

# Optimizing Immunization Strategies in Adult Patients With Chronic Liver Disease and Liver Transplant Recipients

Stacey Rolak, MD, MPH,<sup>1</sup> Adnan Said, MD, MPH,<sup>2</sup> Rita German, MD,<sup>2</sup> Mary S. Hayney, PharmD, MPH,<sup>3</sup> and Freddy Caldera, DO, MS<sup>2</sup>

<sup>1</sup>Department of Internal Medicine, Mayo Clinic College of Medicine and Science, Rochester, Minnesota

<sup>2</sup>Department of Medicine, Division of Gastroenterology and Hepatology, School of Medicine & Public Health, University of Wisconsin–Madison, Madison, Wisconsin

<sup>3</sup>School of Pharmacy, University of Wisconsin–Madison, Madison, Wisconsin

Address correspondence to:

Dr Freddy Caldera

School of Medicine & Public Health

University of Wisconsin–Madison

1685 Highland Avenue

Madison, WI 53705-2281

Tel: (608) 263-1995

Fax: (608) 265-5677

E-mail: fcaldera@medicine.wisc.edu

**Abstract:** Patients with chronic liver disease (CLD) and liver transplant recipients are at increased risk for infections from vaccine-preventable diseases. Gastroenterologists and hepatologists should assess patient immunization history, and necessary vaccinations should be given as soon as possible. Vaccines demonstrate superior immunogenicity when given earlier in the course of liver disease and prior to transplant. This article summarizes recommendations from the Advisory Committee on Immunization Practices for vaccinations in patients with CLD and liver transplant recipients, and includes a discussion of the influenza, herpes zoster, hepatitis A, hepatitis B, pneumococcal, human papillomavirus, and COVID-19 vaccines.

Patients with liver disease are at increased risk for infections through multiple pathophysiologic mechanisms, including intestinal dysbiosis, increased bacterial translocation, portosystemic shunting, and cirrhosis-associated immune dysfunction. Cirrhosis-associated immune dysfunction is a multifactorial state involving dysregulation of both the adaptive and the innate immune systems as well as persistent immune system activation. Other factors contributing to the increased risk for infections in patients with liver disease include malnutrition and, in the case of liver transplant recipients, immunosuppressive medications.<sup>1</sup>

Both patients with chronic liver disease (CLD) and liver transplant recipients are at high risk for acquiring and experiencing complications from vaccine-preventable diseases (VPDs).<sup>2,3</sup> Despite this risk, multiple studies have reported suboptimal vaccination rates in both patients with CLD and liver transplant recipients.<sup>4,5</sup> Reasons for this may include lack of education on the recommended vaccine schedule among providers and patients, concern about vaccine safety and efficacy, and confusion about which medical provider is primarily responsible for recommending vaccines. Clinical practice guidelines for vaccination of immunosuppressed patients recommend that specialists share responsibility for ensuring that

## Keywords

Vaccines, vaccine-preventable diseases, liver transplantation, liver diseases

their patients receive the appropriate vaccines.<sup>6</sup> Therefore, gastroenterologists and hepatologists should assume an active role in the appropriate immunization of their patients with CLD. It is important to address immunization needs as soon as possible, as immunologic responses earlier in the course of liver disease are stronger.<sup>7,8</sup> For patients undergoing liver transplant evaluation, vaccinations should be given prior to transplant when possible, as vaccine responses are typically higher pretransplant.<sup>9</sup> Live vaccines should be administered at least 4 months prior to transplant and are contraindicated after transplant.<sup>10</sup>

The Advisory Committee on Immunization Practices (ACIP) is a committee of medical and public health experts that develops recommendations on the use of vaccines. The Centers for Disease Control and Prevention sets the US adult and childhood immunization schedules based on ACIP recommendations. This article focuses on appropriate immunization strategies both for patients with CLD and for liver transplant recipients, as outlined by the ACIP and the American Society of Transplantation Infectious Disease Community of Practice.<sup>11,12</sup>

## Influenza Vaccine

Influenza is a common respiratory illness that results in significant morbidity and mortality and resulted in an estimated 490,600 hospitalizations and 34,200 deaths from 2018 to 2019 in the United States.<sup>13</sup> Disease complications and hospitalizations are highest among adults ages 65 years and older and immunosuppressed patients, such as patients with CLD and solid organ transplant recipients.<sup>14</sup> Influenza infection in patients with liver disease portends a poor outcome. One global analysis found that, among patients infected with the 2009 influenza A virus (H1N1), patients with liver disease had a 5-fold increased risk of influenza-related hospitalization and a 17-fold increased risk of death compared with healthy individuals.<sup>15</sup> Another study found a 2-fold increased risk of hospital admission for influenza virus from 2013 to 2014 in patients with liver disease.<sup>16</sup> The influenza vaccine can decrease the risk of disease and severity of illness. An observational, prospective, multicenter study demonstrated that solid organ transplant recipients (including liver transplant recipients) and hematopoietic stem cell transplant recipients who had laboratory-confirmed influenza A were less likely to develop pneumonia or require intensive care unit admission if they had received the influenza vaccine during the same influenza season.<sup>17</sup> Influenza infection is also associated with hepatic decompensation in patients with cirrhosis, and administration of the influenza vaccine can reduce the risk of this complication.<sup>18,19</sup>

To decrease morbidity and mortality from influenza, the ACIP recommends annual influenza immunization

for all adults who do not have contraindications (Table). The vaccine should be offered ideally by the end of October in the United States and before the onset of influenza activity in the community.<sup>14</sup> All influenza vaccines in the United States are now quadrivalent, containing 2 influenza A virus strains and 2 influenza B virus strains. The influenza vaccines licensed in the United States are the inactivated vaccine (available in both the quadrivalent high dose [HD], which was licensed by the US Food and Drug Administration [FDA] in 2019, or the quadrivalent standard dose [SD]), adjuvanted quadrivalent vaccine, recombinant quadrivalent vaccine, and live attenuated quadrivalent vaccine. Because the live attenuated influenza vaccine is indicated for healthy individuals 2 to 49 years of age, patients with CLD are not candidates for this vaccine.<sup>14</sup> The live attenuated influenza vaccine should not be given to transplant recipients, along with other live virus vaccines, including the measles, mumps, and rubella vaccine and the varicella vaccine.<sup>12</sup> The HD trivalent vaccine demonstrated superior efficacy against influenza compared with that of the SD trivalent vaccine in a randomized controlled trial among persons ages 65 years and older.<sup>20</sup> The quadrivalent influenza vaccine with an adjuvant demonstrated acceptable vaccine efficacy in individuals ages 65 years and older in a clinical trial during an influenza season with poor vaccine strain match.<sup>21</sup>

Contraindications to the influenza vaccine include history of severe allergic reaction to any component of the vaccine (other than egg) or to a previous dose of any influenza vaccine. Contraindications to the live attenuated vaccine also include concomitant aspirin or salicylate-containing therapy, immunocompromised state, pregnancy, cerebrospinal fluid leak, recent receipt of influenza antiviral medication, and cochlear implants.<sup>14</sup> The inactivated influenza vaccines are safe after solid organ transplant. Several studies have demonstrated that there is no increased risk of allograft rejection or dysfunction following influenza vaccination in solid organ transplant recipients.<sup>22</sup> The influenza vaccine should be given annually to all patients with CLD and to all liver transplant recipients. The ACIP does not express preference among HD, adjuvanted, or SD vaccines for immunosuppressed patients or for the general population.<sup>14</sup>

Although most inactivated vaccines are administered at least 3 months posttransplant to allow for achievement of steady maintenance immunosuppression medication levels, the influenza vaccine can be given as early as 1 month following transplant.<sup>12</sup> In general, the immune response to the influenza vaccine is less robust in solid organ transplant recipients, but the vaccine is still effective and should be given when due.<sup>23,24</sup> Although studies specifically in liver transplant recipients have not been published, a study of kidney transplant patients failed to show

**Table.** Adult Immunization Schedule for Patients With Chronic Liver Disease and Liver Transplant Recipients Based on ACIP Recommendations

Vaccine	Dosing Schedule	
	Patients With Chronic Liver Disease	Liver Transplant Recipients
SD quadrivalent influenza, inactivated	1 dose seasonally for all patients 18-64 years of age	
HD influenza, inactivated	1 dose seasonally for patients ≥65 years of age <sup>a</sup>	1 dose seasonally for liver transplant recipients ≥18 years of age <sup>b</sup>
Influenza, live attenuated	Contraindicated for patients with chronic liver disease and liver transplant recipients	
Herpes zoster (Shingrix)	2 doses (2-6 months apart) for all patients ≥50 years of age	2 doses (2-6 months apart) for patients ≥19 years of age; can be given 1-2 months apart
Hepatitis A (Vaqta; Havrix; Hep A-Hep B [Twinrix])	2 doses of Vaqta (6-18 months apart) or Havrix (6-12 months apart) at higher dose for adults ≥19 years of age OR 3 doses of Hep A-Hep B at 0, 1, and 6 months or accelerated 4 doses at 0, 7, 21-30 days, and 12 months	
Hepatitis B (Engerix-B; Recombivax HB; Hep A-Hep B [Twinrix]; HepB-CpG [Heplisav-B])	3 doses of Engerix-B or Recombivax HB at 0, 1, and 6 months OR 3 doses of Hep A-Hep B at 0, 1, and 6 months or accelerated 4 doses at 0, 7, 21-30 days, and 12 months OR 2 doses of HepB-CpG at 0 and 1 month <sup>c</sup>	
Pneumococcal	<p><u>Vaccine-naive:</u> PCV15 followed by PPSV23 1 year later<sup>d</sup> OR PCV20 alone</p> <p><u>Previously immunized:</u> <i>Received PCV13:</i> If 19-64 years of age, 1 dose of PPSV23 at least 8 weeks after PCV13 and second dose 5 years later If ≥65 years of age, 1 dose of PPSV23</p> <p><i>Received PPSV23:</i> Single dose of PCV15 or PCV20 at least 1 year after PPSV23</p>	
Human papillomavirus (Gardasil 9)	3 doses (0, 1-2, and 6 months) for patients 15-26 years of age; consider 3-dose series for at-risk patients 27-45 years of age	
COVID-19 (Pfizer-BioNTech COVID-19 vaccine [Comirnaty]; Moderna COVID-19 vaccine [Spikevax]; Johnson & Johnson/Janssen COVID-19 vaccine)	Moderna or Pfizer-BioNTech vaccine preferred Pfizer-BioNTech: 2 doses (21 days apart) Moderna: 2 doses (28 days apart) Booster dose of mRNA vaccine at least 5 months after completing initial series	Moderna or Pfizer-BioNTech vaccine preferred Pfizer-BioNTech: 2 doses (21 days apart) Moderna: 2 doses (28 days apart) Additional primary dose of mRNA vaccine at least 28 days after second dose Booster dose of mRNA vaccine at least 3 months after completing initial series Posttransplant, postpone immunization if undergoing treatment for acute rejection

ACIP, Advisory Committee on Immunization Practices; HD, high dose; mRNA, messenger RNA; PCV13, pneumococcal conjugate 13-valent vaccine; PCV15, pneumococcal conjugate 15-valent vaccine; PCV20, pneumococcal conjugate 20-valent vaccine; PPSV23, pneumococcal polysaccharide 23-valent vaccine; SD, standard dose.

<sup>a</sup>The HD influenza vaccine contains 4 times more hemagglutinin than the SD vaccine, and induces higher antibody concentrations. It provides better protection against influenza in adults 65 years of age and older.<sup>20</sup>

<sup>b</sup>The HD influenza vaccine demonstrated better immunogenicity than the SD vaccine in adult transplant recipients in a randomized controlled trial.<sup>26</sup>

<sup>c</sup>A higher dose of vaccine may be offered in the posttransplant setting, although response rates may be poor. Protective antibodies should be closely monitored. Antibodies to hepatitis B surface antigen should be checked at least 4 weeks after completing the series.

<sup>d</sup>For patients who are immunocompromised or anticipating immunosuppressive therapy, an 8-week interval should be used.

superiority of adjuvanted vaccines over nonadjuvanted influenza vaccines.<sup>25</sup> In a randomized, double-blind trial of 172 solid organ transplant recipients, seroconversion rates and postimmunization geometric mean titers were significantly higher in patients who received the HD trivalent influenza vaccine compared with patients who received the SD trivalent vaccine.<sup>26</sup> Both the SD and HD vaccines are acceptable options for liver transplant recipients; however, the HD vaccine has demonstrated superior immunogenicity in liver transplant recipients. The ACIP and the American Society of Transplantation recommend the HD, adjuvanted, or SD influenza vaccine for liver transplant recipients.

### Herpes Zoster Vaccine

Shingles, or herpes zoster (HZ), is caused by reactivation of latent varicella zoster virus, which is the virus that causes chicken pox. HZ often presents with a unilateral, localized vesicular eruption and pain in the affected dermatome. Chronic neuropathic pain following resolution of the acute vesicular eruption, called postherpetic neuralgia (PHN), is a common complication that occurs in approximately 10% of the general population.<sup>27</sup> Other complications include cranial and peripheral nerve palsies, vasculopathies, and ophthalmic involvement. Immunosuppressed patients, including solid organ transplant recipients, have a greater incidence of HZ and a higher risk for severe and disseminated disease.<sup>28</sup> In 1 study, PHN occurred in up to one-third of liver transplant recipients.<sup>29</sup> There is a high incidence of HZ specifically in liver transplant recipients, with an even greater risk among liver transplant recipients older than 50 years of age or those taking mycophenolate mofetil.<sup>3,29</sup>

A population-based study in Taiwan showed that there was no increased risk of HZ in patients ages 18 years and older with liver cirrhosis compared with a matched control population without cirrhosis.<sup>30</sup> However, this study did not differentiate between patients with decompensated liver cirrhosis and those with compensated liver cirrhosis, and it did not consider zoster immunization history. The results of this study suggest that certain patients with cirrhosis may benefit from HZ immunization.

The recombinant HZ vaccine (RZV; Shingrix, GlaxoSmithKline) combines glycoprotein E with a novel adjuvant to amplify immune response, and is administered as a series of 2 doses separated by 2 to 6 months. RZV is highly immunogenic, with 97% efficacy demonstrated in individuals ages 50 years and older and 89% efficacy in individuals ages 70 years and older in 2 clinical trials.<sup>31,32</sup> The live attenuated zoster vaccine (ZVL) that was licensed in 2006 is no longer available in the United States as of November 2020.

The ACIP recommends administration of RZV to immunocompetent adults ages 50 years and older. Adults should receive RZV if they have had shingles or have previously received ZVL. RZV is also now recommended for the prevention of HZ and related complications in immunodeficient or immunosuppressed adults ages 19 years and older. The second dose should be given at least 1 to 2 months after the first in this population (Table).<sup>33</sup>

There are no published studies evaluating the immunogenicity of RZV in liver transplant recipients specifically. The vaccine has been shown to be safe and immunogenic in adults with hematologic malignancies receiving immunosuppressive cancer therapies and in autologous stem cell transplant recipients.<sup>34,35</sup> In a multicenter, randomized, placebo-controlled trial studying RZV in renal transplant recipients ages 18 years and older receiving daily immunosuppressive therapy, RZV was immunogenic and immune response persisted through 12 months postvaccination.<sup>36</sup> Overall occurrence of renal function changes, rejections, and serious adverse events were similar between the vaccine and placebo groups. Local adverse events were more frequent in the RZV group, as expected. History of severe allergic reaction to any component of the vaccine is the only contraindication.<sup>33</sup> RZV is recommended in all adults ages 50 years and older with CLD, and in liver transplant recipients ages 19 years and older who have not yet received the vaccine.

### Hepatitis A Vaccine

Hepatitis A virus (HAV) is a common virus worldwide that is spread through fecal-oral transmission. It typically causes an acute, self-limited infection in healthy adults, although some prolonged or relapsing cases have been reported.<sup>37,38</sup> Patients may be asymptomatic or can develop fever, fatigue, nausea, vomiting, anorexia, jaundice, dark urine, and pale stools. HAV is clinically indistinguishable from other acute viral hepatitis. In severe cases, HAV infection can lead to fulminant hepatitis, which is more likely in adults 50 years of age and older and in patients with underlying CLD.<sup>39</sup> Patients with CLD are not at increased risk for acquiring HAV infection, but they are at an increased risk of mortality and for developing fulminant hepatitis once infected.<sup>40-42</sup>

There are 3 vaccines available in the United States for hepatitis A. Two are single-antigen inactivated hepatitis A vaccines given in 2 doses 6 to 12 months apart (Havrix, GlaxoSmithKline) or 6 to 18 months apart (Vaqta, Merck) (Table). These vaccines are approved for children 12 months of age and older. For adults 19 years of age and older, both vaccines are given at an increased dose. The third available vaccine is a combination-inactivated

vaccine (Twinrix, GlaxoSmithKline), which contains both a hepatitis A and a hepatitis B vaccine (Havrix and Engerix-B, GlaxoSmithKline). This combination vaccine is given on either a standard dosing schedule of 3 doses at 0, 1, and 6 months, or on an accelerated dosing schedule of 4 doses at 0 days, 7 days, and 21 to 30 days, followed by a booster at 12 months. The safety profiles of the hepatitis A vaccines are similar.<sup>43</sup> Contraindications include allergic reaction after a previous dose or to any component of the hepatitis A vaccine, including neomycin and yeast.<sup>44</sup>

The ACIP recommends hepatitis A vaccination for adults at risk for HAV infection or severe disease from HAV infection, and for adults requesting protection against HAV without acknowledgment of a risk factor.<sup>44</sup> The hepatitis A vaccine is indicated in all adults with CLD and in all liver transplant recipients. Limited data are available to guide whether immunocompromised patients should receive booster doses.

As with other vaccines, the hepatitis A vaccine should be given as early as possible in the course of liver disease because vaccine immunogenicity declines with severity of liver disease and in decompensated cirrhosis.<sup>2,8</sup> Sero-protection in liver transplant recipients is variable.<sup>45,46</sup> Because of their risk for severe disease if infected, hepatitis A vaccination for patients with liver disease is a priority.

## Hepatitis B Vaccine

Compared with patients without liver disease, patients with CLD are at greater risk for severe complications and mortality from superimposed acute or chronic hepatitis B virus (HBV) infection.<sup>47</sup> There is also a small risk of HBV infection after orthotopic liver transplant, including from donor-derived hepatitis B acquisition. Despite the risks of HBV, patients with CLD have suboptimal vaccination rates against hepatitis B.<sup>48,49</sup>

Patients with cirrhosis and patients who receive the hepatitis B vaccine after liver transplant have low seroconversion rates from the SD recombinant hepatitis B vaccine series. However, the vaccine is still immunogenic in early mild or moderate CLD.<sup>50,51</sup> Patients with a lower Model for End-Stage Liver Disease score have a greater response to the recombinant hepatitis B vaccine.<sup>52</sup> Therefore, the hepatitis B vaccine should be given as early as possible in CLD. In patients undergoing evaluation for a liver transplant, the vaccine series ideally is completed prior to transplant. Response to the hepatitis B vaccine after transplant varies greatly, and antibody titers may decline more rapidly among transplant recipients.<sup>53</sup>

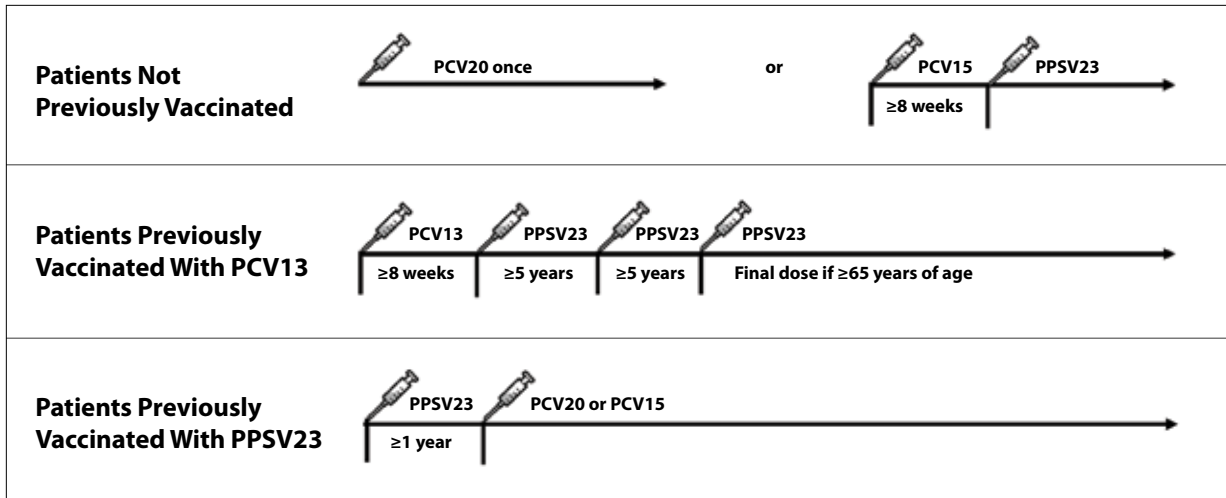
There are several recombinant hepatitis B vaccines licensed in the United States. Engerix-B, Twinrix, and Recombivax HB (Merck) are administered as a 3-dose series at 0, 1, and 6 months. The Twinrix vaccine can also

be given at an accelerated dosing schedule with 4 doses. Each of these products contains an aluminum-based adjuvant. There is a dialysis formulation available for the Recombivax HB vaccine, which contains a higher dose of antigen. HepB-CpG (Heplisav-B, Dynavax) was licensed in 2018 as a 2-dose series with at least 4 weeks between doses. HepB-CpG also contains recombinant hepatitis B surface antigen, but the adjuvant is an oligodeoxynucleotide that acts as a buffer. HepB-CpG has higher seroconversion rates when compared with Engerix-B in patients with type 2 diabetes mellitus, in healthy individuals ages 40 to 70 years, and in healthy adults ages 18 to 55 years.<sup>54,55</sup> At this time, the ACIP recommends the 2- and 3-dose series vaccines, without a preference (Table).<sup>56</sup> The ACIP recommends that the hepatitis B vaccine be given to all adults with risk factors for infection by sexual exposure or intravenous drug use, patients with HIV, persons seeking protection from HBV infection, health care personnel at risk for blood and body fluid exposure, patients on dialysis, household contacts of persons with HBV, and patients with CLD. Hepatitis B vaccines are contraindicated in persons who have had an allergic reaction after a previous dose or to any component of a hepatitis B vaccine, including neomycin and yeast.<sup>56</sup>

Because patients with cirrhosis may have a suboptimal response to the hepatitis B vaccine, patients who have previously been immunized against HBV should undergo testing to confirm their immunity. Antibodies to the hepatitis B surface antigen (anti-HBs) should be checked at least 4 weeks after the completion of the hepatitis B vaccine series. An anti-HBs level of 10 mIU/mL or greater is protective and indicates that no additional doses of hepatitis B vaccine are needed. If the anti-HBs level is less than 10 mIU/mL at this time, a challenge dose of hepatitis B vaccine should be administered, and another anti-HBs level should be obtained 4 weeks later to evaluate for an anamnestic response that would indicate the patient was a vaccine responder for whom antibodies waned. If the anti-HBs level is less than 10 mIU/mL after the challenge dose, the patient should complete another hepatitis B vaccine series.<sup>56</sup> Different strategies to improve the immunogenicity of hepatitis B vaccines in patients with CLD include the use of HD and accelerated vaccine schedules and booster doses.<sup>52,57,58</sup>

A recently published retrospective study showed that the 2-dose series of HepB-CpG resulted in higher rates of seroconversion than the 3-dose Engerix-B vaccine series in patients with CLD.<sup>59</sup> In multivariate analyses, patients who received HepB-CpG had a 2.7-fold greater likelihood of achieving immunity than patients who received the Engerix-B vaccine. The presence of cirrhosis, chronic obstructive pulmonary disease, or renal failure portended a lower likelihood of achieving immunity. This suggests





**Figure 1.** ACIP-recommended pneumococcal vaccine schedule for liver transplant recipients and patients with chronic liver disease who are immunosuppressed.

ACIP, Advisory Committee on Immunization Practices; PCV13, pneumococcal conjugate 13-valent vaccine; PCV15, pneumococcal conjugate 15-valent vaccine; PCV20, pneumococcal conjugate 20-valent vaccine; PPSV23, pneumococcal polysaccharide 23-valent vaccine.

that HepB-CpG may be preferential to the Enderix-B vaccine in patients with CLD; however, prospective studies in this population are needed to determine whether HepB-CpG achieves higher rates of seroconversion than other vaccine series.

Pretransplant serologies should be obtained for HBV. The hepatitis B vaccine is indicated in solid organ transplant candidates who are not immune. The ACIP also recommends testing for anti-HBs level after series completion in these patients. Hepatologists should play an active role in ensuring that their patients are immunized with a hepatitis B vaccine series prior to transplant. Vaccine adherence can be improved by providing the hepatitis B vaccine in clinic.<sup>60</sup> Additionally, initiating the hepatitis B vaccination during hospitalization among patients with CLD and prior to liver transplant is an effective intervention for improving vaccination rates.<sup>61</sup> Because HepB-CpG can be administered in 2 doses with only 4 weeks between doses, using this vaccination series can facilitate vaccine completion prior to transplant.

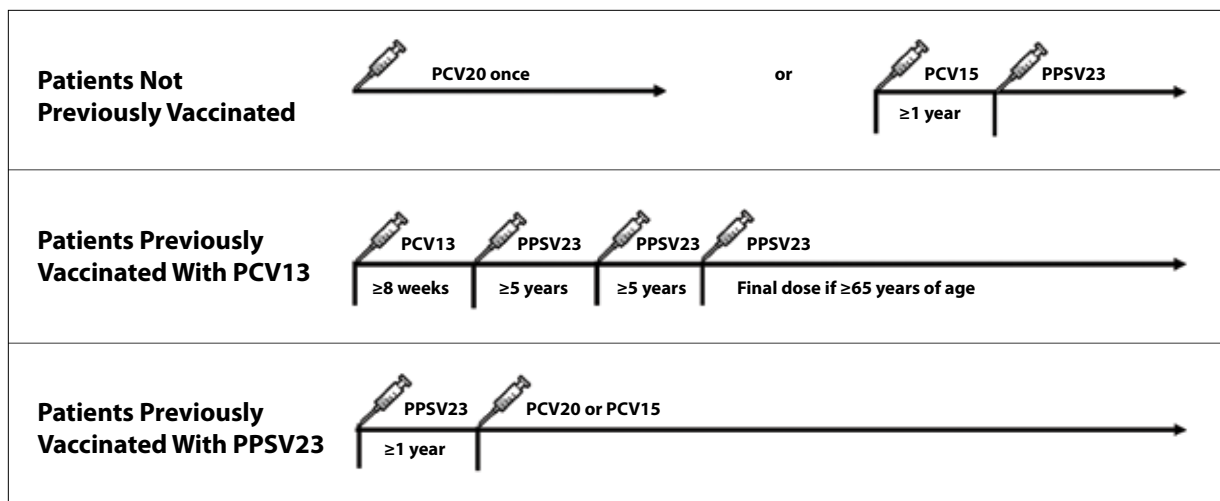
## Pneumococcal Vaccine

Invasive pneumococcal disease (IPD) from *Streptococcus pneumoniae* causes significant morbidity and mortality from infections, including bacteremia, pneumonia, osteomyelitis, and meningitis. There is a greater risk of IPD in solid organ transplant recipients, and there is greater mortality following IPD in patients with cirrhosis than in the general population.<sup>62-64</sup> IPD is most common within the first 3 years posttransplant but can occur at any time.<sup>63</sup>

In hospitalized patients with cirrhosis, pneumonia carries one of the highest risks for mortality, and the most common pathogen for community-acquired pneumonia in these patients is *S pneumoniae*.<sup>65</sup> Spontaneous bacterial peritonitis, a serious complication in patients with cirrhosis and ascites, is caused by *S pneumoniae* in some cases (approximately 3%-5%).<sup>66</sup> Despite the severity of disease in immunosuppressed populations, there remains suboptimal pneumococcal vaccine adherence. In 1 study, only 60% of liver transplant recipients with evaluable vaccination documents had received at least 1 pneumococcal vaccination.<sup>67</sup>

Pneumococcal vaccine recommendations have been updated recently. The pneumococcal conjugate 13-valent vaccine (PCV13) contains 13 serotypes and is no longer recommended for use in adults. The pneumococcal polysaccharide 23-valent vaccine (PPSV23) includes 12 of the serotypes included in PCV13 plus 11 additional serotypes. The pneumococcal conjugate 15-valent vaccine (PCV15) contains the PCV13 serotypes and 2 additional serotypes. The pneumococcal conjugate 20-valent vaccine (PCV20) also contains the PCV13 serotypes and 7 additional serotypes.<sup>68</sup>

Pneumococcal vaccines are recommended for patients with CLD and liver transplant recipients (Figures 1 and 2).<sup>68</sup> Vaccine-naïve patients ages 19 and older should receive PCV20, or PCV15 followed by PPSV23. The interval between PCV15 and PPSV23 should be at least 8 weeks in those who are immunocompromised; the interval should be extended to at least 1 year in the general population. Immunocompromised patients who



**Figure 2.** ACIP-recommended pneumococcal vaccine schedule for patients with chronic liver disease who are not immunosuppressed.

ACIP, Advisory Committee on Immunization Practices; PCV13, pneumococcal conjugate 13-valent vaccine; PCV15, pneumococcal conjugate 15-valent vaccine; PCV20, pneumococcal conjugate 20-valent vaccine; PPSV23, pneumococcal polysaccharide 23-valent vaccine.

have received PCV13 previously should receive PPSV23 at least 8 weeks after PCV13. Patients who have received PPSV23 previously should receive a dose of PCV15 or PCV20 at least 1 year after their PPSV23 dose. Contraindications to any pneumococcal vaccine include severe allergy after a previous dose, allergy to any component of the vaccine, or allergy after any vaccine containing diphtheria toxoid.<sup>68</sup>

Data on the immunogenicity of pneumococcal vaccines in patients with CLD are limited. Results of 1 small study suggest that liver transplant recipients may have a suboptimal response to PPSV23.<sup>69</sup> There was no association between vaccination and allograft rejection or de novo donor-specific antibody formation in solid organ transplant recipients receiving PPSV23.<sup>22</sup>

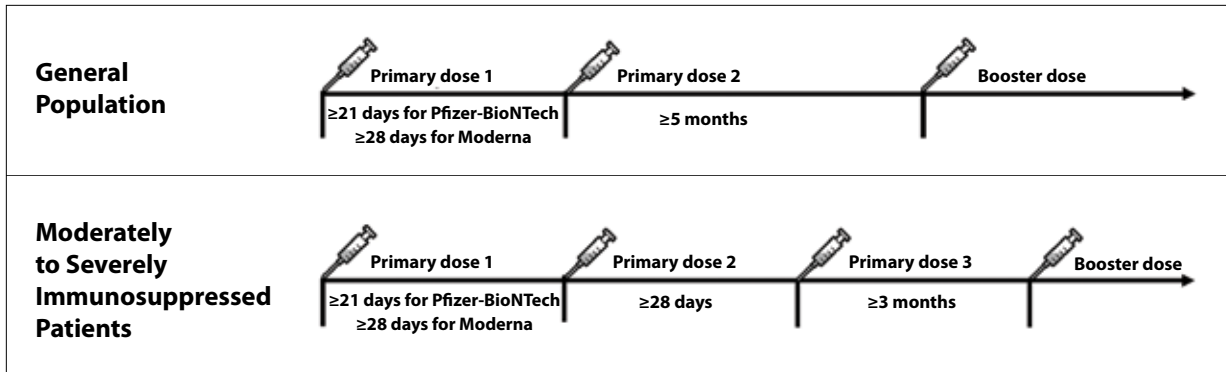
### Human Papillomavirus Vaccine

Human papillomavirus (HPV) is a common and typically asymptomatic sexually transmitted infection that can cause cervical, vaginal, vulvar, penile, anal, and some oropharyngeal cancers.<sup>70</sup> HPV vaccines have been found to be highly effective in reducing HPV infections and HPV-associated cancers.<sup>71</sup> HPV vaccines do not treat existing lesions caused by HPV and do not prevent the progression of HPV infection into disease. There is an increased risk for HPV-associated cancers in solid organ transplant recipients, particularly for vulvar, anal, and penile cancers.<sup>72</sup> This highlights the importance of HPV vaccination, especially among immunosuppressed patients. The 9-valent HPV vaccine (Gardasil 9, Merck)

is available in the United States and protects against oncogenic HPV types 16 and 18 (which cause the majority of HPV-associated cancers), and types 31, 33, 45, 52, and 58, as well as nononcogenic HPV types 6 and 11, which cause genital warts.

The ACIP recommends routine HPV vaccination at age 11 or 12 years, but the series can be initiated at 9 or 10 years of age if the clinician deems it appropriate.<sup>71</sup> The vaccine is recommended for all persons through age 26 years. A 2-dose series is recommended if initiating the HPV series before the individual reaches 15 years old, with the second dose administered 6 to 12 months after the first dose. If the HPV series is initiated when the individual is 15 years or older or is immunosuppressed, a 3-dose series is indicated. The 3-dose series has a scheduled administration at 0, 1 to 2, and 6 months (Table). In June 2019, the ACIP recommended catch-up HPV vaccination for all persons through age 26 years.<sup>71</sup> The ACIP recommends the vaccine series for persons 27 to 45 years old based on shared clinical decision making. Although the ACIP warns that vaccine efficacy may be affected by immunosuppression, the HPV vaccine series should still be administered to adults with risk factors, such as new sexual partners.<sup>71</sup> The HPV vaccine is contraindicated in persons with severe allergic reaction after a previous dose or to a vaccine component, including yeast.<sup>71</sup>

In 1 study, solid organ transplant recipients receiving the quadrivalent HPV vaccine demonstrated lower antibody responses compared with healthy individuals.<sup>73</sup> However, there are limited data on the immunogenicity of the 9-valent HPV vaccine among patients with



**Figure 3.** ACIP-recommended COVID-19 mRNA vaccine schedule.

ACIP, Advisory Committee on Immunization Practices; mRNA, messenger RNA.

CLD and liver transplant recipients, with further studies needed. Solid organ transplant recipients remain at high risk for HPV-associated malignancy.

### COVID-19 Vaccine

COVID-19, the illness caused by SARS-CoV-2, emerged in Wuhan, China, and has spread worldwide since 2019. Many patients with COVID-19 are asymptomatic or have mild symptoms such as fatigue, fever, chills, cough, headache, myalgia, and anosmia. More severe infections result in pulmonary disease, coagulopathies, multiorgan failure, and death.

Older adults and patients with underlying medical comorbidities, including chronic lung disease, heart disease, diabetes, and obesity, are at greater risk for serious complications from COVID-19. Patients with CLD may also be at a higher risk. Patients with cirrhosis experience high rates of hepatic decompensation, acute-on-chronic liver failure, and death from respiratory failure following acute COVID-19 infection.<sup>74</sup> The SECURE-Liver and COVID-Hep registries show that hepatic decompensation events are more frequent with increasing severity of liver disease. Additionally, mortality from COVID-19 is particularly high among patients with alcohol-related liver disease and advanced cirrhosis.<sup>75</sup>

Early data suggest that liver transplant recipients infected with COVID-19 may be at a similar risk for death as the general population.<sup>76</sup> One study demonstrated that mortality and the highest level of supplemental oxygen required during hospitalization did not significantly differ between solid organ transplant recipients and non-solid organ transplant patients hospitalized with COVID-19.<sup>77</sup> These results suggest that chronic immunosuppression may not be an independent driver of poor outcomes in COVID-19 infections. Regardless, infection with COVID-19 in solid organ transplant

recipients portends a poor outcome.<sup>78,79</sup> The 28-day mortality among hospitalized solid-organ transplant recipients is high, and up to 20.5% in 1 study.<sup>78</sup>

Currently, there are 3 vaccines available for COVID-19 in the United States: 2 messenger RNA (mRNA)-based vaccines given in 2 doses (Pfizer-BioNTech [Comirnaty] and Moderna [Spikevax]) and an adenoviral vector vaccine given as a single dose (Johnson & Johnson/Janssen). The Pfizer-BioNTech mRNA-based 2-dose vaccine now has full FDA approval in individuals ages 16 years and older. It has also been granted Emergency Use Authorization (EUA) for children ages 5 to 11 years. The Moderna mRNA-based 2-dose vaccine recently received full FDA approval, and the Johnson & Johnson/Janssen vaccine is available under EUA from the FDA. The COVID-19 vaccines target the viral spike glycoprotein that is necessary for the attachment of SARS-CoV-2 to the angiotensin-converting enzyme 2 receptor on human epithelial cells. The Moderna and Pfizer-BioNTech vaccines contain synthetic nucleoside-modified mRNA that encodes this spike glycoprotein.<sup>80,81</sup> The Johnson & Johnson/Janssen vaccine uses a replication-incompetent adenoviral vector that contains the DNA encoding for this spike glycoprotein.<sup>82</sup>

The ACIP recommends the Pfizer-BioNTech or Moderna mRNA COVID-19 vaccines over the Johnson & Johnson/Janssen COVID-19 vaccine for primary and booster vaccinations.<sup>83</sup> The Pfizer-BioNTech vaccine can be given to individuals 5 years of age and older. An additional primary dose of mRNA vaccine is recommended in certain immunocompromised recipients of an initial mRNA COVID-19 vaccination series. The purpose of an additional primary dose is to confer additional protection to persons who likely did not mount a protective immune response after initial vaccination. Moderately to severely immunosuppressed individuals 12 years of age and older (Pfizer-BioNTech) or 18 years and older (Moderna)



should receive an additional primary mRNA vaccine dose at least 28 days after their second dose (Table).<sup>84,85</sup>

Booster doses are now recommended for all individuals 12 years and older. A booster dose is intended to enhance or restore immune protection that may have waned over time. Booster doses are recommended 5 months after the last dose in the general population, and 3 months after the last dose in patients who are moderately to severely immunosuppressed (including liver transplant recipients) (Figure 3).<sup>85,86</sup>

Adults 18 years and older who received primary vaccination with the Johnson & Johnson/Janssen COVID-19 vaccine should receive a booster dose 2 months later. Individuals who are moderately or severely immunocompromised who had an initial Johnson & Johnson/Janssen COVID-19 vaccine dose should receive an additional primary dose of an mRNA vaccine at least 28 days later. These patients should then receive a booster dose with an mRNA vaccine at least 2 months after the second primary dose, for a total of 3 doses.<sup>85</sup>

The American Association for the Study of Liver Diseases (AASLD) recommends that all adults with CLD and liver transplant recipients receive the COVID-19 vaccine, regardless of prior diagnosis of COVID-19 or the presence of antibodies to SARS-CoV-2.<sup>87</sup> Several studies of the immunogenicity of the mRNA COVID-19 vaccine series among solid organ transplant recipients have demonstrated an antibody response among solid organ transplant recipients that was lower than expected.<sup>88-90</sup> Other studies have demonstrated low serologic response to the mRNA COVID-19 vaccines among solid organ transplant recipients when compared with immunocompetent controls.<sup>91,92</sup> The significant proportion of liver transplant recipients taking antimetabolite immunosuppressants (mycophenolate mofetil) demonstrated even less immunogenicity to the vaccine.<sup>91,92</sup> Overall, immunogenicity in this population is low after vaccination. Currently, there is no evidence to support checking antibody titers to determine which patients need another vaccine dose, as the level of protective antibody is unknown.

The results of a double-blind, randomized controlled trial of a third dose of the Moderna vaccine vs placebo among 120 solid organ transplant recipients demonstrated improved immunogenicity following the third dose.<sup>93</sup> An increase in immunogenicity following a third dose of the Pfizer-BioNTech vaccine among solid organ transplant recipients has also been demonstrated.<sup>94</sup> Therefore, the AASLD recommends a third dose of the mRNA vaccine (Pfizer-BioNTech or Moderna) at least 28 days after the second dose among immunocompromised individuals, including solid organ transplant recipients. The AASLD also recommends this for patients with hepatocellular carcinoma and patients with CLD

receiving prednisone, antimetabolites, and/or biologic therapies.<sup>87</sup>

Liver transplant candidates should proceed with COVID-19 vaccination even if their liver transplant is likely to occur before the second mRNA vaccine dose can be administered. The second dose of mRNA vaccine should be given at the earliest appropriate interval after transplant. If patients are unable to receive the vaccine prior to liver transplant, it should be given at least 3 months posttransplant and as early as 4 weeks posttransplant if there is ongoing community spread.<sup>87</sup> Reduction of immunosuppressive medications to elicit a greater immune response to the vaccine is not recommended owing to risk of acute cellular rejection (ACR). The COVID-19 vaccine should not be given in liver transplant recipients who have active ACR, are being treated for ACR, or are on high daily doses of steroids. Immunization should be initiated after their ACR is resolved and their baseline immunosuppression is reestablished. Patients with CLD who are receiving therapy for HBV, hepatitis C virus, primary biliary cholangitis, or autoimmune hepatitis should continue their medications while receiving the COVID-19 vaccine.<sup>87</sup>

Contraindications to the COVID-19 vaccine include severe allergic reaction after a previous dose, allergy to a component of the COVID-19 vaccine, or development of thrombosis with thrombocytopenia after the Johnson & Johnson/Janssen vaccine.

## Conclusion

Optimizing immunization rates in patients with CLD and in liver transplant recipients can prevent the morbidity and mortality associated with VPDs. Obtaining a careful immunization history, counseling on vaccine recommendations, and providing necessary vaccines are important for the health maintenance of these patients. Gastroenterologists and hepatologists should be aware of ACIP and the American Society of Transplantation vaccine recommendations, and should share responsibility with primary care providers to ensure that their patients' vaccines are up to date.

## Disclosures

*Dr Said has received research support from Intercept Pharmaceuticals, EXACT Sciences, and the Jackson Foundation. Dr Caldera has received research support from Takeda Pharmaceuticals and Sanofi. The other authors do not have any relevant conflicts of interest to disclose.*

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