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REVIEW ARTICLE

Evolving challenges with long-term care of liver transplant recipients

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Abstract

The number of liver transplants (LT) performed worldwide continues to rise, and LT recipients are living longer post-transplant. This has led to an increasing number of LT recipients requiring lifelong care. Optimal care post-LT requires careful attention to both the allograft and systemic issues that are more common after organ transplantation. Common causes of allograft dysfunction include rejection, biliary complications, and primary disease recurrence. While immunosuppression prevents rejection and reduces incidences of some primary disease recurrence, it has detrimental systemic effects. Most commonly, these include increased incidences of metabolic syndrome, various malignancies, and infections. Therefore, it is of utmost importance to optimize immunosuppression regimens to prevent allograft dysfunction while also decreasing the risk of systemic complications. Institutional protocols to screen for systemic disease and heightened clinical suspicion also play an important role in providing optimal long-term post-LT care. In this review, we discuss these common complications of LT as well as unique considerations when caring for LT recipients in the years after transplant.

KEYWORDS
allograft rejection, biliary complications, immunosuppression, liver transplant, post-transplant infection, post-transplant malignancy, post-transplant metabolic syndrome

1 | INTRODUCTION

While there has been a shift in the epidemiology of diseases leading to liver transplantation (LT), the incidence of chronic liver disease and associated complications is rising worldwide.[1–4] Acute complications of LT are well-established and historically led to low rates of long-term patient survival.[5,6] With the advent of modern immunosuppression, LT recipients are living longer with substantial improvements in graft and patient survival.[7] This has led to increasing numbers of transplant recipients requiring lifelong care. In 2020, 98 842 LT recipients were living with a functioning graft, the majority of whom were transplanted as adults.[8] It is well-documented that the leading causes of late mortality after LT are graft failure, renal dysfunction, cardiovascular disease, and malignancy. With this in mind, focus must be turned to long-term care of both the graft and the patient. In this review, we discuss common complications and unique considerations when caring for LT recipients in the years after transplantation (Figure 1).

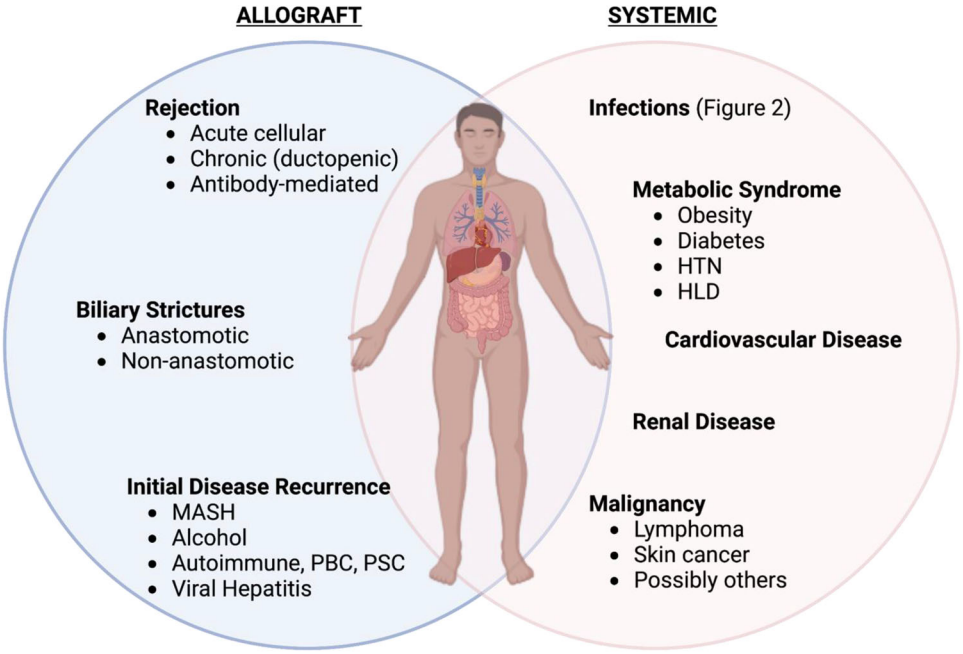

FIGURE 1 Liver transplant recipients are at risk for both graft-specific and systemic complications throughout their lifetime. Optimal long-term care of transplant recipients requires heightened attention to these conditions in addition to usual age-appropriate care. HLD, hyperlipidemia; HTN, hypertension; MASH, metabolic dysfunction-associated steatohepatitis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis. Figure generated using www.biorender.com.

2 | GRAFT DYSFUNCTION AND REJECTION

Careful attention to the allograft is paramount in caring for the LT recipient. Allograft dysfunction has varying clinical presentations at different phases post-LT. Acute causes of graft dysfunction include vascular complications such as hepatic artery thrombosis (HAT), primary graft nonfunction (PNF)/early graft dysfunction, and early acute cellular rejection (ACR). These are discussed here only in the context of their implications for long-term graft function. Long-term graft dysfunction results from various insults including late ACR or antibody mediated rejection (AMR), chronic (ductopenic) rejection, biliary strictures, and recurrence of primary liver disease. Given the significant shortage of donated organs, there is a push to use marginal donors (e.g., donors after cardiac death, donors exposed to hepatitis B and C, and older donors) which can greatly impact long-term graft function.

2.1 | Late ACR and AMR

Late ACR has been variably defined as ACR occurring after 1–6 months post-LT.[9] ACR is a T-cell mediated inflammatory process affecting the bile ducts and vascular endothelium.[10,11] Late ACR occurs after decreasing initial immunosuppression and generally results from being under-immunosuppressed. It is most commonly discovered with asymptomatic transaminase elevations. Definitive diagnosis requires histopathology demonstrating at least two of the following: (i) portal inflammation, (ii) bile duct damage, (iii) subendothelial inflammation in the portal and hepatic venules (endotheliitis).[10] Depending on the severity of the biochemical and histopathological findings, late ACR can be treated by increasing the backbone immunosuppression (e.g., calcineurin inhibitors (CNI)) dose with or without pulse dose steroids. In severe, steroid-refractory cases, lymphocyte depleting therapy with anti-thymocyte globulin may be required. Early recognition and treatment of late ACR has been shown in multiple retrospective cohort studies to decrease the risk of chronic rejection and improve graft and patient survival.[9,12,13]

AMR is increasingly recognized as a cause of liver allograft dysfunction.[14] Traditionally, the liver was thought to be protected from AMR owing to (1) the dense sinusoidal network that "absorbs" antibodies, (2) secretion of soluble HLA1 to neutralize antibodies, and (3) the regenerative capacity of the liver. Diagnosis of AMR is made with (1) positive donor specific antibody (DSA) screen, (2) exclusion of other causes, and (3) characteristic histology, including complement component 4d (C4d) staining.[15] Presentation of AMR varies depending on the time course. In the early post-operative period, AMR presents with early graft dysfunction, and in the later period, it is associated with chronic rejection. However, the correlation with chronic rejection does not imply causation, as ongoing inflammation (e.g., ACR or infection) upregulates allograft class II expression, resulting in circulating DSA binding with subsequent allograft injury.[16] The backbone of AMR treatment is plasmapheresis. Use of T-cell depleting therapy (i.e., anti-thymocyte globulin), B-cell depleting therapy (i.e., rituximab), or IVIG depends on the timing relative to transplant and center-specific protocols.[16] As AMR becomes an increasingly recognized cause of graft dysfunction, it will be important to further elucidate predictive factors to facilitate prevention and early treatment.

2.2 | Chronic (ductopenic) rejection

Chronic allograft rejection is potentially permanent damage to the bile ducts, arterioles and venules, typically resulting from recurrent or persistent ACR.[17] Diagnosis relies on histopathology with (i) biliary atrophy affecting the majority of bile ducts, (ii) foamy arteriopathy, and (iii) bile duct loss affecting >50% of portal tracts.[17] This commonly leads to cholestasis and eventual graft failure. With improvements in immunosuppression, chronic rejection has become far less prevalent with an incidence less than 5% compared to up to 20% in the late 1980s.[18] This significant improvement is attributed to the widespread use of tacrolimus as the backbone of immunosuppression.[19–24] Chronic rejection typically results from persistent or recurrent ACR. Risk factors include medication non-adherence, cyclosporine use (instead of tacrolimus), autoimmune hepatitis (AIH) as primary liver disease, and severity and length of ACR episodes.[20,24,25]

Presentation ranges from asymptomatic liver chemistry elevations (typically in a cholestatic pattern) to significant jaundice and graft dysfunction. Because chronic rejection often coincides with late ACR, it is prudent to adequately treat any active inflammation with pulse dose steroids and increased CNI dose. It is typically accepted that chronic rejection is irreversible, and the goal of treatment is to optimize immunosuppression to (i) treat any component of ACR and (ii) prevent progression. In biliary epithelial cultures, tacrolimus prevents senescence,[26] which may contribute to its observed clinical benefit in preventing progression of ductopenia compared to cyclosporine.[27–29] However, more advanced chronic rejection typically results in graft failure and often requires re-transplantation or palliative care if re-transplant is not an option.

3 | BILIARY COMPLICATIONS

Biliary complications remain a common cause of morbidity in LT patients in both the early and late post-transplant periods. In the first few months after transplant, biliary leaks and technique-related anastomotic strictures are the most common complications. Over time, biliary strictures are more commonly related to fibrosis and vascular insufficiency. Despite decades of trials with preventative strategies, biliary strictures are estimated to occur in 5%–15% of deceased donor LT recipients, with higher rates (up to 40.6%) in living donor recipients.[30–32] Biliary strictures are categorized into anastomotic strictures (AS) and non-anastomotic strictures (NAS). Both AS and NAS are suspected when liver chemistries rise in a cholestatic pattern, but each type of stricture has different pathogenesis, risk factors, management, and prognosis.

3.1 | Anastomotic biliary strictures

Anastomotic strictures are narrowings isolated to the anastomosis between donor and recipient bile ducts arising from focal blood flow abnormalities with subsequent fibrotic healing. Risk factors for AS include high tension on the anastomosis, excessive cautery for hemostasis, suturing techniques, and variant duct anatomy including small duct caliber and duct-duct mismatch. Historically, AS were managed by converting a duct-to-duct anastomosis to a Roux-en-y hepaticojejunostomy; however, endoscopic management is now considered first line treatment. Endoscopic retrograde cholangiopancreatography (ERCP) with balloon dilation and stent placement is superior to balloon dilation alone and has a durable response in the 70%–100% of deceased donor recipients.[33–36] Percutaneous drainage and conversion to a Roux-en-Y anastomosis remain second- and third-line options.

3.2 | Non-anastomotic biliary strictures

Non-anastomotic biliary strictures (NAS) are typically multifocal, irregular, intrahepatic strictures with associated sludge and casts. Both macroscopic and microscopic insults can increase risk for NAS. Macroscopically, HAT cuts off blood supply to the entire biliary tree and if not immediately recognized and managed, can result in NAS. Microscopic risk factors include prolonged cold and warm ischemia time (including organs donated after circulatory death) and prolonged vasopressor use in the perioperative period. Immune-mediated risk factors such as chronic rejection and primary sclerosing cholangitis (PSC) as primary liver disease add additional risk. Initial management involves treating reversible causes, such as urgent revascularization in the event of HAT.

With increasing use of marginal organs, ischemic cholangiopathy (IC) remains a significant clinical concern. Better donor selection, tissue plasminogen activator (tPA),[37] and rapid donor hepatectomy have all decreased donation after cardiac death (DCD) associated IC. Recently, normothermic perfusion has shown great promise in reducing rates of ischemic-type NAS,[38,39] and outcomes may further improve as pumps are increasingly used.

If NAS develop, ERCP is the preferred first-line treatment, with reports suggesting it is highly effective in NAS management.[40] However, success of ERCP relies on the number, size, and location of the strictures. Given the multifocal nature of small, intrahepatic strictures and the often irreversible etiology, it is not surprising that most studies report a disappointing durable success rate. Ultimately, NAS require more frequent interventions and have been associated with increased risk of graft loss.[33,41] Use of peroral cholangioscopy to cannulate across small intrahepatic biliary strictures has shown some promise but has not yet substantially changed practice or outcomes with NAS.[42] Ursodeoxycholic acid is occasionally used as an adjunct therapy for management of sludge, casts, and stones associated with NAS; however, it does not reliably alter the natural history.[43] Fenofibrates have also been used off-label in a small, proof of concept study demonstrating potential utility in altering the natural history of ischemic-type NAS.[44]

Unfortunately, NAS can lead to secondary biliary cirrhosis and ultimately graft loss. NAS from IC remains a common clinical conundrum despite attempts at prevention and treatment. Severity of illness and poor quality of life resulting from NAS/IC is often underestimated

by the MELD score. With this in mind, the Organ Procurement and Transplantation Network (OPTN) updated guidance regarding MELD exception points in July 2022 to include patients with diffuse IC within 12 months of transplant.[45]

4 | RECURRENCE OF THE PRIMARY LIVER DISEASE

Recurrent primary liver disease can affect both graft and patient survival. With the ability to cure hepatitis C virus (HCV) infection with direct acting antiviral agents,[46–50] HCV is no longer the primary indication for LT. Alcohol associated liver disease and metabolic dysfunction-associated steatotic liver disease (MASLD) are now the most common indications for LT in the United States, both of which have significant psychosocial and metabolic risk factors that affect long term outcomes. Autoimmune liver diseases (i.e., primary biliary cholangitis [PBC], PSC, and AIH) can also recur post-LT. Disease recurrence negatively impacts both graft and patient survival, highlighting the importance of ongoing monitoring.

4.1 | Alcohol-associated liver disease (ALD)

Heavy alcohol use is associated with an increased risk of long-term mortality post-transplant.[51] Length of pre-transplant abstinence most consistently correlates with likelihood of recurrent use. Historically, centers required ≥6 months of sobriety prior to listing. Even then, one group reported a relapse rate of 19% of which >40% returned to heavy alcohol use.[52] Despite this, the "6-month rule" is increasingly obviated for patients with severe alcoholic hepatitis (AH) carrying high short-term mortality,[53–55] a practice which is supported by multiple studies demonstrating significantly improved survival with early LT and relatively low rates (~10%) of relapse in highly selected patients.[56–60] As early transplantation for severe AH becomes accepted, reliance on psychosocial and behavioral factors will be more important to help patients maintain sobriety.[52,58]

4.2 | Metabolic dysfunction-associated steatohepatitis (MASH)

Recurrent steatosis is nearly universal in patients transplanted for MASLD and commonly occurs as *de novo* MASLD in those with other indications for transplant;[61,62] however, progression to advanced fibrosis from recurrent MASH is rare.[63] Overall survival of patients transplanted for MASH is similar to those transplanted for other indications,[64,61] and those with recurrent steatosis have 5-year survival rates on par with patients without recurrence.[62] However, a recent study found that patients transplanted for MASH at ≥65 years-old or those with diabetes have worse survival than their counterparts,[65] and similar to the non-LT population,[66] cardiovascular events were common causes of mortality.[62,65] Importantly, statin use improves survival, suggesting that careful attention to metabolic parameters is of utmost importance in this population, where metabolic risk factors typically worsen after LT.[65] Finally, one recent, single arm study reported that the dual peroxisome proliferator activated receptor (PPAR)-α/γ agonist Saroglitizar reduces hepatic steatosis and improves metabolic parameters post-LT.[67,68] This study lays important groundwork for future trials modifying both hepatic and cardiometabolic risks of recurrence post-LT.

4.3 | Viral hepatitis

With the ability to cure HCV infection with direct acting antiviral agents[46–50] recurrence of HCV post-transplant is no longer a major concern. While Hepatitis B infection (HBV) is not curable, introduction of nucleos(t)ide analogue (NA) has seen a significant decrease in cirrhosis from HBV as indication for LT.[69,70] HCC as a result of HBV cirrhosis, however, remains an important LT indication.[71] Predictors of HBV recurrence post-transplant include HCC at the time of transplant, Anti-HBc-positive graft, elevated HBV viral load at the time of transplant, Hepatitis B e-antigen positive and mutation in the HBV S gene.[71] Post LT, recurrence risk should be determined based on HBV DNA, drug resistance, co-infection with hepatitis D or HIV, with high risk patients receiving Hepatitis B virus Immunoglobulin (HBIG) early post-LT in addition to lifelong NA[72] Tenofovir and Entecavir are the preferred agents due to high genetic barrier to resistance and improved long term survival,[71] and some centers are now minimizing HBIG use due to efficacy of high genetic barrier NAs.[73] Five-year survival for HBV related LT is now similar to other indications[74]

4.4 | PSC

PSC is a progressive disease with a transplant free survival of 9–12 years after diagnosis.[75] Recurrence of PSC post-transplant is reported in 8%–27% patients after a median of 4.7 years.[76–78] Diagnosing recurrent PSC is complicated by other potential etiologies of post-transplant bile duct disorders. A strict definition stipulates that diagnosis of PSC is confirmed pre-transplant and requires the presence of intra- and/or extrahepatic biliary stricturing, beading, and irregularity present for greater than 90 days, or histology consistent with PSC.[79] Risk factors for recurrence include increased inflammatory bowel disease activity post-transplant, recurrent cholangitis as indication for transplant, ACR,[80] cholangiocarcinoma pre-transplant, donor age, high MELD score,[81] and younger recipient age.[78] While previously thought to be protective, recent data did not show pre-transplant colectomy to be associated with reduction in PSC recurrence.[80] Recurrence negatively affects graft and patient survival,[76,78] leading to a 33% decrease in 10-year graft survival and increased rates of re-transplantation.[76] Early recurrence within 5 years of transplant is associated with a decrease in long-term graft and patient survival.[76] Although frequently

used, there is no data that ursodeoxycholic acid (UDCA) improves survival or symptoms in recurrent PSC[75] nor does its use prevent recurrent disease.[77]

4.5 | PBC

PBC accounts for about 10% of patients listed for LT in the US and Europe[82] with reported post-LT recurrence ranging from 4% to 46%.[83–85] Diagnosis of recurrent PBC relies on histology, as liver tests can be normal and neither the presence nor titer of anti-mitochondrial antibody (AMA) correlate with recurrence. Rejection, Graft-versus-host disease (GVHD) or biliary obstruction can confound the diagnosis. Donor age, recipient age at LT, recipient age at initial diagnosis of PBC, and warm ischemia time are risk factors for PBC recurrence.[82,85] While previous studies suggested that recurrence did not impact graft survival, more recent data indicates that recurrence confers increased risk of graft loss and death.[82,85] In a recent meta-analysis, empiric ursodiol post-LT reduced incidence of recurrent PBC (16.7% in the ursodiol group vs. 23.1%).[86] As the mechanism of recurrence is not currently understood, impetus should be placed on recognition of risk factors and prevention strategies.

4.6 | AIH

The reported incidence of recurrent AIH is 8%–12% within the first year post-transplant and 36%–68% after 5 years.[87] A recent multinational cohort reported 20% recurrence after 5 years, 31% after 10 years, and 49% after 20 years.[88] Risk factors for recurrent AIH include younger age at transplant (<42 years-old), donor and recipient sex mismatch, higher IgG level pre-transplant,[88] longer time from transplant, discontinuation of steroids, type I AIH, HLA-DRB1 3 or 4 positivity as well as pre-transplant tacrolimus[87] or post-transplant Mycophenolate mofetil (MMF) use.[88] Pre-transplant levels of antinuclear antibody (ANA) and anti-smooth muscle antibody (ASMA) do not predict AIH recurrence.[89] After transplant, elevated bilirubin at 6 months and elevated liver enzymes at 12 months are associated with a higher recurrence risk.[88] Recurrent AIH rarely presents with severe hepatitis, and many disease features may be less pronounced or absent due to concurrent immunosuppression in transplant recipients.[90] Diagnostic criteria are identical to primary AIH. Recurrent AIH is associated with graft loss and death, with higher bilirubin level at diagnosis conferring higher risk of graft loss.[88] Treatment mirrors that of initial AIH with steroids and an anti-metabolite while continuing CNI.[91]

De Novo AIH is defined as the onset of AIH in a patient transplanted for another indication. This occurs in 1%–3% of adult transplant recipients in North America[91] with variable timeline and may represent an atypical form of rejection in genetically predisposed individuals.[87] Risk factors include ACR, steroid dependence, HLA DR3 phenotype, and older female donors.[92] Presentation, histology, and treatment are identical to recurrent AIH.

5 | METABOLIC COMPLICATIONS OF LIVER TRANSPLANT

It is well-established that the metabolic syndrome (obesity, hypertension, diabetes, and cardiovascular disease) has reached epidemic proportions and is rapidly rising in every age group in the United States.[93] Many hallmarks of metabolic syndrome are absent in patients with advanced liver disease as they often have sarcopenia,[94] altered lipid profiles, and a vasodilatory state with relative hypotension and hyperdynamic circulation.[95–97] Nevertheless, vascular disease is quite prevalent in this population. A recent study of protocolized left heart catheterization of 228 patients undergoing LT evaluation detected coronary artery disease in 36.8% of patients with MASH patients comprising >50% of the group.[98] Additionally, all mechanisms of immunosuppression are associated with varying degrees of metabolic derangements (Table 1), increasing this risk in LT recipients compared to the general population. Studies have estimated the prevalence of metabolic syndrome to be up to 58% in transplant recipients,[99,100] and cardiovascular disease remains a major cause of mortality in this group.

5.1 | Obesity

Obesity rates in the United States are increasing at an alarming rate, and current data estimates that 42.2% of adults over the age of 18 qualify as obese (Body Mass Index (BMI) > 30 kg/m^2).[93] The overwhelming majority of patients who are obese at the time of transplant remain obese after transplant, with progressively higher rates over time.[101] Similar to the non-transplant patient, obesity predisposes patients to diabetes, dyslipidemia and cardiovascular disease. *De novo* rates of MASLD post-LT are approximately 40% but even higher in patients transplanted for MASH cirrhosis with 77.6% displaying allograft steatosis 10 years-post-LT.[102]

With these consequences in mind, management of weight gain after LT is critical. Immunosuppression optimization with minimal effective immunosuppression, especially corticosteroid use, is a key first step. Calcineurin inhibitors, however, are also associated with weight gain. While cyclosporine has been associated with higher rates of obesity in the early post-operative period than tacrolimus, this association disappears in longer-term follow up.[101] Adding mammalian target of rapamycin (mTOR) inhibitors to minimize tacrolimus levels has reduced rates of post-transplant obesity in a randomized control trial (RCT)[103]; however, these agents are known to increase the risk of hyperlipidemia and are uncommonly used.[104]

Prior studies of medical management of obesity have not shown sustained effects; however, the addition of multiple glucagon-like peptide 1 (GLP1) receptor agonists, including semaglutide, liraglutide, and tirzepatide, may have significant benefits in this population. While these drugs have not been well-studied in the post-transplant cohort, one small retrospective study published in abstract form demonstrated modest weight loss with the initiation of a GLP1 agonist for diabetes management in solid organ transplant recipients.[105]

TABLE 1 Metabolic, cardiovascular, and systemic complications are frequent in transplant recipients and can be exacerbated by commonly prescribed immunosuppression.

Maintenance immunosuppression		Metabolic complications				Other complications			
Class	Medication	Weight Gain	Diabetes	Hypertension	Hyperlipidemia	Renal	Neuro-psychiatric	Marrow suppressive	Teratogenic
Corticosteroid	Prednisone	+	+++	+	+	–	+	–	–
Calcineurin inhibitor	Tacrolimus	+	++	+	+	+++	++	–	–
	Cyclosporine	+	+	++	++	++	+	–	–
Antimetabolite	Azathioprine	–	–	–	–	–	–	+++	–
	Mycophenolate	–	–	–	–	–	–	++	+++
mTOR inhibitors	Everolimus	–	–	–	+++	+	–	+	+
	Sirolimus	–	–	–	+++	+	–	–	+

Note: +, indicates that a medication has this side effect and the number of + signs indicates severity. –, indicates that a medication does not have a known side effect. Steroids are notorious for exacerbating poor glucose tolerance and worsening diabetes in both the short and long-term. Steroids are well-established to lead to weight gain, hypertension, and hyperlipidemia as well, and can lead to steroid-induced psychosis. The commonly used calcineurin inhibitors (tacrolimus and cyclosporine) have varying effects on all studied metabolic complications. Both tacrolimus and cyclosporine can be neurotoxic and can lead to a wide range of neurologic complications including lowering seizure thresholds, causing peripheral neuropathy, causing headaches, and being associated with posterior reversible encephalopathy syndrome (PRES). Antimetabolites are weaker immunosuppression with minimal metabolic effect but do have unique considerations of marrow suppression (e.g., neutropenia), and MMF should be discontinued prior to pregnancy. The newer mTOR inhibitors significantly worsen dyslipidemia but do not have other known metabolic complications. However, everolimus can exhibit some degree of marrow suppression, and both should be discontinued 8–12 weeks prior to pregnancy (category C).

Another highly effective weight loss option is bariatric surgery. However, there are unique considerations for timing of surgery in patients awaiting LT,[106] and long-term data in the post-transplant setting is lacking.

5.2 | Diabetes and new onset diabetes after transplant

True prevalence of diabetes (DM) prior to transplant is unknown, but glucose intolerance is common due to impaired hepatic glycogen synthesis and increased peripheral insulin resistance. While a minority of patients with insulin resistance improve after LT, most patients remain insulin resistant and many develop new onset diabetes after transplant (NODAT). It is estimated that up to 38% of post-transplant patients have diabetes, and that up to 28% of patients develop NODAT.[107–109] Independent risk factors for developing NODAT historically include HCV infection and steroid boluses[107]; however, immunosuppression regimens also contribute to insulin resistance and diabetes via several distinct mechanisms after transplant (Table 1).

Corticosteroids contribute to hyperglycemia via both inhibiting pancreas islet cell dysfunction and impairing insulin sensitivity in the liver and peripheral tissues (i.e., skeletal muscle and adipose tissue). Calcineurin inhibitors are directly toxic to pancreatic islet cells and inhibit beta-cell proliferation.[110,111] Tacrolimus, specifically, is associated with higher rates of post-transplant diabetes.[80] The effect of mTOR inhibitors on diabetes development is controversial.

Management of DM post-transplant is similar to the general population with a target hemoglobin A1c (HbA1c) of <7%. Notably, HbA1c is not valid in the 3 months following transplant owing to the common need for blood transfusions perioperatively and the high steroid doses commonly used for induction. Treatment is centered around optimizing immunosuppression and minimizing steroids; however, when treatment is required, insulin is often needed. Diabetes in transplant recipients increases the risk of *de novo* steatosis of the allograft with progression to advanced fibrosis[112] and late onset HAT,[109] which reduces both graft and patient survival.[109] While GLP1 receptor agonists have not been extensively studied in this population, they are not expected to have drug-drug interaction with the CNIs.

5.3 | Systemic arterial hypertension

Systemic arterial hypertension (HTN) is diagnosed as either a systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg. This is uncommon in patients prior to LT owing to a vasodilated state with low systemic vascular resistance (SVR) and hypotension. Post-transplant, hemodynamic changes, and immunosuppression regimens both contribute to hypertension, and over 50% of LT recipients are ultimately diagnosed with hypertension.[113] Mineralocorticoid activity of corticosteroids and increases in SVR contribute to steroid-induced HTN; however, steroid use is generally time-limited and therefore not a major contributor to long-term HTN. Calcineurin inhibitors, on the other hand, are the most common culprit for long-term HTN in transplant recipients and contribute through vasoconstrictive effects both systemically and within the renal vascular bed via increased thromboxane and endothelin-1 secretion.[113–115] The renovascular effects impair glomerular filtration and sodium excretion, thereby exacerbating the effect on systemic hypertension.

Given that vasoconstriction is a primary mechanism of CNI-induced hypertension, first line treatment is typically calcium channel blockers, preferentially amlodipine.[116] Nifedipine can increase CNI levels through CYP3A activity although it can be used safely with close monitoring of levels. Ace-inhibitors/Angiotensin-receptor blockers (ACE-I/ARBs) have renal protective effects and should be used if proteinuria is present; however, electrolytes should be monitored closely as they can contribute to hyperkalemia, especially in combination with CNIs. Thiazide diuretics are generally avoided due to the potential for electrolyte disturbances and the additive effect that hypovolemia may have on renal vasoconstriction to propagate renal insufficiency. Treatment goals are similar to the general population and may require multiple anti-hypertensives with different mechanisms.

5.4 | Cardiovascular disease

All of the above metabolic complications increase the risk of cardiovascular disease (CVD) in LT recipients, which is a major cause of late mortality. Given the higher rate of these metabolic complications in LT recipients compared to the general population, it is not surprising that the probability of CVD is also higher.[117] This was shown in a retrospective study of 181 LT recipients, where the Framingham risk calculator was used to calculate 10-year risk both pre- and post-LT.[117] They found that pre-transplant values were similar to the general, local, non-transplant population (6.9% vs. 7%) but that just 1-year post-transplant, this had increased to 11%.[117] This discrepancy may be due to the deranged metabolic profiles in the pre-transplant population which may underestimate the ~25% prevalence of coronary artery disease (CAD) in this group.[118] The incidence of CAD in the pre-LT population is likely rising given the increasing incidence of MASH as an indication for transplant.[87] Together, these data highlight the need for (1) adequate preoperative coronary disease risk stratification and (2) intensive screening and targeted therapy to modify cardiovascular disease risk factors. Recently published data suggest that the use of statins in patients transplanted for MASH conferred mortality benefit post-LT.[65]

5.5 | RENAL DYSFUNCTION

Chronic kidney disease (CKD) in transplant recipients is estimated to be as high as 50% by the 10-year mark.[119] The prevalence of renal failure (diagnosed as glomerular filtration (GFR) rate < 30 or development of end stage renal disease (ESRD)) has been found to be 18% at 5 years and 25% at 10 years post-transplant.[120] Importantly, the prevalence of renal dysfunction after transplant appears to increase over time.[119] New onset renal insufficiency (within 6 months post-transplant) and persistent renal insufficiency post-transplant both increase risk of 1-year mortality,[121] and late onset renal dysfunction (onset 1–5 years post-transplant) is associated with even higher mortality.[119]

Unsurprisingly, pre-existing CKD is associated with increased post-transplant CKD, but it is also associated with inferior graft survival, increased infection, increased post-transplant ESRD, and higher post-operative mortality.[120,122] Increasing numbers of pre-transplant candidates have CKD, in part due to rising prevalence of metabolic risk factors and MASH emerging as the leading cause of LT. The institution of the MELD scoring system in 2002 has both increased the number of transplant candidates with CKD as well as increased donor prioritization to patients with renal dysfunction,[122] and the risk of post-transplant ESRD has increased in each subsequent year.[123]

Etiologies of post-transplant kidney disease are likely multifactorial but include pre-transplant kidney injury, post-operative acute tubular necrosis (ATN), exposure to CNIs, post-transplant DM, HTN, and obesity. Interestingly, among all non-renal solid organ transplant recipients, LT recipients have the second highest incidence of post-operative chronic renal failure despite the lowest level of immunosuppression with CNIs.[120] Elevated creatinine at 1 year, use of cyclosporine as immunosuppression, presence of DM pre-transplant, and post-transplant AKI predict progression to ESRD.[124,125] It is important to review medications that can impact renal function including NSAIDs, antibiotics such as vancomycin, and medications that increase CNI levels (e.g., anti-fungals, anti-epileptics, calcium channel blockers, and protease inhibitors).

Diagnosis requires specific attention as serum creatinine elevation is a late and insensitive marker of renal dysfunction, and while it is recommended to use a Cystatin C based equation,[126] this is more expensive and less widely available. It is also important to note that LT patients often have lower muscle mass (both pre- and post-transplant) which leads to creatinine overestimating the GFR[119] and post-transplant proteinuria may be masked due to the anti-proteinuric effect of CNIs. While biopsy is the gold standard for diagnosis, alternative biomarkers are being investigated to aid in diagnosis including neutrophil gelatinase-associated lipocalin (NGAL), Interleukin-18 (IL-18), and Kidney Injury Molecule-1(KIM-1).[127]

While acute CNI toxicity is rare and usually reversible with cessation of CNI, chronic CNI nephrotoxicity is more difficult to treat. Pathologically, it causes irreversible severe arteriolar hyalinosis, glomerulosclerosis, and interstitial fibrosis.[128] In order to prevent chronic CNI nephrotoxicity, strategies have emerged to decrease post-transplant CNI exposure such as induction with delayed introduction of CNI, CNI minimization protocols, and CNI withdrawal and conversion to MMF or mTOR based regimens.[127–134] A systematic review showed that introduction of everolimus at 4 weeks with early CNI withdrawal led to improved renal function at 12 months without increase in rejection, graft loss or mortality.[131]

For those who develop ESRD post-transplant, survival is significantly increased with subsequent kidney transplantation as opposed to ongoing dialysis[124]; 6-year survival is only 27% for those receiving dialysis.[135] As of 2011, 1% of all renal transplants in the US were performed in LT patients who developed ESRD post-transplant.[136] In 2017, a new policy standardized eligibility for simultaneous liver kidney transplants (SLK). Commonly known as the "safety net", this policy allows patients to undergo LT alone, and if kidney disease persists (dialysis dependence or GFR < 20 2–12 months post-LT) patients are prioritized for subsequent renal transplant.[137]

6 | BONE DISEASE

Cirrhosis is associated with an increased prevalence of osteoporosis (ranging from 12% to 50%) with bone disease present in 20%–40% of patients awaiting LT.[138,139] Corticosteroids accelerate bone loss in nearly all LT recipients in the first 6 months post-transplant,[140] predisposing to low-energy fractures in 20%–35% of patients during this period.[139] Risk factors for these low-energy fractures include low pre-transplant bone density, a history of vertebral fractures, cholestatic liver disease, and advanced age.[138] After 6 months, bone density progressively improves and reaches pre-transplant values within 2–5 years.

Bone loss prevention includes minimizing glucocorticoid exposure, repleting calcium and vitamin D, and regular bone density screening. Guidelines suggest annual BMD measurement in osteopenic patients, those with cholestasis, and those continued on glucocorticoids and every 2–3 years for those with normal BMD without the aforementioned risk factors.[138] There is limited data suggesting that the use of mTOR inhibitors may be beneficial to transplant recipients at high risk for osteoporosis, in addition to its likely byproduct of decreasing need for glucocorticoids.[139] Guidelines further suggest bisphosphonate therapy for patients with a T score ← 2.5 or atraumatic fractures, or T score −1.5 to −2.5 with additional risk factors.[141] Unfortunately, prophylactic bisphosphonate administration to high risk candidates has not been shown to prevent post-transplant fracture development.[142]

7 | MALIGNANCY

7.1 | De novo malignancy

Malignancies are a serious long-term complication of LT and a leading cause of mortality. High incidences of solid tumor formation after LT have been reported in multiple retrospective single-center experiences.[143–146] However, these are not entirely generalizable given different patient populations with varying baseline risks for malignancy and immunosuppression protocols.

One population-based study from Finland included 540 LT recipients from 1982 to 2005 and compared their incidence of cancer to the nation-wide Finnish Cancer Registry.[147] Overall, they found a 13% cumulative risk of *de novo* cancer at 10 years and a 16% risk after 20 years. This corresponded with a 2.59 standardized incidence ratio (SIR) for all cancers and a 2% incidence of cancer-related mortality. Differences were driven primarily by non-melanoma skin cancer and non-Hodgkin's lymphomas (NHL). Non-melanoma skin cancer had an SIR of 38.5 (95% CI 18.5–70.8), and NHL had SIR 13.9 (95% CI 6.01–27.4).[147] The incidence of other solid tumor types is not significantly different between transplant recipients and the general population. It is important to note that in many of the available studies, patients were transplanted prior to modern immunosuppression regimens when azathioprine and cyclosporine were commonly used and maintained at higher levels. One center reported that immunosuppression to avoid all rejection was associated with an increased incidence of *de novo* cancer, and in the Finnish study, having at least one episode of acute rejection appeared protective from *de novo* cancer.[147,148] In both studies, the long-term immunosuppression regimen had the greatest impact on cancer risk. Studies comparing the risk of *de novo* cancer after solid organ transplant in patients receiving cyclosporine versus tacrolimus have shown mixed results.[149,150] It is therefore reasonable to conclude that both CNIs increase risk of *de novo* malignancy. Mammalian target of rapamycin inhibitors (e.g., sirolimus and everolimus) have improved cancer risk profiles; however, they are not commonly used as first line immunosuppression outside of renal-sparing protocols or high-risk HCC populations as discussed below. mTOR inhibitors are, however, important agents to consider in the event of *de novo* malignancy.

While there is no standard recommendation on cancer screening after transplantation, it is reasonable to screen for specific cancers due to a heightened risk in some cancer types and a theoretical risk in others. In addition to minimizing immunosuppression to the lowest effective dose, our practice is summarized in Table 2.[151]

7.2 | Non-melanoma skin cancer

Significantly increased rates of skin cancer is thought to be due to both (i) decreased immune surveillance to tumor antigens and (ii) increased sensitivity to UV-induced DNA damage (which is greater with azathioprine than MMF).[152] This is the basis for recommendations to decrease direct exposure to UV light and have annual dermatology examinations to detect and excise suspicious lesions (Table 2). If diagnosed, it is important for dermatology to consult with the transplant team to consider minimizing immunosuppression as able and/or using mTOR inhibitors. While not always feasible, the benefit of mTOR inhibitors in skin cancer prevention post-transplant was proven in an RCT of renal transplant recipients[153] which demonstrated regression of pre-malignant lesions compared to patients who stayed on the traditional regimen.[153]

7.3 | Kaposi's sarcoma

Kaposi's sarcoma (KS) is an angioproliferative neoplasm caused by Human Herpesvirus-8 (HHV-8). While traditionally associated with HIV/AIDS, solid organ transplants recipients are historically > 50 times more likely to develop KS than immunocompetent counterparts,[154] with one center reporting a 2.1% occurrence rate post-LT.[155] KS traditionally presents early post-transplant with one group reporting a median time of onset of 13 months post-renal transplant.[156] It is important to note that most reports of post-transplant KS are from the era of cyclosporine when higher IS levels was commonplace.

Similar to management of other malignancies, minimizing total immunosuppression while still preventing allograft rejection is the main goal of therapy, and one group reported complete regression of KS in a subset of patients with immunosuppression reduction

TABLE 2 Transplant recipients require life-long care and careful attention to increased screening, prevention, and treatment protocols.

Malignancy	Recommended screening
Lymphoma	No routine screening Maintain high index of suspicion (see text)
Skin	Annual dermatology exam (starting no later than 5 years post-LT) Avoid direct sunlight Use sunscreen with SPF 30 or higher Wear sun protective clothing
Head and Neck	Tobacco cessation counseling Annual otolaryngology for history of tobacco use + liver transplant for alcohol-related liver disease
Lung	Tobacco cessation counseling Annual low dose chest CT
Colon	**General**: Colonoscopy starting at age 45 Consider 5 years post LT as 1st surveillance and base subsequent intervals per CRC guidelines (variable practice) **PSC with IBD or other genetic risk**: Annual colonoscopy Recommend colectomy if dysplasia
Genitourinary	Annual PAP for female patients ages 21–65 years old Annual anorectal PAP for men who have sex with men
Breast	Annual mammogram at age 40
HCC	Cross-sectional imaging of chest, abdomen, and pelvis: Low risk: Every 6 months for 2 years (consider RETREAT score[171]) High risk: Every 3–6 months for year 1 and every 6 months up to year 5 Consider mTOR inhibitor-based immunosuppression[179]
Infectious disease	Vaccine recommendation
General vaccine recommendation	If possible, give vaccines before transplant (better immunogenicity) Most vaccines delayed until at least 3 months post-LT Can give seasonal respiratory virus (e.g., influenza and SARS-CoV-2) vaccine after 1st month post-LT
Live vaccines	Avoid all live vaccines post-transplant
Hepatitis A	All adults Check titers **Preferred vaccine(s)**: Hepatitis A Vaccine, Inactivated (HAVRIX) **Schedule(s)**: two doses, 6–12 months apart
Hepatitis B	All adults Check titers **Preferred vaccine(s)**: Hepatitis B Vaccine (Recombinant), Adjuvanted vaccine (HEPLISAV-B); Hepatitis B Vaccine (Recombinant) (ENGERIX-B) **Schedule(s)**: HEPLISAV-B: two doses, at least 4 weeks apart; ENGERIX-B: three doses, 0, 1, and 6 months Hepatitis B Vaccine (Recombinant), Adjuvanted vaccine is more potent post-LT but theoretical concern of altered immune tolerance
Human papillomavirus	All patients < than 26 years-old (individual basis for patients > than 26 years-old) **Schedule**: three doses, 0, 1, and 6 months If administering post-transplant: Start 3–6 months post-transplant
Shingles	Age > 50 years-old **Preferred vaccine**: RZV (ZVL no longer available in United States) **Schedule**: two doses, 2–6 months apart; revaccinate with RZV if prior ZVL vaccination; wait 1 year after infection prior to RZV vaccination
Tetanus	All adults **Preferred vaccine**: Tdap at least once, Td or Tdap for booster **Schedule**: Prior to transplant and booster every 10 years
Influenza	All adults **Schedule**: Annually (can be given after 1st month of transplant)

(Continues)

TABLE 2 (Continued)

Malignancy	Recommended screening
SARS-CoV-2	Recommendations evolving
Pneumonia	All adults**Possible regimens**: 1. PCV20 alone 2. PCV13 followed by PPSV23 (8 weeks later) and repeat PPSV23 every 5 years until final dose at age 65 3. PPSV23 followed by PCV13 (1 year later) 4. PCV13 followed by PCV20 (8 weeks later) 5. PPSV23 followed by PCV20 (1 year later)
Metabolic health	**Monitoring and treatment recommendation**
Glucose	Monitor glucose with routine labs Check A1c if hyperglycemia (fasting glucose > 100 mg/dL) for more than 3 months. Note that A1c is inaccurate in first 3 months post-transplant. Treatment: target A1c < 7%
Lipids	Fasting lipid profile within first year post-LT and every 2–3 years thereafter Statin if known ASCVD or if 10-year ASCVD risk > 7.5% Consider statin in other groups (improves mortality post-LT for MASH)
Blood pressure	Monitor at each visit post-LT Target BP < 130/90 First line: Amlodipine if no proteinuria ACE-I/ARB with proteinuria (need to monitor electrolytes)
Weight	Monitor at each visit post-LT Lifestyle modifications Immunosuppression optimization Consider GLP1-receptor agonists, especially with diabetes
Bone density	DEXA scan at year 1 and every 2–3 years standard Annual DEXA if osteopenia, ongoing cholestasis, or ongoing steroid use Vitamin D and calcium repletion Endocrinology referral for bisphosphonate if low bone density

Note: Recommendations for malignancy screening intervals, infectious disease prevention, and metabolic health are depicted in this table.
Most vaccines delayed until after 1st 3 months post LT.
Abbreviations: ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensinogen receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; DEXA, Dual-energy X-ray absorptiometry; GLP-1RA, glucagon like peptide 1 receptor agonist; HCC, hepatocellular carcinoma; IBD, inflammatory bowel disease; LT, liver transplant; PCV, pneumococcal conjugate vaccine; PPSV, pneumococcal polysaccharide vaccine; PSC, primary sclerosing cholangitis; RZV, recombinant zoster vaccine; SPF, sun protection factor; ZVL, zoster vaccine live.

or cessation.[156] mTOR inhibitors, which display anti-VEGF activity, are a unique consideration for this vascular tumor in small case series.[155,157]

7.4 | Post-transplant lymphoproliferative disorder (EBV/PTLD)

Lymphoma presentation can be highly variable and requires a high index of suspicion with new onset constitutional symptoms, including fatigue, weight loss, chills, and/or night sweats. Diagnosis requires physical exam, imaging, blood counts with differential, viral studies (i.e., EBV PCR) and often times lymph node biopsy. Any lymphoma in the post-transplant population is considered a post-transplant lymphoproliferative disorder (PTLD), these are classically related to EBV infection.

Epstein-Barr virus infection is ubiquitous in the adult population with over 90% of adults worldwide being seropositive. In immunocompetent individuals, this can present as childhood febrile respiratory illness or as infectious mononucleosis with fever, lymphadenopathy, hepatosplenomegaly, and hepatitis. Post-transplant, seronegative individuals are at risk for primary EBV infection, which increases the risk of post-transplant lymphoproliferative disease (PTLD).[158] The incidence of EBV associated PTLD is estimated to be 1%–2% at 5 years post-transplant.[159] PTLD follows a bimodal distribution with peaks in onset in the first year and then again beyond the 5-year mark.[158] A recent retrospective cohort study evaluating 1849 LT recipients reported PTLD in 3.8% of patients,[160] which was associated with significantly worse survival. Incidence is overall higher in pediatric recipients compared to adults, likely due to an increased number of seronegative recipients, although adults have worse survival outcomes.[160] Approximately 20% of PTLD cases are EBV negative which is more commonly seen in adult transplant recipients and tends to have later onset (5–10 years after transplant).[161] One single center series of 176 PTLD patients found similar outcomes and responses to therapy between EBV negative and EBV positive PTLD.[162]

Traditional therapy of PTLD has involved reduction in immunosuppression with more advanced disease being treated with Rituximab.[161,163,164] Regression of EBV associated lesions is seen in 23%–86% of patients with decreased immunosuppression alone.[164] Surgery is used as adjunctive measure to decreased immunosuppression in cases of localized disease.

7.5 | Hepatocellular carcinoma recurrence

The incidence of HCC and the frequency of HCC as an indication for LT are rising.[1,165,166] When patients are transplanted within Milan criteria, patients have 5-year recurrence-free survival exceeding 70%, making transplant the preferred treatment of HCC at many centers.[167,168] However, as centers transplant patients beyond traditional Milan criteria, there is an increased risk for HCC recurrence.[169] Recurrence risk can be broadly categorized into two factors—primary tumor characteristics and immunosuppression regimens. AFP producing tumors,[170,171] tumors outside of Milan criteria,[169,171] microvascular invasion,[171] and poorly differentiated tumors[172] are all established risk-factors for cancer recurrence. Unfortunately, there are no biomarkers currently available to accurately predict tumor biology and differentiation without histology.

Immunosuppression regimens are a readily modifiable risk factor. High CNI levels are associated with increased HCC recurrence.[173,174] Experimental models have shown that CNIs result in in vitro angiogenesis and promote liver tumor growth and invasion[175] whereas mTOR inhibitors inhibit angiogenesis in vitro and retard HCC growth in mice.[176,177] A retrospective study of 227 patients who underwent LT for HCC showed substantially improved survival in those who received sirolimus based immunosuppression.[178] In this study, mTOR inhibitor use was an independent predictor of recurrence-free survival over time.[178] Additionally, in the SiLVER trial,[179] a multicenter prospective RCT of 525 patients undergoing LT for HCC who were randomized to receive either mTOR-based or mTOR-free immunosuppression after LT, the intention-to-treat analysis demonstrated reduced rates of recurrence from 3 to 5 years post-transplant in patients maintained on mTOR inhibitors. Unfortunately, there was no benefit seen after 5 years. Additionally, the largest benefit was seen in patients within Milan criteria, while no benefit was seen in the high-risk, extended criteria patients, highlighting the importance of tumor-specific risk factors and patient selection.

Since this seminal study, multiple post-hoc analyses have been completed in an attempt to identify groups that may benefit most from mTOR inhibition. These studies have shown patients with AFP ≥10 ng/mL who receive sirolimus for ≥3 months have significantly higher recurrence-free and overall survival.[180] While prolonged sirolimus use appears to be beneficial, there are higher rates of rejection and adverse events including infections, worsening metabolic parameters especially hyperlipidemia, and mouth ulcerations[181]

8 | INFECTIOUS DISEASE

Incidence of infection after LT is high compared to other solid organ transplants. This is likely multifactorial given the complexity of the surgery, risk of abdominal contamination and particularly poor overall health of patients with end stage liver disease.[159] Transplant candidates and donors undergo extensive screening for infectious diseases as the post-transplant immunosuppression puts recipients at high risk of recurrence or reactivation. Routine vaccination prior to transplant is recommended by AASLD to prevent infectious complications post-transplant.[141] Risk of infection post-transplant is traditionally divided into three periods: the first month post-transplant, 1–6 months post-transplant, and beyond 6 months.[158,182] Common infections experienced during these periods and risk factors are summarized in Figure 2.

In the first month post-transplant, infections are most often nosocomial and bacterial in origin, similar to the infections encountered by immunocompetent hosts undergoing hepatobiliary procedures.[159] Opportunistic infections (OIs) are uncommon in this early period and usually occur during the 1–6 month period, and it is standard practice to administer prophylaxis against bacterial, viral, and fungal infections in the early post-LT period (Figure 2). The late post-transplant period is usually notable for fewer infectious complications. For patients with stable graft function post-transplant, infections resemble those seen in the general population. The development of OIs in this period usually suggests excessive maintenance immunosuppression or treatment of recent acute or chronic rejection.[158,159,183] Incidence of graft loss and overall mortality increase significantly in patients with at least one episode of late infection (>6 months post-transplant).[184]

While time course post-transplant is traditionally used to define risk of infection, one should also consider each patient's "net state of immunosuppression," including current and past immunosuppressive therapy, prior exposure to chemotherapy and antibiotics, mucocutaneous barrier integrity, bone marrow suppression (often drug induced), technical complications from surgery, underlying immune defects (including autoimmune disease), metabolic conditions (including diabetes and alcohol use), and concurrent viral infections.[158]

8.1 | Fungal infections

Fungal infections tend to present in the early post-operative period and include aspergillus, candida, and cryptococcus. While less common than candida or aspergillus, cryptococcus tends to have later presentation with symptom onset approximately 30 months post-transplant. It can manifest as pneumonia (46%), isolated meningitis (36%), disseminated disease (11%), and less frequently, involvement of another single organ (such as lymphadenopathy 7%). Mortality rates associated with cryptococcus are as high as 25%[183] rendering early detection and treatment key. Histoplasmosis while rare in LT recipients, can cause pneumonia, hepatosplenomegaly, gastrointestinal involvement or pancytopenia, and can result from primary infection or reactivation

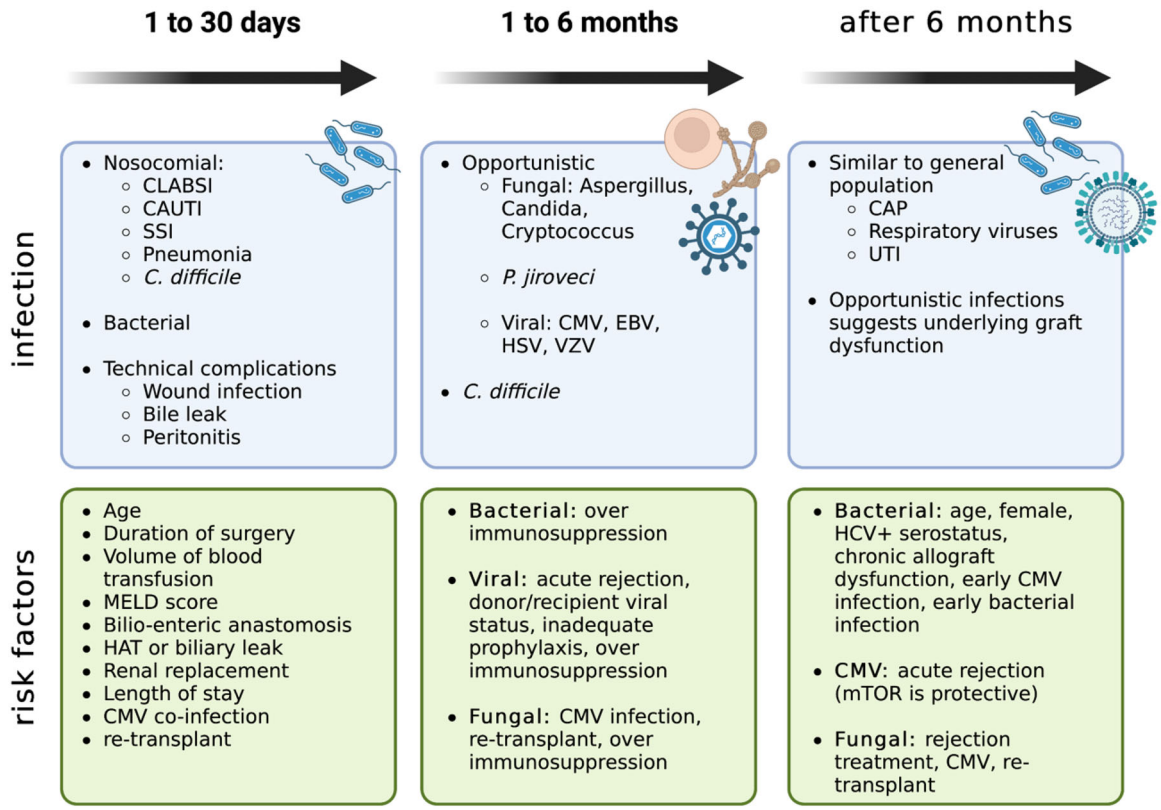

FIGURE 2 Infections are frequent causes of morbidity and mortality in transplant recipients. The type of infection and common offending pathogens (shown in light blue boxes) as well as risk factors for infection (shown in light green boxes) vary depending on the time relative to transplant. Early infections (in the first 30 days) are similar to those commonly seen in hospitalized patients with disease severity and surgical technique contributing to risk. Infections that occur within 1–6 months post-transplant often arise from reactivation of prior infections or new, opportunistic infections. Fungal infections and specific viral illnesses predominate with high doses of immunosuppression increasing risk. After 6 months, immunosuppression is typically weaned, and infections are community acquired. Opportunistic infections after 6 months should raise suspicion for over immunosuppression, graft dysfunction, or both. CAP, community acquired pneumonia; CAUTI, catheter associated urinary tract infection; CLABSI, central line associated blood stream infection; CMV, Cytomegalovirus; EBV, Epstein–Barr virus; HAT, hepatic artery thrombosis; HCV, hepatitis C virus; HSV, herpes simplex virus; MELD, model for end stage liver disease; RRT, renal replacement therapy; SSI, surgical site infection; UTI, urinary tract infection; VZV, varicella zoster virus.

from prior infection.[183] While histoplasmosis is endemic to Ohio and Mississippi river valleys, pre-transplant screening is usually not recommended based on low likelihood of subsequent infection.[185] It is important to note that many anti-fungal medications, particularly azoles increase CNI and mTOR levels.

8.2 | Tuberculosis

Incidence of TB among transplant patients is estimated to be 20–74 times higher than the general population with a mortality rate of up to 30%.[186] Reactivation of latent TB is the most common cause of post-transplant TB. All transplant candidates are screened for TB prior to transplant, although optimal screening methods for both active and latent TB are debated, and screening is itself complicated by the compromised immune system of patients that may not react to tuberculin skin test (TST) and interferon gamma release assays (IGRA).[159,187] Most centers, however, opt for IGRA for TB screening. Both prophylaxis and treatment of infection in LT patients is complicated by drug-drug interactions. Rifampin, which interferes with metabolism of CNIs and mTOR inhibitors, can lead to ACR and should be used cautiously.[187] While isoniazid (INH) can be hepatotoxic, INH related hepatotoxicity in patients with compensated cirrhosis is rare.[188] The majority of solid organ transplant patients who develop TB do so within 9 months of surgery, with the remainder developing > 2 years post-transplant.[189,190] Given the wide array of clinical presentations, TB should be considered in all transplant recipients with fever of unknown origin.[186]

8.3 | Cytomegalovirus

Cytomegalovirus (CMV) is the most common viral infection to influence outcomes post LT.[183] Risk of infection is highly correlated to serologic status of donor and recipient, with seronegative recipients who receive organs from seropositive donors being at highest risk.

Incidence of CMV among LT recipients vary, however, viremia has been reported in as high as 92% of patients and symptomatic infection in 50%–65% of high-risk donor mismatch group.[158,191] Prophylaxis in the first 3–6 months has been the most widely used strategy for CMV prevention; however, delayed onset (post-prophylaxis) CMV disease remains a problem. A recent RCT demonstrated that pre-emptive therapy lowers incidence of delayed onset infection compared to traditional prophylaxis,[192] but this burdensome and uncommonly done.

Cytomegalovirus infection typically presents as a systemic syndrome (fever, malaise, bone marrow suppression) and less frequently, as tissue invasive disease (i.e., colitis, enteritis, esophagitis, gastritis, hepatitis, pneumonitis, encephalitis, or retinitis). Diagnosis of CMV infection should be based on quantitative nucleic acid amplification testing, with biopsy required to confirm tissue invasive disease.[193] Atypical presentations include allograft rejection, vanishing bile duct syndrome, or chronic ductopenic rejection.[191,194] In LT recipients, the gastrointestinal tract is the most common site of involvement of invasive disease, and CMV hepatitis can appear similar to allograft rejection.[195] Late onset CMV disease most commonly presents as CMV syndrome, with factors such as female gender, renal dysfunction, and allograft rejection predisposing to development of late onset CMV disease.[194,196] Chronic allograft dysfunction is an independent risk factor for late CMV disease, and mTOR based immunosuppression has been shown to be protective.[184] First line therapy for CMV infection is oral valganciclovir or IV ganciclovir with concomitant reduction in immunosuppression.[193,194] Weekly viral load monitoring and presence or absence of tissue invasive disease guide duration of therapy.

9 | CONCLUSIONS

Despite increased post-transplant survival with improved immunosuppression and surgical techniques, transplant recipients continue to experience a complex array of late post-transplant complications. Since many of these complications are related to immunosuppression, future advances will require immunosuppressive regimens with improved side effect profiles as well as efforts to minimize and withdraw immunosuppression in select patients. Prospective trials report up to 40% of select recipients can tolerate complete withdrawal of immunosuppression at 10 years post-transplant in adults and at 8.5 years post-transplant for pediatric recipients[197–199] with recent studies shifting to earlier withdrawal times. A recent study by the Immune Tolerance Network assessed early withdrawal of immunosuppression in those transplanted for HCV or non-immune liver disease and found that almost 2/3 of transplant recipients were able to tolerate reduction to 50% or less from baseline monotherapy.[198] This study and others highlight the need for viable biomarkers in every day practice to identify patients who will benefit the most from immunosuppression withdrawal and reliably predict immune tolerance.

AUTHOR CONTRIBUTIONS

Matthew A. Odenwald, Hannah F. Roth, and Anesia Reticker drafted the initial manuscript. Anjana Pillai and Maria Segovia provided critical revision of the manuscript. All authors approved the final manuscript submitted.

CONFLICT OF INTEREST STATEMENT

Matt Odenwald, Hannah Roth, and Anesia Reticker have nothing to disclose. Maria Segovia is a consultant for Takeda Pharmaceuticals. Anjana Pillai is on the medical advisory board of Exelixis, Genentech, AstraZeneca, Eisai Inc, and Replimune.

DATA AVAILABILITY STATEMENT

All data in this review article were previously published in the cited manuscripts, which are available on PubMed.

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