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Long-term management of liver transplant recipients: A review for the internist

ABSTRACT

Outcomes and long-term survival rates after liver transplantation have significantly improved over the last 5 decades, but the improved longevity is accompanied by long-term complications such as metabolic syndrome, obesity, cardiovascular disease, cancer, and bone disease. After the first year, the primary care physician assumes a greater role and provides most of the patient's care. This review provides a source for primary care physicians in managing the long-term medical complications seen in these patients.

KEY POINTS

Tacrolimus and cyclosporine are the most commonly used immunosuppressive agents in liver transplant recipients. Adverse effects include hypertension, hypercholesterolemia, diabetes (more common with tacrolimus), renal insufficiency, and osteoporosis.

Hypertension affects 40% to 85% of liver transplant patients. Dihydropyridine calcium channel blockers (eg, amlodipine, nifedipine) are the first-line agents.

Cardiovascular disease is the third most common cause of death after liver transplantation. Modifying risk factors is essential.

Skin cancers account for 40% of all cancers after liver transplantation. Intensive screening is required and has been proven to lower the risk of death.

SINCE 1963, WHEN Starzl et al performed the first successful liver transplantation,¹ outcomes of this life-saving procedure have continued to improve. Long-term survival rates have increased markedly: the current 5-year rate is 73.8% and the 10-year rate is 60%.²

This success means that internists will be caring for a greater number of liver transplant recipients and managing their long-term problems, such as hypertension, diabetes mellitus, dyslipidemia, obesity, metabolic syndrome, cardiovascular disease, renal insufficiency, osteoporosis, cancer, and gout.

This review will discuss these complications, focusing on the role the primary care physician assumes beyond the first year after transplantation.

■ ROLE OF THE PRIMARY CARE PHYSICIAN

Hepatologists, primary care physicians, and surgeons share the care of transplant recipients. The first several weeks after transplantation require close follow-up by the hepatologist and transplantation team, with particular attention paid to the patient's overall health and well-being, medication compliance, and biochemical and immunosuppression monitoring.

After the first year, the primary care physician assumes a greater role, becoming the main provider of the patient's care.^{3,4} Good communication between the transplant center and the primary care physician should lead to a smooth transition.⁴ Although the hepatologist continues to manage immunosuppressive drugs, allograft rejections, and biliary complications, the primary care physician manages

TABLE 1

Common adverse effects of immunosuppressive agents used in liver transplantation

Immunosuppressants	Side effects
Calcineurin inhibitors (cyclosporine, tacrolimus)	Hypertension Hypercholesterolemia Neurotoxicity Diabetes (more common with tacrolimus) Renal insufficiency Osteoporosis Nausea, abdominal pain, diarrhea Hirsutism (with cyclosporine) Gingival hyperplasia (with cyclosporine)
Mycophenolate mofetil	Bone marrow suppression Abdominal pain, nausea, diarrhea Neurotoxicity (headache, insomnia, dizziness)
Azathioprine	Bone marrow suppression Gastrointestinal side effects, including pancreatitis Dermatitis
Mammalian target of rapamycin (mTOR) inhibitors (sirolimus, everolimus)	Hypercholesterolemia Hypertriglyceridemia Hypertension Abdominal pain, diarrhea, constipation Dermatitis Diabetes

Medication monitoring should be based on trough levels, not random levels

most of the long-term complications and thus needs to be aware of the common ones and feel comfortable managing them. Aims during visits are to screen for and detect common complications and manage them appropriately, in addition to performing annual physical examinations and routine health care. A reasonable interval for liver transplant recipients to visit their primary care physician is every 6 months.

■ IMMUNOSUPPRESSANT MEDICATIONS

Multiple agents are used for immunosuppression after liver transplantation:

- Calcineurin inhibitors (cyclosporine and tacrolimus)
- Antimetabolites (mycophenolate mofetil, azathioprine, and mycophenolate sodium)
- Mammalian target of rapamycin (mTOR) inhibitors (sirolimus and everolimus)
- Corticosteroids.

TABLE 1 lists their common side effects.

Most centers use a combination of two to

four immunosuppressants as induction therapy in the immediate posttransplant period, then taper the doses and eliminate all but a calcineurin inhibitor and an antimetabolite. For example, some start with a combination of tacrolimus, mycophenolate mofetil, and a corticosteroid. The choice in the immediate posttransplant period is frequently made by the transplant center in cooperation with the hepatologist. By the time primary care physicians see these patients, they usually are on a calcineurin inhibitor alone or a calcineurin inhibitor plus mycophenolate mofetil.

Calcineurin inhibitors

Cyclosporine is metabolized by the cytochrome CYP3A4 pathway. With an average half-life of 15 hours, it is given orally, usually every 12 hours.

The dosage is adjusted according to the trough level. Higher levels are needed in the initial posttransplant period to prevent graft rejection, whereas lower levels are preferred

later to decrease the occurrence and severity of adverse effects. Typical long-term trough levels are 50 to 100 ng/mL. Levels should be checked more often if an acute illness develops or the patient starts taking a potentially interfering drug.

Of importance: the dosage should be based on trough levels and not on random levels. Levels are often falsely high if blood samples are not drawn at the trough level. Repeating the measurement and making sure the sample is drawn at the trough level, ie, 12 hours after the last dose, is advised in this condition.

Cyclosporine causes widespread vasoconstriction resulting in decreased renal blood flow and systemic hypertension, often within a few days of starting it. Other important adverse effects include renal insufficiency, dyslipidemia, neurotoxicity (headache, tremor, seizure), and diabetes.

Tacrolimus is superior to cyclosporine in terms of survival, graft loss, acute rejection, and steroid-resistant rejection in the first year.⁵ Currently, it is the agent used most often for maintenance immunosuppression after liver transplantation.

Like cyclosporine, tacrolimus is metabolized in the liver by CYP3A4. Satisfactory trough levels after 1 year are 4 to 6 ng/mL.

The adverse effects of tacrolimus are similar to those of cyclosporine, but diabetes mellitus is more common with tacrolimus. Bone marrow suppression may occur more often with tacrolimus as well.

Antimetabolites

Antimetabolites are generally not potent enough to be used alone.

Mycophenolate mofetil causes adverse effects that include bone marrow suppression and gastrointestinal symptoms such as gastritis, diarrhea, and abdominal pain.

Azathioprine, infrequently used in transplantation in the United States, is nevertheless sometimes substituted for mycophenolate mofetil in pregnant women, as it seems safer for use in pregnancy.

Serum levels of azathioprine and mycophenolate mofetil are not routinely monitored.

mTOR inhibitors

Sirolimus and everolimus are mTOR inhibitors, inhibiting proliferation of lymphocytes.^{6,7}

Unlike calcineurin inhibitors, mTOR inhibitors are not associated with nephrotoxicity, neurotoxicity, renal dysfunction, hypertension, or diabetes. Sirolimus is considered an alternative to calcineurin inhibitors or, in some instances, used as add-on-therapy to lower the dose of the calcineurin inhibitor.

However, sirolimus carries a potential risk of hepatic artery thrombosis, a life-threatening complication.⁸ This has led the US Food and Drug Administration (FDA) to require sirolimus to carry a black-box warning, and most transplant centers avoid using it in the first 30 days after transplantation.

Dyslipidemia is perhaps the most common adverse effect of sirolimus. Others include dose-related cytopenia and wound dehiscence.⁹

Everolimus has yet to be established for use in liver transplantation, although safety trials have been published.^{10,11} The FDA currently recommends against using it in the first 30 days after liver transplantation.

Both sirolimus and everolimus are metabolized by CYP3A4, which is the same metabolic pathway used by cyclosporine and tacrolimus. Hence, drugs that inhibit CYP3A4 may significantly impair clearance of both sirolimus and everolimus.

Corticosteroids

Corticosteroids have been the cornerstone of immunosuppression and remain the first line of treatment for acute allograft rejection. High intravenous doses of corticosteroids are usually started in the peritransplant period and are then switched to oral doses, which are tapered and continued with a fixed dose such as 20 mg of prednisone daily for 3 to 6 months after transplantation. However, some transplant centers keep patients on prednisone 5 mg/day indefinitely.

Adverse effects of corticosteroids include diabetes, salt and fluid retention, hypertension, hyperlipidemia, cosmetic changes (acne, cervical fat pad or "buffalo hump"), delayed wound healing, susceptibility to infection, cataracts, osteopenia, and potential adrenal suppression.¹² There is concern that the use of these drugs may increase hepatitis C virus replication in patients who received a liver

Tacrolimus is superior to cyclosporine in terms of survival, graft loss, and rejection but is more likely to cause diabetes

transplant for hepatitis C cirrhosis. Randomized trials have yielded conflicting results.^{13–15}

Drug interactions

Certain drugs can affect the metabolism of calcineurin inhibitors and mTOR inhibitors by inducing CYP3A4, which results in decreasing the levels of the immunosuppressive drugs, or by inhibiting CYP3A4, which has the opposite effect.

Medications that can decrease the levels of calcineurin inhibitors and mTOR inhibitors:

- Anticonvulsants (carbamazepine, phenobarbital, phenytoin)
- Antibiotics (rifampin, isoniazid)
- St John's wort.

Medications that can increase the levels of calcineurin inhibitors and mTOR inhibitors:

- Antifungals (fluconazole, ketoconazole, itraconazole, voriconazole, asposfungin)
- Antibiotics (azithromycin, erythromycin, clarithromycin)
- Nondihydropyridine calcium channel blockers (diltiazem, verapamil).¹⁶

Selected antibiotics are generally well tolerated, such as penicillins, cephalosporins, quinolones, sulfonamides, and topical antifungal agents.

LONG-TERM COMPLICATIONS

FIGURE 1 summarizes the common long-term complications of liver transplantation.

Hypertension

The prevalence of hypertension after liver transplantation is 40% to 85%, which is markedly higher than in patients with chronic liver disease before liver transplantation.^{17,18}

One of the factors contributing to this increase is the use of immunosuppressive medications. Of these drugs, cyclosporine seems to be the one that most often causes an increase in both the incidence and the severity of hypertension, as it produces widespread vasoconstriction.¹⁹ Corticosteroids cause hypertension through their mineralocorticoid effects.

The diagnostic cutoffs for hypertension (ie, 140/90 mm Hg) and the treatment goals in posttransplant patients are similar to those in the general population. However, at our in-

stitution we target a blood pressure of less than 130/80 mm Hg in transplant patients because they have a high prevalence of other cardiovascular risk factors such as diabetes, obesity, and renal insufficiency.²⁰

Dihydropyridine calcium channel blockers such as amlodipine and nifedipine are considered the best first-line agents because they dilate renal afferent arterioles, an effect that may counteract the vasoconstriction mediated by calcineurin inhibitors. Nondihydropyridine calcium channel blockers such as diltiazem and verapamil tend to have more marked negative inotropic effects and are not recommended in liver transplant recipients because they increase the levels of calcineurin inhibitors.²¹

Diuretics (eg, furosemide) might be the second-line agents, especially in patients with peripheral edema.¹⁶ One should be vigilant for hyperuricemia if thiazide agents are used.

Angiotensin-converting-enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are typically avoided in the early posttransplant period, but they can be started later and have additional benefits in patients with diabetes and congestive heart failure. Starting ACE inhibitors is acceptable in these patients unless there is a contraindication such as allergy to ACE inhibitors, hypotension, history of bilateral renal artery stenosis, significant hyperkalemia, or acute kidney injury. *Monitor the serum potassium level closely for hyperkalemia in patients concurrently using calcineurin inhibitors.*

Alpha-blockers and beta-blockers can be used as add-on therapy in patients with uncontrolled hypertension with the exception of carvedilol, because it increases the levels of calcineurin inhibitors.²²

Blood pressure monitoring by the primary care physician is recommended every 6 months after the early posttransplant period, or more frequently when changes in treatment are being considered.

If hypertension continues to be inadequately controlled despite treatment, changing the immunosuppressive drugs or decreasing the doses can be considered, but the transplant hepatologist must be involved in this decision.^{23,24}

Sirolimus carries a black-box warning about hepatic artery thrombosis

Long-term complications of liver transplantation

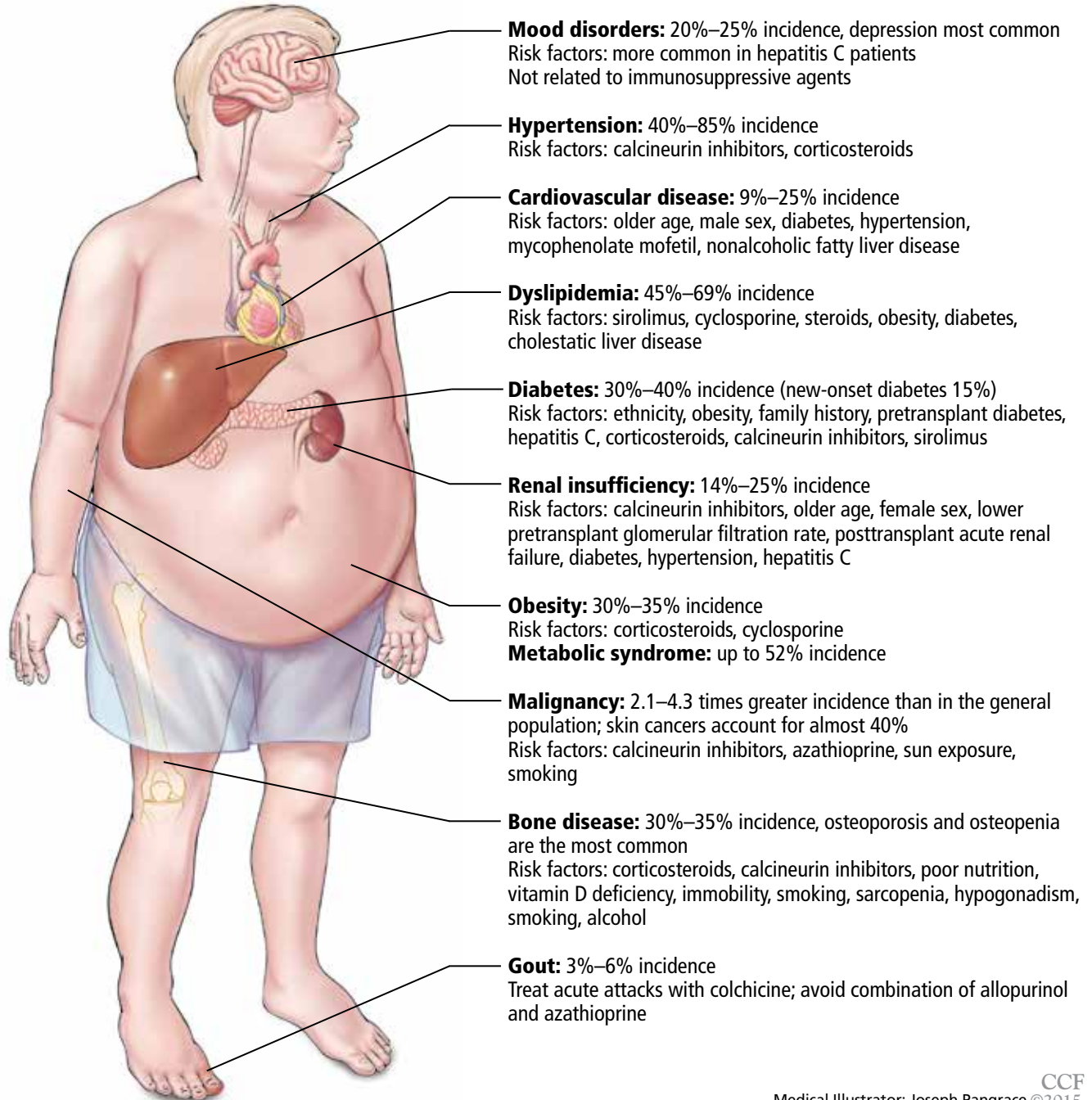


FIGURE 1

Diabetes mellitus

The prevalence of diabetes mellitus is higher in liver transplant recipients than in the general population, reaching 30% to 40%.^{17,25} In addition to preexisting diabetes, 15% of liver transplant recipients develop new-onset diabetes.^{26,27}

Risk factors for developing diabetes after liver transplantation include African American or Hispanic ethnicity, obesity, family history, pretransplant diabetes, hepatitis C virus infection, use of corticosteroids, and use of calcineurin inhibitors (tacrolimus more than

cyclosporine) and sirolimus.²⁶

In addition to increasing the risk of cardiovascular disease and other diseases, diabetes decreases both patient and graft survival after liver transplantation.²⁸

The management of diabetes and the treatment target after transplantation should follow the American Diabetes Association guidelines for the treatment of type 2 diabetes mellitus.²⁹ Lifestyle modifications, diet, and exercise are as important for transplant patients as for the nontransplant population. Insulin therapy is usually needed in the early posttransplant period to control blood glucose levels well, especially with the high doses of corticosteroids used during the first few weeks. No trials to date have compared oral agents in posttransplant patients. Therefore, the choice of oral hypoglycemic agents should be individualized on the basis of the patient's characteristics and comorbidities.

We recommend that primary care providers screen all liver transplant recipients for diabetes regardless of their pretransplant status. This can be done by obtaining regular fasting blood glucose levels or a hemoglobin A_{1c} level every 6 months. Additionally, liver transplant recipients diagnosed with diabetes require annual eye examinations to look for cataracts and diabetes-related changes.³⁰

Dyslipidemia

On November 12, 2013, the American College of Cardiology and the American Heart Association (ACC/AHA) released new clinical practice guidelines for treating blood cholesterol levels.^{31,32} According to these new guidelines, there are four groups of patients for whom treatment with statins is clearly indicated:

- Patients with cardiovascular disease
- Patients with low-density lipoprotein cholesterol (LDL-C) levels ≥ 190 mg/dL
- Patients 40 to 75 years old with type 2 diabetes
- Patients 40 to 75 years old with an estimated 10-year risk of cardiovascular disease of 7.5% or greater.

Liver transplant recipients should be evaluated on an individual basis to see if they fit in any of the four groups and if statin treatment therefore needs to be initiated.

A few things need to be kept in mind. First, the incidence of dyslipidemia after liver transplantation is estimated to be 45% to 69%. Risk factors include obesity, diabetes mellitus, cholestatic liver disease, and immunosuppressant medications.³³ Sirolimus has a significant and well-documented association with dyslipidemia. Cyclosporine and corticosteroids are also strongly associated with dyslipidemia. Tacrolimus has a minor effect, and mycophenolate mofetil and azathioprine have no significant effects on serum lipid levels.¹⁶

Second, of the seven currently marketed statins, pravastatin and fluvastatin are preferred in liver transplant recipients because they are not metabolized by the same cytochrome CYP3A4 pathway that metabolizes calcineurin inhibitors and sirolimus.³⁴ The doses of 40 to 80 mg daily of pravastatin or 40 mg twice daily of fluvastatin lower low-density lipoprotein cholesterol (LDL-C) levels by approximately 30% to 35%. However, these two agents are considered “moderate-intensity” statins according to the new ACC/AHA guidelines. The only two “high-intensity” statins are atorvastatin (40–80 mg) and rosuvastatin (20–40 mg), but they are both metabolized by CYP3A4. Therefore it is prudent to avoid them with the concurrent use of a calcineurin inhibitor or tacrolimus.

Gemfibrozil does not lower LDL-C and should not be used concomitantly with statins due to unacceptable risk of rhabdomyolysis and myopathy. Fenofibrates are usually avoided due to potential nephrotoxicity in patients receiving cyclosporine. Bile acid sequestrants (cholestyramine, colestipol, colesevelam) can decrease plasma mycophenolate mofetil levels by 35%.^{16,35} Thus, these agents should be avoided if mycophenolate mofetil is used.

It is reasonable to screen all liver transplant recipients with a fasting lipid profile at 3, 6, and 12 months after transplantation and annually thereafter. Creatine kinase should be measured if the patient complains of severe muscle pain or weakness but not on a routine basis.

Obesity

Approximately one-third of patients who are of normal weight at the time of transplantation will become obese afterward.^{18,25} Cortico-

Monitor potassium closely in patients on calcineurin inhibitors plus ACE inhibitors or ARBs

steroid use is an important risk factor for post-transplant obesity, and tapering these drugs helps reduce weight.³⁶ Patients treated with cyclosporine are more likely to gain weight than those who receive tacrolimus.³⁷

Of importance: nonalcoholic fatty liver disease, currently the most common cause of chronic liver disease in adults, is rapidly increasing as an indication for liver transplantation. In fact, the proportion of liver transplantation procedures for nonalcoholic steatohepatitis-related cirrhosis increased from 1.2% in 2001 to 9.7% in 2009, and nonalcoholic steatohepatitis is expected to become the leading indication for liver transplantation in the next 20 years. And because nonalcoholic fatty liver disease is directly linked to obesity, the prevalence of obesity as a complication of liver transplantation will most likely increase in the near future.

Overweight liver transplant recipients may have great difficulty losing weight. Treatment starts with patient education on caloric restriction and exercise. If traditional measures fail to result in adequate weight loss, additional options include switching from cyclosporine to tacrolimus.²³

Bariatric surgery may become an option for posttransplant patients. In a recent case series from the University of Minnesota, Al-Nowaylati et al³⁸ reported their experience with seven patients who underwent orthotopic liver transplantation and then open Roux-en-Y gastric bypass. After bariatric surgery, the patients' mean body mass index declined significantly, and glycemic control and high-density lipoprotein cholesterol (HDL-C) levels improved. However, one patient died of multiple organ failure, to which the bariatric surgery might have contributed.³⁸

Heimbach et al³⁹ conducted a study in patients referred for liver transplantation for whom a rigorous noninvasive weight-loss program before transplantation had failed. The researchers performed combined liver transplantation and sleeve gastrectomy in seven carefully selected patients who had failed to achieve weight loss to a body mass index less than 35 kg/m² before transplantation. All seven patients lost weight, decreasing their mean body mass index from 49 kg/m² before the procedure to 29 kg/m² at last follow-up, and none of them developed post-

transplant diabetes or steatosis.

At this time, there is not enough evidence to recommend concurrent orthotopic liver transplantation plus bariatric surgery, or combined orthotopic liver transplantation and sleeve gastrectomy. More study is needed to further evaluate these advanced approaches.

Posttransplant metabolic syndrome

Metabolic syndrome is common after liver transplantation and is strongly associated with increased morbidity in this patient population.^{40,41} The general definition of metabolic syndrome includes a combination of at least three of the following: hypertension, insulin resistance, hypertriglyceridemia, low HDL-C, and obesity.

The prevalence of metabolic syndrome is higher in patients after liver transplantation than in nontransplant patients. In a review of 252 liver transplant recipients, 52% were diagnosed with posttransplant metabolic syndrome, but only 5% had had it pretransplant.⁴²

Careful screening for posttransplant metabolic syndrome and early recognition of risk factors are important. Nevertheless, the treatment of this condition depends on treating its components according to recommended guidelines.⁴¹

Cardiovascular disease

The incidence of cardiovascular morbidity and death is increased after liver transplantation.²⁴ In addition, after liver transplantation, cardiovascular disease is a major cause of death unrelated to liver disease. It accounts for 12% to 16% of deaths and is the third most common cause of late mortality after liver transplantation.⁴³ Of note, a recent study by our group demonstrated that patients undergoing liver transplantation for nonalcoholic steatohepatitis had a significantly higher risk of a cardiovascular event during the 3 years after transplantation than patients undergoing liver transplantation for cholestatic liver disease.⁴⁴

Risk factors for cardiovascular disease after liver transplantation include older age at transplantation, male sex, posttransplant diabetes, posttransplant hypertension, and the use of mycophenolate mofetil.⁴⁴ Modifying the risk factors is essential in decreasing the risk of cardiovascular events.

Screen all liver transplant recipients for diabetes regardless of their pretransplant status

It is reasonable to perform dobutamine stress testing every 3 to 5 years in patients with multiple risk factors for cardiovascular disease, or more frequently in those with preexisting coronary artery disease.^{45,46}

Malignancy

The risk of several malignancies increases after liver transplantation. Liver transplant recipients have an incidence of cancer 2.1 to 4.3 times greater than age- and sex-matched controls.^{24,47–49}

Skin cancers are the most common and account for almost 40% of malignancies in organ transplant recipients.⁵⁰ Whereas basal cell carcinoma is more common in the general population, squamous cell carcinoma is equally common in liver transplant recipients.

Multiple clinical studies have linked calcineurin inhibitors and azathioprine to the development of skin cancer. Annual skin examinations in addition to avoiding other risk factors such as smoking and sun exposure are generally recommended. Changing the immunosuppressants to sirolimus in high-risk patients may lower their chance of developing skin cancer.^{51,52}

Patients with ulcerative colitis who undergo liver transplantation because of sclerosing cholangitis are at higher risk of colon cancer and require annual colonoscopy with surveillance biopsies. Patients who undergo transplantation for alcoholic liver disease seem to have a higher risk of pulmonary and oropharyngeal cancers.^{53,54}

It is important that transplant patients adhere to recommended cancer screening guidelines, in view of their increased risk. Studies have shown improved overall survival in liver transplant recipients who underwent intensive cancer surveillance.⁵⁵

Renal insufficiency

Renal insufficiency is a well-recognized complication of liver transplantation and is associated with an increased long-term death rate.^{56,57}

The incidence of renal insufficiency increases dramatically over time. Ojo et al,⁵⁷ in a study of almost 37,000 liver transplant recipients, found that the incidence of chronic kidney disease (defined as an estimated glomerular filtration rate < 30 mL/min/1.73 m²)

was 13.9% at 3 years, 18% at 5 years, and approximately 26% at 10 years.

Risk factors include the use of calcineurin inhibitors (both cyclosporine and tacrolimus), older age, female sex, lower pretransplant glomerular filtration rate, postoperative acute renal failure, diabetes, hypertension, hepatitis C virus infection, and transplantation before 1998.^{58,59} Replacing a calcineurin inhibitor with mycophenolate mofetil or sirolimus may be considered with communication with the transplant center, as mycophenolate mofetil or sirolimus are associated with a lower risk of renal injury.^{60–64}

Starting 1 year after liver transplantation, primary care providers should screen for renal dysfunction by obtaining kidney function tests every 6 months, including urinalysis and microalbuminuria assessment. Equations for estimating the glomerular filtration rate used in practice, such as the Modification of Diet in Renal Disease Study equation, rely mainly on serum creatinine, which may lead to overestimating renal function in some circumstances. Therefore, other equations can be used to confirm the estimated glomerular filtration rate measured by creatinine clearance, and to more accurately evaluate kidney function. Calculators are available at www.kidney.org/professionals/kdoqi/gfr_calculator.

All liver transplant recipients should avoid nonsteroidal anti-inflammatory drugs and nephrotoxic medications, and should have their hypertension and diabetes adequately controlled.

Bone diseases

Osteopenia is another major complication of liver transplantation. One-third of liver transplant recipients have a bone mineral density below the fracture threshold.⁶⁵

Multiple factors contribute to increased bone loss after transplantation, including use of corticosteroids, use of calcineurin inhibitors (cyclosporine, tacrolimus), poor nutrition, vitamin D deficiency, immobility, sarcopenia (reduced muscle mass), hypogonadism, smoking, and alcohol abuse.⁶⁶ Even at low doses of less than 7.5 mg per day, corticosteroids inhibit osteoblast activity and increase bone resorption.

Studies have reported rapid bone loss at around 6 months after transplantation.^{67–69}

About 1/3 of normal-weight patients become obese after liver transplantation

However, long-term follow-up of bone mineral density up to 15 years after transplantation revealed an improvement mainly in the 2nd postoperative year, with no deterioration afterward.⁶⁵

High-risk patients need to be identified early with appropriate screening and evaluation. Evaluation includes dual-energy x-ray absorptiometry and serum levels of calcium, phosphorous, parathyroid hormone, testosterone (men), estradiol (women), and alpha-25-hydroxyvitamin D. These tests are typically done before transplantation and then every other year afterward.

We recommend a daily dose of calcitriol and a calcium supplement to all our liver transplant patients.⁷⁰ If osteoporosis (a T-score 2.5 or more standard deviations below the mean) or a fragility fracture occurs, then the patient may benefit from an oral bisphosphonate. Calcitonin has also been shown to improve bone mineral density in patients with osteoporosis after liver transplantation.⁷¹

Hyperuricemia and gout

Although hyperuricemia is common in liver transplant recipients (reported in approximately 47%), the development of clinical gout is less common (6%).⁷² Asymptomatic hyperuricemia requires observation only and is not usually treated in liver transplant recipients.

Acute attacks of gout are typically managed with colchicine 0.6 mg every 2 hours, up to five doses. Prednisone can be considered if symptoms persist despite treatment with colchicine. Allopurinol in an initial dose of 100 mg daily is used as maintenance therapy to reduce production of uric acid.⁷³ However, because of the potential for drug interactions, the combination of azathioprine and allopurinol should be avoided.

Psychiatric complications and quality of life

Depression is common in liver transplant recipients, significantly more so in patients who received a transplant because of hepatitis C.⁷⁴ The type of immunosuppressant is not associated with the incidence of depression. When indicated, the internist may start the patient on a selective serotonin reuptake inhibitor such as citalopram 20 mg daily, as these medications are usually effective and well tolerated

in liver transplant patients.⁷³

Liver transplantation has a major positive effect on quality of life. Most patients with end-stage liver disease have poor quality of life before transplantation, but this seems to improve notably afterward. A meta-analysis showed significant improvement in posttransplant physical health, sexual functioning, daily activities, and social functioning compared with before transplantation.⁷⁵

Alcohol abuse and smoking

Patients who underwent liver transplantation because of alcoholic liver disease should be advised to abstain from alcohol.¹⁹ Patients who underwent the procedure for a different indication are advised to avoid excessive alcohol intake, as it is proven to lower the survival rate.²⁰ Alcohol recidivism and smoking (including marijuana) are major problems, and internists are best positioned to address these issues and treat them.

Vaccinations

All liver transplant recipients should be vaccinated against influenza, pneumococcal infection, and tetanus. Hepatitis A and B vaccines are typically given before transplantation. In general, live vaccines such as measles-mumps-rubella and varicella are not recommended after any solid organ transplant.⁷⁶

A study in Germany showed that immunization rates were too low in solid-organ transplant recipients, and almost 90% of patients were not adequately informed about immunizations.⁷⁷ Hence, there may be room for improvement, and primary care providers should take the lead toward better outcomes in this regard.

Recurrence of the primary liver disease after transplantation

Different primary liver diseases recur with different frequencies.

Hepatitis C has the highest rate of recurrence of the liver diseases.^{78,79} Reinfection with hepatitis C virus after liver transplantation is almost universal and can follow different patterns. One of the most aggressive patterns is fibrosing cholestatic hepatitis, which frequently leads to graft failure and death, and hence necessitates urgent detection and treatment.

All liver transplant recipients should avoid nonsteroidal anti-inflammatory drugs and nephrotoxic medications

Hepatocellular carcinoma also has a high recurrence rate.⁸⁰ Surveillance with liver ultrasonography or computed tomography is required every 6 months for the first 5 years after liver transplantation.

Other liver diseases. Nonalcoholic steatohepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, and hepatitis B infection also tend to recur after liver transplantation.^{46,81} On the other hand, alpha-1 antitrypsin deficiency, Wilson disease, hemochromatosis, and metabolic disorders are “cured” after liver transplantation.

It is important to detect any increase in liver enzymes above baseline. An elevation of 1.5 times the upper limit of normal or more should trigger further investigation.

Allograft dysfunction

A number of complications can develop in the liver allograft and result in abnormal liver function tests and, if not treated, graft failure. The most common causes of late graft dysfunction include recurrence of primary liver disease, biliary complications, and chronic rejection.⁴⁶

Vascular complications include hepatic artery thrombosis and stenosis and are usually evaluated by liver ultrasonography and Doppler scan of the hepatic artery and venous structures.²⁴

Biliary strictures give a cholestatic picture,

with elevated bilirubin and greater elevation of alkaline phosphatase than of alanine aminotransferase and aspartate aminotransferase. Strictures are usually treated by endoscopic dilation and stenting, but they may eventually require surgery.

Late acute cellular rejections occur in 10% to 20% of cases and are a risk factor for chronic rejection. Liver biopsy is needed to make the diagnosis, and pulsed doses of corticosteroids remain the backbone of treatment therapy.

Chronic rejection is not common, occurring in 3% to 4% of liver transplant recipients.⁴⁶ Treatment is based on increasing immunosuppression and ensuring compliance with prescribed medications. However, chronic rejection may not respond well, and repeat transplantation may be the last resort for some patients.

■ WHEN TO REFER TO THE HEPATOLOGIST

Some situations require referral to the hepatologist or the transplant center. In general, the following are best managed by a hepatologist: adjustment of immunosuppressive drugs and dosages, allograft dysfunction, vascular and biliary complications, progressing renal dysfunction, and recurrence of primary liver disease. Early communication with a hepatologist and the transplant center is recommended in these cases. ■

■ REFERENCES

1. Starzl TE, Marchioro TL, Vonkaulla KN, Hermann G, Brittain RS, Waddell WR. Homotransplantation of the liver in humans. *Surg Gynecol Obstet* 1963; 117:659–676.
2. Matas AJ, Smith JM, Skeans MA, et al. OPTN/SRTR 2011 annual data report: kidney. *Am J Transplant* 2013; 13(suppl 1):11–46.
3. McCashland TM. Posttransplantation care: role of the primary care physician versus transplant center. *Liver Transpl* 2001; 7(suppl 1):S2–S12.
4. Heller JC, Prochazka AV, Everson GT, Forman LM. Long-term management after liver transplantation: primary care physician versus hepatologist. *Liver Transpl* 2009; 15:1330–1335.
5. McAlister VC, Haddad E, Renouf E, Malthaner RA, Kjaer MS, Gluud LL. Cyclosporin versus tacrolimus as primary immunosuppressant after liver transplantation: a meta-analysis. *Am J Transplant* 2006; 6:1578–1585.
6. Neuhaus P, Klupp J, Langrehr JM. mTOR inhibitors: an overview. *Liver Transpl* 2001; 7:473–484.
7. Sehgal SN. Rapamune (RAPA, rapamycin, sirolimus): mechanism of action immunosuppressive effect results from blockade of signal transduction and inhibition of cell cycle progression. *Clin Biochem* 1998; 31:335–340.
8. Asrani SK, Wiesner RH, Trotter JF, et al. De novo sirolimus and reduced-dose tacrolimus versus standard-dose tacrolimus after liver transplantation: the 2000–2003 phase II prospective randomized trial. *Am J Transplant* 2014; 14:356–366.
9. Montalbano M, Neff GW, Yamashiki N, et al. A retrospective review of liver transplant patients treated with sirolimus from a single center: an analysis of sirolimus-related complications. *Transplantation* 2004; 78:264–268.
10. Everson GT. Everolimus and mTOR inhibitors in liver transplantation: opening the “box.” *Liver Transpl* 2006; 12:1571–1573.
11. Levy G, Schmidli H, Punch J, et al. Safety, tolerability, and efficacy of everolimus in de novo liver transplant recipients: 12- and 36-month results. *Liver Transpl* 2006; 12:1640–1648.
12. Toniutto P, Fabris C, Fumolo E, et al. Prevalence and risk factors for delayed adrenal insufficiency after liver transplantation. *Liver Transpl* 2008; 14:1014–1019.
13. Klintmalm GB, Davis GL, Teperman L, et al. A randomized, multicenter study comparing steroid-free immunosuppression and standard immunosuppression for liver transplant recipients with chronic hepatitis C. *Liver Transpl* 2011; 17:1394–1403.
14. Llado L, Fabregat J, Castellote J, et al. Impact of immunosuppression without steroids on rejection and hepatitis C virus evolution after liver transplantation: results of a prospective randomized study. *Liver Transpl* 2008; 14:1752–1760.
15. Lake JR. Immunosuppression and outcomes of patients transplanted for hepatitis C. *J Hepatol* 2006; 44:627–629.
16. Sohn AJ, Jeon H, Ahn J. Primary care of the liver transplant recipient. *Prim Care* 2011; 38:499–514.
17. Laish I, Braun M, Mor E, Sulkes J, Harif Y, Ben Ari Z. Metabolic

- syndrome in liver transplant recipients: prevalence, risk factors, and association with cardiovascular events. *Liver Transpl* 2011; 17:15–22.
18. **Stegall MD, Everson G, Schroter G, Bilir B, Karrer F, Kam I.** Metabolic complications after liver transplantation. Diabetes, hypercholesterolemia, hypertension, and obesity. *Transplantation* 1995; 60:1057–1060.
 19. **Textor SC, Canzanello VJ, Taler SJ, et al.** Cyclosporine-induced hypertension after transplantation. *Mayo Clin Proc* 1994; 69:1182–1193.
 20. Prevention, detection, evaluation, and treatment of hypertension. The Sixth Report of the Joint National Committee. National Institutes of Health-National Heart, Lung, and Blood Institute. National High Blood Pressure Education Programme. *Indian Heart J* 1999; 51:381–396.
 21. **Frishman WH.** Calcium channel blockers: differences between subclasses. *Am J Cardiovasc Drugs* 2007; 7(suppl 1):17–23.
 22. **Galioto A, Semplicini A, Zanus G, et al.** Nifedipine versus carvedilol in the treatment of de novo arterial hypertension after liver transplantation: results of a controlled clinical trial. *Liver Transpl* 2008; 14:1020–1028.
 23. **Neal DA, Gimson AE, Gibbs P, Alexander GJ.** Beneficial effects of converting liver transplant recipients from cyclosporine to tacrolimus on blood pressure, serum lipids, and weight. *Liver Transpl* 2001; 7:533–539.
 24. **Singh S, Watt KD.** Long-term medical management of the liver transplant recipient: what the primary care physician needs to know. *Mayo Clin Proc* 2012; 87:779–790.
 25. **Bianchi G, Marchesini G, Marzocchi R, Pinna AD, Zoli M.** Metabolic syndrome in liver transplantation: relation to etiology and immunosuppression. *Liver Transpl* 2008; 14:1648–1654.
 26. **Lane JT, Dagogo-Jack S.** Approach to the patient with new-onset diabetes after transplant (NODAT). *J Clin Endocrinol Metab* 2011; 96:3289–3297.
 27. **Wilkinson A, Davidson J, Dotta F, et al.** Guidelines for the treatment and management of new-onset diabetes after transplantation. *Clin Transplant* 2005; 19:291–298.
 28. **Moon JI, Barbeito R, Faradji RN, Gaynor JJ, Tzakis AG.** Negative impact of new-onset diabetes mellitus on patient and graft survival after liver transplantation: long-term follow up. *Transplantation* 2006; 82:1625–1628.
 29. **American Diabetes Association.** Standards of medical care in diabetes—2012. *Diabetes Care* 2012; 35(suppl 1):S11–S63.
 30. **Marchetti P.** New-onset diabetes after liver transplantation: from pathogenesis to management. *Liver Transpl* 2005; 11:612–620.
 31. **Stone NJ, Robinson J, Lichtenstein AH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines.** 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014; 129(suppl 2):S1–S45.
 32. **National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).** Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002; 106:3143–3421.
 33. **Gisbert C, Prieto M, Berenguer M, et al.** Hyperlipidemia in liver transplant recipients: prevalence and risk factors. *Liver Transpl Surg* 1997; 3:416–422.
 34. **Asberg A.** Interactions between cyclosporin and lipid-lowering drugs: implications for organ transplant recipients. *Drugs* 2003; 63:367–378.
 35. **Bullingham RE, Nicholls AJ, Kamm BR.** Clinical pharmacokinetics of mycophenolate mofetil. *Clin Pharmacokinet* 1998; 34:429–455.
 36. **Everhart JE, Lombardero M, Lake JR, Wiesner RH, Zetterman RK, Hoofnagle JH.** Weight change and obesity after liver transplantation: incidence and risk factors. *Liver Transpl Surg* 1998; 4:285–296.
 37. **Canzanello VJ, Schwartz L, Taler SJ, et al.** Evolution of cardiovascular risk after liver transplantation: a comparison of cyclosporine A and tacrolimus (FK506). *Liver Transpl Surg* 1997; 3:1–9.
 38. **Al-Nowaylati AR, Al-Haddad BJ, Dorman RB, et al.** Gastric bypass after liver transplantation. *Liver Transpl* 2013; 19:1324–1329.
 39. **Heimbach JK, Watt KD, Poterucha JJ, et al.** Combined liver transplantation and gastric sleeve resection for patients with medically complicated obesity and end-stage liver disease. *Am J Transplant* 2013; 13:363–368.
 40. **Watt KD, Charlton MR.** Metabolic syndrome and liver transplantation: a review and guide to management. *J Hepatol* 2010; 53:199–206.
 41. **Pagadala M, Dasarathy S, Egtesad B, McCullough AJ.** Posttransplant metabolic syndrome: an epidemic waiting to happen. *Liver Transpl* 2009; 15:1662–1670.
 42. **Alberti KG, Eckel RH, Grundy SM, et al.** Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009; 120:1640–1645.
 43. **Watt KD, Pedersen RA, Kremers WK, Heimbach JK, Charlton MR.** Evolution of causes and risk factors for mortality post-liver transplant: results of the NIDDK long-term follow-up study. *Am J Transplant* 2010; 10:1420–1427.
 44. **Albeldawi M, Aggarwal A, Madhwal S, et al.** Cumulative risk of cardiovascular events after orthotopic liver transplantation. *Liver Transpl* 2012; 18:370–375.
 45. **Gibbons RJ, Balady GJ, Bricker JT, et al.** ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *Circulation* 2002; 106:1883–1892.
 46. **Aberg F, Isoniemi H, Höckerstedt K.** Long-term results of liver transplantation. *Scand J Surg* 2011; 100:14–21.
 47. **Aberg F, Pukkala E, Höckerstedt K, Sankila R, Isoniemi H.** Risk of malignant neoplasms after liver transplantation: a population-based study. *Liver Transpl* 2008; 14:1428–1436.
 48. **Mells G, Neuberger J.** Long-term care of the liver allograft recipient. *Semin Liver Dis* 2009; 29:102–120.
 49. **Herrero JI.** De novo malignancies following liver transplantation: impact and recommendations. *Liver Transpl* 2009; 15(suppl 2):S90–S94.
 50. **Euvrard S, Kanitakis J, Claudy A.** Skin cancers after organ transplantation. *N Engl J Med* 2003; 348:1681–1691.
 51. **Euvrard S, Morelon E, Rostaing L, et al; TUMORAPA Study Group.** Sirolimus and secondary skin-cancer prevention in kidney transplantation. *N Engl J Med* 2012; 367:329–339.
 52. **Salgo R, Gossman J, Schofer H, et al.** Switch to a sirolimus-based immunosuppression in long-term renal transplant recipients: reduced rate of (pre-)malignancies and nonmelanoma skin cancer in a prospective, randomized, assessor-blinded, controlled clinical trial. *Am J Transplant* 2010; 10:1385–1393.
 53. **Narumi S, Roberts JP, Emond JC, Lake J, Ascher NL.** Liver transplantation for sclerosing cholangitis. *Hepatology* 1995; 22:451–457.
 54. **Knechtle SJ, D'Alessandro AM, Harms BA, Pirsch JD, Belzer FO, Kalayoglu M.** Relationships between sclerosing cholangitis, inflammatory bowel disease, and cancer in patients undergoing liver transplantation. *Surgery* 1995; 118:615–620.
 55. **Finkenstedt A, Graziadei IW, Oberaigner W, et al.** Extensive surveillance promotes early diagnosis and improved survival of de novo malignancies in liver transplant recipients. *Am J Transplant* 2009; 9:2355–2361.
 56. **Fisher NC, Nightingale PG, Gunson BK, Lipkin GW, Neuberger JM.** Chronic renal failure following liver transplantation: a retrospective analysis. *Transplantation* 1998; 66:59–66.
 57. **Ojo AO, Held PJ, Port FK, et al.** Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med* 2003; 349:931–940.
 58. **Klintmalm GB, Gonwa TA.** Nephrotoxicity associated with cyclosporine and FK506. *Liver Transpl Surg* 1995; 1:11–19.
 59. **A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression in liver transplantation. The US Multicenter FK506 Liver Study Group.** *N Engl J Med* 1994; 331:1110–1115.
 60. **Neff GW, Montalbano M, Slapak-Green G, et al.** Sirolimus therapy

- in orthotopic liver transplant recipients with calcineurin inhibitor related chronic renal insufficiency. *Transplant Proc* 2003; 35:3029–3031.
61. **Cotterell AH, Fisher RA, King AL, et al.** Calcineurin inhibitor-induced chronic nephrotoxicity in liver transplant patients is reversible using rapamycin as the primary immunosuppressive agent. *Clin Transplant* 2002; 16(suppl 7):49–51.
 62. **Manzia TM, De Liguori Carino N, Orlando G, et al.** Use of mycophenolate mofetil in liver transplantation: a literature review. *Transplant Proc* 2005; 37:2616–2617.
 63. **Schlitt HJ, Barkmann A, Boker KH, et al.** Replacement of calcineurin inhibitors with mycophenolate mofetil in liver-transplant patients with renal dysfunction: a randomised controlled study. *Lancet* 2001; 357:587–591.
 64. **Hodge EE, Reich DJ, Clavien PA, Kim-Schluger L.** Use of mycophenolate mofetil in liver transplant recipients experiencing renal dysfunction on cyclosporine or tacrolimus-randomized, prospective, multicenter study results. *Transplant Proc* 2002; 34:1546–1547.
 65. **Hamburg SM, Piers DA, van den Berg AP, Slooff MJ, Haagsma EB.** Bone mineral density in the long term after liver transplantation. *Osteoporos Int* 2000; 11:600–606.
 66. **Maalouf NM, Shane E.** Osteoporosis after solid organ transplantation. *J Clin Endocrinol Metab* 2005; 90:2456–2465.
 67. **Crosbie OM, Freaney R, McKenna MJ, Curry MP, Hegarty JE.** Predicting bone loss following orthotopic liver transplantation. *Gut* 1999; 44:430–434.
 68. **Giannini S, Nobile M, Ciuffreda M, et al.** Long-term persistence of low bone density in orthotopic liver transplantation. *Osteoporos Int* 2000; 11:417–424.
 69. **Monegal A, Navasa M, Guanabens N, et al.** Bone disease after liver transplantation: a long-term prospective study of bone mass changes, hormonal status and histomorphometric characteristics. *Osteoporos Int* 2001; 12:484–492.
 70. **Neuhaus R, Lohmann R, Platz KP, et al.** Treatment of osteoporosis after liver transplantation. *Transplant Proc* 1995; 27:1226–1227.
 71. **Valero MA, Loinaz C, Larrodera L, Leon M, Moreno E, Hawkins F.** Calcitonin and bisphosphonates treatment in bone loss after liver transplantation. *Calcif Tissue Int* 1995; 57:15–19.
 72. **Neal DA, Tom BD, Gimson AE, Gibbs P, Alexander GJ.** Hyperuricemia, gout, and renal function after liver transplantation. *Transplantation* 2001; 72:1689–1691.
 73. **Schiff ER, Sorrell MF, Maddrey WC, editors.** Schiff's Diseases of the Liver. 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007.
 74. **Tombazzi CR, Waters B, Shokouh-Amiri MH, Vera SR, Riely CA.** Neuropsychiatric complications after liver transplantation: role of immunosuppression and hepatitis C. *Dig Dis Sci* 2006; 51:1079–1081.
 75. **Bravata DM, Olkin I, Barnato AE, Keeffe EB, Owens DK.** Health-related quality of life after liver transplantation: a meta-analysis. *Liver Transpl Surg* 1999; 5:318–331.
 76. **Danziger-Isakov L, Kumar D; AST Infectious Diseases Community of Practice.** Vaccination in solid organ transplantation. *Am J Transplant* 2013; 13(suppl 4):311–317.
 77. **Chesi C, Gunther M, Huzly D, et al.** Immunization of liver and renal transplant recipients: a seroepidemiological and sociodemographic survey. *Transpl Infect Dis* 2009; 11:507–512.
 78. **Berenguer M, Lopez-Labrador FX, Wright TL.** Hepatitis C and liver transplantation. *J Hepatol* 2001; 35:666–678.
 79. **Forman LM, Lewis JD, Berlin JA, Feldman HI, Lucey MR.** The association between hepatitis C infection and survival after orthotopic liver transplantation. *Gastroenterology* 2002; 122:889–896.
 80. **Benten D, Stauffer K, Sterneck M.** Orthotopic liver transplantation and what to do during follow-up: recommendations for the practitioner. *Nat Clin Pract Gastroenterol Hepatol* 2009; 6:23–36.
 81. **Kotlyar DS, Campbell MS, Reddy KR.** Recurrence of diseases following orthotopic liver transplantation. *Am J Gastroenterol* 2006; 101:1370–1378.

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