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Beyond Graft Survival: A Practical Guide to Long-Term Care After Liver Transplantation


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LIVER

STRUCTURED ABSTRACT

Question: What are the best practices for preventing and managing non-graft-related complications in adult liver transplant (LT) recipients beyond the first 90 days post-transplant?

Design: Multidisciplinary practice guideline developed jointly by American Association for the Study of Liver Disease (AASLD) and American Society of Trasplantation (AST). Clinical questions were structured in PICO format. A systematic literature search was conducted through Ovid MEDLINE and Embase (January 2016 to May 2023), supplemented by an updated search in December 2024. Recommendations were graded using the Oxford Center for Evidence-Based Medicine framework and classified as strong or weak based on evidence quality, risk-benefit ratio, and patient preferences. Consensus required at least 80% agreement among panel members.

Setting: All clinical settings where adult liver transplant recipients are followed beyond the early postoperative period, including transplant centers and primary care practices.

Patients: Adult liver transplant recipients more than 90 days post-transplant with non-graft-related comorbidities including metabolic, cardiovascular, renal, oncologic, infectious, and musculoskeletal complications.

Intervention/Exposure: Key recommendations include

- Annual screening for hypertension, diabetes, obesity, and dyslipidemia in all recipients; early corticosteroid withdrawal in those with metabolic comorbidities.
- Glucagon-like peptide-1(GLP-1) receptor agonists and sodium-glucose cotransporter-2 (SGLT-2) inhibitors as first-line therapy for diabetic recipients at high cardiovascular or renal risk; metformin for those without such risk factors.
- Hydrophilic statins as first-line therapy for dyslipidemia; amlodipine or felodipine as preferred antihypertensives in recipients without cardiovascular or renal comorbidities.
- Calcineurin inhibitors (CNI) minimization combined with mycophenolate or everolimus within the first year for chronic kidney disease (CKD); beyond 1 year, in CKD patients, CNIs should be minimized but not eliminated.
- Pre-emptive weekly cytomegalovirus (CMV) monitoring with polymerase chain reaction (PCR) testing for 100 days is preferred if either the recipient or donor is CMV+; if this cannot be performed, then Valganciclovir 900 mg daily (or renally dosed) for 3 months (D±/R+) or 6 months (D+/R-) is advised.
- *Pneumocystis jiroveci* pneumonia prophylaxis is recommended for 6 months post-transplant with trimethoprim-sulfamethoxazole or atovaquone.
- Annual total full-body skin examination, given that the most common post-LT cancer is non-melanoma skin cancer.
- Colonoscopy is the preferred modality for colon cancer screening. Screening cadence follows the general population but may consider every 5 years.
- Dual-energy x-ray absorptiometry (DXA) at 6 months post-transplant; pharmacologic therapy for T-score ≤ -2.5 or fracture risk assessment tool (FRAX) $\geq 20\%$ for major fracture risk.
- Delay pregnancy until 1-year post-transplant and with at least 6 months of graft stability. Mycophenolic acid products should be discontinued at least 6 weeks before conception in women and 90 days in men.

Calcineurin inhibitors, azathioprine and steroids are safe in pregnancy.

Outcomes: Patient survival, graft survival, cardiovascular events, renal function, de novo malignancy incidence, infection-related mortality, and quality of life.

Data Analysis: Recommendations were graded strong or weak using the Oxford Center for Evidence-Based Medicine framework. The recommendations are derived from retrospective cohort studies, systematic reviews, and extrapolations from the general population, reflecting a persistent evidence gap in prospective transplant-specific data.

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Results: The guideline provides 87 recommendations across 9 clinical domains. Long-term mortality after LT is driven predominantly by complications of immunosuppression, recurrent disease, and medical comorbidities rather than graft failure. Highlights are presented below, with key recommendations summarized (**Table 1**) and the temporal trajectory of post-transplant infections illustrated (**Figure 1**).

Rates of gastrointestinal and cardiovascular events were modestly increased during the first year after screening but became similar to controls over time. All-cause mortality did not differ between groups.

Metabolic syndrome affects more than half of LT recipients, with de novo incidence of 24.7% (95% CI 18% to 32.9%) over 15 months post-transplant.[1] Hypertension is present in 53 to 62%, dyslipidemia in 30 to 71%, diabetes in 25 to 40%, and obesity in 36 to 41% of recipients.[2] Early corticosteroid withdrawal within the first 2 months significantly reduces post-transplant diabetes and hypertension, supported by a Cochrane review of 17 randomized trials, with only a modest increase in rejection risk.[3] GLP-1 receptor agonists and SGLT-2 inhibitors are recommended as first-line agents in high-risk recipients, with referral to obesity specialists suggested as early as 3 to 6 months post-transplant in those with a body mass index above 30.[4] Hydrophilic statins (e.g. pravastatin or rosuvastatin) are preferred for dyslipidemia given their favorable CYP3A4 profile and minimal interaction with CNIs.[5] In recipients without cardiovascular or renal comorbidities, amlodipine or felodipine are the preferred first-line antihypertensive agents given the mechanism of reversal of CNI-induced renal vasoconstriction.

LT recipients have the highest risk of incident advanced CKD, with early end-stage renal disease rates rising from 21.8 to 36.3 per 1,000 patient-years between the pre-model for end-stage renal disease and end-stage renal disease eras.[6] CNI reduction combined with mycophenolate or everolimus within the

first year is strongly recommended. The landmark H2304 trial demonstrated sustained estimated glomerular filtration rate improvement with everolimus plus reduced tacrolimus through 36 months with comparable rejection rates.[7] The EVEROLIVER registry confirmed that early conversion within 3 months allowed 55% of patients with baseline estimated glomerular filtration rate below 60 mL/min/1.73 m² to recover above that threshold at month 36, with no benefit observed in those converted after 12 months.[8] Use of Belatacept and discontinuation of calcineurin inhibitors in the early postoperative period is not recommended due to high rates of graft failure.[9]

Infection timing follows a well-described trajectory: nosocomial and donor-derived infections predominate in the first month, opportunistic infections from months 1-12, and community-acquired infections thereafter (**Figure 1**). In a randomized trial of 205 CMV D+/R recipients, CMV disease incidence was significantly lower with pre-emptive weekly PCR monitoring than with universal valganciclovir prophylaxis (9% vs 19%, P=0.04), with superior CMV-specific immune reconstitution in the pre-emptive arm.[10] In refractory or resistant cases with low levels of viremia (≤20,000 IU/mL), Maribavir 400 mg twice daily is preferred, supported by a phase 3 randomized trial.[11]

LT recipients carry a 2.45-fold increased overall cancer risk compared with the general population.[12] While non-Hodgkin lymphoma carries the highest standardized incidence ratio, non-melanoma skin cancer is the most common, yet annual skin exams remain inconsistently performed. For colon cancer screening, colonoscopy is preferred over stool-based testing given an adjusted odds ratio of 2.38 (95% CI 1.07 to 5.3) for advanced adenomas in solid organ transplant recipients.[13] Serial Epstein-Barr virus PCR for post-transplant lymphoproliferative disorder screening is not supported.[14]

Post-transplant osteopenia, osteoporosis, and fractures are reported in 35%, 12%, and 20% of recipients respectively, with an incidence of 11% for vertebral fractures.[15] DXA at 6 months post-transplant and every 1 to 2 years in those with baseline abnormalities is strongly recommended. Pharmacologic therapy is indicated for T-scores ≤−2.5 or FRAX ≥20%.

Pregnancy within 12 months of transplant is associated with significantly lower live birth rates (80% vs 98%) and higher rates of rejection (46% vs 11%) compared with after 12 months.[16] Mycophenolic acid is contraindicated in pregnancy and should be discontinued at least 6 weeks before conception in women and 90 days in men.[17]

COMMENTARY

Why Is This Important?

Scientific Registry of Transplant Recipients data demonstrate excellent long-term outcomes after liver transplantation with 5- and 10-year survival approaching 82% and 69%, respectively. As graft survival continues to improve, the major threats to long-term survival shifted from graft failure to cardiovascular disease, malignancy, renal failure, and infection. Despite this transition, management of non-graft complications remains highly variable across transplant centers and primary care settings. This guideline provides the first comprehensive, evidence-based framework for long-term management of adult liver transplant recipients. Importantly, many recommendations address conditions commonly managed outside transplant centers, emphasizing the critical role of coordinated care between transplant hepatologists, primary care physicians, and other specialists.

Key Study Findings

One of the most notable observations is the unexpectedly high burden of CKD among liver transplant recipients. The EVEROLIVER registry makes a compelling case for early reduction in calcineurin inhibitors and conversion to mTOR inhibitors, while conversion after 12 months provided no benefit.[8] These data suggest a narrow therapeutic window during which renal recovery remains achievable.

The introduction of GLP-1 receptor agonists has offered a paradigm shift for therapeutic options for post-LT patients with diabetes mellitus or obesity. Additional favorable properties include their renal protective and anti-inflammatory effects. Adjusting immunosuppression while on a GLP-1 receptor agonist is not needed.[4]

Regarding post-LT malignancy, non-melanoma skin cancer is the most common, yet annual skin exams remain one of the most inconsistently performed interventions in this population. The preference for colonoscopy over stool-based testing and consideration of every 5-year surveillance should be acknowledged.[13]

The reproductive data are among the most actionable in the guideline. An 18-percentage-point difference in live birth rates and a 35-percentage-point difference in rejection rates based solely on timing of conception suggest that family planning is an integral part of every pre-transplant and post-transplant conversation.[16]

Caution

Several strong recommendations, including annual metabolic screening, are based on level 5 evidence reflecting expert consensus rather than robust data. Equity considerations are minimally

Domain	Key Recommendation	Strength/Level
Metabolic screening	Annual screening for hypertension, diabetes, obesity, and dyslipidemia in all recipients	Strong, Level 5
Corticosteroids	Early withdrawal within 2 months in recipients with diabetes mellitus or hypertension	Strong, Level 1
Diabetes, no CV/renal risk	Metformin is first-line	Strong, Level 5
Diabetes, high CV or renal risk	GLP-1 receptor agonists and/or SGLT-2 inhibitors are first-line	Strong, Level 5
Obesity (BMI >30kg/m2)	Referral to obesity specialist at 3–6 months; GLP-1 RA if diet and exercise insufficient	Strong, Level 3–5
Hypertension, no CV/CKD	Amlodipine or felodipine are first-line	Strong, Level 5
Hypertension, with CV disease or CKD	RAS inhibitors are first-line	Strong, Level 5
Dyslipidemia	Hydrophilic statins are first-line; consider ezetimibe or PCSK9 inhibitors for refractory cases	Strong, Level 5
CKD, immunosuppression	CNI reduction combined with mycophenolate or everolimus within the first year; thereafter, CNIs minimized but not eliminated	Strong, Level 1
CKD, belatacept	Contraindicated due to increased mortality risk	Strong, Level 1
CKD surveillance	Creatinine-based estimated glomerular filtration rate every 6–12 months (stages 1–3); every 1–3 months (stages 4–5)	Strong, Level 4
CMV prophylaxis, preferred strategy	Pre-emptive weekly CMV PCR for 100 days when feasible	Strong, Level 1
CMV prophylaxis, alternative	Valganciclovir prophylaxis (3 months D±/R+; 6 months D+/R−)	Strong, Level 1
CMV, refractory or resistant	Maribavir 400 mg BID (viral load ≤20,000 IU/mL); IV foscarnet for high viral load or severe disease	Strong, Level 1
Pneumocystis jiroveci pneumonia prophlaxis	Trimethoprim-sulfamethoxazole or atovaquone for 6 months	Strong, Level 2

Domain	Key Recommendation	Strength/Level
Candida prophylaxis	Risk-based assessment; fluconazole 2-4 weeks	Strong, Level 2
Post-transplant lymphoproliferative disorder screening	Serial assessment of Epstein-Barr virus PCR is not advised	Weak, Level 3
Skin cancer	Annual full-body skin examination	Strong, Level 2
Colorectal cancer	Colonoscopy preferred over stool-based testing; consider every 5 years in average-risk recipients ≥45 years	Weak, Level 3
Colorectal cancer, IBD with or without PSC	Annual colonoscopy with random biopsies	Strong, Level 1–2
Colorectal cancer, PSC without IBD	Colonoscopy every 5 years with biopsies	Strong, Level 3
Bone health	DXA at 6 months post-transplant; pharmacotherapy for T-score ≤−2.5 or FRAX ≥20%	Strong, Level 1–2
Pregnancy timing	Delay pregnancy ≥12 months post-transplant	Strong, Level 3
Pregnancy, immunosuppression	Discontinue MPA ≥6 weeks before conception in women; ≥90 days in men	Strong, Level 1

Table 1. Key recommendations from the AASLD/AST Practice Guideline on non-graft–related complications after adult liver transplantation.
BID, twice a day; BMI, body mass index; CKD, chronic kidney disease; CMV, cytomegalovirus; CNI, calcineurin inhibitor; CV, cardiovascular; DXA, dual-energy x-ray absorptiometry;GLP-1, glucagon-like peptide-1; IBD, inflammatory bowel disease; FRAX, fracture risk assessment tool; MPA, mycophenolic acid PCR, polymerase chain reaction; PSC, primary sclerosing cholangitis; RAS, renin–angiotensin system; SGLT2, sodium-glucose cotransporter-2.

addressed: differential access to GLP-1 receptor agonists and subspecialists across socioeconomic and geographic strata, an omission that implementation-focused readers should account for in local adaptation of these recommendations.

Our Practice

This guideline reinforces several aspects of my current practice while highlighting opportunities for earlier intervention. I routinely emphasize aggressive cardiovascular risk-factor modification after transplantation, but these recommendations support earlier incorporation of GLP-1 receptor agonists and SGLT-2 inhibitors in appropriate high-risk recipients. This point highlights the need for integration in a multidisciplinary fashion with other specialists such as endocrinologists, dieticians, primary care providers, and pharmacists. In this manner, we are able to identify at risk patients earlier, though access to care

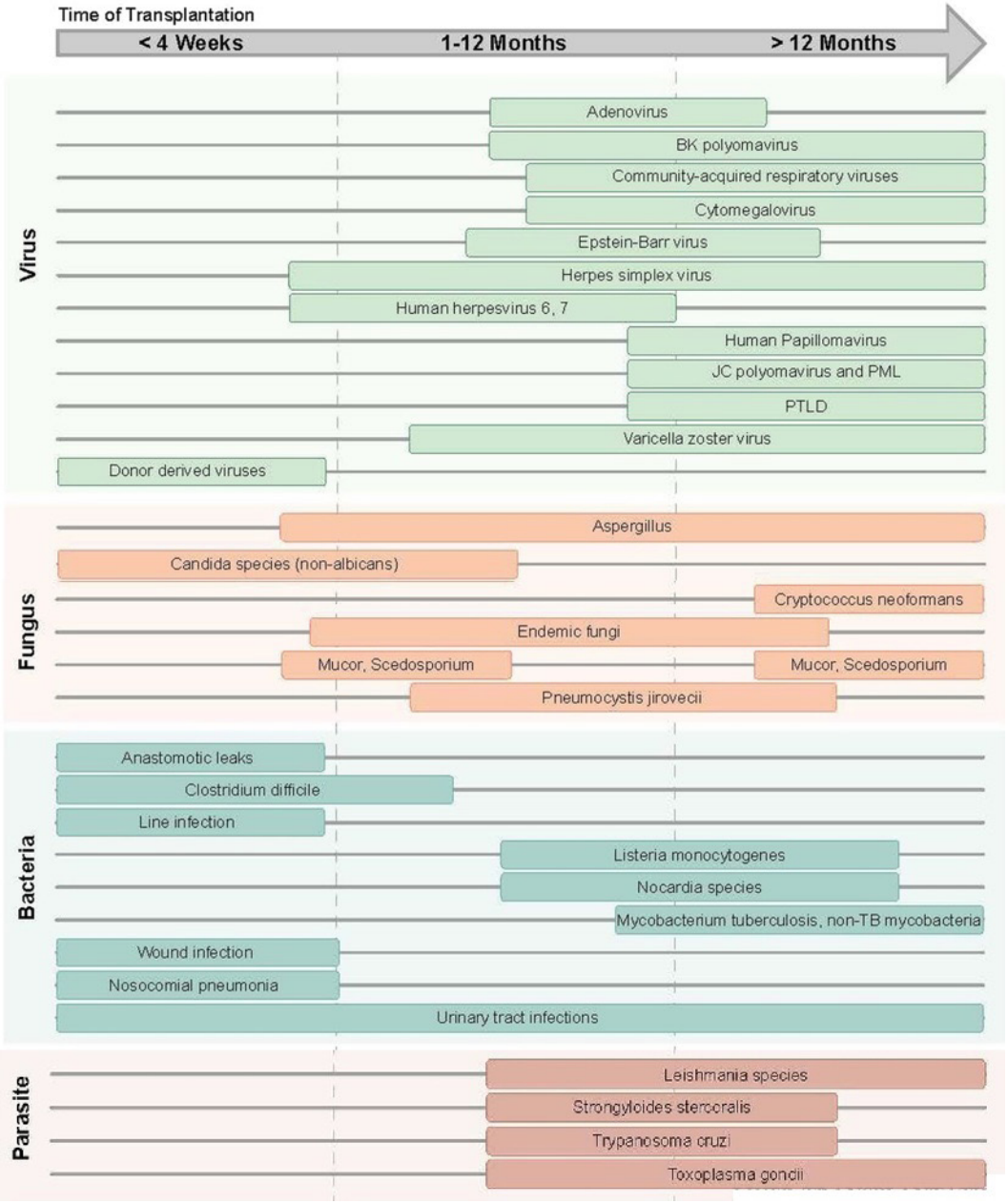

Figure 1. Timeline of common post-transplant infections. Time course of infection based upon time from the index liver transplant. PTLD, post-transplant lymphoproliferative disorder.

is often still limited by insurance barriers.

The data regarding early calcineurin inhibitor minimization are particularly compelling and reinforce the importance of recognizing chronic kidney disease before irreversible injury develops. Although we hope for renal recovery within the first year post-LT, we want to identify patients earlier before the window for safety net closes. Novel biomarkers for detecting early kidney dysfunction could aid risk stratification.

The guideline also serves as a reminder that cancer surveillance should remain a priority long after transplant follow-up intervals become less frequent. Annual dermatologic examinations and transplant-specific colorectal cancer

surveillance are interventions that can easily be overlooked during long-term care. As graft function stabilizes with time, visits with my post-LT patients focus on well-being, including quality of life, sexual health, family planning, and mental health, among others. Providers can use dot phrases to ensure all aspects are addressed, and pre-visit surveys to screen for topics that patients may not traditionally feel comfortable discussing. It takes a village to help our patients get through transplant, and the same can be said post-transplant. Integral to the care of our patients is communicating with primary care providers to ensure that these post-transplant screening metrics are addressed.

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Future Research

Future research should prioritize prospective transplant-specific studies evaluating immunosuppression strategies, metabolic therapies including GLP-1 receptor agonists, and interventions that reduce cardiovascular risk after transplantation. Biomarkers to detect early chronic kidney disease and post-transplant lymphoproliferative disorder are needed. Equally important are implementation studies evaluating how transplant centers can improve adherence to cancer surveillance, bone health screening, and preventive care recommendations across diverse patient populations.

Conflict of Interest

The authors have no conflicts of interest to disclose.

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