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The Gastroenterologist's Guide to Management of the Post-Liver Transplant Patient

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The management of the post-liver transplant patient is complex and involves a large interdisciplinary team. After referral to a transplant center, evaluation and listing, and eventual transplantation, the patient is cared for closely by the transplant center. Once deemed ready for discharge, the patient returns to the primary care provider for ongoing management of the various issues that increase in incidence post transplant such as osteoporosis, cardiovascular, and renal diseases, as well as metabolic syndrome. The role of the gastroenterologist is not well defined, but certainly, he or she may be called upon for the initial evaluation and ongoing management of gastrointestinal as well as hepatobiliary issues. This includes but is not limited to the investigation of abnormal liver tests, non-specific gastrointestinal complaints such as nausea, vomiting, or diarrhea, biliary complications, and even recurrent hepatic disease. Having familiarity with post-transplant immunosuppressive agents, drug interactions, and potential infectious and malignancy-related complications of transplant is essential, as the primary gastroenterologist may be expected in some situations to field the initial work-up, if patient access to the transplant center is limited. The aim of this review is to summarize the gastroenterologist's role in the management of the post-liver transplant patient.

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INTRODUCTION

Liver disease is insidious, progressive, and often without medical cure. Liver transplantation (LT) remains the treatment for appropriate candidates with uncontrollable symptoms or complications related to chronic liver disease. The US transplantation rate remains stable near 6300 per year, despite nearly 15,000 patients waiting [1]. Improved transplantation techniques afford the LT recipient greater life expectancy. However, metabolic syndrome, cardiovascular disease (CVD), and malignancy have increased prevalence post LT.

The pre-LT and peri-LT candidate can expect intimate involvement from a large interdisciplinary team, usually linked to the LT center. As the first post-LT anniversary approaches many patients depart the transplant center, returning to their primary care providers (PCPs). While many transplant centers continue to manage immunosuppression and certain post-LT complications, the onus of care shifts. PCPs are held accountable for managing comorbidities including: metabolic syndrome, diabetes, vaccinations, and bone health [2]. The gastroenterologist may manage surveillance for primary gastrointestinal (GI) malignancy, diagnosis and management of abnormal liver injury tests (LITs), biliary complications, and assessment of GI symptoms [3].

IMMUNOSUPPRESSION

Post-LT immunosuppression is typically deferred to the transplant center. As suggested by the 2012 American Society of Transplantation, immunosuppressive regimen will be determined by the indication for transplant and a patient's medical comorbidities [4]. The aim is the use of the lowest effective dose of immunosuppression to prevent allograft rejection and minimize medication-induced side effects. As an example, we present Mayo Clinic's practice (Table 1). However, it should be noted that there are significant center, national, and international variations in practice. Additionally, there may be specific circumstances where immunosuppressive regimens are altered based on the underlying disease process or underlying comorbidities. An example is the minimization of calcineurin inhibitor (CNI) exposure, a known nephrotoxin, in patients with renal dysfunction through the use of mammalian target of rapamycin (mTOR) inhibitors or mycophenolate (MMF) preparations or anti-metabolites (Table 4). The time of maximal immunosuppression is within the first 4 months post LT. Immunosuppression is continued lifelong. The withdrawal of immunosuppression has been successful in a minority of adult patients and is not currently recommended [5].

The medication list should be carefully reviewed as common medications used to treat GI symptoms may significantly

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Table 1 Common post-transplant immunosuppressant agents and trough levels

Name	0-4 months	4–12 months	1 year and beyond
Tacrolimus trough (ng/mL)	7–10	4–7	4–6
Cyclosporine trough (ng/mL)	200–250	150–200	50–100
Prednisone	Tapering dose	Off	Off
Mycophenolate mofetil	1000 mg BID	Off	Off
Sirolimus (ng/mL)	10–14	8–14	8–12
Everolimus (ng/mL)	4–8	4–8	4–8

Mayo Clinic's practice protocol is presented as an example. Patients are typically left on monotherapy indefinitely with few exceptions. There is wide practice variation based on LT center.

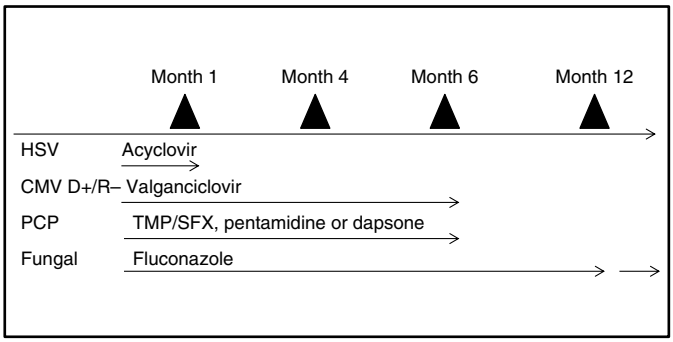

Fig. 1 Post-liver transplant infection prophylaxis. Infectious prophylaxis is LT center specific and widely variable based on patient risk factors and LT center location. Mayo Clinic's protocol is summarized graphically. Herpes (HSV) prophylaxis is continued for 1 month. In cytomegalovirus (CMV) mismatches, donor (D)-positive recipient-negative patients are treated with valganciclovir for 6 months; for positive recipients (R) weekly CMV PCR is checked for 4 months post LT; for D−/R− no CMV prophylaxis is instituted. Pneumocystis prophylaxis begins with trimethoprim/sulfamethoxazole (TMP/SFX), unless there are contraindications. Inhaled pentamidine or dapsone may be considered. Fluconazole serves as fungal prophylaxis

interact via the CYP450 enzyme pathways with immunosuppressants. Examples include: direct-acting anti-viral (DAA) therapies to treat hepatitis C virus (HCV), macrolides (e.g., clarithromycin) used for *Helicobacter pylori*, calcium channel blockers used for esophageal symptoms, and azoles used as fungal prophylaxis or to treat candidal infections [6].

Patients should be counseled on birth control post LT. While fertility may return sooner, outcomes are significantly improved by waiting to conceive for >1 year post LT [7]. MMF is associated with significant teratogenicity and prescribing providers should be aware of the Risk Evaluation and Mitigation Strategy proposed by the Food and Drug Administration [8].

INFECTION

The largest cause of morbidity and mortality post LT is infection, occurring in 75% of patients [9]. A fever at any time post LT should be aggressively evaluated regardless of an elevated white blood cell count. Cultures and imaging should be obtained to identify a pathogen and source. Immediately post-operatively, hospital-acquired and bacterial wound infections abound. Gram-negative rod (GNR) and multi-drug-resistant GNR pathogens are most common [10]. Biliary sources should be suspected. Patients receiving deceased after cardiac death (DCD) allografts are at particular risk for GNR sepsis-related mortality [11]. Viral infections such as cytomegalovirus (CMV) and Epstein–Barr virus predominate within the first 6 months. CMV-mismatched patients (donor-positive/recipient-negative) are at highest risk; CMV-negative recipients of negative donor allografts are at lowest risk [12].

Bacterial, viral, and fungal prophylaxis is routinely administered during the period of maximal immunosuppression; however, prophylactic regimens are dependent on the transplant centers and their locations (Fig. 1). Mayo Clinic protocol relies on CMV status of the donor and recipient to determine prophylactic regimen. If both donor and recipient are CMV-negative, herpes simplex virus prophylaxis alone with acyclovir (inactive against CMV) is instituted. Fungal prophylaxis may decrease the incidence but not severity of fungal infections [13]. The duration and agent used for fungal prophylaxis is widely dependent on center practice and the overall risk of patient exposure to fungi [14]. There is no specific recommendation to prevent infection from endemic fungi such as histoplasmosis or blastomycosis [15]. A special example of tailored anti-fungal would be at Mayo Clinic in Arizona, an endemic region for coccidioidomycosis. Prophylaxis is routinely instituted for the first year [16]. In patients with known exposure, prophylaxis may be continued lifelong.

Active tuberculosis (TB) is a contraindication to LT [17]. Latent TB may reactivate, and is associated with mortality rates approaching 30% [18]. Given that the incidence of TB may be 7–74 times higher than the general population, all patients undergoing evaluation for LT should be evaluated for TB [19, 20]. Those with latent TB should be treated once clinically stable post LT, as treatment may universally prevent the development of active TB [21]. Regimens include isoniazid and pyridoxine for 9 months, or rifampin for 4 months [20]. Rifampin reduces plasma levels of CNIs and mTOR inhibitors. As these medications are associated with hepatotoxicity, involvement of a transplant infectious disease specialist is likely beneficial [21].

EVALUATION OF ABNORMAL LITS

Abnormal LITs post LT may occur for a variety of reasons, some of which include emergencies. The broad categories include: biliary, vascular, and parenchymal complications. These will be discussed sequentially in depth in the following sections. Unfortunately, classical presentations are often the exception rather than the rule and as such evaluation should be thorough, given that multiple factors may occur concomitantly. While approaches may differ, our approach to the evaluation of abnormal LITs will start with a transplant Doppler ultrasound (US) to give an initial albeit insensitive evaluation of the liver parenchyma, assess for biliary ductal dilation, and to evaluate the hepatic arterial and venous flow (Fig. 2). Identification of structural abnormalities

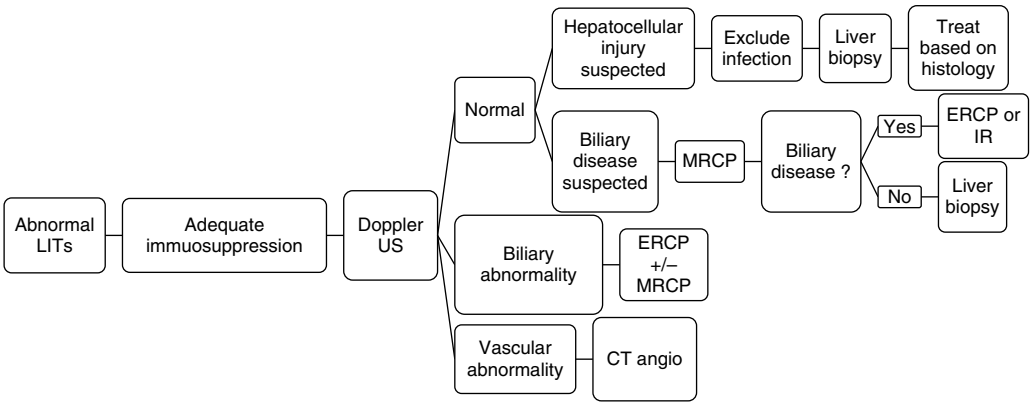

Fig. 2 Evaluation of abnormal liver injury tests. A proposed algorithm for the evaluation of abnormal liver injury tests starting with confirmation of therapeutic immunosuppression. Doppler US is a cheap and quick insensitive test to evaluate for parenchymal, vascular, or biliary disease. Definitive vascular imaging may require CT angiography (CT angio) or direct angiography in some instances. Magnetic resonance cholangiography (MRCP) is the preferred next step for evaluating the biliary tree followed by endoscopic retrograde cholangiopancreatography (ERCP). If ERCP is not feasible, then interventional radiology (IR) intervention may be pursued. Liver biopsy should be considered to rule out rejection or recurrent disease

should be pursued with more definitive testing such as computed tomography (CT) or magnetic resonance imaging (MRI). Post-LT biliary complications are best initially evaluated with MRI/magnetic resonance cholangiography (MRCP). Vascular or venous abnormalities are best evaluated with appropriately protocoled CT imaging. If clinical suspicion is raised for intrahepatic infection (e.g., abscess) CT is a reasonable assessment option. Once structural abnormalities are excluded, focus shifts toward hepatocellular causes such as rejection and recurrence of the primary disease. Serologic testing and in many cases biopsy will be necessary. Biopsy is especially important for the diagnosis and staging of severity of rejection.

BILIARY COMPLICATIONS

Biliary complications post LT may occur in up to 5–30% of patients [22–24]. Etiologies include: bile leaks and bilomas, anastomotic strictures, and non-anastomotic strictures often due to ischemic cholangiopathy, stones and casts, or recurrent cholestatic liver disease. Clinical signs and symptoms of biliary tract pathology vary, but include malaise, anorexia, weight loss, early satiety, and/or abdominal pain with or without fever. LIT patterns lack adequate sensitivity and specificity to diagnose biliary tract disease, but may be the only clinical sign [25]. Lower bilirubin levels argue against significant biliary tract disease [26]. US is often considered the first diagnostic test of choice to evaluate the presence of biliary pathology, but has low sensitivity (29–70%) and specificity (69%) [24, 25, 27].

If US is non-diagnostic and suspicion for biliary tract disease remains, the next non-invasive test of choice is MRCP. MRCP has a sensitivity and specificity well above 90% for detection of biliary pathology; however, not all biliary pathology (e.g., sludge and small stones) will present with a dilated duct [26, 28]. If US is diagnostic, it is debatable whether to proceed directly to ERCP or perform MRCP first. While MRCP is costly, it provides additional anatomic characterization which may help with the interventional endoscopist's therapeutic plan. A negative MRCP does not rule out biliary tract disease, and there may be discordance between US and MR findings.

If MRCP is negative, it is additionally debatable whether one should proceed with diagnostic ERCP or first obtain a liver biopsy which may hint at the disturbance causing the LITs, distinguishing features of large bile duct obstruction from other causes of elevated LITs such as drug effect, infection, rejection, or recurrent disease [24]. A study by Elmunzer et al. [29] showed that over 90% of ERCPs performed for therapeutic intent ultimately resulted in intervention; of those performed for diagnostic purposes only, >65% still resulted in intervention. Complication rates were low, and cost savings occurred by avoiding MR. We would recommend diagnostic ERCP only when the clinical scenario warrants the risks of the procedure. While many LT patients undergo Roux-en-Y biliary reconstruction, which makes ERCP technically more challenging, it is still feasible, especially with the use of balloon-assisted ERCP [30, 31]. Overall management requires multidisciplinary input from the surgical team, transplant hepatologist, therapeutic endoscopist, and interventional radiologist. Failure of endoscopic therapy would warrant interventional radiologic therapy, and certain refractory biliary complications may require combined therapeutic endoscopic and interventional radiology intervention (e.g., rendezvous procedures which utilize ERCP to internalize percutaneous biliary tubes).

STRICTURES

Biliary strictures may be anastomotic or non-anastomotic. Anastomotic strictures are by far the most common, accounting for 80% of stricturing disease [32]. They tend to occur early in the post-LT period; typically within the first 6 months, thereafter decreasing in incidence [24, 33]. Non-anastomotic strictures are likely the sequelae of hepatic arterial insufficiency, prolonged ischemic times, and/or immunologic mechanisms [24, 33, 34]. They tend to occur slightly later in the post-LT period but with increasing incidence during the first year. While the management of anastomotic and non-anastomotic strictures with balloon dila-

tion or stenting with exchange every 3 months is largely similar, anastomotic strictures are more likely to respond to endoscopic intervention. Data from Pasha et al. [35] suggest that maximal balloon dilation up to 10 mm limited only by duct size, in combination with maximal stent placement up to 4 ranging in size up to 11.5 French should be the treatment of choice, preventing the need for surgical revision to a Roux-en-Y choledochojejunostomy in over 90% of cases. This aggressive upfront approach may shorten the duration of therapy from a mean of 12 to <5 months.

Anastomotic strictures may predispose to bile leaks. Symptoms are non-specific and usually consist of pain. High suspicion of a bile leak clinically with evidence of rising bilirubin leads to a confirmatory ERCP in approximately 65% of cases. Additionally, sampling a fluid collection and assessing the fluid to serum bilirubin ratio is useful, as a ratio >3.25 has 73% sensitivity and 95% specificity for diagnosis [36]. Hepatic artery disease, seen in up to 53% of cases, should be suspected when refractory bile leaks occur [37].

VASCULAR COMPLICATIONS

The liver receives dual blood supply via the portal venous and hepatic arterial systems. The majority of blood supply comes from the portal venous system; however, the hepatic artery is the sole blood supply to the biliary tree. While the native liver may be able to overcome vascular insults due to the presence of collaterals, the transplanted liver typically lacks this ability and may be quite susceptible to stenoses, thromboses, and aneurysms.

Arterial complications include thrombosis, stenosis, pseudoaneurysm, or rupture. Thrombosis risk is approximately 3–12% and may present early on or late [38, 39]. Early occurrence is usually marked with abnormal LITs, fever, and, in some cases, signs of graft insufficiency or failure, which could warrant need for repeated transplantation. Stenosis may present with abnormal LITs, and reduced resistive indices on US. Hepatic artery aneurysms may develop and predispose to life-threatening bleeding with a clinical presentation ranging from an asymptomatic abnormality identified on imaging to hemodynamically significant hemobilia. Typically, Doppler US will be insufficient to characterize the vascular anatomy and CT angiography or direct angiography may be required. Given that arterial abnormalities can have dire consequences, we perform Doppler US on postoperative days 7, 21, 4 months, and annually. Reduced resistive indices on Doppler in some cases may be managed conservatively with anti-platelet therapy. Other lesions may require endovascular intervention or surgical revision. Therapy should be guided by multidisciplinary evaluation with transplant hepatology, surgery, and interventional radiology.

Portal vein thrombosis or stenosis occurs in up to 12% of cases. Severe cases may present with portal hypertension including recurrent ascites or variceal bleeding. Treatments consist of anticoagulation, thrombectomy either through interventional radiology or surgical repair [38]. The hepatic veins and inferior vena cava may also become stenosed or thrombosed and require intervention. Clinically, hepatomegaly and signs of portal hypertension may become evident.

REJECTION

Full discussion of allograft rejection is beyond the scope of this review article. However, the primary gastroenterologist should monitor for signs of rejection in transplant patients. In the majority of cases, management should occur with input from the LT center. Rejection rates have declined, but acute cellular rejection may occur in nearly a quarter of patients [40]. While most patients can overcome rejection episodes with appropriate management, up to 10% may ultimately require re-listing for transplant. Clinically, signs are non-specific, including fatigue, pain, and, in some cases, fever. There is a rise in LITs, but the pattern is non-specific as there may be a rise in transaminases or cholestatic tests such as alkaline phosphatase and bilirubin. If rejection is considered the cause of a rise in LITs, biopsy should be obtained to evaluate the severity and to rule out other causes of allograft injury or dysfunction. Biopsy is generally safe with a complication rate of about 1%, including a higher infectious risk in patients with choledochojejunostomy or biliary tract obstruction [41]. The three histologic hallmarks of rejection are: a mixed inflammatory infiltrate in the portal triad, nonsuppurative cholangitis, and endothelitis/venulitis [42]. Rejection episodes may be treated with increasing immunosuppression trough goals, intravenous Solu-Medrol, or in refractory or severe cases anti-thymocyte globulin under the supervision of practitioners familiar with these agents.

RECURRENCE OF PRIMARY DISEASE

Hepatitis C virus

HCV recurs in >90% of LT recipients; is associated with increased episodes and severity of rejection; and a recurrence of cirrhosis in as many as 10–30% of patients within 5 years, which reduces graft survival [43–45]. Organ access may be increased by leaving patients with end-stage liver disease viremic and eligible to receive infected allografts. The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America have set forth guidelines for the management of HCV post LT (Table 2). Treatment duration is 12 weeks. Significant alterations in CNI levels may occur when initiating DAA therapy. As an example, paritaprevir/ritonavir/ombitasvir/dasabuvir may increase tacrolimus to such an extent that tacrolimus may only need to be dosed weekly. In patients with known exposure to hepatitis B virus (HBV), vigilance is recommended to survey for HBV reactivation, as HCV is known to suppress HBV and treatment of HCV may result in a HBV flare [46].

Hepatitis B virus

HBV was largely a contraindication to transplant due to near universal recurrence and severe post-LT complications. With combination use of HBV immunoglobulin and viral suppression with oral agents, survival rates approach those for other LT recipients, though about half of patients will develop recurrent HBV within 5 years [47, 48]. Elevated LITs should prompt HBV DNA testing and if positive assessment for mutations. Tenofovir alafenamide may be a good option for viral suppression given the low resistance rates with tenofovir and the decreased risk of renal toxicity [49].

Table 2 IDSA/AASLD post-liver transplant hepatitis C virus treatment guidelines

Genotype	Treatment experience	Cirrhosis	Regimen	Duration (weeks)
1,4,5,6	Naïve or experienced	Noncirrhotic	Glecaprevir/Pibrentasvir OR Ledipasvir/Sofosbuvir OR Daclatasvir/Sofosbuvir OR Simeprevir/Sofosbuvir[a]	12
		Compensated	Ledipasvir/Sofosbuvir	
		Decompensated	Ledipasvir/Sofosbuvir with ribavirin	
2,3		Noncirrhotic	Glecaprevir/Pibrentasvir OR Daclatasvir/Sofosbuvir with ribavirin	
		Compensated	Daclatasvir/Sofosbuvir with ribavirin OR Glecaprevir/Pibrentasvir OR Sofosbuvir/Velpatasvir with ribavirin	
		Decompensated	Daclatasvir/Sofosbuvir with ribavirin OR Sofosbuvir/Velpatasvir with ribavirin	

Current HCV treatment guidelines as recommended by the IDSA/AASLD.
[a]Genotypes 1 and 4 only.
HCV hepatitis C virus, *AASLD* American Association for the Study of Liver Diseases, *IDSA* Infectious Diseases Society of America

Primary biliary cholangitis

While adverse outcomes and the need for re-transplantation are rare, primary biliary cholangitis recurs in as many as 50% of patients and may be affected by the choice of immunosuppressant with cyclosporine appearing to reduce the risk of recurrence compared with tacrolimus [43, 50, 51]. Anti-mitochondrial antibody titers are not helpful. Diagnosis relies on histology showing plasma cell-rich infiltrate. Recurrence typically becomes apparent within 3–6 years post LT [52, 53]. Ursodeoxycholic acid at 13–15 mg/kg per day in divided doses may reduce the risk of recurrence by up to 40% [54].

Primary sclerosing cholangitis

While LT for primary sclerosing cholangitis (PSC) accounts for a small percentage of LT in the United States, recurrence rates exceed 45% and require re-transplantation in 15% [43, 55]. Recurrence is associated with worse outcomes [51]. The diagnosis of recurrent PSC can be challenging given that post-LT cholangiopathy may mimic PSC. Mayo Clinic's practice is to attempt to avoid DCD organ implantation in these patients as outcomes may be worse [56]. However, with optimal selection of high-quality DCD organs outcomes may be equivalent to brain dead allografts [57]. Ongoing management of coexistent inflammatory bowel disease (IBD) must continue post LT. Annual colorectal cancer surveillance is recommended [58].

Autoimmune hepatitis

Recurrence rates for autoimmune hepatitis (AIH) approach 25–50% with a mean time to recurrence of 2 years [43, 55]. Significant elevations in LITs in an hepatocellular pattern may suggest recurrent disease. Biopsy should be pursued. However histologic differentiation between recurrent AIH and rejection may be difficult [59]. Adequate immunosuppression is essential and as such more aggressive therapy with the use of CNIs in combination with steroids, MMF, and/or azathioprine should be considered [60, 61].

Alcohol-related liver disease

Alcohol-related liver disease (ALD) is a common cause for LT and may surpass HCV as the leading indication for LT listing in the United States [62]. Significant effort is expended to choose candidates committed to sobriety. Despite reports of as many as half of patients transplanted for ALD resuming alcohol consumption in some form post LT, <20% will drink to such an extent to become harmful. The recurrence of ALD post LT is <5% [63]. The natural history of transplantation for ALD is similar to that of LT for other indications. Patients should continue to be monitored for alcohol use, and counseled in abstinence post LT.

Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis

Nonalcoholic steatohepatitis (NASH)-related cirrhosis will be a leading indication for LT in the United States [62]. Seventy-five to 100% of patients transplanted for cryptogenic or NASH-related cirrhosis develop steatosis by 5 years post LT. NASH may recur in 11–38% of patients [43, 64, 65]. Recurrent disease rarely necessitates re-transplantation but does increase risk of death from CVD, in keeping with an increased risk of CVD in patients with NASH not undergoing LT [63, 66]. De novo nonalcoholic fatty liver disease (NAFLD) is also of great concern post LT given that high post-LT incidence of metabolic syndrome. De novo NALFD occurs in about one-third of patients and de novo NASH in 4% [63, 67]. Rising LITs and body mass index suggest NASH. Transient elastography with controlled attenuation parameter may be useful in monitoring the degree of fibrosis and steatosis.

MANAGEMENT OF GI SIGNS AND SYMPTOMS

GI complaints are common post LT including: anorexia, nausea, vomiting, diarrhea, dyspepsia, and abdominal pain. GI bleeding may occur. The evaluation is per the current recommended guidelines as set forth by major GI societies. However, infectious causes should be aggressively pursued. Additionally, the medication list should be thoroughly screened.

Dyspepsia may be caused by infectious, medication, or anatomic causes. Endoscopy should be pursued early if serologic testing does not reveal a cause and no offending medication is identified. MMF commonly causes GI distress, including diarrhea. A trial of discontinuation or dose reduction will often prove whether or not MMF is the culprit.

Diarrhea post LT occurs commonly, but in many instances the exact cause remains elusive [68, 69]. The evaluation of acute diarrhea should exclude infectious causes such as *Clostridium difficile* and CMV. An enteric stool culture and GI pathogen panel which excludes *C. difficile* and common viruses such as adenoviruses and enteroviruses is advised. Flexible sigmoidoscopy or colonoscopy with biopsies to look for MMF-related colitis, de novo IBD, or infection is reasonable. Rarely, graft-versus-host disease may be the cause of diarrhea.

Post-LT ascites even in the absence of recurrent cirrhosis may occur in patients without significant pre-LT ascites. Causes are typically anatomic, including vena-caval or hepatic-venous stenosis, or chylous leak. Ascitic fluid assessment including albumin, total protein, and triglycerides is recommended. Transjugular liver biopsy with portal pressure measurements can determine whether an elevated hepatic-venous portal pressure gradient is present, to assess for an anatomic stenosis—potentially amenable to angioplasty—and allow tissue procurement to assess for parenchymal abnormalities.

Anemia occurs in up to 14% of LT patients with causes including: blood loss, vitamin or mineral deficiencies, and/or medications [70]. Evaluation should be pursued especially in the setting of iron deficiency anemia. Medications may account for up to 11% of cases, but in 30% of cases the cause remains cryptogenic.

INFLAMMATORY BOWEL DISEASE

IBD may complicate pre-LT and post-LT management. Eighty-five percent of PSC patients will have coexistent IBD, though interestingly the severity of PSC and thus need for LT exists in an inverse relationship with the severity of IBD and need for colectomy [71–73]. However after LT, IBD severity and neoplasia risk may be increased [74]. As a general rule, approximately a third of patients with pre-existing IBD will experience improvement, a third stability, and a third worsening of symptoms post LT [75]. De novo IBD may occur after solid organ transplant with an incidence in excess of ten times the general population, and is most apt to occur after LT specifically likely owing to its association with disease treated by LT [76]. The incidence may be as high as 30% with a median time to occurrence of 4 years [77].

There are limited data on treatment of IBD in the setting of LT. Tacrolimus is associated with increased risk of IBD relapse [78]. This is debatable however. Tacrolimus has been shown to be a superior immunosuppressant and the risk of rejection may outweigh consideration of alternate agents which have dual activity to prevent allograft rejection and treat IBD [79]. Cyclosporine has been shown to be protective, and has been used outside the LT setting to treat IBD [78]. Azathioprine may serve a dual purpose of transplant immunosuppression and IBD management. Multiple new biologics are available, though data are limited even with older agents such as infliximab or adalimumab. While the minimally available data suggest biologic treatment response similar to non-LT patients, the risk of hepatitis, infection, and malignancy remain of concern [79–81]. Vedolizumab has shown promise with 60% remission rate in those with refractory IBD post LT [82]. There do not appear to be significant adverse events yet reported, though data are limited to a very small number of patients. The lack of data and clinical complexity may warrant early consultation with the transplant center and IBD subspecialist. The data regarding the outcomes for surgical intervention are mixed [77, 79]. Data do suggest that colectomy post transplant, specifically ileo-anal pouch anastomosis, may worsen liver allograft survival [83].

METABOLIC COMPLICATIONS OF TRANSPLANT

Most LT recipients do not succumb to graft failure but to metabolic complications. Greater than 20% of LT patients die of CVD [84]. Immunosuppression accelerates CVD, weight gain, and metabolic syndrome [85]. Hyperlipidemia exacerbated by steroids may persist even after steroid withdrawal and should be managed aggressively [86]. Statins may be used post LT but there are several interactions via the CYP450 pathway. This is avoided by use of pravastatin. New-onset diabetes post LT occurs in up to 15% of patients and is likely related to immunosuppression use including corticosteroids and tacrolimus [87].

Pre-LT obesity remains a problem post LT. Morbid obesity may require surgical interventions such as the lap band or combined LT and gastric sleeve [88, 89]. Vigorous over moderate intensity exercise has been shown to improve outcomes in NAFLD, but the optimal exercise strategy is unknown for LT recipients [90].

RENAL DYSFUNCTION

Renal dysfunction is one of the most common complications of LT immunosuppression [91]. Twenty percent of patients will develop chronic kidney disease by 5 years post LT; 25% will develop end-stage renal disease by 10 years [92]. Few patients will require renal transplantation. Renal-sparing protocols which consist of lower trough CNIs in combination with MMF or mTOR inhibitors may delay kidney injury [93, 94].

MALIGNANCY INCIDENCE AND SCREENING

Cancer risk is increased 11-fold post LT. The risk is most pronounced in younger patients <65 years and highest within the first 2 years post LT [95]. However, the overall risk of any malignancy exceeds 40% by 20 years post LT [96]. Skin cancer is the most common malignancy. Yearly dermatologic evaluation is warranted. Three major classes of malignancy occur post LT: those related to recurrent primary hepatic malignancy: hepatocellular carcinoma (HCC), cholangiocarcinoma, or neuroendocrine tumor; malignancy related to transplant: post-transplant lymphoproliferative disorder; and an increased incidence of malignancies seen in the general population.

Liver cancer is the second most common solid organ malignancy post LT following lung [97]. Transplantation for HCC

Table 3 Post transplant malignancies and screening recommendations

Cancer	Incidence %	Standardized incidence ratio	Screening[a]
Skin	3.3–8	13.9	Annual skin exam
Lung	0.9	13.77	Annual chest radiograph
Liver	0.5	77.94	CT or MRI first 2 years post LT at 6–12 month intervals, then annual liver ultrasound
Colorectal	0.4	7.61	Screening colonoscopy every 5–10 years Annual colonoscopy if PSC and IBD with chromoendoscopy or random biopsies
Prostate	0.4	2.34	Yearly PSA and digital rectal examination
Breast	0.3	4.00	Yearly mammogram
Head and Neck	0.3	19.29–61.59	Panorex in smokers or those with alcohol-related liver disease
Pancreas	0.1	12.08	No specific guideline PMNs managed as per non-LT
Renal	0.1	8.71	Urinalysis
Esophagus	0.1	22.69	No specific guideline
Stomach	0.07	10.90	No specific guideline
Small Intestine	0.03	14.44	No specific guideline
PTLD/lymphoma	1.2	52.90	No specific guideline

[a]There is significant practice variation based on LT center.
CT computed tomography, *MRI* magnetic resonance imaging, *LT* liver transplantation, *PSA* prostate-specific antigen, *PSC* primary sclerosing cholangitis, *IBD* inflammatory bowel disease, *PTLD* post-transplant lymphoproliferative disorder, *IPMN* intraductal papillary mucinous neoplasm

within Milan (tumor size <5 cm and no more than 3 tumors equal or <3 cm) or the University of California, San Francisco criteria (single lesion no >6.5 cm or no more than 3 tumors, the largest of which is <4.5 cm) has produced excellent results. Recurrence rates for HCC approach 15%, with the highest risk within the first 2 years.

As part of a transplant evaluation, many abnormalities may be incidentally discovered. Common occurrence is the detection of pulmonary nodules and cystic lesions of the pancreas. We follow Fleischner society guidelines with regards to pulmonary nodules. Intraductal papillary mucinous tumors of the pancreas are followed per current standard guidelines in the non-transplant population given the largely benign course; however, malignant potential exists [98]. Overall cancer risk, as summarized from a study by Zhou et al. [97], and screening recommendations are found in Table 3.

The risk of colon cancer may be twice as high in patients with liver disease compared with the general population, and risk does not decrease post LT [99]. Additionally, post-LT patients may develop GI malignancy a median decade earlier than non-LT patients [96]. Various strategies have been recommended from aggressive strategies to following routine guidelines for non-LT patients. Strategies are again largely based on local practice Table 3.

Tobacco and alcohol use are strongly discouraged post LT due to worse outcomes [100]. Tobacco may increase head and neck cancers as well as accelerating post-LT CVD. Alcohol use may be a difficult discussion to have with patients, especially those who may have been transplanted for reasons other than ALD. For those with a history of alcohol abuse, approximately 12% will relapse into a pattern of harmful drinking. Age >50 years at the time of transplant, short-term sobriety <6 months and higher high-risk alcoholism relapse (HRAR) score (based on duration of alcohol use, number of drinks per day, and prior inpatient rehab) all increase risk. Regarding the HRAR score, if >3, relapse rates are 100%; if no risk factors are present, the risk is <5% [101]. The median rate of relapse to any drinking is 261 days, and while overall graft survival is lower in patients who drink it is not statistically significantly so [102]. However excessive alcohol consumption decreases survival regardless of the indication for transplant and as such should be discouraged [103].

ELECTIVE SURGERY

At Mayo Clinic, elective procedures are deferred for a minimum of 4 months. Abdominal hernia repairs are most common. Clinical experience suggests patients fare well. In a large cohort of organ transplant recipients, colorectal surgery appeared to be safe with no patient suffering a postoperative mortality for an elective procedure [104]. mTOR inhibitors impair wound healing and should be avoided peri-operatively in deference to CNIs.

CONCLUSION

Management of the post-LT patient is complex and requires continued input from the LT center, PCP and primary gastroenterologist. The exact role expected of each may be blurred but communication between providers is essential to ensure the delivery of optimal care. The primary gastroenterologist may be called

Table 4 Immunosuppressant side effect profile

Name	Class	Toxicity						Special consideration
		Renal	Neuro	DM	HTN	BMS	HLD	
Tacrolimus	CNI	X	X	X	X		X	Hyperkalemia
Cyclosporine	CNI	X	X	X	X		X	Hyperkalemia GingivalHyperplasia Hypertrichosis
Mycophenolate	A-M					X		Teratogen GI side effects and colitis Increased risk for viral infections
Prednisone	CS			X	X		X	Osteoporosis Weight gain Impaired wound healing
Sirolimus/everolimus	mTOR	X	X*			X	X	Impaired wound healing PneumonitisProteinuria
Azathioprine	A-M					X		Hepatotoxicity Lymphoma risk Drug interaction with allopurinol

Toxicities include nephrotoxicity (renal), neurotoxicity (neuro) such as headache, in the case of everolimus (*) mood effects and depression have been noted, DM, BM, and HLD. Given high potential for drug interactions, pharmacy consultation is advised when new medications are prescribed. As a general rule, we recommend against herbal or dietary supplement use to avoid unintended drug interactions

CNI calcineurin inhibitors, *A-M* anti-metabolite, *CS* corticosteroid, *mTOR* mechanistic target of rapamycin, *HTN* hypertension, *BMS* bone marrow suppression, *HLD* hyperlipidemia, *DM* diabetes mellitus, *HLD* hyperlipidemia

upon to address the treatment of ongoing or recurrent hepatic disease such as HCV, biliary complications, ongoing screening for GI-related malignancies, and for the evaluation of GI symptoms.

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CONFLICT OF INTEREST

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REFERENCES

1. UNOS. https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/.
2. Heller JC, Prochazka AV, Everson GT, Forman LM. Long-term management after liver transplantation: primary care physician versus hepatologist. Liver Transplant. 2009;15:1330–5.
3. McCashland TM. Posttransplantation care: role of the primary care physician versus transplant center. Liver Transplant. 2001;7 Suppl 1:S2–12.
4. Lucey MR, Terrault N, Ojo L, et al. Long-term management of the successful adult liver transplant: 2012 Practice Guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Liver Transplant. 2013;19:3–26.
5. Devlin J, Doherty D, Thomson L, et al. Defining the outcome of immunosuppression withdrawal after liver transplantation. Hepatology (Baltim, Md). 1998;27:926–33.
6. Pillai AA, Levitsky J. Overview of immunosuppression in liver transplantation. World J Gastroenterol. 2009;15:4225–33.
7. Coscia LA, Constantinescu S, Moritz MJ, et al. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. Clin Transpl. 2010:65–85.
8. Risk Evaluation and Mitigation Strategy. https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm318880.htm.
9. Torbenson M, Wang J, Nichols L, Jain A, Fung J, Nalesnik MA. Causes of death in autopsied liver transplantation patients. Mod Pathol. 1998;11:37–46.
10. Patel G, Huprikar S. Infectious complications after orthotopic liver transplantation. Semin Respir Crit Care Med. 2012;33:111–24.
11. Qiao B, Wu J, Wan Q, Zhang S, Ye Q. Factors influencing mortality in abdominal solid organ transplant recipients with multidrug-resistant gram-negative bacteremia. BMC Infect Dis. 2017;17:171.
12. Weigand K, Schnitzler P, Schmidt J, et al. Cytomegalovirus infection after liver transplantation incidence, risks, and benefits of prophylaxis. Transplant Proc. 2010;42:2634–41.
13. Holt C, Winston DJ. Transplantation of the liver. 3 ed. Amsterdam: Elsevier; 2015.
14. Giannella M, Bartoletti M, Morelli M, et al. Antifungal prophylaxis in liver transplant recipients: one size does not fit all. Transplant Infect Dis. 2016;18:538–44.
15. Miller R, Assi M. Practice ASTIDCo. Endemic fungal infections in solid organ transplantation. Am J Transplant. 2013;13 Suppl 4:250–61.
16. Blair JE. Coccidioidomycosis in liver transplantation. Liver Transplant. 2006;12:31–39.
17. Aguado JM, Herrero JA, Gavalda J, et al. Clinical presentation and outcome of tuberculosis in kidney, liver, and heart transplant recipients in Spain. Spanish Transplantation Infection Study Group, GESITRA. Transplantation. 1997;63:1278–86.
18. Holty JE, Gould MK, Meinke L, Keeffe EB, Ruoss SJ. Tuberculosis in liver transplant recipients: a systematic review and meta-analysis of individual patient data. Liver Transplant. 2009;15:894–906.
19. Liu J, Yan J, Wan Q, Ye Q, Huang Y. The risk factors for tuberculosis in liver or kidney transplant recipients. BMC Infect Dis. 2014;14:387.

20. Subramanian AK, Morris MI. Practice ASTIDCo. *Mycobacterium tuberculosis* infections in solid organ transplantation. Am J Transplant. 2013;13 Suppl 4:68–76.
21. Sidhu A, Verma G, Humar A, Kumar D. Outcome of latent tuberculosis infection in solid organ transplant recipients over a 10-year period. Transplantation. 2014;98:671–5.
22. Johnston TD, Gates R, Reddy KS, Nickl NJ, Ranjan D. Nonoperative management of bile leaks following liver transplantation. Clin Transplant. 2000;14(4 Part 2):365–9.
23. Rerknimitr R, Sherman S, Fogel EL, et al. Biliary tract complications after orthotopic liver transplantation with choledochocholedochostomy anastomosis: endoscopic findings and results of therapy. Gastrointest Endosc. 2002;55:224–31.
24. Balderramo D, Navasa M, Cardenas A. Current management of biliary complications after liver transplantation: emphasis on endoscopic therapy. Gastroenterol Y Hepatol. 2018;41:107–15.
25. Kohli DR, Vachhani R, Shah TU, BouHaidar DS, Siddiqui MS. Diagnostic accuracy of laboratory tests and diagnostic imaging in detecting biliary strictures after liver transplantation. Dig Dis Sci. 2017;62:1327–33.
26. Catalano MF, Van Dam J, Sivak MV Jr. Endoscopic retrograde cholangiopancreatography in the orthotopic liver transplant patient. Endoscopy. 1995;27:584–8.
27. Sharma S, Gurakar A, Jabbour N. Biliary strictures following liver transplantation: past, present and preventive strategies. Liver Transplant. 2008;14:759–69.
28. Jorgensen JE, Waljee AK, Volk ML, et al. Is MRCP equivalent to ERCP for diagnosing biliary obstruction in orthotopic liver transplant recipients? A meta-analysis. Gastrointest Endosc. 2011;73:955–62.
29. Elmunzer BJ, Debenedet AT, Volk ML, et al. Clinical yield of diagnostic endoscopic retrograde cholangiopancreatography in orthotopic liver transplant recipients with suspected biliary complications. Liver Transplant. 2012;18:1479–84.
30. Chahal P, Baron TH, Poterucha JJ, Rosen CB. Endoscopic retrograde cholangiography in post-orthotopic liver transplant population with Roux-en-Y biliary reconstruction. Liver Transplant. 2007;13:1168–73.
31. Dellon ES, Kohn GP, Morgan DR, Grimm IS. Endoscopic retrograde cholangiopancreatography with single-balloon enteroscopy is feasible in patients with a prior Roux-en-Y anastomosis. Dig Dis Sci. 2009;54:1798–803.
32. Thethy S, Thomson B, Pleass H, et al. Management of biliary tract complications after orthotopic liver transplantation. Clin Transplant. 2004;18:647–53.
33. Seehofer D, Eurich D, Veltzke-Schlieker W, Neuhaus P. Biliary complications after liver transplantation: old problems and new challenges. Am J Transplant. 2013;13:253–65.
34. de la Mora-Levy JG, Baron TH. Endoscopic management of the liver transplant patient. Liver Transplant. 2005;11:1007–21.
35. Pasha SF, Harrison ME, Das A, et al. Endoscopic treatment of anastomotic biliary strictures after deceased donor liver transplantation: outcomes after maximal stent therapy. Gastrointest Endosc. 2007;66:44–51.
36. DeBenedet AT, Scheiman JM, Elta GH, Elmunzer BJ. Peritoneal fluid bilirubin to serum bilirubin ratio for the diagnosis of bile leaks in orthotopic liver transplant recipients. Dig Dis Sci. 2013;58:3044–8.
37. DaVee T, Geevarghese SK, Slaughter JC, Yachimski PS. Refractory anastomotic bile leaks after orthotopic liver transplantation are associated with hepatic artery disease. Gastrointest Endosc. 2017;85:984–92.
38. Pawlak J, Grodzicki M, Leowska E, et al. Vascular complications after liver transplantation. Transplant Proc. 2003;35:2313–5.
39. Piardi T, Lhuaire M, Bruno O, et al. Vascular complications following liver transplantation: a literature review of advances in 2015. World J Hepatol. 2016;8:36–57.
40. Nacif LS, Pinheiro RS, Pecora RA, et al. Late acute rejection in liver transplant: a systematic review. Arq Bras De Cir Dig. 2015;28:212–5.
41. Larson AM, Chan GC, Wartelle CF, et al. Infection complicating percutaneous liver biopsy in liver transplant recipients. Hepatol (Baltim, Md). 1997;26:1406–9.
42. Demetris AJ, Batts KP, Dhillon AP, et al. Banff schema for grading liver allograft rejection: an international consensus document. Hepatology (Baltimore, Md). 1997;25:658-63.
43. Kotlyar DS, Campbell MS, Reddy KR. Recurrence of diseases following orthotopic liver transplantation. Am J Gastroenterol. 2006;101:1370–8.
44. Berenguer M, Ferrell L, Watson J, et al. HCV-related fibrosis progression following liver transplantation: increase in recent years. J Hepatol. 2000;32:673–84.
45. Garcia-Retortillo M, Forns X, Feliu A, et al. Hepatitis C virus kinetics during and immediately after liver transplantation. Hepatol (Baltim, Md). 2002;35:680–7.
46. Bersoff-Matcha SJ, Cao K, Jason M, et al. Hepatitis B virus reactivation associated with direct-acting antiviral therapy for chronic hepatitis c virus: a review of cases reported to the U.S. Food and Drug Administration Adverse Event Reporting System. Ann Intern Med. 2017;166:792–8.
47. Anselmo DM, Ghobrial RM, Jung LC, et al. New era of liver transplantation for hepatitis B: a 17-year single-center experience. Ann Surg. 2002;235:611–20.
48. Oldakowska-Jedynak U, Paczek L, Foroncewicz B, et al. Prevention of hepatitis B recurrence after liver transplantation using lamivudine and hepatitis B immune globulin. Ann Transplant. 2007;12:28–32.
49. Bam RA, Yant SR, Cihlar T. Tenofovir alafenamide is not a substrate for renal organic anion transporters (OATs) and does not exhibit OAT-dependent cytotoxicity. Antivir Ther. 2014;19:687–92.
50. Dmitrewski J, Hubscher SG, Mayer AD, Neuberger JM. Recurrence of primary biliary cirrhosis in the liver allograft: the effect of immunosuppression. J Hepatol. 1996;24:253–7.
51. Pena Polanco NA, Levy C, Martin EF. Cholestatic liver diseases after liver transplant. Clin Liver Dis. 2017;21:403–20.
52. Sylvestre PB, Batts KP, Burgart LJ, Poterucha JJ, Wiesner RH. Recurrence of primary biliary cirrhosis after liver transplantation: histologic estimate of incidence and natural history. Liver Transplant. 2003;9:1086–93.
53. Liermann Garcia RF, Evangelista Garcia C, McMaster P, Neuberger J. Transplantation for primary biliary cirrhosis: retrospective analysis of 400 patients in a single center. Hepatology (Baltim, Md). 2001;33:22–27.
54. Bosch A, Dumortier J, Maucort-Boulch D, et al. Preventive administration of UDCA after liver transplantation for primary biliary cirrhosis is associated with a lower risk of disease recurrence. J Hepatol. 2015;63:1449–58.
55. Gautam M, Cheruvattath R, Balan V. Recurrence of autoimmune liver disease after liver transplantation: a systematic review. Liver Transplant. 2006;12:1813–24.
56. Sundaram V, Choi G, Jeon CY, et al. Donation after cardiac death liver transplantation in primary sclerosing cholangitis: proceed with caution. Transplantation. 2015;99:973–8.
57. Trivedi PJ, Scalera I, Slaney E, et al. Clinical outcomes of donation after circulatory death liver transplantation in primary sclerosing cholangitis. J Hepatol. 2017;67:957–65.
58. Desai D, Desai N. Colorectal cancer surveillance in inflammatory bowel disease: a critical analysis. World J Gastrointest Endosc. 2014;6:541–8.
59. Hubscher SG. Recurrent autoimmune hepatitis after liver transplantation: diagnostic criteria, risk factors, and outcome. Liver Transplant. 2001;7:285–91.
60. Edmunds C, Ekong UD. Autoimmune liver disease post-liver transplantation: a summary and proposed areas for future research. Transplantation. 2016;100:515–24.
61. Mottershead M, Neuberger J. Transplantation in autoimmune liver diseases. World J Gastroenterol. 2008;14:3388–95.
62. Goldberg D, Ditah IC, Saeian K, et al. Changes in the prevalence of hepatitis C virus infection, nonalcoholic steatohepatitis, and alcoholic liver disease among patients with cirrhosis or liver failure on the waitlist for liver transplantation. Gastroenterology. 2017;152:1090–9 e1091.
63. Burra P, Lucey MR. Liver transplantation in alcoholic patients. Transplant Int. 2005;18:491–8.
64. Contos MJ, Cales W, Sterling RK, et al. Development of nonalcoholic fatty liver disease after orthotopic liver transplantation for cryptogenic cirrhosis. Liver Transplant. 2001;7:363–73.
65. Kim WR, Poterucha JJ, Porayko MK, Dickson ER, Steers JL, Wiesner RH. Recurrence of nonalcoholic steatohepatitis following liver transplantation. Transplantation. 1996;62:1802–5.
66. Dureja P, Mellinger J, Agni R, et al. NAFLD recurrence in liver transplant recipients. Transplantation. 2011;91:684–9.
67. Dumortier J, Giostra E, Belbouab S, et al. Nonalcoholic fatty liver disease in liver transplant recipients: another story of "seed and soil". Am J Gastroenterol. 2010;105:613–20.
68. Ginsburg PM, Thuluvath PJ. Diarrhea in liver transplant recipients: etiology and management. Liver Transplant. 2005;11:881–90.
69. Wong NA, Bathgate AJ, Bellamy CO. Colorectal disease in liver allograft recipients—a clinicopathological study with follow-up. Eur J Gastroenterol Hepatol. 2002;14:231–6.
70. Corless I, Preston C, Millson C. Anaemia in the post liver transplant population—an under-investigated problem. Gut. 2009;58:A71–A72.
71. Loftus EV Jr, Sandborn WJ, Lindor KD, Larusso NF. Interactions between chronic liver disease and inflammatory bowel disease. Inflamm Bowel Dis. 1997;3:288–302.
72. Filipec Kanizaj T, Mijic M. Inflammatory bowel disease in liver transplanted patients. World J Gastroenterol. 2017;23:3214–27.

73. Navaneethan U, Venkatesh PG, Mukewar S, et al. Progressive primary sclerosing cholangitis requiring liver transplantation is associated with reduced need for colectomy in patients with ulcerative colitis. Clin Gastroenterol Hepatol. 2012;10:540–6.
74. Ho GT, Seddon AJ, Therapondos G, Satsangi J, Hayes PC. The clinical course of ulcerative colitis after orthotopic liver transplantation for primary sclerosing cholangitis: further appraisal of immunosuppression post transplantation. Eur J Gastroenterol Hepatol. 2005;17:1379–85.
75. Singh S, Loftus EV Jr, Talwalkar JA. Inflammatory bowel disease after liver transplantation for primary sclerosing cholangitis. Am J Gastroenterol. 2013;108:1417–25.
76. Verdonk RC, Dijkstra G, Haagsma EB, et al. Inflammatory bowel disease after liver transplantation: risk factors for recurrence and de novo disease. Am J Transplant. 2006;6:1422–9.
77. Indriolo A, Ravelli P. Clinical management of inflammatory bowel disease in the organ recipient. World J Gastroenterol. 2014;20:3525–33.
78. Haagsma EB, Van Den Berg AP, Kleibeuker JH, Slooff MJ, Dijkstra G. Inflammatory bowel disease after liver transplantation: the effect of different immunosuppressive regimens. Aliment Pharmacol Ther. 2003;18:33–44.
79. Schnitzler F, Friedrich M, Stallhofer J, et al. Solid organ transplantation in patients with inflammatory bowel diseases (IBD): analysis of transplantation outcome and IBD activity in a large single center cohort. PLoS ONE. 2015;10:e0135807.
80. Mohabbat AB, Sandborn WJ, Loftus EV Jr, Wiesner RH, Bruining DH. Anti-tumour necrosis factor treatment of inflammatory bowel disease in liver transplant recipients. Aliment Pharmacol Ther. 2012;3:569–74.
81. Sandhu A, Alameel T, Dale CH, Levstik M, Chande N. The safety and efficacy of antitumour necrosis factor-alpha therapy for inflammatory bowel disease in patients post liver transplantation: a case series. Aliment Pharmacol Ther. 2012;36:159–65.
82. Olmedo Martin RV, Amo Trillo V, Gonzalez Grande R, Jimenez Perez M. Efficacy and safety of vedolizumab as a treatment option for moderate to severe refractory ulcerative colitis in two patients after liver transplant due to primary sclerosing cholangitis. Rev Esp De Enferm Dig. 2017;109:659–62.
83. Trivedi PJ, Reece J, Laing RW, et al. Ileo-anal pouch anastomosis negatively impacts graft survival following liver transplantation for primary sclerosing cholangitis. J Hepatol. 2017;66:S6–7.
84. Pruthi J, Medkiff KA, Esrason KT, et al. Analysis of causes of death in liver transplant recipients who survived more than 3 years. Liver Transplant. 2001;7:811–5.
85. Gill JS. Cardiovascular disease in transplant recipients: current and future treatment strategies. Clin J Am Soc Nephrol. 2008;3 Suppl 2:S29–37.
86. Moench C, Barreiros AP, Schuchmann M, et al. Tacrolimus monotherapy without steroids after liver transplantation–a prospective randomized double-blinded placebo-controlled trial. Am J Transplant. 2007;7:1616–23.
87. Marchetti P. New-onset diabetes after liver transplantation: from pathogenesis to management. Liver Transplant. 2005;11:612–20.
88. Campsen J, Zimmerman M, Shoen J, et al. Adjustable gastric banding in a morbidly obese patient during liver transplantation. Obes Surg. 2008;18:1625–7.
89. Heimbach JK, Watt KD, Poterucha JJ, et al. Combined liver transplantation and gastric sleeve resection for patients with medically complicated obesity and end-stage liver disease. Am J Transplant. 2013;13:363–8.
90. Kistler KD, Brunt EM, Clark JM. et al. Physical activity recommendations, exercise intensity, and histological severity of nonalcoholic fatty liver disease. Am J Gastroenterol. 2011;106:460–8; quiz 469.
91. Millis JM, McDiarmid SV, Hiatt JR, et al. Randomized prospective trial of OKT3 for early prophylaxis of rejection after liver transplantation. Transplantation. 1989;47:82–88.
92. Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med. 2003;349:931–40.
93. Manzia TM, De Liguori Carino N, Orlando G, et al. Use of mycophenolate mofetil in liver transplantation: a literature review. Transplant Proc. 2005;37:2616–7.
94. Neff GW, Montalbano M, Slapak-Green G, et al. Sirolimus therapy in orthotopic liver transplant recipients with calcineurin inhibitor related chronic renal insufficiency. Transplant Proc. 2003;35:3029–31.
95. Chak E, Saab S. Risk factors and incidence of de novo malignancy in liver transplant recipients: a systematic review. Liver Int. 2010;30:1247–58.
96. Finkenstedt A, Graziadei IW, Oberaigner W, et al. Extensive surveillance promotes early diagnosis and improved survival of de novo malignancies in liver transplant recipients. Am J Transplant. 2009;9:2355–61.
97. Zhou J, Hu Z, Zhang Q, et al. Spectrum of de novo cancers and predictors in liver transplantation: analysis of the scientific registry of transplant recipients database. PLoS ONE. 2016;11:e0155179.
98. Lennon AM, Victor D, Zaheer A, et al. Liver transplant patients have a risk of progression similar to that of sporadic patients with branch duct intraductal papillary mucinous neoplasms. Liver Transplant. 2014;20:1462–7.
99. Komaki Y, Komaki F, Micic D, Ido A, Sakuraba A. Risk of colorectal cancer in chronic liver diseases: a systematic review and meta-analysis. Gastrointest Endosc. 2017;86:93–104.e105.
100. Liu Q, Yan L, Xu C, Gu A, Zhao P, Jiang ZY. Increased incidence of head and neck cancer in liver transplant recipients: a meta-analysis. BMC Cancer. 2014;14:776.
101. De Gottardi A, Spahr L, Gelez P, et al. A simple score for predicting alcohol relapse after liver transplantation: results from 387 patients over 15 years. Arch Intern Med. 2007;167:1183–8.
102. Rice JP, Eickhoff J, Agni R, Ghufran A, Brahmbhatt R, Lucey MR. Abusive drinking after liver transplantation is associated with allograft loss and advanced allograft fibrosis. Liver Transplant. 2013;19:1377–86.
103. Faure S, Herrero A, Jung B, et al. Excessive alcohol consumption after liver transplantation impacts on long-term survival, whatever the primary indication. J Hepatol. 2012;57:306–12.
104. Reshef A, Stocchi L, Kiran PR. Colorectal resection in transplant recipients: is it safe? Gastroenterology. 2011;1:S1048.