



Infection prophylaxis and management of viral infection

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Abstract: Viral infections are associated with significant morbidity and mortality in lung transplant recipients. Importantly, several viral infections have been associated with the development of chronic lung allograft dysfunction (CLAD). Community-acquired respiratory viruses (CARV) such as influenza and respiratory syncytial virus (RSV), are frequently associated with acute and chronic rejection. Cytomegalovirus (CMV) remains a significant burden in regards to morbidity and mortality in lung transplant recipients. Epstein-Barr virus (EBV) is mostly involved with the development of post-transplant lymphoproliferative disorder (PTLD), a lymphoid proliferation that occurs in the setting of immunosuppression. On the other hand, the development of direct acting antivirals for hepatitis C virus (HCV) is changing the use of HCV-positive organs in transplantation. In this article we will focus on reviewing common viral infections that have a significant impact on lung transplant recipients looking at epidemiology, prevention and potential treatment.

Keywords: Viral infections; lung transplant; prophylaxis

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Community-acquired respiratory viruses (CARV)

CARV are common after lung transplantation. In immunocompromised patients these infections can involve the lower respiratory tract and are often associated with significant mortality (1,2). The viral pathogens frequently reported include: influenza A and B, respiratory syncytial virus (RSV), adenovirus, parainfluenza (PIV), human metapneumovirus (hMPV).

CARV infection can occur at any time after lung transplantation, but seasonal variability often occurs. Few cases of donor-derived influenza and adenovirus infection have been reported and associated with significant morbidity (1,3). The most sensitive diagnostic tools available for the detection of CARV infections are nucleic acid amplification assays including polymerase chain reaction (PCR). These assays usually allow for simultaneous detection of a multiple viral pathogens. All patients with a suspected respiratory

viral infection should have a nasopharyngeal swab, wash or aspirate for testing (4,5). A prolonged shedding of CARV have described in lung transplant patients, in particular with rhinovirus (6,7). However, the effect of prolonged shedding on the graft is unclear.

In a recent prospective analysis of 98 adult lung transplant recipients, the overall incidence of CARV was 0.76 patient/year. Interestingly, 11.5% of asymptomatic patients had positive nasopharyngeal swabs compared with 55.4% positive tests in symptomatic patients. Higher incidences of respiratory viral infection were observed in winter and fall. Picornavirus (rhinovirus and enterovirus), coronaviruses and influenza were the most frequently isolated viral pathogens. While asymptomatic infections were seen mostly with picornaviruses and coronaviruses, infections with Paramyxoviruses and influenza viruses were significantly associated with pneumonia and higher risk of hospitalization (2). Similar findings were reported from a

prospective Swiss study with overall incidence of respiratory viral infection of 0.83 per patient-year. Respiratory viral infection was detected in 14% of the screening visit and 34% of the emergency visits. Picornaviruses were the most commonly identified, while influenza and PIV were associated with 50% hospitalization rates.

Outcomes associated with respiratory viral infections including acute cellular rejection (ACR) and development of CLAD have been studied in the literature. Often within few months after a BAL-positive respiratory viral infection, lung transplant recipients developed biopsy-proven ACR or decline for FEV1 greater or equal to 20% compared to recipients without viral isolation (5). However, there are contrasting reports regarding the development of ACR following respiratory viral infection. Despite the Swiss prospective study failed in finding a temporal association between viral infection and ACR (8), in nested case-control analysis from a Spanish group, the presence of respiratory viral infection within the previous 3 months was associated with the development of ACR (2). In a retrospective study including 250 LTR patients, symptomatic CARV infections was independently associated with development of CLAD. The association was stronger in the first months after respiratory viral infections but it was present when all follow-up time was measured (9).

RSV

RSV is one of the most commonly isolated CARV with incidence up to 16% after LTR. RSV is transmitted via droplet secretions. The incidence of RSV usually follows community outbreaks with peak incidence from September to April. However, hospital outbreaks have been described as well. The overall mortality for RSV among immunocompromised patients can be as high as 20%. Moreover, in LTR the overall mortality for RSV infections ranges from 10% to 20%.

RSV infection is associated with significant morbidity and mortality. Acutely, RSV infection is associated with development of bronchiolitis, lower respiratory infection and respiratory failure. A persistent decline greater than 20% of FEV1 suggestive of development of bronchiolitis obliterans syndrome (BOS) had been described following RSV isolation in lung transplant recipients (10). RSV is therefore considered a distinctive risk factor for the development of CLAD (11,12). Moreover, mortality rates range between 10% and 20% after RSV infection in lung transplant recipients (11,13).

To prevent spreading of RSV infections, patients with known or suspected RSV should be isolated from other patients using standard contact precautions. There is no approved vaccine for the prevention of RSV. Recently a humanized RSV-specific monoclonal antibody palivizumab demonstrated to be effective for high risk infants and children with specific underlying clinical conditions. However, no studies have been completed to assess the use of palivizumab in the setting of solid organ transplant (SOT). Due to lack of randomized clinical trials, the treatment of RSV infection is still matter of debate. Primarily, therapy for RSV infection is supportive. Several case series have described therapeutic regimens including ribavirin aerosolized, intravenous (IV) or oral with or without IV immunoglobulin and steroid. Oral ribavirin is the most frequently used due to lower cost compared to aerosolized form despite limited studies comparing the efficacy and safety in the management of RSV infections. In a recent single-center study involving 46 patients (of which 22 lung transplant recipients) showed no differences in mortality, length of stay and resolution of symptoms but an enormous cost avoidance attributable to use of oral ribavirin (14). In two placebo-controlled trials involving lung transplant recipients AL-RSV01, which is a small interfering RNA (siRNA) that acts preventing viral replication, had been studied. In the first trial the nebulized ALN-RSV01 was administered to 24 lung transplant recipients with RSV infection for 3 days demonstrating safety and tolerability. Moreover, new or progressive FEV1 decline consistent with BOS at 90 day was decreased compared with placebo (15). Similarly, in the subsequent phase 2b study nebulized ALN-RSV01 was well tolerated for 5 days and demonstrated a significant treatment effect when initiated early from symptoms onset on the development of BOS on day 180 compared with placebo (16).

Influenza

Influenza virus A and B belong to the virus family Orthomyxoviridae and are able to cause a contagious respiratory disease in humans (17). Influenza A viruses generally surface from a zoonotic reservoir before spreading among human. On the other hand, influenza B virus is almost exclusively found in human host. Influenza A viruses in particular present two peculiar antigenic properties that allow to evade host responses and perpetuates seasonal epidemics and pandemic. Minor changes induced by the point mutations that usually involve the hemagglutinin and

neuraminidase are called antigenic drift. More complex arrangement that allow for the mixing genetic information of different viral strains giving rise to novel and gene-reassorted virus strains is called antigenic shift, which is associated with development of pandemics as in 2009 (18,19).

Influenza viruses are the cause of annual epidemics of respiratory illness that is associated with significant morbidity and mortality in immunocompetent and immunosuppressed population. The annual outbreaks have a seasonal distribution that mostly occur during winter months. Interestingly, there is still a limited understanding on influenza transmission, but the generally accepted way of transmission are direct contact from infected patients, droplets and aerosols (20). The cumulative incidence of influenza virus infection in SOT recipients is estimated to be up to 13% (4). According to a single-center retrospective study evaluating in 33 immunosuppressed patients, 39% of all respiratory infections were caused by influenza viruses (21) Influenza virus infection can present mild respiratory complains but it is often associated with progression to lower respiratory tract infection, bacterial superinfection, respiratory failure and later with the development of chronic rejection (22,23). Severe influenza disease is usually observed in early post-transplant periods likely due to more intense immunosuppression. Mortality ranges between 2–4% but it can increase up to 21% in lung transplant recipients with pre-existing grade 3 BOS during the recent H1N1 pandemic (24). Several tests are available for the diagnosis of influenza including rapid antigen detection, direct fluorescent antibodies (DFA), but PCR assay is considered the gold standard for diagnosis.

In order to prevent the spread of influenza viruses is recommended to use appropriate droplet precautions and vaccination of recipients and their close contacts. Annual vaccination is recommended to all lung transplant recipients (25). Influenza vaccine should be administered after the first 3 months from transplantation or intensified immunosuppression following treatment of rejection. Vaccine can be given as early as 1 month after transplantation in case of high influenza activities or pandemic (26). There is different type of vaccine: trivalent vaccine, containing two strains of influenza A and one strain of influenza B, and a quadrivalent vaccine that comprises two strains of each influenza virus. Responses in terms of immunogenicity are variable in all SOT recipients, mostly affected by type of transplanted organ and immunosuppression regimens and intensity. Mycophenolate mofetil appears to be associated with poorer antibody

response, while contrasting data are available for other anti-rejection drugs (27). In a large multicenter prospective studies including 616 transplant patients, of which 116 lung transplant recipients, influenza vaccination was associated with decrease disease severity (28). There are some concerns that vaccination might be associated with development of *de novo* DSA and/or allograft rejection. The evidence is poor and a recent systematic review on vaccine safety provided reassurance on the safety of vaccination in SOT recipients (29).

There are only few retrospective studies including lung transplant patients of the use of oseltamivir for the treatment of influenza infection (24,30). Therefore, there are no recommendation on the optimal timing, dose and duration in lung transplant recipients with confirmed influenza infection. However, it has been suggested that antiviral therapy should be given to all lung transplant recipients with suspected or confirmed influenza infection despite severity or onset of symptoms. Oseltamivir is generally well-tolerated and has shown to improve outcomes particularly if initiated within 48 hours from symptoms onset (24). Recently, a new antiviral drug, baloxavir marboxil, had been approved for the treatment of influenza A and B (31). Studies in SOT recipients are currently not available.

Adenovirus

Adenoviruses are a widespread group of viruses with over 60 serotypes known to cause a variety infections including respiratory, gastrointestinal and febrile disease in immunocompetent hosts (32). Adenoviruses are divided in seven species (from A to G) depending on several viral characteristics (33). The incidence of adenovirus among lung transplant recipients or for that matter all SOTs is not well-defined. More data exists for bone marrow transplant populations with estimates a cumulative incidence of 3% in adult bone marrow transplant recipients, with those having an allogeneic versus an autologous transplant having disproportionately higher risk (34).

Among pediatric lung transplant recipients, a single center has reported a cumulative incidence of 7% for adenovirus pneumonia (35) while a cumulative incidence of 2.5% was observed in an adult cohort (13). Adenovirus infection can be acquired *de novo* but in most of adult SOT recipients it manifest as reactivation of a latent infection of the recipient or from the graft itself. In immunocompromised patients, endogenous reactivation

of adenovirus seems to be the predominant cause of disease based on studies demonstrating identical strain of adenovirus isolated prior and post-transplant in allogeneic hematopoietic stem cell transplant recipients (36). Usually, the primary site of adenovirus disease is the transplanted graft with manifestations including necrotizing pneumonias, nephritis, hemorrhagic cystitis and disseminated disease (37,38). With regards to outcomes, adenovirus infection in lung transplant recipients has been associated with graft failure, particularly with FEV1 decline consistent with BOS (3). Mortality from adenovirus infection has been reported in both pediatric and lung transplant populations (13,35).

Multiple diagnostic tests exist for adenovirus but real-time PCR assays are the recommended standard and can be used for detection in most specimen types (39,40). However, these results should be correlated with clinical presentation and histopathology in order to distinguish asymptomatic infection, adenovirus disease and disseminated disease. This recommendation derives from the fact that asymptomatic patients can shed for prolonged periods of time. Despite the lack of general consensus, the American Society of Transplantation has recommended to define an asymptomatic adenovirus infection as the detection of adenovirus from patient samples (blood, urine, stools, BAL) in absence of signs or symptoms. While the detection of adenovirus in biopsy specimen or from BAL along with the presence signs or symptoms of organ involvement should be considered as adenovirus disease. Finally, a disseminated infection is characterized by the involvement of 2 or more organs not including viremia (33,38). With regards to prevention of adenovirus, there are no vaccines or standard prophylaxis regimens available in hospital settings, strict droplet and contact precautions are recommended for those that test positive for adenovirus.

Similar to immunocompetent hosts, treatment of adenovirus infection in lung transplant recipient starts with supportive care. If possible, reduction in immunosuppressive therapy is recommended to aid with clearance (39). Potential antiviral agents against adenovirus include ribavirin and cidofovir. Use of IV ribavirin for adenovirus infection in bone marrow transplant patients has not shown any clear benefit (34) and is not recommended (39). There has been some success with the use of IV cidofovir but usage is significantly limited by nephrotoxicity (35). Brincidofovir is an oral, lipid derivative of cidofovir that has shown acceptable tolerability, safety, and efficacy in bone marrow transplant recipients (41,42). Further research of

the utility of brincidofovir among other SOT is ongoing.

It is worth to mention that other respiratory viruses are often identified in lung transplant recipients and are linked with development of decline of lung function consistent with CLAD (43,44). The after lung transplant, a cumulative incidence of 5–7% have been described for PIV virus and hMPV (2). Currently, only supportive therapy is recommended, due to the lack of vaccines or approved antiviral drugs with clinical benefits.

Cytomegalovirus (CMV)

The cumulative incidence of CMV disease among lung transplant recipients has remained at 20% to 50% with some reports up to 80%, even in the era of preventive prophylactic strategies (45-47). Active CMV infection manifests as fever, bone marrow suppression, and tissue invasive disease including pneumonitis and colitis. Aside from direct effects of CMV infection itself, CMV has long been associated with increased acute rejection episodes (48) and FEV1 decline consistent with BOS (49,50). Donor (D) and recipient (R) mismatch, specifically CMV D+R- recipient are at significantly higher risk of developing CMV disease (51). Along with increased risk of CMV disease, CMV D+R- recipients have higher overall mortality than CMV D-R- for lung transplant recipients (52).

Given the serious implications of CMV disease, most lung transplant centers practice universal prophylaxis in the initial months post-transplant regardless of CMV status, with valganciclovir being an effective oral regimen (53). Optimal duration of prophylaxis has been the subject of much study, with evidence supporting extending duration of prophylaxis to minimum of 1 year post-transplant, particularly for CMV D+R- recipients (54,55). Use of CMV prophylaxis after treatment of rejection with anti-lymphocyte antibodies is also recommended. Hematologic adverse events related to valganciclovir are not uncommon and newer alternative oral regimens are becoming more available. Letermovir has been shown effective in stem cell transplant populations and could be considered an off-label alternative for prophylaxis that is not myelosuppressive (56). The role of CMV immunoglobulin in post-transplant prophylaxis is not well-supported by what evidence exists (57) though it is still in use as an adjunct therapy for CMV disease treatment at some centers (58).

Recommended treatment regimens for CMV disease with normal renal function include oral valganciclovir 900 mg twice daily and intravenous (IV) ganciclovir 5 mg/kg/dose

twice daily (59). For any CMV disease that is tissue invasive or considered clinically severe, IV ganciclovir is recommended first-line over oral valganciclovir. Treatment response is monitored with once weekly quantitative CMV nucleic acid amplification. For those that do not also have evidence of rejection, decreasing immunosuppression regimens from 3 to 2 drugs during the duration of CMV treatment may result in sooner disease resolution (60).

Incidence of ganciclovir resistant CMV have been reported at 6–11.9% among lung transplant recipients in prior decades but likely is higher in the current era with the increase in use of CMV prophylaxis, increase in number of lung transplants, and increase in use of induction agents at time of transplant (61,62). Transplant recipients with recurrent CMV infection or persistent CMV on prolonged therapy should undergo testing, particularly for UL97 and UL54 gene mutations (59). An option for ganciclovir resistance is IV foscarnet which at times is also given in combination with ganciclovir, particularly if there is also cidofovir resistance present. Cidofovir can be considered as salvage therapy in strains with both foscarnet and ganciclovir resistance but there are limits with nephrotoxicity and possible rapid development resistance. Maribavir is a UL97 inhibitor that has shown activity against CMV strains resistant to ganciclovir and foscarnet (63). A phase II study of Maribavir 400 mg twice daily showed effectiveness against resistant and refractory CMV infection in hematopoietic cell transplant recipients (64) and is undergoing further study among SOT populations. Improvements in testing and treatments of CMV resistance continue to evolve but guidelines are based upon expert consensus statements.

Epstein-Barr virus (EBV)

EBV is widely disseminated herpesvirus that is transmitted by contact with oral secretions. Approximately 90% of adults worldwide have antibodies to EBV and the majority of the primary infections are asymptomatic. In adolescent and adults, EBV is primary agent of infectious mononucleosis but it is also associated with several malignancies including B and T cell lymphomas, Hodgkin's lymphoma, gastric carcinoma and nasopharyngeal carcinoma (NPC).

Following the initial infection, EBV utilizes different programs of gene expression to establish a quiescent but persistent infection of B cells. In immunocompetent hosts, these events are constantly monitored by the immune

system: active viral replication induces NK cell activation, production of serum antibodies to different EBV proteins and a large expansion of cytotoxic CD8+ T lymphocytes (65,66). In the setting of immunosuppression, likely due to blunting of these immune responses, EBV is associated in 70–80% of the cases with the development of post-transplant lymphoproliferative disorder (PTLD).

The development of an adaptive T-cell immune response is central to controlling EBV-infected B cell proliferation and virus replication. Despite high variability in the EBV-specific CD8+ T cell counts, no difference was noted among patients with PTLD when compared to SOT patients with EBV reactivation or healthy controls (67). Studies by Martinez and colleagues have shown that pediatric transplant patients are able to mount a primary T-cell response to EBV. However, the magnitude of the response to EBV lytic and latent proteins by polyfunctional T cell response is attenuated when compared to healthy subjects (68,69). Collectively all these prior studies illustrate that T-cell immune responses to EBV vary post-transplant and may favor the development of PTLD.

PTLD presents as a clinically and pathologically heterogeneous group of lymphoproliferative diseases. Data from international transplant registries suggest that the overall prevalence of EBV-associated PTLD ranges between 1–20% after SOT (70,71). In adult lung transplant recipients a cumulative incidence up to 10% of PTLD had been observed, higher than most other commonly transplanted organs (72,73). Despite the low incidence, PTLD represents one of the most serious complications in SOT recipients. Mortality after PTLD in lung transplant is up to 50% with recipients dying due to treatment failures or complications of chemotherapy (74–76). Based on small studies, the risk of developing PTLD is highest in the first year after transplant. However, a second peak of PTLD is evident many years after transplantation (77). Several efforts have been done to identify the patients who are at risk of developing PTLD. Currently, EBV status mismatch, CMV seronegativity and intense immunosuppression are considered the major risks factors for the development of PTLD (73–75,78). Other associations have also described including certain HLA types and the expression of specific viral genes (79). Regarding treatment, reduction of immunosuppression is cornerstone and the initial step in treating patients with PTLD, in order to reduce the disequilibrium between immunosuppression and immunosurveillance. This approach is often associated with increased risk of graft failure. Rituximab, anti-CD20

monoclonal antibody, is now considered the standard therapy along with reduction of immunosuppression based on results from several phase 2 trials (80,81). Other chemotherapy regimens, including R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine and prednisone), can be used in case of lack of responses to initial management. Recently, trials on EBV-specific cytotoxic T cells generated from blood donors have shown interesting results in patients with PTLD who failed conventional treatments (82,83).

Prevention of the development of PTLD depends on limiting the immunosuppression. Routine EBV PCR to monitor the presence of EBV viremia have been suggested especially in lung transplant recipients with negative EBV serostatus. There are some caveats. First, although a PCR is a standard and reliable method to measure EBV loads, there are no standard protocols, kits, or machines. Individual centers and laboratories will develop their own cutoff values. Therefore, the World Health Organization (WHO) International Standard for EBV was developed based on the results of a worldwide collaborative study group, and was released for the standardization of quantitative PCR (84). Secondly, there is no consensus on monitoring EBV loads in plasma versus whole blood. Immunocompetent healthy EBV-carriers have a measurable EBV DNA in their whole blood, but EBV DNA is hardly detectable in plasma. Similarly, EBV loads measure in whole blood were higher compared to plasma samples from 10 PTLD patients as described by Wagner *et al.* (85). Currently, there are no clear recommendations to monitor EBV viral loads in SOT.

The role of antiviral agents is equivocal. Valganciclovir or ganciclovir, used for CMV prophylaxis, are able to block EBV replication *in vitro*. While acyclovir acts in the lytic phase of EBV replication but has no effect on reactivation of latent virus as observed in malignancies. Evidence of a beneficial effect of ganciclovir comes from a retrospective studies of pediatric liver recipients. In this study 18 patient considered at high-risk of developing PTLD due to EBV mismatch (donor EBV positive/recipient EBV negative) received intravenous ganciclovir, 22 low-risk patients (EBV recipients positive) received intravenous ganciclovir during hospitalization followed by acyclovir. There were no cases of PTLD in the high-risk liver transplant patients, and 2 cases of PTLD in the low-risk which resolved with reduction of immunosuppression (86). A different approach using preemptive rituximab has been described in hematopoietic stem cell transplants presenting with detectable EBV PCR.

This strategy appeared to be safe and effective in preventing the development of PTLD (87). There are no studies in lung transplant recipients to explore this option yet.

Other herpesviruses

Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) are common infections in immunocompetent hosts and are linked to reactivation after organ transplantation. HSV1 present a prevalence in the general population of 70–90% while HSV is approximately 20% (88). Clinically, HSV viruses reactivation include oral and genital mucocutaneous vesicular rash. Rarely, severe cases of disseminated HSV disease can be observed in SOT recipients (89). The antiviral prophylaxis given for CMV prophylaxis is including ganciclovir, acyclovir or valganciclovir is also effective in preventing HSV reactivation. Treatment of HSV reactivation consists of oral acyclovir (90).

Varicella-zoster virus (VZV) is associated with the development of two clinically distinct diseases: varicella and herpes-zoster (HZ) or shingles. VZV presents a seroprevalence close to 100% in Europe and North America. Interestingly the incidence of HZ is growing in immunocompetent hosts, with a median incidence of 4–4.5 per 1,000 person-year (91). Due to the immunosuppression and decreased T cell immunity, SOT recipients are at increased risks of developing HZ (92). HZ can be observed in SOT recipients and in particular in lung transplant with a cumulative probability up to 20% (92). VZV reactivation usually occurs after the use of antiviral prophylaxis is discontinued. Therapy for VZV infection consists of administration of oral acyclovir, valganciclovir. Despite rare, cases of fatal disseminated VZV have been described in lung transplant recipients. IV acyclovir is drug of choice in this case (93). Strategies to attenuate VZV reactivation include: pre-transplant vaccination with live attenuated Oka vaccine as recommended in general elderly population (94). A positive vaccine history or VZV antibody titers before SOT protect against VZV disease after SOT. Recently, a dead recombinant zoster vaccine was tested in selected group of kidney transplant recipients, demonstrating safety and immunogenicity (95). More studies regarding clinical benefits and lung transplant recipients are still lacking.

Hepatitis virus

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are cause of acute and chronic hepatitis after transplantation (96).

However, vaccination and the recent development of direct acting anti-viral drugs have helped in increasing the use of organs from donors with known viral hepatitis.

HBV is a major cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma worldwide. Its prevalence and associated mortality have started to decrease following effective vaccination. Lung transplant candidate should be screened prior to transplantation (97). Patients who had received HBV vaccine (anti-HBs IgG positive) and patients who have been previously infected (anti-HBs IgG and anti-HBc IgG positive) are considered candidate for lung transplantation. Patients without immunity should receive HBV vaccination. Accelerated schedules can also be given but may be less immunogenic (94). According to recent guidelines from the ISHLT, chronic HBV infection should be considered a relative contraindication and selected candidates should be screened for presence of cirrhosis or hepatocellular carcinoma (98). Antiviral therapy should be continued indefinitely after transplantation with drugs of choice including entecavir, tenofovir and lamivudine (96).

Similarly, HCV is associated with development of chronic hepatitis, cirrhosis and hepatocellular carcinoma (99). There is no vaccine for the prevention of HCV transmission. Initial screening for antibody to HCV should be done at the time of transplant assessment. In case of positive HCV serology, further studies including genotyping, liver scan and biopsy are necessary (100). Chronic HCV infection remains an absolute contraindication. However, a recent analysis of the UNOS database showed that HCV-seropositive recipients have a similar 5-year survival when compared to HCV-negative (101). In selected cases with absence of cirrhosis and hepatocellular carcinoma lung transplantation may be considered.

The use of HBV and HCV positive donors has been reported in the literature. The risk of HBV transmission is insignificant in candidate with proven immunity (102). Therefore, efforts should be made to vaccinate prior to transplantation. In HBV non immune patients, protocols to monitor the development of transaminitis, seroconversion or infection are recommended (102). The 5-year mortality was not significantly different between 333 recipients of anti-HBc positive lungs and heart-lung transplantation and 13,233 recipients of anti-HBc negative organs. Prophylaxis following anti-HBc positive organ transplant with lamivudine is suggested for 12 months in case of positive HBV DNA in the blood (96). Transplantation of HCV-positive organs almost always results in viral transmission. Currently, the use of HCV positive organs is

limited to HCV-positive recipients. However, recently the use of HCV-positive organs in HCV-negative recipients is growing due to the newer direct acting anti-viral drugs such sofosbuvir, ledipasvir and velpatasvir which allow eradication of HCV infection (103-105).

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