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COUNSELING LIVER DISEASE PATIENTS ABOUT COVID-19 VACCINATION

See main document [“AASLD EXPERT PANEL CONSENSUS STATEMENT: VACCINES TO PREVENT COVID-19 IN PATIENTS WITH LIVER DISEASE”](#)

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There are numerous questions from patients, their caregivers, and providers regarding the use, safety, and efficacy of COVID-19 vaccination in patients with chronic liver disease (CLD) and solid organ transplant (SOT) recipients. In general, vaccination is rarely contraindicated because of comorbidities or pre-existing allergies or intolerances, particularly for persons at risk for severe COVID-19. Therefore, there are few if any people at risk who should defer vaccination. In the appropriate clinical context, patients should be counseled that the overall safety, efficacy, and clinical benefit of available COVID-19 vaccines outweigh 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.¹

Preferred COVID-19 vaccines for patients with liver disease

At this time, there are insufficient data to recommend any of the currently authorized COVID-19 vaccines (e.g., Pfizer-BioNTech, Moderna, or Johnson & Johnson/Janssen) over another for CLD patients. While there are differences between vaccines, the currently authorized vaccines are nearly equivalent in preventing severe disease, hospitalization, or death. All trials included patients with stable liver disease. Only the adenoviral vector vaccine trial included a few SOT patients. One notable difference between the vaccines is the minimum age authorized to receive vaccination (Moderna and Johnson & Johnson/Janssen ≥ 18 years, Pfizer-BioNTech ≥ 16 years). However, trials in patients ≥ 12 years are ongoing with all three vaccines. There are insufficient data to consider vaccine efficacy among emerging SARS-CoV-2 variants as a reason to select one vaccine over another.

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 can 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 only to spike proteins that are 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

If receiving one of the mRNA COVID-19 vaccines, we recommend completing both 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) after the first dose. 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.¹ Vaccine administration errors and side effects should be reported to the VAERS. There are no convincing data to support a single-dose vaccination schedule with the available mRNA COVID-19 vaccines or two doses of

the adenoviral vector COVID-19 vaccine. A double dose of any of the available COVID-19 vaccines is NOT recommended.

Vaccination timing relative to SARS-CoV-2 infection

We recommend that vaccination be delayed until recovery from acute COVID-19 and after completion of isolation precautions, both for infection occurring prior to initial dose or between mRNA COVID-19 vaccine doses. Delay of vaccination is reasonable (particularly while vaccination distribution remains limited) as evidence suggests that reinfection risk is low in the months following infection. We recommend vaccination for all previously infected persons because reinfection does occur. There is no recommended minimum interval between infection and vaccination.

Vaccination timing relative to SARS-CoV-2 exposure

Vaccination as post-exposure prophylaxis is not recommended as the onset of protective immune response from vaccination is thought to be longer than the incubation period for SARS-CoV-2 and would thus not provide benefit in preventing infection. Patients with a known SARS-CoV-2 exposure should wait to receive vaccination until completion of quarantine restrictions. Outside of this timing, prior exposure should not alter the recommendation for vaccination.

Vaccination timing relative to other vaccinations

We recommend COVID-19 vaccination be given at least 14 days from other vaccinations when clinically feasible.

Vaccination timing after SARS-CoV-2 monoclonal antibody (MAB) or convalescent plasma infusion

We recommend delaying vaccination, both initial or second dose, for 90 days after SARS-CoV-2 monoclonal antibody or convalescent plasma infusion. This delay may decrease interactions between antibody therapy and the vaccine-induced immune responses. Other monoclonal antibody therapies (i.e., non-COVID-19 therapies) do not require a delay in COVID-19 vaccination.

Vaccination in patients with autoimmune hepatitis or other autoimmune diseases

We recommend administration of a COVID-19 vaccine to patients with autoimmune hepatitis and/or CLD patients with autoimmune diseases. All of the clinical trials included participants with autoimmune disease; however, a small number of participants on immunosuppressive medications were included in the Johnson & Johnson/Janssen phase 3 trial. In all studies, neither side effects nor efficacy were provided for these subgroups. There are no data to support delaying or holding immunosuppression prior to administration of the COVID-19 vaccine.

Vaccination in post-liver transplant patients

Limited data exist regarding vaccination in SOT recipients. A real-world trial of mRNA vaccines in SOT recipients, including liver transplant (LT) patients, confirmed similar severity and rates of reactogenicity when compared to non-transplant patients. None of these patients experienced severe allergic reactions, acute cellular rejection (ACR), or COVID-19. Vaccine efficacy data in SOT recipients are lacking.

Although the Johnson & Johnson/Janssen phase 3 trial enrolled a small number of SOT recipients, specific data on LT recipients were not described. Limited data from this trial precludes clear conclusions regarding the safety or efficacy of adenoviral vaccines in LT recipients.

At this time, COVID-19 vaccination is recommended for all LT recipients. Consideration may be given to waiting for 6 weeks after LT when immunosuppression and other medications can be more safely minimized. All immunosuppressive medications related to liver transplantation should be continued as instructed by the care team. Empiric reduction of immunosuppression is NOT RECOMMENDED in an effort to increase immune response as the risk for ACR outweighs any theoretical benefit. Vaccination prior to LT is recommended when feasible.

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. None of the phase 3 study protocols advised for or against use of antipyretics following vaccination. Additionally, the protocols did not mandate use of these agents as a protocol violation or addressed timing of participants' baseline medication use relative to vaccination. Therefore, 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. None of the study protocols addressed concurrent medication use or timing in relationship to the vaccination.

COVID-19 vaccination of inpatients versus outpatients

All of the participants in the COVID-19 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 ([Table 1](#)). Prior anaphylaxis to any other allergen (including venom, food, and medication) does not preclude the use of 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 ([Table 1](#)). The individual components of each vaccine are available from the CDC.¹ 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 mRNA or adenoviral vector 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. However, the CDC has [eased restrictions](#) in some circumstances. It should be noted that SARS-CoV-2 infections have occurred in vaccinated participants in the clinical trials .

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, fatigue, swelling, and headache are also commonly reported. Younger patients may experience symptoms more commonly than older recipients ([Figure 3](#)).

Distinguishing COVID-19 symptoms 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 the available COVID-19 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.

Addressing patient hesitancy to receive COVID-19 vaccination

For patients who are reluctant to be vaccinated or decline COVID-19 vaccination, we recommend an engaged discussion with their health care provider to determine the factors in their decision and address misconceptions. Common themes include the pace of vaccine authorization and fear of the novelty of the vaccines. Particularly among minority patients, there is distrust and skepticism of the medical community generally and “experimental drugs” specifically that is historically well founded. It is critical to address this distrust, especially because the COVID-19 pandemic has disproportionately impacted this demographic.

In a NAACP-supported survey,² 14% of Black respondents and 34% of Latinx respondents reported trust in the safety of the COVID-19 vaccines and 18% and 31%, respectively, reported definitely planning to get the COVID-19 vaccination. In the same survey, 72% of Black respondents and 66% of Latinx respondents rated their health care provider positively as a source of clear information for decision making.

In order to elicit potentially modifiable barriers to vaccination, we recommend starting with an open-ended question to assess vaccine readiness, such as, “Are you planning to get the COVID-19 vaccine?” From this starting point, a “no” answer more easily leads to a follow-up question (e.g., “Would you mind telling me about

your concerns?” or “Tell me more about that decision.”). Sharing the following facts and others about the clinical trials and EUA process may help them make an informed decision:

- EUA does not mean less rigorous safety or efficacy standards.³ EUA submission requires completion of phase 1 and 2 studies followed by phase 3 trials with median follow up of at least 2 months. EUA requests must include phase 3 safety data for >3000 participants. The speed at which COVID-19 vaccinations were authorized and became available to the public was because of unique trial designs (rolling and overlapping cohort assessment) and the short timeline for assessing vaccine response (as opposed to drugs that may require 6 months or more of data accumulation to demonstrate efficacy).
- Minority representation in the COVID-19 vaccine clinical trials was higher than typical in clinical trials. Black participation was near 10% in the Pfizer-BioNTech and Moderna trials. Hispanic participation was 26% and 20%, respectively. American Indian/Alaska Native participation was proportionate to the US population. There were no reported differences in safety or efficacy in these subpopulations.

References

1. 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.
2. Langer Research Associates. Coronavirus vaccine hesitancy in Black and Latinx communities. Covid Collaborative. Published November 23, 2020. <https://www.covidcollaborative.us/content/vaccine-treatments/coronavirus-vaccine-hesitancy-in-black-and-latinx-communities>. Accessed March 2021.
3. FDA. Emergency Use Authorization for vaccines explained. Published November 20, 2020. <https://www.fda.gov/vaccines-blood-biologics/vaccines/emergency-use-authorization-vaccines-explained>. Accessed March 2021.

Table 1. Triage of Persons Presenting for COVID-19 Vaccination

	May Proceed with Vaccination	Precaution to Vaccination	Contraindication to Vaccination
CONDITIONS	<p>Conditions</p> <ul style="list-style-type: none"> Immunocompromising conditions Pregnancy Lactation <p>Actions</p> <ul style="list-style-type: none"> Additional information provided 15 minute observation period 	<p>Conditions</p> <ul style="list-style-type: none"> Moderate/severe acute illness <p>Actions</p> <ul style="list-style-type: none"> Risk assessment Potential deferral of vaccination 15-minute observation period if vaccinated 	<p>Conditions</p> <ul style="list-style-type: none"> None <p>Actions</p> <ul style="list-style-type: none"> N/A
ALLERGIES	<p>Allergies</p> <p>History of allergies that are unrelated to components of an mRNA COVID-19 vaccine*, other vaccines, injectable therapies, or polysorbate, such as:</p> <ul style="list-style-type: none"> 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 <p>Actions</p> <ul style="list-style-type: none"> 30-minute observation period: Persons with a history of anaphylaxis (due to any cause) 15-minute observation period: All other persons 	<p>Allergies</p> <ul style="list-style-type: none"> 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) <p>Actions</p> <ul style="list-style-type: none"> Risk assessment Consider deferral of vaccination and/or referral to allergist-immunologist 30-minute observation period if vaccinated 	<p>Allergies</p> <p>History of the following are contraindications to receiving either of the mRNA COVID-19 vaccines*:</p> <ul style="list-style-type: none"> 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 <p>Actions</p> <ul style="list-style-type: none"> 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 March 2021