

Practice Guideline



AASLD AST Practice Guideline on adult liver transplantation: Diagnosis and post-transplant management of non-graft-related complications

Abstract

Long-term mortality after liver transplantation (LT) largely reflects complications of immunosuppression, recurrent disease, and medical and surgical comorbidities, including metabolic syndrome, chronic kidney disease, cardiovascular disease, malignancies, and hernias. This document aims to provide best practice guidelines for the preventative and disease-specific management of non-graft-related complications in adult recipients beyond the first 90 days after liver transplant. A multidisciplinary writing group of transplant experts was tasked to formulate clinical questions (in PICO format) that arise during routine management of adult LT recipients. A systematic literature search was performed by a medical librarian. The expert panel reviewed the literature, generated guideline recommendations, and rated the level of evidence for each recommendation based on the Oxford Center for Evidence-Based Medicine. The panel categorized the strength of recommendations based on the level of evidence, risk–benefit ratio, and patient preferences. Multidisciplinary care and partnership between the transplant center and the primary care physician are essential for long-term care of the transplant recipient. Significant components of non-graft management guidelines are derived from retrospective cohort studies, systematic reviews, and extrapolation of data from the general population. This gap highlights the unmet need for robust prospective studies addressing the long-term care of liver transplant recipients.

Keywords: chronic kidney disease, de-novo cancers, metabolic disease, non-graft, quality of life, survival benefit

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Abbreviations: AASLD, American Association for the Study of Liver Diseases; ACS, American Cancer Society; AKI, acute kidney injury; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BMD, bone mineral density; CI, confidence interval; CKD, chronic kidney disease; CMV, cytomegalovirus; CNI, calcineurin inhibitors; COVID-19, coronavirus disease 2019; CRC, colorectal cancer; CVD, cardiovascular disease; DCD, donation after cardiac death; DDI, donor-derived infection; DHHS, Department of Health and Human Services; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; EVEROLIVER, Everolimus Liver Registry; GLP-1 RA, glucagon-like peptide-1 receptor agonists; HPV, human papillomavirus; HTN, hypertension; IBD, inflammatory bowel disease; ILTS–SETH, International Liver Transplant Society and the Spanish Society of Liver Transplantation Consensus Conference; IU, international unit; KDIGO, Kidney Disease Improving Global Outcomes; LDLT, living donor liver transplantation; LT, liver transplantation; MeTS, metabolic syndrome; MPA, mycophenolic acid; mTORi, mammalian target of rapamycin inhibitor; NAT, nucleic acid test; OR, odds ratio; PCP, primary care physician; PCSK9, proprotein convertase subtilisin/kexin type 9; PSC, primary sclerosing cholangitis; PTLT, post-transplant lymphoproliferative disorder; QOL, quality of life; RAS, renin–angiotensin system; RCT, randomized controlled trial; RSV, respiratory syncytial virus; SGLT2i, sodium–glucose cotransporter-2 inhibitors; SIR, standardized incidence ratio; SRTR, Scientific Registry of Transplant Recipients; uNGAL, urinary neutrophil gelatinase–associated lipocalin; USPSTF, United States Preventive Services Task Force.

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INTRODUCTION

Liver transplantation (LT) remains a curative therapy for end-stage liver disease and certain primary liver malignancies. Advances in surgical techniques, organ procurement, and immunosuppression have led to significant improvement in long-term post-transplant survival.^[1] Data analysis from the Scientific Registry of Transplant Recipients (SRTR) for patients transplanted between 2012 and 2024 showed 5- and 10-year patient survival of 82% and 69%, respectively, with 11,436 patients having >10 years of functioning graft (personal communication with SRTR).

Long-term post-LT mortality is mainly due to the complications of immunosuppression, recurrent disease, medical comorbidities, and malignancies. Improvement in these outcomes would improve post-transplant patient and graft survival and quality of life (QOL). Partnership between the transplant center and primary care physician (PCP) is important in long-term care of LT recipients.

The purpose of this guideline document is to assist in the prevention, diagnosis, and management of medical and surgical comorbidities not related to liver allograft per se in adult recipients beyond the first 90 days of transplant. Evaluation and management of graft-related complications are discussed in a separate document.^[2]

METHODS

Literature search strategies were developed in collaboration with a medical librarian for the concepts of wellness, pregnancy, medical complications, and non-graft-related surgical issues after transplantation in adult LT recipients. Databases searched included Ovid MEDLINE and Embase.com, and searches for gray literature were run in the Cochrane Library and relevant associated websites. The initial search was completed on May 15, 2023. All searches were limited to English, humans, and from January 1, 2016, to the date of the search. MEDLINE and conference abstract records were excluded from the Embase search.

Studies were selected for inclusion in the systematic review of evidence if they met the following criteria: (1) peer-reviewed full-text articles; (2) included LT recipients; and (3) included one of the outcomes of interest. Articles were excluded from the systematic review if they

were conference abstracts not published in peer-reviewed journals, editorials, commentaries, case reports, narrative reviews, consensus documents, and letters; full-text articles that were not available in English; and studies that did not report on outcomes of interest.

A total of 1461 unique studies met the search requirements. Based on titles and abstracts, 296 articles were continued to full-text review, and 83 articles were excluded from data extraction. A total of 83 studies provided data that informed the recommendations. Data were not extracted from excluded articles, but these were available as discussion or background references. An updated search was conducted in December 2024, and relevant articles were also included. Additional articles not identified in the search but thought to be key to the evidence needed to formulate recommendations were occasionally included.

Guideline statements were developed based on available evidence, with the level of evidence assessed by the Oxford Grading system.^[3] The strength of recommendations was based on the level of evidence, risk–benefit ratio, and patient preferences. Recommendations were graded as “strong” when supporting evidence was robust and consistent to allow adoption as standard of care. Recommendations were graded as weak when the evidence was weaker or inconsistent and alternative approaches were available, to allow clinicians to be flexible in their decision-making. Agreement or disagreement on each guideline or guidance statement was voted upon by each workgroup member via the Alchemer survey platform. Consensus, defined as at least 80% agreement among members, was achieved on all statements within this document.

Panel composition, review process, and funding

The guideline was developed by a multidisciplinary writing group. The guidelines were reviewed by the Practice Guidelines Committee, made available for public comment, approved by the American Association for the Study of Liver Disease (AASLD) Governing Board, and the AST Board of Directors. The AASLD Governing Board approved the final version on October 16, 2025. Conflict of interest was managed according to AASLD’s Code for the Assessment and Management of Conflict of Interest.^[4] This guideline was funded by AASLD.

WELLNESS AFTER TRANSPLANTATION

Nutrition and exercise

Question 1: What dietary recommendations should be made to adult liver transplant recipients?

Guidelines statements

1. Liver transplant recipients should be counseled to limit added sugar and saturated fats to <10% each of total daily calories, and sodium to <2300 mg/day (Strong, Level 5).
2. Liver transplant recipients should not use herbal and dietary supplements without discussing with their transplant providers (Strong, Level 4).
3. Liver transplant recipients should avoid foods known to interact with immunosuppressive therapy, particularly grapefruit (Strong, Level 3).
4. Liver transplant recipients should avoid the consumption of untreated water from lakes and rivers (Strong, Level 3).
5. Liver transplant recipients should avoid unpasteurized milk products, and raw or undercooked eggs and meats (particularly uncooked pork, poultry, fish, and seafood) (Strong, Level 3).

Rationale and background

Weight gain is common after LT, with high rates (exceeding 40%) of obesity [body mass index (BMI) >30 kg/m²], reflecting behavioral patterns and effects of immunosuppressive therapy.^[5,6] Post-LT obesity is associated with metabolic dysfunction, recurrent or de novo metabolic dysfunction–associated steatotic liver disease (MASLD), cardiovascular disease, and poor long-term outcomes.^[7–10] While there are no specific studies to inform dietary recommendations for LT recipients, in the absence of metabolic comorbidities,^[11] the Dietary Guidelines for Americans from the United States Department of Health and Human Services (DHHS) are widely applicable.^[12] They recommend a varied diet that limits added sugar and saturated fats to <10% each of daily calories, and sodium to <2300 mg/day. Office-based weight loss counseling often has limited efficacy in achieving weight loss in LT,^[13] but it can favorably impact metabolic risk factors such as diabetes control.^[14]

Herbal and dietary supplements (excluding mineral supplements like magnesium, calcium, and zinc) should be discouraged as they may affect calcineurin inhibitors (CNI) metabolism or lead to drug-induced liver injury.^[15,16] For example, ingestion of grapefruit, pomegranate, clementines, and black licorice may increase CNI levels, while St. John's Wort may reduce CNI levels.^[17,18] Consumption of untreated river and

lake water, untested well water, unpasteurized milk products, and raw and undercooked eggs and meats (pork, poultry, fish, and seafood) should be avoided.^[19–27]

Question 2: What types of exercises are best for adult liver transplant recipients?

Guidelines statement

6. Liver transplant recipients should participate in at least 150–300 minutes of moderate intensity or 75–150 minutes of vigorous intensity aerobic activity per week, along with muscle-strengthening activities of all major muscle groups at least 2 days a week (Strong, Level 2).

Rationale and background

Aerobic and strength training in LT recipients, who have adequately healed from the transplant procedure, is safe and may improve physical function, muscular and cardiorespiratory fitness, and QOL.^[28–30] A 12-month supervised program that combined aerobics with strength training for 1 hour 3 times per week was associated with improvement in general health, vitality, and mental health at 12 months, whereas the control group had decreased QOL over time.^[28] The Physical Activity Guidelines for Americans from the US DHHS recommend at least 150–300 minutes of moderate intensity or 75–150 minutes of vigorous intensity aerobic activity per week, along with muscle-strengthening activities of all major muscle groups at least 2 days a week.^[31]

Health behaviors

Question 3: What factors influence self-management and health behaviors after adult liver transplantation?

Guidelines statements

7. Liver transplant recipients with medical nonadherence (missed appointments, missed laboratory testing, subtherapeutic immunosuppression levels) should be screened for substance use disorder, anxiety, and depression (Strong, Level 3).
8. Liver transplant recipients with medical nonadherence should be screened for food insecurity, transportation insecurity, and insufficient social support (Strong, Level 4).

9. Liver transplant recipients should avoid alcohol intake irrespective of the etiology of liver disease (Strong, Level 4).
10. Discussion of lifestyle changes to improve sleep with at least 7 hours of sleep per night in adult liver transplant recipients may be considered (Weak, Level 4).
11. Liver transplant recipients should receive annual depression screening and assessment of alcohol use (Strong, Level 3).

Rationale and background

Health behaviors significantly influence self-management and QOL, especially in chronic conditions. Physical function, appetite, dietary issues, and medications are major challenges at 3–6 months post-LT.^[32] A randomized controlled trial of postoperative remote monitoring intervention improved physical function and general health at 90 days after LT.^[33] Figure 1 shows targets to improve QOL, intervention, and areas of future research. Factors such as anxiety, depression, fatigue, physical health, cognition, social and emotional well-being, mental functioning, medication side effects, and nonadherence impact QOL.^[34] In a meta-analysis of 48 articles, pooled depression among 5170 LT recipients was 24.5% (95% CI: 19.5%–30.4%). Recipients transplanted for alcohol-associated liver disease had 14% higher odds of depression compared with those without. Moreover, depression was associated with increased odds of mortality (OR = 1.82; 95% CI 1.08–3.07), graft loss (OR = 2.82; 95% CI 1.64–4.24), and graft rejection (OR = 1.76; 95% CI 1.12–2.77).^[35]

Impaired sleep quality, insomnia, sleep disturbance, or sleep dissatisfaction affects about half of LT recipients and is more common than in other solid organ transplant recipients.^[36] Li et al., using data from the United Kingdom Biobank for participants primarily of European ancestry aged 38–73 years, identified a nonlinear association between sleep duration (~7 h as the optimal sleep) and cognitive function, mental health, and brain structure.^[37] Extrapolating this data to LT recipients who have poor quality sleep may benefit from at least 7 hours of sleep. Post-LT alcohol use is associated with graft steatosis, steatohepatitis, and more rapid progression to cirrhosis^[38] and has been implicated in graft rejection.^[39] Return to work occurred in less than half of recipients after LT and is higher among those with higher level education, pre-LT employment, and less physically demanding (eg, “desk”) occupations.^[40]

Bone health after LT

Question 4: What are the optimal management strategies for prevention and pharmacological

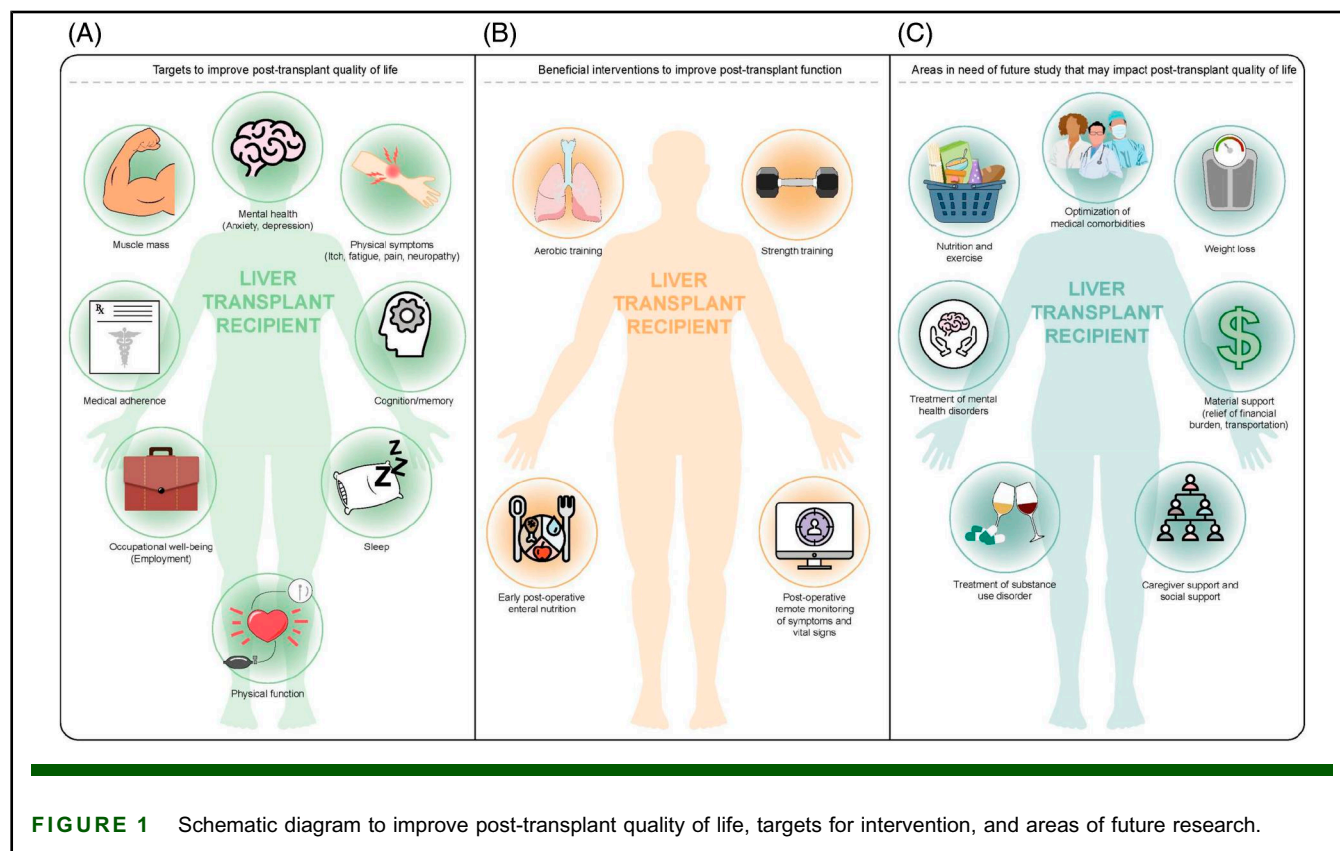
management of osteopenia and osteoporosis in adult liver transplant recipients?

Guidelines statements

12. Liver transplant recipients should undergo a bone density scan once they are on stable immunosuppression, typically after 6 months of transplant (Strong, Level 2).
13. In liver transplant recipients with osteoporosis or osteopenia, serial dual-energy x-ray absorptiometry (DEXA) monitoring should be performed every 1–2 years until findings are stable (Strong, Level 3).
14. Liver transplant recipients with osteoporosis or osteopenia should be counseled to maintain a daily calcium intake of > 1200 mg per day (including diet plus supplement, if needed) (Strong, Level 3).
15. Liver transplant recipients with osteoporosis should maintain serum 25-hydroxyvitamin D (25[OH]D) $\geq$ 30 ng/mL with a preferred range of 30–50 ng/mL (Strong, Level 3).
16. Liver transplant recipients with osteoporosis and with 25[OH]D < 30 ng/mL should receive vitamin D3 supplementation at a daily dose of 1000–2000 IU daily (Strong, Level 3).
17. Pharmacologic therapy should be initiated for liver transplant recipients with (1) osteopenia and a history of fragility fractures of the hip or spine (osteoporosis equivalent), (2) a T-score of ≤ -2.5 or lower, or (3) Fracture risk assessment tool (FRAX) 10-year probability for major osteoporotic fracture $\geq$ 20% or the 10-year probability of hip fracture $\geq$ 3%. Appropriate initial pharmacologic therapy for patients who fit the criteria includes, but is not limited to, alendronate, denosumab, risedronate, and zoledronate (Strong, Level 1).
18. Liver transplant recipients meeting criteria for osteoporosis should be referred for physical therapy to prevent falls (Strong, Level 1).

Rationale and background

Established risk factors for low bone mineral density (BMD) include female sex, older age, low BMI, diabetes, malnutrition, sedentary lifestyle, vitamin D and calcium deficiency, long-term heparin or warfarin use, corticosteroids, medical comorbidities, low



ambient light exposure, hypogonadism, previous falls and fractures, parental history of hip fracture, tobacco, and alcohol intake.^[41,42] Patients are usually weaned off corticosteroids within 3–6 months after LT. Although there is no data on starting BMD monitoring in LT recipients, it should be started once the patients are on stable immunosuppression, typically 6 months after LT. BMD in the lumbar spine recovers after LT, but this is not observed in the femoral neck or thoracic spine. Pre-LT low BMD, pre-LT fractures, post-LT duration of corticosteroid use, and age are the factors implicated in fragility fractures.^[41] In a meta-analysis, the incidence of post-LT osteopenia, osteoporosis, and fractures was 35%, 12%, and 20%, respectively, with vertebral fracture incidence at 11% and hip fracture at 0.9%.^[43] Age ≥ 60 years, post-LT DM, and cholestatic liver disease were associated with post-LT fractures despite bisphosphonate therapy.^[44] Older post-transplant studies had suggested efficacy for bisphosphonate therapy in improving BMD.^[45,46] Given the lack of large, prospective studies in the LT population, recommendations (Table 1) are adapted from existing guidelines for the general population.^[47]

Vaccinations after LT

Question 5: What is the recommended vaccination schedule for adult liver transplant recipients?

Guidelines statements

19. Liver transplant recipients should discuss vaccinations with their providers in addition to following the guidance by the Advisory Committee on Immunization Practices of the Centers for Disease Control recommendations for immunocompromised adults (Strong, Level 1).
20. Liver transplant recipients should not receive live virus vaccines (Strong, Level 1).
21. Household contacts of liver transplant recipients should avoid vaccinia/smallpox and polio vaccine but may receive other live attenuated vaccines when no inactivated alternatives are available, as with measles, mumps, or rubella, while exercising diligent handwashing for 2 weeks (Strong, Level 4).
22. Liver transplant recipients should consult with a travel medicine specialist before traveling to regions with higher rates of infection and be advised on vaccine-preventable illnesses and antimicrobial prophylaxis based on destination-associated infection risks (Strong, Level 4).

TABLE 1 Preventing major osteoporotic fractures in liver transplant recipients

Strategy (reference, online sources)	Recommendations	Indications	Frequency of monitoring
BMD assessment	- DXA scan	Pre-LT At least 6 mo post-LT	Every 1–2 y if baseline osteopenia or osteoporosis Age-appropriate if normal baseline BMD
Vitamin D status assessment	- Assess serum 25(OH)D levels - Target ≥ 30 ng/mL	All LT recipients	Not established
Nutrition supplementation	- Calcium 1200 mg/day - Vitamin D 600 IU/day	Osteopenia or osteoporosis	Not established
Lifestyle	- Assess for prior falls - Assess for prior fracture without trauma - Weight-bearing exercise - Improving balance to reduce falls risk - Correct visual impairment - Avoiding sedatives, tranquilizers, muscle relaxants - Avoid postural hypotension - Using canes or walkers for stability - Avoiding house clutter - Avoiding slippers, wearing supportive footwear - Avoiding alcohol/tobacco	Osteopenia or osteoporosis	Not established
Assess additional causes of bone loss	- Assess thyroid function - Assess-free testosterone (males), menopausal status (females)	Osteopenia or osteoporosis	Not established
First-line medical therapy	- Oral bisphosphonates +calcium and vitamin D	Osteoporosis Osteopenia and FRAX 10-year probability for major osteoporotic fracture $\geq 20\%$ or the 10-year probability of hip fracture $\geq 3\%$ (in the United States)	BMD via DXA scan every 1–2 y
Second-line medical therapy consult with specialist (eg, rheumatology, endocrinology)	- IV bisphosphonates - Calcitonin - Selective estrogen receptor modulators - Estrogen hormone therapy - Parathyroid hormone analogues RANK ligand inhibitors - Sclerostin inhibitors	Intolerance or lack of efficacy of first-line therapy	N/A

Note: Osteopenia: T-score between -1.0 and -2.5 .

Osteoporosis: T-score < -2.5 or history of fragility fracture irrespective of BMD. Fragility fracture is defined as a fracture sustained from a force similar to a fall from a standing position or less that would not have occurred in healthy bone, except for fractures of the skull, face, fingers, and toes. T-score between -1.0 and -2.5 and high FRAX score www.shef.ac.uk/FRAX.

Abbreviations: BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; LT, liver transplantation.

Rationale and background

Recommended vaccinations in adult LT recipients mirror those for the general population. However, distinguishing themes in LT recipients include: strict avoidance of live vaccines,^[48] expanded age-based thresholds compared with the general population,^[49] and deferring vaccinations for 3–6 months after LT or after the treatment of acute allograft rejection due to a reduced response to the vaccine (immunogenicity of vaccines remains attenuated but to a lesser extent under subsequent maintenance immunosuppression).^[50,51] Recommended vaccinations for LT recipients are summarized in Table 2.^[51,86,88] Influenza and coronavirus disease of 2019 (COVID-19) vaccinations are discussed in the section on post-LT infections. Household contacts of LT recipients should generally avoid live vaccines, particularly vaccinia/smallpox vaccines and oral polio vaccines, if there are alternative vaccines available (eg, for influenza and varicella).^[50,51,89,90] If live attenuated viral vaccines are the only option, household members may still get vaccinated (eg, measles, mumps and rubella, or rotavirus for infants) while exercising infection prevention measures such as frequent hand-washing for the first 2 weeks, when viral shedding is likely to be at its peak (longer if oral polio vaccine).^[51,91,92]

Vaccination recommendations change with new vaccines and evolving infection patterns and risks, hence the continually updated Centers for Disease Control (CDC) guidance on vaccinations is a valuable resource.^[88] LT recipients are advised to discuss vaccinations with their providers as well, in case the CDC guidance is controversial. LT recipients should consult a travel medicine specialist before traveling to destinations with higher rates of endemic infections, such as yellow fever or hepatitis A, for guidance on additional vaccinations, passive immunization, and prophylactic antimicrobials depending on the destination and patient factors.^[93–95]

Reproductive health

Question 6: How can maternal, fetal, and graft outcomes be optimized in adult liver transplant recipients?

Guidelines statements

23. In liver transplant recipients of childbearing age, addressing contraception and pregnancy is recommended (Strong, Level 5).
24. In adult liver transplant recipients, pregnancy should be delayed for at least one year after transplant and until graft function has been stable for at least six months (Strong, Level 3).

25. In adult liver transplant recipients, a multidisciplinary approach is advised for pregnancy care involving transplant providers and maternal-fetal medicine specialists (Strong, Level 5).

Rationale and background

The number of childbearing aged women LT recipients continues to increase.^[96] In a meta-analysis of 1131 pregnancies in 833 LT recipients, mean maternal age at pregnancy was 20–32.2 years (pooled rate=27.8 y) and time from LT to pregnancy was 10.7–184.8 months (pooled rate=59.7 months).^[97] Improved pregnancy outcomes occur when graft function and immunosuppression regimens are stable, typically within 12–24 months post-LT. An interval of <12 months from LT to pregnancy compared with >12 months is associated with significantly lower live birth rates (80% vs. 98%) and higher rejection rates (46% vs. 11%).^[98,99] Another report found the lowest birth weight (2213 g) and highest preterm (<37 wk) birth rates (58.7%) when the time from LT to pregnancy is <2 years.^[94] A longer interval from LT to pregnancy permits graft stability and modification of immunosuppression to avoid teratogenic medications before conception. Unintended pregnancies frequently occur within 12 months of LT, often due to a lack of patient awareness of restored reproductive function and insufficient contraception use.^[100] Patients often prefer to discuss pregnancy and contraceptive options with transplant providers.^[101–103] A discussion of family planning to understand their reproductive intentions and to address knowledge gaps ideally should occur pre-LT and continue during post-LT care to help prevent unintended pregnancy and consequent worse outcomes.^[101,104,105] Guidance on immunosuppression and pregnancy-related issues in LT recipients was comprehensively reviewed in the AASLD reproductive health and liver disease practice guidelines, including a discussion of reproductive considerations for male LT recipients.^[104]

Overall, live birth rates compare favorably to the general population, with reported ranges 71%–85.6% in LT patients.^[97,106,107] Preterm delivery rates in LT recipients were 27.8%–32.1% compared with 10.4% in the general population.^[96,97,107] Pregnant LT recipients are at higher risk for gestational diabetes, and hypertensive disorders, including preeclampsia, occur more frequently.^[97,104,106] Hypertension and preeclampsia are associated with preterm delivery and intrauterine growth restriction in LT recipients, with rates ranging from 12.5% to 21.9%, compared with 4%

TABLE 2 Recommended vaccinations in liver transplant recipients

Organism and currently available vaccines	Recommendation	CEBM level of evidence and references
<i>Influenza A/B vaccines</i> <i>Inactivated</i> (inactivated vaccine is most well-studied) High dose inactivated quadrivalent MF59-adjuvanted inactivated (caution, the live virus vaccine is administered as a nasal spray and should be avoided)	One dose seasonally	1 ¹ [52–59]
^b <i>Streptococcus pneumoniae vaccines</i> Polysaccharide conjugated vaccine (PCV) 13, 15, 20, and 21 valent are available Pneumococcal polysaccharide (unconjugated) vaccine (PPSV) 23 valent	ACIP <i>No previous PPSV23 or PCV 13, 15, or 20:</i> Give 1 dose of PCV15 followed by PPSV23 $\geq$ 8 wk later, or 1 dose PCV20 or PCV21. <i>Only PPSV23 previously:</i> Give 1 dose of PCV15 or PCV20 or PCV21 $\geq$ 1 y after PPSV23. Do not redose PPSV23. <i>Only PCV13 previously:</i> Give 1 dose of PCV20 or PCV21 $\geq$ 1 y after PCV13 or give PPSV23 $\geq$ 8 wk later. <i>PCV13 and 1 dose PPSV23 previously:</i> Give 1 dose of PCV20 or PCV21 $\geq$ 5 y after last vaccine dose or give PPSV23 $\geq$ 8 wk after the last PPSV23 dose. IDCOP Give PCV13 followed by PPSV23 $\geq$ 8 wk later. Repeat PPSV23 every 5 y.	1 ¹ [60–62]
<i>Varicella, recombinant zoster vaccine</i> (caution: the live vaccine is also injectable and should be avoided)	The US CDC recommends that all adult liver transplant recipients aged $\geq$ 19 y receive 2 doses of VZVr once; if given pre-transplant, no additional doses are needed.	2 ² [63–65]
<i>Tetanus and diphtheria (toxoids) (Td) with acellular pertussis (antigens) (Tdap)</i>	ACIP and IDCOP 1 dose Tdap, then Td or Tdap booster every 10 y. At least 1 dose of pertussis vaccine (TdAP) in adulthood for women of childbearing age and those in contact with children.	2 ² [66,67]
<i>COVID-19 vaccines</i> mRNA vaccines (use the latest version) Protein subunit adjuvanted vaccine	ACIP Patients may receive a booster of any approved SARS-CoV-2 vaccine at least once every 6 mo; additional doses no more frequently than every 2 mo can be considered at the direction of a clinical provider.	1 ¹ [68–71]
<i>Hepatitis A</i> (inactivated and recombinant)	ACIP (at-risk patients, which would include LT recipients) and IDCOP 2 or 3 dose regimens, depending on the vaccine. Boosters may be required for waning immunity, especially if at risk, eg, planned travel to an endemic area.	2 ² [72,73]
<i>Hepatitis B</i> Recombinant and includes conventional (single dose and high dose) and CpG-adjuvanted vaccines	ACIP and IDCOP Vaccinate with 3 or 4 doses (conventional, high dose age $\geq$ 20) or 2 doses (CpG-adjuvanted) regimens and check titers $>$ 4 wk post-vaccination. <i>Vaccinated but anti-hepatitis B surface antibody titer $<$ 10 IU/L:</i> Repeat vaccination series or give single dose vaccine (consider high dose vaccine) and recheck titers $>$ 4 wk post-vaccination.	2 ² [74–76]
<i>Human papillomavirus</i> Inactivated vaccine (since 2016, only the 9-valent vaccine is available in the United States)	IDCOP 3 dose regimen (complete series if started before LT) in both female and male adults up to age 45. ACIP recommends up to age 26, and case by case for ages 27–45).	2 ² [77,78]
<i>Respiratory syncytial virus</i> Recombinant protein subunit vaccine	ACIP Considers use in adults age $\geq$ 50 y, single dose Anticipated evolving guidance given recent FDA approval.	4 ⁴ [79]
<i>Polio, inactivated</i> (caution: the live vaccine is administered orally and should be avoided)	ACIP and IDCOP If unvaccinated (rare)	2 ² [80]

TABLE 2. (continued)

Organism and currently available vaccines	Recommendation	CEBM level of evidence and references
<i>Neisseria meningitides</i> Quadrivalent ACWY (MenACWY) and serogroup B vaccines (MenB)	ACIP and IDCOP For at-risk unvaccinated groups or if >5 y since last vaccination <i>College students, members of military, travel to endemic areas:</i> 1 dose MenACWY (booster q 5 y), if age 18–23 consider course of MenB (booster 1 y later and then q 2–3 y) <i>Asplenia, eculizumab or ravulizumab therapy, HIV infection:</i> 2 doses MenACWY ≥ 8 wk apart (booster q 5 y) and course of MenB (booster 1 y later and then q 2–3 y)	2 ^[81,82]
<i>Hemophilus influenza type B</i> Polysaccharide conjugate vaccine	Not routinely recommended in adult SOT (routine in children) recipients except if asplenia (serologic assessment recommended)	3 ^[83]
<i>Rabies virus</i> Inactivated vaccine	Not routinely recommended. Post-exposure vaccination recommended (5-dose regimen days 0, 3, 7, 14, and 28) with immunoglobulin day 0 Travel to endemic areas requires serologic monitoring post-vaccination.	4 ^[84]
<i>Mpox</i>	ACIP Not routinely recommended for the general population For at-risk adults only.	4 ^[85]

Note: These recommendations are based on the Advisory Committee on Immunization Practices of the Centers for Disease Control recommendations for immunocompromised adults (age 19 or older) and supported by the American Society of Transplantation Infectious Disease Community of Practice guidance in adult solid organ transplant recipients.^[51,86,87]

^aThe ACIP recommends annual vaccination in immunocompromised adults with either inactivated or recombinant quadrivalent influenza vaccines. The IDCOP broadly recommends annual influenza vaccination in SOT recipients. At present, only quadrivalent influenza vaccines are available in the United States.

^bConjugated vaccine administration preceding unconjugated vaccine administration increases the response and extends serotype coverage. This is recommended by the ACIP and the ASTIDCP.

Abbreviations: ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control; CEBM, Centre for Evidence-Based Medicine; FDA, Food and Drug Administration; HIV, human immunodeficiency virus; IDCOP, Infectious Diseases Community of Practice (American Society of Transplantation); LT, liver transplant; SOT, solid organ transplant.

in the general US population.^[97,98,106] Cesarean delivery rates, severe maternal morbidity, hospital length of stay, and cost are higher in LT recipients.^[96,97,108] The high prevalence of obstetric complications supports a higher risk classification of post-LT pregnancies.^[107]

Question 7: What is an ideal approach to immunosuppression and monitoring graft function during pregnancy in adult liver transplant recipients?

Guidelines statements

26. Mycophenolic acid products are contraindicated in pregnancy due to the risk of miscarriage and birth defects and should be discontinued at least 6 weeks before conception for women and 90 days for men (Strong, Level 1).
27. Calcineurin inhibitors may be used during pregnancy, and trough levels should be monitored along with liver tests to guide dosing. Trough levels should be obtained more frequently during pregnancy (Strong, Level 4).

28. Azathioprine and corticosteroids are acceptable to be used during pregnancy (Strong, Level 4).

Rationale and background

In a meta-analysis of 12 studies with 838 pregnancies, tacrolimus, sirolimus, cyclosporine, azathioprine, and mycophenolic acid (MPA) products use were 60%, 27%, 20%, 16%, and 3%, respectively.^[107] In a meta-analysis of 38 studies with 1131 pregnancies, pooled live birth rates (78%), preterm birth rates (30%), and miscarriages (18%) were similar in tacrolimus or cyclosporine predominant regimens.^[97] Live birth rates are lower (70%), and rates of miscarriage are higher (21%) in MPA-containing regimens.^[97,99] Data on rejection during pregnancy are limited to a few studies, with reported rates ranging from 4% to 7.7%.^[96,99]

CNI is considered compatible with pregnancy.^[104] Trough levels should be closely monitored due to physiological changes affecting tacrolimus

metabolism.^[109] A suggested frequency for monitoring levels during pregnancy is every 2–4 weeks, but this should be individualized based on the patient's medical history, graft function, and course of pregnancy.^[104] MPA is contraindicated in pregnancy due to the risk of congenital malformation and spontaneous abortion. The Food and Drug Administration (FDA) recommends MPAs should be discontinued at least 6 weeks before conception for women and 90 days for men.^[104] Mammalian target of rapamycin inhibitors (mTORi) use is not recommended due to limited safety and outcomes data in pregnancy.^[104]

Infectious complications

Question 8: What are the optimal non-vaccine strategies to prevent infection after liver transplant?

Guidelines statements

29. In treatment-naïve liver transplant recipients with latent tuberculosis, therapy with isoniazid 300 mg once a day plus pyridoxine (vitamin B6) 50 mg once a day should be instituted within 6 months post-transplant once graft function is stable. If therapy is started pre-transplant, rifampin 300 mg once a day for 4 months can be used as well (Strong, Level 1).
30. In liver transplant recipients, prophylaxis of *Pneumocystis jiroveci* pneumonia should be continued for 6 months post-transplant with trimethoprim-sulfamethoxazole or atovaquone (Strong, Level 2).
31. Liver transplant recipients with two or more risk factors (renal replacement therapy pre-, peri- or post-transplant, needing re-operation including anastomotic leakage or repeat laparotomies, re-transplant, receiving transfusion of ≥ 40 units of cellular products or having had a choledochojejunostomy) should receive prophylaxis with fluconazole for 2–4 weeks due to increased risk of invasive fungal infections, particularly candidemia (Strong, Level 2).
32. Liver transplant recipients should avoid exposure to high-risk pets, which include rodents, reptiles, and birds (Strong, Level 5).

Rationale and background

Infection is a leading cause of death in LT recipients.^[110–112] Nosocomial infections and donor-

derived infections (DDI) typically occur during the first month of LT; opportunistic infections like cytomegalovirus, *Pneumocystis jiroveci* pneumonia (PJP), and tuberculosis occur from 1 to 12 months post-LT; and community-acquired infections usually occur after 6 months post-LT (Figure 2).^[112,113] Respiratory viral infections, including COVID-19, influenza, and respiratory syncytial virus (RSV), are more severe in LT recipients.^[114]

Pre-LT infections closer to the timing of LT increase postoperative morbidity.^[112] In the early post-LT period, bacterial, including multidrug-resistant infections (25%) and fungal infections (40%), are common with high mortality rates ranging from 25% to 67%.^[115–117] Risk factors for these infections are pre-LT infections,^[112] mechanical ventilation or prolonged intensive care unit stay, renal insufficiency including renal replacement therapy, and re-operation or hepatic artery complications, needing re-operation including anastomotic leakage or repeat laparotomies, re-transplantation, transfusion of ≥ 40 units of cellular products, choledochojejunostomy, and *Candida* colonization in multiple sites.^[116,118,119] Additional risk factors for fungal infections are MELD ≥ 30 and living donor liver transplant (LDLT). Patients with ≥ 2 risk factors are given 2–4 weeks of antifungal prophylaxis.^[120–122] Oral azole-based therapy is most utilized, although low-dose amphotericin (1 mg/kg/d) and echinocandins have been proven safe and effective in preventing invasive fungal infection.^[123–125] Pre-LT testing for latent tuberculosis is indicated. If latent infection is noted, then therapy can be started before LT or within 6 months of LT once graft function is stable.

While response to COVID-19 vaccines is diminished in LT recipients, vaccination is still recommended (statement 19, Table 3). Monoclonal antibodies are effective at reducing the risk of COVID-19 infection among LT recipients as supplement to vaccination although availability is determined by activity against circulating variants.^[151–153] Influenza infection has been associated with a higher rate of pulmonary and extrapulmonary complications, development of rejection with graft dysfunction, prolonged shedding of influenza virus, and increased drug resistance.^[154] Annual vaccination is critical to prevent infection and is associated with improved outcomes among those who develop breakthrough infections despite vaccination (Table 3).^[51,52,155] Given reduced humoral responses in LT recipients, especially within the first 3 months post-transplant or following treatment of rejection, vaccination of all close contacts is recommended.^[51] Two doses of the influenza vaccine separated by 1–3 months, as well as use of either high-dose or adjuvanted vaccine, may improve vaccine responses.^[156] Live attenuated influenza vaccines are not recommended for transplant patients or their close contacts.^[157,158] Post-exposure prophylaxis with oseltamivir, zanamivir, or baloxavir is approved. Prophylaxis

Timeline of Common Post-transplant Infections

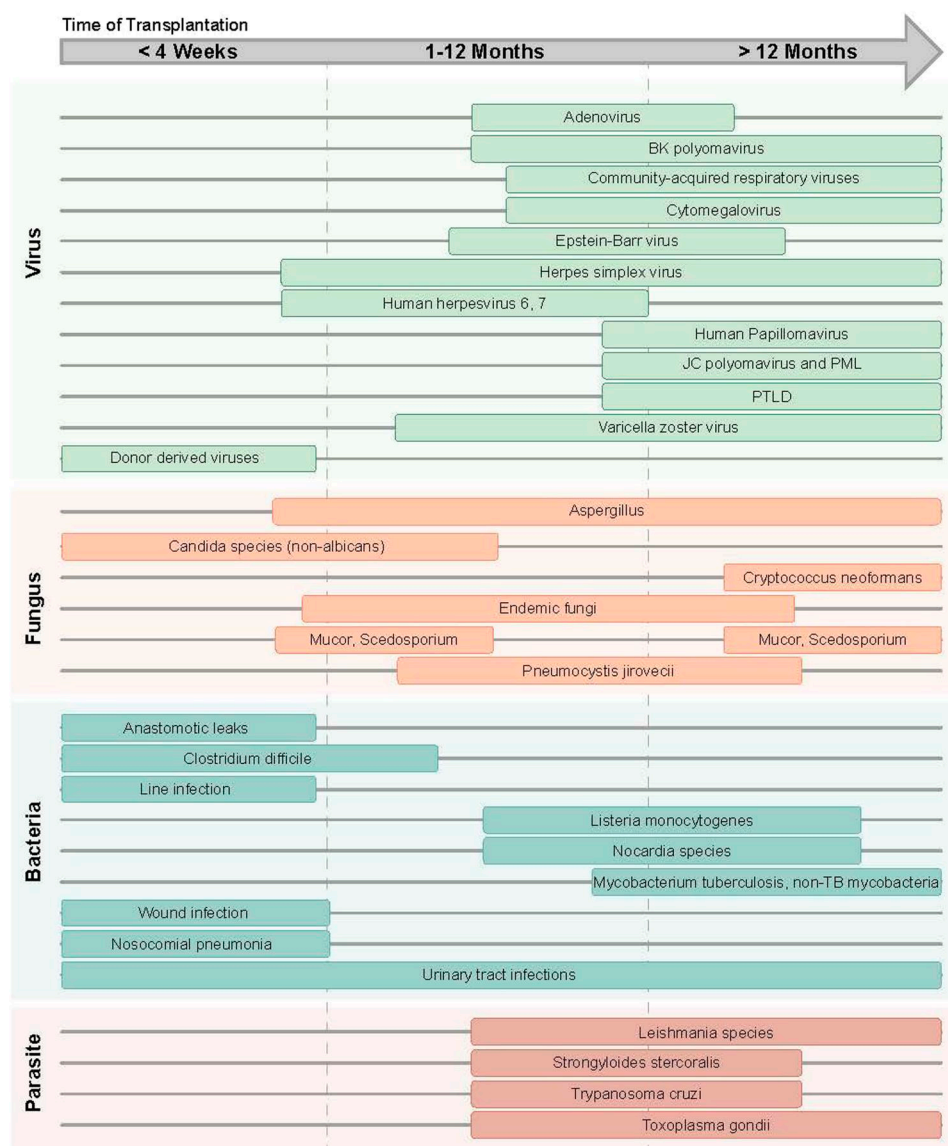


FIGURE 2 Time course of infection based upon time from the index liver transplant. Abbreviation: PTLD, post-transplant lymphoproliferative disorder.

is not recommended in vaccinated but exposed LT recipients. For those with exposure, rapid initiation of empiric treatment is preferred; if therapy is not started within 48 hours of first exposure, defer therapy until symptoms develop.^[158] Early treatment of individuals in close contact with the patient can reduce the risk of transmission.^[159]

Any approved neuraminidase inhibitor (oral oseltamivir, intravenous peramivir, or inhaled zanamivir) can be used for influenza treatment with dosing based on renal function. While the best results occur when therapy is started within 48 hours of symptom onset,

therapy may be effective in hospitalized patients and immunocompromised patients beyond this time.^[160] Baloxavir marboxil is approved for treatment of influenza, but is not routinely recommended for immunocompromised patients because of the risk of resistance emergence; improved activity against influenza B and limited emergence for resistance in influenza B subtypes would favor its use even in LT patients with influenza B.^[159]

The impact of RSV is not well defined in LT recipients. One of the recently approved RSV vaccines should be recommended for all recipients and their

TABLE 3 Cancer screening recommendations in adult liver transplant recipients based on the American Cancer Society (ACS) and United States Preventive Services Task Force (USPSTF) guidelines, and are supported and supplemented by the International Liver Transplant Society and the Spanish Society of Liver Transplantation Consensus Conference (ILTS-SETH) working group

Cancer type by organ system	Screening guidance	OCEBM level of evidence [references]
Skin	^a <i>All patients</i> Annual full-body skin exam (more frequent surveillance in those with skin cancer) ACS recommends: monthly skin self-exams Limiting exposure to ultraviolet rays	2 ^[126–130]
Colorectal cancer	<i>All other patients (age ≥ 45) (ACS and USPSTF)</i> <i>Per the general population, but may consider colonoscopy every 5 y.</i> ^b <i>IBD (any age) without PSC:</i> Annual colonoscopy (not stool-based testing) with random biopsies if meeting surveillance criteria based on extent and duration of IBD ^b <i>IBD (any age) with PSC,</i> Annual colonoscopy (not stool-based testing) with random biopsies <i>PSC without IBD (any age)</i> Colonoscopy (not stool-based testing) every 5 y with biopsies (to assess for IBD)	1 ^[127,131–133] 1 2 3
Cervical and vulvar (also anal if HPV+)	<i>Female (age 21–65 USPSTF, 25–65 ACS)</i> <i>Per the general population,</i> includes pelvic exam, PAP and/or HPV testing If HPV+ and age ≥ 21 or sexually active, consider annual Pelvic exam, PAP with anal PAP testing	1 ^[77,126,127,134–140] 4
Breast	<i>Female (age ≥ 40)</i> <i>Per the general population</i>	1 ^[141]
Prostate	<i>Male (age 55–70 USPSTF, age ≥ 50 with 10 y life expectancy ACS)</i> <i>Per the general population</i> Consider annual PSA testing and DRE (joint decision making with the patient)	2 ^[142,143]
Lung cancer	<i>Smokers age 50–80 (current or within 15 y and ≥ 20 pack years).</i> <i>Per the general population</i> Annual low-dose CT chest All tobacco users should receive smoking cessation education and related medical intervention	1 ^[144–148] 1
^a Oropharyngeal	<i>Smokers (current or former), HPV infection, ALD</i> Referral to ear, nose, and throat exam within a year of LT	2 ^[77,144,149,150]

^aCancer-specific recommendations in LT recipients. There are no general population guidelines for clinical screening.

^bLT recipient subgroups are at increased risk for colorectal cancer, and colonoscopy is recommended over fecal-based test screening and surveillance.

Abbreviations: ACS, American Cancer Society; ALD, alcohol-associated liver disease; CT, computed tomography; DRE, digital rectal exam; HPV, human papilloma virus; IBD, inflammatory bowel disease; LT, liver transplantation; MASH, metabolic dysfunction-associated steatotic liver disease; OCEBM, Oxford Centre for Evidence-Based Medicine; PAP, Papanicolaou test; PSA, prostate-specific antigen; PSC, primary sclerosing cholangitis; USPSTF, United States Preventive Services Task Force.

close contacts consistent with approved indication of individual vaccine (Table 3).^[161,162] As there are no approved therapies for RSV, supportive measures are recommended. Guidelines for solid organ transplant recipients exist for most other post-transplant infections and can generally be applied to LT recipients.

Caution is also needed to minimize the recognized risk of bacterial, viral, and protozoal infection through consumption of contaminated food and water in immunosuppressed individuals, which can be extrapolated to LT recipients. In addition, caution to minimize the risk of zoonotic infection by avoiding high-risk pets, such as birds and reptiles, is also recommended for LT recipients.^[163,164]

Question 9: What is required if a donor-derived transmission is suspected in an adult liver transplant recipient?

Guidelines statements

33. In liver transplant recipients, suspicion of donor-derived infection must be reported by the Organ Procurement Organization and/or transplant center within 24 hours to the Organ Procurement and Transplant Network Patient Safety Portal (Strong, Level 5).
34. The transplant team should secure residual blood samples from donor and recipient(s) and retain all relevant cultures for further investigation by the Disease Transmission Advisory Committee or the Centers for Disease Control when donor-derived infections are suspected (Strong, Level 3).

35. The transplant team should review available donor serology and cultures for all early post-transplant infections, and transplant infectious diseases or infectious diseases specialists should be consulted when a donor-derived infection is suspected (Strong, Level 3).

Rationale and background

DDI can be anticipated when the donor is known to have an infection or unanticipated if infection is not known in the donor and inadvertently transmitted to the recipient.^[165,166] Expected DDI are common and can be prevented or mitigated through routine prophylaxis, monitoring, or early treatment.^[167,168] Unexpected DDI are rare (0.18% of all transplants performed); the risk is significantly greater from deceased donors, but disease transmission from living donors and indirect transmission from blood products have been described as well.^[169–171] Although rare, DDIs are associated with graft loss or death in about a third of cases, with higher rates when parasitic or fungal diseases are transmitted.^[169] If there is a substantial concern for the unexpected DDI, then a report must be made within 24 hours after learning about the event (OPTN Policy 15.5.B). A DDI should be suspected in all early post-LT infections, particularly if it involves an unusual pathogen or the recipient has an atypical post-LT course, including unexplained fever, unexplained hepatitis, or unexplained alteration of mental status. When DDI is suspected, careful review of donor cultures and history as well as other recipients from the same donor is indicated.^[172,173] Residual laboratory specimens should be preserved for further investigation by the Disease Transmission Advisory Committee or the Centers for Disease Control. Disclosing DDI to patients is the standard of care and should be documented according to the transplant center's policy.

Question 10: What is the optimal strategy for Cytomegalovirus prevention and treatment in adult liver transplant recipients?

Guidelines statements

36. In liver transplant recipients, when either the donor or recipient is cytomegalovirus seropositive, pre-emptive monitoring with weekly cytomegalovirus polymerase chain reaction testing for 100 days should be used for prevention, if the transplant center can implement the monitoring reliably (Strong, Level 1).

37. In liver transplant recipients, if the pre-emptive monitoring for cytomegalovirus cannot be performed reliably, then start valganciclovir 900 mg once a day (or renally adjusted) for 3 months (Cytomegalovirus Donor $\pm$ /Recipient+) or 6 months (Cytomegalovirus Donor +/Recipient-) (Strong, Level 1).
38. In the absence of herpes simplex and varicella zoster virus seropositivity in adult liver transplant recipients, letermovir can be substituted for valganciclovir if there is persistent neutropenia from valganciclovir prophylaxis (Strong, Level 2).
39. Letermovir does not have any activity for *Herpes simplex virus* or *Varicella zoster virus*. Hence, liver transplant recipients on letermovir for persistent neutropenia should receive prophylaxis with acyclovir, valacyclovir, or famciclovir if seropositive for *Herpes simplex virus* or *Varicella zoster virus* (Strong, Level 2).
40. In liver transplant recipients with Cytomegalovirus donor-/recipient- status or where pre-emptive monitoring is being used, oral acyclovir, valacyclovir, or famciclovir should be used to prevent herpes simplex virus and varicella zoster virus for at least 3 months after liver transplant (Strong, Level 2).
41. In liver transplant recipients, oral valganciclovir is the preferred treatment of cytomegalovirus infection (900 mg twice daily or renally adjusted) except when the viral load is $\geq 100,000$ IU/mL, impaired gastrointestinal absorption, or presence of severe infection, especially pneumonia, in which case intravenous ganciclovir is recommended (Strong, Level 1).
42. In liver transplant recipients, maribavir 400 mg twice daily is the preferred therapy for refractory or resistant cytomegalovirus with low viral load ($\leq 20,000$ IU); intravenous foscarnet should be used for patients with refractory disease and high viral load ($> 20,000$ – $50,000$ IU/mL), severe disease, or concern for poor gastrointestinal absorption (Strong, Level 1).
43. In liver transplant recipients on treatment for cytomegalovirus infection, monitoring of cytomegalovirus viral load should be performed once a week while on therapy. Therapy should be continued until cytomegalovirus viral load becomes undetectable, and then the patient should have weekly monitoring for 4 weeks off therapy; secondary prophylaxis is not recommended (Strong, Level 1).

Rationale and background

With routine prophylaxis, the incidence of herpes viral infections, including cytomegalovirus (CMV), is around 19%, with relatively low mortality.^[174] Risk of CMV infection is directly related to donor and recipient serostatus; the highest risk is with primary infection (donor seropositive, recipient seronegative or D+/R–), with intermediate risk in seropositive recipients (D–/R+ or D+/R+).^[175,176] CMV risk is low (<2%) if both the donor and recipient are seronegative (D–/R–). Prevention of CMV can be accomplished through serological matching of donors; however, this is not practical for every case, as it would significantly increase the wait times for LT. No CMV vaccine is approved to date.^[177] Universal antiviral prophylaxis with valganciclovir for 3–6 months after LT is the most widely used strategy.^[178,179] Pre-emptive therapy involves monitoring patients for viremia by CMV polymerase chain reaction (PCR) at regular intervals and administering antiviral medications if CMV replication occurs. In a randomized controlled trial (RCT) of 205 LT recipients D+/R– CMV status, the incidence of CMV disease was significantly lower with pre-emptive therapy (valganciclovir, 900 mg, twice daily until 2 consecutive negative tests a week apart) for viremia detected by weekly plasma CMV PCR for 100 days of LT) than with universal antiviral prophylaxis of valganciclovir 900 mg daily for 100 days (9% vs. 19%, $p=0.04$) with no significant difference in the rates of allograft rejection (28% vs. 25%), graft loss (2% vs. 2%), neutropenia (13% vs. 10%), or all-cause mortality at last follow-up (15% vs. 19%).^[174] Moreover, patients in the pre-emptive therapy arm had better CMV-specific immune responses, likely to reduce the late-onset CMV reactivation risk. Although there are clearly logistical challenges in pre-emptive monitoring in practice, it results in generally better outcomes.^[174,180–182] Prevention strategies for most patients should be for 3 months, and 6 months for those who receive lymphocyte-depleting therapies.

While valganciclovir is the most widely utilized antiviral for prevention, letermovir was noninferior to valganciclovir for prophylaxis of CMV disease over 52 weeks in kidney transplant recipients, with lower rates of leukopenia or neutropenia, supporting its use for this indication.^[183] The higher cost of letermovir limits its use to patients unable to tolerate valganciclovir prophylaxis, due to persistent neutropenia. Letermovir should not be routinely prescribed for treatment of active infections due to resistance risk.^[184] Letermovir also does not have activity against other herpes viruses, such as herpes simplex or varicella zoster.

CMV infection can present at any time post-transplant with a variety of symptoms, including asymptomatic viremia, CMV syndrome (fatigue, myalgias, fevers, neutropenia, and viremia), or CMV end-

organ disease. CMV infection typically occurs within 1–2 months of stopping prophylaxis, and within the first 3 months after LT or rejection treatment.^[185,186] CMV end-organ disease most commonly affects the gastrointestinal tract, including the liver; it is unique as viremia may be below the limit of detection and, if detectable, it may not correlate well with disease severity.^[185,186] While absolute treatment thresholds have not been established, persistent or rising viral load or detection in a non-immune host are common triggers for therapy.^[187] While valganciclovir is equally effective for most patients with CMV replication, intravenous ganciclovir is preferred for patients with gastrointestinal disease and poor oral absorption, patients with central nervous system disease, and patients with persistent replication despite 2 weeks of oral therapy. Many centers favor intravenous therapy for patients with high viral loads, above 50,000–100,000 IU/mL.^[179] Therapy is continued until viral load is undetectable by a sensitive assay for at least 1 assessment (most centers will ensure 2 negative tests before stopping) and clinical symptoms have resolved. Patients who have persistent replication or are refractory to current therapy, including persistent neutropenia, should have resistance assessed by genotypic analysis, which can guide therapy. For most LT recipients with refractory or resistant CMV infection, maribavir can be used as an oral option.^[188] However, those with resistant or refractory CMV infection with high viral loads (>20,000–50,000 IU/mL) require hospitalization, or failure of maribavir will require intravenous therapy, typically with foscarnet.^[189,190] Management of refractory or resistant CMV should be directed by a transplant infectious diseases specialist.^[185,186]

Oncological complications

Question 11: What are the recommendations for de novo cancer screening in adult liver transplant recipients, and do they differ from the general population?

Guidelines statements

44. Liver transplant recipients should receive age-appropriate cancer screening according to the United States Preventive Services Task Force or other organizations (Strong, Level 1).
45. Liver transplant recipients should undergo yearly clinical skin exams for skin cancer screening (Strong, Level 2).
46. Liver transplant recipients who use tobacco should receive smoking cessation education and related medical intervention (Strong, Level 1).

47. Female liver transplant recipients aged ≥ 21 or who are sexually active and have positive human papillomavirus testing may consider undergoing annual pelvic exam, cervical and anal Papanicolaou testing (Weak, Level 4).
48. Liver transplant recipients with a history of tobacco or alcohol-associated liver disease, or human papillomavirus infection, may consider referral to ear, nose, and throat specialists for head and neck cancer surveillance within the first year of transplant (Weak, Level 3).
49. Liver transplant recipients who are otherwise at average risk may consider undergoing colonoscopy for colorectal cancer surveillance every 5 years (Weak, Level 3).
50. Liver transplant recipients with primary sclerosing cholangitis and inflammatory bowel disease should undergo colonoscopy annually with random biopsies for colorectal cancer screening (Strong, Level 2).
51. Liver transplant recipients with primary sclerosing cholangitis (PSC) but without inflammatory bowel disease (IBD) should undergo colonoscopy, with ileal intubation, and with colon biopsies every 5 years for inflammatory bowel disease and colorectal cancer screening (Strong, Level 3).

Rationale and background

Oncologic complications of LT can be divided into donor-derived cancers, recurrent cancers, and de novo cancers. Donor-derived cancers are rare, with <100 cases reported.^[191] Recurrent cancers include extrahepatic cancers in remission before LT, and intrahepatic cancers such as hepatocellular carcinoma and cholangiocarcinoma—the latter are outside the scope of this guideline. De novo cancers represent the greatest burden on LT recipients and include post-transplant lymphoproliferative disorder (PTLD), and commonly occur in the general population, such as breast, prostate, lung, and colorectal cancer (CRC).

A systematic review reported 92 cases of donor-derived cancer (most common were lymphoma, melanoma, and neuroendocrine tumors) diagnosed in the first year after transplant and outcomes varied substantially by tumor type (good for lymphoma, dismal for melanoma).^[191] The risk of recurrence for patients with a history of extrahepatic cancer in remission at the time of LT is low (1 per 100 person-years) because those with high risk (> 10%) for recurrence pre-LT are usually deemed not transplant candidates.^[192]

LT recipients demonstrate a 2.45-fold overall increase in cancer risk compared with the general population.^[193] Figure 3 shows the 10 most common malignancies by incidence in the general population and standardized incidence ratio (SIR, akin to relative risk) among LT recipients.^[194] The largest relative risk is with non-Hodgkin lymphoma, but since the general population incidence is low, the absolute risk in transplant recipients remains fairly low. By far, the greatest absolute risk increase of any cancer is with non-melanoma skin cancer, since it has a high baseline population incidence and a large SIR.

Cancer screening is an important component of post-LT care.^[195] Screening recommendations by the United States Preventive Services Task Force (USPSTF) for the general population can serve as a guide (Table 3) with several important exceptions.^[196] Recommendations informed by cancer-specific guidance in high-risk subgroups are summarized in Table 3 and supported by a systematic review of practice guidelines^[126] and a recent International Liver Transplant Society and Spanish Society of Liver Transplantation Consensus Conference (ILTS-SETH) working group.^[127] Based on this systematic review of practice guidelines from various professional societies on cancer screening in recipients of solid organ transplant^[126] the recommendation is yearly skin cancer screening. Some societies recommend annual cancer screening^[77,127,134] for human papillomavirus (HPV)-related cancers, particularly among high-risk patients with HPV, where anal cancer risk is also increased.^[135,136,196] More intensive CRC screening may be justified given the SIR of 1.89 is similar to the relative risk of having a positive family history in a first-degree relative (1.87)^[197] and the adjusted odds ratio for advanced adenomas is 2.38 (95% CI 1.07–5.3).^[198] Given the limited sensitivity of stool-based testing for advanced adenoma in solid organ transplant recipients, colonoscopy is preferred over stool-based testing.^[199] Furthermore, LT recipients with IBD and PSC, and patients with IBD in the absence of PSC but meeting surveillance criteria based on the extent and duration of IBD, also warrant more intense CRC surveillance by colonoscopy with ileal intubation. LT recipients with PSC but without IBD should undergo colonoscopy with biopsies every 5 years to screen for IBD and CRC, given the incidence rate ratio (2.72 [95% CI, 1.64–4.52]).^[131,132,200]

The risk of head and neck cancers is significantly higher in LT recipients with a history of smoking, alcohol-associated liver disease, or HPV, and may warrant early referral for screening with ear nose and throat specialists.^[77,144,149] Likewise, cervical cancer risk is significantly higher in LT recipients, and thus annual screening may be appropriate for those with other risk factors such as HPV.^[126,127]

All tobacco users should receive smoking cessation education and related medical intervention to minimize

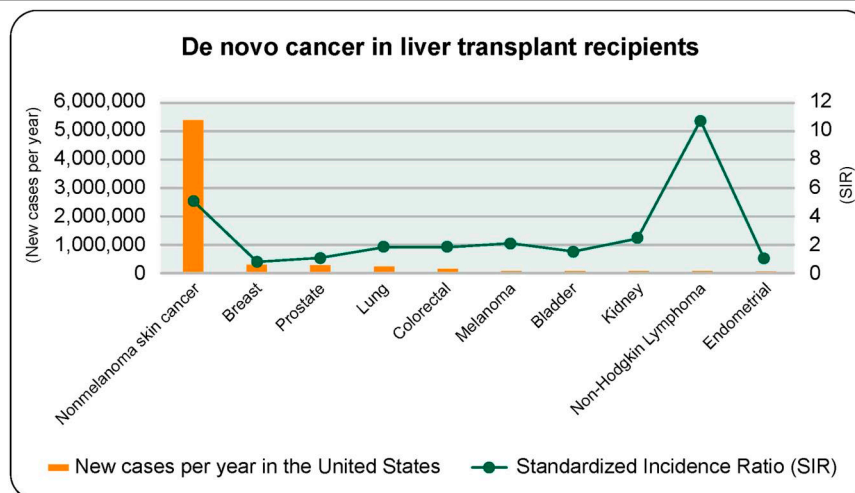


FIGURE 3 Top 10 most common malignancies by incidence in the general population and standardized incidence ratio among liver transplant recipients.

the risk of tobacco-associated malignancies and cardiovascular disease.^[201,202]

Question 12: What is the recommended approach to screening for post-transplant lymphoproliferative disorder in adult liver transplant recipients?

Guidelines statement

52. In liver transplant recipients, the screening for post-transplant lymphoproliferative disorder with serial Epstein–Barr virus polymerase chain reaction is not supported (Weak, Level 3).

Rationale and background

PTLD occurs in approximately 2% of adult LT recipients, most commonly in the first 3 years of LT, although patients may present many years later.^[203] Clinical presentation is often nonspecific, with no or vague symptoms such as fevers, night sweats, or weight loss. Imaging may show bulky lymphadenopathy, with a confirmatory diagnosis subsequently made by biopsy. Survival is >50% at 10 years, with older age and monomorphic type being negative prognostic factors.^[204] Patients who are EBV negative at the time of LT are at the highest risk. Although markedly elevated EBV viral load can identify those at increased risk, the role of EBV screening for PTLD is not well established.^[205] Once diagnosed, management of PTLD involves a reduction in immunosuppression. For patients with monomorphic PTLD, treatment involves chemotherapy like other lymphomas.^[204]

Metabolic and cardiovascular complications

Metabolic syndrome

Question 13: What changes in immunosuppression should be considered in adult liver transplant recipients with metabolic comorbidities?

Guidelines statements

53. In all liver transplant recipients, annual screening for hypertension, obesity, diabetes, and hyperlipidemia should be performed (Strong, Level 5).
54. In liver transplant recipients with metabolic comorbidities, namely diabetes mellitus and hypertension, early withdrawal of corticosteroids is recommended while balancing the risk of rejection (Strong, Level 1).
55. In liver transplant recipients with poor glycemic control despite aggressive medical management, conversion from tacrolimus to cyclosporine may be considered (Weak, Level 3).
56. In liver transplant recipients with uncontrolled hypertension despite aggressive medical management, conversion from cyclosporine to tacrolimus may be considered (Weak, Level 3).

57. In liver transplant recipients with hyperlipidemia despite aggressive medical management, calcineurin inhibitor minimization with or without the addition of antimetabolite may be considered (Weak, Level 5).

Rationale and background

Metabolic syndrome (MetS) represents a constellation of ≥ 3 of the following: hypertension (HTN), dyslipidemia, obesity, and type 2 diabetes mellitus (DM). MetS and its individual components (Figure 4) commonly affect LT recipients and add to cardiovascular morbidity and mortality, with overall MetS prevalence exceeding 50% (persistent from pre-LT and de novo post-LT).^[206] A meta-analysis of 2683 LT recipients found that the incidence of de novo MetS was 24.7% (CI: 18%–32.9%) over 15 months after LT, with older age, pre-LT MASLD, and pre-LT DM being the major predictors.^[207] Of the various manifestations of MetS, HTN has the highest incidence post-LT, followed by DM.^[207]

Figure 5 summarizes the management strategies for post-LT cardiometabolic care. Corticosteroids are most implicated in impaired glycemic control.^[208,209] Contemporary immunosuppression protocols emphasize early withdrawal of corticosteroids within the first two months while continuing antimetabolites, namely MPA, for 3–6 months (or longer) post-LT, balancing the risk of rejection. A Cochrane review of 17 RCT in LT recipients showed that steroid withdrawal or avoidance resulted in significant decrease in post-LT DM and HTN albeit with an increased risk of rejection.^[210] Conversely, antimetabolites (eg, azathioprine and MPA) have not been associated with any metabolic comorbidity.^[210] CNIs have been associated with dyslipidemia, DM, HTN, and chronic kidney disease (CKD) with HTN and dyslipidemia are more commonly observed with cyclosporine while hyperglycemia is more typical with tacrolimus.^[211,212] In those with post-LT obesity, significantly less weight gain was seen among patients randomized to reduced tacrolimus with everolimus (6.69 ± 8.37 kg) or eliminated tacrolimus with everolimus alone regimen (6.01 ± 9.98 kg), compared with those on standard tacrolimus dosing (9.54 ± 10.21 kg).^[213] This intervention may be considered as a second-line approach to post-LT obesity management, with first line being lifestyle modifications along with the new generation of anti-obesity medications. Furthermore, mTORi increase the risk of dyslipidemia, especially hypertriglyceridemia.^[214] The data, however, are conflicting regarding the association of mTORi use with post-LT DM.^[215–217]

Question 14: What is first-line therapy for long-term non-insulin-based management of type 2 diabetes mellitus in adult liver transplant recipients?

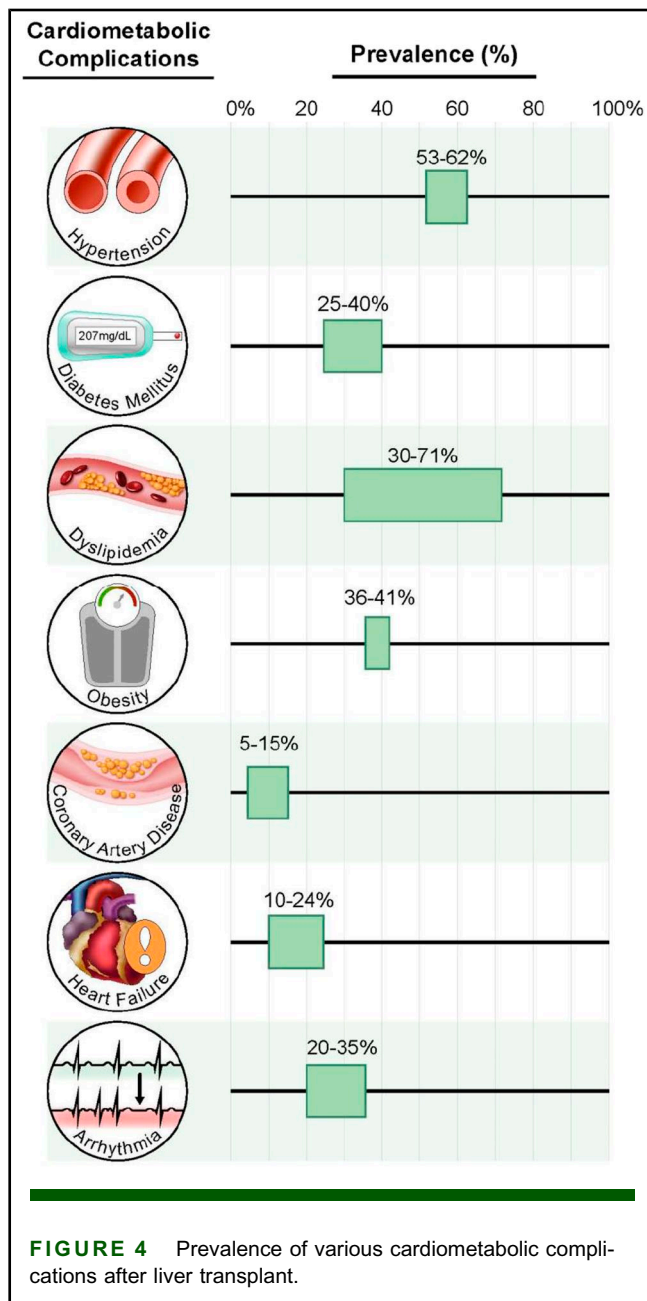
Guidelines statements
58. In liver transplant recipients with type 2 diabetes mellitus and no other risk factors for cardiovascular disease, metformin should be the first-line therapy (Strong, Level 5).
59. In liver transplant recipients with type 2 diabetes mellitus, glucagon-like peptide-1 receptor agonists, and/or sodium-glucose cotransporter-2 inhibitors should be considered as first-line therapy for those at high-risk for atherosclerotic cardiovascular disease, heart failure, stroke, or chronic kidney disease (Strong, Level 5).

Rationale and background

Insulin-based therapies are not discussed here and should be practiced as in a non-transplant setting. The availability of newer non-insulin-based therapies is changing long-term management of DM post-LT (Figure 5).^[218] Glucagon-like peptide-1 receptor agonists (GLP1-RA) and sodium-glucose cotransporter-2 inhibitors (SGLT2i) have expanded treatment options post-LT. In 2023, the American Association of Clinical Endocrinology recommended GLP1-RA and/or SGLT2i as first-line therapy in patients at high risk for atherosclerotic cardiovascular disease (ASCVD; eg, those with proteinuria or albuminuria, HTN, left ventricular hypertrophy, systolic or diastolic dysfunction, ankle-brachial index < 0.9), heart failure, stroke, or CKD.^[219] In patients without these conditions, metformin is used as first-line therapy, but not sulfonylureas. Although prospective studies with SGLT2i and GLP1-RA are lacking in LT recipients, the potential for drug-induced liver injury or interaction with CNI appears minimal, if any. One study showed increased canagliflozin (SGLT2i) levels in patients on cyclosporine, though there were no clinical consequences.^[220]

Question 15: What is the first-line therapy for hypertension in adult liver transplant recipients?

Guidelines statements
60. In liver transplant recipients with a history of cardiovascular disease and/or chronic kidney disease, the long-term antihypertensive regimen should include a renin-angiotensin system inhibitor, unless contraindicated due to difficult-to-control hyperkalemia (Strong, Level 5).



61. In liver transplant recipients with no evidence of cardiovascular disease and chronic kidney disease, use of amlodipine or felodipine as first-line antihypertensive therapy is recommended (Strong, Level 5).

Rationale and background

Initial management of HTN (defined as systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg) includes lifestyle changes (eg, low salt

diet, regular exercise, weight reduction, smoking cessation) and pharmacotherapy (Figure 5). In the absence of clinical trials, management of HTN in LT recipients mirrors that in the general population. The most recent international guidelines for HTN tailor the choice of pharmacotherapy to the patient's comorbidities.^[221] Renin-angiotensin system (RAS) blockers and beta blockers are first-line therapy in patients with concurrent coronary artery disease or heart failure. In patients with prior stroke, RAS blockers, calcium channel blockers, and diuretics are initial options. RAS blockers are also first-line therapy for patients with CKD. In the absence of these comorbidities, the use of calcium channel blockers (amlodipine and felodipine) in LT recipients is reasonable given the mechanism of action, which involves reversal of renal vasoconstriction, and minimal interaction with CNI.^[206] The goal of antihypertensive pharmacotherapy is to lower BP to $\leq 130/80$ mm Hg.

Question 16: What is the optimal lipid-lowering strategy for adult liver transplant recipients?

Guidelines statements

62. In liver transplant recipients with hyperlipidemia, hydrophilic statins are recommended as first-line therapy in combination with lifestyle modifications. Ezetimibe and/or proprotein convertase subtilisin/kexin type 9 inhibitors can be considered for refractory cases (Strong, Level 5).
63. In liver transplant recipients with hypertriglyceridemia despite statin use, addition of omega-3 with or without fibrates should be considered (Strong, Level 5).

Rationale and background

Pharmacologic management of dyslipidemia is based upon risk stratified approach based on risk factors (age, DM, HTN, CKD, smoking, elevated LDL, and family history of ASCVD) and 10-year risk assessment per the ASCVD risk score.^[222,223] This risk stratification approach also determines the target cholesterol level and appropriate statin use (high intensity vs. low intensity statin). Notably, hydrophilic statins (pravastatin for medium intensity and rosuvastatin for high intensity) are preferred in LT recipients since they are not cytochrome P450 3A4 substrates; a feature that reduces the potential for interaction with CNIs that are substrates or inhibitors of cytochrome P450 3A4.^[224]

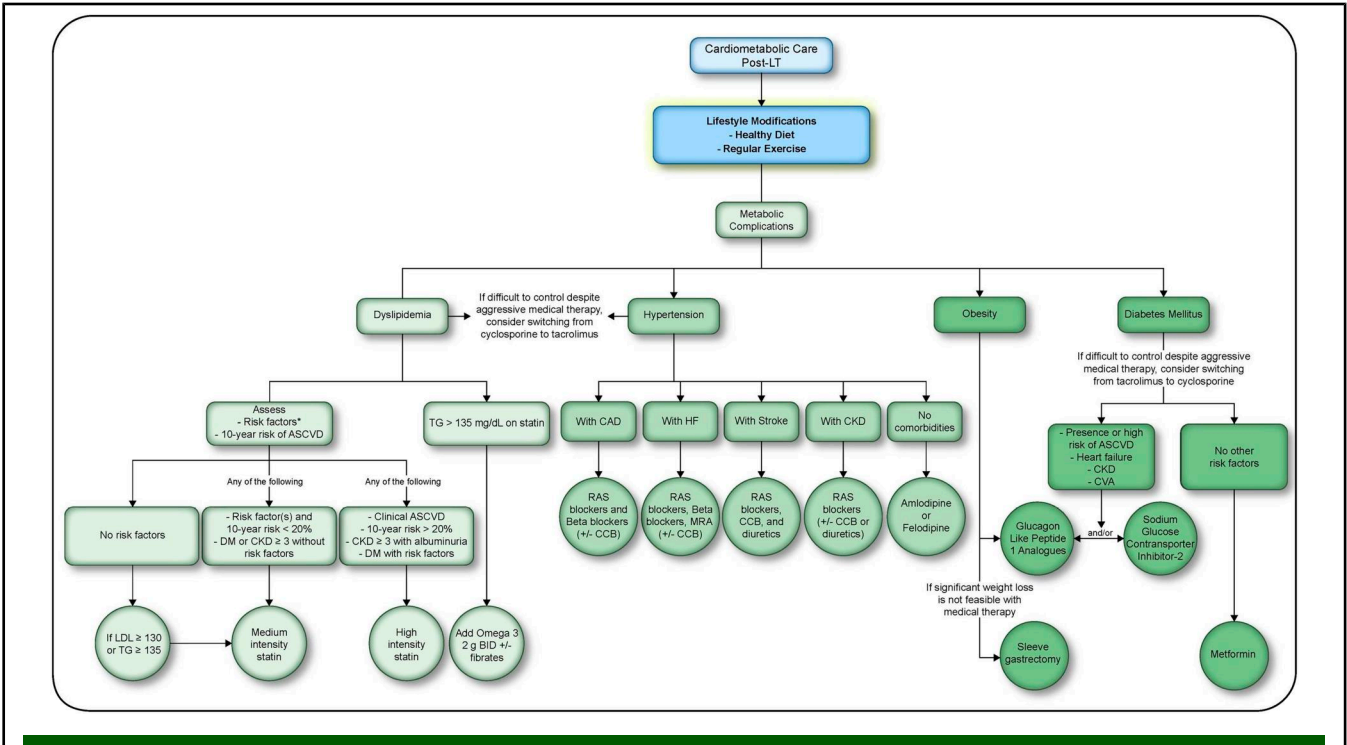


FIGURE 5 Management of cardiometabolic complications after liver transplant. *Risk factors: advanced age, high non-high-density cholesterol, low high-density cholesterol, diabetes mellitus, hypertension, chronic kidney disease, cigarette smoking, and family history of atherosclerotic vascular disease. Abbreviations: ASCVD, atherosclerotic vascular disease; CAD, coronary artery disease; CCB, calcium channel blockers; CKD, chronic kidney disease; CVA, cerebrovascular accident; DM, diabetes mellitus; HF, heart failure; LDL, low-density lipoprotein; MRA, mineralocorticoid antagonists; RAS, renin-angiotensin system; TG, triglyceride.

Statin therapy should be initiated at a low dose, with a gradual increase, if needed. If statins are ineffective in lowering cholesterol to the target range, ezetimibe, which is safe and effective in LT recipients,^[225] can be added. While there are no clinical trials using proprotein convertase subtilisin/pcskexin type 9 (PSCK9) inhibitors, which are novel humanized antibodies, in LT recipients, there have been no reports of liver toxicity or interaction with immunosuppression medications. If hypertriglyceridemia (> 135 mg/dL) persists despite statin use, addition of omega-3 is recommended, and if triglyceride level remains elevated, addition of fibrates should be considered^[222] while exercising caution in view of potential interactions with CNIs and statins leading to increased risk of muscle toxicity.

Post-transplant obesity management

Question 17: Should weight loss pharmacotherapy be considered for the treatment of obesity in adult liver transplant recipients?

Guidelines statements

64. In adult liver transplant recipients with obesity who are unable to lose sufficient weight with diet and exercise, use of GLP1-RA should be considered, in collaboration with providers in primary care, obesity medicine, and/or endocrinology (Strong, Level 3).
65. In adult liver transplant recipients with obesity (body mass index > 30), referral to obesity specialists should be considered as early as 3–6 months post-transplant (Strong, Level 5).

Rationale and background

A prospective study confirmed that weight loss counseling alone is ineffective in LT recipients.^[13] A retrospective study of 44 LT recipients (predominantly diabetic) showed that those who were started on GLP1-

RA experienced significant weight loss averaging 8% of total body weight as early as 9 months of therapy, mirroring weight loss seen in non-LT recipients with T2DM.^[226,227] However, the rate of adverse events (mainly nausea and vomiting) was 7%. No immunosuppression adjustment was needed because of GLP1-RA. Data about the use of other anti-obesity medications [eg, phentermine-topiramate, naltrexone-bupropion, and tirzepatide (a novel glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist)] in LT recipients are lacking.

Question 18: When should weight loss surgery be recommended to adult liver transplant recipients?

Guidelines statements

66. In liver transplant recipients, weight loss surgery should be considered if medical management is unsuccessful or if the recipient needs weight loss of > 15%–20% of current weight (Strong, Level 3).
67. Weight loss surgery after a liver transplant should be considered only after the recipient is medically and surgically stable (Strong, Level 3).

Guidelines statements

68. In liver transplant recipients with a history of cardiovascular disease, cardiac-focused clinical assessment should be performed on every visit at primary care, hepatology, and cardiology clinics (Strong, Level 5).
69. In adult liver transplant recipients with a history of cardiovascular disease, annual follow-up with a cardiologist should be considered (Strong, Level 5).
70. In adult liver transplant recipients with systolic dysfunction, diastolic dysfunction, or more than mild valvular disease, echocardiographic surveillance should be considered and individualized based on the patient's risk profile (Weak, Level 5).

Rationale and background

Bariatric surgery is the most effective intervention for weight loss that can be performed during or after LT.^[228] Bariatric surgery after LT is an attractive option given the resolution of portal hypertension. If performed during LT, then it adds to the complexity of the transplant procedure. A systematic review of 28 studies (pre-LT = 6, at LT = 6, and post-LT = 16) of 144 patients from 2001 to 2020 revealed that weight loss was greatest with Roux-en-Y gastric bypass, and least with the gastric band.^[229] However, postoperative complications were significantly higher with Roux-en-Y gastric bypass.^[229] Sleeve gastrectomy, which is often performed laparoscopically, is an option that has gained popularity in LT patients as it achieves a significant degree of weight loss, with decreased complications and preserved access to the biliary tree compared with Roux-en-Y gastric bypass.^[229–235] There is an emerging field of Endobariatrics where weight loss procedures can be performed endoscopically; however, there is insufficient data to provide recommendations.

Cardiovascular complications

Question 19: In liver transplant recipients with pre-existing cardiovascular disease, is post-transplant cardiovascular surveillance warranted?

Rationale and background

Pre-LT cardiovascular disease (CVD) is an independent predictor of post-LT cardiovascular events, a leading cause of post-LT morbidity and mortality.^[236–238] While studies evaluating the impact of surveillance in LT recipients are lacking, recently published multidisciplinary practice-based recommendations proposed a comprehensive approach, including monitoring for signs and symptoms of coronary artery disease.^[239] Annual visit with a cardiologist for patients with CVD should be considered. There is insufficient evidence to recommend serial assessments of coronary arteries post-LT although the available observational data suggests expedited course for coronary atherosclerosis in LT recipients with MetS.^[240] In patients with valvular heart disease that is more than mild, echocardiographic surveillance is recommended every 1–2 years, as in the general population. The group also suggested echocardiographic surveillance every 6 months in patients with subclinical cardiac dysfunction until the latter has been resolved. However, the Cirrhotic Cardiomyopathy Consortium recommends echocardiographic surveillance of LT recipients with cirrhotic cardiomyopathy (ie, systolic or diastolic dysfunction) for only 2 years post-LT due to increased risk for post-LT cardiac events.^[241–243] Surveillance echocardiography can prompt surgical intervention for valvular heart disease, or initiation or augmentation of anti-remodeling therapy for cardiac dysfunction, although studies evaluating the optimal interval for echocardiographic surveillance are needed.

Question 20: What cardio-preventive strategies should be considered in adult liver transplant recipients?

Guidelines statements
71. In liver transplant recipients, lifestyle modifications (ie, diet and exercise) and aggressive management of metabolic complications are essential for primary prevention of cardiovascular disease (Strong, Level 5).
72. In liver transplant recipients, the use of aspirin or statin should be guided by the same cardiovascular risk stratification approach used in the general population (Strong, Level 5).
73. In liver transplant recipients with recurrent cardiovascular events, minimization of calcineurin inhibitors with introduction of mammalian target of rapamycin inhibitors (eg, everolimus) may be considered (Weak, Level 3).

Rationale and background

Lifestyle changes including diet, exercise, smoking cessation, and alcohol cessation are essential for primary prevention of cardiovascular complications post-LT.^[239] HTN control has been associated with a significant reduction in cardiovascular events and mortality post-LT.^[244] Statins offer a survival benefit in LT recipients, albeit underutilized.^[245,246] Cyclosporine has been linked to increased risk of cardiovascular events; thus, minimizing or substituting it with other immunosuppressants is recommended in patients with or at high risk of CVD.^[236] Anti-remodeling therapy (eg, beta blockers, RAS blockers, aldosterone antagonists) should be considered in patients with systolic dysfunction even if asymptomatic given its utility in recovery of left ventricular ejection fraction.^[239] GLP1-RA and SGLT2i have cardioprotective effects and should be considered in LT recipients, especially those with DM or obesity.^[239] It is noteworthy that post-LT CKD is associated with increased risk for cardiac events.^[238,247] A post-hoc data analysis from an international RCT showed that tacrolimus minimization, together with introduction of everolimus improved renal function and mitigated the risk for cardiac events.^[248] Secondary prevention of CVD in LT recipients should follow guidelines for the general population.

Chronic kidney disease

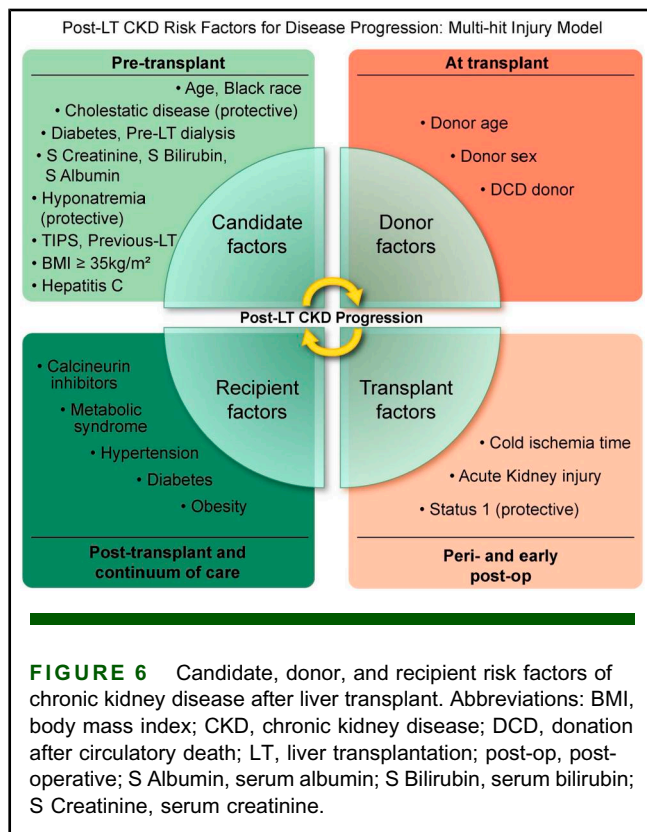
Question 21: What are the risk factors and optimal strategies for chronic kidney disease surveillance among adult liver transplant and simultaneous liver–kidney transplant recipients?

Guidelines statement
74. In liver transplant and simultaneous liver–kidney recipients, active chronic kidney disease surveillance using serial serum creatinine-based estimated glomerular filtration rate should be performed every 6–12 months in the early and moderate (stages 1–3) and 1–3 months in advanced chronic kidney disease (stages 4–5) (Strong, Level 4).

Rationale and background

Despite the lowest level of immunosuppression in LT recipients compared with heart and lung transplant recipients, the risk of incident advanced (stages 4–5) CKD is highest among LT recipients.^[249] Incident end-stage renal disease (ESRD) poses a substantial mortality risk for LT recipients.^[249,250] The adjusted relative risk of post-LT incident ESRD has increased in the MELD era (HR = 1.15, $p < 0.0001$);^[251] since 2002, there has been a 7.6% annual rise in post-LT ESRD risk, contrasting with a previously decreasing trend from 1995 to 2001.^[251] While late post-LT ESRD (after 6 months of LT) incidence remains stable, early ESRD rates (within 6 months of LT) have surged from 21.8 to 36.3 per 1000 patient-years between pre-MELD and MELD eras.^[252] A systematic review of 14 studies reveals varied CKD incidence and progression, influenced by treatment regimens.^[253] Figure 6 demonstrates the unique candidate, donor, and transplant-related risk factors influencing the post-LT CKD progression. Acute kidney injury (AKI), common in the early postoperative period, is strongly associated with post-LT CKD. Moreover, CNIs' side effects include, besides renal dysfunction, HTN, DM, obesity, and dyslipidemia, which expedite the CKD progression among LT recipients.^[249,252,254,255]

The cumulative incidence of stages 4–5 CKD was 10%, 12%, and 16% at 1-, 3-, and 5-year after SLKT, respectively.^[256] Pre-transplant DM (HR = 1.45; 95% CI, 1.00–2.15), MASLD (HR, 1.58; 95% CI, 1.01–2.45), and delayed kidney graft function (HR, 1.72; 95% CI, 1.10–2.71) were the recipient factors independently associated with high risk of post-SLKT stages 4–5



CKD. The use of tacrolimus compared with cyclosporine reduced the risk of stages 4–5 CKD by 66%.^[256]

CKD surveillance should be performed in patients with LT and SLKT. Serum creatinine-based estimated glomerular filtration rate (eGFR) equations demonstrated reasonable precision in LT recipients.^[257] According to the Kidney Disease Improving Global Outcomes (KDIGO) 2024 clinical practice guidelines, those at risk for CKD should undergo CKD surveillance using creatinine-based eGFR.^[258] However, if cystatin C is available, then eGFR should be estimated from the combination of creatinine and cystatin C.^[259] Increased proteinuria (spot protein-to-creatinine ratio >0.3) may be absent even in the presence of advanced CKD because of the antiproteinuric effect of CNIs. KDIGO recommends CKD surveillance annually for early-stage CKD (stages 1–2), every 6 months for moderate CKD (stages 3a and 3b), and every 1–3 months for advanced CKD (stages 4–5).^[260] Referral to nephrology should be considered if the eGFR <30 mL/min. Patients can be referred early (stage 3) if they have significant urine findings suggestive of nephritides. These data are extrapolated from the non-transplant patients with risk factors for CKD, such as HTN, DM, and MetS.^[261]

Question 22: What is the role of risk factor modification in preventing the progression to advanced chronic kidney disease among adult liver transplant recipients?

Guidelines statements

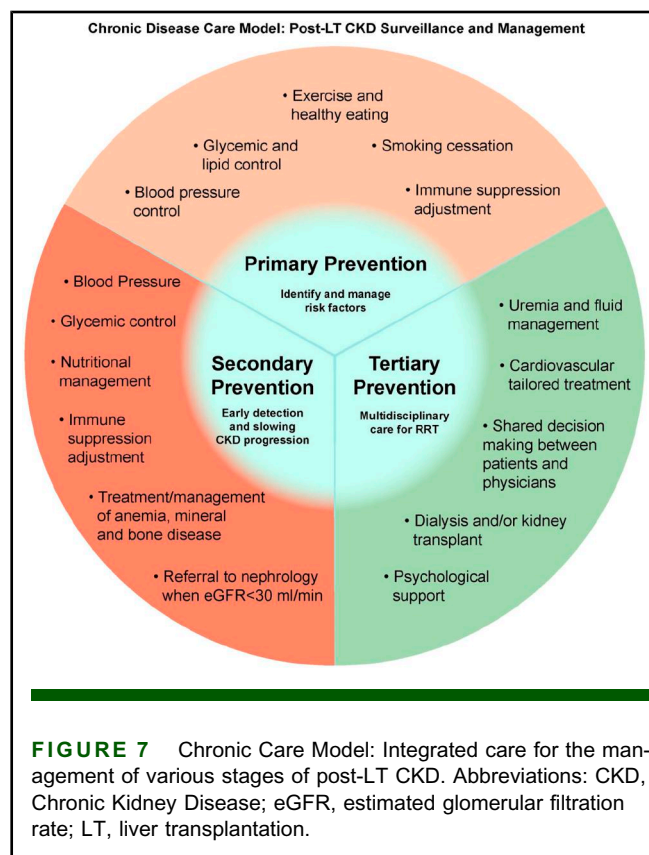
75. In liver transplant recipients with chronic kidney disease, aggressive management of hypertension, diabetes, obesity, and dyslipidemia should be performed in collaboration with primary care providers, nephrologists, and transplant providers to prevent progression to stages 4–5 disease (Strong, Level 5).
76. In adult liver transplant recipients with chronic kidney disease, referral to nephrology should be considered at stage 4 disease (Strong, Level 5).

Rationale and background

Multiple studies have used the risk factors for CKD progression to construct risk-predicting models.^[251,252,254,262] Renal risk index uses 14 recipient factors at transplant to estimate post-LT ESRD risk.^[254,263] Another study developed the risk prediction model using age, female sex, hemoglobin, uric acid, and average concentration of cyclosporine at 3 months for new onset CKD defined as eGFR <60 mL/min/ 1.73 m^2 for 3 months after LT, regardless of the presence or absence of structural kidney damage.^[262] Urinary Neutrophil Gelatinase-Associated Lipocalin (uNGAL) at 24 hours post-perfusion independently predicted the incident post-LT CKD in a prospective study, with uNGAL >93 ng/mL demonstrating high specificity and 100% positive predictive value.^[264]

The Wagner Chronic Care Model delineates an integrated care continuum for various stages of CKD in the general population.^[265,266] Figure 7 shows the adaptation of this model for integrated care for the management of post-LT CKD. There is limited data on interventions for risk factor modification on CKD progression among LT recipients. Extrapolating from the non-transplant patients with risk factors for CKD progression, KDIGO 2024 clinical practice guidelines can also be applied to LT recipients with CKD.^[258] LT recipients with CKD should practice lifestyle modifications, achieve and maintain optimal BMI, avoid tobacco products, consume plant-based foods compared with animal-based foods, and have a lower consumption of ultra-processed foods with sodium intake <2 g per day and stricter control of HTN and DM.

LT recipients should receive education regarding post-LT CKD risk to foster engagement and self-management. A survey of 163 LT recipients with stages 1–3 CKD demonstrated lower CKD knowledge scores than the non-



transplant population.^[267] The survey also showed that more than two-thirds of the LT recipients were interested in learning about the risk factors and prevention.^[267] Implementation of a CKD educational and goal-setting tool among 81 LT recipients with stages 1–3 CKD significantly improved their CKD knowledge scores, helped participants identify their most crucial self-management goal, and expressed motivation to pursue it.^[268]

There is little data on the timing of nephrology assessment for LT recipients with CKD. However, data suggest that early referral to nephrology for CKD care improves clinical and patient-related outcomes in the CKD general population.^[269–271] Therefore, KDIGO recommends that patients with stage 4 CKD should be referred to nephrology.^[260]

Question 23: What is the role of immunosuppression-based strategies in preventing the progression of chronic kidney disease in adult liver transplant recipients?

Guidelines statements

77. In liver transplant recipients with peri- or early post-transplant acute kidney injury, delayed introduction of calcineurin inhibitors in conjunction with induction immunosuppression may be considered for renal protection (Weak, Level 2).

78. In liver transplant recipients with chronic kidney disease within the first year of transplant, calcineurin inhibitor dosing should be reduced, typically in combination with an adjunctive non-nephrotoxic immunosuppressive agent (mycophenolate or everolimus) to improve long-term renal function (Strong, Level 1).
79. In liver transplant recipients with chronic kidney disease, calcineurin inhibitors should be minimized but not eliminated within the first year of liver transplant to prevent deterioration in renal function (Strong, Level 1).
80. In liver transplant recipients with chronic kidney disease, use of belatacept for renal protection is not recommended due to an increased risk of mortality (Strong, Level 1).
81. In liver transplant recipients with chronic kidney disease, mycophenolate monotherapy is not recommended to prevent kidney disease progression because of a strong association with acute cellular rejection (Strong, Level 2).
82. In liver transplant recipients with chronic kidney disease, calcineurin inhibitors should be minimized but not stopped beyond 1 year post-transplant for renal protection (Strong, Level 3).

Rationale and background

The post-transplant period is divided into perioperative, very early (0–1 month), early (1–12 months), and late (≥ 12 months) to summarize the evidence for immunosuppression-based renal protective strategies (Table 4). There is no high-quality evidence supporting any renal protective strategies during the intraoperative period or ≥ 12 months of LT.^[255]

There is evidence for the use of induction agents with delayed introduction of CNIs for renal protection in those with stage 2 or higher peri- or postoperative AKI during very early post-transplant patients (0–1 month) (Table 4). This approach provides time for renal recovery from perioperative AKI. An RCT that compared induction therapy comprising daclizumab, MPA, corticosteroids, along with delayed low-dose tacrolimus (trough levels 8–12 ng/dL), demonstrated improved median eGFR in the daclizumab+delayed low-dose tacrolimus groups without any significant differences in rates of acute cellular rejection (ACR).^[272] One retrospective study from a single center that used the approach of delaying tacrolimus initiation combined with basiliximab induction in LT patients with severe

TABLE 4 Selected studies that examined the effect of immunosuppression regimen on renal function among liver transplant recipients

Author (N)	Study design	Major findings
Very early post-transplant period (< 1 mo) CNi minimization studies		
Yoshida et al. [272] N = 148	Immediate post-LT: DAC+reduced TAC delayed 6 d vs. standard TAC	- Improved GFR in reduced, delayed TAC - No difference in AR rates
Neuberger [273] N = 525	Immediate post-LT: standard TAC vs. reduced-dose TAC+MMF/MPA vs. DAC+reduced TAC delayed 5 d +MMF/MPA	- Significantly less drop in GFR in reduced, delayed TAC - Less AR in reduced, delayed TAC
Calmus et al. [274] N = 199	Immediate post-LT: DAC+standard TAC delayed 5 d vs. standard TAC	- No difference in month 12 SCr > 1.43 mg/dL - No difference in AR rates
Boudjema et al. [275] N = 195	Immediate post-LT: reduced TAC+MMF/MPA vs. standard TAC	- Significantly better GFR at month 12 in reduced TAC +MMF/MPA - Significantly less AR in reduced TAC+MMF/MPA
Klintmalm et al. [276] N = 250	Immediate post-LT: BAS+BELA MI+MMF/MPA vs. BELA MI+MMF/MPA vs. BELA LI+MMF/MPA vs. TAC +MMF/MPA vs. TAC	- Significantly better month 12 GFR in all BELA groups - Significantly higher AR rates in all BELA groups - Significantly diminished month 12 survival in BELA LI +MMF
Asrani et al. [277] N = 222	Immediate post-LT: standard TAC vs. reduced TAC +SRL	- No difference in GFR - Graft loss, death, vascular thrombosis, and sepsis are higher in reduced TAC+SRL
Nair et al. [278] N = 110	Immediate post-LT: rATG+standard TAC delayed 10 d vs. standard TAC	- Difference in delta SCr at 9 but not at 12 mo - No difference in AR rates
Trunečka et al. [279] N = 893	Immediate post-LT: PR-TAC (0.2 mg/kg/d)+MMF/MPA+bolus steroids vs. PR-TAC (0.15–0.175 mg/kg/day) +BAS+MMF/MPA+bolus steroid vs. PR-TAC (0.25 mg/kg/day delayed day 5)+BAS+MMF/MPA +bolus steroid	- eGFR (MDRD4) was higher in arms 2 and 3 versus 1 ($p = 0.001$, $p = 0.047$) - ACR incidence was significantly lower in arm 2 versus 1 and 3 ($p = 0.016$, $p = 0.039$)
Cillo et al. [280] N = 140	Steroids, TAC, and basiliximab were randomized (2:1) to EVR (day 8) and taper TAC vs. continued TAC	- eGFR was higher in the EVR arm - No difference in AR rates - Inc rate of dyslipidemia, wound complication, and incisional hernia in the EVR arm
Early post-transplant period (1–12 mo) CNi minimization studies		
Teperman et al. [281] N = 293	Week 4–12 post-LT: CNi+MMF/MPA vs. CNi to SRL+MMF/MPA	- Significant month 12 eGFR increase in SRL+MMF/MPA - High side effects and discontinuation in SRL+MMF/MPA - Higher rejection rate in SRL+MMF/MPA
De Simone et al. Saliba et al. Fischer et al. [282–284] N = 719	Week 4 post-LT: TAC elimination plus EVR vs. reduced TAC+EVR vs. standard TAC	- Month 12/24/36 eGFR superior for reduced TAC+EVR - Reduced incidence and severity of AR in reduced TAC +EVR - TAC elimination arm stopped due to high AR rates
Fischer et al. [285] N = 203	Week 4 post-LT: BAS induction for all; CNi to EVR vs. CNi continuation	- Significant improvement in GFR with EVR conversion - No difference in AR rates
Abdelmalek et al. [286] N = 607	Month 6–144 post-LT: CNi to SRL vs. CNi continuation	- No improvement in GFR with SRL conversion - Higher AR rates with SRL conversion
Sterneck et al. [287] N = 81	Week 4 post-LT: BAS induction for all; CNi to EVR vs. CNi continuation. Five-year f/u of the PROTECT study	- Significant improvement in GFR with EVR conversion at 5 y f/u - No difference in AR rates
Jeng et al. N = 284 Sung-Gyu Lee et al. N = 1544 Sapisochin et al.	Week 4 post-living donor LT: CNi vs. reduction of CNi plus EVR	- EVR+rTAC was noninferior to CNi in terms of efficacy and renal function at 12 mo - Significantly better renal function in patients with HCC on EVR+rTAC at 24 mo - Significant improvement in GFR on EVR+rTAC at 5 y in HCC patients

TABLE 4. (continued)

Author (N)	Study design	Major findings
(N = 117) [288–290]		
Buchholz et al. [291] N = 508	Weeks 4–6 post-LT: CNI vs. 50% reduction of CNI plus SIR	- Month 3 eGFR superior for reduced TAC+SIR, but this did not lead to better kidney function long-term - Subgroup of reduced TAC+sustained SIR at least during 1 post-LT year showed improved eGFR and lowest rate of CKD ($\geq$ stage 3) from year 1 onward until 5 y
Saliba et al. [292] N = 188	Week 4 post-LT: BAS induction for all. TAC elimination plus EVR vs. standard TAC	- Significant improvement in GFR with EVR conversion - Higher rejection rate in EVR arm
Late post-transplant period (> 12 mo)		
Abdelmalek et al. [286] N = 607	Month 6–144: CNI to SRL vs. CNI continuation	- No improvement in GFR with SRL conversion - Higher AR rates with SRL conversion
De Simone et al. [293] N = 145	Prospective randomized controlled: EVR+low dose CNI/ CNI elimination vs. standard dose CNI $\times$ 6 mo, GFR 20–60 at enrollment Time from LT to enrollment: 12–60 mo	No difference in eGFR or AR in both groups
Pageaux et al. [294] N = 56	Prospective randomized controlled: MMF/MPA+low dose CNI vs. standard CNI for chronic renal failure Time from LT to enrollment: 1 y post-LT	- Significant improvement in eGFR in MMF/MPA+ low dose CNI at 1 y - No AR in either group
Beckebaum et al. [295] N = 90	Prospective randomized controlled (2:1): MMF/MPA +low dose CNI vs. standard CNI for SCr > 1.2 mg/dL Time from LT to enrollment: 1 y post-LT	- Significant improvement in eGFR in MMF/MPA+ low dose CNI at 1 y - No AR in either group

Abbreviations: ACR, acute cellular rejection; AR, acute rejection; BAS, basiliximab; BELA, belatacept; CKD, chronic kidney disease; CNI, calcineurin inhibitors; DAC, dacluzimab; eGFR, estimated glomerular filtration rate; EVR, everolimus; LT, liver transplantation; MMF, mycophenolate; MPA, mycophenolic acid; PR-TAC, prolonged tacrolimus; rTAC, reduced tacrolimus; SCr, serum creatinine; SRL, sirolimus; TAC, tacrolimus.

renal dysfunction (pre-LT dialysis/eGFR < 30 mL/min/1.73 m² or post-LT AKI) did not show any durable effect on long-term renal outcomes.^[296] The use of belatacept and avoidance of CNI therapy in the early postoperative period is not recommended because of the prohibitively high rates of ACR that led to increased patient deaths and graft loss,^[276] despite improvement in eGFR at the 12-month mark in belatacept groups. This resulted in the issuance of an FDA boxed warning for the use of belatacept in LT recipients.

There is quality evidence for 2 renal protective strategies during the very early and early post-transplant period (1–12 months): (1) low dose CNI and MPA, and (2) low dose CNI and mTOR inhibitors (Table 4). In a multicenter randomized prospective study, the group receiving reduced tacrolimus with MPA had higher GFR levels 1 year post-LT compared with the standard tacrolimus group. In addition, the reduced tacrolimus group had lower ACR rates (30% vs. 46%).^[275] In a phase II study investigating the use of the mTORi sirolimus during the very early postoperative phase, there were no discernible differences in GFR.^[277] However, the arm receiving sirolimus in conjunction with tacrolimus exhibited higher incidences of graft loss, death, vascular thrombosis, and sepsis. As a result, sirolimus has an FDA boxed warning about its use in LT.

The safety profile of mTORi in conjunction with CNI after the first month of LT appears to be more

favorable.^[281,282,285] The pivotal H2304 trial studied everolimus with reduced tacrolimus dose, commencing at the fourth week after LT.^[282–284] In this RCT, the standard tacrolimus arm. This trial had a dedicated arm to assess everolimus and tacrolimus elimination by the fourth month of LT, which was terminated early because of high rates of ACR in this arm compared with the standard tacrolimus arm. The everolimus+reduced tacrolimus arm showed a remarkable improvement in eGFR up to 36 months post-LT, with similar rates of ACR. This led to the FDA's approval of this regimen beyond the initial month following LT. However, discontinuation of drug regimen due to adverse events was more frequently seen in the everolimus+reduced tacrolimus group (25.7%) versus the standard tacrolimus group (14.1%).

When data from 2 RCTs [N = 772; H2304 (deceased donor, n = 488), H2307 (living donor, n = 284)] comparing everolimus+reduced tacrolimus and standard tacrolimus groups were pooled, there was comparable efficacy and safety in patients with normal or mildly decreased renal function (CKD stages 1–2) at 24 months in both groups^[288] suggesting standard dose tacrolimus regimen is acceptable in stages 1–2 CKD. The observational Everolimus Liver registry (EVEROLIVER) from France evaluated renal function among LT recipients who were converted to

everolimus. A total of 1045 LT recipients received everolimus after a mean time of 3.6 ± 5.1 years. Among patients with CKD (baseline eGFR < 60 mL/minute/ 1.73 m²), 55% in the early conversion group (within 3 months) and 39.4% in the mid-conversion group (between 4 and 12 months) had improvement in eGFR (≥ 60 mL/minute/ 1.73 m²) at month 36. In an adjusted analysis, the time to conversion ≥ 12 months was associated with no improvement in eGFR.^[297]

Combining MPA or mTORi with low-dose CNI to improve renal function in the later post-LT period (> 12 mo) does not have the same benefits as in the early post-LT period^[293–295,298–301] (Table 4). The trials are limited because of small sample sizes, uncontrolled designs, or retrospective observational methodologies. The investigations examining the concept of late (> 12 mo) conversion to MPA alone or in combination with low-dose CNI have reported improvements in eGFR with no adverse events.^[301] Interestingly, eGFR improvement was observed even in patients with GFR levels below 30 mL/min. However, MPA monotherapy conversion was linked to elevated risks of ACR, albeit without graft loss or mortality.^[294,302,303] The greatest benefits of CNI reduction were observed when the regimen was altered within 1–2 years following LT. Several studies that explored the concept of late conversion to everolimus with or without low-dose CNI demonstrated either minimal or insignificant improvements in GFR and an increased rate of discontinuation attributed to side effects.^[293,298,300]

Surgical considerations in LT recipients:

Question 24: What is the timing and perioperative immunosuppression management after elective surgery in adult liver transplant recipients?

Guidelines statements

83. In liver transplant recipients, elective surgery should occur at least 3 months after transplant when the patients have stable allograft function (Strong, Level 5).
84. In liver transplant recipients undergoing elective surgery, a transplant professional should be involved in the management of immunosuppression before and after elective surgery (Strong, Level 5).

Rationale and background

There is limited literature about the timing of elective surgery, such as hernia repairs, dental procedures, or orthopedic interventions after LT. Centers recommend

waiting at least 3 months post-LT for such procedures. While there are no trials to support this recommendation, this is followed at most centers as it is usually a safe period to allow for settling of acute surgical issues, transition to a stable immunosuppressive regimen, and stabilization of graft function. It is not recommended to hold CNI for the surgery or after the surgery. If patients are on high-dose steroids, these should be reduced if possible. Given the long half-life, consider holding mTORi (everolimus or sirolimus) ~4–6 weeks before elective surgery to facilitate wound healing. It is prudent to have the transplant providers and pharmacists be involved to guide when to restart mTORi after the surgery.

Question 25: What is the timing and management of hernia in adult liver transplant recipients?

Guidelines statements

85. In liver transplant recipients, use of mTOR inhibitors, nutritional status and obesity should be optimized before a hernia repair is planned (Strong, Level 2).
86. In liver transplant recipients, the use of mesh is recommended for ventral repair because of the large defect. Avoiding tension is key to successful ventral hernia repair and essential to minimize the risk of recurrence (Strong, Level 2).
87. In liver transplant recipients, the method of surgical repair (open vs. minimally invasive) should be based on the surgeon's expertise. While open and minimally invasive approaches have equivalent outcomes in terms of recurrence, the latter are associated with shorter recovery times, decreased pain, and less early complications (Strong, Level 2).

Rationale and background

Incisional hernias are a common surgical issue with an incidence ranging from 5% to 35% within the first 2 years after LT.^[304,305] Advanced age, obesity, postoperative wound infections, and poor nutritional status are the major risk factors for hernia formation after LT.^[306,307] In addition, the type of incision used is an important risk factor, with the standard "Mercedes" type incision associated with a higher incidence than an inverted L-shaped incision or a vertical midline incision. Moreover, mTORi-based immunosuppression is an important risk factor.^[308,309] Introduction of mTORi is delayed until the transplant incision heals (usually 1–2 months post-LT), and providers usually change from mTORi to a CNI-based regimen before the time of hernia repair.

TABLE 5 Future directions and areas of research

Overall	• Evaluation of care coordination models between primary care and transplant clinics to optimize focus on preventing metabolic and oncologic complications
Wellness and quality of life	• Prospective studies to identify the optimal dietary and exercise recommendations for LT recipients
Reproductive health	• Analysis of the ongoing database registry of transplant recipients to effectively study reproductive health
Infectious diseases	• Prospective studies for management of opportunistic infections
Oncologic complications	• Development of biomarkers for early detection of PTLT • Decision support for individualized cancer screening recommendations (personalized medicine) • Evaluation of pharmaco-prophylaxis for prevention of skin cancer
Metabolic and cardiovascular	• Randomized studies to examine the impact of mTORi on post-transplant cardiovascular disease • Investigation of novel anti-obesity pharmacotherapy (eg, tirzepatide) in the treatment of post-LT obesity and mitigating the long-term risk of post-transplant diabetes mellitus • Assessing the cardiometabolic benefits of using newer therapies for diabetes mellitus (ie, GLP1-RA and SGLT2i) in liver transplant recipients • Investigation of post-LT evolution of cardiovascular diseases (eg, coronary artery disease, valvular disease, cardiomyopathy)
Chronic kidney disease	• Critical need to understand nephroprotective strategies during the perioperative and immediate postoperative periods after LT • Prospective randomized trials to evaluate the safety and efficacy of proposed regimens, particularly in the context of co-stimulation blockade agents • Explore management options, including optimal timing for referral to nephrology specialists, to mitigate long-term renal decline • Novel biomarkers that can detect early renal injury prior to the onset of reduced GFR are urgently needed • Evaluate the predictive accuracy, clinical applicability, and cost-effectiveness of these biomarkers to enable timely intervention • Prospective studies to understand treatment adjustments and strategies aimed at improving renal function during the later stages post-LT, particularly beyond the first year • Prospective studies to examine the role of SGLT-2 and GLP1 receptors antagonist on mitigating post-LT CKD progression
Post-transplant hernias	• Optimal timing of elective surgery and immunosuppression management • Refining of surgical techniques to reduce ventral hernias

Abbreviations: GLP-1RAs, glucagon-like peptide-1 receptor agonists; LT, Liver transplantation; mTORi, mammalian target of rapamycin inhibitor; PTLT, post-transplant lymphoproliferative disorder; SGLT2i, Sodium-glucose cotransporter-2 inhibitors.

The incisional hernias present as asymptomatic bulges or with vague symptoms of abdominal pain and/or fullness. Patients may present with severe pain and bowel obstruction when abdominal contents become incarcerated and/or strangulated. Hernias should be repaired when diagnosed, especially those that are symptomatic, of significant size, or enlarging. It is important to palpate and assess the size of the hernia defect and determine if the hernia is reducible. A computed tomography scan and/or ultrasound can help if the diagnosis is not certain, especially in obese patients. Addressing risk factors such as abdominal obesity is always advisable, if possible. Many of these hernias will require a mesh repair as the defects are too large to easily allow for a tension-free primary repair.^[310] The most important step is to avoid tension because this is essential for minimizing recurrence. Various techniques for mesh repair techniques (onlay or underlay) and various mesh materials (synthetic, biologic, and hybrid) have been described.^[310] A meta-analysis suggests that a laparoscopic approach has equivalent outcomes in terms of recurrence and has associated benefits of shorter recovery times, decreased pain, and less early complications.^[311,312]

FUTURE DIRECTIONS AND CONCLUSIONS

Table 5 highlights the priorities for future research for non-graft-related complications. Many recipients enjoy a meaningful and normal life span, with many living over 30 years post-LT due to advances in surgical techniques, immunosuppressive therapies, and post-transplant care. Partnership with primary care physicians and transplant physicians is the key to improved long-term survival in this population. Continued advancements in medical care and patient management are expected to further enhance these outcomes, offering hope and a better future for those undergoing LT.

CONFLICTS OF INTEREST

Manhal Izzy consults for Madrigal and Mirum. Virginia C. Clark consults for Takeda. Bilal Hameed consults for Surrozen, Madrigal, Gilead, Pleiogenix, and Malinckrodt. The remaining authors have no conflicts to report.

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