Supplemental Text

AASLD Expert Panel Consensus Statement: Vaccines to Prevent COVID-19 Infection in Patients with Liver Disease

Non-COVID-19 Vaccines in Patients with Chronic Liver Disease

Innate immunity provides the first line of defense through a system of cell surface and intracellular pattern recognition receptors that recognize pathogen- and danger-associated molecular patterns (PAMPs or DAMPs). Adaptive immunity, mediated by B- and T-cells, is required for effective and durable pathogen-specific protective immunity that forms the basis for vaccination. Recent reviews have highlighted the range of immune dysfunction observed in the setting of cirrhosis.(1,2) (**Supplemental Figure 1**) In addition, lack of T-cell help has been associated with nonalcoholic fatty liver disease,(3) altered B-cell function has been reported in HCV-related cirrhosis, and chronic HBV has been associated with global and virus-specific B- and T-cell dysfunction.(4–6) Although the degree of immune dysregulation is higher in patients with more severe or decompensated liver disease compared to those with compensated liver disease, this has not been precisely quantified.(7)

The available evidence suggests that, while influenza virus does not directly target the liver, it contributes to collateral liver damage(8) and promotes hepatic decompensation.(9,10) In several studies, patients with CLD had a significantly increased risk of hospitalization and death related to influenza infection.(11,12) The available evidence suggests that, while influenza vaccine may not protect against all-cause mortality, it triggers an effective antibody response and may reduce the risk of all-cause hospitalization in patients with CLD.(11) Therefore, the CDC and others recommend routine annual vaccination in CLD patients.

Guidelines from the CDC and AASLD also recommend vaccination against HAV and HBV in patients with CLD.(13,14) (**Supplemental Figure 1**) Furthermore, while HBV vaccination is associated with >95%

response among young, healthy subjects,(15) a recent review of HBV vaccination in cirrhotic patients highlighted a weaker immune response of 47% on average, with slightly greater responses noted in higher dose compared to standard dose vaccination (53% vs 38%).(16) Lower immunogenicity has been associated with more advanced liver disease as measured by model for end-stage liver disease or Child-Turcotte-Pugh score, as well as age and genetic factors.(17,18) Although improved responses have been noted with double-dose vaccination and booster vaccination,(17,19) such measures were met with low rates of response among patients with end-stage liver disease.(20) A small, non-randomized clinical trial of cirrhotic patients showed a slightly greater overall HBV vaccine response rate for high dose accelerated compared to standard vaccine regimens (78.6% vs 67.4%, *P*=0.19).(21) In the same study, however, the overall vaccine response to HAV was 100% for high dose accelerated versus 94.3% for standard dose, suggesting that cirrhotic patients can indeed mount an effective vaccine response. More recently, a novel adjuvanted HBV vaccine (HepB-CpG with 20 μg antigen) has been found to be more immunogenic in patients with CLD, with response rates that were 2.7 times that of patients receiving standard recombinant HBV vaccine.(22)

Non-COVID-19 Vaccines in Immunosuppressed Patients

The immunosuppression used in SOT recipients including corticosteroids, calcineurin inhibitors (cyclosporine, tacrolimus), and purine synthesis inhibitors (mycophenolate mofetil) acts to inhibit the immune response via various mechanisms that culminate in a net inhibition in T- and B-cell function and adaptive immunity. This raises concerns about the efficacy of vaccination in SOT and other immunosuppressed patients compared to age- and sex-matched population controls.(23) Additionally, hypogammaglobulinemia has been described post-SOT. An immunoglobulin (Ig) G level <600 mg/dL is associated with insufficient antibody production in 15%-30% of patients depending on the inoculant.(24) One of the strategies to augment posttransplant antibody response sufficient to provide protection includes vaccination prior to transplant and preferably prior to the onset of end stage organ failure

when immunity is lower and immune dysregulation higher.(25) Vaccination within 6 months after transplantation is associated with the lowest response rate because of high levels of immunosuppression during this period. Therefore, vaccinations should ideally be administered at the time of diagnosis of CLD long before transplantation may be needed and preferably before the onset of more advanced liver disease.

The American Society of Transplantation,(26) ACIP,(27) and CDC all recommend that SOT recipients should receive various vaccinations preferably prior to transplantation and periodically after SOT (pneumovax, HAV, HBV, influenza, Haemophilus influenza type b, and tetanus-diphtheria-pertussis). (**Supplemental Table 1**) Such FDA-licensed vaccines are safe with little risk for inducing graft rejection.(9)

There is significant concern for administering live vaccines to SOT recipients because of the risk of uncontrolled replication of the live virus in the host. The ACIP recommends avoiding live vaccines in those receiving high-dose corticosteroids, defined as ≥2 mg/kg of body weight or ≥20 mg/day of prednisone or equivalent for ≥14 consecutive days.(27) Administration of a live vaccine should be delayed by a minimum of one month after stopping high-dose steroids. A similar waiting period of one month is also recommended to initiate high-dose steroids after receiving a live vaccine. Although research suggests that certain live virus vaccines (varicella, and measles-mumps-rubella) can be administered safely to selected pediatric liver transplant recipients, live viral vaccines are currently not recommended in most circumstances following transplantation.(26,28)

Assays to Detect Immunity to COVID-19

Effective vaccine strategies provide durable protective immune responses to prevent infection and limit disease onset and severity. Some vaccines such as measles-mumps-rubella provide long-lasting immunity over decades while others may provide shorter duration of immunity (e.g., inactivated pertussis). The duration and durability of a vaccine response may also be driven by the rate of viral

escape mutations in the population. While neutralizing antibody responses have provided correlates of vaccine efficacy and protection for both DNA (e.g., HBV and papillomavirus) and RNA viruses (e.g., HAV and poliovirus), SARS-CoV-2 vaccine strategies using mRNA and adenoviral vectors can also induce potent CD8 T-cell responses.

Antibodies That Bind SARS-CoV-2

Currently, over 60 assays are commercially available to detect IgG and/or IgM antibodies to SARS-CoV-2 spike glycoprotein and/or nucleoprotein under EUA.(29) Most of these assays have a high sensitivity, specificity, and negative predictive value (median 97%-100%), but variable positive predictive value (median 87%, range 50%-100%) for detecting prior exposure to SARS-CoV-2. While these assays measure previous viral infection, they do not necessarily reflect protective immunity. Furthermore, the durability of antibody response to SARS CoV-2 is not well established at this time, although antiviral IgM and IgG titers may wane over 6 months of initial infection, particularly among asymptomatic subjects.(30–32) An immune response to spike protein (e.g., antibody and/or T-cell response) may be detected after natural infection as well as successful vaccination.(23) By contrast, immune response to nucleoprotein or other viral proteins will be detected after natural infection but not after vaccination with current mRNA approaches.

Assays That Measure Virus Neutralizing Antibodies

Currently, there is no FDA-authorized commercial assay to measure neutralizing antibody response to SARS-CoV-2. However, neutralizing activity can be measured in research laboratories by incubating live virus or pseudovirus with patient serum or plasma (containing antibodies) before inoculating permissive cells in laboratories approved for biosafety level 3 or 2 work. Such antibody assays are being used in COVID-19 vaccine development programs to determine levels that define protective immunity against SARS CoV-2.(33)

Assays to Measure T-cell Responses

Various assays can measure the frequency, phenotype, and function of host immune cells, such as the gamma-interferon release (tuberculosis) and intracellular cytokine staining (cytomegalovirus) that detect *in vitro* response of host T-cells to specific pathogens. Currently there are no commercially available T-cell response assays that evaluate response to SARS-CoV-2 vaccine or infection.

Safety and Efficacy of FDA EUA mRNA COVID-19 Vaccines

Pfizer-BioNTech Vaccine

The Pfizer-BioNTech vaccine (BNT162b2) is an intramuscular vaccine administered as a series of two 30 µg doses (0.3 mL each) given three weeks apart.(34) The multiple-dose vials must be stored between -80 °C to -60 °C. Once thawed and diluted, the multiple-dose vials must be used within 6 hours.

An EUA was granted by the FDA on December 11, 2020 based on median 60-day follow-up data from an ongoing registration Phase 1/2/3 randomized, observer-blind, placebo-controlled trial (C4591001).(35) The Phase 2/3 trial enrolled adult participants stratified by age (younger, 18-55 years of age; older, >55 years of age); adolescents (older, 16-17 years of age; younger, 12-15 years of age) were added later. Inclusion criteria included medical conditions or exposure that conferred a higher risk for acquiring COVID-19, including CLD, stable chronic HBV or HCV, and autoimmune disease. Exclusion criteria included treatment with immunosuppressive therapy, diagnosis of an immunocompromising condition, or prior known COVID-19. The phase 3 study is ongoing and being conducted in the US and several other countries. Additional studies are planned to evaluate BNT162b2 in pregnant women, children younger than 12 years of age, and immunocompromised persons.

In the Phase 2/3 Pfizer-BioNTech trial, participants were randomized 1:1 to receive BNT162b2 (n=21,720) or placebo (n=21,728).(35) Median age was 52 years and 50.6% were male. Most participants

were White (82.9%), 9.4% Black, 4.3% Asian, <3% other racial groups, and 28% were Hispanic/Latino. About 35% were obese (BMI ≥30.0 kg/m^2) and 21% had at least one coexisting condition.

VE for the primary endpoint (confirmed COVID-19 occurring at least 7 days after the second dose in participants without serological or virological evidence of past SARS-CoV-2 infection) was 95.0% (95% confidence interval, 90.3-97.6). (**Figure 2**) There were 8 COVID-19 cases in the BNT162b2 group and 162 COVID-19 cases in the placebo group. There was evidence for some efficacy after the first dose with a VE of 52.4% between the first and second doses. Host immunity from vaccination is not immediate and full protection may take up to two weeks from the second dose. There was also evidence that BNT162b2 was protective against severe COVID-19, with only 1 case of severe COVID-19 in the BNT162b2 group and 9 cases in the placebo group. Similar VE was observed across subgroups defined by age, sex, race, ethnicity, BMI, and the presence of coexisting conditions, including participants ≥65 years of age (94.7%). The efficacy of the vaccine in potentially preventing spread of SARS-CoV-2 could not be determined.

Safety data are available from 43,448 participants, including 37,706 participants with a median of 2 months of follow-up after the second dose. Reactogenicity and adverse events (AEs) were generally milder and less frequent in the older than the younger group. (**Figure 3**) Local reactions including pain at the injection site, redness, and swelling were most frequently observed and generally similar in frequency after the first and second doses. Systemic events (fatigue, headache, muscle pain, chills, joint pain, fever, vomiting, diarrhea) were more frequent and more severe in the younger versus older age group. The frequency and severity of systemic events generally increased with the number of doses (except vomiting and diarrhea). In vaccine recipients, the most commonly reported systemic events were fatigue and headache (39%-59% depending on age group and dose number). Of particular interest were AEs of lymphadenopathy, reported in 64 participants (0.3%) in the BNT162b2 group and 6 participants (<0.1%) in the placebo group, usually in the arm or neck region within 2 to 4 days after vaccination.

Hypersensitivity adverse events (2 in BNT162b2 group and 1 in the placebo group) were assessed as unrelated to the vaccine. Serious autoimmune disorders were considered when reporting adverse events of clinical interest. Four participants in the vaccine group developed Bell's palsy, which is consistent with the expected background rate in the general population.(34) The incidence of serious adverse events and deaths was low and comparable for BNT162b2 and placebo, and no deaths were considered to be related to the vaccine or placebo.

Moderna Vaccine

The Moderna vaccine (mRNA-1273) is an intramuscular vaccine administered as a series of two 100 µg doses (0.5 mL each) given 1 month apart.(36) The multiple-dose vials must be stored between -25 °C to -15 °C. Once thawed, vials can be stored between 2 °C to 8 °C for up to 30 days or between 8 °C to 25 °C for up to 12 hours. Once the first dose is withdrawn, the vial must be used within 6 hours.

An EUA was granted by the FDA on December 18, 2020 based on an ongoing Phase 3 randomized, observer-blind, placebo-controlled trial (mRNA-1273-P301).(37) Participants were stratified into three groups: 18 to <65 years of age and not at risk for progression to severe COVID-19 (58.6%), 18 to <65 years of age and at risk for progression to severe COVID-19 (16.7%), and ≥65 years of age (24.8%). Underlying comorbidities included diabetes, chronic lung disease, severe obesity, significant cardiovascular disease, CLD, or HIV infection.

In the Phase 3 Moderna trial, participants were randomized 1:1 to receive mRNA-1273 (n=15,181) or placebo (n=15,170). Median age was 52 years and 52.6% were male. Most participants were White (79.4%), 9.7% Black, 4.7% Asian, <3% other racial groups, and 20% were Hispanic/Latino.

VE for the primary endpoint (COVID-19 occurring at least 14 days after the second dose in participants who were negative for SARS-CoV-2 at baseline) was 94.1%, with 11 COVID-19 cases in the mRNA-1273 group and 185 COVID-19 cases in the placebo group. (**Figure 2**) VE was lower in participants ≥65 years of age compared to those 18 to <65 years of age (86.4% vs 95.6%). Similar to the Pfizer-

BioNTech Phase 3 trial, there was evidence for some efficacy after one dose of mRNA-1273. There was also similar evidence for a protective effect of mRNA-1273 on preventing severe COVID-19, with 0 cases of severe COVID-19 in the mRNA-1273 group and 30 cases in the placebo group.

Safety data are available for 30,350 participants with a median follow-up of 9 weeks after the second dose. The most common AEs were injection site pain (91.6%), fatigue (68.5%), headache (63.0%), muscle pain (59.6%), joint pain (44.8%), and chills (43.4%). (**Figure 3**) Similar to the Pfizer-BioNTech vaccine, lymphadenopathy was reported in 173 participants (1.1%) in the mRNA-1273 group and 95 participants (0.63%) in the placebo group. There were more hypersensitivity AEs in the mRNA-1273 group (1.5%) compared to the placebo group (1.1%), but no anaphylactic or severe hypersensitivity reactions. There were 3 reports of Bell's palsy in the mRNA-1273 group and 1 case in the placebo group. The incidence of serious adverse events was low but more frequent after the second dose than after the first dose and generally less frequent in older (≥65 years of age) compared to younger participants. The safety profile of mRNA-1273 was generally similar across subgroups, including participants with medical comorbidities, except for more frequent and generally mild to moderate reactogenicity in the younger age group. Safety conclusions could not be made about pediatric populations, pregnant and lactating individuals, and immunocompromised individuals but studies are underway.(38)

GENERAL GUIDANCE FOR COVID-19 VACCINATION

- **Persons ≥16 years (Pfizer-BioNTech) or ≥18 years (Moderna) with CLD are recommended to receive a COVID-19 vaccine (Phase 1c).**
- **The FDA and CDC recommend that all COVID-19 vaccine recipients should receive two doses of the mRNA vaccines as close to the recommended interval as possible.**
- **The second dose of the mRNA COVID-19 vaccines may be given up to 6 weeks after the first dose if necessary; however, the vaccine series should not be restarted if there is a longer delay before the second dose.**(39)

- **Each vaccine series should be completed with the same vaccine used initially. However, in exceptional situations, any available mRNA COVID-19 vaccine may be given at least 28 days after the first dose.**(39)
- **The FDA and CDC DO NOT RECOMMEND testing for serum IgM or IgG antibodies to the SARS-CoV-2 spike glycoprotein before or after COVID-19 vaccination.**
- **Administration of the COVID-19 vaccines should be at least 14 days after administration of other elective vaccines to minimize the likelihood of reduced efficacy and adverse events.**
- **The CDC recommends that people with a history of severe allergic reactions to medications or foods, and those with a history of Guillain-Barre syndrome, should receive an mRNA COVID-19 vaccine.**
- **CONTRAINDICATION: Individuals with an immediate allergic reaction of any severity (including hives) to a previous dose of an mRNA COVID-19 vaccine, to any of its components, or to polysorbate (with which there can be cross-reactive hypersensitivity to PEG) should NOT receive an mRNA COVID-19 vaccine unless they have been evaluated by an allergy expert who determines that it can be given safely.**
- **All patients who receive a COVID-19 vaccine should be monitored for a minimum of 15 minutes after the injection for an allergic reaction. Individuals with a history of an anaphylactic or anaphylactoid reaction to any prior drug or vaccine should be monitored for a minimum of 30 minutes.**
- **COVID-19 vaccines should be administered in an area and facility where immediate allergic reactions can be managed appropriately.**
- **To facilitate ongoing safety evaluation, vaccine providers should report vaccine administration errors, serious adverse events associated with vaccination, cases of multisystem inflammatory syndrome, and cases of COVID-19 that result in hospitalization or death through the VAERS.**

- **Safety of the COVID-19 vaccines has not yet been established in children or pregnant women. However, pregnancy is NOT a contraindication to COVID-19 vaccine administration and should be discussed with the patient's obstetrician.**
- **See Supplemental Text for recommendations for counseling patients about COVID-19 vaccines.**

Counseling Liver Disease Patients About COVID-19 Vaccination

Many questions will arise related to the use, safety, and efficacy of COVID-19 vaccination in patients with CLD and SOT recipients. However, vaccination is rarely contraindicated because of comorbidities or pre-existing allergies or intolerances. Few people are at risk who should defer vaccination. It is important to counsel patients about the overall safety, efficacy, and clinical benefit of mRNA COVID-19 vaccines compared to the risk of becoming ill with COVID-19. The following are summarized recommendations to address patient-specific concerns. The CDC has developed a more extensive guide for patient counseling concerns.(39)

Preferred COVID-19 vaccines for patients with liver disease

At this time, there are insufficient data to recommend one mRNA COVID-19 vaccine (e.g., Pfizer-BioNTech or Moderna) over another. While there are differences between vaccines, the currently authorized mRNA vaccines are nearly equivalent in terms of efficacy, each demonstrating a 95% VE. One notable difference is the minimum age authorized to receive vaccination (Moderna ≥18 years, Pfizer-BioNTech ≥16 years).

Pre-vaccination serological testing

We do not recommend pre-vaccination testing for SARS-CoV-2 IgG or IgM antibodies. Multiple commercially available assays under EUA measure antibodies to various SARS-CoV-2 proteins. They are

primarily used to monitor antibody response during and after COVID-19. Notably, while they may confirm prior exposure, they may not represent protective immunity. Furthermore, limited data exist describing the durability of these antibodies. Given the lack of evidence in demonstrating protective immunity, we do not recommend serological testing prior to COVID-19 vaccination.

Post-vaccination serological testing

We do not recommend post-vaccination testing for SARS-CoV-2 IgG or IgM antibodies until new and validated studies show detection of an effective immune response that correlates with disease prevention or amelioration. Commercially available antibody assays are directed toward SARS-CoV-2 spike glycoprotein and/or nucleoproteins. Current vaccines stimulate an immune response to spike proteins detectable after both vaccination and natural infection. In contrast, assays directed toward other non-spike proteins will be detected only after natural infection. Data related to the utility of post-vaccination serological testing are lacking and such testing is not currently recommended.

Administration and timing of vaccination

We recommend completing both mRNA COVID-19 vaccine doses in the timeline recommended. The CDC currently recommends administration of the second dose of the Pfizer-BioNTech mRNA vaccine at 3 weeks (21 days) and the Moderna mRNA vaccine at 4 weeks (28 days). The second dose can be given up to 4 days early (i.e., 17 and 24 days, respectively). If patients are unable to receive the second dose at this recommended interval, the CDC recommends administration no later than 6 weeks after the first dose; however, the vaccine series should not be restarted if there is a longer delay before the second dose.(39) Vaccine administration errors and side effects should be reported to the VAERS. There are no convincing data to support a single-dose vaccination schedule.

Vaccination in patients with autoimmune hepatitis or other autoimmune diseases

We recommend administration of the vaccine to patients with autoimmune hepatitis and/or CLD patients with autoimmune diseases. The Pfizer-BioNTech and Moderna clinical trials included participants with autoimmune disease; however, participants on immunosuppressive medications were excluded. In both studies, neither side effects nor efficacy were provided for these subgroups. The exclusion of immunosuppressed participants in these trials precludes conclusions on VE in this population. There are no data to support delaying or holding immunosuppression prior to administration of the COVID-19 vaccine.

Use of antipyretics as pre-vaccination prophylaxis or post-vaccination treatment

We do not recommend antipyretics or NSAIDs pre-vaccination as prophylaxis for local or systemic reactions because of the absence of data on the impact of these medications on vaccine immunogenicity.

We support the use of antipyretics or NSAIDS post-vaccination to treat local or systemic reactions as needed. Neither Pfizer-BioNTech nor Moderna study protocol advised for or against use of antipyretics following vaccination. Neither protocol mandated use of these agents as a protocol violation or addressed timing of participants' baseline medication use relative to vaccination. There is no evidence to suggest that use of antipyretics or NSAIDs following vaccination will affect safety or efficacy of the COVID-19 vaccination.

Concurrent medication timing or use

We do not recommend withholding baseline medications before or after vaccine administration. Neither the Pfizer-BioNTech nor Moderna study protocol addressed concurrent medication use or timing in relationship to the vaccination.

Consistent with CDC guidance, patients who received monoclonal antibodies or convalescent plasma for the treatment of COVID-19 should wait to be vaccinated at least 90 days from the time of dosing of these medications. If monoclonal antibodies or convalescent plasma for COVID-19 are administered after receiving the initial vaccine dose, the second dose should be delayed for 90 days following this therapy. Other monoclonal antibody therapies (i.e., non-COVID-19 therapies) do not require a delay in COVID-19 vaccination.

COVID-19 vaccination of inpatients versus outpatients

All of the participants in the mRNA vaccine trials were stable outpatients at the time of enrollment. Therefore, there are no data to guide the use of COVID-19 vaccination in individuals who are currently hospitalized. A review of overall risk versus benefit and potential for adverse events should be considered on a case-by-case basis.

History of anaphylaxis

We recommend vaccination in all patients unless there is a history of prior anaphylaxis to the mRNA COVID-19 vaccine or any of its components. (**Supplemental Table 2**) Prior anaphylaxis to any other allergen (including venom, food, and medication) does not preclude the use of mRNA COVID-19 vaccination, but those individuals should be observed for adverse events for a minimum of 30 minutes after vaccination compared to the standard 15-minute observation period. Vaccine side effects should be reported to the VAERS.

The CDC has provided a table that may be helpful to clinicians in counseling patients. (**Supplemental Table 2**) The individual components of each vaccine are available from the CDC.(39) Neither vaccine contains eggs, gelatin, latex, or preservatives. The common anaphylaxis-inducing allergens of insect venom, milk, eggs, animal dander, and oral medications are not a contraindication or precautions with use of the Pfizer-BioNTech or Moderna mRNA COVID-19 vaccines.

Post-vaccination continuation of behaviors to avoid exposure to SARS-CoV-2

We recommend that everyone continue behaviors to mitigate the risk of SARS-CoV-2 exposure (e.g., masking, hand hygiene, social distancing, etc.) regardless of vaccination status. The onset of protective immunity post-vaccination is not clear and infection occurred in vaccinated participants in the clinical trials even after the second dose.

Common side effects of COVID-19 vaccination and distinguishing these from true infection

Injection site pain is the most common complaint, with "severe pain" occurring in 1% of recipients within 12-24 hours. Fever, myalgia, and headache are also commonly reported. Younger patients may experience symptoms more commonly than older recipients. (**Figure 3**)

Distinguishing COVID-19 from vaccination reaction can be challenging given the nonspecific symptoms associated with both conditions. High fevers and respiratory symptoms (e.g., cough or shortness of breath) are uncommon after vaccination. If observed, clinicians should consider testing for SARS-CoV-2 or another infectious etiology. As most side effects of vaccination should subside within 1-2 days, additional testing should be considered in patients with symptoms persisting beyond this time frame. It should be noted that mRNA vaccines do not cause positive nucleic acid (PCR) or antigen-based tests for SARS-CoV-2. A positive test after vaccination should be considered a true SARS-CoV-2 infection.

References

1. Sipeki N, Antal-Szalmas P, Lakatos PL, Papp M. Immune dysfunction in cirrhosis. World J Gastroenterol 2014 March 14;20:2564–2577.

2. Noor MT, Manoria P. Immune dysfunction in cirrhosis. J Clin Transl Hepatol 2017 March 28;5:50–58.

3. Ma C, Kesarwala AH, Eggert T, Medina-Echeverz J, Kleiner DE, Jin P, et al. NAFLD causes selective CD4(+) T lymphocyte loss and promotes hepatocarcinogenesis. Nature 2016 March 10;531:253–257.

4. Doi H, Iyer TK, Carpenter E, Li H, Chang K-M, Vonderheide RH, et al. Dysfunctional B-cell activation in cirrhosis resulting from hepatitis C infection associated with disappearance of CD27-positive B-cell population. Hepatology 2012 March;55:709–719.

5. Burton AR, Pallett LJ, McCoy LE, Suveizdyte K, Amin OE, Swadling L, et al. Circulating and intrahepatic antiviral B cells are defective in hepatitis B. J Clin Invest 2018 October 1;128:4588–4603.

6. Park J-J, Wong DK, Wahed AS, Lee WM, Feld JJ, Terrault N, et al. Hepatitis B virus--specific and global T-cell dysfunction in chronic hepatitis B. Gastroenterology 2016 March;150:684-695.e5.

7. Kalra A, Wedd JP, Bambha KM, Gralla J, Golden-Mason L, Collins C, et al. Neutrophil-to-lymphocyte ratio correlates with proinflammatory neutrophils and predicts death in low model for end-stage liver disease patients with cirrhosis. Liver Transpl 2017 February;23:155–165.

8. Polakos NK, Cornejo JC, Murray DA, Wright KO, Treanor JJ, Crispe IN, et al. Kupffer cell-dependent hepatitis occurs during influenza infection. Am J Pathol 2006 April;168:1169–1178.

9. Duchini A, Viernes ME, Nyberg LM, Hendry RM, Pockros PJ. Hepatic decompensation in patients with cirrhosis during infection with influenza A. Arch Intern Med 2000 January 10;160:113–115.

10. Song JY, Cheong HJ, Ha SH, Hwang IS, Kee SY, Jeong HW, et al. Clinical impact of influenza immunization in patients with liver cirrhosis. J Clin Virol 2007 July;39:159–163.

11. Van Kerkhove MD, Vandemaele KAH, Shinde V, Jaramillo-Gutierrez G, Koukounari A, Donnelly CA, et al. Risk factors for severe outcomes following 2009 influenza A (H1N1) infection: a global pooled analysis. PLoS Med 2011 July;8:e1001053.

12. Härmälä S, Parisinos C, Shallcross L, O'Brien A, Hayward A. Effectiveness of pneumococcal and influenza vaccines to prevent serious health complications in adults with chronic liver disease: a protocol for a systematic review. BMJ Open 2018 March 16;8:e018223.

13. CDC. Vaccination of adults with liver disease. Published May 2, 2016. https://www.cdc.gov/vaccines/adults/rec-vac/health-conditions/liver-disease.html. Accessed February 2021.

14. Younossi ZM, Stepanova M. Changes in hepatitis A and B vaccination rates in adult patients with chronic liver diseases and diabetes in the U.S. population. Hepatology 2011 October;54:1167–1178.

15. Venters C, Graham W, Cassidy W. Recombivax-HB: perspectives past, present and future. Expert Rev Vaccines 2004 April;3:119–129.

16. Aggeletopoulou I, Davoulou P, Konstantakis C, Thomopoulos K, Triantos C. Response to hepatitis B vaccination in patients with liver cirrhosis. Rev Med Virol 2017 November;27:e1942.

17. Gutierrez Domingo I, Pascasio Acevedo JM, Alcalde Vargas A, Ramos Cuadra A, Ferrer Ríos MT, Sousa Martin JM, et al. Response to vaccination against hepatitis B virus with a schedule of four 40-µg doses in cirrhotic patients evaluated for liver transplantation: factors associated with a response. Transplant Proc 2012 August;44:1499–1501.

18. Walayat S, Ahmed Z, Martin D, Puli S, Cashman M, Dhillon S. Recent advances in vaccination of non-responders to standard dose hepatitis B virus vaccine. World J Hepatol 2015 October 28;7:2503–2509.

19. Bonazzi PR, Bacchella T, Freitas AC, Osaki KT, Lopes MH, Freire MP, et al. Double-dose hepatitis B vaccination in cirrhotic patients on a liver transplant waiting list. Braz J Infect Dis 2008 August;12:306–309.

20. Arslan M, Wiesner RH, Sievers C, Egan K, Zein NN. Double-dose accelerated hepatitis B vaccine in patients with end-stage liver disease. Liver Transpl 2001 April;7:314–320.

21. Wigg AJ, Wundke R, McCormick R, Muller KR, Ramachandran J, Narayana SK, et al. Efficacy of high-dose, rapid, hepatitis A and B vaccination schedules in patients with cirrhosis. Clin Gastroenterol Hepatol 2019 May;17:1210-1212.e1.

22. Amjad W, Alukal J, Zhang T, Maheshwari A, Thuluvath PJ. Two-dose hepatitis B vaccine (Heplisav-B) results in better seroconversion than three-dose vaccine (Engerix-B) in chronic liver disease. Dig Dis Sci 2020 July 2. doi: 10.1007/s10620-020-06437-6. [Online ahead of print]

23. Dan JM, Mateus J, Kato Y, Hastie KM, Yu ED, Faliti CE, et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. Science 2021 January 6. doi: 10.1126/science.abf4063. [Online ahead of print]

24. Goldfarb NS, Avery RK, Goormastic M, Mehta AC, Schilz R, Smedira N, et al. Hypogammaglobulinemia in lung transplant recipients. Transplantation 2001 January 27;71:242–246.

25. Avery RK. Immunizations in adult immunocompromised patients: which to use and which to avoid. Cleve Clin J Med 2001 April;68:337–348.

26. Danziger-Isakov L, Kumar D, AST ID Community of Practice. Vaccination of solid organ transplant candidates and recipients: Guidelines from the American society of transplantation infectious diseases community of practice. Clin Transplant 2019 September;33:e13563.

27. CDC. ACIP general best practice guidelines for immunization. Published November 20, 2020. https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html. Accessed February 2021.

28. Posfay-Barbe KM, Pittet LF, Sottas C, Grillet S, Wildhaber BE, Rodriguez M, et al. Varicella-zoster immunization in pediatric liver transplant recipients: safe and immunogenic. Am J Transplant 2012 November;12:2974–2985.

29. FDA. Independent evaluations of COVID-19 serological tests. https://open.fda.gov/apis/device/covid19serology. Accessed February 2021.

30. Gaebler C, Wang Z, Lorenzi JCC, Muecksch F, Finkin S, Tokuyama M, et al. Evolution of antibody immunity to SARS-CoV-2. Nature 2021 January 18. doi: 10.1038/s41586-021-03207-w. [Online ahead of print]

31. Fenwick C, Croxatto A, Coste AT, Pojer F, André C, Pellaton C, et al. Changes in SARS-CoV-2 spike versus nucleoprotein antibody responses impact the estimates of infections in population-based seroprevalence studies. J Virol 2021 January 13;95:e01828-20.

32. Long Q-X, Tang X-J, Shi Q-L, Li Q, Deng H-J, Yuan J, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nat Med 2020 August;26:1200–1204.

33. Walsh EE, Frenck RW, Falsey AR, Kitchin N, Absalon J, Gurtman A, et al. Safety and immunogenicity of two RNA-based Covid-19 vaccine candidates. N Engl J Med 2020 December 17;383:2439–2450.

34. Pfizer and BioNTech. FDA Briefing Document: Pfizer-BioNTech COVID-19 Vaccine. Vaccines and Related Biological Products Advisory Committee Meeting. Published December 10, 2020. https://www.fda.gov/media/144245/download. Accessed February 2021.

35. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020 December 31;383:2603–2615.

36. Moderna. FDA Briefing Document: Moderna COVID-19 Vaccine. Vaccines and Related Biological Products Advisory Committee Meeting. Published December 17, 2020. https://www.fda.gov/media/144434/download. Accessed February 2021.

37. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021 February 4;384:403–416.

38. ModernaTX, Inc. A phase 2/3, randomized, observer-blind, placebo controlled study to evaluate the safety, reactogenicity, and effectiveness of mRNA-1273 SARS CoV 2 vaccine in healthy adolescents 12 to <18 years of age. Published January 19, 2021. https://clinicaltrials.gov/ct2/show/NCT04649151. Accessed February 2021.

39. CDC. Interim clinical considerations for use of mRNA COVID-19 vaccines currently authorized in the United States. Published January 21, 2021. https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html. Accessed February 2021.

Supplemental Table 1. Recommended Vaccines in Adults with CLD and SOT Recipients

Vaccine	Dosing	CLD	SOT recipients	Comments
Influenza	1 dose yearly	Inactivated Recombinant Live intranasal*	Inactivated Recombinant Live contraindicated	Live intranasal contraindicated in SOT recipients and those >50 years
Tdap (tetanus, diphtheria, pertussis)	1 dose 10 years			
Pneumococcal 13	1 dose			
Pneumococcal polysaccharide 23	1, 2, or 3 doses 3-5 years			
Hepatitis B (Engerix, Recombivax HB) (Heplisav B)	0, 1, and 6 months 0 and 1 month	Increased immunogenicity		
Hepatitis A	0 and 6 months			
Zoster (Shingrix)		≥50 years	>1 year post SOT (not studied)	
Human papillomavirus (HPV)	2 or 3 doses depending on age, condition			Adults up to age 25 and some 27-45 years

Measles, mumps, and rubella (MMR)	1 or 2 doses at 0 and 6 months		Contraindicated	If born after 1957 or no prior immunity
Varicella	2 doses		Contraindicated	
Meningococcus	1-3 doses			
H. Influenzae	1 dose			

*only if age <50 years

Adapted from the CDC: Vaccination of adults with liver disease. Published May 2, 2016. https://www.cdc.gov/vaccines/adults/rec-vac/health-conditions/liver-disease.html. Accessed February 2021

Supplemental Table 2. Triage of Persons Presenting for mRNA COVID-19 Vaccination

	May Proceed with Vaccination	Precaution to Vaccination	Contraindication to Vaccination
CONDITIONS	**Conditions** • Immunocompromising conditions • Pregnancy • Lactation **Actions** • Additional information provided • 15 minute observation period	**Conditions** • Moderate/severe acute illness **Actions** • Risk assessment • Potential deferral of vaccination • 15-minute observation period if vaccinated	**Conditions** • None **Actions** • N/A

ALLERGIES	**Allergies** History of allergies that are unrelated to components of an mRNA COVID-19 vaccine*, other vaccines, injectable therapies, or polysorbate, such as: • Allergy to oral medications (including the oral equivalent of an injectable medication) • History of food, pet, insect, venom, environmental, latex, etc., allergies • Family history of allergies **Actions** • 30-minute observation period: Persons with a history of anaphylaxis (due to any cause) • 15-minute observation period: All other persons	**Allergies** • History of any immediate allergic reaction to vaccines or injectable therapies (except those related to component of mRNA COVID-19 vaccines* or polysorbate, as these are contraindicated) **Actions** • Risk assessment • Consider deferral of vaccination and/or referral to allergist-immunologist • 30-minute observation period if vaccinated	**Allergies** History of the following are contraindications to receiving either of the mRNA COVID-19 vaccines*: • Severe allergic reaction (e.g., anaphylaxis) after a previous dose of an mRNA COVID-19 vaccine or any of its components • Immediate allergic reaction‡ of any severity to a previous dose of an mRNA COVID-19 vaccine or any of its components^ (including polyethylene glycol) • Immediate allergic reaction of any severity to polysorbate **Actions** • Do not vaccinate** • Consider referral to allergist-immunologist

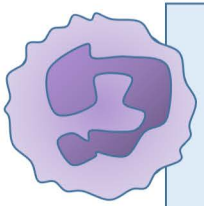
*Refers only to mRNA COVID-19 vaccines currently authorized in the United States (i.e., Pfizer-BioNTech, Moderna COVID-19 vaccines)

**These persons should not receive mRNA COVID-19 vaccination at this time unless they have been evaluated by an allergist-immunologist and it is determined that the person can safely receive the vaccine (e.g., under observation, in a setting with advanced medical care available)

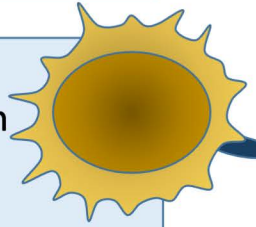
Adapted from the CDC: Interim clinical considerations for use of mRNA COVID-19 vaccines currently authorized in the United States. Published January 21, 2021. https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html. Accessed February 2021

Innate Immunity

Altered PRR expression/Signaling
Reduced Complement C3/C4



Neutrophils
Persistent Activation
Reduced Migration
Reduced Phagocytosis

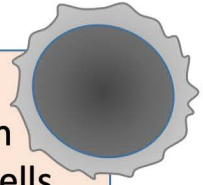


Monocytes/Macrophages
Decreased Ag presentation
Reduced Chemotaxis
Reduced Phagocytosis
Defective Superoxide Degeneration

Cirrhosis-Associated Immune Dysfunction

Adaptive Immunity

T Cells
Persistent Activation
Reduced CD4 helper-Cells
Increased Apoptosis
T Cell Exhaustion



B Cells
Persistent Activation
Reduced Memory Cells
Increased Apoptosis
Altered Ig production