

Vaccination in Chronic Liver Disease: An Update

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Patients with chronic liver disease (CLD) with or without cirrhosis remain at risk of developing hepatic decompensation when infected with viral or bacterial pathogens. The Advisory Committee on Immunization Practices (ACIP) currently recommends vaccination in CLD against hepatitis A virus (HAV), hepatitis B virus (HBV), influenza, pneumococcus, herpes zoster, tetanus, diphtheria, pertussis, and SARS-CoV-2. Inactivated vaccines are preferred over live attenuated ones, especially in transplant recipients where live vaccines are contraindicated. As the severity of the liver disease progresses, vaccine efficacy declines, and therefore, vaccines should be ideally administered early in the disease course for optimal immune response. Despite the strong recommendations, overall vaccination coverage in CLD remains poor; however, it is encouraging to note that in recent years coverage against influenza and pneumococcus has shown some improvement. Inadequate access to healthcare, lack of information on vaccine safety, poor financial reimbursement for healthcare providers, and vaccine misinformation are often responsible for low immunization rates. This review summarizes the impact of vaccine-preventable illness in those with CLD, updated vaccine guidelines, seroconversion rates in the vaccinated, and barriers faced by healthcare professionals in immunizing those with liver disease. (J CLIN EXP HEPATOL 2022;12:937-947)

Chronic liver disease (CLD) and cirrhosis are important causes of morbidity and mortality in the western world. The prevalence of CLD in the United States has consistently increased over the last three decades from 12% in the early 1990s to ~15% in 2008.^{1,2} According to the CDC, nearly 4.5 million Americans were diagnosed with CLD and cirrhosis in 2018, corresponding to approximately 1.8% of the total adult population.³ CLD was responsible for 44,358 deaths in the United States in 2019, with a crude death rate of 13.5 per 100,000. In the era of direct-acting antiviral drugs (DAA), the etiology of CLD has shifted from Hepatitis C virus (HCV) infection to one primarily driven by nonalcoholic fatty liver disease (NAFLD) and alcohol-related liver disease (ALD). The etiology of CLD varies considerably by race and ethnicity, with ALD being the predominant cause in Caucasians and HCV in African Americans, while NAFLD stemming from the obesity epidemic is the leading cause of cirrhosis in Hispanics, Native Americans, Hawaiians, and Japanese Americans.⁴

Cirrhosis-related immune dysfunction characterized by alterations in innate (decreased complement activity, reduced chemotaxis, and phagocytosis) and adaptive immunity (decreased memory cells, CD4 helper cells, T cell exhaustion) leads to an inadequate immune response against a wide range of pathogens.^{5,6} Defects in adaptive immunity may also perhaps explain hypo-responsiveness to vaccines in this patient population. As a result, patients with CLD, especially those with cirrhosis, remain at risk of developing hepatic decompensation when infected with vaccine-preventable viral infections such as hepatitis A and B, pneumococcal disease, influenza, or coronavirus disease-19 (COVID-19). Moreover, coinfection with hepatitis B virus (HBV) in CLD also increases the risk of hepatocellular cancer (HCC). The CDC, Advisory committees on immunization practices (ACIP), and the AASLD recommend vaccination in CLD against hepatitis A virus (HAV), HBV, influenza, pneumococcus, and herpes zoster early in the disease course for optimal immune response. Ideally, inactivated vaccines are preferred over live attenuated ones, especially in immunocompromised (transplant recipients) where live vaccines are contraindicated. Despite these strong recommendations, the vaccination rate in this vulnerable population remains suboptimal. In this review, we discuss the current guidelines on vaccinations, seroconversion rates in the vaccinated, challenges faced by the healthcare professionals in immunizing those with liver disease, and the potential solutions to overcome these shortfalls.

INFLUENZA VACCINE

Based on the modeling data, the CDC estimates that every year since 2010, in the United States, influenza has resulted

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Abbreviations: ACLF: acute on chronic liver failure; ACIP: Advisory Committee on Immunization Practices; ALD: alcohol-related liver disease; CLD: Chronic liver disease; CLIF-C: Chronic Liver Failure Consortium; DAA: direct-acting antiviral drugs; HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; LT: liver transplant; NAFLD: nonalcoholic fatty liver disease; SOFA: sequential organ failure assessment

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in approximately 9–45 million illnesses, 140,000–810,000 hospitalizations, and 12,000–61,000 deaths.⁷ At the same time, in 2018–19 influenza vaccinations averted an estimated 58,000 hospitalizations and 3500 deaths. Influenza illness is caused predominantly by two different viruses, Influenza A, which includes subtypes H1N1 and H3N2, and Influenza B, which are further separated into two distinct genetic lineages (Yamagata and Victoria).⁸ AALSD guidelines recommend annual inactivated influenza A and B vaccinations in all adults with CLD.⁹ The live attenuated vaccine is not recommended. Currently available inactivated vaccines include the trivalent (2 strains of influenza A and 1 of influenza B) and the quadrivalent (2 strains of influenza A and two strains of B).

Impact of Influenza on Cirrhosis

Patients with cirrhosis infected with the influenza virus are not only at increased risk of developing severe illness but also have higher mortality compared to those without liver disease.^{10–13} Based on available evidence, it appears that influenza, an extrahepatic respiratory virus, may not cause direct damage to the liver parenchyma. Rather it causes collateral damage in which a pulmonary infection triggers an immune response resulting in recruitment of CD8⁺T cells to the liver resulting in clinically significant hepatitis.¹¹ One study that looked at 96 hospitalized patients with influenza found that underlying cirrhosis was associated with nearly four times higher risk of death.¹⁴ Another study that analyzed 22 cirrhotic patients with influenza in the intensive care unit (ICU) reported an 82% mortality despite timely antiviral treatment. In that study, creatinine >1.8 mg/dL and PaO₂/FiO₂ ratio <200 at presentation were independent risk factors for death.¹² A more recent study conducted during a serious flu outbreak in Germany in 2017–18 found that influenza infection could trigger acute on chronic liver failure (ACLF) in patients with cirrhosis and make them prone to developing secondary bacterial infections.¹⁰ The authors also found that the mean sequential organ failure assessment (SOFA) and mean acute physiology and chronic health evaluation (APACHE -2) scores were higher in cirrhosis than those with no liver disease.

Efficacy of Influenza Vaccine

There are no large randomized, double-blind case–control studies on the efficacy of influenza vaccine in those CLD and cirrhosis. A small study from Japan that looked at immunogenicity in 80 patients with chronic hepatitis C, of which 23 had cirrhosis, found that a single subcutaneous dose of monovalent inactivated influenza A (H1N1) vaccine mounted 72% seroconversion rate of 72%.¹⁵ Immunogenicity was robust regardless of cirrhosis, while older age and lower body mass index were associated with poor immune response. In another study, 20 patients with

decompensated cirrhosis (Child-Pugh class B = 10, Child-Pugh class C = 10) inoculated with trivalent influenza vaccine found seroconversion rates of 75% to H1N1 strain, 80% to H3N2 strain, and 85% to B strain.¹⁶ A recent systematic review and meta-analysis of 12 studies (six studies looked at clinical outcomes following flu vaccination and six studies looked at serological response) found that the seroconversion rate in CLD was ~80% for A/H1N1 strain and ~87% for B strain, clearly well above the 40% recommended lower thresholds for these vaccines.¹⁷ While there was no significant impact on all-cause mortality, vaccination reduced hospital admissions from 205 per 1000 to 149 per 1000.¹⁷ Vaccinated CLD patients were 27% less likely to be admitted to a hospital than the unvaccinated (risk ratio 0.73, 95% CI 0.66 to 0.80). These data suggest that the influenza vaccine is effective in those with CLD, including those with cirrhosis.

Influenza Vaccination Coverage in CLD

Despite strong recommendations and compelling data on efficacy, vaccination coverage against influenza in those with CLD has been poor.^{18–20} A 2015–16 survey in the United Kingdom reported that only 42% of patients with CLD (age 16 years to 65) received an annual influenza vaccine, while in Italy, only 27% of patients less than 65 years received the vaccine in 2019.^{19,20} In that study, patients with alcoholic liver disease and individuals born in foreign countries had lower immunization rates than the general population. Lack of adequate information regarding immunization in minority communities was the primary reason cited for these shortcomings. These findings suggest that primary care physicians, hepatologists, and the medical community need to develop better communication strategies and improvise on already existing tools to enhance vaccination coverage in those with CLD.

PNEUMOCOCCAL VACCINE

The pneumococcal immunization series consists of 2 vaccines, the pneumococcal conjugate vaccine (PCV 13 or Prevnar 13, Pfizer) and the pneumococcal polysaccharide vaccine (PPSV23 or Pneumovax 23, Merck). PCV-13 consists of 13 serotypes of *Streptococcus pneumoniae* (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, 18C, and 23F) conjugated with diphtheria toxin, whereas Pneumovax-23 contains polysaccharide antigens from 23 serotypes of *S. pneumoniae*.

Vaccine Regimen and Recommendation

In 2019, the CDC and ACIP updated their guidelines on pneumococcal vaccination and no longer recommended routine PCV 13 in adults with CLD between the ages of 19–64 years. Patients >65 years remain at risk of invasive

pneumococcal disease/pneumonia, and physicians may offer them the vaccine after shared clinical decision making.²¹ However, a one-time dose with PPSV 23 is recommended in CLD patients between 19 and 64 years, and those ≥ 65 years should receive a second dose after ≥ 1 year if they had previously received PCV 13 or ≥ 5 years after the first dose of PPSV 23. Adult liver transplant (LT) recipients should receive routine vaccination with one dose of PCV13. PPSV-23 is recommended for a total of 3-lifetime doses in this population. The first dose is given ≥ 8 weeks after PCV 13 and a second dose ≥ 5 years after the first dose of PPSV23. When these patients turn 65 years, they should receive a 3rd and final dose at least 5 years apart from the second dose of PPSV 23 (Table 1).

Pneumococcal Disease in CLD

Infection with *S. pneumoniae* can result in a wide range of illnesses such as pneumonia, bacteremia, meningitis, and spontaneous bacterial peritonitis (SBP). Fortunately, following the introduction of the pneumococcal conjugate vaccine in 2000, there has been a significant and consistent drop in the incidence of invasive pneumococcal disease in all age groups (19–64 years and ≥ 65 years).²² However, patients with CLD remain at a higher risk of contracting pneumococcus than those without any underlying conditions. A recent analysis of 1549 cases (inpatients, outpatients, and emergency room visits) of invasive pneumococcal disease (IPD) found that, compared to the general population, those with CLD have twice the risk of developing IPD, and this relative risk was similar to those with underlying chronic obstructive pulmonary disease (COPD).²³ A report from Spain that looked at hospital discharge data found that the annual incidence rate of hospitalization due to streptococcal pneumonia in CLD patients (18–64 years) was 541/100,000 while it was only 6/100,000 in those with no risk factors.²⁴ More importantly, patients with CLD ≥ 65 years had an incidence rate of 1264/100,000.

Despite appropriate and timely use of antibiotics, bacterial infections in cirrhosis are associated with significantly high mortality (7%–40%).^{25,26} *S. pneumoniae* is the most

frequent cause of pneumonia in cirrhotics and noncirrhotics. Numerous studies have demonstrated poor outcomes in cirrhotics following streptococcal pneumonia and/or bacteremia.^{27–30} *S. pneumoniae* is also the third most frequent cause of SBP after *Escherichia coli* and *Klebsiella*. A case-control study found that patients (n = 50) with spontaneous pneumococcal peritonitis had a higher incidence of bacteremia (84.0% vs. 59.0%; $P = 0.002$) and variceal bleeding (10.0% vs. 1.0%; $P = 0.02$) compared to patients with SBP due to other causes.³¹ However, the 30-day mortality (10.0% vs. 24.0%; $P = 0.04$) and in-hospital mortality (16.0% vs. 32.0%; $P = 0.04$) rates were significantly lower in patients with spontaneous pneumococcal peritonitis compared to the control group.

Efficacy of Pneumococcal Vaccine

Robust data on the immunogenicity of pneumococcal vaccine in CLD are not available. The most recent study regarding this was conducted approximately two decades ago. In that study, 45 patients with CLD (Child-Pugh classification: A, 19%; B, 56%; and C, 25%) were injected with Pneumovax-23, and antibody response was compared to healthy controls at 1 and 6 months.³² They found that although IgG, IgM, and IgA levels increased at 1 month, by 6 months, there was a waning of immunity with a rapid decline in antibodies. Moreover, patients who underwent LT (n = 25) had declining antibody levels as early as 3 months post-transplant compared to their baseline. Vaccine hypo-responsiveness may perhaps explain the current CDC recommendation of three doses of PPSV23 in patients post LT.

Pneumococcal Vaccination Coverage in CLD

According to the CDC, in 2018, only 23% of adults (19–64 years) with underlying risk factors received a pneumococcal vaccine, while in older adults (>65 years), coverage was 69%.³³ Data on pneumococcal vaccination coverage exclusively in CLD patients are limited. A survey conducted in 2003 found that the vaccination rate against pneumococcus in CLD was 39% in primary care clinics compared to only 19% in specialist clinics.³⁴ Centers that had a policy

Table 1 Pneumococcal Vaccination Regimens and Recommendations.

Medical condition	PCV13 for patients aged 19–64 years	PPSV23 for patients aged 19–64 years	PCV13 for patients aged ≥ 65 years	PPSV23 for patients aged ≥ 65 years
Chronic liver disease/cirrhosis	No recommendations	1 dose	After shared clinical decision making, one dose given at least 1 year after the first dose of PPSV23	Second dose, if PCV13 has been given, then give PPSV23 ≥ 1 year after PCV13 and ≥ 5 years after the most recent dose of PPSV23
Liver transplant recipients	1 dose	First dose ≥ 8 weeks after PCV13, second dose ≥ 5 years after first PPSV23	1 dose if no previous vaccination with PCV13	3rd dose ≥ 8 weeks after PCV13 and ≥ 5 years after most recent dose of PPSV23

for on-site vaccination had higher coverage. A more recent study from the Mayo Clinic that analyzed vaccine-eligible CLD patients (n = 285) from 2007 to 2015 had more encouraging results and reported an overall coverage rate of 63%,¹⁸ however, coverage in those older than 65 years was relatively low at 54%.

SARS-COV-2 VACCINES

Coronavirus disease (COVID-19) caused by SARS-CoV-2 was declared as a pandemic by the WHO in March 2020. Hospitalizations due to COVID-19 have resulted in significant resource utilization and have overwhelmed health-care systems worldwide.

Impact of COVID-19 on CLD and Liver Transplant Recipients

Patients with CLD, especially those with cirrhosis, when infected with SARS-CoV-2 have increased mortality risk than those without liver disease. To date, the largest report on the impact of COVID-19 in CLD comes from two combined international liver registries (SECURE-Cirrhosis and COVID-Hep.net) that analyzed 745 CLD patients, of which 386 had cirrhosis.³⁵ While the mortality in CLD patients without cirrhosis was 8%, it was 32% in those with cirrhosis. With the increasing severity of liver disease, there was a stepwise increase in the risk of all major adverse outcomes, including ICU admissions, invasive mechanical ventilation, renal replacement therapy, and death. Age, Child-Pugh class, and alcoholic liver disease were independent predictors of mortality; 79 patients with cirrhosis (79/386) developed acute hepatic decompensation characterized by worsening ascites (28%), hepatic encephalopathy (27%), spontaneous bacterial peritonitis (3%), and variceal hemorrhage (3%) and 89 patients met criteria for ACLF. There was a strong correlation between case fatality rates and Chronic Liver Failure Consortium (CLIF-C) organ failure scores.

Numerous studies have looked at the outcome of COVID-19 in LT recipients, and based on available data, it appears that while liver transplantation is associated with increased hospitalization, it may not be a major risk factor for increased mortality.³⁶⁻³⁸ The reported mortality in this cohort is anywhere between 8% and 18%, and this is lower than those with underlying cirrhosis. A study that included 151 LT recipients infected with SARS-CoV-2 found that they were not at increased risk of death from COVID-19 when matched to patients without liver transplants with similar comorbidities.³⁹ Respiratory failure was the predominant cause of death, and independent risk factors for mortality included advanced age, renal failure, and the presence of non-liver cancers.

COVID-19 Vaccines in CLD and LT Recipients

Several vaccines have been developed against COVID-19, and regulatory bodies, such as the FDA and European Medical Association (EMA), have approved (emergency use authorization) several of them. These include mRNA vaccines, such as BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), and vaccines that use an adenovirus vector platform such as AZD1222 (Oxford-AstraZeneca) and Ad26.COVS.2 (Johnson & Johnson).⁴⁰⁻⁴² Although the registration trials of mRNA vaccines enrolled patients with CLD (217 patients in Pfizer trial and 196 patients in Moderna trial), the vaccine efficacy, immunogenicity, and safety of these cohorts are currently not available. A recent study from the United States found that 75% of patients with CLD without cirrhosis and 77% of patients with cirrhosis had adequate antibody response to COVID-19 vaccines.⁴³ In that study, the use of a single-dose Johnson and Johnson vaccine was associated with poor immunogenicity. Currently, all major liver societies recommend vaccination against COVID-19 in CLD and cirrhosis, given the high risk of mortality in this population,^{44,45} however, there is not enough data to recommend one vaccine over the other.

Studies in solid organ transplant recipients that analyzed immunogenicity following two doses of COVID-19 mRNA vaccines have demonstrated suboptimal humoral immune response.⁴⁶ However, few studies that looked at vaccine efficacy exclusively in LT recipients have shown mixed results.⁴⁷⁻⁴⁹ One study involving 161 LT recipients (53% received Pfizer and 47% received Moderna) reported a robust immune with 81% of participants producing detectable antibodies 30 days after the second shot.⁴⁷ Contrary to this, a study from Israel found that only 47% of LT recipients elicited an antibody response to the Pfizer vaccine.⁴⁹ Similarly, we have shown that 61% (38/62) of LT recipients did not mount a good response after two doses of mRNA vaccine.⁴³ Overall, these vaccines appear to be safe in both CLD and LT recipients, and no major adverse effects have been reported.

Few studies have recently reported excellent responses after a booster dose of vaccine. This should be a consideration in all immunocompromised subjects, especially in organ transplant recipients.⁵⁰⁻⁵²

HEPATITIS B VACCINE

In the United States, from 2010 to 2019, the reported incidence of acute HBV infections has relatively been stable except for a mild increase in 2017, which was attributed to the surge in injected drug abuse. Since the introduction of childhood HBV vaccination, the incidence of new chronic HBV infections has dramatically reduced, but the

poor vaccination coverage in adults at high risk continues to pose a serious threat of acute hepatitis B.

Hepatitis B Infection in CLD

It is well documented that coinfection with chronic HBV and chronic HCV is associated with an increased risk of cirrhosis and HCC.^{53–55} A study that looked at liver histology in patients with chronic HBV and HCV found a higher prevalence of moderate or severe chronic hepatitis or cirrhosis (63% of 65 patients) compared to those with chronic HBV alone (47% of 90 patients) or chronic HCV alone (41% of 98 patients).⁵⁶ Patients with coinfection also had higher levels of serum aspartate transaminase, suggesting a more vigorous immune response. Data on superinfection with hepatitis B virus (HBV) in those with CLD are limited. There are isolated reports of adverse outcomes, including fulminant hepatitis following acute HBV infection in patients with chronic hepatitis C virus (HCV) infection.^{57–59} A small case-control study from Italy found that patients with chronic HCV infected with acute HBV are at increased risk of developing ascites and hepatic encephalopathy compared to those with acute HBV alone.⁶⁰

Immunogenicity of Hepatitis B Vaccine in CLD

Hepatitis B vaccination is recommended for all patients with CLD with and without cirrhosis. Currently, both single antigen vaccines such as Engerix-B, Heplisav-B, Recombivax-HB and combination vaccines such as Twinrix (combined hepatitis A and B vaccines) are available. Although these vaccines are highly immunogenic in healthy individuals (>90%), multiple studies have shown that factors such as advanced age, male gender, obesity, diabetes mellitus, and chronic kidney disease are associated with reduced immune response.^{61–64} Similarly, seroconversion is poor in those with CLD, and vaccine efficacy wanes with the increasing severity of the liver disease. Studies that evaluated the efficacy of the 3-dose vaccine in cirrhosis have reported highly variable seroconversion rates ranging anywhere from 16% to 79%. Although high-quality randomized prospective trials are lacking, it is safe to say that vaccine efficacy in CLD is suboptimal.^{65–68}

Multiple strategies have been proposed to improve immunogenicities, such as accelerated vaccine regimens and increased vaccine dosing. One study compared the standard-dose vaccine of Twinrix or Engerix B in 97 cirrhotics (20 μ g at 0, 1, and 6 months with a 40- μ g booster of Engerix-B if nonimmune) against a high-dose accelerated vaccine in 51 patients (40 μ g at 0, 1, and 2 months, with the schedule repeated as a booster in those who are nonimmune) and found that seroconversion in the high-dose group was only 45% while in the standard dose group it was 51.5%;⁶⁹ however, when a booster dose was given, there was a significant improvement in the high-dose

group, and vaccine efficacy of 79% was achieved. A recent study found that the newly approved 2-dose vaccine (Heplisav-B) offered higher seroprotection (63% vs. 45%, $P = 0.03$) in CLD compared to the traditional 3-dose vaccine (Engerix-B).⁷⁰ Patients who received Heplisav-B were almost three times as likely to achieve immunity compared to those who received Engerix-B (aOR: 2.74, 95% CI 1.31–5.71, $P = 0.01$) after adjusting for comorbidities. Patients who had cirrhosis, COPD, or renal failure were at risk of a poor immune response.

Vaccination in those with Occult HBV Infection

Vaccination of patients with previous exposure to HBV and have low-level viremia (HBV DNA) in the absence of positive HBsAg is a controversial area. Often referred to as occult HBV infection, these patients may be either seropositive (anti-HBc positive \pm anti-HBs) or seronegative (both anti-HBc and anti-HBs negative).^{71,72} There is a consensus that these patients should have prophylactic treatment with either entecavir or tenofovir if they were to undergo chemotherapy or potent immunosuppression. There have been few small studies with discordant results after HBV vaccination in those with occult HBV infection.^{73,74} Based on the current evidence, there is no role for HBV vaccination in these patients.

HEPATITIS A VACCINE

Increased mortality from HAV superinfection in those with CLD is well documented.^{75–77} A CDC study between 1983–88 that analyzed 2311 cases of acute HAV in CLD reported a 28% mortality.⁷⁵ Another prospective study that looked at 17 cases of HAV superinfection in 17 patients with chronic HCV over a 7-year period found that 7 of 17 developed fulminant hepatic failure with a mortality rate of 35%.⁷⁶ Interestingly HAV superinfection in those with underlying chronic HBV had an uncomplicated course. There are also reports of fatal outcomes following HAV superinfection in those with underlying alcoholic cirrhosis.^{78,79}

Immunogenicity of Hepatitis A Vaccine in CLD

Currently approved vaccinations against HAV include Havrix and Vaqta. While regulatory bodies in the United Kingdom and United States recommend HAV vaccine in those with CLD, in certain countries like India, where the prevalence of HAV antibodies in CLD is reportedly greater than 90%, routine vaccination is not recommended.⁸⁰ The safety and efficacy of HAV vaccines in CLD are well documented.^{81,82} A multicenter trial found that seroconversion following the 2-dose vaccine was 98% in those with chronic HBV, 94% in chronic HCV, and 95% in those with miscellaneous CLD; however, vaccine efficacy in patients with advanced liver disease is poor. For instance, one study demonstrated a 98% seroconversion in patients with

CLD and compensated cirrhosis, while the response rate in Child-Pugh B cirrhosis was only 71% and 57% in those with Child-Pugh class C.⁸³ On multivariate analysis, increasing Child-Pugh class was associated with reduced immunogenicity. These data clearly indicate the need for vaccination early in the disease course in those with cirrhosis, so that vaccine efficacy is optimum. A more recent analysis of approximately 80,000 chronic HCV cases in the United States through the Veterans Affairs (VA) case registry found that the incidence of HAV superinfection in those not vaccinated against HAV was 0.16%, while it was only 0.01% in those vaccinated (incidence rate ratio 14.25; 95% CI 2.23–595.5; $P = 0.0003$) demonstrating strong clinical support in favor of vaccination in this vulnerable patient population.⁸⁴

Vaccination Coverage for Hepatitis A and Hepatitis B

Despite recommendations by multiple consensus panels, vaccination coverage against hepatitis A and B among CLD patients is poor, but it is improving. According to data from National Health and Nutrition Examination Surveys (NHANES), vaccination against HAV in CLD increased from 13% in 1999–2004 to 20% in 2005–2008.⁸⁵ Similarly, for HBV, coverage increased from 23% to 32% during the same period. By using the same database, it was reported that in 2013–14 nearly 40% of adults with CLD received at least one dose of hepatitis A, while 51% of CLD patients received one dose of hepatitis B vaccine.⁸⁶ The coverage in CLD against HBV is higher than that of the general population. Younger age, having health insurance, and having a college degree, were independent predictors for being vaccinated. Although underlying CLD was associated with increased odds of HBV vaccination, it did not have an impact on HAV vaccination.

HERPES ZOSTER VACCINE

The annual incidence of Herpes zoster in adults is approximately 4 cases/1000 US population, while in those 60 years or older, it is 1 case per 100 US population.⁸⁷ Based on available data, it appears that those with CLD may not be at a higher risk of developing Herpes zoster infection compared to the general population. However, LT and subsequent immunosuppression increase the risk substantially.^{88–90} A study from Spain that looked at 201 LT recipients found that the incidence of Herpes zoster was 12%, with nearly a third developing postherpetic neuralgia.⁸⁹ The use of azathioprine and mycophenolate mofetil were independent risk factors for the development of Herpes zoster.

Currently available vaccines to prevent zoster includes Zoster Vaccine Live (Zostavax), which is a one-dose live attenuated strain of VZV, and the more recently approved

Zoster Vaccine Recombinant (Shingrix), a nonlive 2-dose subunit vaccine that contains VZV recombinant glycoprotein-E in combination with a novel adjuvant. As of November 2020, Zostavax is no longer available for use in the United States.⁸⁷ Data on the efficacy and safety of Zostavax in CLD patients and LT recipients are currently lacking; however, RCTs in immunocompetent individuals have demonstrated a vaccine efficacy of 97%.⁹¹ The ACIP recommends that patients with CLD receive two doses of Shingrix after the age of 50 years 2–6 months apart.⁹² Although Shingrix is not contraindicated in immunocompromised patients, ACIP currently does not recommend this vaccine in LT recipients. Shingrix should ideally be given in this population prior to LT. It is interesting to note that recent trials that evaluated the efficacy of Shingrix in renal transplant recipients and stem cell transplant recipients demonstrated a robust immune response, indicating that the vaccine may be perhaps effective in LT recipients as well.^{93,94} In our practice, we have been recommending Shingrix to all our liver transplant recipients despite no such recommendations from ACIP.

TETANUS, DIPHTHERIA, AND PERTUSSIS VACCINE

There are limited data on the efficacy of these vaccines in those with CLD. ACIP currently recommends one dose of Tdap in those with CLD followed by a Td or Tdap booster every 10 years.^{95,96} Given these vaccines are inactivated, they are generally considered safe in LT recipients and currently recommended by the American Society of Transplantation (AST) in LT recipients.⁹⁷ A small study involving pediatric patients with CLD ($n = 29$) and LT ($n = 52$) demonstrated vaccine efficacy >95% following immunization with tetanus toxoid while efficacy against diphtheria was >80%.⁹⁸ Although there are no studies in adult LT recipients, trials in renal transplant patients have demonstrated an adequate short-term immune response to these vaccines, with the waning of immunity after 12 months that necessitates the need for boosters every 10 years.^{99,100}

VACCINATION IN SPECIAL POPULATIONS WITH CLD

Acute Liver Failure and Acute on Chronic Liver Failure

Because of a limited window for liver transplantation in acute liver failure and acute-on-chronic liver failure, vaccination is not a priority, and moreover, the immune response in these patients is likely to be poor. The general rules of vaccination are applicable to these patients if they were to recover with or without liver transplantation. It is perhaps prudent to wait for a few weeks after liver

transplantation to start the vaccination protocol for a better response.

Renal Failure or HIV

Vaccination in those with CLD and renal failure or HIV is similar to that of CLD without these comorbidities. In those with HIV, vaccination for Hemophilus influenza (especially in the presence of asplenia), human papillomavirus (if ≤ 26 years), and meningococcus could be considered. Live vaccine should be avoided in those with CD4 count <200 cells/mm³.

Pregnant Women

Pregnant women with CLD should be vaccinated against hepatitis A and B, SARS-CoV-2, influenza (inactivated), and DTaP.^{101,102} Vaccination against pneumococcus with PPSV23 is also a consideration in pregnancy, although safety data are lacking. Reassuringly, no adverse events were reported in infants whose mothers were inadvertently vaccinated with PPSV23 during the pregnancy.¹⁰³ It is mandatory to administer hepatitis B immune globulin (HBIG) along with the first dose of HBV vaccine to newborns of HBV positive mothers during the first 12 h of birth to reduce risk of perinatal transmission. Vaccines contraindicated during pregnancy include MMR, HPV, varicella, and zoster.

Children

Children with CLD should receive all routine immunizations as recommended by the Center for Disease Control. This includes vaccination against hepatitis A and B, influenza, DTaP, Hemophilus influenza, pneumococcus, polio, MMR, varicella, meningococcal ACWY, and HPV. It is also important to vaccinate household contacts with age-appropriate immunizations to reduce the risk of transmission to the child. Children listed for LT should ideally be immunized prior to transplant, but a recent study showed that only 29% of pediatric LT candidates had age-appropriate vaccinations.¹⁰⁴ Although there are concerns in administering live attenuated vaccines, such as MMR and varicella to children after LT, the American Society of Transplantation Infectious Disease Community of Practice (AST IDCOP) revised its guidelines in 2019 and now recommend live vaccines in pediatric transplant recipients provided they are more than 1 year after transplant, more than 2 months after an episode of acute rejection and are on low levels of immunosuppression.¹⁰⁵

SUMMARY AND CONCLUSIONS

Patients with CLD with or without cirrhosis remain at risk of developing serious illness when infected with viral or

bacterial pathogens. Complications resulting from these preventable infections remain an important cause of hospitalizations and readmissions in those with CLD leading to significant healthcare resource utilization. Vaccination offers a safe and cost-effective strategy to reduce morbidity in this vulnerable population. It is better to administer all vaccinations early in the liver disease course for optimal immune response. Vaccination of HAV and HBV should be prioritized in those with CLD. Although the ACIP recommends simultaneous vaccination with Tdap, inactivated influenza, and pneumococcus in immunocompetent individuals, its efficacy in CLD patients is unknown. In the absence of any reliable data, it is reasonable to give these vaccines simultaneously for the sake of better adherence. In individuals with CLD and underlying respiratory disorders, pneumococcal and influenza vaccination should be a priority. It is also safe to give simultaneous COVID and influenza vaccines, preferably at two different injection sites, as per the Center for Disease Control.

Despite the long-standing recommendations by multiple expert consensus panels and regulatory bodies, vaccination coverage in CLD is unsatisfactory. Inadequate access to healthcare, poor awareness among providers and patients regarding vaccine recommendations, vaccine costs, lack of information on vaccine safety, poor financial reimbursement for healthcare providers, poor compliance with completion of vaccine regimens (if more than one dose necessary), and vaccine misinformation are some of the common factors for low immunization rates. Various strategies have been proposed to improve vaccination coverage, such as incentives for patients returning to complete vaccination series or vaccine documentation in the electronic medical records as a “quality” measurement for primary care physicians. Patients may also be sent notifications via email/text messages and social media reminding them about pending immunizations. Additional interventions that could be implemented at the physician level include assessing the vaccination status of patients during every clinic visit using electronic health record pop-up reminders, reducing out-of-pocket costs and copays for patients, and scheduling home visits for vaccinations. Local pharmacies can also play a role by proactively identifying at-risk patients and offering them on-site vaccination by coordinating care with the primary care physicians. Improving vaccination coverage in CLD involves many hurdles and requires a multidisciplinary approach for optimal implementation.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

JJ and HN did do the research and drafted the manuscript. PJT revised it and checked it for accuracy.

CONFLICTS OF INTEREST

The authors have none to declare.

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