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SUPPLEMENTAL MATERIALS

See main document "AASLD EXPERT PANEL CONSENSUS STATEMENT: VACCINES TO PREVENT COVID-19 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 (Supplemental Figure 1).[1,2] 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 chronic liver disease (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 Centers for Disease Control and Prevention (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 (Supplemental Figure 1).[13,14] 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 solid organ transplant (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] Advisory Committee on Immunization Practices (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.

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.[33] 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).[34] 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).[34] 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.

Viral efficacy (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.[33] 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.[35] 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).[36] 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.[37]

Prioritization During Limited Supply of COVID-19 Vaccines

The COVID-19 vaccines are currently a limited resource that requires rational selection of the highest-risk candidates for priority access. Providers must administer COVID-19 vaccines in accordance with prioritization groups determined by appropriate public health authorities.[38,39] The CDC has published a dynamic document that ranks groups at high risk for exposure or poor outcome from COVID-19 (phases 1a, 1b, 1c, and 2).[39,40] Health care workers are prioritized by the CDC (phase 1a) to receive the COVID-19 vaccines because of their high risk of exposure to SARS-CoV-2, the need to protect patients from infection, and the need to preserve the capacity to care for patients.[41] Patients with underlying medical conditions, including liver disease (e.g., compensated and decompensated cirrhosis, liver cancer), SOT, and immunosuppression, are at risk for severe COVID-19 and are included in phase 1c.[42–46]

Because of the scarcity of COVID-19 vaccines and the observation that SARS-CoV-2 reinfection is uncommon within 90 days of first infection, the CDC recognizes that persons with recent SARS-CoV-2 infection may want to defer vaccination for up to 90 days. In addition, early work suggests that COVID-19 vaccine-related side effects may be more common in those with previous SARS-CoV-2 infection, particularly when vaccinated soon after infection.[47]

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

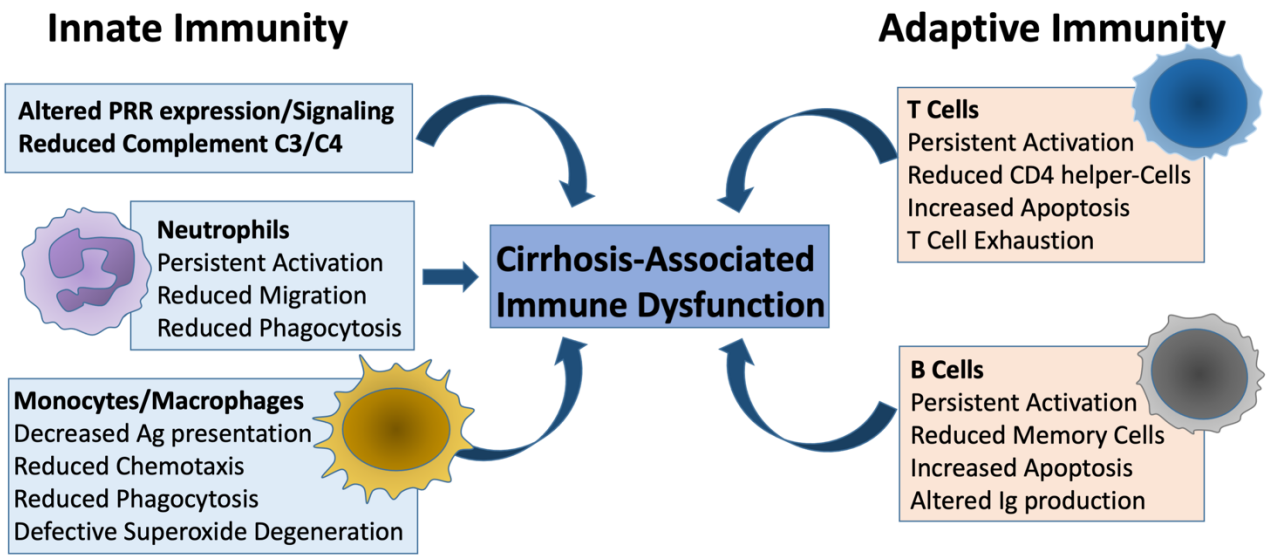
Vaccine	Dosing	CLD	SOT recipients	Comments
Influenza	1 dose yearly	Inactivated Recombinant Live intranasal*	Inactivated Recombinant Live contraindicated	Live intranasal contraindicated in SOT recipients and those >50 years
Tdap (tetanus, diphtheria, pertussis)	1 dose 10 years			
Pneumococcal 13	1 dose			
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 Figure 1. Immune Dysfunction in Cirrhosis

Alterations in innate and adaptive immune function occur in cirrhosis which may contribute to vaccine hyporesponsiveness in this population.



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