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Long-term Management of the Liver Transplant Patient: Recommendations for the Primary Care Doctor

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No official document has been published for primary care physicians regarding the management of liver transplant patients. With no official source of reference, primary care physicians often question their care of these patients. The following guidelines have been approved by the American Society of Transplantation and represent the position of the association. The data presented are based on formal review and analysis of published literature in the field and the clinical experience of the authors. These guidelines address drug interactions and side effects of immunosuppressive agents, allograft dysfunction, renal dysfunction, metabolic disorders, preventive medicine, malignancies, disability and productivity in the workforce, issues specific to pregnancy and sexual function, and pediatric patient concerns. These guidelines are intended to provide a bridge between transplant centers and primary care physicians in the long-term management of the liver transplant patient.

Key words: Immunosuppression, liver, long-term, management, transplantation

Abbreviations: ACE, angiotensin converting enzyme; ACIP, Advisory Committee on Immunization Practices; ACS, American Cancer Society; AIH, autoimmune hepatitis; AZA, azathioprine; CCBs, calcium channel blockers; CKD, chronic kidney disease; CMV, cytomegalovirus; CNI(s), calcineurin inhibitor(s); CRF, chronic renal failure; CsA, cyclosporine; CT, computed tomography; DEXA, dual energy x-ray absorptiometry; EBV, Epstein Barr virus; ERCP, endoscopic retrograde cholangiopancreatogram; ETOH, alcohol; GFR, glomerular filtration rate; HBIg, Hepatitis B immune globulin; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDL, high density lipoprotein; HPV, human papilloma virus; LAIV, live attenuated influenza vaccine; LDL, low density lipoprotein; LT, liver transplantation; MDRD, modification of diet in renal disease; MELD, model for end-stage liver disease; MMF, mycophenolate mofetil; MPA, mycophenolic acid; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; NSAIDs, non-steroidal anti-inflammatory drugs; NTPR, National Transplantation Pregnancy Registry; PBC, primary biliary cirrhosis; PCP(s), primary care physician(s); PCR, polymerase chain reaction; PSC, primary sclerosing cholangitis; PTC, percutaneous transhepatic cholangiogram; PTLD, post-transplant lymphoproliferative disease; QOL, quality of life; SCC, squamous cell carcinoma; TAC, tacrolimus; USA, United States; USFDA, US Food and Drug Administration; VLDL, very low density lipoprotein.

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Introduction

Liver transplantation (LT) outcomes have evolved dramatically since the development of the surgical procedure in the 1960s. Today, the 1-year expected survival rate is over 85% and LT has become the treatment of choice for chronic liver failure, acute liver failure and selected patients with early stage unresectable liver cancer. With increasing numbers of long-term survivors, primary care physicians (PCPs) are seeing larger numbers of solid organ recipients in their practice.

A survey of transplant centers published in 2001 found that a majority of centers expected PCPs to assume responsibility for the overall care of liver transplant patients after the first 6 months of transplant (1). In addition to routine healthcare needs, unrelated to the transplant, PCPs are faced with complex management of chronic illness and cancer screening that have unique implications due to chronic immunosuppression. However, most PCPs have no formal training in transplantation. This article is intended to serve

as a guideline to assist the PCP in long-term care of liver transplant recipients.

Immunosuppressive Medications

Knowledge of immunosuppressive medications and their side effects, as well as potential individual drug interactions, is important in the management of liver transplant patients. The complications associated with immunosuppressive medications accrue with longer exposure. Over half of the deaths in liver transplant patients are related to complications attributable to antirejection medications including cardiovascular disease, renal failure, infection or malignancy (2). To prevent acute rejection and manage potential adverse effects, there is a general strategy of using multiple immunosuppressive medications at high doses early after LT and fewer immunosuppressive medications at lower doses later after LT.

Early after LT, most centers use a combination of two to four immunosuppressive medications, including a calcineurin inhibitor (CNI), an antimetabolite, sirolimus, and/or corticosteroids. Later, most centers taper doses of immunosuppressive drugs and eliminate all but the CNIs. There is considerable variation between centers as to the particular medications used and the specific timing of their tapering and discontinuation, but most in the field agree that immunosuppression management is the primary responsibility of the transplant center (1). Therefore, the transplant centers review laboratory tests (including complete blood count, renal function, hepatic function and drug levels) on all recipients on a regular basis (most often monthly, but more or less frequently based on patient health, organ function and center-specific protocols). These laboratory tests can be obtained close to the patients' homes with the results monitored by the transplant center.

Calcineurin inhibitors (CNIs)—cyclosporine (CsA) and tacrolimus (TAC)

All forms of CsA [Sandimmune (Novartis, East Hanover, NJ), Neoral (Novartis, East Hanover, NJ) and Gengraf (Abbott, North Chicago, IL)] and TAC [Prograf (Astellas, Deerfield, IL)] suppress the immune system through the inhibition of calcineurin, a protein that drives production of cytokines, such as IL-2, involved in the activation of T cells (the immune cell that attacks the liver allograft). Collectively, CsA and TAC are called CNIs. The majority of patients are maintained on one or the other lifelong after transplant. Both are oral agents usually taken every 12 h. A modified release preparation of TAC should be available soon and can be given every 24 h. CsA is available in 25 and 100 mg capsules and TAC in 0.5, 1 and 5 mg capsules. The dosage is based on trough levels of the drugs and is highly individualized. Higher trough levels are sought initially after transplant when the risk of rejection is high and lower levels are sought later when concerns about adverse effects start to predominate. Typical trough levels for CsA are 200–300 ng/ml initially, and levels of 50–150 ng/ml long term. Typical trough levels for TAC are 5–15 ng/ml initially and levels of about 5 ng/ml after a year. Due to the very narrow therapeutic window of these medications, caution must be exercised when substituting generic CNIs. For example, switching from one formulation of a CNI to a generic CNI may result in low serum levels and precipitate an episode of rejection. Any switch in the formulation of CNI should be associated with more frequent monitoring with laboratory tests. Generic CNIs have met FDA criteria demonstrating bioequivalence, but in most cases have not been fully evaluated in potentially at-risk patient populations (specifically African Americans or pediatric populations) (3).

There are several side effects common to both CNIs including hyperkalemia, hypertension, neurotoxicity (headaches, tremors, neuropathy and seizures) and nephrotoxicity. Renal insufficiency is a major cause of morbidity and mortality after liver transplant. CsA is more commonly associated with dyslipidemia and gingival hyperplasia, while TAC is more frequently associated with diabetes. TAC is currently used in a majority of liver transplant patients in the United States (USA) and associated with less rejection than CsA (4).

Antimetabolites

Azathioprine (AZA) [Imuran (Prometheus, San Diego, CA), Azasan (Salix, Morrisville, NC)], mycophenolate mofetil (MMF) (CellCept (Roche, Nutley, NJ)] and mycophenolic acid (MPA) [Myfortic (Novartis, East Hanover, NJ)] are antimetabolites. Antimetabolites refer to a group of drugs that interfere with purine nucleotide synthesis, which leads to preferential inhibition of T and B lymphocytes. The antimetabolites are not generally potent enough to be used alone, but are important as adjunct agents. Typically MMF or MPA are also discontinued within a year after transplant. However, there is evidence that if MMF or MPA is continued, lower doses of CNIs can be used with a resulting improvement in renal function (5). AZA was used early in liver transplant, but in recent years MMF and MPA are used more frequently. AZA can be associated with cholestatic hepatitis. MMF and MPA do not exhibit this rare side effect and are more potent. Frequent side effects of MMF and MPA include bone marrow suppression and gastrointestinal issues including gastritis, nausea, diarrhea and abdominal pain.

Sirolimus/rapamycin

Sirolimus [Rapamune (Wyeth-Ayerst, Philadelphia, PA)] is a newer immunosuppressant agent that inhibits T cell proliferation through cell cycle inhibition. It is touted as an agent that is potent enough to be used as a primary immunosuppressive agent but without the nephrotoxicity of CNIs. Sirolimus is therefore considered as an alternative to CNIs or in some instances in combination with lower doses of one of the CNIs. Sirolimus has been associated

Table 1: Drugs and substances that may decrease levels of cyclosporine, tacrolimus and sirolimus[1]

Anti-convulsants	Antibiotics	Others
Carbamazepine	Rifabutin	St. John's Wort
Phenobarbital	Rifampin	Orlistat
Phenytoin		

[1]This table is not all inclusive.

with an increased risk for hepatic artery thrombosis (in some but not all trials) and, as a result, has received a 'black box' warning for liver transplant recipients suggesting avoidance in the first month after transplant. Other side effects include rash, dyslipidemia, cytopenias, poor wound healing, lymphoceles and oral ulcerations. There is also an association with an unusual but potentially fatal interstitial pneumonitis. Due to side effects, 20–30% of those patients who receive the drug are not able to tolerate it.

Corticosteroids

Corticosteroids (prednisone or prednisolone) are generally given in large doses during the first week after LT and tapered rapidly to low levels or completely eliminated within weeks or months following LT (6). Given the substantial long-term side effects of corticosteroids, most transplant centers are trying to eliminate or minimize corticosteroids use in transplant recipients. However, in patients with autoimmune liver diseases or recurrent rejection, steroids are frequently continued indefinitely.

Drug interactions of immunosuppressants

TAC, CsA and sirolimus have dose-related toxicity and relatively narrow therapeutic windows. The two pathways that are important for CNIs metabolism are cytochrome P-450 3A4 and P-glycoprotein. Certain drugs can induce or inhibit the cytochrome P-450 3A4 pathway resulting in rapid or slow metabolism of CNIs. Tables 1 and 2 provide a list of substances that can increase or decrease levels of immunosuppressants, but are not exhaustive, and therefore it is advisable to notify the transplant center whenever new medications are initiated in the liver transplant recipient. For example, the inadvertent use of clarithromycin, an inhibitor of the cytochrome P-450 3A4 pathway, for a simple urinary tract infection can double the serum TAC level and result in significant nephrotoxicity. P-glycoprotein is a cell membrane-associated protein that transports a variety of drug substances and influences drug absorption (in the intestine) and elimination (in the liver and kidney) (7). Carvedilol, a nonselective beta-blocker with alpha-blocking properties is metabolized by the cytochrome P-450 2D6, but not the P-450 3A4 pathway. Carvedilol has been shown to increase serum levels of CNIs by inhibiting the P-glycoprotein pathway (7,8). Other frequent potential interactions include allopurinol (which can increase levels of antimetabolites to toxic levels, especially AZA), nonsteroidal anti-inflammatory medications (NSAIDs) (which can potentiate CNI-induced nephrotoxicity) and spironolactone, which can increase CNI-induced hyperkalemia.

Drugs that are generally well tolerated include amlodipine, nifedipine, clonidine, angiotensin converting enzyme (ACE) inhibitors, angiotensin II AT1 receptor blockers and beta-blockers (excluding carvedilol) for hypertension; oral hypoglycemics, metformin, sulfonylureas and thiazolidinediones for diabetes; selected antimicrobial agents including any of the penicillins, cephalosporins, quinolones, sulfonamides and topical (not oral) anti-fungal agents; and gabapentin and evetiracetam for seizures. Statin drugs, ezetimibe, niacin and intestinal binders of bile acids have been used to treat dyslipidemia. Due to interactions between CNIs and statins or ezetimibe, these lipid-lowering drugs should be given at lower dosages and monitored for side effects and serum trough levels of CNIs (9). Intestinal binders of bile acids should be given 2 h before or after CNIs and should not be used in patients also taking MMF or MPA (10). Narcotics are usually safe outside their addictive potential and antidepressants are typically well tolerated. Up to 4 g/day of acetaminophen can be given to liver transplant recipients with functioning livers without reservation.

Recommendations

- With the narrow therapeutic ranges for CNIs, it is recommended to avoid all medications that will affect the metabolism of the CNIs (Tables 1 and 2) or contribute to their toxicity. This would include avoiding all NSAIDs and any agent that is primarily metabolized by the same (cytochrome P450 3A4 or P-glycoprotein) pathways as TAC, CsA or sirolimus.
- Before prescribing any new medication, it is imperative to review them for possible drug interactions with the liver recipient's immunosuppressive agents and consult the transplant center. Websites to look

Table 2: Drugs and substances that may increase levels of cyclosporine, tacrolimus and sirolimus[1]

Antifungals	Antibiotics	Calcium channel blockers	Others
Caspofungin	Azithromycin	Diltiazem	Protease inhibitors for HBV
Fluconozole	Clarithromycin	Verapamil	Protease inhibitors for HIV
Itraconozole	Erythromycin		Grapefruit products
Ketoconozole			Danazol
Terbinafine			
Voriconozole			

[1]This table is not all inclusive.

for drug interactions include www.epocrates.com and www.pdr.net.

Causes of Liver Allograft Dysfunction

Salvage of the dysfunctional liver allograft depends on accurate diagnosis and prompt treatment. The differential diagnosis of hepatic allograft dysfunction includes the following: rejection; viral hepatitis including cytomegalovirus (CMV) and other herpes family viruses, hepatitis A, B or C; recurrent primary liver disease (viral hepatitis B or C, autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), recidivism with alcohol (ETOH) and recurrent hepatocellular carcinoma (HCC)); exposure to hepatotoxins; vascular complications including hepatic artery thrombosis and portal or hepatic vein thrombosis; and biliary complications.

Rejection

Acute rejection may occur in up to 10% of liver transplant recipients (11). It is most common within the first 3 months following LT, but can occur at any time. Rejection (as with immunosuppressive levels) is usually managed by the transplant center. When rejection occurs some years following LT, it is often associated with low CNI levels and noncompliance. Rejection is often suspected by hepatocellular abnormalities of serum liver function tests, but can be seen with cholestatic abnormalities of serum liver function tests. Fever, jaundice and abdominal pain may suggest advanced rejection. Chronic rejection resulting in fibrosis and disappearance of bile ducts may develop (vanishing bile duct syndrome or ductopenic rejection), resulting in severe biliary obstruction and jaundice, frequently associated with renal dysfunction. Chronic rejection may be treated by increasing CNI levels or the addition of sirolimus, but retransplantation should be considered if significant allograft synthetic dysfunction or portal hypertensive complications exist.

Cytomegalovirus

CMV infection is the most common cause of acute allograft dysfunction due to infection in the first few months following LT, although other herpes family viruses may also cause hepatotoxicity and similar symptomatology. CMV disease may result from reactivation of a remote infection in the recipient or a new infection acquired following LT. Patients at highest risk are CMV negative prior to LT and receive a liver from a CMV positive donor. The typical timing for disease is 1–4 months posttransplant, but can be delayed after prophylaxis with an antiviral agent. Acute CMV disease may manifest with fevers, headaches, myalgias, leukopenia, thrombocytopenia, pneumonitis, nausea, diarrhea, retinitis and/or hepatitis. The diagnosis can be made from blood (CMV polymerase chain reaction (PCR) and/or CMV antigenemia) or tissue samples (intestines or liver). When a liver biopsy is obtained, giant cells with viral inclusions suggest the diagnosis of CMV hepatitis, which can then be confirmed by immunohistochemistry of the biopsy specimen. Intravenous ganciclovir is the most common treatment, but oral valganciclovir and CMV-specific immunoglobulin have also been utilized (12). CMV infection can also precipitate acute rejection by inflammatory and immune-mediated mechanisms.

Recurrence of primary liver disease

Liver transplant recipients may develop recurrence of their primary liver disease.

Hepatitis C recurrence is universal following LT and generally leads to slowly progressive graft dysfunction. At 5 years after LT, up to 30% of patients undergoing LT for hepatitis C virus (HCV)-induced liver disease develop cirrhosis (13). Currently, the only available treatment option is interferon and ribavirin therapy following LT, but treatment is associated with frequent hematologic complications and viral clearance is achieved in only 20–30% of transplant recipients (13). Anti-viral therapy for HCV should be administered by a clinician experienced in the treatment of viral hepatitis.

Hepatitis B recurrence following LT can lead to rapid graft loss if untreated, but with the use of Hepatitis B immune globulin (HBIg) and the availability of multiple antiviral agents (lamivudine, adefovir, entecavir, telbivudine and tenofovir), and a better understanding of hepatitis B virus (HBV), resistance mutations have reduced this problem to negligible rates of recurrence (14). A significant limitation in preventing recurrent HBV is the high long-term costs of these therapies. Current protocols include using HBIg with an antiviral agent, but ongoing studies to identify lower cost alternative treatment protocols are underway.

Autoimmune diseases including AIH, PBC and PSC recur in approximately 11–22% of patients despite the use of immunosuppressive medications following LT. Additional treatment at the time of recurrence has variable effectiveness to prevent graft dysfunction or graft loss (15).

Patients transplanted for *ETOH*-induced cirrhosis are at risk of drinking after LT, and hence should be counseled against ETOH use. Recent data suggest that up to 20% of patients transplanted for ETOH-related liver disease will return to some degree of drinking at some time after LT (16).

Hepatocellular carcinoma (HCC) is the primary indication in 15–20% of all adult patients listed for a liver transplant. Patients transplanted with HCC and within Milan criteria (one lesion less than 5 cm in diameter, two or three lesions all less than 3 cm in diameter, and no evidence of vascular involvement and no metastasis) have recurrence rates less than 10%, but patients that are transplanted with HCC outside of Milan criteria have recurrence rates as high as 34% (17). Recurrent cancer, either in the liver allograft,

lungs, bone, central nervous system, adrenal glands or some other site is usually identified by imaging.

Vascular complications

Vascular complications occur in up to 10% of liver transplant recipients, usually within the first month after LT, but can occur at any time. Hepatic artery thrombosis may cause destruction of the bile ducts leading to biliary strictures or bilomas. Secondary infection of a biloma may result in a hepatic abscess. Patients may present with elevated liver tests, jaundice or fevers. Percutaneous or endoscopic stenting of the biliary strictures, as well as percutaneous drainage of any existing bilomas, may lead to restoration of normal function, but frequently patients require retransplantation. If hepatic artery thrombosis is identified within the first week, usually manifested by acute and dramatic increase in serum transaminase levels, the graft may be occasionally salvaged by thrombectomy or thrombolytic therapy. Portal and hepatic vein thrombosis can also occur, and may manifest symptomatically as recurrent ascites or variceal hemorrhage. There is no universal approach to the treatment of these problems, however, vascular stenting or anastomotic revision may be considered and patients should be referred back to the transplant center for urgent evaluation and treatment (18).

Biliary complications

Biliary complications represent some of the more frequent problems encountered by the posttransplant patient with an incidence rate of 10–25% (19,20). Right-lobe living donor transplants are associated with higher rates of biliary abnormalities (28–32%) than deceased donor transplants (5–15%) (21). Recipients of livers from donors after cardiac death have the highest rate of biliary complications (60%), which has limited this potential source of donor organs (22). The various types of biliary complications include bile leaks, bilomas, anastomotic strictures, diffuse biliary strictures, sludge, stones, Sphincter of Oddi dysfunction and cystic duct mucoceles. Biliary complications can also be related to a T-tube used by some surgeons to stent the biliary anastomosis and allow access to the biliary system.

To understand biliary complications, it helps to understand the two types of biliary reconstruction during a liver transplant. The primary technique is a duct-to-duct anastomosis (also called a choledochocholedochostomy). This method preserves recipient Sphincter of Oddi function as a defense against enteric organisms and allows for future endoscopic access of the duct. The second method makes use of a Roux-en-Y choledochojejunostomy or hepaticojejunostomy. In this procedure, the donor bile duct is sewn directly into a jejunal limb. This second method has been preferred in patients with PSC, cholangiocarcinoma, biliary atresia, inadequate bile duct size and a large disparity between the donor and recipient ducts (23). This method is also used for surgical correction of biliary complications from a duct-to-duct anastomosis.

Bile leaks can occur at the biliary anastomosis, at the T-tube exit site, from the cystic duct stump and from the liver edge and occur in 5–15% of patients. They are associated with T-tubes, liver biopsies or hepatic artery thrombosis. The leaks can be asymptomatic or can be associated with fever, abdominal pain or even signs of sepsis.

Treatment depends on the etiology of the bile leak (24–27). Bile leaks related to the T-tube can be managed by percutaneous drainage, endoscopic placement of a stent across the Sphincter of Oddi or the site of the leak, or surgical hepaticojejunostomy. Infected bilomas should be treated with antibiotics and either percutaneous or surgical drainage.

Biliary strictures can either be anastomotic or nonanastomotic. Strictures can occur any time after LT and in both duct-to-duct anastomosis and Roux-en-Y choledochojejunostomy. The causes of anastomotic strictures include local ischemia, scarring and narrowing resulting from suturing. Since these strictures are focal, nonsurgical treatment with endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiogram (PTC) can be used for successful treatment (28–30). Nonanastomotic strictures are more difficult to treat with ERCP or PTC as they tend to be in multiple locations at the hilum or in the intrahepatic biliary radicals (28,30). In one study, hepatic artery thrombosis was responsible for 7 of the 12 (58%) nonanastomotic strictures identified (31). Other factors contributing to strictures include prolonged organ ischemia, donor organs obtained after cardiac death, CMV infection, immunologic rejection, and recurrence of PSC (19,31).

Other biliary complications have been reported in the liver transplant patient. Sphincter of Oddi dysfunction as a result of denervation may occur in up to 5% of liver transplant patients (27,28). Sphincterotomy and conversion to a Roux-en-Y heptaticojejunostomy are suggested treatments (32). Mucoceles (within the cystic duct) and stones have led to biliary obstruction and can require Roux-en-Y reconstruction (27). Hemobilia is rare, but may present as gastrointestinal bleeding or as biliary obstruction from clot formation within the biliary tree resulting from peri-operative procedures (biopsy or PTC).

Recommendations

- If liver function tests are abnormal (1.5 times above normal) in liver recipients, the liver transplant center should be contacted.
- Various studies should evaluate the cause of hepatocellular injury (generally an elevation of serum aminotransferases compared to alkaline phosphatase) include the following:
  a. ultrasound of the liver and Doppler of the allograft vasculature system and

b. liver biopsy.
- Various studies should evaluate the cause of cholestasis (generally elevated serum alkaline phosphatase compared to aminotransferases) include the following:
  a. endoscopic retrograde cholangiopancreatography (ERCP),
  b. magnetic resonance cholangiopancreatography (MRCP) and
  c. percutaneous transhepatic cholangiogram (PTC).
- Biliary complications should be considered in any patient who presents with cholestatic liver function tests, jaundice and/or fever. Since the transplanted liver is not innervated, patients do not always have right upper quadrant abdominal pain.
- Any patient with biliary complications should have their hepatic artery evaluated for possible thrombosis.

Renal Dysfunction

Liver transplant recipients have the second highest rate of chronic renal failure [CRF; defined as a glomerular filtration rate (GFR) of $\leq$ 29 ml/min/1.73 m^2 BSA] among recipients of nonrenal, solid organs with an 18% cumulative incidence 5 years after LT (33). Among all solid organ recipients, the development of CRF is associated with a 4.5 greater probability of death compared to organ recipients with normal renal function (34). As much as 25% of the decline in GFR can occur within the first posttransplant year (35,36). Signs and symptoms of patients with CRF include anemia, renal osteodystrophy and electrolyte abnormalities. Pretransplant factors, immunosuppression posttransplant, hypertension and diabetes mellitus are the four most important factors that influence long-term renal function after LT. Hypertension and diabetes can occur independently or as adverse effects of commonly prescribed posttransplant CNIs or corticosteroids and will be discussed in the next section (Metabolic Disorders).

Pretransplant factors

Pretransplant factors associated with an increased risk for CRF include: female sex, chronic kidney disease (CKD) prior to LT (especially dialysis therapy), diabetes mellitus and infection with HCV (34). With the introduction of the Model for End-Stage Liver Disease (MELD) for organ allocation in 2002, serum creatinine has emerged as a major determinant for timing of LT with priority increasing proportionally to serum creatinine (37). The effect of the change in organ allocation policy on the burden of CKD post-LT is unknown.

Immunosuppression

Though critical to the success of organ transplantation, CNI-based immunosuppressive medications can cause substantial nephrotoxicity. Acute nephrotoxicity from CNIs results from vasoconstriction of intrarenal vessels causing decreased renal blood flow. The effect is reversible with dose reduction or medication withdrawal. In contrast, chronic CNI nephrotoxicity is characterized by tubulointerstitial fibrosis and is clinically manifested by declining GFR with time and is the most common cause of CKD postliver transplant (38). Management of chronic CNI-induced renal injury is minimization of CNIs or conversion to sirolimus.

Measurement of renal dysfunction

The two most accessible formula-based estimates of GFR are the Modification of Diet in Renal Disease (MDRD) and Cockcroft–Gault equations. Both calculations underestimate the true GFR in liver transplant recipients. MDRD is the preferred method to estimate GFR as it is more precise and accurate, with only 65% of the estimates within 30% of the measured GFR (39).

Recommendations

- Contact the liver transplant center and discuss minimization of CNIs.
- Optimize treatment of diabetes and hypertension (if present) to minimize further renal injury (see the next section).
- Evaluate with urine analysis.
- Consider early referral to a nephrologist for evaluation and management of renal dysfunction if
  a. abnormal urine analysis (proteinuria or hematuria),
  b. MDRD GFR $<$ 60 ml/min/1.73 m^2 BSA and
  c. rapid decline in renal function.

Metabolic Disorders

There are common medical conditions occurring in many liver transplant recipients that require special attention from PCPs including: diabetes, hypertension, dyslipidemia, obesity, gout and metabolic bone disease.

Diabetes

In liver transplant recipients, the prevalence of overt diabetes may be as high as 33% (40,41). Risk factors include use of corticosteroids, TAC at high dosages, hepatitis C seropositivity, ethnicity, pretransplant diabetes and obesity (42). LT sometimes cures hepatogenous diabetes; however, many pretransplant insulin-dependent patients remain on insulin after LT (43). In one cohort study of 618 liver recipients, 56% (37/66) of pretransplant diabetics were free of diabetes 1 year from LT. However, 7% (39/552) of recipients developed new onset diabetes within that year (44). Incidence of *de novo* posttransplant diabetes is greatest during the first year after LT (26% at 1 year, 9% at 2 years and 1% at 3 years) (45). Patients transplanted for hepatitis C are more likely to have diabetes after LT compared to patients transplanted for other causes (46).

Management of posttransplant diabetes is similar to patients without liver disease with the same treatment goals to prevent renal failure, neuropathy, retinopathy, cardiovascular and cerebrovascular disease. Diabetic diet, exercise and education are important in managing diabetes. Many

patients require insulin therapy in the early stages. Oral hypoglycemics can be used for a lesser degree of hyperglycemia with little concern of interaction with immunosuppressive medications or damage to the transplanted liver (47). Early withdrawal or dose reduction of corticosteroids may improve glycemic control. Another beneficial therapeutic maneuver may be lowering of TAC dosages.

Hypertension

Hypertension is a common complication in the posttransplant patient (48). Corticosteroids and CNIs increase the risk of hypertension in the posttransplant patient. The latter medication causes sympathetic stimulation with resultant renal vasoconstriction and sodium retention (49). CsA is associated with a higher incidence of hypertension following LT as compared to TAC (25–82% vs. 17–64%, respectively) (48,50,51).

The goal of antihypertensive therapy should be a blood pressure below 130/80 (52). Treatment of hypertension may include thiazide or loop diuretics especially in those patients with peripheral edema, but must be used with caution, since they can increase the risk of hyperuricemia. The calcium channel blockers (CCBs), particularly the dihydropyridine class, are a particularly attractive choice because their vasodilatory effects may overcome the vasoconstriction induced by the CNIs. Diltiazem, verapamil and nicardipine should be avoided as they can increase serum levels of the CNIs (48). Antisympathetic antihypertensives (clonidine and doxazosin) are frequently used for posttransplant hypertension, but can cause depression. Beta-blockers are less effective generally than CCBs, but can be used and do not affect CNI levels. The exception is carvedilol, which can cause elevated levels of CNIs and usually requires reduction in CNIs dosages to maintain therapeutic serum levels (8). ACE inhibitors and angiotensin II receptor blockers are not used initially for hypertension, because of the increased risk of renal insufficiency and hyperkalemia in early posttransplant recipients. However, once the acute problems early after LT have resolved, these agents may have a role to prevent diabetic nephropathy and the effect of CsA upregulating angiotensin II receptors (53). Another treatment option that can be considered in conjunction with the transplant center is steroid withdrawal.

Dyslipidemia

Between 16 and 43% of liver transplant recipients have increased plasma cholesterol (54–57). Most patients with noncholestatic liver disease have low serum cholesterol levels due to impaired hepatic synthesis and esterification. Risk factors for posttransplant hypercholesterolemia include female gender, cholestatic liver disease, pretransplant cholesterol elevation, diabetes, obesity and use of beta-blockers, diuretics or immunosuppressive agents (55). CsA, steroids and sirolimus have a significant effect on serum lipid levels. TAC has a minor effect, whereas MMF and AZA have no significant effect on serum lipids. CsA increases serum total cholesterol, low-density lipoprotein (LDL)-cholesterol and triglycerides (58). Steroids increase serum very low-density lipoprotein (VLDL)-cholesterol, total cholesterol and triglycerides levels, and decrease high-density lipoprotein (HDL)-cholesterol levels (58).

Initial treatment for dyslipidemia is lifestyle changes. If lifestyle changes are unsuccessful, the next step is switching medications that are associated with increased dyslipidemia, including oral contraceptives, thiazides, beta-blockers, CsA, steroids and sirolimus. The transplant center should be contacted to consider reducing or eliminating steroids and substituting TAC for CsA (59). If alterations of medications are unsuccessful, then drug therapy should be initiated. All agents correcting lipoprotein metabolism have been used successfully in liver transplant patients, but have potential side effects. Nicotinic acid can cause significant flushing, hyperglycemia, hyperuricemia, gastrointestinal distress or rarely hepatotoxicity. Bile acid sequestrants (cholestyramine, colestipol and colesevelam) can decrease plasma MMF and MPA levels by 35% (10). In addition, bile acid sequestrants can decrease absorption of CNIs. Thus, bile acid sequestrants should not be used in patients taking MMF or MPA and should be given greater than 2 h before or after CNI dosing. Fibric acids (gemfibrozil, fenofibrate and clofibrate) can cause biliary sludge, dyspepsia or myopathy. Ezetimibe can be used, but with monitoring of CNI levels. Statins can cause myopathy or increased liver enzymes. If a statin is used, hydrophilic statins (pravastatin or fluvestatin) are preferred since they are not metabolized by the same cytochrome 450 3A4 metabolic pathway that metabolizes CNIs and sirolimus. The lipophilic statins (atorvastatin, lovastatin and simvastatin) are metabolized by the cytochrome P-450 3A4 metabolic pathway and must be used with caution, since they are associated with higher rates of myotoxicity at dosages greater than 20 mg/day (9). The combination of a lipophilic statin and a fibric acid can significantly increase the risk of myotoxicity. Management of dyslipidemia requires close patient follow-up to observe for possible side effects from the medications.

Obesity

In one study, up to 28% of patients who had a liver transplant had a body mass index > 30. Obese patients undergoing a liver transplant are at higher risk of poor wound healing and infections immediately after LT compared to nonobese patients. Unfortunately, 22% of nonobese transplant recipients became obese over a 2-year follow-up (60). It is common for patients posttransplant to have an improved sense of well-being, contributing to overeating. Liver recipients, who were overweight preoperatively, tend to gain more weight. Corticosteroids definitely contribute to weight gain, and one study suggests that CsA is associated with more weight gain compared to TAC (46% vs. 27%, respectively) (61). Patients transplanted for nonalcoholic steatohepatitis can develop recurrent steatosis in their liver if they gain weight after LT (62).

Treatment for obesity involves sensible diet, abstinence from ETOH, aerobic exercise programs and considering altering immunosuppressive medications (lowering or discontinuing corticosteroids or switching from CsA to TAC). Orlistat as an antiobesity agent is not recommended for patients also receiving CsA, since the combination may decrease CsA absorption. Orlistat has been safely used with TAC-based immunosuppression, but efficacy is unknown (63). Isolated case reports have reported on weight loss surgery after LT (64).

Gout

Hyperuricemia is common in posttransplant recipients. Frequently, this condition occurs as a result of decreased uric acid excretion related to CNIs. Preventing attacks usually consists of allopurinol and avoiding contributing medications, including thiazide diuretics, low-dose aspirin and nicotinic acid. Allopurinol can be used in patients on immunosuppressive agents, except with AZA, since the combination may increase the risk of AZA toxicity, including mylosuppression. Acute gout attacks are treated with colchicine and corticosteroids as second line treatment. NSAIDs should be avoided in patients taking CNIs, since the combination can induce nephrotoxicity.

Metabolic bone disease

Many patients with chronic liver disease have decreased bone density as compared with age-matched controls. Factors causing bone disease in cirrhotic patients include ETOH consumption in patients with ETOH-induced cirrhosis, immobility with advanced disease, smoking history, hypogonadism, older age, impaired conversion to 25-hydroxylation of vitamin D by the liver, poor nutritional status and calcium malabsorption (65).

Bone loss occurs at an accelerated rate after LT and nadirs 6 months after the surgery. At 1 year after LT, bone densities are usually equivalent to the bone density at the time of transplant (65). The prevalence of skeletal fractures within 2 years after liver transplant is about 13% (66). Increased bone resorption is the prime contributor to the decline in bone density. In patients transplanted due to cholestatic-related cirrhosis, additional factors contributing to osteoporosis include vitamin D malabsorption and unconjugated bilirubin impairing the proliferation of osteoblasts (67). Corticosteroids are an additional factor causing bone disease after LT. In animal models, conversion from CsA to TAC leads to a reversal of CsA-induced bone loss although there are no good studies evaluating bone loss in humans on CNIs (68). AZA, sirolimus or mycophonolate do not appear to be associated with bone loss (69).

Adult liver transplant recipients should be evaluated for osteoporosis if they have any possible risk factors, including a history of smoking, heavy ETOH intake, physical inactivity, cholestatic liver disease, postmenopausal state, advanced age, hypogonadism, a fracture with minimal trauma or corticosteroid use for more than 6 months. The preferred method to evaluate for osteoporosis is a dual energy x-ray absorptiometry (DEXA) scan. If the DEXA scan is abnormal, treatment is indicated.

Nonpharmacologic therapies include ETOH and smoking cessation, increased physical activity and a balanced diet with 1500 mg of calcium and 800 IU of vitamin D daily. Studied pharmacologic treatments include testosterone replacement in male patients with low serum testosterone levels, replacement of additional vitamin D (25 000–50 000 IU orally two to three times per week) if a deficiency is present and bisphosphonates. Agents that have not been well studied in liver transplant recipients include parathyroid hormone, calcitonin, and selective estrogen-receptor modulators. These agents have been proven to be effective in nontransplanted patients with postmenopausal osteoporosis. Treatment for osteoporosis in liver transplant recipients is not different from other patients and drugs used for treatment are not usually toxic to the liver.

Another important metabolic bone disease is osteonecrosis of the femoral head, which presents as hip pain due to corticosteroid use. This is diagnosed by magnetic resonance imaging (MRI) and may require hip replacement.

Recommendations

- Discuss with the transplant center to minimize any medication that could be contributing to or causing any metabolic disorder(s).
- Diabetes and metabolic bone disease management should include standard therapies.
- Hypertension treatment should avoid using diltiazem, verapamil or carvedilol to a patient who is on a CNI; all other agents are safe to use.
- Dyslipidemia treatment can be associated with significant drug interactions. The preferred statin of choice is a hydrophilic statin (pravastatin or fluvestatin), since they will not interact with CNIs. The lipophilic statins (atorvastatin, lovastatin and simvastatin) will interact with CNIs and are associated with higher rates of myotoxicity at dosages greater than 20 mg/day. Dose a bile sequestrant more than 2 h before or after a CNI dose and do not use in patients also taking MMF or MPA.
- Obese patients on CsA should not receive orlistat, otherwise use standard treatment.
- Gout management should include standard therapies, but avoid interactions between allopurinol with azathioprine and NSAIDs with CNIs.

Preventive Medicine

Transplant recipients are usually highly motivated to maintain their recovered health status by adhering to pharmacotherapy regimens and medical follow-up. This motivation

Table 3: Vaccines that are safe to give to immunosuppressed patients or household contacts

Diphtheria
Hepatitis A, B or the combination of A and B
Haemophilus influenzae type b (Hib)
Human papillomavirus
Influenza inactivated
Meningococcal
Pertussis
Pneumococcal
Tetanus
Tick-borne encephalitis

affords the treating physician the opportunity to implement preventive medicine measures. Besides the routine blood testing for monitoring immunosuppressive drug levels, liver transplant recipients require immunization boosters or primary series, dental care, counseling against smoking and cannabis, and screening for malignancies. Given the increased risk of certain cancers, issues with malignancies will be discussed in the next section.

Vaccinations

Immunosuppression severely inhibits T cell function and increases risks of developing infections, resulting in significant morbidity and mortality in transplant patients. Thus, to decrease risks of viral and bacterial infections certain vaccines can and should be given to transplant recipients (70). The ideal time to vaccinate patients requiring immunosuppression is prior to immunosuppression, when possible, recognizing that not all patients with chronic liver disease respond to vaccinations. Posttransplant, vaccines that are widely agreed to be safe when administered to immunosuppressed patients or their household contacts are listed in Table 3. In addition, immune globulin can be given for patients who are exposed to an acute case of hepatitis A, hepatitis B and varicella-zoster. Although many centers recommend against vaccinations with the live-attenuated vaccines listed in Table 4 due to the theoretical risks from potential shed of live virus, several small studies have demonstrated safe administration of live-attenuated vaccines after transplantation (71–73). When possible, inactivated vaccines should be administered. For example, the injected influenza-inactivated vaccine [Afluria (CSL Biotherapies, King of Prussia, PA), Fluvirin (Novartis, Cambridge, MA), Fluzone (Sandofi Pasteur, Swiftwater, PA), FluLaval and Fluarix (GlaxoSmithKline, Research Triangle Park, NC)] is recommended for immunosuppressed patients and their household contacts instead of the inhaled live-attenuated influenza vaccine (LAIV) (FluMist, Medimmune Vaccines, Gaithersburg, MD).

Table 4: Live attenuated vaccines

Bacille calmette-guerin (BCG)
Live attenuated influenza (LAIV)
Measles
Mumps
Polio (oral)
Rotavirus
Rubella
Typhoid (oral-TY21a)
Vaccinia (smallpox vaccine)
Varicella
Yellow fever

A study in 165 renal transplant recipients vaccinated with trivalent inactivated influenza vaccine showed the vaccine was safe with seroprotection rates of 79–93% (74). Since liver recipients receive less overall immunosuppression compared to renal transplant recipients, seroprotection and seroresponse rates from influenza vaccinations would be anticipated to be at the same level or improved compared to renal transplant recipients. Although seroresponse does not appear to be altered based on the use of CNI or sirolimus for immunosuppression therapy, seroresponse was decreased 2.6- to 5-fold in patients receiving MMF in the above study (74).

Dental care

Routine dental care is important both before and following LT as oral infections can cause significant morbidity and even mortality. There has been a recent change regarding dental prophylaxis with antibiotics in immunosuppressed transplant recipients for routine dental maintenance. Currently, according to the American Heart Association, antibiotic prophylaxis is not needed unless the patient has an underlying cardiac condition that increases the risk of developing infective endocarditis, including patients with a previous history of endocarditis, prosthetic valves, cardiac transplants with graft valvulopathy and certain forms of congenital heart disease (75). A dental issue unique to transplant patients using CsA and calcium channel blockers is gingival overgrowth. Management of gingival hypertrophy includes periodontal surgery and intensive hygienist support and brushing. TAC is not associated with gingival hyperplasia. Thus, switching from CsA to TAC may be helpful in preventing further hyperplasia (76).

Counseling against smoking and marijuana

Smoking tobacco has been shown to increase the risk of complications after LT. Cigarette smoking increases the risk of coronary heart disease, stroke, certain cancers, chronic obstructive lung disease, and adverse vascular events and graft loss in liver transplant recipients (77). The vascular events arise due to a predisposition of a hypercoagulable state post-LT that increases the risk for hepatic artery thrombosis, hepatic artery stenosis, portal vein thrombosis and deep vein thrombosis (78). A retrospective study of liver transplant recipients showed that vascular events are increased in 18% of smokers versus 8% of nonsmokers ($p = 0.02$) (78). When hepatic artery thrombosis develops,

it is associated with significant graft loss, morbidity and mortality (79).

Many transplant centers also discourage the use of cannabis in liver transplant patients. There is no data citing increased risks of complication for cannabis use after LT but several studies have shown that cannabis use is associated with increased prevalence of fibrosis and steatosis in patients with chronic liver disease (80–82). Finally, contamination of fungal spores in cannabis may increase the risk of respiratory infections (83).

Recommendations

- Vaccinations should be given according to the guidelines established by the 'Advisory Committee on Immunization Practices (ACIP)', but the use of live attenuated vaccines (Table 4) on patients and their household contacts should be cleared by the transplant center.
- Encourage routine dental care. Gingival hyperplasia can be caused by CsA. Contact the transplant center and discuss switching from CsA to TAC.
- In addition to all of the risks of increased morbidity and mortality associated with cigarette smoking to the general population, liver transplant patients are at additional risks of vascular events and graft loss and cigarette smoking should be discouraged. Standard therapies should be used to stop smoking including smoking-cessation programs, nicotine replacement, bupropion and/or varenicline.
- Cannabis use may increase fibrosis and steatosis and may contain fungal spores, thus use should be discouraged.

Malignancies

Malignancies are serious causes of morbidity and mortality after solid organ transplantation. Newer immunosuppression agents are more intense, and prolonged graft survival has resulted in extended exposure to immunosuppressive therapy. Both of these factors have led to the development of malignancies after LT (84,85). Cutaneous malignancies are the most common *de novo* malignancies with an estimated incidence up to a hundred times that observed in an age-matched group from the general population (86). Many viral-related malignancies, such as Kaposi's sarcoma from human herpes virus 8; anogenital lesions, the result of human papillomavirus (HPV); cervical carcinoma secondary to HPV and posttransplant lymphoproliferative disease (PTLD); and B-cell lymphomas related to Epstein Barr virus (EBV) infection are increased in liver transplant recipients. Colon and upper aerodigestive cancers are more prevalent in liver transplant recipients when they are associated with risk factors such as PSC with ulcerative colitis and alcoholic liver disease, respectively. Risk factors such as age, smoking and alcohol seem to play a role in the higher risk for malignancies, but the presence of long-term immunosuppression is the basis for the higher incidence.

Cutaneous malignancies

Carcinomas of the skin and lip are frequently reported. Squamous cell carcinomas (SCC), basal cell carcinomas and melanomas are frequently observed in transplanted recipients. Cutaneous malignancies, especially SCC, develop at a younger age, are more aggressive, metastasize and tend to be multiple in transplant recipients than those in the general population. The peak incidence of cutaneous malignancies is 3–5 years after organ transplantation (87,88). Risk factors for SCC after organ transplantation include a history of skin cancer and/or actinic keratosis, fair skin, chronic sun exposure and/or sunburn, older age, duration and intensity of immunosuppression, history of HPV infection, and CD4 lymphopenia. Patients at high risk for SCC require close monitoring before and after LT and should be followed by a dermatologist (89).

Treatment of all premalignant and malignant skin lesions is not unique for a liver transplant recipient and should be performed by an expert in the field. Minimizing immunosuppression may decrease the occurrence of these lesions and there are data supporting conversion for CNIs to sirolimus (90), but should be done by the transplant center in order to maintain graft function.

Posttransplant lymphoproliferative disorders (PTLD)

PTLD occurs in about 2% of adult transplant recipients and up to 15% of pediatric transplant recipients, generally within the first year after transplant (91,92) and is usually (80–90%) associated with EBV infection (93). Two other types of PTLD which are B-cell marker CD20 negative include a plasmacytic variety resembling multiple myeloma and a T cell malignancy (94).

Symptoms associated with PTLD include fever, night sweats, malaise, weight loss and other constitutional symptoms. PTLD can occur in the absence of lymphadenopathy. The work-up for a suspected PTLD should include biopsy of enlarged lymph nodes or identified mass (94). Staging recommendations from the World Health Organization include contrast computed tomography (CT) of the chest, abdomen and pelvis; serum lactate dehydrogenase for prognosis only and EBV PCR which may be helpful in both diagnosis and monitoring response to therapy (95).

PTLD therapy includes reduction of immunosuppression which should be individualized for each patient's allograft type and severity of disease, while monitoring for allograft dysfunction. After minimizing immunosuppression, patients may notice symptomatic improvement in as little as 1–2 weeks and a clinical response may be noted within 4 weeks (92). Patients unable to tolerate reduction of immunosuppression and those with aggressive

disease should be treated with rituximab (CD20 expressing B cells tumors) or chemotherapy (CD20 negative B cells tumors).

Recommendations

- Screening for most malignancies in transplant recipients should follow the same guidelines proposed by the American Cancer Society (ACS) and various other societies. Screening for breast, prostate and colon cancer should be performed at the appropriate sex, age and frequency as recommended by the ACS.
- Patients with PSC and pan-ulcerative colitis should undergo yearly colonoscopies with multiple biopsies.
- All transplant recipients should receive a thorough dermatologic exam yearly and should be educated on the use of sun screen and avoidance of sun exposure.
- Management of virally mediated malignancies (Kaposi's sarcoma, anogenital lesions and PTLD) requires significant reductions in immunosuppression for effective treatment. Contact the transplant center to minimize immunosuppression, while preventing rejection.
- Other cancers such as breast, lung, colon and prostate, which do not occur in greater frequency in liver transplant recipients, may require minimal immunosuppression adjustment.

Pregnancy and Sexual Function

More than 50% of females with end-stage liver disease experience amenorrhea and infertility is also common (96). More than 90% of LT recipients recover sexual function after LT (97). Time to recovery of fertility is variable and prophylaxis should begin at the time of return of sexual activity if patients wish to avoid pregnancy. Approximately 50% of female transplant recipients are within reproductive age when LT occurs (98).

The National Transplantation Pregnancy Registry (NTPR) database is a voluntary registry that has outcomes on over 2700 pregnancies in solid organ recipients and describes a live birth rate of over 70%, in addition to favorable child and maternal outcomes for the majority of recipients (99). Although this success is encouraging, these pregnancies are still considered high risk and are believed to carry increased morbidity and risk of mortality to both the transplant recipient and her fetus.

Risks of immunosuppression therapy with pregnancy

There are risks for complications during pregnancy for the liver transplant recipient as well as risk of exposure to immunosuppressive therapy and infection for the fetus. According to many authors, a 12-month period between organ transplantation and pregnancy is strongly advised to allow graft function and immunosuppressive regimen to stabilize (96–98).

Risks associated with the fetus/child

Premature and low weight births are the most common fetal complications after LT with frequencies from 10% to 55% (96–98). The fetus is also at risk for TORCH infections such as CMV and herpes simplex virus related to the immunosuppressive state of the mother (100). A common risk involved in maternity and paternity after organ transplantation arises from the potential teratogenic effects of the required immunosuppressive therapy. The NTPR reports a rate of congenital anomalies of 4–5% among patients born to transplant patients using immunosuppressive drugs compared to the baseline rate of 3% for all pregnancies in the USA. Most immunosuppressive agents are classified by the USA Food and Drug Administration (USFDA) for pregnancy safety as C (animal reproductive studies have shown an adverse effect on the fetus or are lacking, and there is no well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks). The exceptions are MMF and AZA, which are classified by the USFDA for pregnancy safety as D (positive evidence of human fetal risk, but potential benefits may warrant use of the drug in pregnant women despite potential risk). In 33 pregnancies exposed to MMF in 24 transplant patients, there were 15 spontaneous abortions and 18 live births (101). Structural malformations were seen in four of 18 (22%) infants. Common structural malformations include ear abnormalities, which were similar to findings in animal reproductive studies (102). TAC-based immunosuppressive regimens are associated with lower rates of hypertension and preeclampsia and a lower incidence of maternal and fetal complications compared to CsA-based immunosuppressive regimens (96–104). Long-term follow-up demonstrates that the majority of the children exposed to immunosuppressant therapy *in utero* are developing normally (103).

Other risk factors associated with pregnancy

Pregnancies in patients with hypertension, diabetes or both tend to have worse outcomes (105). Also, preconceptional renal dysfunction has a very strong association with adverse outcomes of pregnancy in liver transplant patients (97–100).

The most frequent maternal complication after LT is pregnancy-induced hypertension and occurs in 25–45% of patients (96). Preeclampsia, intrauterine infections, anemia, cholestasis and pyelonephritis are other maternal complications. Spontaneous abortion occurs in 39% of these pregnancies which accounts for most of the lost pregnancies (97–103).

Rejection

Pregnancy is associated with increases in plasma proteins, which can increase the bound fraction of CNIs and other protein-bound drugs. Frequent monitoring of serum levels of CNIs are needed during pregnancy to keep

within the therapeutic range. The incidence of rejection is approximately 10% (98–104). Mild-to-moderate elevation of liver enzymes is common in pregnant liver recipients. When acute rejection is suspected, percutaneous liver biopsy does not appear to be contraindicated in pregnant patients (100).

Postpartum medical issues

There were no peripartum deaths reported in the NTPR. Recurrence of primary disease, and not rejection, is responsible for most graft and patient loss after pregnancy. The number of infants who have been breast-fed is still small, so it is not possible to state any conclusion on its effects.

Male sexual function

Sexual function is extremely poor in male cirrhotic patients but returns quickly in the male transplant recipients after transplant. Over half of all males report normal return of libido after transplant (106). Analysis of semen reveal about half of all males have normal density, motility and normal forms (107). Management of erectile dysfunction should include standard therapies including hormonal therapies, intraurethral alprostadil, intracavernous vasoactive drug injection, vacuum constriction devices, penile prosthesis implantation and oral phosphodiesterase type 5 inhibitors.

The NTPR reports that outcomes of pregnancies fathered by male transplant recipients are similar to the general population (105). Precautions are needed after transplant to prevent unwanted pregnancies.

Recommendations

- Pregnancy is discouraged within the first year after LT.
- Patients within reproductive age should receive counseling on family planning. Management for prevention of pregnancy should include standard therapies.
- Patients should receive preconception counseling.
- Mycophenolate mofetil and azathioprine are associated with an increased risk of miscarriages and birth defects. Contact the transplant program to discontinue or replace them at least 6 weeks prior to conception.
- Physicians are encouraged to report all pregnancies to the National Transplantation Pregnancy Registry.
- Management of erectile dysfunction should include standard therapies.

Disability and Productivity in the Workforce

LT prolongs life and achieves long-term survival rates that exceed those associated with the natural history of liver disease. In addition, it gives most patients the opportunity to improve their quality of life (QOL) and return to daily activities including employment. In adults, employment is a key factor associated with success in both economic and psychosocial health (108,109). Several recent studies have examined the frequency of factors associated with rates of employment and disability after LT, and their findings are summarized below.

Quality of life (QOL) after liver transplant

Unequivocally, when the transplant is successful, a patient's QOL improves after LT compared to pre-LT (108,110–113). However, for many patients, health-related QOL is lower than that in the general population (109,114). A lower QOL and physical functioning has been seen in liver transplant recipients with numerous readmissions after the surgery, if delayed wound healing was present or if hepatitis C recurred (115). A study comparing liver transplant recipients and their health practitioners found that there was a striking discrepancy between the health practitioner's objective health assessment and the patient's perception of health status and ability to work. This was most marked in the group of unemployed patients who noted that they had difficulty with behavioral and physical performance of everyday activities. The authors suggested that interventions should be instituted to change health perceptions and to encourage return to work. Occupational counseling and instituting an exercise program postoperatively are recommended to increase a perception of good health (112,113).

A meta-analysis of health-related QOL studies after LT showed that there was significant improvement after LT in physical health, sexual function, daily activities, general health-related QOL and social function, but smaller improvements in psychological health. The authors recommend that psychological and social support be increased both pre- and post-LT and that patients be informed pre-LT about QOL improvements and limitations after LT (111).

Employment after liver transplant

Patients returning to work after LT in the USA range from 27% to 60%; the range is wide because some studies identify students and homemakers as employed, some exclude retirees in the sample and some include part-time workers while others do not (108,109,112,114,115). Most patients who return to work do so within the first 6 months after LT (108). Many transplant centers have arbitrarily chosen 6 months to allow time for the incision to heal and to decrease the risk of incisional hernias. Factors that have been associated with posttransplant employment include private insurance, pretransplant employment, younger age, high level of physical function and a higher general health score (109). Medicaid patients are more likely to remain unemployed after LT, while patients who have private health insurance strive to remain employed to maintain their health insurance after LT (108). Patients have a varying degree of time that is needed for recovery from LT; however, permanent disability is very rare.

Recommendations

- Psychological issues should be evaluated and treated.
- Social support lowers the rate of depression and noncompliance.
- Physical activity should include an aerobic exercise program and should be started early after LT.
- Due to the risk of developing incisional hernias, exercises that may strain abdominal muscles are restricted within the first 6 months after LT.
- Patients may return to the workforce once the incision has healed and the patient is able to perform activities of daily living.

Issues Specific to the Pediatric Patient

Approximately 500–600 pediatric liver transplants are performed annually in the USA and currently there are well over 5000 pediatric recipients with functioning allografts (116). Long-term patient and graft survival continue to surpass that of adult liver recipients, a finding that may be due to multiple factors, including less established comorbidities and the rarity of recurrent liver disease (117). Children surviving 1 year after transplant enjoy a 94% patient and 89% graft survival at 5 years (118).

The PCP is increasingly likely to encounter children who have had a liver transplant (119). Knowledge of several key distinctions in children undergoing transplant will facilitate these patients' care: surgical implications; immunosuppression and rejection risk; infection, malignancy, and long-term risks of immunosuppression; and immunization recommendations.

Surgical implications

Children are more likely to receive technical variant liver grafts than adults; about 50% of children receive whole organs from deceased donors, the remainder are divided between recipients of living donor segments (20%) and deceased donor reduced or split grafts (30%) (120,121). These technical variants and the small size of anatomic structures contribute to an increased incidence of technical complications in children. Vascular complications most often present in the first few months after transplant whereas biliary obstruction may present later in the postoperative course. Often these complications may be asymptomatic and are diagnosed on the basis of appropriate diagnostic studies because of elevated liver injury tests.

Immunosuppression and rejection risk

The majority of children are managed on TAC after liver transplant (116). Corticosteroids are commonly used in combination with TAC and withdrawn at variable times after LT (122). Acute rejection is encountered in up to 50% of children in the posttransplant period (120), but single acute episodes are not associated with poor outcome or chronic rejection. Adherence to medical regimen may especially become a concern in the adolescent population and can lead to graft loss (117). Chronic rejection is uncommon (<5%) in compliant liver transplant recipients with a TAC-based immunosuppression (123).

Infection, malignancy and long-term risks of immunosuppression

Since recurrent disease is rare in pediatric transplant, the major determinant of long-term morbidity is related to immunosuppression and includes infection, renal insufficiency, osteoporosis, cardiovascular disease risk, and impaired growth and development. Several unique areas of concern to children include viral illnesses such as EBV-related PTLD and CMV, which are more common in sero-negative children who receive sero-positive allografts. Serial monitoring of EBV and CMV viral loads has significantly contributed to decreasing the incidence of these viral illnesses following transplant (124), since empiric therapies and immunosuppression reduction can be initiated prior to the onset of clinical illness.

Immunizations

A list of vaccines that are safe to give to immunosuppressed patients or household contacts are listed in Table 3. Limited data are available on the risks and benefits of using live attenuated vaccines (Table 4) in transplant patients or their household contacts. A complete discussion of immunizations can be found in the 'Preventive Medicine' section, subheading 'Vaccinations'.

Recommendations

- If liver function tests are abnormal (one and half above normal) in liver recipients, the liver transplant center should be contacted.
- Various studies to evaluate for abnormal liver function tests include the following:
  a. ultrasound of the liver and Doppler of the allograft vasculature system,
  b. liver biopsy and
  c. cholangiogram of the biliary system with ERCP, MRCP or PTC.

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