skeletal muscle, and brain at autopsy [32, 33]. Tissue viral loads were significantly higher in transplant recipients than in their immunocompetent counterparts [34]. The last of the nearly 8000 reported cases of SARS-CoV was reported in May 2004, after which no additional cases have been reported, for unclear reasons.

In September 2012, initial reports of infection with another novel human coronavirus began in Saudi Arabia, with rapid spread to neighboring Egypt, Iran, Jordan, Kuwait, Lebanon, Qatar, Oman, Yemen, and the United Arab Emirates, then to other continents with airline travel [35]. Middle East Respiratory Syndrome Coronavirus (MERS CoV) has been reported to cause severe respiratory tract infection in adult patients, with a mortality rate as high as 60%, most commonly in those with diabetes mellitus and end stage renal disease [36]. After a median incubation period of 5 days (range, 2–14 days), patients often present with fever, cough, dyspnea, and diarrhea after close contact with an infected case and/or travel from an area where infection is active. Coryza, headache, nausea, vomiting, and abdominal pain have also been reported [37]. Laboratory findings include thrombocytopenia, leukopenia, lymphopenia, and elevated

transaminases and LDH. Coinfection with other respiratory viruses has been reported [38]. As with SARS-CoV, health care workers are at risk for infection [39, 40]. Dromedary camels have been reported to harbor infection in the Arabian Peninsula, although the mode of transmission of infection has not yet been elucidated [41].

Several cases of MERS CoV infection have been reported in hematopoietic stem cell and solid organ transplant recipients, who have developed bilateral pulmonary infiltrates with respiratory failure, acute renal failure, leukopenia, thrombocytopenia, and elevated transaminases, at times without fever [36, 42].

While difficult to grow in cell culture, MERS CoV may be diagnosed by RT-PCR on respiratory secretions. Virus has been detected with these techniques in urine and stool as well. To increase the yield of testing, it is recommended that multiple specimens from different sites (e.g., nasopharyngeal swab, sputum, BAL fluid, serum, and stool) be tested using RT-PCR, which is available from the CDC and local health departments in the USA [37]. Due to the risk of transmission of infection to health care workers, contact and airborne precautions are recommended in caring for the suspected MERS-CoV infected patient [39, 40].

While there have been no randomized, controlled clinical trials of antivirals against MERS-CoV, ribavirin and mycophenolate mofetil (an immunosuppressive agent used commonly in transplantation) have in vitro activity against the virus [43]. Ribavirin (in combination with interferon α-2b) has demonstrated promise in decreasing lung injury and viral replication in rhesus macaques infected with MERS-CoV [44]. A retrospective cohort study describing the use of ribavirin and interferon α-2a in twenty patients with severe infection demonstrated an early survival benefit [45].

Whereas coronaviruses made world headlines with the SARS epidemic in 2002–2004 and the MERS-CoV emergence in 2012, coronaviruses OC43 (group 1) and 229E (group 2) have been known for decades to cause upper respiratory tract infections during the fall and winter months. Coronavirus NL63 (group 1) has been reported to cause upper and lower respiratory tract infections in immunocompetent hosts in the Netherlands, and coronavirus HKU1 (group 2) has been reported to cause pneumonia in Hong Kong and France [21]. Non-SARS coronaviruses have recently been associated with severe lower respiratory tract infections in hospitalized patients, including lung and liver transplant recipients [46]. Coronavirus 229E has been isolated from hematopoietic stem cell transplantation recipients with fever and cough associated with interstitial and alveolar pulmonary infiltrates [46]. Pancytopenia may be present. Radiographic infiltrates are most commonly interstitial, although 28% are alveolar. Pleural effusions may be present, and pneumothorax has been noted in a minority of patients. Diagnosis may be made by culture in human hepatoma HUH7 cell line, or by RT-PCR [46, 47].

49.5 Hepatitis E

Hepatitis E is endemic in developing countries and has been reported to cause epidemic disease in Asia, Africa, and Latin America via fecal–oral transmission [48]. Travel-related infection has been reported in those returning from endemic areas with poor sanitation. Recent reports have highlighted the important role of this infection in transplant recipients.

Hepatitis E virus (HEV) is an RNA virus with four major genotypes with presumed reservoirs in pigs, wild boars, deer, and mollusks [49, 50]. Seroprevalence surveys indicate that infection in blood donors, even in France and the USA, is significant; in some areas, hepatitis E is more prevalent than hepatitis A [51, 52]. Epidemics of infection have been described from ingestion of contaminated water, mollusks, and undercooked deer, boar, or pig meat [53–55]. Blood transfusion-transmitted infection has also been described [56–59]. After an incubation period of two to nine weeks, patients develop jaundice, abdominal pain, anorexia, and nausea. Fever and chills may occur as well, although rash is unusual. Diagnosis can be made by RT-PCR detection of HEV RNA, which is present between 2 and 6 weeks after infection, as symptoms occur [60]. IgM antibodies develop as symptoms resolve, approximately 4 weeks after infection. Elevated transaminases occur, peaking approximately 6 weeks after infection. While viremia resolves within 6 weeks of infection, virus remains detectable in stool for several weeks after viremia resolves and IgG appears. Serum IgG antibodies persist for years after acute infection.

Approximately 10% of patients with acute HEV infection develop fulminant hepatitis with acute hepatic failure; the presence of pregnancy or underlying chronic liver disease (e.g., chronic hepatitis C infection or cirrhosis) increases the risk for severe infection [61, 62]. Histopathologic findings on liver biopsy include lymphocytic infiltration of portal triads. Chronic hepatitis appears to be rare in immunocompetent hosts.

Disease in organ transplant recipients has been characterized by a high incidence of chronic infection (in up to 60% of acutely infected patients) with progressive fibrosis and eventual cirrhosis [63–66]. Reactivation of infection has been described in liver and allogeneic HSCT recipients, in whom nearly half of infections became chronic [67–69]. Liver transplant recipients appear to be at increased risk for chronic infection resulting from reactivation of HEV after transplantation, as well as acute graft hepatitis from reactivation or primary infection [70]. Extrahepatic manifestations of infection in transplant recipients have included glomerulonephritis and neurologic involvement [69, 71].

There are no FDA-approved therapies for HEV infection, although decreasing immunosuppression appears to have helped control viremia in some chronically infected transplant recipients. In small studies, interferon alpha and ribavirin have been reported to decrease viremia in these patient populations [72, 73].

49.6 Lymphocytic Choriomeningitis Virus

Lymphocytic choriomeningitis virus (LCMV) gained notoriety as a pathogen in solid organ transplantation in 2005, when the first two outbreaks of donor-transmitted infection were described [74–76]. Additional donor-transmitted outbreaks have recently occurred in the USA and Australia [77–80]. Four clusters of donor-derived infection have occurred in the USA to date.

LCMV is a rodent-borne Old World arenavirus that causes asymptomatic or mild, self-limited illness in the immunocompetent host. Rodents, especially common house mice, laboratory mice, and hamsters, often acquire infection congenitally, resulting in lifelong, asymptomatic excretion of virus in urine, saliva, and feces [81–84]. Human infection occurs via direct contact with infected rodents or aerosolized infected excreta (e.g., with cleaning soiled cage bedding). Symptoms described in immunocompetent humans include fever, headache, and myalgias, with CSF findings consistent with aseptic meningitis (e.g., lymphocytic pleocytosis). In the normal host, infection is self-limited and carries a mortality rate of less than 1% [85].

In the transplant clusters, infection with LCMV has been fatal in more than 80% of cases [74, 78, 80]. Patients have presented within the first month posttransplant with fever, diarrhea, abdominal pain, and dyspnea. Rash, headache, lethargy, hypotension, and the presence of pulmonary infiltrates are variable. Thrombocytopenia and anemia have been present, with variable peripheral leukocyte and lymphocyte counts. Acute hepatitis with elevated transaminases has been noted, as well as coagulopathy with prolonged protimes. Patients have developed rapidly progressive multisystem failure with encephalopathy prior to death. In one cluster, while the donor had no evidence of infection in multiple tissues tested, a pet hamster present in the donor's home for several weeks prior to donation was found to have LCMV in multiple tissues [74]. Virus isolated from the hamster was identical to that isolated from the infected transplant recipients. The survivor in that cluster, a kidney recipient, was treated with discontinuation of all immune suppression except corticosteroids and with intravenous ribavirin. Similar approaches have been used in more recent cases [80].

With four donor-derived infection outbreaks in the USA alone, LCMV infection is likely more common than previously recognized in transplant recipients. Detailed workup of potential organ donors with aseptic meningitis or meningoencephalitis may prevent transmission in some cases. Whether LCMV infection occurs posttransplant in recipients with exposure to pet hamsters or house mice is unknown.

49.7 Metapneumovirus

Human metapneumovirus is a single-stranded RNA paramyxovirus of worldwide endemicity that causes respiratory tract infection in children, the elderly, and immunocompromised adults, with outbreaks reported in long-term care facilities [86–90]. Infection occurs in the late winter and early spring (January through April), similar to the seasonality of respiratory syncytial virus (RSV). Upper and lower respiratory tract symptoms, including rhinorrhea, sore throat, cough, dyspnea, and fever, have been described.

Infection has been described following lung and heart–lung transplantation, resulting in acute pneumonia with diffuse alveolar damage and hyaline membrane formation [91, 92]. Lung transplant recipients with metapneumovirus pneumonia have a 14% mortality rate and are at higher risk for acute and chronic rejection [92, 93]. In renal transplant recipients, pneumonitis due to metapneumovirus has been reported 3 years posttransplant [94]. In one study of HSCT recipients, human metapneumovirus was isolated via RT-PCR in 26% of symptomatic patients undergoing bronchoscopy and carried a mortality rate of 80% [95]. Infection occurred within the first few weeks following transplant, and was characterized by fever, nasal congestion, and cough, with rapid development of hypoxia, hypotension, and progressive pneumonia, with diffuse alveolar hemorrhage in three of five patients [94–96]. Pleural effusions and nodular infiltrates may be seen, which may help differentiate infection from RSV. Coinfection with RSV, rhinovirus, and CMV has been described following lung transplantation [97].

Ribavirin has been demonstrated to decrease human metapneumovirus replication in the lungs in a mouse model [98], and intravenous ribavirin has been effective in the treatment of several lung transplant recipients with metapneumovirus infection [99].

49.8 Measles

Measles outbreaks have occurred in multiple states in recent years, with an attack rate of greater than 90% among susceptible patients, including unvaccinated children and adults [100–108]. Affected patients develop fever, cough, and coryza, associated with a characteristic rash. Infection may be complicated by pneumonia, encephalitis, or dissemination, with significant mortality noted in solid organ and HSCT recipients [109]. Infection has been associated with waning immunity and is diagnosed serologically. There are no data on antivirals for treatment of measles.

49.9 Mumps

Mumps has been increasingly reported in the USA, with more than 10,000 cases reported in a large multistate outbreak in 2005–2006 [110–116]. Patients present with acute onset of unilateral or bilateral parotitis; infection may be complicated by orchitis, oophoritis, pancreatitis, mastitis, meningitis, and encephalitis [117]. Infection may be diagnosed serologically or via PCR [118, 119]. No antivirals have been investigated in the treatment of mumps. Enhanced efforts at immunization against measles and mumps pretransplant as well as active surveillance posttransplant are warranted.

As a result of the re-emergence of these vaccine-preventable viruses, recent guidelines suggest vaccination with the measles, mumps, and rubella (MMR) vaccine 2 years following hematopoietic stem cell transplantation in patients without evidence of graft-versus-host disease [120, 121]. If at all possible, patients undergoing solid organ transplantation who do not have evidence of protection against measles and mumps (e.g., positive IgG antibody to each) should be vaccinated prior to the initiation of immunosuppressive therapy.

49.10 Norovirus

Noroviruses are caliciviruses that cause over 20 million cases of gastroenteritis annually in the USA and over half of all epidemics of gastroenteritis worldwide [122–129]. Infection is acquired via consumption of contaminated foods (including raw oysters, fruit, and vegetables) or via ingestion of or swimming in contaminated water, with spread via fomites and from person to person [130–145]. Infection is extremely contagious and often spreads rapidly as a result of prolonged fecal shedding in affected patients after resolution of symptoms. Outbreaks of infection have been described in multiple settings including military barracks, restaurants, hospitals, long-term care facilities, schools, and cruise ships [122].

Infection may be asymptomatic or present with the sudden onset of nausea, vomiting, and diarrhea after an incubation period of less than 48 h. Some studies have suggested that vomiting is more common in children, with diarrheal symptoms predominating in infants and adults [138, 148]. Infection is most common in the winter months, with symptoms lasting 1–7 days [122, 142, 148]. Attack rates in some outbreaks have been 50–90%, with health care workers at substantial risk for infection [127, 130, 137–139, 144–147].

Noroviruses cannot be cultured in vitro, but RT-PCR and enzyme immunoassay (EIA) assays are available for diagnosis in stool specimens [148–150].

Norovirus infection in solid organ transplant recipients is common, and marked by risk for chronic and relapsing infection [150]. Infection presents with watery diarrhea, which can cause volume depletion and acute renal failure in renal transplant recipients [126, 142, 149, 151]. Patients may be symptomatic for months and may shed virus in stool for years. Hematopoietic stem cell transplant recipients have been reported to develop acute and chronic diarrheal disease from norovirus infection, which has been associated with the subsequent development of chronic GVHD [151, 152]. Receipt of cord blood, induction with fludarabine, and receipt of alemtuzumab have been reported to be risk factors for norovirus infection in this setting. Nosocomial outbreaks of infection in HSCT units have resulted in infection of staff and patients, with sepsis from bacterial translocation complicating several cases [152, 153].

Treatment of norovirus infection in transplant recipients has not been investigated in randomized, controlled trials to date. Reduction of immunosuppression resulted in clearance of infection in one intestinal transplant recipient with norovirus infection [154]. There are no available antiviral therapies to date. Noroviruses are highly resistant to disinfectants, propagating prolonged transmission in many environments.

49.11 Parvovirus B19

Parvovirus B19 infection is common, with 60–90% of adults having serologic evidence of prior infection [155]. In children, parvovirus infection causes erythema infectiosum, a febrile illness with a characteristic “slapped cheek” rash. Adults with acute parvovirus infection develop a flu-like illness, sometimes with resultant arthropathy. A pathogen of erythroid progenitor cells, parvovirus B19 causes severe anemia in patients with underlying hemolytic disorders and hydrops fetalis in pregnancy. In recent years, neurologic involvement including meningoencephalitis has been described, which may be more common in immunocompromised hosts [156, 157].

In transplant recipients, anemia is the most common presentation of infection. Fever occurs in 25% of patients and arthralgia or rash occurs in less than 10% of those affected [158]. Pancytopenia may be present. Other manifestations described in the transplant population include hepatitis, myocarditis, pneumonitis, encephalitis, meningitis, peripheral neuritis, and collapsing glomerulopathy [155, 157–160]. Those with CNS infection may develop sequelae including seizures, cognitive deficits, stroke, and muscle wasting [157]. Donor-transmitted infection has been described, presenting with allograft dysfunction, fever, arthralgia, and pancytopenia, often without a rash [161–164]. Chronic or recurrent anemia may be seen posttransplant, as well as pure red cell aplasia [165, 166]. Parvovirus B19 infection has also been associated with the subsequent development of thrombotic microangiopathy in kidney transplant recipients, including a cluster of cases in Iran; hemophagocytic lymphohistiocytosis has also been described in this population [167, 168]. The significance of the frequent finding of parvovirus DNA in renal allografts pre- and posttransplant is under investigation [169]. In other transplant populations, parvovirus may be associated with chronic cellular allograft rejection [170].

Diagnosis of parvovirus B19 infection may be made by serology, PCR, or bone marrow examination in immunocompetent hosts. The yield of serologic testing (especially IgM) is limited in transplant recipients who may not mount an adequate antibody response to infection, so that RT-PCR on blood, bone marrow, or other involved tissues is necessary to detect infection in many cases [155].

Infection may respond to intravenous immunoglobulin (IVIg), with relapses occurring in up to 25% of immunosuppressed hosts [155]. There are no published data on the use of antivirals in parvovirus infection.

49.12 Polyoma Viruses (KI, WU, and Merkel Cell Carcinoma Polyomaviruses)

Human polyoma viruses such as BK virus and JC virus are well known pathogens in transplantation and are discussed elsewhere. In recent years three additional polyoma viruses have been described as potential pathogens in immunocompromised hosts. Like BK and JC, these viruses frequently cause asymptomatic primary infection in healthy patients and are capable of establishing latent infection which can be reactivated in the setting of immune suppression. KI and WU viruses (named for the institutions in which they were discovered, Karolinska Institutet and Washington University) have been isolated in children with acute respiratory symptoms including wheezing as well as in the setting of pneumonia [171, 172]. Respiratory infection has also been described in HIV-infected patients, in whom higher viral loads have been demonstrated in those with lower CD4 counts [173].

KI and WU polyomaviruses have been isolated in nasopharyngeal, sputum, and bronchoalveolar lavage specimens in hematopoietic stem cell and solid organ transplant recipients [174, 175]. These viruses have also been detected in transbronchial biopsy specimens in lung transplant recipients, who in many cases were asymptomatic. Coinfection with other viral and bacterial pathogens has been reported. RT-PCR results should be interpreted with caution in transplant recipients, in whom severe infection has not been described to date. There are no available data on the role of decreasing immunosuppressive therapy or the use of antiviral agents in the development or treatment of infection with KI and WU polyomaviruses.

Merkel cell carcinoma is a neuroendocrine malignancy of the skin which is most common in immunocompromised hosts including transplant recipients [173, 176]. Over 80% of these tumors contain a polyoma virus named Merkel Cell polyomavirus (MCPyV); virus has also been found in respiratory secretions in asymptomatic transplant recipients. Further study of each of these polyomaviruses is ongoing in the transplant population.

49.13 Rotavirus

Rotavirus, the most common cause of enteritis worldwide and a common pathogen in healthy children under the age of 3, has become increasingly recognized as a pathogen in pediatric and adult recipients of solid organ transplants [177]. Epidemics have occurred through fecal–oral transmission, primarily in the winter and spring. Affected patients present with watery diarrhea, nausea, vomiting, abdominal pain, and, in some cases, gastrointestinal bleeding from colonic ulcers. Infection may be diagnosed by antigen detection in stool specimens using ELISA, latex agglutination, or quantitative PCR. Infection is generally self-limited with weaning immunosuppression during the acute phase of illness. There are no published data on antiviral activity against rotavirus; treatment remains symptomatic.

Rotavirus has been associated with a high risk of acute cell-mediated rejection in intestinal transplant recipients, which has been proposed to be related to poor absorption of immunosuppressive agents in the setting of vomiting and diarrhea, as well as immune reactivation of gastrointestinal tract-associated lymphocytes in the setting of infection [178]. In HSCT recipients, rotavirus infection may be difficult to differentiate clinically and histopathologically from GVHD.

In 1998, a live, oral, tetravalent rhesus–human reassortment rotavirus vaccine (RotaShield, Wyeth-Ayerst Laboratories, St. David, PA) was licensed and recommended for routine immunization of infants in the USA; it was voluntarily withdrawn from the market in 1999 due to its association with intestinal intussusception noted in postmarketing surveillance [179–181]. Two additional Rotavirus vaccines have been studied (RotaTeq, Merck & Company, Whitehouse Station, NJ; Rotarix, GlaxoSmithKline Biologicals, Rixensart, Belgium). Both vaccines are oral and contain live virus, and are thus contraindicated in highly immunocompromised patients. Fecal virus shedding has been noted with both vaccines, with transmission of vaccine-associated virus to household members noted with Rotarix [181].

Current vaccination guidelines in immunocompromised hosts recommend that HSCT and solid organ transplant recipients not receive this live virus vaccine. Household contacts of patients with immune deficiency may be vaccinated, but the transplant recipient should not change diapers for 4 weeks after vaccination, the usual duration of viral shedding in stool [182].

49.14 West Nile Virus

West Nile virus (WNV) was initially isolated from a febrile patient in the West Nile Province in Uganda in the 1930s and has been enzootic in Africa, Asia, the Middle East, and parts of the Mediterranean and Europe, causing asymptomatic disease

or a self-limited febrile flu-like illness [183]. This flavivirus was first detected in the northeastern USA in 1999 and has caused outbreaks of infection in the late summer and early fall throughout the USA since then [184, 185]. Birds are the primary reservoir of infection. Mosquitoes acquire lifelong infection after biting viremic birds, spreading infection from their salivary glands to other species, including humans, with a subsequent bite. In human infection, the incubation period is 2–14 days [186]. While approximately 80% of infections are asymptomatic, 20% of patients develop West Nile fever, characterized by fever, malaise, anorexia, nausea, myalgias, headache, and occasionally lymphadenopathy [187]. One in 150 symptomatic patients develops meningitis and/or encephalitis [188]. Meningitis presents with photophobia, phonophobia, meningismus, and hyperreflexia; CSF analysis reveals a lymphocytic pleocytosis (<500 leukocytes/mm^3, glucose usually normal). Patients with encephalitis develop altered mental status, cranial nerve palsies, seizures, and movement disorders. A minority of patients develop rapid asymmetric weakness that may progress to flaccid paralysis mimicking poliomyelitis, associated with hyporeflexia or areflexia [184, 189, 190]. Acute neuromuscular respiratory failure may develop, which carries a mortality rate of more than 50% [188]. Hemorrhagic fever characteristic of other flaviviruses has also been described [191]. The presence of severe weakness and hyporeflexia in a patient with meningoencephalitis should raise the suspicion of WNV infection. MRI may demonstrate meningeal or periventricular enhancement, sometimes mimicking ischemic changes [186].

Transmission of WNV via dialysis has been suggested [192], and transmission via blood transfusion and organ transplantation has been well documented [193–197]. In immunocompromised hosts, central nervous system involvement is common, although CSF pleocytosis may be minimal [198–200]. Community-acquired infection has been reported following solid organ transplantation, occurring 2 months to 10 years posttransplant [185, 199–202]. A study of WNV infection during an outbreak in Toronto noted that liver, kidney, and heart transplant recipients had 40 times the risk of symptomatic infection as normal hosts [203]. In all cases, the recipients had participated in outdoor activities without the use of insect repellant or other personal protective measures. Fever often preceded neurologic symptoms. A delayed serologic response was noted in the transplanted cohort in which infection carried a mortality rate of 25%, versus 9% in the general population. In a Colorado outbreak in 2003, 11 transplant recipients (4 kidney, 2 liver, 2 kidney/pancreas, 1 lung, and 2 HSCT) developed infection requiring hospitalization [204]. Ten (91%) developed meningoencephalitis, one developed acute flaccid paralysis without encephalitis, and three patients had meningoencephalitis and paralysis. Two patients died (18% mortality), and three suffered significant neurologic sequelae. It appears that transplant recipients are more likely to develop meningoencephalitis in the setting of acute West Nile virus infection than immunocompetent hosts, perhaps with a higher mortality rate. Prolonged infection can also occur [205].

Several cases of WNV infection have been reported in HSCT recipients [206, 207]. Infection occurred 3–5 months posttransplant in the most well-described cases, after engraftment but while on calcineurin inhibitor-based prophylaxis or treatment of chronic graft-versus-host disease. Fever, lethargy, progressive bilateral extremity weakness, and hyporeflexia or areflexia were present. CSF contained 0–6 white blood cells/μL; IgG and IgM were negative in CSF and blood in most cases. Diagnosis of WNV infection was made by PCR performed on serum and CSF. All of the described patients died.

Diagnosis of WNV infection in immunocompetent hosts may be made serologically or via RT-PCR. An IgM antibody capture assay is available and becomes positive in CSF 3–5 days after onset of symptoms in nonimmunosuppressed hosts [202, 207], before serum antibody develops; CSF IgG appears approximately 5 days later. Antibody presence may be confirmed with viral neutralization studies. IgM antibodies may persist in serum for up to 12 months after infection resolution, and IgG may persist for years. As in the hematopoietic stem cell recipients noted above, immunocompromised patients demonstrate delayed seroconversion, making diagnosis of acute infection difficult at times. Nucleic acid testing in plasma and/or CSF is the most useful diagnostic test in this setting [208].

There are no antiviral agents that have proven efficacy in the treatment of WNV infection. Ribavirin possesses in vitro activity but demonstrates poor clinical efficacy [186, 209]. IVIg with high titers of anti-WNV antibodies (e.g., from Israel, where infection is endemic) has demonstrated significant clinical benefits in animal models, although antibody titers are low in immune globulin derived from the US donors, which have proven ineffective in treating acute infection [184, 210, 211]. A report of successful treatment of donor-transmitted WNV infection in a liver transplant recipient by reducing immunosuppression and administering plasma from seropositive blood donors has been published [212]. Overall case fatality rates of infection with WNV are 4–20% [189, 192], with significantly higher rates in transplant recipients.

Unlike the case in other neuroinvasive viral infections, the severity of initial clinical presentation does not predict the prognosis of WNV infection [187, 190, 213]. Survivors frequently suffer from prolonged fatigue, myalgias, cognitive deficits, memory loss, and tremors. Parkinsonism, excessive somnolence, and postural instability are reported. Phase I trials of a vaccine have been promising [214]. Transplant recipients should be educated about the transmission of West Nile virus and urged to remove any stagnant water collections and to use insect repellant when outdoors at dusk during the later summer and fall in order to prevent infection.

49.15 Conclusion

Viruses remain the most significant and elusive pathogens infecting patients following solid organ and hematopoietic stem cell transplantation. The days of "it's just a virus" are clearly behind us, as immunosuppression has changed, post-transplant longevity is increasing, and molecular diagnostic methods have dramatically improved [215]. Serology may be of limited value in immunocompromised hosts in the diagnosis of acute infection as well as in detecting reactivation of latent infections. Multiplex, quantitative real-time PCR assays are now available to detect multiple viruses, including panels of PCRs for detection of respiratory viruses and CNS pathogens [216, 217]. These sensitive techniques are being evaluated carefully in transplant populations for their specificity and for their potential utility as markers of early infection with surveillance monitoring. The impact of community-acquired respiratory viral infections on the development of acute rejection and bronchiolitis obliterans in lung transplantation appears to be significant and warrants further study [218, 219]. Continued vigilance in detecting emerging viral infections and continued study of potential antiviral therapies in the transplant population will likely improve patient survival.

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