PAPER ID: PMC7107977

TITLE:
Rare and Emerging Viral Infections in Transplant Recipients

ABSTRACT:
Emerging viral pathogens include newly discovered viruses as well as previously known viruses that are either increasing, or threatening to increase in incidence. While often first identified in the general population, they may affect transplant recipients, in whom their manifestations may be atypical or more severe. Enhanced molecular methods have increased the rate of viral discovery but have not overcome the problem of demonstrating pathogenicity. At the same time, improved clinical diagnostic methods have increased the detection of reemerging viruses in immunocompromised patients. In this review, we first discuss viral diagnostics and the developing field of viral discovery and then focus on rare and emerging viruses in the transplant population: human T-cell leukemia virus type 1; hepatitis E virus; bocavirus; KI and WU polyomaviruses; coronaviruses HKU1 and NL63; influenza, H1N1; measles; dengue; rabies; and lymphocytic choriomeningitis virus. Detection and reporting of such rare pathogens in transplant recipients is critical to patient care and improving our understanding of posttransplant infections.

INTRODUCTION:
Emerging infectious diseases are caused by pathogens that are newly recognized or whose incidence has either increased in the preceding 2 decades or threatens to increase. Viral diseases account for a large proportion of such infections. In the context of transplant recipients, important emerging viruses can be considered to be 1 of 3 types: (1) novel viruses; (2) known viruses increasing in incidence in the general population and, potentially, in transplant recipients; and (3) previously known viruses that cause disease of increased severity in the immunocompromised host. In this review, we begin by discussing viral diagnostics and the evolving field of viral discovery, which has increased the speed of virus identification but has created new challenges. Our focus then shifts to specific emerging and reemerging viral pathogens in the transplant community. Viruses described in case series or multiple case reports are listed in Table 1. Viruses described only in single case reports are listed in Table 2. The potential risks of viral transmission as the result of xenotransplantation will not be addressed [1].

VIRAL DISCOVERY:
Viral discovery has typically relied on the ability to detect new viruses in cell culture. Although clinical virology laboratories affiliated with transplant centers routinely perform viral culture, many pathogens do not grow well or do not grow at all, and viral detection using culture is further limited by the number of cell lines a laboratory can realistically maintain. Pathogen detection in the clinical laboratory is also limited by the available tests, which often target conserved sequences (polymerase chain reaction [PCR] or real-time [RT]–PCR) or specific antigens or antibodies to detect known viruses. Multiplex testing for clinical syndromes, particularly for respiratory-tract infections, allows for a less biased approach to viral diagnosis but still faces limitations in identifying emerging pathogens [2]. In rare situations, an unusual virus may be detected by testing for known pathogens, as in the case of a woman who presented with Usutu viremia, which gave a low-positive result by West Nile virus RT-PCR [3].
A number of more rapid molecular methods are now being employed in viral discovery, categorized as sequence dependent (such as the pan-viral microarray) or sequence-independent techniques [4]. The pan-viral microarray is an array spotted with oligonucleotide sequences representing known viral pathogens. Novel viruses can be identified if sufficient similarity exists between sequences in the new virus and those on the array. Amplicons can then be recovered from the array, then cloned and sequenced [5]. This technology was used in the identification of SARS coronavirus from a cultured patient isolate [4]. PCR based on conserved sequences generally has limited applicability in viral diagnostics, as viruses do not contain highly conserved sequences analogous to 16S ribosomal RNA sequences utilized in bacterial identification [6].
The sequence-independent amplification and sequencing of viral nucleic acids in biological samples has been termed viral metagenomics [4, 7]. Sequence-independent approaches include subtractive hybridization or representation difference analysis, sequence-independent single-primer amplification, and rolling circle amplification. These techniques have been used to identify agents such as human herpes virus 8, torque teno viruses (TTV), hepatitis E virus (HEV), Norwalk

virus, parvovirus 4, and human bocavirus (HBoV) [4, 7]. Viral metagenomics has been aided by the development of a number of new sequencing platforms. Termed next-generation sequencing (NGS, or deep-sequencing), such technologies allow for the rapid and parallel generation of 106 to over 109 sequences per run. Most current technologies rely on nonspecific amplification of viral DNA or RNA from samples treated to remove host nucleic acids. Amplification is followed by sequencing by synthesis using different technologies to detect base incorporation [6–8]. NGS has been utilized to identify novel viruses in patient samples and in studies of fevers of unknown origin [9, 10].
NGS has a great ability to detect both known and previously unknown (divergent) viruses, but mere detection does not demonstrate causation. For many of these viruses, classical Koch's postulates cannot be applied, and as demonstrated with TTV and HBoV, establishing a causative role for these agents can be difficult [6, 11, 12]. Mokili and colleagues [6] proposed “Metagenomic Koch's Postulates,” but whether they are sufficient remains moot. At this time, NGS is largely a tool for research purposes. Sequencing reactions take a good deal of time to set up and perform [8]. These runs generate massive amounts of data that must be filtered prior to analysis using various alignment programs designed to handle the large numbers of short reads [8, 9]. Finally, results must be interpreted carefully. Contaminants from the laboratory and even from commercial reagents are often identified (eg, xenotropic murine leukemia virus–related virus), and confirming the presence of a virus identified with small numbers of reads may not be possible [9, 13].

Human T-cell Leukemia Virus Type 1 ::: EMERGING AND REEMERGING VIRAL PATHOGENS:
Human T-cell leukemia virus type 1 (HTLV-1) seroprevalence rates range from 3% to 30% in endemic areas, to <1% in Western countries [14]. Chronic HTLV-1 infection is associated with adult T-cell leukemia (ATL) and HTLV-1–associated myelopathy (HAM) in 5% or fewer of those infected, but there is concern that immunosuppression in HTLV-1–positive transplant recipients may trigger progression to these complications [15–17]. Yoshizumi et al [17] identified 26 HTLV-1–positive, living donor liver transplant recipients. ATL developed in 4 patients at 181–1315 days post transplantation; all 4 patients died, including 3 from ATL. Overall survival rates did not differ between HTLV-1–positive recipients and 305 HTLV-1–negative liver transplant recipients from the same institution [17]. Case reports of ATL following renal transplantation in HTLV-1–positive patients have been documented, though in case series of renal transplant recipients (totaling 46 patients with 5–17 years of follow-up), no cases of ATL or HAM developed [18–21]. HAM has been reported in 1 HTLV-1 D+/R+ living-related liver transplant recipients [22].
ATL responds poorly to conventional chemotherapy, with the highest median survival rates reported in clinical trials being approximately 13 months [23]. As a consequence, hematopoietic stem cell transplantation (HSCT) has been evaluated for the treatment of ATL in HTLV-1–positive patients. (HSCT will be used to describe the transplantation of multipotent stem cells from bone marrow, peripheral, or cord blood.) The largest study of HSCT for ATL involved the retrospective analysis of 386 patients with ATL who had undergone an allogeneic HSCT at 3 centers in Japan [23]. Their 3-year survival rate was 33%; ATL recurred in 41% of patients who survived to 30 days post transplant. Those who received transplants from a related HTLV-1 seropositive donor had a higher risk of disease-associated mortality relative to those whose related donor was HTLV-1 negative. HSCT recipients in complete remission at the time of transplantation had a higher rate of survival compared to patients not in complete remission (51% vs 26%) [23].
The transmission of HTLV-1 through transplantation or transfusion has been documented. In Spain, 3 HTLV-1–negative recipients of organs from a single HTLV-1–positive donor (1 liver and 2 kidney transplants) developed HAM within 2 years of transplantation [24]. Two case reports document the occurrence of HAM in a heart transplant recipient and an HSCT recipient who acquired HTLV-1 through blood transfusions [16, 25]. In low-prevalence areas, however, universal donor screening with Enzyme-linked immunosorbent assay followed by Western blotting resulted in many false positives, and the practice is no longer recommended by the United States Organ Procurement and Transplantation Network [14].

Hepatitis E virus ::: EMERGING AND REEMERGING VIRAL PATHOGENS:
HEV is a common cause of acute liver disease in the developing world, primarily from fecal-oral spread through contaminated drinking water. Infections in developed nations are well described, but typically result from the consumption of undercooked pork products. In immunocompetent hosts, HEV acute infection is self-limited with rare progression to fulminant liver failure. However, in the immunosuppressed host, chronic infection marked by persistent viremia and abnormal liver function with eventual progression to cirrhosis can occur [26–28]. Cases have been described in

recipients of a variety of transplants, including kidney, liver, heart, and lung [27, 28]. In a multicenter review of 85 cases of acute HEV infection, 65.9% of the solid organ transplant (SOT) recipients developed chronic hepatitis of whom 14.3% developed cirrhosis. The use of tacrolimus compared with cyclosporine A was an independent predictor of chronic infection [28]. Rare cases of encephalitis and polyradiculopathy with HEV RNA detection in the cerebrospinal fluid (CSF) have also been described [26].
The majority of HEV infections following SOT result from de novo infections and are unlikely to represent virus reactivation [26, 29]. Rare instances of transmission through blood transfusion or the donated graft have been reported [26]. Determining the overall incidence of HEV-related disease following transplantation is hampered by the available diagnostic tests, none of which are Food and Drug Administration (FDA) approved. Commercial serological assays have variable test characteristics, and tests for HEV RNA detection in serum or stool samples are not routinely available [26].
Reports of HEV infection following HSCT are limited. While an individual case of HEV reactivation following HSCT has been reported, a review of 32 anti-HEV immunoglobin G–positive patients prior to HSCT showed no evidence of disease reactivation [30].
Treatment of prolonged HEV viremia often involves reducing immunosuppression. Pegylated interferon administration has been shown to induce a sustained virologic response in a limited group of patients [26]. Both approaches to viral control may increase the risk of graft rejection. Ribavirin monotherapy has induced sustained virologic responses without the risk of rejection and may represent the first-line agent for treatment [26].

Coronaviruses ::: EMERGING AND REEMERGING VIRAL PATHOGENS:
There are 5 clinically relevant non-SARS human coronaviruses (HCoV): OC43; 229E; HKU1 and NL63, both identified in the last decade; and the Middle East Respiratory Syndrome HCoV (MERS-CoV), identified in 2012. A prospective study found that 41% of HCoV infections were asymptomatic and none of 22 infected allogeneic HSCT recipients developed lower-respiratory-tract infection, although prolonged viral excretion is frequent [30]. Nonetheless, there have been reports of fatal HCoV infection following HSCT. There is evidence among SOT recipients that HCoV can cause severe lower-respiratory-tract infections and increase the risk of graft rejection [31, 32]. HCoV-HKU1 and NL63 do not appear to be more virulent than the previously discovered HCoV-OC43 and 229E; however, the recently identified MERS-CoV has been associated with severe pneumonia and a high mortality rate. Cases have not yet involved immunocompromised hosts.

Polyomaviruses and Bocavirus ::: EMERGING AND REEMERGING VIRAL PATHOGENS:
Efforts to identify novel respiratory pathogens have led to the discovery of HBoV and KI and WU polyomaviruses (KIPyV and WUPyV) [12, 33–35]. While these viruses have been detected in patients with respiratory symptoms, evidence to support a causative role for these agents in severe disease is lacking [12, 33]. Studies evaluating HBoV as a respiratory pathogen in immunocompromised adults have detected the virus infrequently and have not documented an effect on patient outcomes [2, 12]. The establishment of HBoV as a respiratory pathogen has also been complicated by high rates of copathogen detection and HBoV detection in asymptomatic patients [2, 12]. Viral dissemination in transplant recipients occurs, with HBoV detected in blood and stool. However, patients often had HBoV detected after weeks of hospitalization, and other pathogens were also detected during these episodes [36, 37]. Some commercial platforms for multiplex detection of respiratory pathogens include HBoV. No specific antiviral treatment is available [2].
KIPyV and WUPyV have been detected in nasopharyngeal and bronchoalveolar lavage samples from SOT and HSCT recipients [33–35]. Detection of these viruses has been associated with sputum production and wheezing following HSCT [34]. However, similar to HBoV, these viruses are often codetected with other pathogens, and they have not been associated with severe respiratory tract disease or mortality [34, 35].

Influenza ::: EMERGING AND REEMERGING VIRAL PATHOGENS:
Immunocompromised hosts are more susceptible to complications of influenza; however, it is not clear that emerging strains will necessarily cause more severe disease. One case series of 237 SOT patients with H1N1 influenza showed that 16% required ICU admission and 4% died [38]. A series among HSCT recipients showed similar findings [39]. In a comparison of outcomes in kidney transplants and immunocompetent patients with H1N1, there were no differences in

morbidity or mortality [40]. To date, no cases of H5N1 or H7N9 influenza have been reported in transplant recipients.

Measles Virus ::: EMERGING AND REEMERGING VIRAL PATHOGENS:
The recent rise in measles incidence brings it into consideration here. The most significant manifestation may be subacute measles encephalitis (SME), though severe cases of pneumonia have been documented [2]. SME has developed in renal transplant recipients and a single HSCT recipient. Patients may present with a measles-compatible illness, which improves. They develop altered mental status and seizures 2–4 weeks later; fever is uncommon. The first imaging changes are seen by magnetic resonance imaging, and diagnosis is confirmed by immunoglobin M (IgM) seroconversion or RT-PCR. The clinical course is one of deteriorating mental status and treatment-refractory seizures [2]. Four of 6 transplant cases of SME have died. The 2 survivors both had significant neurological deficits [41]. The incidence of measles in transplant recipients, as well as the proportion with severe disease, is unclear. Two series identified 2 cases of interstitial pneumonia (1 fatal) among 24 HSCT recipients diagnosed with measles, though methodological limitations existed in both studies [2].

Dengue Virus ::: EMERGING AND REEMERGING VIRAL PATHOGENS:
Dengue virus (DENV) is the most common vector-borne viral disease worldwide and has been detected in an increasing number of countries over the last 40 years. In 2 case series involving 33 renal transplant recipients, only a single case of severe dengue developed, with no fatalities or loss of graft function [42, 43]. Severe cases of dengue, including 4 deaths, have been reported in renal transplant recipients along with fatal cases in a liver transplant recipient and an HSCT recipient [2]. In patients who died, disease typically developed within the first month post transplant. Human-to-human transmission of DENV as a result of SOT or HSCT has been postulated, and transfusion-related DENV infections have been reported [44]. FDA-approved diagnostics include tests for IgM detection and a Centers for Disease Control and Prevention–developed RT-PCR; management consists of supportive care.

Rabies Virus ::: EMERGING AND REEMERGING VIRAL PATHOGENS:
Seventeen cases of rabies have been reported in transplant recipients, and to date, all have been transmitted through the transplanted tissue or organ [2, 45]. Nine cases followed corneal transplantation, including 8 deaths [2]. The sole survivor, reported in 1981, began postexposure prophylaxis (PEP) on postoperative day 1 [46]. Two clusters (Texas, 2004, and Germany, 2005), totaling 7 rabies cases, have occurred following SOT [47, 48]. These cases followed the transplantation of liver, lung, kidney, kidney-pancreas, and iliac artery grafts. Patients typically developed encephalitis between 30 and 60 days post transplant, and all symptomatic patients died [48]. Patients in Germany received PEP and antiviral treatment, though not until postoperative day 45 [47]. The liver recipient in this cluster had been previously vaccinated and never developed disease [2]. Both donors were later determined to have rabies exposures (bat and dog bites, respectively) [47, 48]. A recent report (Maryland) documented a fatal case of rabies developing a year after kidney transplant. Transmission of raccoon-variant rabies through the donated graft was confirmed. Three other graft recipients from the same donor are alive, though full details are not available [45].
The management of rabies focuses on prevention with vaccination in high-risk patients or PEP. Transplant recipients who receive PEP can mount adequate responses (antibody titers of 0.5 international units/mL), though titers are lower than in immunocompetent patients [2]. Based on the experience of the German liver transplant recipient, rabies vaccination may remain effective even after transplantation.

Lymphocytic Choriomeningitis Virus ::: EMERGING AND REEMERGING VIRAL PATHOGENS:
Cases of lymphocytic choriomeningitis virus (LCMV) transmitted through organ transplantation (4 clusters, including 14 cases and 11 deaths) document the ability of this pathogen to cause severe disease in the immunocompromised host [10, 49–51]. Another cluster involved the transmission of a related arenavirus in Australia, with similar outcomes (1 liver and 2 kidney recipients; 3 deaths) [10]. As with rabies infections post transplant, all cases resulted from transmission through organ transplantation [10, 49–51]. At this time, cases have not been described in the HSCT population. The 4 case clusters of LCMV infection occurred in the United States and involved kidney, liver, and lung transplants [49–51]. Symptoms developed between 2 and 23 days post transplant and included fever, abdominal pain, nausea, diarrhea, and altered mental status. Patients often

developed a peri-incisional rash and tenderness. CSF findings included elevated protein (often marked), normal to low glucose, and a mild pleocytosis [49–52]. Three patients survived LCMV infection following SOT, 2 kidney recipients and a liver recipient. Ribavirin has been employed in some cases, though the benefit remains unclear [2]. Three corneal transplant recipients were potentially exposed to LCMV, though none of them developed symptoms or seroconverted [2]. Contact investigation revealed exposure to rodents or positive testing for LCMV in 3 donors [49–51]. Investigation into the fourth donor revealed no exposure, and all testing performed on remaining tissues was negative [50]. It has been advised that immunocompromised patients avoid contact with rodents, including pets, though this was not the mode of LCMV acquisition in these outbreaks [53].

Prevention and Reporting ::: EMERGING AND REEMERGING VIRAL PATHOGENS:
For the majority of viral infections discussed here, data are insufficient to determine the true incidence of disease in transplant recipients. Measles, mumps, and yellow fever are vaccine-preventable illnesses, though these vaccines are live-attenuated and not recommended following transplantation. Also, antibody response to vaccines is less than in immunocompetent patients. Donor-transmitted rabies carries a dire prognosis, and though limited data exist, the use of PEP in transplant recipients appears safe.
Given their apparent rarity, screening for many of these diseases in organ donors is not recommended. The examples of HTLV-1 (discussed earlier) and LCMV are illustrative of some of the difficulties involved with donor screening. In the outbreak investigations for LCMV, only 1 of 4 donors had detectable antibodies. Indeed, RT-PCR from multiple samples failed to detect LCMV from 1 donor, and yielded a positive result in only a single lymph node in another [49–51]. It seems prudent to obtain a comprehensive history of potential organ donors, though it remains unclear how certain findings, such as rodent ownership, should affect one's donor status. Reporting rare infections in transplant recipients will help to identify agents for which more research is needed and screening may be warranted. However, it is likely that these infections are underdiagnosed as symptoms may be attributed to more common, and potentially coincident, posttransplant infections.