Vaccination Strategies for a Liver Transplant Recipient

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Patients with cirrhosis and liver transplant recipients are at increased risk of infections. Malnutrition, multiple hospital admissions, immune dysfunction related to cirrhosis, and immunosuppressive agents used for liver transplantation predispose the recipient to various life-threatening infections. Some of these infections are preventable with vaccines. With the COVID-19 pandemic, there has been an accelerated research in vaccination technology and platforms, which in turn may also improve awareness of physicians regarding this healthy and often ignored aspect of management of patients with cirrhosis and transplant recipients. The organ transplant candidates should complete the recommended vaccination schedule as early as possible (especially patients with compensated cirrhosis) or at least during their pretransplant work-up so as to prevent or reduce the severity of various infections. (J Clin Exp Hepatol 2025;15:102421)

Patients with acute or chronic end-stage liver disease (ESLD) and liver transplant (LT) recipients are at increased risk for infections, some of which can be prevented by timely vaccination of these individuals. There is often a lack of awareness regarding vaccination among physicians attending these sick patients.[1] Various pathophysiologic mechanisms that may predispose these individuals to an increased risk of infection include intestinal dysbiosis, enhanced bacterial translocation, portosystemic shunting, malnutrition, and immunosuppressive medications (following LT).[2] These infectious complications significantly increase the morbidity and mortality among the liver transplant recipients. Some of these infections are vaccine preventable. However, the efficacy of these vaccines is lower in these patients than in the healthy individuals due to the underlying immunosuppression along with use of post-transplantation immunosuppressive therapy.[2] Pretransplant immunization provides higher protective antibody titers and reduces morbidity significantly as compared to vaccination done in the post-transplant period.[7]

On the first visit to the transplant clinic itself, the vaccination status of the recipient should be reviewed. At the same time, an appropriate vaccination strategy should be prepared. Review of the vaccination strategy and its implementation should be undertaken when the patient is listed for transplantation. Every effort should be made to ensure completion of vaccination prior to transplantation, with inactivated vaccines and live viral vaccines to be completed 2 weeks and 4 weeks prior to transplantation, respectively. An infectious disease consultation should be sought for patients who are unvaccinated or partially vaccinated prior to transplantation. It is important to address immunization needs in recipient at the earliest opportunity, as immunologic response at an earlier course of liver disease are stronger.[8] Unfortunately, a dedicated immunization schedule for adult patients with chronic liver disease (CLD) planned for LT is lacking in India. Moreover, despite knowledge regarding need of vaccination in these immunocompromised individuals, there remains a huge gap in attitude and practice of gastroenterologist and hepatologists of India to ensure complete vaccination in these patients.[9] The risk of infection is the highest especially during the peritransplant period (Before LT till the 6th month following LT when the intensity of immunosuppression is the highest). Vaccination in these individuals act as possible method to prevent these infections.[10]

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Abbreviations: ACIP: Advisory Committee on Immunization Practices; ACLF: Acute-on-chronic liver failure; AST: American Society of Transplantation; BCG: Bacillus Calmette–Guerin; CDC: Centres for Disease Control and Prevention; CLD: Chronic liver disease; ESLD: End-stage liver disease; FDA: US Food and Drug Administration; GBS: Guillian–Barre syndrome; HAV: Hepatitis A virus; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HD: High dose; HPV: Human papillomavirus; HZ: Herpes zoster; ICU: intensive care unit; IgG: Immunoglobulin G; IPD: Invasive pneumococcal disease; JEV: Japanese encephalitis virus; LD: Liver disease; LT: Liver transplantation; LZV: Live attenuated zoster vaccine; MenACWY: Meningococcal ACWY; MMR: Measles, mumps, and rubella; PCV: Pneumococcal conjugate vaccine; PPSV: Pneumococcal polysaccharide vaccine; RZV: Recombinant Zoster Vaccine; SD: Standard dose; SOT: Solid organ transplant; TB: Tuberculosis; dap: Tetanus, diphtheria, acellular pertussis; vWF: von Willebrand factor; VZV: Varicella zoster virus

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IMMUNE DYSFUNCTION IN PROSPECTIVE LT RECIPIENTS, NEED OF VACCINATION, AND PRINCIPLE OF VACCINATION

Pathophysiology of Immune Dysfunction in Cirrhosis (Cirrhosis-associated Immune Dysfunction)

Patients with advanced decompensated cirrhosis often have immune dysfunction, which may be due to the following: i) destruction and shunting of intrahepatic reticuloendothelial system; ii) disturbed innate immunity due to impaired phagocytosis and reduced complement synthesis; iii) impaired activity of B cell, T cell, and NK cells and decreased globulin synthesis. iv) These patients are often malnourished and ethanol abusers, which leads to secondary immunodeficiency. The term cirrhosis-associated circulatory dysfunction comprises of a distinct spectrum of immune alterations ranging from systemic inflammation to immune paralysis. v) Immune and circulatory changes in patients with cirrhosis lead to a vasodilation that increases severity of infection, leading to septic shock and multiorgan dysfunction. Severe bacterial infections lead to about 38% mortality in patients with cirrhosis as compared to 10% in healthy individuals.[3,4]

Need of Vaccination in Patients With Cirrhosis

With worsening of decompensation, patients with cirrhosis have progressively worsening of cirrhosis-associated immune dysfunction. There is progressive loss of function of both T cells and B cells. The liver, acting as a gatekeeper, plays key role in mediating immune response to various gut-derived pathogens. This makes the patients with decompensated cirrhosis susceptible to various bacterial and viral infections.[5] Moreover, the severity of illness is also increased significantly in these patients and leads to higher morbidity and mortality.[3] Similarly, patients following LT are also prone to these infections due to intensive care unit (ICU) stay and use of potent immunosuppressive agents at high doses (HDs) (especially during the first 6 months of LT). Moreover, incidence of acute cellular rejection is also the highest during this period, which leads to use of bolus corticosteroids and increasing doses of immunosuppressive agents, leading to increased risk of various infections.[6] Thus, timely vaccination in all patients with cirrhosis is essential to prevent or reduce severity of these infections.

Principles of Vaccination in Patients With Cirrhosis and LT Recipients

Patients with cirrhosis should be vaccinated at an early stage of illness (ideally compensated cirrhosis) for a better immune response as suboptimal response to vaccine has been observed in these patients. With waning immunity, response to vaccines also reduces with decompensation.[7] Similarly, vaccination in unvaccinated transplanted individuals should be postponed at least up to 6 months, with the exception of the seasonal influenza vaccine, which can be given as early as 1 month following LT. After 6 months of LT, live vaccines may be given after explaining potential risks and benefits to the recipient. In general, live vaccines are contraindicated in patients after LT, and a gap of at least 4 weeks must be ensured between vaccination and LT.[8] However, in specific circumstances (e.g., measles outbreaks), some of these live vaccines may be used after explaining the due advantages and risks.[9] Fearing the risk of disseminated infection, the live vaccines are also contraindicated in patients with ESLD. However, the patients in LT waiting list are generally sick and are referred late for vaccination. Moreover, survival of patients with acute-on-chronic liver failure (ACLF) is usually few days without emergency LT. In such a scenario, the patients may be given vaccines just few days prior to LT. In contrast, patients who are posted electively for LT should be vaccinated at the earliest opportunity to health care. However, clinical data to support this are very few, and higher-quality studies are needed.

The principle of vaccination in these individuals has been summarized in Figure 1.

COMMON VACCINE-PREVENTABLE DISEASES

Though patients with advanced cirrhosis and liver transplant recipients are susceptible to various bacterial or viral infections, not all these infections are vaccine preventable. Diseases that can be prevented by vaccination can be classified on basis of aetiology (bacterial/viral). These common infections are summarized in the following in Table 1.

ROUTE OF VACCINE ADMINISTRATION IN CIRRHOSIS

Most of the patients with advanced decompensated cirrhosis tend to have both thrombocytopenia and coagulopathy. There is also reduction in protein C and S levels along with increased factor VIII and von Willebrand factor (vWF) activity in patients with cirrhosis. While thrombocytopenia and increased nitric oxide inhibit platelet aggregation, increased factor VIII and vWF level promote platelet aggregation. Thus decompensated cirrhosis may be described as a state of rebalanced homeostasis.[10] Moreover, presence of thrombocytopenia or coagulopathy in these patients rarely predicts a bleeding episode. Despite having thrombocytopenia, residual platelets are able to provide normal thrombin generation and thus normal primary hemostasis (at least at platelet count of 50,000–60,000/mL). Similarly, a prolonged prothrombin time rarely predicts the risk of bleeding in these patients.[11] Thus till robust data are available, these vaccines should be given by an

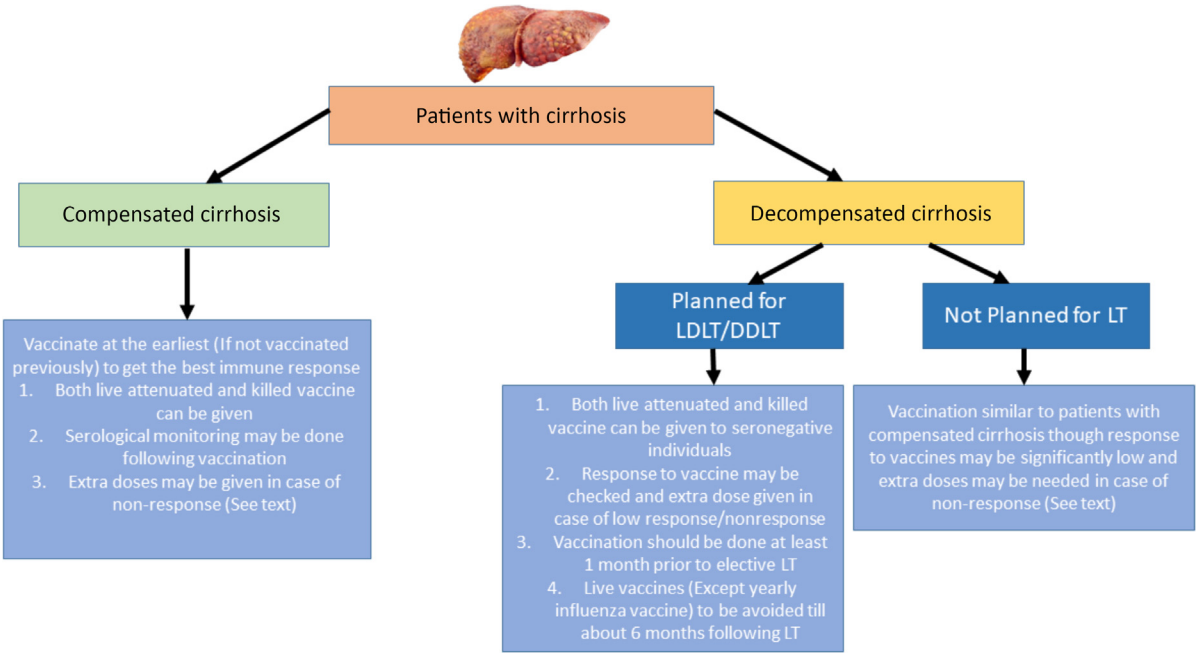

Figure 1 Principle of vaccination in patients with cirrhosis. LT, liver transplantation; LDLT, live-donor liver transplantation; DDLT, dead-donor liver transplantation.

Table 1 Vaccine-preventable Diseases.

Bacterial infections	Viral infections
1. Invasive pneumococcal infection	1. Varicella zoster infection
2. Diphtheria	2. Mumps
3. Tetanus	3. Measles
4. Pertussis	4. Rubella
5. Meningococcal infection	5. Human Papilloma virus
	6. Hepatitis A virus
	7. Hepatitis B virus
	8. Influenza
	9. COVID-19

intramuscular route/subcutaneous route, as prescribed routinely for patients without cirrhosis.

INDIVIDUAL VACCINES

Influenza Vaccine

Influenza is a common endemic viral respiratory illness associated with a higher morbidity and mortality among solid organ transplant (SOT) recipients as than in immunocompetent individuals. Influenza is mainly caused by 2 different viruses: influenza A (subtypes: H1N1 and H3N2) and influenza B.[12] Pandemic influenza A H1N1 in 2009 resulted in 57–70% organ transplant recipients requiring hospitalization and a mortality rate of as high as 4–21%.[13] Studies also indicate that organ transplant recipients mount a poor antibody response to influenza vaccination as compared to the healthy controls.[14] Other factors associated with a poor antibody response include the type and intensity of immunosuppression, an age >65 years, and early post-transplant period.[15,16] As shown in several studies, the risk of disease and severity of the illness, chances of developing pneumonia, and requiring ICU admission are significantly reduced if the person has received the influenza vaccine of the same season.[17,18] For the same reason, the American Association for Study of Liver Disease recommends annual vaccination of all patients with CLD.[19] Inactivated seasonal influenza vaccine should be administered annually in pretransplantation and post-transplantation periods.[20,21] In contrast to most other inactivated vaccines, influenza vaccine can be given as early as 1 month following LT.[22] Seroconversion and seroprotection rates vary from 60% to 90% and 7–50%, respectively, in various studies when measured at 3–6 weeks following vaccination.[23] Both quadrivalant and trivalent inactivated vaccines are available. The standard dose (SD) and HD vaccines are both acceptable options for liver transplant recipients, but the HD vaccine showed a better immunogenicity among liver transplant recipients.[24] The live attenuated influenza vaccine, which is administered intranasally, is associated with mild to severe respiratory symptoms, owing to viral replication and is contraindicated in immunosuppressed population, including patients with cirrhosis and SOT recipients. Safety and no increased risk of allograft rejection or organ dysfunction have been demonstrated in SOT recipients following influenza vaccination. Generally speaking, there are no absolute contraindications to inactivated influenza

vaccine in liver transplant recipients, unless there is prior history of anaphylaxis.[25]

Influenza vaccine is associated with multiple adverse events such as encephalitis and encephalopathy, seizures, acute disseminated encephalomyelitis, transverse myelitis, optic neuritis, Guillian–Barre syndrome (GBS), neuromyelitis optica, multiple sclerosis, and anaphylaxis,[26] though not all these adverse events can be definitely attributed to the vaccine *per se*. Anaphylaxis constitutes the most clinically significant adverse event following influenza vaccination. Though rare, anaphylaxis is very convincingly associated with influenza vaccination. As anaphylaxis can be life threatening or even fatal, health authorities recommend the vaccines be given in facilities having trained personnel and appropriate resuscitation instruments for early detection and treatment of anaphylaxis.[27] As the influenza vaccine contains egg protein, it may cause anaphylaxis in patients who develop systemic reactions (e.g., angioedema, respiratory distress, light-headedness, and vomiting requiring epinephrine or other emergency medical intervention) on consumption of eggs. Thus influenza vaccine should be given cautiously in these individuals under close supervision. Alternatively, these individuals may be given the cell culture–based inactivated influenza vaccine.[28,29] Gelatin is commonly used as the stabilizer in various vaccines (including influenza vaccine). Thus patients with a history of anaphylaxis to gelatin must also avoid the vaccine.[30] A possible association between the development of GBS and influenza vaccination is a matter of concern since last 40 years. In the meta-analysis by Martín Arias, L. H *et al.* found out that all types of influenza vaccines are associated with development of GBS. The pandemic-adjuvant vaccine was found to be associated with a higher risk than the nonadjuvented vaccine.[31] In addition, development of GBS was associated with molecular mimicry and host factors (genetic susceptibility).[32] Following influenza vaccination, recipients may develop thrombocytopenia. This adverse event is thought to be immune mediated (a combination of molecular mimicry, T-cell-mediated destruction of platelets, and bone marrow suppression).[33] Finally, narcolepsy (excessive day-time sleepiness) has been associated with influenza vaccination. The mechanism of development of narcolepsy includes immunology (molecular mimicry with enhanced T-cell immunity against viral epitopes [neuraminidase 175–189 and nucleoprotein 214–228]) that mimics brain self-epitope (protein-O-mannosyltransferase-1). Other immune mechanism includes upregulation of interferons, perforin-1 and granzyme-B.[34] In addition, genetic factors (HLA-DQB1*06:02) has also shown to associated with narcolepsy following influenza vaccination.[35]

Pneumococcal Vaccine

Streptococcus pneumoniae causes invasive pneumococcal disease (IPD), including pneumonia, bacteremia, meningitis, and osteomyelitis and is associated with severe morbidity and mortality. Elderly patients, smokers, chronic ethanol abusers, and patients with underlying cirrhosis are at a high risk of developing IPD.[36] These Gram-positive bacteria also cause spontaneous bacterial peritonitis in these patients.[37] The SOT recipients are at a greater risk of severe disease and mortality than the general population. The first 3-year post-transplant period carries the highest risk of IPD, although it may occur at any time during the post-transplant period.[38] The incidence of IPD in transplant recipients is high, which is about 28–36 per 1000 patients per year, which is much higher than that in the healthy population.[39]

Currently available two main formulations of pneumococcal vaccine are the pneumococcal polysaccharide 23-valent vaccine (PPSV23 or Pneumovax 23) and the pneumococcal conjugate 13-valent vaccine (PCV13 or Prevenar 13). The PPSV-23 vaccine is cheap and has higher serotype coverage than PCV13. The latter contains the 7 serotypes present in PCV-7, 5 serotypes in PPSV23, and 1 serotype present in neither of PCV7/PPSV23.[40] The protein-conjugated vaccines help in inducing a T-cell-dependent response, augmentation of the production of antibodies of higher avidity, and formation of memory B cells. This leads to a boosting effect on revaccination. Moreover, the conjugated vaccine is highly efficacious and prevents nasopharyngeal carriage. In contrast, the polysaccharide vaccine induces a T-cell-independent immune response, and unlike PCV, there is no formation of memory B cell. There is no boosting effect of revaccination unlike PCV. In addition, PPSV23 does not prevent nasopharyngeal carriage.[41]

Older studies showed similar immunogenicity of PCV when used in patients with alcoholic cirrhosis, chronic obstructive pulmonary disease, or healthy patients.[42] However, recently, a study by McCashland *et al.*, compared immune response to PPSV23 in 45 patients with cirrhosis as compared to 13 age-matched controls at 1 and 6 months following vaccination and before/after LT. They noted a higher immunoglobulin G (IgG) response in control group. Though immunoglobulin M and IgG responses were higher in patients with cirrhosis, the levels gradually decreased after LT, and sometimes antibody titers were even lower than preimmunization levels, suggesting lower efficacy of PPSV23 vaccine after LT.[7] Despite this, pneumococcal vaccines must be given in all patients with cirrhosis and prior to LT. There is uncertainty regarding the optimal monitoring strategies and interventions for the declining titers.[43]

In a randomized control trial done on the adult liver transplant recipients, in whom the conjugate vaccine was used for priming, followed by the polysaccharide vaccine PPSV23 eight weeks later, individuals did not show any boosting of titers with the dose of PPSV23.[7] However, the PPSV23 provides coverage against 11 additional serotypes of pneumococcus not covered in the conjugate vaccine. Hence, the recommendations for pneumococcal vaccine

in immunocompromised individuals suggest a single dose of PCV13, followed by PPSV23 after 8 weeks. A second dose of PPSV23 should be administered after five years of the first dose. Patients who have received a single dose of PPSV as per previous immunization regimens, should receive a dose of PCV13 at least 1 year after the last PPSV injection.[7]

There has been a recent update in the pneumococcal vaccine recommendations. PCV13 is not recommended for use in adults anymore in the newer guidelines.[7] PPSV23, pneumococcal conjugate 15-valent vaccine (PCV15), and pneumococcal conjugate 20-valent vaccine (PCV20) are recommended for use in this updated guideline.[44]

In the Indian scenario, as PCV15 and PCV20 are not available commercially, vaccination of adults should be done as per previous guidelines. Pneumococcal vaccines are recommended for all CLD patients and liver transplant recipients. As both PCV and PPSV are inactivated vaccines, they can be used in both pretransplant and post-transplant patients.[45]

Severe allergy to any previous dose of pneumococcal vaccine, allergy to any of the components of the vaccine, or allergy after any vaccine containing diphtheria toxoid are the contraindications for the pneumococcal vaccine. PCV13 and meningococcal vaccine MenACWY-D (Menectra) should be given at least 4 weeks apart as both of them, when administered together, produce lower pneumococcal titers.[46] (Tables 1 and 2).

Adverse events associated with PCV include local-site pain redness and swelling. Other adverse events include nausea, headache, myalgia, low-grade fever, rash, and vomiting.[47] Similar to influenza vaccines, patients receiving pneumococcal vaccines may also develop thrombocytopenia (immune-mediated or due to bone marrow suppression).[33]

Hepatitis A Vaccine

Patients of underlying hepatic fibrosis or ESLD are likely to develop ACLF when infected with hepatitis A virus (HAV), which is associated with high morbidity and mortality (especially in elderly patients with underlying hepatitis C virus (HCV) infection or hepatitis B virus [HBV] carriers).[48,49] Currently, three inactivated vaccines are available in the United States. These are Havrix (GlaxoSmithKline biologicals), TWINRIX (GlaxoSmithKline biologicals), and Vaqta (Merck & co). Havrix and Vaqta are given 2 doses at an interval of 6–12 months. Hepatitis A vaccine is recommended in all seronegative patients with ESLD.[50] Ideally, serological assays for hepatitis A should be undertaken prior to transplantation. While previous epidemiological studies conducted in India showed that most of the persons are immune to HAV infection by adulthood, recently conducted studies have shown contrary results. With improved sanitation and urbanization, the seroprevalance rate is gradually decreasing in adults.[51] The available hepatitis A vaccines, though highly effective, show reduced efficacy in patients with ESLD, and the antibody titers tend to decline rapidly as compared to healthy individuals.[52,53] Patients with compensated cirrhosis tend to mount a similar immune response as healthy individuals (94–98%).[54] In contrast, patients with advanced decompensated cirrhosis tend to mount a weaker immune response.[55,56] Seroprotection offered by the hepatitis A vaccine is variable in liver transplant recipients. After LT, immunogenicity of HAV vaccine is also reduced (especially in early period after LT) with a rapid decline in protective antibody titers.[57,58] Presence of high neutrophil and lymphocyte counts in liver transplant recipients has been shown to be associated with a higher immune response.[57] As seroprevalence of HAV is gradually decreasing, it is recommended that all seronegative patients with cirrhosis should receive HAV vaccine at the earliest stage of illness so as to provide optimal benefit of vaccination.

Adverse events following hepatitis A vaccine are usually mild and include local-site pain, redness, and swelling. Following vaccination, some of the recipients may develop low-grade fever. In addition, thrombocytopenia related to decreased platelet production and immune-mediated destruction of platelets has also been noted with this vaccine.[33]

Hepatitis B Vaccine

HBV infection in an immunocompromised patient is associated with an increased incidence of progression to chronicity, progression of cirrhosis, and development of Hepatocellular carcinoma (HCC). Acute HBV infection is also a leading cause of acute liver failure or ACLF (especially in Asian countries) and is associated with high morbidity and mortality.[59] In liver transplant recipients, *de novo* HBV infection may ultimately lead to loss of the allograft. Thus all patients with ESLD who are negative for Hepatitis B surface antigen, total anti-Hbc, and anti-Hbs and are in LT waiting list must receive the complete course of HBV vaccination at the earliest opportunity prior to transplantation. Till very recently, 2 single-antigen vaccines (Recombivax HB and Engerix-B) along with a combined HAV/HBV vaccine (TWINRIX) have been approved by the US Food and Drug Administration (FDA). These vaccines contain nonglycosylated sHbsP24, with aluminum hydroxide being the adjuvant. On other hand, these vaccines differ from each other with respect to concentration of the surface antigen and nature of aluminum adjuvants. The standard course of HBV vaccine (TWINRIX/Recombivax HB/Engerix-B) consists of 3 doses (each dose 20 μg) given intramuscularly at 0, 1, and 6 months. Though the vaccine efficacy is very high, older males, immunosuppressed patients, smokers, alcoholics, patients with chronic kidney disease, and obese individuals often mount very poor immune response.[60] Recently, the FDA has approved an HBV vaccine composed of

Table 2 Summary of Commonly Recommended Vaccines in Potential Liver Transplant Recipients.[26,73,74]

Inactivated vaccine			
Name of vaccine	**Target population**	**Vaccination schedule**	**Special remarks**
Pneumococcal vaccine	All unvaccinated or incompletely vaccinated liver transplant recipients	**Unvaccinated individuals—**1 dose of PCV13 followed 2 months later by 1 dose of PPSV23 **Patient previously vaccinated by PPSV23—**1 dose of PCV13 at least 1 year of PPSV23 and one dose of PPSV23 after 5 years of PPSV23	**S**imilar dosing schedule can be followed in unvaccinated individuals after liver transplant. Patients between 19 and 65 years of age should receive 1 dose of PPSV23 at least 1 or 5 years after PCV 13 or PPSV
Seasonal influenza vaccine	All patients with cirrhosis and liver transplant recipients	1 dose of tetravalent vaccine every year	Can be given to patients as early as 1 month following liver transplant
HAV vaccine	All LT recipients and patients with compensated/decompensated cirrhosis	Two doses of inactivated vaccine at 6- to 12-month interval Three dose of TWINRIX at 0, 1, and 6 months	A third booster dose can be given in individuals with inadequate response to vaccination
HBV vaccine	All liver transplant recipients and patients with compensated/decompensated cirrhosis	Three dose of vaccines (Engerix-B/Recombivax HB/ TWINRIX) to be admitted at 0, 1, and 6 months Alternately, 2 doses of HAPLISAV-B 4 weeks apart	In contrast to immune competent individuals liver transplant recipients and patients with cirrhosis should be given a higher dose (40 μg) of vaccine
Diphtheria, tetanus and acellular pertussis vaccine	All patients with cirrhosis and liver transplant recipients	1 dose every 10 years	None
HPV vaccine	All patients with cirrhosis and liver transplant recipients between 9 and 45 years of age	3 doses at 0,2 and 6 months	Patients up to 55 years may be vaccinated with the vaccine with favorable safety and immunogenicity profile
Zoster recombinant (Shingrix)	Not recommended in patients with cirrhosis. If at all given to be to be administered prior to LT	Patients who are more than 50 year of age should receive 2 doses 2–6 month apart regardless of previous herpes zoster or history of zoster live vaccine	None
Live attenuated vaccines			
Name of vaccine	**Target population**	**Vaccination schedule**	**Special remarks**
MMR	Seronegative patients with cirrhosis prior to LT	2 doses 4 weeks apart	Patients who have received only one dose must receive the second dose prior to LT
VZV	Seronegative patients with cirrhosis prior to LT	2 doses 4–8 weeks apart	Should be given only if benefit of vaccination outweighs the risks

PCV, pneumococcal conjugate vaccine; PPSV, pneumococcal polysaccharide vaccine; HAV, hepatitis A virus; HBV, hepatitis B virus; HPV, human papilloma virus; LT, liver transplantation; MMR, mumps, measles, and rubella; VZV, varicella zoster virus.

Recombinant Hepatitis B surface antigen mixed with a synthetic oligonucleotide (CpG motif). The purpose of adding the synthetic motif is to stimulate innate immune response through toll-like receptor-9. In contrast to the older vaccines, HEPLISAV-B is given as 2 doses at an interval of 4 weeks.[61] A systematic review by Lee GH *et al.* included 4 randomized studies (7056 patients receiving 2 doses of HEPLISAV-B and 3214 patients receiving 3 doses of Engerix-B). Immune response was found to be significantly higher in patients receiving HEPLISAV-B. More importantly, the response was better in poor responders (old patients/obese and immunosuppressed individuals).[62] At 4–8 weeks of receiving the last dose of vaccine, anti-HBs titer should be determined. Vaccinated individuals with an anti-HBs titer of more than 10 IU/L are considered protected against HBV infection. However, the rate of seroconversion using SD of vaccine may be low (16–20%) in the immunosuppressed patients with decompensated cirrhosis in contrast to patients with compensated cirrhosis, where the rate of seroconversion may be up to 88%.[63,64] To overcome these challenges, various strategies have been tried. In a retrospective study from Brazil, a double-dose HBV vaccination (40 μg) was used in 43 patients at a standard schedule of 0, 1, and 6 months. About 68% patients achieved the desired antibody response.[65] Improvement in seroconversion using double-dose HBV vaccination in conventional schedule in immunocompromised patients has also been replicated in various other studies.[65,66]

The other commonly used strategy to improve immune response to HBV vaccine in patients with cirrhosis is to use an accelerated vaccination schedule. A retrospective study from Spain included 62 patients with cirrhosis. Out of these, 50 patients received double-dose HBV vaccination in an accelerated schedule. Only 22 patients (44%) developed a protective antibody titer. Furthermore, 15 patients were revaccinated using the same dose and schedule, after which 9 patients (60%) developed protective antibody titers. Similar results were also replicated in another study from Mayo clinic. In contrast, vaccination following LT resulted in adequate response in only 32% of individuals. More importantly, only 11.6% and 8% patients retained protective antibody titer at 1 and 2 years following vaccination. Pre-LT anti-HBs titer was the primary determinant of persistence of protective antibody titer at 1 and 2 years.[67] Young age, early child status, and HCV coinfection were associated with better immune response in the study.[67] The underlying etiology of cirrhosis is another determinant of immune response to vaccination. Patients with ethanol-related cirrhosis have been shown to be having an inferior immune response to HBV vaccine as compared to cirrhosis due to other etiology.[68,69]

Use of adjuvants has also shown to boost immune response to vaccines e.g., aluminum hydrophosphate sulfate, thiomersal, and aluminum hydroxide. About a quarter of approved HBV vaccines contain various adjuvants. However, studies with respect to increased immunogenicity are scarce. A double-adjuvant HBV vaccine Fendrix has shown to improve immune response in patients with decompensated cirrhosis when compared with ENERGIX-B. However, FDA approval of Fendrix is pending at present.[70]

Thus, it can be safely concluded from all these studies that patients with early or compensated cirrhosis may be given a standard regimen of HBV vaccination. In contrast, in patients with decompensated cirrhosis, double-dose vaccine/accelerated-schedule vaccination may be used well prior to LT to achieve the protective antibody titer level. Similarly, use of double adjuvant–based HBV vaccine may improve immunogenicity in patients with advanced cirrhosis. The efficacy of recently approved HEPLISAV-B vaccine needs to be studied in these patients.

Similar to hepatitis A vaccine, following hepatitis B vaccination, patients may develop local swelling, redness, and low-grade fever. Anaphylaxis is rare, though patients with prior history of allergy to the vaccine should avoid vaccine in future. Though various neurological complications such as GBS and multiple sclerosis have been shown to be associated with the vaccine, none of these associations have been proven conclusively.[71]

Herpes Zoster Vaccine

Reactivation of the latent varicella-zoster virus (VZV) leads to herpes zoster (HZ). The most common presentation of the later is a painful dermatomal rash. The most common complication of HZ is postherpetic neuralgia, a chronic pain that may persist for months or even years after resolution of zoster rash.[72] Immunocompromised patients and transplant recipients are at a greater risk of complications such as, disseminated VZV, and mortality in severe cases, due to poor cellular immunity against the virus, as compared to the healthy controls. Two HZ vaccines are currently available, namely the live attenuated zoster vaccine (LZV, Zostavax) and a recombinant subunit zoster vaccine (RZV, Shingrix). The recombinant zoster vaccine (RZV) is a nonlive vaccine that consists of a truncated form of VZV glycoprotein along with the GSK-AS01$_B$ adjuvant system. This vaccine is recommended for use in adults more than 50 years of age to prevent HZ and postherpetic neuralgia.[72] In these patients, the efficacy of the vaccine is more than 90%, though it has been shown to be lower in patients on immunosuppressive therapy.[72–74] The recommended vaccination schedule is 2 doses at an interval of 1–2 months. A phase III randomized controlled trial was done in 264 renal transplant recipients by Vink P *et al.* A total of 132 patients received 2 doses of RZV at interval of 1–2 months. Another 132 patients received placebo. At 1 month and 12 months following the second dose, the response to vaccine was optimal and superior compared to placebo.[75] The RZV has been shown to have higher efficacy than LZV in the prevention of shingles.[76] More importantly, LZV is not

recommended after transplantation, whether or not the recipient is VZV seropositive, due to the risk of vaccine-related viral disease. Live vaccines, if need to be given, should be administered at least 4 weeks prior to transplantation.[77] In a study, after VZV administration in a group of pediatric liver transplant recipients; majority of them (97%) were seroprotected at a follow-up (median follow-up time: 1.7 years) and had no reported VZV-related disease.[78]

Varicella Vaccine

Severe complications can occur following primary varicella infection in transplant recipients. Most adult transplant recipients already have immunity to varicella, owing to natural infection or childhood vaccination but can cause potentially severe complications in the immunocompromised population following transplantation.[79] Routine vaccination in children and susceptible individuals who are at high risk of serious complications with varicella is recommended.[80,81] The varicella vaccine is live attenuated and is contraindicated in immunocompromised population and following LT. Serological tests for varicella antibodies should be undertaken prior to transplantation, and seronegative transplant candidates should be administered the vaccine at least 4 weeks prior to transplantation.

Adverse events following varicella vaccination are rare and include only minor local-site reactions such as swelling, redness, and pain. Development of seizures with or without fever has been noted in individuals after 6–7 days after vaccination. However, this association has not been proven conclusively.[35]

Human Papillomavirus Vaccine

An increased incidence of human papillomavirus (HPV)-related genital warts and malignancies has been observed in SOT recipients. Anecdotally, HPV is also implicated in development of HCC, though recent studies have suggested that HPV infection may actually lower the risk of development of HCC in HCV-infected patients.[82,83] Female recipients with HPV infection are at a 20- to 100-fold increased risk of developing cervical intraepithelial neoplasia, whereas both male and female recipients are at an increased risk of developing other anogenital cancers.[84,85] Currently, only 2 HPV vaccines (bivalent vaccine—CERVARIX and quadrivalent vaccine—GARDASIL) are approved to be used in India.[86] The 9-valent vaccine (GARDASIL-9) is not available in India. Three doses of these vaccine at 0, 1, and 6 months provide seroprotection in more than 90% of patients for 10 years.[86] The vaccine is currently approved for girls between 9 and 26 years of age and is not approved for use in boys. High-quality data are lacking regarding HPV vaccination in patients with cirrhosis.[87,88] However, in post-transplant setting, a reduced but acceptable immunogenicity (up to 68%) of HPV vaccines has been described in observational studies.[87] High serum tacrolimus level has been shown to be associated with lower immunogenicity. However, the rate of seropositivity remains high at 12 months following vaccination despite progressive decline in the antibody titers.[87] Patients at a risk of HPV-related malignancies include males or females between 9 and 45 year of age, though use of the vaccine in patients up to 55 years has been shown to have favorable safety and immunogenicity profile.[89] Thus, it is recommended to give a 3-dose vaccination to all eligible patients prior to LT. If it is not possible to complete the entire schedule by transplantation, the extra doses may be given 3–6 months after LT, once the period of intense immunosuppression is over.

A number of local and systemic adverse events have been ascribed to HPV vaccination. These include local-site pain, tenderness, and swelling, which may occur in about 25% patients. Systemic side effects such as fever may occur in about 4% patients.[90] No serious vaccine-related adverse event has been reported. Patients with prior history of hypersensitivity to yeast or any vaccine component should not receive the vaccine. As postural symptoms such as dizziness and tachycardia have been documented with use of HPV vaccines, the vaccine should be given in sitting or lying-down position. Following vaccination, patient should be observed for 15 min for possible development of side-effects.[86]

Measles, Mumps, and Rubella

Infection with measles, mumps, and rubella (MMR) viruses are extremely rare in patients following SOT. There has been a recent resurgence of measles in the form of worldwide epidemics.[91] In immunocompromised individuals, severe measles infections have been observed. However, given the severity of these infections, all the eligible patients should receive the vaccine whenever feasible. The traditional schedule of MMR vaccine is 2 doses separated by at least 4 weeks. For optimal immune response, the age of vaccination in children should be more than 1 year of age to reduce interference by maternally derived antibodies. However, in immunocompromised individuals, the response to vaccination is often poor. A prospective study, by Schulman *et al.*, included 10 children on maintenance hemodialysis; all the children were given 2 doses of MMR vaccine 4 weeks apart. It was noted that only 70%, 50%, and 80% patients developed immune response against MMR infection, respectively. However, only 30% patients developed protective antibody against all three infections.[92] Data regarding vaccine response in patients with cirrhosis are lacking at present. However, all the LT candidates should be vaccinated at least 4 weeks prior to scheduled transplantation. Antibody titers may be checked after vaccination as response to vaccine is variable in these immunosuppressed individuals. Despite poor response to the vaccines in children less than 1 year of age, some of the infants (<1-year age) or neonates (<28 days' age) may

need LT. In such a scenario, the American Society of Transplantation (AST) and Infectious Disease Society of America recommend MMR vaccination in infants more than 6 months' age. Being a live vaccine, MMR vaccination is generally not warranted following LT. However, few small studies have documented safety of use of MMR vaccine following transplantation though immune response may be low in these patients. In a small study which included 18 children who received measles vaccine, 7 patients out of them developed immune response. There were no adverse events directly attributable to the vaccine *per se*.[93] Moreover, larger recent retrospective, cohort, and prospective studies have established safety and immunogenicity of MMR vaccine in liver transplant recipients. In these studies, the rate of seroconversion was 44%–63% for measles, 73%–100% for mumps, and 100% for rubella vaccine.[94–96] More importantly, only mild adverse events such as rash and local reactions have been reported in these studies.[96] Based on these studies, the AST in 2019 have revised their guidelines and advocated administration of MMR vaccine in carefully selected patients following solid organ transplantation with appropriate education and close follow-up.[96]

Tetanus, Diphtheria Toxoid, and Pertussis

Data on the risk of these diseases or their vaccination in liver transplant recipients or cirrhotic patients are lacking.[97–99] The tetanus, diphtheria, and pertussis vaccine are inactivated vaccines and should be given as per same indications and schedule similar to general population. Being inactivated vaccines, they can be given safely after LT when needed. Vaccination with these agents *per se* does not increase risk of rejection. However, when given to transplant recipients, immune response may be blunted.[8,99] The prospective study by Baloni A *et al.*, looked into efficacy of diphtheria, tetanus, and poliomyelitis in patients undergoing liver and kidney transplant. They compared immune response to these vaccines in healthy individuals. They found a normal immune response in patients undergoing LT. In fact, patients with cirrhosis may actually have a better immune response for diphtheria and poliomyelitis.[97] At present, it is recommended by AST that tetanus titers to be monitored in children at least 4 weeks following vaccination. A rapid decrease of antibody titers especially for diphtheria has been noted in the post-transplant state. Booster injections in renal transplant recipients have been found to be well tolerated. Based on this, a recommendation for booster injections every 10 years has been made for patients with cirrhosis and liver transplant recipients.[100–102]

Meningococcal Vaccine

Higher risk of invasive meningococcal disease has not been documented in SOT recipients. Therefore, no recommendation for meningococcal vaccination has been proposed in this patient population. If patients waiting for liver transplant need to receive meningococcal vaccines because they have functional or anatomic asplenia, they should receive two doses of meningococcal B vaccine as well as two doses of meningococcal A, C, Y, and W vaccines. While in case of meningococcal B vaccine, the gap between the two doses of the vaccine should be one month; in other meningococcal vaccines, the gap should be six months.[21,87,88]

Tuberculosis Vaccine

Despite availability of highly effective and safe oral therapies, tuberculosis (TB) remains the leading fatal infectious disease worldwide. More importantly, patients with cirrhosis are at high risk for developing TB as compared to the general population.[103] In a Danish nation–based study, prognosis of these patients is poor with case fatality rate reaching up to 27% at 30 days and 48% at 1 year.[104] Moreover, most of the commonly used bactericidal antitubercular drugs (Isoniazid, rifampicin and ethambutol) are hepatotoxic. Deranged liver function at the baseline along with presence of hypoalbuminemia increases the risk of developing hepatotoxicity further.[105] The only approved vaccine to prevent TB is Bacillus Calmette–Guerin (BCG) which is administered in New Born to reduce severity of childhood TB. Efficacy and safety of the BCG vaccine are not established in adults or patients with cirrhosis. Thus, at present, it is not recommended to vaccinate adult patients with cirrhosis or liver transplant recipients.

COVID-19 Vaccine

Patients with decompensated cirrhosis are at a high risk of acquiring COVID-19 infection and are associated with higher morbidity and mortality. Patients with alcoholic liver disease, nonalcoholic fatty liver disease, and chronicHCV infection are at an increased risk of developing COVID-19 infection. In contrast, patients with autoimmune liver disease remain at a lower risk. About 20–50% patients may develop acute decompensation or ACLF with consequent increased morbidity and mortality.[106] An exaggerated immune response (cytokine strom) in these patients may be responsible for increased morbidity and mortality in these patients. Similarly, liver transplant recipients are immunosuppressed and are at high a risk of developing severe COVID-19 with increased morbidity and mortality.[106–108]

Between 2020 and 2022, several COVID-19 vaccines were approved for emergency use. These include the messenger RNA (mRNA) vaccines (BNT162b2 Pfizer-BioNTech and mRNA-1273 Moderna), an adjuvented recombinant protein vaccine (NVX-CoV2372 Novavax), or a replication incompetent adenovirus vaccine (Ad26.COV2.S Janssen/Johnson & Johnson and AZD1222

Oxford-AstraZeneca). However, most studies based on use of these vaccines excluded patients with cirrhosis and liver transplant recipients.[61]

D'Offizi *et al.*, in their study, found that liver transplant recipients had a significantly lower serological response to mRNA vaccines than healthy controls. After 2 doses of the vaccine, the LT group showed a blunted but coordinated humoral and T-cell-mediated response.[109] Real-life studies exploring serological response to mRNA vaccines in liver transplant recipients have demonstrated antibody responses between 47.5% and 81%.[110–117] A Chinese multicentre prospective study by Jingwen Ai *et al.*, compared immune response to inactivated whole-virion vaccine in patients with cirrhosis and normal individuals. Protective antibody titers were assessed in 437 patients with CLD and were compared with 144 healthy volunteers. It was noted that about 75% of patients with compensated cirrhosis/decompensated cirrhosis and noncirrhotic CLD developed protective antibodies in contrast to about 90% of healthy volunteers who had adequate response to the vaccine.[118] Two COVID-19 vaccines commonly used in India were COVISHIELD (ChAdOx1nCoV-19 vaccine, the replication deficient chimpanzee adenovirus vaccine) and COVAXIN (BBV152, the whole-virion vaccine). A cross-sectional study by Singh A *et al.* included 784 patients with cirrhosis. Out of them, 134 patients received 2 doses of COVISHIED, whereas 97 patients received a single dose of vaccine. Seroconversion was documented in 82 of 88 (90%) patients. Breakthrough infection occurred in about 3% of patients (receiving single dose/2 doses). The vaccine was tolerated well, and none of the recipients developed any major adverse events.[119] As per the Global Hepatology Society Statement, patients with liver disease including liver transplant recipients should receive vaccination against SARS-COV2 with any authorized COVID 19 vaccine.[120,121] If the patient has not received the vaccine prior to LT, at the earliest, the patients should be vaccinated is at 3 months following LT. Withholding immunosuppression to improve immune response to COVID-19 vaccine has not been recommended. As the protection from vaccinated gradually declines over time, need for booster vaccinations in this immunocompromised group would be required even though the long-term efficacy of vaccines has not been specifically studied in this population. More studies are required in this field before concrete recommendations can be made regarding booster vaccination.

In liver transplant recipients, reduced immune response to various COVID-19 vaccines has also been noted. The cohort study from Italy by Guarino M *et al.* enrolled 492 liver transplant recipients who received 2 doses of mRNA vaccine. At 3 months following vaccination, antispike protein antibody titer was determined by chemiluminescent assay. Antibody to the spike protein was detected in 75% of patients at 3 months of vaccination. On multivariate analysis, older age of recipient (>40 years), shorter time from LT (<5 years), and immunosuppression with antimetabolites were associated with low response to vaccination. Moreover, the vaccine response was significantly lower in liver transplant recipients than in the controls.[122] Immunosuppression protocols using mycophenolate mofetil has been shown to be associated with lower response to COVID-19 vaccine.[123] In such a scenario, use of 3 doses of mRNA vaccine has shown to be associated with a higher immunogenicity in SOT recipients.[124] Moreover, using three doses of vaccine has not shown to increase the risk of rejection despite an increased immune response.

Another concern regarding COVID-19 vaccination in liver transplant recipients is the risk of rejection due to immune response to the vaccine. Though rare, this phenomenon has been documented in cornea, kidney, liver, and pancreas transplant recipients. Most of the rejection episodes were treated conservatively followed by complete recovery of organ function.[125] As the benefit associated with COVID-19 vaccination significantly outweighs the risk, pending further high-quality studies, no eligible patients with cirrhosis or liver transplant recipient should be deprived of COVID-19 vaccination.

Common adverse events following COVID-19 vaccination include local-site pain, redness, and swelling. Patients may also develop systemic adverse events such as fever, arthralgia, and rashes. These adverse events are usually mild and respond to symptomatic treatment. However, life-threatening adverse events such as pericarditis, myocarditis, GBS, anaphylaxis, acute disseminated encephalomyelitis, thrombosis with thrombocytopenia syndrome, or vaccine-induced immune thrombocytopenia have been described in the vaccine recipients. However, data regarding these adverse events in patients with cirrhosis are scarce. Moreover, COVID-19 infection in unvaccinated individual may be life-threatening. Thus, all the eligible patients with cirrhosis must be vaccinated prior to LT.[35]

STRATEGIES TO IMPROVE IMMUNE RESPONSE TO VACCINES IN PATIENTS WITH CIRRHOSIS AWAITING LT AND POST LT

While patients with advanced decompensated cirrhosis and liver transplant recipients are immunosuppressed, patients with compensated or early decompensated cirrhosis may have vaccine response similar to that of patients without cirrhosis. Thus, patients should be vaccinated at the earliest opportunity.[55,126] Smokers and ethanol abusers often have inferior response to vaccines. Moreover, the antibody titer also reduces progressively over time, requiring additional doses of vaccines,[127,128] so all vaccine recipients should be advised to abstain from smoking and ethanol abuse. Similarly, in liver transplant recipients, vaccination should be done at least 4 weeks prior to transplant to obtain optimal immune response. Patients with

diabetes mellitus also mount poor response to HBV vaccine. The newly approved HAPLISAV vaccine has been shown to provide better immune response in patients with cirrhosis and diabetes.[129,130] Use of albumin infusion, modulation of gut microbiota, and use of novel vaccine adjuvants may be helpful to improve vaccine response, though more high-quality studies are needed at present before their routine use can be advocated.[61]

Patients with ESLD posted for LT are immunocompromised and prone to various life-threatening infections. It is a routine practice in most Indian LT centers to vaccinate these individuals well before the time of transplantation. However, some of them are too sick (e.g., patients with ACLF) who require urgent LT to salvage. In such a scenario, emphasis should be given on routine vaccination of individuals with cirrhosis at the earliest opportunity by the primary healthcare personnel. Unfortunately, there is lack of a dedicated adult immunization program in India. Moreover, an immunization program for immunocompromised patients and patients posted for transplantation is lacking at the present. Implementation of mandatory immunization of all patients with cirrhosis (Even compensated cirrhosis) may lead to significant reduction in mortality due to various vaccine-preventable infections.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Monalisa Sahu: conceptualization, methodology, writing—original draft. Dibya Lochan Praharaj: review and editing; Ajeet Singh Bhadoria: writing—review and editing.

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The authors who have taken part in this study declare that they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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DISCLOSURE

None.

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