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Review

# Clinical Approach to the Management of Infections before and after Liver Transplantation

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**Abstract**

The infectious complications before and after liver transplant (LT) are affected by the severity of liver disease and immunosuppression intensity after transplantation. Both cirrhosis and immunosuppression contribute to dysfunction of defensive mechanisms of the host. When a patient is evaluated for transplantation, the opportunity arises to assess the individual's risk for infection and how one may modify those risks through prophylactic and therapeutic strategies. Pretransplant infectious disease evaluation focuses on exposure history, prior infections, serologic testing for latent infections, distant exposures, identify colonization patterns of MDRO, and administration of vaccines. The risk of acquiring rare infections are increasing because of greater global mobility. Additional evaluation should be considered for some endemic infectious diseases, beyond recommended standard testing for transplant candidates and donors. It is important to have knowledge of risk factors, local epidemiology and resistance pattern of organisms for management of infections in post-transplant period. Infections are often recipient or donor derived or can be associated with surgical and nosocomial complications during 1$^{st}$ month after LT. Opportunistic infections are common during first year after transplantation due to higher intensty of immunosuppression,

while the risk goes down with time but is never zero as intermittent augmentation of immunosuppression can bring the risk back. The risk factors for infection after LT is both donor and recipient derived, as well as aspects related to the transplant operation. In recent studies genetic polymorphisms in the innate immune system , from both donor and recipient, have been identified as important risk factor for infection after LT. Early diagnosis of infections using advanced diagnostic approaches, closer surveillance and targeted treatment protocols are required to manage infectious complications in LTR. Rigorous screening of both donor and recipient for latent and active infections is essential for best outcome after liver transplantation. Most of the liver transplant centers have dedicated physicians with expertise in transplant infectious disease and it is advisable if these experts are consulted when the patients admitted to non transplant centers.

**Keywords**
Liver transplant candidates; recipients; infection; bacteria; multidrug resistant organisms; viruses; fungus; donor; opportunistic infection

## 1. Introduction

Liver transplant (LT) has radically changed the outcome of patients with chronic liver disease, acute liver failure and malignancies. Liver is the second most common organ after kidney to be transplanted worldwide [1]. The patient and graft survival have improved over the years and one year survival after LT is exceeding 85%. The various factors which have contributed to this are; advances in surgical techniques, judicious use of newer immunosuppressive agents and improved diagnostic methods for identifying and preventing infections [1]. However, infections still continue to evolve and remain the leading cause of mortality and hospital costs among transplant recipients [2-7]. We describe in this review our current clinical approach to evaluate and manage commonly encountered infections in LT candidates and recipients.

## 2. Pre-Transplant Infectious Disease Evaluation

Pre transplant infectious disease evaluation is an important component of the transplantation process [8-12]. This permits identification of occult active infections that merit treatment before transplant and other latent infections that may reactivate after transplant. This evaluation helps to determine the post-transplant prophylactic strategies, or may disqualify the recipient from receiving a transplant. It should be a standard of care to obtain good patient history to identify underlying disease risk factors for infections, thorough physical examination and comprehensive infectious disease work up (Table 1). Although screening practices vary from centre to centre but certain screening tests, such as serological testing for human immunodeficiency virus (HIV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), varicella zoster virus (VZV), hepatitis B virus (HBV), hepatitis C virus (HCV) and *Treponema pallidum* (TP) are obtained by most transplant centres [8-12]. Screening for certain infections should be considered depending on the endemicity of fungal, viral, parasitic and multidrug resistant bacterial infections.

**Table 1** Pre-Transplant infectious disease routine screening test for liver transplant candidate and for potential donor.

| | **Screening test for transplant candidate and donor** |
|---|---|
| ***Screening for colonisation of MDRO** | Rectal swabs culture : (CPE, VRE,)<br>Nasal, axilla, groin swab culture : MRSA |
| **Tuberculosis** | *Mycobacterium tuberculosis: Tuberculin and IGRA test* |
| **Syphilis** | Rapid plasma reagin (RPR) or other serological test for syphilis |
| **CMV** | CMV IgG antibody |
| **EBV** | EBV IgG antibody |
| **HIV** | HIV 1& 2 antibody & HIV antigen combo |
| **HTLV I &II** | HTLV I&II antibody |
| **HBV** | HBV surface antigen (HBsAg), |
| | HBV total core antibody (HBcAb) & HBsAb |
| **HCV** | Hepatitis C virus antibody (Anti HCV IgG ) |
| **HEV** | HEV RNA, HEV antibody |
| **West Nile virus** | West Nile virus IgM antibody if positive perform PCR testing. |
| **Parasitic infections** | Toxoplasma IgG antibody,<br>Strongyloides serology in endemic areas |
| ***Endemic Mycoses** | Coccidioidomycosis serology in endemic area |

*; Screening should be considered in transplant candidate, MDRO ; multidrug-resistant organism, VRE; Vancomycin-resistant *Enterococcus faecium,* MRSA; Methicillin-resistant *S. aureus*, CPE; CPE; carbapenemase producing *Enterobacteriaceae,* IGRA;interferon gamma release assay, CMV; Cytomegalovirus, EBV; Epstein-Barr virus, HPV; Human papilloma virus, HIV; Human immunodeficiency virus, HBV; Hepatitis B virus, HCV; Hepatitis C virus.

### *2.1 Identifying Active Bacterial Infections*

LT candidates with end stage liver disease are at high risk of bacterial infections. The patients with cirrhosis have alteration of both innate and acquired immunity known as cirrhosis – associated immune dysfunction (CAID) [13, 14]. Spontaneous bacterial peritonitis (SBP) is one of the serious complication in these patients and has led to long term use of antibiotic prophylaxis. Emerging evidence suggests high prevalence of multi-drug resistant organisms (MDRO) and associated mortality of >35% in patients with decompensated cirrhosis [15, 16]. In patients with active infections before transplant such as SBP and blood stream infections, transplant should be delayed where possible. However, there are no data to suggest, what should be a safe interval between infection and transplantation. It is important to fully treat and investigate by repeating cultures, serology, radiography, or other tests required to diagnose the infection. This may not be practical in situations of emergency transplant or very sick patients who are offered a deceased donor organ, where management should be individualized in consultation with a microbiologist or infectious-disease consultant knowledgeable in transplant infectious disease [17]. Patients who have received pre transplant immunosuppression with steroids or other immunosuppressive medications are prone to broader range of opportunistic infections. Some of these infections in

*active* form, such as histoplasmosis, tuberculosis (TB) and aspergillosis are contraindications to transplantation. It is important to detect and fully treat such infections prior to transplant. Transplantation should be considered once such an infection has been fully treated.

### *2.2 Latent Bacterial Infections and Colonisation*

#### 2.2.1 Multidrug Resistant Organisms (MDRO)

Colonisation and infection with emerging MDRO is an increasing problem in patients awaiting transplantation [16]. Pre transplant screening depends on local transplant centres' prevalence and epidemiology. The common MDRO include, vancomycin-resistant *Enterococcus faecium* (VRE), methicillin-resistant *S aureus* (MRSA), extended spectrum beta-lactamase producing *Enterobacteriaceae* (ESBLE-E), and carbapenem resistant *Enterobacteriaceae* (CRE) [17]. VRE infection and colonization are increasing problems in liver patients and are associated with higher morbidity and mortality [18-21]. Gastrointestinal tract and biliary tract colonization are common in patients with cirrhosis and LTR and invasive infection is most common in those with biliary and surgical complications [21]. Other risk factors for increased colonisation and infection with VRE are SBP prophylaxis, rifaximin use, patients on dialysis, and high MELD score [18]. . Although there is no effective agent for VRE decolonisation, but isolation and effective infection control measures do help to control the spread. As with VRE, screening for MRSA should be done to identify patients who are at higher risk and consider eradication and appropriate infection-control measures [21, 22]. Eradication of MRSA colonization with nasal mupirocin ointment and chlorhexidine washes must be attempted. MRSA infection has been found to have a high mortality in LTR with a deep intra-abdominal focus of infection or bacteraemic pneumonia [22].

The CRE is emerging new superbug that is posing a serious threat to immunocompromised hosts [23, 24]. In endemic areas, CRE colonisation and infection, particularly those due to carbapenem-resistant *Klebsiella pneumoniae* (CRKP), have become increasingly common in patients with liver disease and transplant recipients [24, 25]. CRE colonisation and infections are associated with very high morbidity and mortality in patients with cirrhosis and LTR [25-27]. Therapeutic options for treating CRE (especially for metallo-beta-lactamase producing coliforms) are limited and therefore prevention of CRE is crucial. Our experience shows that pre transplant screening of CRE have significant impact on reducing the spread and infection rate of CRE in LT candidates and recipients. CRE colonisation of donors or recipients is not a contraindication for transplant, while knowing the status of CRE colonisation allows the appropriate management and prompt isolation and treatment of recipients in order to avoid transmission or infection [27]. An additional rationale for screening gastrointestinal CRE colonization is that colonized patients could be candidates for decolonization. Although there is limited evidence for decolonisation, small studies has demonstrated that selective digestive decontamination (SDD) with oral gentamicin with or without oral colistin, significant decline in CRKP carriage rates [28, 29].

#### 2.2.2 Latent Syphilis

Potential LT candidates are screened for latent syphilis with a rapid plasma reagin (RPR) assay. If the results are positive, the patient should undergo a specific treponemal test (fluorescent treponemal antibody absorption test or micro hemagglutination assay for *Treponema pallidum*).

Positive RPR assay result with positive treponemal test results should be considered an indication of active or latent syphilis and should be treated according to standard guidelines [30].

#### 2.2.3 Latent Mycobacterial Infection

All transplant candidates and donors, particularly those from areas where *Mycobacterium tuberculosis* is endemic, should be screened for latent tuberculosis (TB) infection [31-33] with tuberculin skin test and or interferon gamma release assay (IGRA) [31-33]. IGRAs include the Quanti-FERON-TB Gold Plus (Cellestis, Australia) and the T-SPOT test (Oxford Immunotec, UK). However, there are potential drawbacks associated with screening. Patients with positive PPD test and IGRA results should be considered for prophylactic therapy with isoniazid (INH) under expert supervision due to risk of hepatotoxicity [32-33]. If transplantation is urgent, a patient may be listed prior to completion of prophylactic treatment but should continue INH therapy after transplantation with careful monitoring of liver function tests and cyclosporine or tacrolimus levels [34].

### *2.3 Latent Fungal Infections*

The endemic fungi and Cryptococcus are important causes of morbidity and mortality in transplant patients [34]. However serologic screening and secondary prophylaxis have been recommended for coccidioidomycosis in transplant candidates and recipients in areas where these diseases are endemic. Approximately half of coccidioidal infections in transplant recipients are due to reactivation of pre-existing disease. Prophylactic antifungal therapy should be considered in recipients who continue to reside in endemic areas during the period of maximum immunosuppression. Routine pre-transplant screening for histoplasmosis and blastomycosis for donors and transplant candidates is not currently recommended even in endemic areas because of low incidence of infection post transplantation. Testing for blastomycosis should be considered in transplant candidates and donors in endemic areas that have skin and lung lesions of unknown etiology.

Patients with cirrhosis has a unique predilection to cryptococcosis and the disease usually leads to fulminant course and poor outcomes. Cryptococcal meningitis may be missed in patients with hepatic encephalopathy and, peritonitis due to *Cryptococcus* is also under diagnosed. Cryptococcal antigen testing of serum, ascitic and cerebrospinal fluids, can aid in the identification of cases pre-transplant. In clinically stable patients with pre--transplant cryptococcosis liver transplantation may be cautiously considered with adequate antifungal therapy [35].

### *2.4 Latent Viral Infection*

Although a number of viral infections have been transmitted through donor organ transplantation, but routinely tested viruses for both LT candidates and donors are CMV, EBV, HIV, VZV, HBV, and HCV (Table2). However there is considerable centre-to-centre variation for screening of other viruses e.g. herpes simplex virus (HSV), human T-lymphotropic virus (HTLV I/II), HEV and human herpes viruses 6, 7&8 (HHV6, 7&8).

**Table 2** Recommended vaccines for adult liver transplant (LT) candidate and recipient.

| Vaccine | Time of last dose of vaccine before LT / doses | **Time of vaccine after LT / doses | Comments |
|---|---|---|---|
| PCV-13 | 2wks./1life time dose | 3-6 mo./one life time dose | Interval between PCV-13 and PPSV-23 should be at least 8 weeks. Booster PPSV-23 after 5 years |
| PPSV-23 | 2 wks./2 doses 5 years apart | 3-6 mo. / 2 doses 5 years apart | |
| Influenza | 2 wks./one dose | 1 mo./ 1dose | Administer every year before season |
| HBV | 2 wks./3doses at 0,1,and 6 mo. | 3-6 mo./ if seronegative for HBs-Ab repeat series with double dose | Serial HBs-Ab titters should be assessed both before and every 6–12 months after transplantation to assess ongoing immunity |
| HAV | 2 wks. / 2doses at 0 and 6 month | 3-6 mo. / Complete series after transplant | Must have HAV before visiting to endemic area |
| *HPV | 2 wks. / 3doses | 3-6 mo./ 2-3doses | Recommended up to 45 years of age |
| Tdap or dt | 2 wks./one dose | 3-6mo / one dose | Administer Tap or dt vaccine according to previous immunisation status, booster every 10 years |
| HIB | 2 wks./ one dose | 3-6 mo./ one dose | Candidates who may need splenectomy, or functional spleen or on eculizumab |
| *Men B | 2 wks./2 dose | 3-6 mo./ 2doses | |
| *Men ACWY | 2 wks./one dose | 3-6 mo./ one dose | Recommended at risk population, planning to travel to endemic areas or adolescent or anatomic asplenia |
| VZV | 1 mo./ 2 doses , a month apart | MMR & VZV are live vaccines and are contraindicated after transplant | MMR and VZV live vaccines can be considered after transplant when meet specific criteria of "low-level" immune suppression –ref 67 |
| MMR | | | |
| Zoster vaccine | 2wks/2 doses, 2-6 month apart | 6 mo./2 doses 2-6month apart | Shingrix® should be preferred as it is killed recombinant zoster vaccine (RZV) |
| BCG | 6 mo. / one dose | BCG is live vaccine contraindicated | Administer in instances in which exposure is unavoidable |

PCV-13, 13-valent pneumococcal conjugate vaccine; PPSV-23, 23-valent pneumococcal polysaccharide vaccine; HBsAb, Hepatitis B surface antibody; HPV, human papillomavirus; dT, diphtheria and tetanus; Tdap, tetanus, reduced diphtheria toxoid & acellular pertussis; MMR, mumps, measles, rubella; VZV, varicella zoster virus; Men, Meningococcal; TB, tuberculosis; * Immunogenicity in the post-transplant setting has not been studied extensively. **Complete doses of all killed vaccines if not given before transplant.

### 2.4.1 CMV

The CMV donor and recipient's serostatus determines what CMV prophylaxis or pre-emptive therapy should be used [36]. Antiviral prophylaxis is a most common prevention strategy for all donor/recipient subtypes except D+R+, D-/R- who often receive no prophylaxis [37]. The donor-seropositive, recipient-seronegative ($D^+/R^-$) combination represents the highest risk for severe and late CMV disease, CMV recurrence, and ganciclovir resistance; therefore this group require regular monitoring to prevent CMV associated complications [38, 39]. Prophylaxis is usually given for 3 -6 months after LT with valganciclovir the most frequently used agent for high risk patients In our experience D-R+ was associated with increased biopsy proven hepatitis in pediatric LTR and associated with increased morbidity [39]. This group can be considered for antiviral prophylaxis, although will need more data on its benefit for adult LTR. Some centres utilize the pre-emptive approach for all patients and treatment is commenced when positive CMV viremia is identified. Pre-emptive therapy require regular monitoring usually weekly screening and rapid turnaround time of results [36].

### 2.4.2 EBV

EBV is associated with the devastating disease known as post-transplant lymphoproliferative disease (PTLD) in LTR. The highest risk for PTLD is found in the EBV $D^+/R^-$ combination [40]. Although more than 50% adult population may be EBV seropositive but it is important to determine the serostatus of donor and recipients in pediatric and adult population. Similar to CMV, EBV-seropositive recipients can also reactivate the virus, especially under the influence of intensive immunosuppression such as antilymphocyte therapy. With recently published strategies for EBV, quantitative EBV DNA monitoring of high-risk LTR should be done [40-42]. In response to elevated or rising EBV loads, most accepted preventive strategy is pre-emptive reduction in immunosuppression to prevent EBV disease and PTLD [43]. Limited data on EBV monitoring in adult patients suggest that, it is associated with lower incidence of PTLD in EBV seronegative patients [44]. There is no consensus on time intervals for EBV monitoring, it varies from centre to centre. In our centre this is done weekly while patient is in the hospital, after that on hospital follow up visits or earlier in suspected EBV related infections or disease.

### 2.4.3 Other Herpesvirus

Viral screening for other members of the herpesvirus family also provides useful information. Although some centres screen for herpes simplex virus (HSV)-1 seropositivity, and administer antiviral therapy to all recipient using agents with activity against HSV. Approximately 90% of adults are seropositive for varicella-zoster virus (VZV), but those few who are seronegative are at risk for primary varicella after transplantation, which can be severe [11, 12]. If time permits prior to the anticipated transplantation, varicella vaccination should be administered for seronegative candidates.

### 2.4.4 HIV

HIV screening is done routinely by transplant centres for donor and transplant candidates and HIV positive donors offered to HIV-positive LT candidates [45]. In patients with HIV infection currently, organ transplantation is performed with no detectable viral replication, a CD4+ lymphocyte count above 200 cells/ $mm^3$ and over 100 cells/ $mm^3$ in patients who have hyper-spleenism and the use of antivirals [46].

Many centres screen for human T-lymphotropic virus (HTLV) I and II. HTLV-I is a retrovirus that is endemic in certain areas, can cause tropical spastic paraparesis or adult T cell leukaemia/lymphoma, but seropositive individuals are frequently asymptomatic for decades and may never develop disease [12]. Areas with a high rate of infection due to HTLV I/II include Southeast Asia and the Pacific Islands including Japan, Western Africa, parts of South America, and the Caribbean islands. HTLV-II is a related virus that is difficult to distinguish by serological testing and is not currently known to be associated with any disease. The detection of HTLV I/II seropositivity has not been considered a contraindication to transplantation because there is little literature on the magnitude of the risk of progressing to overt disease under the influence of immunosuppression. Recipients of confirmed or suspected HTLV-1 infected organs or HTLV-positive LTR should undergo regular monitoring for complications of infection, using both serological and nucleic acid based testing (NAT) [47].

### 2.4.5 Hepatitis Viruses

Both donor and LT candidate should be screened for Hepatitis B virus (HBV) and Hepatitis C virus (HCV) infection by doing serology and /or NAT tests [2, 11, 12]. HBV screening for LT candidates is carried out sequentially using serological tests [48]. The key marker is HBV surface antigen (HBsAg), if negative and in immunised patients should determine the HBV surface antibody (HBsAb). However if HBsAg is positive the candidate should have full diagnostic profile of HBV including; HBeAb and HDV Ab serology and HBV DNA quantification. All these markers are particularly relevant for establishing either treatment or prophylaxis patterns before and after transplantation [49-51]. Donors are screened for serological evidence of HBsAg and total HBV core antibody (HBcAb). HBcAb positive (HBsAg negative) donor liver can be used in special circumstances where there are no other potential donor sources. [52, 53]. When HBcAb positive donor is given to an HBsAg positive recipient, the standard approach to prevent HBV reactivation should be adopted [50]. In case of HBcAb positive donor is given to a HBV immune or non-immune recipient, prophylactic lamivudine should be given from the time of transplantation, and should be continued indefinitely [54, 55]. HBsAg positive donor livers can be given to HBsAg positive recipients as long as the recipient is known to be HDV negative, but must be treated with entecavir or tenofovir after transplant [48]. All these recipients require laboratory monitoring for acquired HBV infection after transplantation. The risk of de novo infection is high in naïve HBsAb recipients. Accelerated vaccination against Hepatitis B should be offered while patient is awaiting the transplant surgery. Use of HBV specific immunoglobulins is practised by some centres to avoid allograft infection [56].

2.4.6 HCV

Similar to HBV, HCV screening is done routinely for recipients and donor. In addition, despite negative serology testing, some donors with high-risk category may be at risk for transmitting HCV because of the window period, which is the time between infection and detection by a specific testing method. NAT assay is recommended for these high-risk donors, which detects the presence of HCV viral RNA in the donor's blood. If HCV positive recipients not treated pre-transplant, HCV reinfection of the transplanted liver occur in 100% of patients without effective antiviral treatment post-transplant and can be a cause of graft failure. Historically HCV seropositive organs were excluded from transplantation, but only offered to HCV+ transplant candidates [57]. However current availability of safe and highly effective direct acting antiviral (DAA) regimens has revolutionised the approach to HCV management in LT candidates and recipients [58-60]. All transplant recipients with HCV infection can be cured, while early data also suggest excellent outcomes in recipients of organs from HCV viremic donors [60]. Up to 4% of HCV seropositive donors are viraemic, several single-centre reports of using HCV-viremic organs for HCV-uninfected (HCV-) recipients reported early graft outcomes similar to those of HCV-negative recipients [60]. The DAA regimen is highly effective in treating HCV infection before and after transplantation. These results support utilization of HCV Ab+/NAT- and HCV-viremic organs in selected high risk recipients both with and without HCV infection [61].

Hepatitis E virus (HEV): Until recently the occurrence of HEV in the western world was not of clinical concern, due to its benign and usually subclinical evolution in comparison to Asia and Africa where large epidemics associated with high mortality. HEV infections are not a risk for transplantation except in cases of acute infection in the donor. The HEV is known to cause acute hepatitis, but increasing evidence suggests this to be an agent leading to chronic hepatitis in LTR [62]. HEV may be acquired from donor organ, from de novo acquisition from blood products, or as reactivation in seropositive LT candidates. HEV screening is considered by many centres routinely in all organ donor. The UK advisory Committee for the Safety of Blood , Tissue and Organs recommend HEV screening for all liver donors and for high risk transplant candidates [63] . The detection of HEV viremia in a donor is not an absolute contra-indication to use organ from that donor. HEV can be treated with peg interferon or ribavirin, which was routinely used for treatment of HCV.

### *2.5 Latent Parasitic Infections*

The screening for toxoplasma in transplant and donor varies from centre to centre. In Europe, of 29 countries included in the Eurotransplant network, toxoplasma serology is mandatory in 11countries [64]. Toxoplasmosis results mainly from transmission of the parasite with the transplanted organ from a *Toxoplasma* seropositive donor to a *Toxoplasma* seronegative recipient. The risk of toxoplasma reactivation is high in cases of transplantation of organs that are recognized sites of encystation of the parasite such as the heart and is markedly low after liver transplantation. The D+R- group is considered for prophylaxis with trimethoprim-sulfamethoxazole or pyrimethamine (centre dependent) after transplantation [64]. In pre transplant seropositive recipients, reactivation of latent infection is rare and less severe than donor –transmitted infection. The serological tests do not often contribute to the diagnosis of

toxoplasmosis; it is based mainly on the demonstration of parasites or parasitic DNA in blood, bone marrow, cerebrospinal fluid, and Broncho alveolar lavage fluid or biopsy specimens**.**

The risk of transmission of rare infections is increasing with greater global mobility. The screening should be considered for all geographically restricted infections for both transplant candidates and donors depending on the origin. Extended screening for specific infections such as; S*trongyloides stercoralis, Schistosoma* spp., malaria, *Trypanosoma cruzi,* rabies and West Nile virus, is recommended. Strongyloidiasis may persist at low levels in the intestines of recipients who have lived in areas where strongyloidiasis is endemic. It is helpful to consider S*trongyloides* serological screening of international transplant candidates, those who have lived in areas where infection is endemic and all patients who are HTLV-1 positive [9, 45].

## 3. Vaccination before and after Liver Transplantation

Pre-transplant period gives the best opportunity for updating vaccination status and providing education regarding the reduction of post-transplant infection risks and need to complete vaccinations after transplantation [65, 66]. Ideally, every effort should be made to administer full complement of vaccines before transplant, because of the better immune response to vaccines and general contraindications of live vaccine use after transplantation. Vaccines noted to be safe for administration after transplantation may not be sufficiently immunogenic because of the effect of immunosuppressive therapy. All the available vaccines should be administered according to normal immunisation schedule and other vaccines recommended for LT candidate and recipient (Table 2). Many transplant centres will do routine pre-transplant serology for vaccine-preventable diseases such as Hepatitis B, Varicella, measles, mumps and rubella to guide individual vaccine recommendations. LT candidate who have never received the pneumococcal vaccine, a single dose of PCV13 is recommended first, followed by PPSV-23, eight weeks later (Table2). In general, all the killed vaccines can be resumed after transplant. Although there is no consensus as to the ideal time to vaccinate after transplantation, most centres restart vaccinations at approximately 6 months after transplantation in patients who are on standard immunosuppressive regimens [65, 66]. Live vaccines are generally contraindicated after transplantation because of the perceived risk of transmission of vaccine-derived strains to the recipient. Around 10% of organ transplant patients get shingles. Shingrix® is a killed recombinant zoster vaccine (RZV) which is approved to prevent herpes zoster in patients ≥ 50 years. It is also imperative to determine if the donor has received live vaccination during the past 4 weeks against; influenza (inhaled live vaccine), varicella, measles, mumps, rubella, BCG, cholera (oral vaccine), yellow fever and *Salmonella typhi* (oral vaccine) or polio (oral vaccine).

Growing evidence in pediatric transplant recipients suggest that live-attenuated viral vaccines especially Varicella zoster (VZV) and measles, mumps, rubella (MMR) are safe and can be offered to solid organ transplant (SOT) recipients who are on “low-level" immune suppression [67]. Two doses of MMR and Varicella are recommended one month apart if recipient is antibody naïve for these viruses. Immunogenicity of many vaccines especially HPV and meningococcal vaccines in the post-transplant setting has not been studied extensively. Healthcare workers, family members and close contacts of transplant candidates should be fully immunized. All these close contacts should receive a yearly inactivated influenza vaccine rather than the live-attenuated influenza vaccine.

## 4. Intra or Peri-Operative Antimicrobial Prophylaxis in LTR

Preoperative antibiotics are administered prior to performing surgery to help decrease the risk of postoperative infections. The timing of antibiotic administration may vary, but the goal of administering preoperative systemic prophylactic antibiotics is to have the concentration in the tissues at its highest at the start and during surgery. The appropriate choice of antibiotic selection include antibiotics which cover most organisms we want to target and have narrow spectrum of activity. Further the antibiotics choice is also based on multiple other factors including cost, safety, and ease of administration, pharmacokinetic profile, bactericidal activity, and hospital resistance patterns, and epidemiology of organisms [68]. Commonly by addressing all of these factors during antibiotic selection, surgical site infections (SSIs) and post-operative infections are minimized. There is no universal consensus on type of antibiotic and appropriate duration of surgical antibiotic prophylaxis in LT. Currently there is no data to support the recommendations of a universal antibiotic prophylaxis protocol rather than an antibiotic regimen is individualized to a patient's comorbidities. In a study of 102 LTR Berry et al demonstrated, there is no significant difference in surgical site infections (SSIs) and nosocomial infections when given antibiotic prophylaxis intraoperative alone vs extended to 72 hours preoperatively [69]. Deep and organ/space -SSIs, caused by MDR bacteria, were common after LT despite prophylaxis with broad-spectrum antimicrobials. There is limited literature that supports the beneficial effect of selective digestive decontamination (SDD) on gram-negative infection following LT but increased the risk of antimicrobial resistance [70].

## 5. Commonly Encountered Infections after Liver Transplantation and Management

The estimated incidence of infections after LT is more than 50% [3, 10, 71-74]. Bacterial infections account for most post-transplant infections (up to 70%), followed by viral and fungal infections. LTR of deceased donor has higher rate of infections in comparison to living donor [74]. The timing and risk of infections in LTR is determined by the intensity of exposure to infectious agents in hospital or community and the level of immunosuppression [2, 4, 75, 76]. The net state of immunosuppression depends on the dose, duration and choice of immunosuppressive medications, underlying immune deficiencies and other risk factors. The timing of specific infections after LT historically has been divided in 3-time frames (Table 3).

**Table 3** Timeline of risk Factors and infection type after liver transplant**.**

| **Risk factors for infections after transplant** | | |
|---|---|---|
| **1st Month** | **Between 1st - 6th month** | **After 6th month** |
| Prolonged hospital stay before LT, Co-morbidity e.g. diabetes, COPD, hemodialysis, ECMO, underlying disease; HBV, HCV and HIV, ALF, autoimmune hepatitis, high MELD score >30, Donor organ: ischaemia times, infected OPF, Post-transplant: level and type of immunosuppression, PNF graft, HAT and biliary strictures, prolonged ICU-stay, dialysis, prolonged ventilation, Roux-en-Y, T-tube drainage, re-transplantation, environment, prior colonization with MDRO, indwelling vascular and urinary catheterization, donor-transmitted diseases | General risks: over-immunosuppression, D+/R- mismatch status for viruses, allograft rejection, repeated biliary tract manipulations, re-transplantation, prolonged hospitalisation, | General risks: Only high-risk patients include those with recurrent rejection and allograft dysfunction that would require intense immunosuppression, |
| **Timeline for various infections after transplant** | | |
| **Bacterial infections**: SSI, intra-abdominal abdomen (infected ascites, abscesses, cholangitis), BSI, urosepsis, respiratory tract, *Clostridium difficile colitis* Viral infection: HSV, CMV, Fungal infection: *Candida* spp, rarely Aspergillus spp | Opportunistic pathogens: CMV, EBV, HHV 6&7, *Aspergillus* spp., *Pneumocystis, Nocardia* spp, TB, *Toxoplasma gondii and* endemic mycoses, recurrent cholangitis, HCV recurrence, | Community acquired infections, RTI, urosepsis, opportunistic infections, varicella-zoster, recurrent cholangitis, HCV recurrence |

SSI; surgical site infection, ALF; acute liver failure, BSI; blood stream infection, HAT; hepatic artery thrombosis, PNF; primary non-functioning graft, OPF; organ preservation fluid, MDRO;multidrug resistant organisms, CMV;cytomegalovirus, EBV;Epstein-Barr virus, HHV;human herpesvirus, HCV; Hepatitis C virus, HBV; Hepatitis B virus, HSV;Herpes simplex virus, ECMO; extracorporeal circulation membrane oxygenation,RTI, respiratory tract infections.

### *5.1. Infections in First Month after Liver Transplantation*

In the first month after LT, patient susceptibility to infection is affected by donor derived infections, surgical complications, environment, immunosuppression, and antimicrobial prophylaxis (Table 3). Opportunistic infections are rare in this period unless the patient has been on immunosuppression before transplant e.g. for autoimmune liver disease or re-transplant.

### 5.1.1 Unexpected Donor Derived Infections

Unexpected donor derived infections may be transmitted via contaminated organ perfusion fluid, or infected tissue or systemic infection of the donor. Mostly routinely tested donor derived infections (CMV, EBV, HIV, HTLV1&2, HBV, HCV, HEV and MDRO) testing relies on serology, NAT and culture (Table 2). However, unexpected transmissions are more difficult to detect. They often manifest within the first month after LT [77-80]. In deceased donor because of time limitations between organ procurement and transplantation, donor infectious disease work-up is not always complete [77]. These can be of common infections (e.g., MRSA, multidrug resistant gram-negatives) or more unusual pathogens such as *Cryptococcus*, lymphocytic choriomeningitis virus, or microsporidium, or West Nile Virus, dengue, arboviruses or ZIKA virus [77-79]. Clinicians should investigate more thoroughly for rare pathogens for the patients with unusual clinical symptoms or persistent fever on antimicrobials and without a focus or source identified by routine clinical testing.

Most common sites of bacterial infections are; surgical site infections (SSI), intra-abdominal, pneumonia and urosepsis [80-83]. Predominant infections are caused by endogenous gram-negative bacteria colonised in the bowel or biliary system [82, 83]. The overall incidence ranges between 20-80%. Surgical site infections (SSI) and intrabdominal infections are most common post-surgery. The incidence of SSI in LTR varies between 10–37% [81]. The increased risk is due to prolonged and complex surgery or if there is ongoing intra-abdominal infection before transplant. Other factors that contribute to SSI are bile leak, split or partial allograft and Roux-en-Y biliary anastomosis [2, 81]. After SSI, there are a number of other health-care associated infections (HCAI) that are often procedure or device-related. These include hospital-acquired pneumonia, *Clostridium difficile* and central line associated infections [2, 84]. Unfortunately, infections may also result from modification of endogenous microbial flora in the recipient or due to new colonization from healthcare environment. Surgical complications like bile leak or hepatic artery thrombosis can first present as infection positive blood culture for gut derived organisms and should prompt investigations to exclude these events.

### 5.1.2 Multidrug-Resistant Organisms (MDRO)

In LTR the Incidence with MDRO infections has increased in the last decade and is associated with a 3-fold increase in mortality. Incidence for SSI with MDRO varied from 53- 85%, predominant isolates were *Klebsiella pneumoniae* and *E*. *coli*. Fifty percent of these were carbapenem resistant. In endemic areas, the incidence of infections due to carbapenem-resistant Enterobacteriaceae (CRE) is 5%, most of which occur within 2 to 4 weeks of transplantation [24-26]. The LTR colonized with CRE are associated with higher mortality [84]. Newer beta-lactamase inhibitor including ceftolozane-tazobactam, ceftazidime-avibactam and meropenem-vaborbactam, have good activity against KPC, OXA carbapenemases but they lack activity against metallo betalactamases (e.g. NDM, VIM) producing coliforms. These agents have shown a mortality advantage compared to older agents such as polymyxin and colistin [85] . In our experience combination antibiotic therapy for CRE infection was effective and improved the outcome . Among gram positive bacteria VRE is commonest. More than 50% mortality has been reported due to VRE infection in LTR. However in our experience VRE is indirect indicator of morbidities' in LTR. Only drugs that have been effective

in treating VRE are linezolid and daptomycin but also with a risk of emerging resistance due to their increasing usage [19-22, 86]. CRE and VRE can spread rapidly in the hospital environment therefore with limited treatment options infection prevention and control remains crucial to prevent widespread dissemination of these organisms.

### 5.1.3 Fungal Infections

Invasive fungal infections (IFI) remains important cause of morbidity and mortality in LTR . The reported incidence of IFI is 18–42% in the absence of prophylaxis and 5–15 % with prophylaxis [87]. The contributory factors for reduced incidence of IFI are evolving immunosuppressive agents, improved surgical technique and improved diagnostic test. The most common fungal infection in LTR are due to *Candida* (90%) and *C albicans* is the most common species. However, with increasing use of fluconazole for antifungal prophylaxis in LTR there is higher prevalence of non –*C albicans* yeast such as *C*. *glabrata*, *C parapsilosis,* or *C*. *krusei*. Risk factors for *Candida* include prolonged or repeat operation, re-transplantation, high intraoperative transfusion requirements, renal failure, prolonged broad spectrum antibiotic exposure, choledochojejunostomy, and *Candida* colonization [87-89]. Antifungal prophylaxis in LTR at high risk of developing IFI is widely agreed on, but there is no universal consensus on the type of antifungal agent and duration [90]. Fluconazole and echinocandins are recommended for prophylaxis, but increasingly associated with resistance [89, 90]. The treatment with echinocandin is recommended for IC, although the risk of breakthrough infections for intra-abdominal candida infections should be recognised [90].

Invasive Aspergillus (IA) being second common cause of IFI in LTR. Compared with candidiasis, aspergillosis usually occurs later in post-transplant period, 75% of cases occur within 6 months [91]. Associated mortality varies from 30-100 % in LTR . Risk factors for IA are fulminant hepatic failure, CMV infection, MELD score of >30, requirement for dialysis, chronic lung disease with colonisation of *Aspergillus,* building works in the close vicinity of transplant ward, ECMO and neutropenia. The LTR with risk factors for IA should be considered for mould active antifungal prophylaxis either posaconazole/ voriconazole or echinocandin. Voriconazole remains the drug of choice to treat IA , isavuconazole and liposomal amphotericin B are alternative antifungals [91, 92]. Role of combination antifungals for primary treatment remains controversial. Risk factors for invasive candidiasis (IC) and IA continue to evolve, and thus strategies for their prevention should be constantly updated and targeted.

The early diagnosis of IFI is crucial for effective treatment. The diagnosis of IFI is challenging because current diagnostic methods lack sensitivity and specificity. The standard diagnostic methods include direct microscopic examination of clinical samples, culture, histopathology and imaging. However non-culture methods such as biomarkers beta-d glucan (BDG) or galactomannan (GM ), or molecular tests are increasingly used as an adjunct for the diagnosis of IFI [87, 93]. BDG is major component of fungal cell wall is useful in diagnosis for invasive candidiasis, IA , *Pneumocystis jiroveci* and other many fungal infections thus not specific. The GM assay is specific and sensitive test for diagnosis of IA, although it is found in cell walls of *Histoplasma capsulatum* and *Fusarium* spp . In select cases of abnormal lesions in lung on imaging, obtaining secretions and biopsies via bronchoscopic approach may be helpful for diagnosis of IA. Although GM can be tested in serum, CSF or pleural fluid but testing in bronchoalveolar lavage

(BAL) is highly specific for diagnosis of IA. In LTR fewer studies has shown limited accuracy of BDG and GM in diagnosis of IFI and there is need for further evaluation of these tests in high risk transplant recipients [94]. Serological testing for fungal antibodies has more value in diagnosis of endemic mycoses. Early biopsy or aspiration should be considered in suspected tissue invasive fungal infection ( brain, liver, spleen, oesophagus and skin). Beside microscopy and culture, it is crucial to do histology, fungal stain and PCR.

5.1.4 Polymicrobial Infections

It is not uncommon to observe multiple microbial infections at the same time in LTR. The risk factors for polymicrobial infections could be higher need of immunosuppression and particularly use of monoclonal antibodies like OKT3 or ATG. Surgical complications like bile leaks or hepatic artery thrombosis predispose to both bacterial and fungal infections. Mixed viral and bacterial infections are usually encountered in the first 3 month and the management may be challenging as antiviral drugs usually have bone marrow or renal toxicity, hence close therapeutic drug monitoring is recommended.

### *5.2. Infections between 2- 6 Months Post-Transplant*

The risk of classic opportunistic infections is highest in the first year after LT when the recipient is on high immunosuppression to a stable maintenance regimen [2, 3, 95]. The infectious complications due to *Pneumocystis jiroveci*, CMV, HSV, herpes zoster (VZV), EBV, HHV 6 or 7, relapsed hepatitis (HBV, HCV), and the community-acquired respiratory viruses (adenovirus, influenza, parainfluenza, respiratory syncytial virus, and metapneumovirus) were recognised to occur [2, 3]. In addition Bacterial infections continue to occur in some patients; such as *Clostridium difficile* or MDROs, or TB. In high risk LTR fungal infections due to Aspergillosis and endemic mycoses could occur [92, 96].

5.2.1 *Pneumocystis Jiroveci* Pneumonia (PJP)

*P jiroveci* is now one of several organisms known to cause life-threatening opportunistic infections in immunocompromised hosts. It is classified as a fungus but does not respond to antifungal treatment. It causes acute lung injury in immunocompromised hosts. Reported incidence in LTR ranged from 1–11% in large studies of patients not on prophylaxis and 0–2% in patients on prophylaxis with mortality rate of 7–88% [97, 98]. The major risk factor for PJP in LTR is augmented immunosuppression, particularly high steroid dose and induction with lymphocyte-depleting agents or alemtuzumab [98]. Neutropenia, low CD4 counts, hypogammaglobulinemia and CMV disease are also associated with increased risk [97, 98]. Patients presentation include dyspnoea with hypoxemia, fever and cough. Chest x-ray and CT shows diffuse interstitial or ground glass changes. Specific diagnosis is made using PCR or immunofluorescent staining on BAL. Elevated serum level of BDG, lactic dehydrogenase are adjunct to diagnoses and can be performed routinely as non-invasive procedure. Trimethoprim-sulfamethoxazole (TMP-SMX) is both the treatment and prophylactic agent of choice. Routine PJP prophylaxis is recommended for at least 6-12-month post-transplant .

### 5.2.2 CMV

Despite antiviral prophylaxis CMV infections and associated complications are still most common after LT with significant impact on the morbidity and mortality [99]. The incidence of CMV disease in the first year after transplant ranges from 44–65% for the highest risk group (D+/R−) to 8–19% for the D-R+ LTR) [100]. Immunosuppression, particularly lymphocyte-depleting agents, viral co-infections, and allograft rejection also increase the risk for CMV disease [101]. CMV has both direct and indirect effects on a patient's post-transplant course. CMV syndrome is most common in LTR and characterized by fever and myelosuppression and affects 60% of CMV disease post liver transplant [102]. Tissue-invasive diseases are CMV esophagitis, gastritis, colitis, hepatitis or pneumonitis. The indirect effects of CMV refer to those changes in the host that occur as a result of the viral replication; these include immunomodulation leading to increased immunosuppression, oncogenesis or allograft injury [38].CMV infection has also been reported as risk factor for chronic rejection. In LTR, CMV may increase the risk of bacterial or fungal superinfection; CMV infection is an independent predictor of mortality in LTR, with one study demonstrated 11 times increased risk of infection-related mortality [103]. Post-transplantation, viral load detection has become the standard of care, [35, 104, 105]. Diagnosis of CMV tissue invasive disease is made via histopathology with the finding of either viral inclusion bodies or detection of viral antigens using immunohistochemistry [35]. PCR of tissue is possible but positive results may not always indicate tissue injury [35]. For pe-emptive CMV infection/ disease treatment, ganciclovir, foscarnet and valganciclovir remains the classical first line options. Intravenous ganciclovir is preferred treatment for CMV disease. Treatment is continued until the clinical symptoms have resolved and patients have at least two negative CMV PCR results 1 week apart [104]. To prevent CMV associated complications high risk patients D+R- are given oral valganciclovir prophylaxis for 3 months which has been found effective in reducing the risk of CMV infection and disease [106-108]. The pre-emptive therapy has become more feasible approach because of improved diagnostic testing. Pre-emptive therapy has been shown to reduce CMV disease by 70% [108]. The emerging issues with antiviral prophylaxis are the late onset CMV disease and antiviral resistance [39, 99]. In the future other three experimental CMV antivirals with different antiviral mechanisms brinicidofovir , UL97 kinase inhibitor maribavir and terminase inhibitor letermovir may become option. These antivirals used singly or in combination may also offer better options for treating drug resistant CMV infections [109].

### 5.2.3 Post-Transplant Lymphoproliferative Disease (PTLD)

EBV infection can range from mononucleosis to frank non-Hodgkin lymphoma. The most serious complication after transplant is PTLD and mainly occur pediatric LTR. The primary EBV infection, D+R- serostatus for EBV, immunosuppression and certain underlying autoimmune disorders were found to increase the risk for PTLD [110]. The most effective intervention in case of high EBV DNA is reduction or cessation of immunosuppression but can increase the risk of graft loss. More recently, the anti-CD20 monoclonal antibody (rituximab) has been shown to improve survival in various transplant populations with PTLD. Other therapeutic options are chemotherapy, surgery or radiotherapy. EBV-directed cytotoxic T cells have shown promise in the management of PTLD but its clinical use is limited by lack of technical facilities [41]. Treatment includes reduction

or stopping all immunosuppression, or administration of anti-CD20 in case of a B-cell PTLD. EBV-DNA monitoring has played an important role in the diagnosis and management of EBV – associated PTLD and should be done in all high risk patients in the first year post LT. The treatment of established PTLD is best carried out by an oncology centre [111].

### *5.3 Infections 6 Months Post Liver Transplantation*

Late in the post-transplant period most LTR are on lower immunosuppression reducing the risk of infections [112]. The community acquired infections e.g. viruses and food borne gastroenteritis are most common [113]. Occasionally, some recipients will develop primary or late CMV infection, papillomavirus and relapsing viral infections HBV, HCV and HIV [39, 114]. Subgroup of LTR who are on higher level of maintenance immunosuppression or have biliary/arterial complications suffer from recurrent infections requiring repeated hospitalisations and antimicrobial therapy. They are at risk of developing colonisation and infection by MDRO and C*. difficile* colitis and other common opportunistic pathogens (e.g. *P. jiroveci*, *L. monocytogenes*, *N. asteroides*, *Aspergillus* species, or *Cryptococcus neoformans*). Recurrent cholangitis is one of late infectious complication in fewer number of LTR particularly those who develop biliary complications [112]. Community-acquired pneumonia (CAP) occurs in significant proportion of patients late after LT [113]. The main agents causing CAP are viruses (influenza, RSV) and bacterial pathogens are less common (*Streptococcus pneumoniae*, *Haemophilus influenza* and the atypical pathogens such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae).* Other late infectious complications most commonly reported are late CMV and herpes zoster [39, 114, 115]. Late onset CMV disease has been shown to occur in up to 8 -26% of high risk LTR recipients after 2 years post transplantation [114]. Patients can present with evidence of CMV syndrome or end-organ disease. The biggest risk is if the diagnosis is delayed as clinicians may be less vigilant about it occurring beyond the immediate post-transplant period. Patients should be treated similarly to those with early-onset CMV. Rarely infections due *Cryptosporidium, Microsporidium*, moulds (mucormycosis, Phaeohyphomycoses), and common diseases (herpes zoster, HSV) or TB of unusual severity are also reported [2, 3, 116].

## 6. Infection Prevention Strategies in the Post-Transplant Period

The patient and their close contacts should be instructed in hand hygiene, environmental cleanliness, and the contact precaution with ill persons, especially during the early post-operative period of maximal immunosuppression. Close contacts of recipients should keep their immunizations up to date in an effort to establish herd immunity and thus decrease the possibility of infection in the transplant recipients. Risks related to the patient's occupation, hobbies, social and travel habits, and animal contacts should also be explained. The key infection-prevention strategies in LTR improving primary or pre-emptive prophylaxis with antimicrobials and vaccination, adherence to infection-control recommendations in healthcare or home settings, promoting healthy behaviour and risk reduction in various settings after transplant, e.g. pretravel consultation [117, 118]. Travel, hobbies, young children, and work environments provide exposures to contaminated food and water (*Listeria, Cryptosporidium*), soil (*Aspergillus* or *Nocardia*), birds (*Cryptococcus*), and geographically restricted mycoses (*Blastomyces dermatitidis*, *Coccidioides immitis*, *Paracoccidioides* species, and *Histoplasma capsulatum*) in addition to outbreaks of respiratory viruses and arthropod-borne diseases.

## 7. Conclusions

Comprehensive pre-transplant infectious diseases workup, immunizations, and perioperative and prophylactic antimicrobials are vital to decrease the rate of infections after liver transplantation of certain infectious diseases. Screening of recipients and donors is crucial to minimize the reactivation or the risk of transmission. In post-transplant period diagnostic work-up and therapy (empirical or targeted), should be performed by an expert with experience in transplant infectious diseases in multidisciplinary team. Early diagnosis and treatment of infections are usually associated with improved outcomes.

## Author Contributions

Each authors contributed equally for writing and editing the manuscript.

## Competing Interests

The authors have declared that no competing interests exist.

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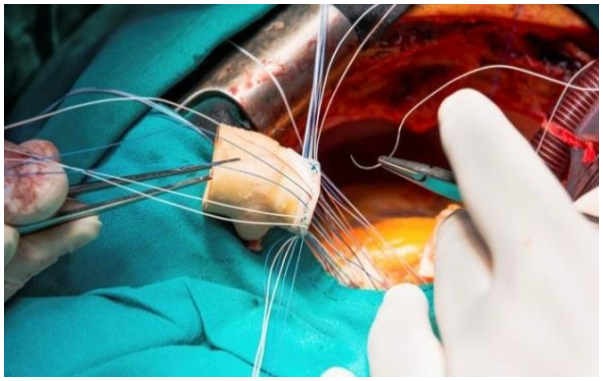

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