Optimizing Vaccination in Adult Patients With Liver Disease and Liver Transplantation

Yoona Rhee, M.D., Sc.M., Beverly E. Sha, M.D., and Carlos A.Q. Santos, M.D., M.P.H.S.

KEY TAKE-HOME POINTS

• Clinicians should actively vaccinate patients with LD and following LT to reduce vaccine-preventable illnesses.
• Early vaccination prior to progression of LD and prior to LT provides the best chance of optimal vaccine response.
• Vaccines are safe; however, live vaccines should not be provided in immunosuppressed patients with LD or after liver transplant (LT) because of risk for secondary disseminated disease. Transplant candidates should not receive live vaccines within 4 weeks of anticipated LT.
• Heplisav-B and Shingrix are new inactivated recombinant vaccines with improved immunogenicity and better safety profiles. Gardasil-9 can now be given to adults up to 45 years old.
• Travel-related health counseling and vaccination in patients with LD and LT recipients is crucial and should be performed months prior to anticipated travel.

Patients with end-stage liver disease (ESLD) and LT recipients remain at high risk for vaccine-preventable infections in the pre- and post-LT period.1-3 Despite higher risks, vaccine adherence remains low.4-6 Timing of vaccination remains crucial, because immunological responses are anticipated to be optimal in early liver disease (LD) and prior to LT7; therefore, every effort should be made to immunize prior to transplantation when possible. Guidelines

Abbreviations: ACIP, Advisory Committee on Immunization Practices; AST, American Society of Transplantation; CDC, Centers for Disease Control and Prevention; CLD, chronic liver disease; ESLD, end-stage liver disease; FDA, US Food and Drug Administration; HAV, hepatitis A virus; HBV, hepatitis B virus; HPV, human papillomavirus; HZ, herpes zoster; IDSA, Infectious Diseases Society of America; IgG, immunoglobulin G; JEV, Japanese encephalitis virus; LD, liver disease; LT, liver transplantation; MenACWY, meningococcal ACWY; MMR, measles, mumps, and rubella; RZV, recombinant herpes zoster; SOT, solid organ transplantation; Tdap, tetanus, diphtheria, pertussis; VZV, varicella zoster virus.

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### TABLE 1. RECOMMENDED ROUTINE VACCINES IN CLD/ESLD AND LT

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Brand Name(s)</th>
<th>Clinical Description</th>
<th>CLD/ESLD</th>
<th>LT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactivated</td>
<td></td>
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<tr>
<td>HAV*</td>
<td>Havrix, Vaqta</td>
<td>HAV can be acquired by fecal-oral transmission and can cause severe acute LD.</td>
<td>Yes. If HAV IgG antibody is not detected in the blood, two doses should be given at 0 and 6-12 months. The CDC does not recommend checking postvaccination serology because response is generally good, there are no current standard booster recommendations, and tests may not be sensitive enough to detect low-level protective antibodies.</td>
<td>Yes. Same as for CLD/ESLD. However, suboptimal responses to two doses of HAV vaccine may occur in transplant recipients. HAV IgG should be checked in high-risk patients (i.e., travelers) with consideration of booster doses.</td>
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<tr>
<td>HBV*</td>
<td>Engerix-B, Recombivax-HB, Heplisav-B (HepB-CpG)</td>
<td>HBV is a blood-borne pathogen that causes acute and/ or chronic infection. There is a risk for hepatocellular carcinoma in chronic disease.</td>
<td>Yes. Indicated if HBV surface IgG antibody is not detected in the blood. Recommend Heplisav-B at 0 and 1 month. Alternatives are Engerix-B/Recombivax-B 40 μg/mL at standard (0, 1, and 6) or accelerated (0, 1, 2, and 12 months) schedules. Check HBV surface IgG antibody at least 1 month after vaccination; if remains nonresponder, consider one-time booster dose or repeat vaccination series. If isolated HBV core IgG antibody is detected, vaccine consideration depends on suspected reason.</td>
<td>Yes. Same as for CLD/ESLD.</td>
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<td>RZV</td>
<td>Shingrix</td>
<td>Shingles (HZ) disease is a reactivation of prior chickenpox (VZV) infection. Shingles can cause a painful local vesicular rash or disseminate.</td>
<td>Yes. Recommend if ≥50 years old, regardless of VZV serostatus or prior chickenpox or shingles disease.</td>
<td>Yes. Same as for CLD/ESLD.</td>
</tr>
<tr>
<td>HPV</td>
<td>Gardasil-9</td>
<td>The most feared complication of HPV infection is malignancy (genital, anal, oropharyngeal), but it can also cause common and genital warts. Prognosis may be worse after LT because of immunosuppression.</td>
<td>Yes. Recommended for adult men and women up to 45 years old. Given in three-dose series at 0, 1-2, and 6 months. Protects against nine serotypes: 6, 11, 16, 18, 31, 33, 45, 52, and 58.</td>
<td>Yes. Same as for CLD/ESLD.</td>
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<tr>
<td>Influenza virus</td>
<td>Multiple</td>
<td>Both influenza A and B viruses can cause infection. Due to high mutation rates, seasonal vaccine will try to match a combination of the most likely circulating strains.</td>
<td>Yes. Should be received once yearly during the fall-winter months.</td>
<td>Yes. Same as for CLD/ESLD.</td>
</tr>
<tr>
<td>Pneumococcal conjugate</td>
<td>Prevnar (PCV-13)</td>
<td>Streptococcus pneumoniae is a bacteria that can cause pneumonia, meningitis, and other invasive disease. PCV13 protects against 13 serotypes: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F.</td>
<td>Yes. Should be received once as an adult, if not received during childhood primary series. Should be given ≥1 year after PPSV23, so preference is to give PCV13 first if both needed (see later).</td>
<td>Yes. Same as for ESLD/CLD.</td>
</tr>
<tr>
<td>Pneumococcal polysaccharide</td>
<td>Pneumovax (PPSV23)</td>
<td>Another pneumococcal vaccine. PPSV23 protects against 23 serotypes: 1, 2, 3, 4, 5, 6A, 7F, 8, 9N, 14, 18C, 19A, 20, 22F, 23F, and 33F.</td>
<td>Yes. Can receive up to three lifetime doses separated by ≥5 years. Up to 2 doses at &lt;65 years old and a final dose at ≥65 years old. Give ≥8 weeks after PCV13 for optimal antibody response (see earlier).</td>
<td>Yes. Same as for CLD/ESLD.</td>
</tr>
<tr>
<td>Tetanus, diphtheria, pertussis (Td, Tdap)</td>
<td>Tetnvac, Adacel, Boostrix</td>
<td>Tetanus is a nervous system infection that is caused by the bacteria Clostridium tetani. Diphtheria is caused by the bacteria Corynebacterium diptheria and causes respiratory or other invasive disease. The bacteria Bordetella pertussis causes pertussis, otherwise known as &quot;whooping cough&quot;.</td>
<td>Yes. Tdap vaccine should be provided once, followed by Td booster every 10 years. If pertussis protection is desired, there is no minimum time interval between last Td and Tdap administration.</td>
<td>Yes. Same as for CLD/ESLD.</td>
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<tr>
<td>Live*</td>
<td>Live Herpes Zoster (ZVL)</td>
<td>Another vaccine to prevent shingles disease (see earlier).</td>
<td>No. Recommend the newer inactivated vaccine (Shingrix) due to better immunogenicity.</td>
<td>No. Live vaccines are generally contraindicated after LT. Provide inactivated RZV vaccine (see earlier).</td>
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</tbody>
</table>

*‡ Live Herpes Zoster (ZVL) Live vaccines are generally contraindicated after LT. Provide inactivated RZV vaccine (see earlier).
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recommend inactivated vaccines to be given 2 weeks and live vaccines 4 weeks prior to LT to maximize response and safely proceed with immunosuppression. After LT, recommendations are to wait 3-6 months when immunosuppression is at maintenance, except inactivated influenza vaccine, which can be given effectively 1 month after LT. Vaccines should not be given during treatment for acute rejection, because increased immunosuppression may blunt vaccine response. Live vaccines should be avoided in immunosuppressed patients with LD and after LT.

Although there are theoretical risks of rejection with vaccination after solid organ transplantation (SOT; e.g., nonspecific immune activation or induction of T/B-lymphocyte responses against alloantigens), there are no clinical data to support this concern. Therefore, vaccination in patients with LD and LT far outweigh any potential risk and should be encouraged.

Routine vaccine schedules recommended for patients with LD and LT recipients are noted in Table 1, according to the Infectious Diseases Society of America (IDSA), American Society of Transplantation (AST) Infections Diseases Community of Practice, and the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP).

Table 1. Continued
<table>
<thead>
<tr>
<th>Vaccine*</th>
<th>Brand Name(s)</th>
<th>Clinical Description</th>
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<tr>
<td>Inactivated</td>
<td>JEV</td>
<td>Ixiaro</td>
<td>JEV is transmitted by mosquitoes and is endemic to Asia and the Western Pacific. It causes neuroinvasive disease.</td>
<td>Yes, for travel to endemic areas. Two-dose series at 0 and 28 days is recommended for long-term travelers (≥1 month) or those with short-term frequent or extensive rural travel. Consider booster dose if at continued risk and primary series received ≥1 year prior.</td>
</tr>
<tr>
<td>MenACWY†</td>
<td>Menactra, Menevo</td>
<td>Infection with the bacteria Neisseria meningitides can lead to meningitis and disseminated infection (meningococcemia) with shock. MenACWY protects against four serogroups: A, C, W, and Y.</td>
<td>Yes, for travel to high endemicity areas such as the meningitis belt of sub-Saharan African and prior to Saudi Arabia travel for Hajj or Umrah. If primary series not received, two doses at 0 and ≥2 months with booster every 5 years if continued risk for exposure.</td>
<td>Yes, Same as for CLD/ESLD.</td>
</tr>
<tr>
<td>Inactivated poliovirus (IPV)</td>
<td>Ipol, multiple combination vaccines</td>
<td>Poliovirus causes neuroinvasive disease and is transmitted by fecal-oral and pharyngeal route. Endemic in certain parts of Africa and Asia.</td>
<td>Yes, for travel to high-risk areas. If primary series not received, three doses total at 0 and 1-2 months, followed by 6-12 months after second dose. Vaccinated adults are candidates for one lifetime booster if traveling to high-risk region.</td>
<td>Yes, Same as for CLD/ESLD.</td>
</tr>
<tr>
<td>Rabies</td>
<td>Imovax, RabAvert</td>
<td>Rabies is a neuroinvasive infection caused by several neurotropic lyssaviruses. Prevalent in all continents, except Antarctica; transmitted by dogs and wild animals.</td>
<td>Yes, if potential risk for exposure. Pre-exposure and postexposure vaccinations are given as a three-dose (0, 7, and 21-28 days) or a four-dose (0, 3, 7, and 14 days) series, respectively. Pre-exposure vaccination is indicated for long-term travelers (≥1 month), planned animal contact, and/or remote from medical care. Booster doses every 6 months to 2 years may be recommended in certain high-risk individuals at ongoing risk to maintain appropriate serum titers.</td>
<td>Yes, Same as for CLD/ESLD. In immunocompromised hosts, a fifth dose of postexposure vaccination is recommended at day 28.</td>
</tr>
<tr>
<td>Inactivated typhoid</td>
<td>Typhim Vi (intramuscular)</td>
<td>Typhoid (enteric) fever is caused by the bacteria Salmonella typhi and is transmitted by the fecal-oral route. Fever and intestinal disease/diarrhea are most common, but extraintestinal disease can occur. Endemic worldwide but most prominent in low-resource areas with poor sanitation.</td>
<td>Yes, for travel to rural areas of tropical countries. One-dose injection, at least 2 weeks prior to travel to develop immunity. Booster dose every 2 years if ongoing risk.</td>
<td>Yes, Same as for CLD/ESLD.</td>
</tr>
<tr>
<td>Live‡</td>
<td>Cholera</td>
<td>Vaxchora (oral)</td>
<td>Infection with the bacteria Vibrio cholerae can lead to severe watery diarrhea and dehydration with electrolyte wasting.</td>
<td>Yes, for travel to areas of active cholera transmission. One oral dose should be received ≤10 days prior to potential exposure. Maybe, for travel to rural areas of tropical countries. Recommend inactivated vaccine if advanced LD due to better safety profile and comparable efficacy. Four oral capsule doses on days 1, 3, 5, and 7. Last dose should be ≥1 week prior to travel to develop immunity. Booster dose every 5 years if ongoing risk. Consider timing if LT anticipated.</td>
</tr>
<tr>
<td>Live typhoid</td>
<td>Vivotif (oral)</td>
<td>Another vaccine to prevent typhoid fever (see earlier).</td>
<td>Yes, for travel to rural areas of tropical countries. Consider timing if LT anticipated.</td>
<td>No. Live vaccines are generally contraindicated after LT. Provide inactivated typhoid vaccine (see earlier).</td>
</tr>
<tr>
<td>Yellow fever virus</td>
<td>YF-Vax</td>
<td>Yellow fever virus is transmitted by mosquitoes and is endemic to Africa and South America. It causes viral hemorrhagic fever and can lead to multiorgan failure.</td>
<td>Yes, if traveling to endemic areas. One dose provides lifelong immunity. Potential rare but serious adverse events include vaccine-associated viscerotropic disease (YEL-AVD) and neurological disease (YEL-AND). Consider timing if LT is anticipated.</td>
<td>No. Live vaccines are generally contraindicated after LT. Travel to endemic regions with yellow fever should be avoided.</td>
</tr>
</tbody>
</table>

* Anthrax, oral poliovirus, and smallpox vaccines are not readily available in United States.
† Additional indication for meningococcal vaccine includes asplenic patients, who should receive both MenACWYW and MenB (Bexsero, Trumenba).
‡ Risks and benefits of live vaccines in patients with advanced LD and decompensated cirrhosis should be carefully considered. An equivalent inactivated vaccine is preferred when available. Live vaccines are contraindicated in immunosuppressed patients with LD.
reduction in the incidence of HZ infection in subjects who were ≥70 years old. Although immunosuppressed patients were excluded from all of the aforementioned phase 3 studies, demonstrated efficacy of the new HBV and HZ vaccines in patients with expected decreased immunogenicity response (e.g., diabetes mellitus, stem cell transplantation) shows promise for improved immunogenicity in patients with LD and LT recipients, as compared with older vaccine preparations. Lastly, in October 2018, the FDA approved the expanded use of Gardasil-9 (Merck & Co., Inc., Kenilworth, NJ, USA), a recombinant vaccine against nine serotypes of human papillomavirus (HPV), to include men and women up to 45 years old. Studies on use of HPV vaccine in patients with LD or LT recipients are limited and suggest suboptimal serological response, with one study of 50 SOT recipients who received the quadrivalent HPV vaccine resulting in 52.6% to 68.4% serological response against the four serotypes. Nonetheless, SOT recipients remain at high risk for HPV-associated malignancy, and all eligible adults up to 45 years old should undergo vaccination.

Patients with LD and LT recipients who wish to travel should be evaluated months in advance by a travel clinic. In addition to vaccination, extensive counseling should be provided on destination-specific safe travel behaviors, food safety, minimizing exposure to endemic infections, prophylaxis for traveler’s diarrhea and malaria (and interactions with transplant rejection medications), insect protection, and posttravel care. Routine vaccines should be updated, with particular focus on HAV, HBV, tetanus, diphtheria, pertussis (Tdap), and measles, mumps, and rubella (MMR) vaccines. Table 2 lists the most common travel vaccines that may be indicated in patients with LD and LT recipients, as recommended by the AST and ACIP. The CDC Yellow Book provides additional in-depth information about travel health and infection prevention.

In conclusion, vaccine optimization in patients with LD and LT recipients is integral to the prevention of many communicable diseases. Vaccination should ideally occur in early LD and prior to LT, especially for live vaccines that are contraindicated after LT. Comprehensive counseling on travel health and vaccinations should be provided for travelers who are LT candidates and recipients.

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