Liver transplantation in adults: Long-term management of transplant recipients

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INTRODUCTION

Liver transplantation is the treatment of choice for appropriately selected patients with end-stage liver disease. With improved long-term survival, more patients are being cared for outside of a transplant center, requiring more widespread familiarity with the complications seen in this patient population. Several medical problems are routinely encountered by clinicians caring for patients after liver transplantation. These include:

- Acute or chronic rejection.
- Complications of immunosuppression including hypertension, renal insufficiency, infection, malignancy, a variety of dermatologic conditions, and metabolic diseases such as diabetes mellitus, obesity, hyperlipidemia, and bone disease.
- Biliary complications.
- Recurrence of the primary liver disease.

This topic will review the general management of patients following liver transplantation and the nonimmunologic complications of liver transplantation. Acute and chronic rejection, infectious complications of liver transplantation, recurrent hepatitis, and recurrent hepatocellular carcinoma are discussed in detail elsewhere. (See "Liver transplantation in adults:

Clinical manifestations and diagnosis of acute T-cell mediated (cellular) rejection of the liver allograft" and "Infectious complications in liver transplantation" and "Hepatitis C virus infection in liver transplant candidates and recipients" and "Liver transplantation in adults: Preventing hepatitis B virus infection in liver transplant recipients" and "Liver transplantation for hepatocellular carcinoma".)

ROLE OF THE PRIMARY CARE CLINICIAN

Immediately following liver transplantation, patients are managed by transplant surgeons and/or transplant hepatologists. However, after several months, the general medical care of a liver transplant recipient is often transferred back to the patient's primary care clinician [1]. While practices vary in different transplant centers, the transplant center typically continues to manage the administration of immunosuppressive agents, to treat recurrent liver disease, and to manage biliary complications. In addition, the transplant center may also manage some of the complications of immunosuppression, such as renal disease. The patient's other medical issues, including other complications of immunosuppression, are often managed by the primary care clinician.

PREVENTIVE MEDICINE

General health maintenance for liver transplant recipients is similar to that for the general population (see "Overview of preventive care in adults"). However, certain disorders require more intensive screening because they are more common following liver transplantation (eg, hypertension, diabetes, dyslipidemia, renal disease, and malignancy). In addition, because there are numerous drugs that interact with immunosuppressive agents, at each visit patients should be asked about any new medications or supplements they are taking (including over-the-counter medications) and be reminded not to start any new medications or supplements without first talking to their clinicians (table 1). (See 'Immunosuppression' below.)

Screening for nonmalignant disease — Our approach to screening for nonmalignant diseases in liver transplant recipients includes:

- General assessment – Annual history and physical examination, annual dental evaluations in addition to routine (twice-yearly) cleanings.
- Hypertension – For the first six months following transplantation, self-monitoring every week and blood pressure monitoring by a healthcare provider every month. In patients without hypertension after six months, blood pressure monitoring by a healthcare

provider every six months. (See "Overview of hypertension in adults", section on 'Diagnosis'.)

- Diabetes mellitus – Screening every six months (typically with either a fasting plasma glucose or a hemoglobin A1C), and, in patients with diabetes, an annual eye examination. (See "Screening for type 2 diabetes mellitus", section on 'A suggested approach'.)

- Dyslipidemia – Annual fasting lipid profile. (See "Measurement of blood lipids and lipoproteins".)

- Cardiovascular disease – Some centers perform stress testing every five years in patients with risk factors for coronary artery disease and more frequently in patients with preexisting coronary artery disease. However, not all insurance covers cardiovascular disease screening in this setting, which may influence whether testing is performed. Exercise stress testing is preferred for those who are able to do the test. For those unable to do exercise stress testing, adenosine and dobutamine stress tests are alternatives. (See "Stress testing for the diagnosis of obstructive coronary heart disease".)

- Renal disease – We measure the creatinine/glomerular filtration rate (GFR) every two to three months for the first year. After the first year, we measure creatinine/GFR every three to six months, and we perform annual urinalysis to assess for microalbuminuria. (See 'Acute and chronic renal disease' below and "Diagnostic approach to adult patients with subacute kidney injury in an outpatient setting", section on 'Evaluation'.)

- Metabolic bone disease: Bone mineral density measurement prior to transplantation and every other year after transplantation. (See "Overview of dual-energy x-ray absorptiometry".)

Screening for malignancies — Both skin cancer and nonskin malignancies are more common following liver transplantation compared with the general public. As a result, we perform intensive screening in this population. (See 'De novo malignancy' below.)

Immunizations — Immunizations recommended for patients receiving solid organ transplantations include vaccinations for influenza, pneumonia, COVID-19, and hepatitis A and B virus. In addition, the recombinant zoster vaccine (RZV) can be given posttransplantation (table 2).

Because immunosuppression can affect the patient's ability to mount an immune response to vaccinations, it is recommended that many of the vaccinations (eg, hepatitis A and B vaccines) be administered prior to transplantation when possible. In addition, live virus vaccinations

should be avoided. The role of immunizations in patients undergoing solid organ transplantation is discussed in detail elsewhere. (See "Immunizations in solid organ transplant candidates and recipients".)

Physical activity — Increasing physical activity provides a potential means to reduce metabolic complications after liver transplantation. In a prospective study, lack of physical exercise was associated with abdominal obesity in liver transplant recipients [2]. Another study showed a reduction in percent body fat in liver transplant patients who participated in a structured 12-week exercise program [3]. A retrospective analysis of patients greater than one-year posttransplant found an inverse association between exercise intensity and metabolic syndrome [4]. (See 'Metabolic syndrome' below.)

Recommendations regarding alcohol consumption — All patients should be advised to avoid alcohol consumption following liver transplantation. Patients who consume excessive alcohol following liver transplantation have lower survival rates than those who do not, regardless of the indication for liver transplantation. In a study of 441 patients who underwent liver transplantation for various indications, the five-year survival rates for those with and without sustained excessive alcohol consumption (>20 g/day for females and >30 g/day for males (figure 1)) were 49 and 75 percent, respectively [5]. In another study including 147 patients who had a liver transplant for alcoholic hepatitis, sustained alcohol use posttransplant was associated with increased mortality [6].

In particular, it is recommended that patients with alcohol-associated liver disease abstain from alcohol consumption completely [7]. Prevention and management of recurrent alcohol use in patients with alcohol-associated liver disease is presented separately. (See "Liver transplantation for alcohol-associated liver disease", section on 'Recurrent harmful alcohol use'.)

Studies have not addressed whether light to moderate alcohol consumption following liver transplantation for non-alcohol-related indications is safe. As a result, we take a conservative approach and suggest that patients abstain from alcohol following liver transplantation.

IMMUNOSUPPRESSION

Most transplant centers use either two or three agents to prevent allograft rejection in the immediate posttransplantation period (table 3). This typically involves a combination of a glucocorticoid such as prednisone, a calcineurin inhibitor (CNI) such as tacrolimus or cyclosporine, and a third agent such as mycophenolate mofetil. Once patients achieve adequate

liver function and are free from rejection for six months, ongoing immunosuppression can often be with monotherapy, typically a CNI. Some centers use sirolimus or everolimus as part of a CNI-sparing regimen in selected patients after the immediate posttransplant period and in patients with recurrent or de novo malignancy. Mycophenolate mofetil may be continued in patients at increased risk for acute or chronic rejection. (See "Liver transplantation in adults: Initial and maintenance immunosuppression".)

All immunosuppressive agents have undesired effects, the spectrum of which vary and in some cases overlap (table 3). Common side effects include hypertension, diabetes mellitus, and renal dysfunction. In addition, there are numerous medications that may interact with immunosuppressive agents, leading to changes in the serum concentrations of the immunosuppressants (table 1). In order to decrease the risk of graft rejection or toxicity due to drug interactions, potential interactions should be reviewed prior to starting any new medications or supplements. As an example, in our protocol for the administration of the antiviral combination of nirmatrelvir and ritonavir for SARS-CoV-2 infection, tacrolimus and cyclosporine are held during treatment and resumed 48 hours after completion of nirmatrelvir and ritonavir therapy. Approaches to the use of nirmatrelvir and ritonavir vary in patients receiving everolimus and sirolimus, from avoiding it altogether to discontinuing everolimus or sirolimus until 48 hours after completion of nirmatrelvir and ritonavir. If there are any concerns about the safety of a given medication or supplement, they should be discussed with the patient's transplant center prior to initiation.

The approach to immunosuppression and issues related to acute and chronic rejection following liver transplantation are discussed in detail elsewhere. (See "Liver transplantation in adults: Initial and maintenance immunosuppression" and "Liver transplantation in adults: Clinical manifestations and diagnosis of acute T-cell mediated (cellular) rejection of the liver allograft" and "Liver transplantation in adults: Treatment of acute T cell-mediated (cellular) rejection of the liver allograft".)

COMPLICATIONS OF IMMUNOSUPPRESSION

Infections — The leading cause of mortality following liver transplantation is infection. As an example, in a cohort study including 577 liver transplant recipients, 55 percent of recipients experienced an infection within 12 months after transplant and infection accounted for 42 percent of deaths during the study period [8]. Serious infections occur most frequently within the first three months posttransplantation, which is the time of greatest immunosuppression [9,10]. However, patients with poor graft function who require increased levels of immunosuppression to treat recurrent cellular rejection or chronic rejection continue to be at

risk for opportunistic infections [11]. A variety of pathogens can cause infections posttransplantation, including bacteria, fungi, and viruses (figure 2). (See "Infectious complications in liver transplantation".)

Liver transplant recipients who develop a fever or other signs of infection require urgent evaluation because even common infections, such as pharyngitis or urinary tract infections, can rapidly progress to sepsis with multiorgan failure [1]. In addition, patients with signs of sepsis should be transferred to a transplant center whenever possible. (See "Sepsis syndromes in adults: Epidemiology, definitions, clinical presentation, diagnosis, and prognosis", section on 'Definitions'.)

In the setting of suspected SARS-CoV-2 infection, even in patients who have been vaccinated, the patient should contact their transplant program for advice regarding therapy and assessment of potential drug interactions. These issues are addressed in detail separately. (See "COVID-19: Epidemiology, virology, and prevention", section on 'Post-exposure management' and "COVID-19: Issues related to solid organ transplantation" and "COVID-19: Evaluation of adults with acute illness in the outpatient setting".)

Our approach to patients with a fever following liver transplantation begins with a thorough history and physical examination (table 4). Laboratory and radiographic evaluation consists of complete blood count, comprehensive metabolic panel, urinalysis, urine culture, blood cultures, and chest radiograph. Abnormalities on chest radiograph or persistent pulmonary symptoms are evaluated by chest computed tomography (CT) and/or bronchoscopy, and abdominal symptoms are evaluated by abdominal imaging such as CT or magnetic resonance imaging with magnetic resonance cholangiopancreatography (MRCP).

Other testing is based upon the clinical setting:

- Patients with arthralgia, fever, and leukopenia, recent treatment for rejection, or those within 90 days of transplant are tested for cytomegalovirus (CMV) by quantitative polymerase chain reaction. (See "Overview of diagnostic tests for cytomegalovirus infection".)

- An abdominal ultrasound with Doppler examination is performed in patients with cholestatic laboratory abnormalities or known biliary disease to evaluate for evidence of biliary obstruction and for hepatic artery thrombosis. We proceed to an MRCP or endoscopic retrograde cholangiopancreatography when there is clinical suspicion of a biliary stricture. (See "Liver transplantation in adults: Endoscopic management of biliary adverse events", section on 'Evaluation' and "Acute cholangitis: Clinical manifestations, diagnosis, and management", section on 'Diagnostic approach'.)

- A CT scan of the head and a lumbar puncture for patients presenting with headache and fever without an identified source for the fever, since meningeal signs are frequently absent in immunosuppressed transplant patients with meningitis. (See "Clinical features and diagnosis of acute bacterial meningitis in adults".)

Sputum cultures including a SARS-CoV-2 swab and stool studies are obtained in the appropriate setting.

If a source of infection is identified, appropriate treatment should be initiated immediately and antibiotic choice may be guided by the patient's previous microbiologic culture and sensitivity data. (See "Infectious complications in liver transplantation", section on 'Time course of infections' and "Infection in the solid organ transplant recipient", section on 'Evaluation and management'.)

However, not all fevers in transplant recipients are due to infection. Graft rejection or the development of malignancy should also be considered. Liver biopsy is indicated if the above studies fail to identify a source for the fever.

Metabolic syndrome — The metabolic syndrome is common among patients who have undergone liver transplantation [12]. It is defined by a combination of hypertension, insulin resistance/diabetes, dyslipidemia, and obesity (table 5). Liver transplant recipients may meet criteria for the metabolic syndrome prior to transplantation, in which case immunosuppressive medications can exacerbate the problem. In addition, many patients will develop the metabolic syndrome de novo. A study of 252 liver transplant patients found that 52 percent had metabolic syndrome following transplantation, compared with only 5 percent prior to transplantation [13]. A second study with 455 liver transplant recipients found that the rate of obesity increased from 24 percent four months after transplantation to 41 percent three years after transplantation [14].

Immunosuppressant use is associated with all aspects of metabolic syndrome (table 3):

- Hypertension: Glucocorticoids, cyclosporine, tacrolimus
- Diabetes mellitus: Glucocorticoids, tacrolimus>cyclosporine
- Obesity: Glucocorticoids, cyclosporine>tacrolimus
- Dyslipidemia: Glucocorticoids, sirolimus, cyclosporine>tacrolimus

It is important to recognize and treat the components of metabolic syndrome because it is strongly associated with increased morbidity and mortality in liver transplant recipients [15]. (See "Metabolic syndrome (insulin resistance syndrome or syndrome X)".)

Hypertension — Approximately 65 to 70 percent of liver transplant recipients develop hypertension following transplantation [16-18]. In addition, some patients lose the normal circadian blood pressure patterns and develop nocturnal hypertension [19]. Because hypertension is common posttransplantation, we suggest that for the first six months following transplantation, the patient's blood pressure be assessed at home with self-monitoring every week and by a healthcare provider every month. In patients without hypertension after six months, blood pressure monitoring should be performed by a healthcare provider every six months. (See "Overview of hypertension in adults", section on 'Diagnosis'.)

The cause of hypertension is multifactorial but is mostly related to the use of calcineurin inhibitors (CNIs; eg, cyclosporine or tacrolimus) and glucocorticoids [20]. CNIs act by increasing both systemic vascular resistance and renal vascular resistance (primarily affecting the afferent arterioles) [21]. How this occurs is incompletely understood, but increased release of vasoconstrictors, particularly endothelin, has been thought to play an important role. (See "Pharmacology of cyclosporine and tacrolimus", section on 'Hypertension' and "Hypertension after kidney transplantation".)

By comparison, glucocorticoids are usually not a major risk factor for chronic hypertension in transplant recipients because of rapid dose reduction. However, they may play a contributory role, and gradual withdrawal of glucocorticoid therapy results in a fall in blood pressure in most patients. (See "Major side effects of systemic glucocorticoids".)

There are conflicting data concerning the frequency of hypertension induced by tacrolimus compared with cyclosporine. Two long-term trials, the European FK506 Multicentre Liver Study Group and the US Multicenter FK506 Liver Study Group, found no difference in the frequency of hypertension between the two drugs [22,23]. By comparison, other trials in liver transplant recipients have found a lower incidence of late-onset hypertension with tacrolimus [24,25]. A meta-analysis of randomized trials in heart transplant recipients included eight studies that compared tacrolimus and cyclosporine with regard to hypertension [26]. Patients who received tacrolimus were at decreased risk for developing hypertension compared with patients who received cyclosporine (relative risk 0.80; 95% CI 0.69-0.93). A lesser degree of weight gain and lower doses of prednisone used with tacrolimus may have been contributing factors [24]. Because of inconclusive data among liver transplant recipients, switching from cyclosporine to tacrolimus solely for treating hypertension is not recommended. (See "Pharmacology of cyclosporine and tacrolimus" and "Cyclosporine and tacrolimus nephrotoxicity".)

Most transplant centers approach hypertension with a stepwise approach, including limiting salt intake, assessing CNI serum levels, and modulating CNI dose if the level is inappropriately elevated. If antihypertensive medications are required, we suggest initiating therapy with a

calcium channel blocker since part of the mechanism of hypertension is thought to be due to renal arteriolar vasoconstriction (table 6). Amlodipine, felodipine, and nicardipine are preferred as first-line agents since they are long-acting, minimally interact with CNIs, and have limited side effects. First-generation calcium channel blockers (eg, nifedipine or verapamil) may inhibit cytochrome P450, increasing CNI levels, and should be avoided.

Up to 30 percent of patients will require more than one agent to control their blood pressure [27]. If calcium channel blockers are not effective or are not tolerated, we suggest the addition or substitution of a cardioselective beta blocker such as metoprolol or atenolol (nonselective beta blockers may decrease portal blood flow). An angiotensin-converting enzyme (ACE) inhibitor or angtioensin-2 receptor blocker (ARB) can also be used in patients with difficult-to-control hypertension. ACE inhibitors and ARBs are preferred in patients with diabetes [28]. However, ACE inhibitors and ARBs may induce hyperkalemia in patients taking CNIs, and the potential risks with ACE inhibitors/ARBs are discussed in more detail separately. (See "Moderately increased albuminuria (microalbuminuria) in type 2 diabetes mellitus", section on 'ACE inhibitors and ARBs' and "Hypertension after kidney transplantation".)

Diuretics are not used as primary therapy for hypertension due to concerns related to the potential to exacerbate electrolyte disturbances and dyslipidemias induced by CNIs but sometimes are used in combination with other agents. (See "Pharmacology of cyclosporine and tacrolimus", section on 'Hypertension'.)

A goal blood pressure of less than 125 to 130/<80 mmHg is reasonable for liver transplant recipients since most have multiple risk factors for cardiovascular disease (eg, diabetes, obesity, dyslipidemia). (See "Treatment of hypertension in patients with diabetes mellitus".)

Diabetes mellitus — Glucocorticoids, cyclosporine, tacrolimus, and weight gain predispose to the development of diabetes following liver transplantation. The risk also appears to be increased in patients transplanted for hepatitis C virus [29,30]. To screen for diabetes, we obtain fasting plasma glucose levels or hemoglobin A1C every six months. We also obtain annual eye examinations in patients with diabetes mellitus. (See "Screening for type 2 diabetes mellitus".)

Patients who are diabetic prior to transplantation frequently require insulin following transplantation. In addition, 5 to 30 percent of recipients develop de novo diabetes [16,31-37]. A meta-analysis that included 16 studies with 3813 liver transplant recipients found that the risk of developing de novo insulin-requiring diabetes was significantly higher among patients treated with tacrolimus compared with those treated with cyclosporine (relative risk 1.38; 95% CI 1.01-1.86) [38]. (See "Kidney transplantation in adults: Posttransplantation diabetes mellitus".)

The development of diabetes does not adversely affect survival in the first year following transplantation, but it is associated with decreased survival after 5 to 10 years [39-41]. This was illustrated in a series in which 26 of 497 liver transplant recipients (5 percent) who developed diabetes mellitus posttransplantation were compared with matched nondiabetic posttransplantation controls [39]. The total number of days in the hospital, graft survival, renal function, and the type and number of infections were similar between the groups during the subsequent 12 months. However, increased 10-year mortality related to infection was reported in a cohort of liver transplant recipients with sustained new-onset diabetes compared with a group of patients with established diabetes pretransplant, transient posttransplantation diabetes, or without diabetes [40]. Similarly, in a database study that looked at more than 35,000 patients who received a liver transplant and had at least five years of follow-up, development of diabetes mellitus posttransplant was associated with increased mortality (adjusted odds ratio 1.06; 95% CI 1.02-1.11) [41].

The lack of deleterious effects of diabetes in the first year is important clinically because diet, weight loss, and tapering of immunosuppressant medications results in amelioration or resolution of de novo diabetes in many patients. In one series of 88 patients who were not diabetic prior to liver transplantation, the prevalence of diabetes fell from 27 percent at one year to 7 percent at three years, in association with a reduction in the mean daily prednisone dose from 13 to 2 mg [31]. Furthermore, some patients who remain diabetic on low doses of glucocorticoids become euglycemic after prednisone withdrawal [42].

Treatment of diabetes posttransplantation includes standard medical and nutritional therapy, including limiting caloric intake, an appropriate diet with weight loss, and the initiation of pharmacologic agents for treatment of diabetes [43] (see "Initial management of hyperglycemia in adults with type 2 diabetes mellitus"). In the peri- and early postoperative period, insulin is generally required. In addition, modulating immunosuppression, including lowering or stopping glucocorticoids, may be of benefit. As steroids are tapered, treatment with lifestyle modification with or without oral hypoglycemic medications may be possible. Finally, switching from tacrolimus to cyclosporine in patients with difficult-to-control diabetes following liver transplantation is also an option [44]. (See "General principles of insulin therapy in diabetes mellitus".)

Obesity — Patients with end-stage liver disease frequently have a compromised nutritional status. Despite this, over one-third of patients are obese [45,46]. Following transplantation, improved health and treatment with glucocorticoids or cyclosporine predispose to weight gain. Approximately one-third of patients who are normal weight at the time of transplantation will become obese following transplantation [16,46-48]. Body weight tends to increase during the

first two years after transplantation and then stabilizes. As an example, in one series of 774 patients, mean body mass index increased from 24.8 kg/m^2 at baseline to 27.0 kg/m^2 at year 1, to 28.1 kg/m^2 at year 2; there was very little change with subsequent observations [47]. (See "Obesity in adults: Prevalence, screening, and evaluation", section on 'BMI-based classifications'.)

The dose of prednisone has been identified as an independent predictor of the development of obesity [47]. However, once obesity is established, tapering of prednisone may not lead to weight loss [16]. In addition, patients treated with cyclosporine are more likely to have weight gain than those who receive tacrolimus (46 versus 27 percent in one study) [49].

Overweight liver transplant recipients may have great difficulty losing weight. Excessive weight gain often leads to reduced physical activity, which predisposes to further weight gain and a sedentary lifestyle. Thus, prevention of excessive weight gain through patient education, nutritional counseling, and an exercise program is important for reducing posttransplantation morbidity. (See "Obesity in adults: Behavioral therapy".)

Treatment of obesity includes caloric restriction, encouraging exercise, and tapering steroids, with an initial goal of losing one to two pounds per week [1]. If those measures fail to result in adequate weight loss, additional treatment options include switching from cyclosporine to tacrolimus and possibly bariatric surgery [15,50]. Small studies have shown potential for pretransplantation sleeve gastrectomy in patients with obesity and low MELD scores [51] and for sleeve gastrectomy at the time of transplantation [52,53], or in the posttransplant period [54-56]. For example, for patients who had failed a weight loss program, sleeve gastrectomy at the time of liver transplantation was effective in achieving weight loss and reducing metabolic complications posttransplant [52,57]. In a follow-up report, weight loss and metabolic improvement persisted for >3 years after combined sleeve gastrectomy and liver transplantation [53]. In addition, endobariatric procedures are emerging as potential options to achieve weight loss in patients who are not surgical candidates; however, data are limited in a posttransplantation population [58].

However, a history of bariatric surgery (particularly Roux-en-Y gastric bypass) was correlated with adverse outcomes for patients on the liver transplant waiting list. In a study of 78 patients with a history of bariatric surgery (Roux-en-Y gastric bypass in most patients) prior to liver transplantation, bariatric surgery was associated with higher rates of removal from the transplant waiting list or mortality compared with controls matched for age and liver disease severity (33 versus 10 percent) [59]. In addition, Roux-en-Y gastric bypass may impair access to the biliary tree (which may be required if biliary complications develop posttransplant) and decreases intestinal drug absorption, which could affect immunosuppression levels. For these

reasons, sleeve gastrectomy is preferred for liver transplant candidates and recipients who are candidates for a surgical weight loss intervention. (See "Bariatric surgery for management of obesity: Indications and preoperative preparation" and "Liver transplantation in adults: Endoscopic management of biliary adverse events".)

Dyslipidemia — Dyslipidemia is common after liver transplantation, and patients should have a fasting lipid profile obtained annually [60]. Hypercholesterolemia develops in 16 to 43 percent of patients and hypertriglyceridemia in 40 to 47 percent; reduced serum HDL-cholesterol is also common [61,62]. Hypertriglyceridemia usually develops within the first month posttransplantation and then remains stable throughout the first year. By comparison, serum cholesterol increases gradually and plateaus at six months [62]. Patients with elevated pretransplantation cholesterol levels are most likely to develop hypercholesterolemia following transplantation [62]. (See "Measurement of blood lipids and lipoproteins".)

The hyperlipidemia observed in liver transplant recipients is mostly related to the side effects of glucocorticoids, cyclosporine, and tacrolimus. Immunosuppression consisting of tacrolimus monotherapy with early glucocorticoid withdrawal, which is common at many centers, has been associated with lower rates of hypercholesterolemia and hypertriglyceridemia at six months posttransplantation compared with dual therapy with tacrolimus and glucocorticoids [63]. Furthermore, tacrolimus appears to have a less prominent effect on lipids than cyclosporine [64]. (See "Kidney transplantation in adults: Lipid abnormalities after kidney transplantation".)

Treatment begins with dietary modification and, if possible, reducing the dose of or discontinuing glucocorticoids [42]. Another option is substituting tacrolimus for cyclosporine. In one study of renal transplant recipients, 53 patients with serum cholesterol concentrations greater than 240 mg/dL (6.2 mmol/L) were randomized to either the continuation of maintenance cyclosporine or conversion to tacrolimus [65]. Substitution with tacrolimus resulted in significant reductions in total and LDL-cholesterol levels (by 16 and 25 percent, respectively) at six-month follow-up, but no change in renal function or glycemic control.

Dyslipidemia improves in many patients over time when glucocorticoids are discontinued and maintenance trough levels of tacrolimus (eg, 4 to 5 ng/mL) or cyclosporine (eg, 100 to 120 ng/mL) are reached. Thus, medical therapy is rarely indicated in the early posttransplant period.

If dyslipidemia persists after the early transplant period, treatment is similar to treatment in nontransplant recipients. However, treatment is complicated by interactions of the drugs used to treat dyslipidemia with immunosuppressive agents (table 1). These interactions can lead to alterations in immunosuppressant levels and/or increased toxicities, including rhabdomyolysis. Thus, agents to treat dyslipidemia must be chosen carefully based upon the

patient's immunosuppressive regimen, and immunosuppressant levels should be monitored if interactions are anticipated (table 7).

Most patients are treated with a statin. Pravastatin and fluvastatin are preferred due to decreased interactions with immunosuppressants (table 7). However, more potent statins such as rosuvastatin, atorvastatin, and simvastatin may be used in patients who are taking tacrolimus, and with caution in patients taking cyclosporine. The goals of treatment depend upon whether the patient has a history of cardiovascular disease or other risk factors for cardiovascular disease. (See "Low-density lipoprotein cholesterol-lowering therapy in the primary prevention of cardiovascular disease" and "Hypertriglyceridemia in adults: Management" and "Management of low density lipoprotein cholesterol (LDL-C) in the secondary prevention of cardiovascular disease".)

Ezetimibe has also been studied alone or as an adjunct to a statin in liver and kidney transplant recipients. It has been shown to reduce LDL levels with generally stable levels of immunosuppression and a low risk of serious side effects. However, there have been reports of myalgia, rhabdomyolysis, hepatitis, acute pancreatitis, and thrombocytopenia [66-68]. In addition, studies in patients outside of the transplant setting have failed to show convincing evidence of clinical benefits from ezetimibe. (See "Statins: Actions, side effects, and administration" and "Low-density lipoprotein cholesterol lowering with drugs other than statins and PCSK9 inhibitors", section on 'Ezetimibe'.)

We avoid treatment with cholestyramine because it can raise triglyceride levels and may significantly impair the absorption of medications, including calcineurin inhibitors. We also avoid nicotinic acid because it can decrease glucose tolerance and raise uric acid levels, leading to symptomatic gout in some patients. (See "Low-density lipoprotein cholesterol lowering with drugs other than statins and PCSK9 inhibitors", section on 'Nicotinic acid (niacin)' and "Low-density lipoprotein cholesterol lowering with drugs other than statins and PCSK9 inhibitors", section on 'Bile acid sequestrants'.)

Cardiovascular risk — Because of the high rates of hypertension, diabetes, obesity, and dyslipidemia following liver transplantation, it is not surprising that coronary heart disease is also common. A meta-analysis that included 4792 patients following liver transplantation with 28,783 person-years of follow-up found that the 10-year risk of cardiovascular events was 14 percent and was particularly high among those with the metabolic syndrome [69]. Factors that have been associated with cardiovascular events include older age at transplantation, male sex, posttransplantation diabetes, posttransplantation hypertension, history of coronary artery disease, and history of nonalcoholic steatohepatitis [14,70,71].

Liver transplant recipients have a greater risk of cardiovascular death and ischemic events than age- and sex-matched nontransplanted patients [69]. As an example, one study compared 1312 liver transplant recipients with age- and sex-matched controls [72]. The relative risk of death due to cardiovascular disease in liver transplant recipients was 2.6 (95% CI 1.5-4.0) compared with controls. When excluding infection, recurrent disease, graft loss due to technical complications, and de novo malignancy, coronary heart disease represents the most common cause of death following liver transplantation [73]:

- In a report that described the cause of death in 299 adult liver transplant recipients who lived for more than three years, 8 out of 38 deaths (21 percent) were due to cardiovascular complications [74].
- Similarly, in a study of 433 patients who survived at least one year after liver transplantation, cardiovascular events accounted for 18 of 43 nongraft-related deaths (42 percent) [75].
- A study from the Netherlands evaluated cardiovascular morbidity in 37 liver transplant recipients who survived more than 15 years posttransplantation [76]. Cardiovascular events including myocardial infarction, angina, claudication, and transient ischemic attacks occurred in 19 percent of patients.

As in any patient with cardiovascular disease, modification of risk factors both before and after liver transplantation is essential to maximize outcomes. Thus, treatment and prevention of obesity, hyperlipidemia, diabetes, and hypertension are priorities. At present, no clear guidelines exist related to invasive modalities (coronary angiography) or noninvasive modalities (cardiac stress testing) to assess cardiac function and coronary artery patency following liver transplantation. One approach is to consider performing exercise or adenosine or dobutamine stress testing every three to five years in patients with risk factors for coronary artery disease.

Acute and chronic renal disease — Acute and chronic kidney injuries are common in liver transplantation. For the first year following transplantation, we screen patients every two to three months with measurement of the creatinine/glomerular filtration rate (GFR). After the first year, we measure creatinine/GFR every three to six months and perform annual assessment for microalbuminuria. (See "Diagnostic approach to adult patients with subacute kidney injury in an outpatient setting", section on 'Evaluation'.)

The best data on the incidence of chronic kidney disease come from a cohort study of almost 37,000 liver transplant recipients who were followed for a median of 36 months [77]. The incidence of chronic kidney disease (defined as an estimated GFR <30 mL/min per 1.73 m^2) was 14 percent at three years and 18 percent at five years (figure 3). Risk factors for chronic renal

failure included calcineurin inhibitor (CNI) therapy (given in at least 89 percent), older age, lower pretransplant GFR, female sex, postoperative acute renal failure, baseline diabetes and hypertension, hepatitis C virus infection, and transplantation before 1998.

Another study evaluated changes in kidney function in 432 patients maintained on tacrolimus who were followed for a mean of 3.7 years [78]. Estimated GFR declined ≥30 percent after transplant in 36 percent of patients. Following a decline during the first six months posttransplantation, mean GFR remained stable for the duration of follow-up.

The cause of kidney injury is multifactorial. Important contributing factors are preexisting chronic kidney disease, renal failure prior to liver transplantation, acute tubular necrosis around the time of transplantation, hypertension, diabetes mellitus, and CNI toxicity. CNI-related acute renal failure is due to renal vasoconstriction and improves with dose reduction. Chronic renal disease can also be induced by these drugs, warranting continued monitoring of the plasma creatinine concentration and urinalysis. There are conflicting data about whether chronic nephrotoxicity in liver transplant recipients is more common with cyclosporine or tacrolimus [22,23,77]. (See "Cyclosporine and tacrolimus nephrotoxicity" and "Kidney function and non-kidney solid organ transplantation".)

Attempts to prevent or reverse CNI-related chronic kidney disease have been largely unsuccessful [79]. Several renal-sparing strategies have been proposed, including reduction or complete withdrawal of the CNI and use of antibody induction therapy to delay initiation of CNI-based therapy [80,81].

A reduction in the dose of the CNI does not typically improve renal function, but may minimize disease progression. Since cyclosporine and tacrolimus appear to be associated with similar degrees of nephrotoxicity, substituting one agent for the other is unlikely to improve renal function and is not recommended [22,23,82]. However, substitution with mycophenolate mofetil (MMF), or a mammalian (mechanistic) target of rapamycin (m-TOR) inhibitor (eg, everolimus, sirolimus) in patients who do not have proteinuria is an option since these agents are associated with a lower risk of renal injury. This strategy may result in a significant decrease in serum creatinine values, particularly when used prior to irreversible renal impairment [83,84]. A multicenter open-label trial utilizing early introduction of everolimus with reduced tacrolimus levels revealed improved renal function at two years postliver transplantation compared with tacrolimus alone [85]. An improvement in renal function was also observed in a retrospective study that examined 157 liver transplantation recipients with renal impairment who were converted to everolimus [86]. The mean glomerular filtration rate increased by 10.9 mL/min/1.73 m^2 at three months after conversion, and by 6.8 mL/min/1.73 m^2 at six months after conversion. However, immunosuppression with MMF, sirolimus, everolimus monotherapy

may be associated with an increased risk of acute rejection, requiring vigilance to recognize and appropriately treat this complication. (See "Pharmacology of mammalian (mechanistic) target of rapamycin (mTOR) inhibitors".)

It has been suggested that calcium channel blockers might offer long-term protection against cyclosporine nephrotoxicity because they block CNI-induced renal vasoconstriction. However, the bulk of evidence suggests that this is not the case [87], probably because interstitial fibrosis and tubular injury (rather than transient renal vasoconstriction) appears to be responsible for chronic nephrotoxicity due to CNIs. (See "Cyclosporine and tacrolimus nephrotoxicity", section on 'Calcium channel blockers'.)

Care should be taken to avoid exposing patients to additional causes of renal injury. Nonsteroidal antiinflammatory drugs can precipitate renal failure in patients receiving CNIs, while other drugs, such as aminoglycoside antibiotics, amphotericin B, and trimethoprim-sulfamethoxazole, can produce renal failure by other mechanisms. Hypertension and diabetes should also be adequately controlled. (See 'Hypertension' above and 'Diabetes mellitus' above.)

Metabolic bone disease — Bone loss is an important source of morbidity in liver transplant recipients (figure 4), and we assess bone mineral density prior to transplantation and every other year after transplantation to assess for osteopenia or osteoporosis. The majority of bone loss and fractures occur within the first six months following transplantation, and fractures often involve the spine [88]. Patients transplanted for cholestatic liver disease are particularly vulnerable to the development of bone loss before and after liver transplantation. (See "Evaluation and treatment of low bone mass in primary biliary cholangitis (primary biliary cirrhosis)" and "Primary sclerosing cholangitis in adults: Clinical manifestations and diagnosis", section on 'Metabolic bone disease' and "Prevention and treatment of osteoporosis after solid organ or stem cell transplantation", section on 'Pretransplantation evaluation'.)

Osteopenia following transplantation mostly results from the use of glucocorticoids, although animal studies suggest that cyclosporine and tacrolimus also increase bone resorption. Other contributing factors may include immobility, hypogonadism, and certain chronic liver diseases (eg, primary biliary cholangitis or autoimmune hepatitis treated with glucocorticoids, alcohol-related liver disease). Treatment of patients with osteoporosis is often with a bisphosphonate. Osteoporosis following solid organ transplantation is discussed in detail elsewhere. (See "Prevention and treatment of osteoporosis after solid organ or stem cell transplantation".)

De novo malignancy — The incidence of malignancy is increased in liver transplant recipients [89]. Because of the increased risk, we pursue more intensive screening than is done in the general population. (See 'Screening and prevention' below.)

Incidence of de novo malignancy — Both skin cancer and nonskin malignancies are more common in liver transplant recipients compared with the general population, with skin cancers being the most common malignancies seen [90]. (See "Malignancy after solid organ transplantation" and "Epidemiology and risk factors for skin cancer in solid organ transplant recipients".)

In a systematic review that included nine studies with a minimum of 400 patients each, the rates of de novo malignancy in patients following liver transplantation were [91]:

- Skin cancer: 0.9 to 3.2 percent, mean time to diagnosis of 36 to 50 months
- Posttransplant lymphoproliferative disorder: 0.9 to 2.6 percent, mean time to diagnosis of 26 to 32 months
- Colorectal cancer: 0 to 0.6 percent, mean time to diagnosis of 16 to 51 months
- Head and neck cancer: 0.1 to 5 percent, mean time to diagnosis of 34 to 61 months
- Lung cancer: 1 to 1.2 percent, mean time to diagnosis of 42 to 50 months
- Breast cancer: 0.2 to 0.7 percent, mean time to diagnosis of 41 to 124 months
- Cervical, uterine, or ovarian cancer: 0 to 1.5 percent, mean time to diagnosis of 1 to 59 months
- Prostate cancer: 0 to 0.3 percent, mean time to diagnosis of 6 to 18 months
- Bladder or renal cancer: 0 to 0.4 percent, mean time to diagnosis of 20 to 55 months

An analysis of a United States national database published after the systematic review included 798 liver transplant recipients and identified 171 adult patients who developed 271 de novo malignancies [89]. Most were skin-related, whereas 29 were hematologic and 95 were solid-organ cancers. (See "Overview of dermatologic problems following liver transplantation".)

The probability of developing any nonskin malignancy varied according to the underlying diagnosis. It was highest in patients with primary sclerosing cholangitis (22 percent at 10 years) and alcohol-related liver disease (18 percent at 10 years) and was approximately 10 percent for all other diagnoses. The risk increased with advancing age and with smoking.

Other studies have demonstrated an association of specific cancers with particular underlying liver diseases. Examples include:

- Primary sclerosing cholangitis and ulcerative colitis with colon cancer [92]. (See "Primary sclerosing cholangitis: Inflammatory bowel disease and colorectal cancer".)

- Recurrent viral hepatitis with hepatocellular carcinoma. (See "Epidemiology and risk factors for hepatocellular carcinoma".)

- Alcohol-associated cirrhosis with oropharyngeal and esophageal squamous cell carcinoma [93,94].

Screening and prevention — Our approach to cancer screening is as follows [95-97]:

- Annual physical examination including examination of the oropharynx and a full body dermatologic examination.
- Some centers perform annual prostate-specific antigen (PSA) testing in male patients. (See "Screening for prostate cancer".)
- Annual Papanicolaou (Pap) test and mammography in females. (See "Screening for cervical cancer in resource-rich settings", section on 'Screening in higher risk patients' and "Screening for breast cancer: Strategies and recommendations".)
- Surveillance for hepatocellular carcinoma with abdominal ultrasound with alpha-fetoprotein (AFP) measurement every six months and/or annual magnetic resonance imaging (MRI) in patients with recurrent viral hepatitis who progress to bridging fibrosis or cirrhosis, and in patients who were transplanted for hepatocellular carcinoma or were found to have hepatocellular carcinoma in their explanted liver.
- We follow the Multi-Society Task Force of Colorectal Cancer guidelines for colonoscopy for colorectal cancer screening, surveillance after screening and polypectomy, and for more frequent screening (every one to two years) in patients with ulcerative colitis or Crohn disease [98].
  - (See "Screening for colorectal cancer: Strategies in patients at average risk".)
  - (See "Screening for colorectal cancer in patients with a family history of colorectal cancer or advanced polyp", section on 'Screening approach'.)
  - (See "Surveillance and management of dysplasia in patients with inflammatory bowel disease".)
  - (See "Overview of colon polyps".)
- There are no national guidelines related to screening for head, neck, or esophageal neoplasia. We generally do not pursue routine screening for these cancers. However, for patients at high risk for one of these cancers (eg, patients who have a history of smoking and alcohol use disorder), the need for periodic evaluation by an ear, nose, and throat surgeon and/or an upper endoscopy is individualized, depending on the patient's specific risk factors.

We do not obtain routine screening of the chest or abdominal imaging (with the exception of screening for hepatocellular carcinoma, described above). Patients with a 20-pack-year history of smoking cigarettes may opt for lung cancer screening with low-dose chest CT, and this is discussed in detail separately. (See "Screening for lung cancer".)

In addition to screening, patients should be instructed to use high sun protection factor sunblock. Cigarette smokers should be counseled to quit and preferably should do so prior to transplantation. (See "Selection of sunscreen and sun-protective measures" and "Overview of smoking cessation management in adults".)

Neurologic events — Neurologic complications, such as vascular damage, infections, immunosuppressive-associated leukoencephalopathy, and metabolic abnormalities, occur in 16 to 80 percent of liver transplant recipients [99-104]. Clinical symptoms are usually mild, but major neurologic sequelae are observed in some patients.

The development of serious neurologic events in the first month posttransplantation was evaluated in a series of 168 liver transplant recipients [103]. The most common events consisted of encephalopathy (19 percent) and seizures (5 percent). Less common complications included ischemia with seizures (related to heparin-induced thrombocytopenia), osmotic demyelination syndrome (formerly called central pontine myelinolysis), stroke, and posterior leukoencephalopathy syndrome. (See "Osmotic demyelination syndrome (ODS) and overly rapid correction of hyponatremia" and "Reversible posterior leukoencephalopathy syndrome" and "Hyponatremia in patients with cirrhosis".)

With inclusion of serum sodium as a factor in the Mayo End-Stage Liver Disease (MELD) score, some patients undergoing liver transplantation may be at increased risk for osmotic demyelination syndrome if they undergo transplantation with a baseline serum sodium of <125 mEq/L [105]. In a study of over 1200 patients who underwent liver transplantation, osmotic demyelination syndrome was diagnosed by neuroimaging in 11 patients (0.9 percent) [106].

Central nervous system (CNS) complications have been identified less frequently in patients receiving immunosuppressive regimens aimed at maintaining low blood levels of tacrolimus [104]. In a study of 395 such patients, major neurologic symptoms or complications were noted in 64 patients (16 percent). None of the complications were caused by infections. Complications included:

- Tacrolimus-related leukoencephalopathy – 0.8 percent
- Cerebrovascular disease – 4 percent
- Osmotic demyelination syndrome – 0.5 percent
- CNS symptoms with no identified cause – 11 percent

Pretransplant variables associated with an increased risk of CNS complications included the presence of portosystemic encephalopathy, higher peak serum bilirubin levels, and lower serum cholesterol levels.

Hearing impairment — At least one report suggested that hearing impairment may be common following transplantation [107]. The most common hearing complaints in a survey of 521 transplant recipients were hearing loss (52 percent), tinnitus (38 percent), and otalgia (30 percent). An association with tacrolimus-based immunosuppression was suggested in one analysis [108].

Hyperuricemia and gout — Hyperuricemia is common in liver transplant recipients, although clinical evidence of gout occurs in only a small proportion of cases. Both cyclosporine and tacrolimus can decrease uric acid excretion.

- An analysis of 134 consecutive liver transplant patients found that 47 percent had hyperuricemia and 6 percent developed gout a mean of 25 months posttransplantation [109]. The incidence of hyperuricemia and gout was similar between patients receiving cyclosporine and tacrolimus.

- A study of 75 liver transplant recipients identified hyperuricemia in 86 percent, whereas gout developed in only 2.6 percent of cases [110].

Asymptomatic hyperuricemia is not treated in liver transplant recipients since the development of gout is uncommon. If gout does develop, treatment of the acute attack is similar to the approach used in renal transplant recipients. The acute attack is typically treated with colchicine. Treatment with prednisone can be considered as a second-line therapy. Nonsteroidal antiinflammatory medications should be avoided since they can worsen renal function. Maintenance therapy for gout often consists of allopurinol. However, for patients receiving azathioprine (rather than the more commonly utilized antimetabolite mycophenolic acid), the combination of azathioprine and allopurinol can lead to myelosuppression; therefore, dose adjustments and close monitoring are required. In addition, switching from azathioprine to mycophenolic acid is an option. (See "Kidney transplantation in adults: Hyperuricemia and gout in kidney transplant recipients".)

Dermatologic complications — A variety of dermatologic conditions have been described following liver transplantation, including cancer, infections, drug-induced lesions, and conditions related to the underlying liver disease. The dermatologic complications of liver transplantation are discussed in detail separately. (See "Overview of dermatologic problems following liver transplantation".)

HEPATOBILIARY COMPLICATIONS

Hepatobiliary complications following liver transplantation include acute and chronic rejection, biliary complications, and recurrence of the primary liver disease.

Acute and chronic rejection — Issues related to acute and chronic rejection following liver transplantation are discussed in detail elsewhere. (See "Liver transplantation in adults: Initial and maintenance immunosuppression" and "Liver transplantation in adults: Clinical manifestations and diagnosis of acute T-cell mediated (cellular) rejection of the liver allograft" and "Liver transplantation in adults: Treatment of acute T cell-mediated (cellular) rejection of the liver allograft".)

Biliary complications — The most common biliary complications following liver transplantation are strictures and leaks [111,112]. The approach to patients with biliary complications is presented separately. (See "Liver transplantation in adults: Endoscopic management of biliary adverse events".)

Recurrence of primary liver disease — A major challenge for many patients following liver transplantation is recurrence of the primary disease that caused the original liver injury. Diseases that do not recur following liver transplantation include congenital anatomic anomalies (biliary atresia, polycystic liver disease, Caroli disease, Alagille syndrome, congenital hepatic fibrosis), metabolic diseases (Wilson disease, alpha-1 antitrypsin deficiency), and acute hepatic insults (drug-induced liver failure), provided the source of injury is removed. However, all other causes of liver disease, including hepatitis B and C virus infection, primary biliary cholangitis, primary sclerosing cholangitis, autoimmune hepatitis, nonalcoholic fatty liver disease, hemochromatosis, alcohol-associated liver disease, and hepatocellular carcinoma may recur after liver transplantation and can be associated with graft injury and failure.

The disorders most commonly associated with recurrence include hepatitis B virus (HBV) and hepatitis C virus (HCV). Fortunately, recurrence of HBV after liver transplantation can be prevented by administering hepatitis B immune globulin at the time of transplantation and at regular intervals thereafter in combination with antivirals such as tenofovir or entecavir. Strategies to minimize or eliminate the use of hepatitis B immune globulin are evolving, including the use of entecavir or tenofovir. (See "Liver transplantation in adults: Preventing hepatitis B virus infection in liver transplant recipients", section on 'Diagnosis'.)

HCV recurrence following liver transplantation was a significant source of morbidity and mortality prior to the advent of direct antiviral agents. HCV viremia and histologic injury following transplantation is essentially universal. The management of HCV recurrence after liver

transplantation is presented separately. (See "Hepatitis C virus infection in liver transplant candidates and recipients".)

Recurrences of other diseases following liver transplantation are discussed elsewhere. (See "Liver transplantation in primary biliary cholangitis", section on 'Recurrence of PBC in the transplanted liver' and "Primary sclerosing cholangitis in adults: Management", section on 'Liver transplantation' and "Liver transplantation for alcohol-associated liver disease" and "Liver transplantation for hepatocellular carcinoma" and 'Preventive medicine' above and "Management of autoimmune hepatitis", section on 'Liver transplantation'.)

ADDITIONAL ISSUES

Patients with end-stage liver disease may struggle with fatigue and sexual dysfunction, problems that can also be seen following liver transplantation. In addition, many female patients regain fertility following transplantation, so issues surrounding pregnancy also need to be addressed.

Fatigue — Fatigue is a major problem after liver transplantation. One of the most detailed studies included 96 transplant recipients who were followed for up to 15 years [113]. Sixty-six percent of patients reported fatigue, while 44 percent reported severe fatigue based upon validated quality of life instruments. A decrease in health-related quality of life correlated with the severity of fatigue. Fatigue did not appear to improve with time. Structured exercise programs might benefit patients with fatigue. In a study of 18 liver transplant recipients who experienced fatigue, a 12-week program of exercise training and physical activity counseling improved fatigue and aerobic capacity [2].

Sexual dysfunction — Sexual dysfunction is common before liver transplantation and often continues afterward [114,115]. (See "Evaluation of male sexual dysfunction" and "Overview of sexual dysfunction in females: Epidemiology, risk factors, and evaluation".)

Pregnancy — Amenorrhea and decreased fertility are common among female patients with end-stage liver disease [116]. However, premenopausal women often regain reproductive function following liver transplantation. It is important to avoid the use of potentially teratogenic immunosuppressive agents in female patients of child-bearing potential who wish to become pregnant. In this circumstance, we recommend conversion from mycophenolic acid to azathioprine, with follow-up at both the liver transplant center and with an obstetrician who manages high-risk pregnancies if the patient becomes pregnant. The approach to pregnancy in patients with preexisting liver disease, including those who have undergone liver

transplantation, is discussed in detail elsewhere. (See "Pregnancy in women with pre-existing chronic liver disease", section on 'Liver transplantation'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Liver transplantation".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here is the patient education article that is relevant to this topic. We encourage you to print or e-mail this topic to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Liver transplant (The Basics)").

SUMMARY AND RECOMMENDATIONS

- **Multidisciplinary care –** Many patients are managed by primary care clinicians following liver transplantation. However, issues related to immunosuppression (including infections, organ rejection, and renal disease) and biliary complications are typically managed by a transplant hepatologist and/or surgeon. (See 'Role of the primary care clinician' above.)

- **Risk of drug interactions –** Numerous drugs interact with immunosuppressive agents, so patients should be asked about any new medications or supplements they are taking (including over-the-counter medications) and be reminded not to start any new medications or supplements without first speaking with their clinicians (table 1). (See 'Immunosuppression' above.)

- **Complications of immunosuppression –** Several medical problems in addition to rejection are common following transplantation, many of which are the result of, or are made worse by, immunosuppression (table 3). In addition to the standard treatments used in the nontransplantation population, the treatment of many of these problems may include changes in the patient's immunosuppressive regimen.

  Common problems include:

  - Infections (see 'Infections' above).
  - Hypertension (see 'Hypertension' above).
  - Diabetes (see 'Diabetes mellitus' above).
  - Obesity (see 'Obesity' above).
  - Dyslipidemia (see 'Dyslipidemia' above).
  - Renal disease (see 'Acute and chronic renal disease' above).
  - Metabolic bone disease (see 'Metabolic bone disease' above).
  - Malignancy (see 'De novo malignancy' above).

- **Preventive health screening –** We suggest the following screening tests for nonmalignant disease in liver transplant recipients (**Grade 2C**) (see 'Screening for nonmalignant disease' above):

  - General assessment **–** Annual history and physical examination, annual dental evaluations in addition to routine (twice-yearly) cleanings.

  - Hypertension **–** For the first six months following transplantation, self-monitoring every week and blood pressure monitoring by a healthcare provider every month. In patients without hypertension after six months, blood pressure monitoring by a healthcare provider every six months. (See "Overview of hypertension in adults", section on 'Diagnosis'.)

  - Diabetes mellitus **–** Screening every six months (typically with either a fasting plasma glucose or a hemoglobin A1C) and, in patients with diabetes, an annual eye examination. (See "Screening for type 2 diabetes mellitus", section on 'A suggested approach'.)

  - Dyslipidemia **–** Annual fasting lipid profile. (See "Measurement of blood lipids and lipoproteins".)

  - Cardiovascular disease **–** Some centers perform stress testing every three to five years in patients with risk factors for coronary artery disease. However, not all insurance

covers cardiovascular disease screening in this setting, which may influence whether testing is performed. Exercise stress testing is preferred for those who are able to do the test. For those unable to do exercise stress testing, adenosine and dobutamine stress tests are alternatives. (See "Stress testing for the diagnosis of obstructive coronary heart disease".)

- Renal disease **–** During the first year, we obtain creatinine/glomerular filtration rate every two to three months. After the first year, we measure creatinine/glomerular filtration rate every three to six months and perform an annual assessment for microalbuminuria. (See "Diagnostic approach to adult patients with subacute kidney injury in an outpatient setting", section on 'Evaluation'.)

- Metabolic bone disease **–** Bone mineral density measurement prior to transplantation and every other year after transplantation. (See "Overview of dual-energy x-ray absorptiometry".)

- **Cancer screening –** We suggest the following screening tests for malignant disease in liver transplant recipients (**Grade 2C**) (see 'Screening for malignancies' above):

  - Annual physical examination including examination of the oropharynx and a full body dermatologic examination.

  - Some centers perform an annual prostate-specific antigen (PSA) in male patients. (See "Screening for prostate cancer".)

  - Annual Pap test and mammography in female patients. (See "Screening for cervical cancer in resource-rich settings", section on 'Screening in higher risk patients' and "Screening for breast cancer: Strategies and recommendations".)

  - Surveillance for hepatocellular carcinoma with abdominal ultrasound and alpha-fetoprotein measurement every six months and/or annual magnetic resonance imaging in patients with recurrent viral hepatitis who progress to bridging fibrosis or cirrhosis and in patients who were transplanted for hepatocellular carcinoma or were found to have hepatocellular carcinoma in their explanted liver.

  - We follow the Multi-Society Task Force of Colorectal Cancer guidelines for colonoscopy for colorectal cancer screening, surveillance after screening and polypectomy, and for more frequent screening (every one to two years) in patients with ulcerative colitis or Crohn disease.

- **Immunizations –** Patients receiving solid organ transplantations should be vaccinated for, among other things, influenza, pneumonia, COVID-19, and hepatitis A and B virus (table 2). (See "Immunizations in solid organ transplant candidates and recipients" and "COVID-19: Issues related to solid organ transplantation", section on 'Prevention'.)

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Topic 4589 Version 45.0

GRAPHICS

Examples of common drug interactions of immunosuppressants used in solid-organ transplant: Cyclosporine, tacrolimus, sirolimus, and everolimus

Common types of drug interactions	Examples of interacting drugs	Approach to management in the absence of appropriate noninteracting alternatives
Coadministration of drugs that inhibit CYP3A metabolism and/or P-gp efflux can **increase immunosuppressant serum concentrations**, leading to significant toxicities.	▪ Amiodarone ▪ ART-boosting agents (eg, ritonavir, cobicistat) ▪ Azole antifungals (eg, fluconazole, posaconazole, voriconazole) ▪ HIV protease inhibitors (eg, atazanavir, nelfinavir, saquinavir) ▪ Macrolide antibiotics ▪ Non-dihydropyridine calcium channel blockers ▪ Ombitasvir-paritaprevir-ritonavir with or without dasabuvir (an HCV, direct-acting antiviral regimen) ▪ Grapefruit juice	▪ Closely monitor immunosuppressant concentrations and signs of toxicity (eg, tremors and headaches). ▪ Substantial, including preemptive, dose reduction of immunosuppressant drug may be needed (eg, on average, only 25% of the standard dose of cyclosporine is required if administered concomitantly with HIV protease inhibitors). ▪ Some combinations are considered contraindicated according to product labeling; refer to appropriate topic reviews for detail. ▪ Lists of CYP3A and P-gp **inhibitors** are provided as separate tables within UpToDate.
Coadministration of drugs that induce CYP3A metabolism and/or P-gp efflux pumping can **decrease immunosuppressant serum concentrations**, increasing the risk of organ rejection.	▪ Antiseizure medications, enzyme inducing (eg, carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) ▪ Enzalutamide ▪ Nafcillin ▪ Rifamycins (eg, rifabutin, rifampin, rifapentine) ▪ St. John's wort	▪ Closely monitor immunosuppressant serum concentrations and signs of organ rejection. ▪ Significant immunosuppressant dose increases may be needed. ▪ Enzyme induction can require up to 2 weeks to achieve maximum effect and persists for up to 2 weeks after discontinuation of the interacting medication. Clinically significant effects can occur

		within hours to days of starting a CYP inducer. ▪ Lists of CYP3A and P-gp **inducers** are provided as separate tables within UpToDate.
Coadministration of nephrotoxic drugs with cyclosporine or tacrolimus can cause **additive or synergistic kidney injury**.	▪ Aminoglycosides ▪ Amphotericin B ▪ Colchicine ▪ Nonsteroidal anti-inflammatory drugs (NSAIDs)	▪ Concomitant administration of cyclosporine and tacrolimus with other potentially nephrotoxic drugs should be avoided. ▪ Suggested dose adjustments for use with colchicine are available in the Lexicomp drug interactions database included within UpToDate.
Coadministration of drugs that increase serum potassium with cyclosporine or tacrolimus may cause **severe hyperkalemia**.	▪ ACE inhibitors/ARBs ▪ Amiloride ▪ Spironolactone ▪ Triamterene ▪ Trimethoprim, trimethoprim-sulfamethoxazole (cotrimoxazole)	▪ Closely monitor serum potassium levels.
Coadministration of cyclosporine with sirolimus can **increase sirolimus concentrations**.	▪ Cyclosporine	▪ Separate administration of sirolimus from cyclosporine by 4 hours; give sirolimus at a consistent time with respect to cyclosporine. ▪ Closely monitor immunosuppressant serum concentrations.
Coadministration of statin drugs with cyclosporine can **increase statin levels and risk of myotoxicity**.	▪ Atorvastatin ▪ Lovastatin ▪ Pitavastatin ▪ Rosuvastatin ▪ Simvastatin	▪ Pravastatin and fluvastatin are preferred due to decreased interactions. ▪ Tacrolimus may be preferred over cyclosporine in patients receiving statin therapy. ▪ Cyclosporine and simvastatin should not be used together. ▪ Some combinations are considered contraindicated or statin daily dose limits are recommended in the product labeling; refer to the Lexicomp drug interactions database

		included within UpToDate for detailed information.

- **Important note:** The interactions listed in this table illustrate some of the common types of interactions with immunosuppressive drugs; this is **not** a complete list, and many other significant drug interactions can occur. When initiating or altering drug therapy, use of a drug interactions database, such as Lexicomp drug interactions, is advised.
- Cyclosporine, tacrolimus, sirolimus, and everolimus are highly dependent upon CYP3A metabolism for clearance and are also substrates of P-gp drug efflux pump. Some interactions can lead to subtherapeutic or dangerously toxic levels of immunosuppressant concentrations.
- When appropriate noninteracting alternatives are readily available, consider modifying treatment to avoid combined use with potent metabolic inhibitors/inducers or agents known to have additive toxicities with immunosuppressants.
- Drug therapy should be managed by transplant specialists with expertise in therapeutic drug monitoring, and doses should be adjusted based upon measurement of immunosuppressant concentrations, particularly whenever drug therapy is altered. If there are any concerns about the safety of a given medication or supplement, they should be discussed with the patient's transplant center prior to initiation.

CYP: cytochrome P450 metabolism; P-gp: P-glycoprotein drug efflux pump; ART: HIV antiretroviral therapy; HIV: human immunodeficiency virus; HCV: hepatitis C virus; ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker.

Graphic 110436 Version 19.0

Vaccinations for solid organ transplant (SOT) candidates and recipients

Vaccine type	Vaccine target	Indications
Nonlive (inactivated, killed, subunit, or recombinant)	Pneumococcal vaccines	All SOT candidates and recipients not previously vaccinated. Vaccine formulation of choice depends on age, national guidelines, and availability.*
	Seasonal influenza virus	Annually for all patients ≥6 months old.¶
	Hepatitis B virus	All SOT candidates and recipients who are nonimmune based on serologic testing (eg, HBsAb-negative patients).
	Hepatitis A virus	If not previously vaccinated: ▪ All adult liver transplant candidates and recipients ▪ All pediatric SOT candidates and recipients ▪ At-risk adult nonliver transplant recipients (eg, travel to or residence in an endemic area)
	Meningococcus	At-risk patients who have not been previously vaccinated, including those treated with eculizumab and those with impaired splenic function.
	Haemophilus influenzae	At-risk patients ≥5 years old who have not been previously vaccinated, including those with impaired splenic function. Children <5 years old should be vaccinated according to the routine schedule.
	Human papillomavirus	All SOT candidates and recipients not previously vaccinated who meet age-based indications for vaccination.
	Tetanus, diphtheria, pertussis (DTaP, Tdap) or tetanus, diphtheria (Td)	All SOT candidates and recipients per guidelines for healthy persons (eg, per routine for children).
	Recombinant zoster vaccine (RZV)	SOT candidates and recipients aged ≥19 years old.
	COVID-19 vaccines[Δ]	All SOT candidates and recipients. Choice of vaccine depends on age, national guidelines, and availability.
Live, attenuated[◇]	Zoster vaccine, live (ZVL)	SOT candidates aged >50 years old. NOTE: RZV is preferred, when available, over ZVL. **(ZVL contraindicated post-transplantation).**
	Varicella vaccine	Nonimmune SOT candidates prior to transplantation; can be given as early as 6 months of age in children.

		Contraindicated post-transplantation and/or for immunosuppressed patients.[§]
	Measles, mumps, rubella	SOT candidates who have not been previously vaccinated and/or lack evidence of measles, mumps, or rubella immunity (ie, IgG seronegative); can be given as early as 6 months of age in children. **Contraindicated post-transplantation and/or for immunosuppressed patients.[§]**
	Rotavirus	Per usual guidelines for infants prior to transplantation; not indicated for older children and adults. **Contraindicated post-transplantation and/or for immunosuppressed patients.**

As part of the pretransplant evaluation, we review each patient's vaccination history and ensure that the above vaccinations have been received when appropriate. For maximal protection, vaccinations should be given pretransplantation and prior to the start of immunosuppressive therapy. This increases the likelihood of developing a protective immune response and allows for administration of any needed live vaccines, which should be given at least 4 weeks prior to transplantation and are generally contraindicated once immunosuppressive therapy has started.

For complete information on timing of vaccine administration and vaccine schedules, refer to the UpToDate topic on vaccinations in solid organ transplantation. For more detailed description of at-risk populations, refer to the UpToDate topics regarding each vaccine.

HBsAb: hepatitis B virus surface antibody; COVID-19: coronavirus disease 2019; IgG: immunoglobulin G.

* In the United States, children <2 years old should receive the pneumococcal conjugate vaccine (PCV) series, children ≥2 years old should receive both the PCV series and 23-valent pneumococcal polysaccharide vaccine (PPSV23), and adults should receive either 20-valent PCV (PCV20) alone or 15-valent PCV (PCV15) followed by PPSV23 at least 8 weeks later. Dosing intervals and schedule may vary if either one of these vaccines has been given previously. Other national guideline recommendations may vary in regard to vaccine selection.

¶ For adults, we prefer the high-dose influenza vaccine as it augments immune response and does not appear to increase the risk of rejection. However, using the standard dose is also acceptable and preferred for children.

Δ Refer to the UpToDate content on COVID-19 vaccines in SOT patients for additional information.

◇ Other live attenuated vaccines include the influenza nasal spray, oral typhoid, and some formulations of the Japanese encephalitis vaccine. These are typically not indicated apart from in selected circumstances (eg, travel) and/or alternative nonlive formulations are available (eg, influenza vaccines and typhoid vaccines).

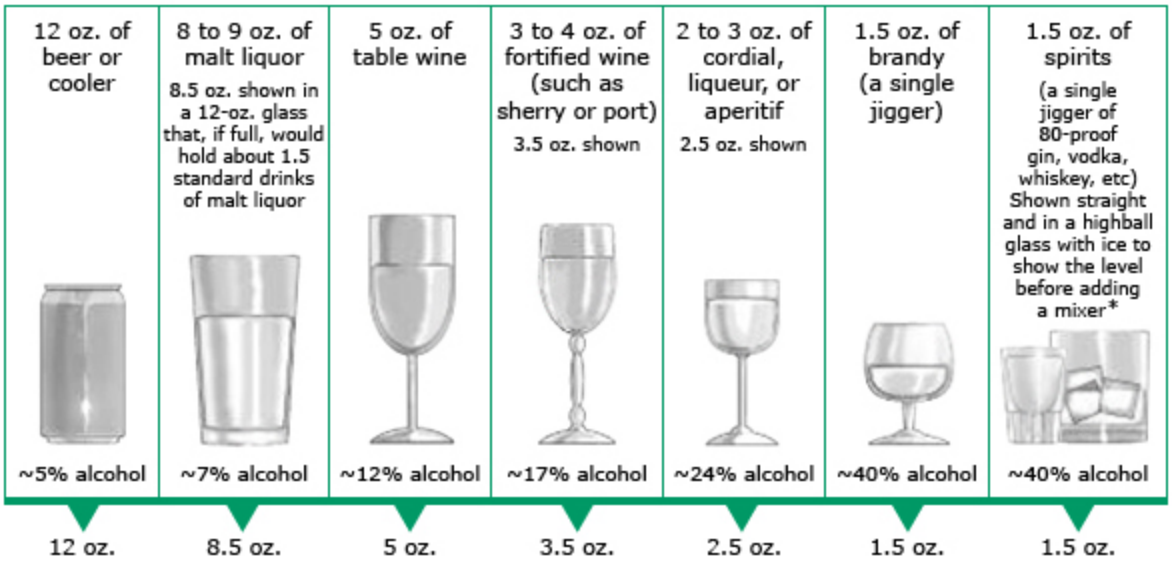
§ Possible exceptions are measles- and varicella-nonimmune pediatric transplant recipients who are receiving minimal or no immunosuppression and who have had no recent allograft rejection; such

individuals may receive the varicella vaccine or measles vaccines with appropriate education and close follow-up.

Graphic 122440 Version 2.0

What is a standard drink?

A standard drink in the United States is any drink that contains about 14 grams of pure alcohol (about 0.6 fluid ounces or 1.2 tablespoons). Below are US standard drink equivalents. These are approximate, since different brands and types of beverages vary in their actual alcohol content.



Many people don't know what counts as a standard drink and so they don't realize how many standard drinks are in the containers in which these drinks are often sold. Some examples:

- For **beer**, the approximate number of standard drinks in:
  - 12 oz. = 1
  - 16 oz. = 1.3
  - 22 oz. = 2
  - 40 oz. = 3.3
- For **malt liquor**, the approximate number of standard drinks in:
  - 12 oz. = 1.5
  - 16 oz. = 2
  - 22 oz. = 2.5
  - 40 oz. = 4.5
- For **table wine**, the approximate number of standard drinks in:
  - a standard 750-mL (25-oz.) bottle = 5
- For **80-proof spirits**, or "hard liquor," the approximate number of standard drinks in:
  - a mixed drink = 1 or more*
  - a pint (16 oz.) = 11
  - a fifth (25 oz.) = 17
  - 1.75 L (59 oz.) = 39

US: United States; oz.: ounces.

* It can be difficult to estimate the number of standard drinks in a single mixed drink made with hard liquor. Depending on factors such as the type of spirits and the recipe, a mixed drink can contain from 1 to 3 or more standard drinks.

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Graphic 56818 Version 5.0

Immunosuppressive agents in liver transplantation

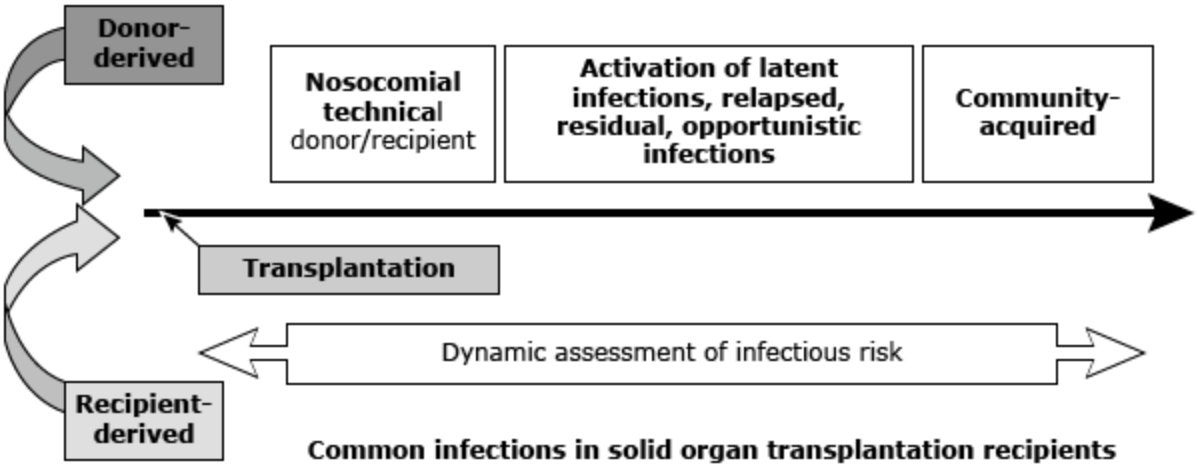
Agent	Mechanism of action	Selected adverse effects*
Prednisone	Suppresses leukocyte, macrophage, and cytotoxic T-cell activity Decreases cytokines, prostaglandins, and leukotrienes	Hypertension Dyslipidemia Glucose intolerance Bone abnormalities Peptic ulcers Psychiatric disorders
Cyclosporine	Inactivates calcineurin Decreases IL-2 production Inhibits T-cell activation	Hypertension Renal insufficiency Neuropathy Hyperlipidemia Gingival hyperplasia Hirsutism Insulin resistance
Tacrolimus	Inactivates calcineurin Decreases IL-2 production Inhibits T-cell activation	Hypertension Renal insufficiency Insulin resistance Neuropathy Hyperlipidemia
Azathioprine or 6-mercaptopurine	Inhibits adenosine and guanine production Inhibits DNA and RNA synthesis in rapidly proliferating T cells	Leukopenia Anemia Thrombocytopenia Pancreatitis
Mycophenolate mofetil or mycophenolic acid	Inhibits production of inosine monophosphate dehydrogenase (IMPDH) Prevents T and B cell proliferation	Leukopenia Anemia Thrombocytopenia GI side effects
Sirolimus or everolimus	Inhibits mTOR, (target of Rapamycin) Prevents T-cell replication	Leukopenia Thrombocytopenia Anemia (microcytic) Hyperlipidemia

		Hepatic artery thrombosis Inhibited wound healing Peripheral edema Pulmonary toxicity

* Not a complete list of adverse effects. See individual Lexicomp drug monographs for additional information.

Graphic 67917 Version 9.0

The timeline of infections following solid organ transplantation[1-3]



Common infections in solid organ transplantation recipients

Antimicrobial-resistant species: • MRSA • VRE • *Candida* species (non-*albicans*) Aspiration Line infection Wound infection Anastamotic leaks/ischemia *Clostridium difficile* colitis **Donor-derived (uncommon):** HSV, LCMV, rabies, West Nile **Recipient-derived (colonization):** *Aspergillus, Pseudomonas*	**With PCP and antiviral (CMV, HBV) prophylaxis:** • BK polyomavirus nephropathy • *Clostridium difficile* colitis • Hepatitis C virus • Adenovirus, influenza • *Cryptococcus neoformans* • *Mycobacterium tuberculosis* **Anastamotic complications** **Without prophylaxis add:** *Pneumocystis* Herpes viruses (HSV, VZV, CMV, EBV) Hepatitis B virus *Listeria, Nocardia, Toxoplasma, Strongyloides, Leishmania, Trypanosoma cruzi*	**Community-acquired pneumonia, urinary tract infection:** *Aspergillus*, atypical molds, *Mucor* species *Nocardia, Rhodococcus* species Late viral: • CMV (colitis/retinitis) • Hepatitis (HBV, HCV) • HSV encephalitis • Community-acquired (SARS, West Nile) • JC polyomavirus (PML), skin cancer, lymphoma (PTLD)

Common patterns of opportunistic infection are observed following solid organ transplantation based on epidemiologic exposures and the "net state of immunosuppression." The timeline is altered based on the immunosuppressive regimen and prophylactic medications. The dynamic assessment of infectious risk represents assays that will measure an individual's risk for infection due to specific pathogens or in general.

CMV: cytomegalovirus; EBV: Epstein-Barr virus; HSV: herpes simplex virus; MRSA: methicillin-resistant *Staphylococcus aureus*; PML: progressive multifocal leukoencephalopathy; PTLD: posttransplant lymphoproliferative disorder; SARS: severe acute respiratory syndrome; VRE: vancomycin-resistant enterococcus; VZV: varicella-zoster virus.

Modified from:

1. Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med 2007; 357:2601.

2. Rubin RH, Wolfson JS, Cosimi AB, Tolkoff-Rubin NE. Infection in the renal transplant recipient. Am J Med 1981; 70:405.

3. Fishman JA, Rubin RH. Infection in organ-transplant recipients [see comments]. N Engl J Med 1998; 338:1741.

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Graphic 58770 Version 5.0

Evaluation of fever after liver transplantation

Initial studies
History and physical examination
Laboratory testing ▪ Complete blood count, liver enzymes ▪ Urinalysis, urine culture ▪ Blood cultures
Radiologic testing ▪ Chest X-ray
Additional studies based upon clinical setting
▪ CMV rapid antigen or CMV quantitative PCR testing ▪ Chest CT and/or bronchoscopy ▪ Ultrasound of liver ± cholangiogram ▪ Head CT and lumbar puncture ▪ Abdominal imaging: CT with contrast, MRI with MRCP

CT: computed tomography; CMV: cytomegalovirus; MRI: magnetic resonance imaging; MRCP: magnetic resonance cholangiopancreatography; PCR: polymerase chain reaction.

Graphic 75619 Version 6.0

Definitions of the metabolic syndrome

Parameters	NCEP ATP3 2005*	IDF 2009	EGIR 1999	WHO 1999	AACE 2003
Required			Insulin resistance or fasting hyperinsulinemia (ie, in top 25% of the laboratory-specific reference range)	Insulin resistance in top 25%[Δ]; fasting glucose ≥6.1 mmol/L (110 mg/dL); 2-hour glucose ≥7.8 mmol/L (140 mg/dL)	High risk of insulin resistance[◇] or BMI ≥25 kg/m^2 or waist ≥102 cm (men) or ≥88 cm (women)
Number of abnormalities	**≥3 of:**	**≥3 of:**	**And ≥2 of:**	**And ≥2 of:**	**And ≥2 of:**
Glucose	Fasting glucose ≥5.6 mmol/L (100 mg/dL) or drug treatment for elevated blood glucose	Fasting glucose ≥5.6 mmol/L (100 mg/dL) or diagnosed diabetes	Fasting glucose 6.1 to 6.9 mmol/L (110 to 125 mg/dL)		Fasting glucose ≥6.1 mmol/L (110 mg/dL); ≥2-hour glucose 7.8 mmol/L (140 mg/dL)
HDL cholesterol	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women) or drug treatment for low HDL cholesterol[§]	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women) or drug treatment for low HDL cholesterol	<1.0 mmol/L (40 mg/dL)	<0.9 mmol/L (35 mg/dL) (men); <1.0 mmol/L (40 mg/dL) (women)	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women)

Triglycerides	≥1.7 mmol/L (150 mg/dL) or drug treatment for elevated triglycerides§	≥1.7 mmol/L (150 mg/dL) or drug treatment for high triglycerides	or ≥2.0 mmol/L (180 mg/dL) or drug treatment for dyslipidemia	or ≥1.7 mmol/L (150 mg/dL)	≥1.7 mmol/L (150 mg/dL)
Obesity	Waist ≥102 cm (men) or ≥88 cm (women)¥	Waist ≥94 cm (men) or ≥80 cm (women)	Waist ≥94 cm (men) or ≥80 cm (women)	Waist/hip ratio >0.9 (men) or >0.85 (women) or BMI ≥30 kg/m^2	
Hypertension	≥130/85 mmHg or drug treatment for hypertension	≥130/85 mmHg or drug treatment for hypertension	≥140/90 mmHg or drug treatment for hypertension	≥140/90 mmHg	≥130/85 mmHg

NCEP: National Cholesterol Education Program; IDF: International Diabetes Federation; EGIR: Group for the Study of Insulin Resistance; WHO: World Health Organization; AACE: American Association of Clinical Endocrinologists; HDL: high-density lipoprotein; CVD: cardiovascular disease; BMI: body mass index.

* Most commonly agreed upon criteria for metabolic syndrome. Note that abdominal obesity is **not** a prerequisite for diagnosis; the presence of any 3 of the 5 risk criteria constitutes a diagnosis of metabolic syndrome.

¶ For South Asian and Chinese patients, waist ≥90 cm (men) or ≥80 cm (women); for Japanese patients, waist ≥90 cm (men) or ≥80 cm (women).

Δ Insulin resistance measured using insulin clamp.

◇ High risk of being insulin resistant is indicated by the presence of at least 1 of the following: diagnosis of CVD, hypertension, polycystic ovary syndrome, non-alcoholic fatty liver disease or acanthosis nigricans; family history of type 2 diabetes, hypertension or CVD; history of gestational diabetes or glucose intolerance; non-White race; sedentary lifestyle; BMI 25 kg/m^2 or waist circumference 94 cm (men) or 80 cm (women); and age 40 years.

§ Treatment with 1 or more of fibrates or niacin.

¥ In Asian patients, waist ≥90 cm (men) or ≥80 cm (women).

References:

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Graphic 53446 Version 14.0

Pharmacologic agents to treat hypertension

Pharmacologic agent	Class	Standard dose	Common side effects
Nifedipine	Calcium channel blocker	10 to 20 mg three times daily, or extended release once daily	Hypotension, peripheral edema, headache, dizziness
Amlodipine		5 to 10 mg once daily	
Felodipine		2.5 to 10 mg once daily	
Nicardipine		20 to 40 mg three times daily	
Metoprolol	Beta blocker	50 to 200 mg po twice daily, or extended release once daily	Hypotension, fatigue, dizziness, bradycardia
Atenolol		50 to 100 mg once daily	
Enalapril	ACE inhibitor	5 to 40 mg once daily	Cough, dizziness, fatigue
Lisinopril		10 to 40 mg once daily	
Losartan	A2 receptor blocker	25 to 100 mg once daily	Dizziness, headache, fatigue, URI symptoms
Valsartan		80 to 320 mg once daily	

Graphic 81578 Version 1.0

Pharmacotherapy for hyperlipidemia after liver transplantation

	Usual starting dose*	Metabolism and elimination¶	Selected drug interactionsΔ	Adverse effects
HMG CoA reductase inhibitors ("statins")				
Pravastatin	10 or 20 mg once per day	Approximately 50% is renally cleared as unchanged drug. Smaller amounts are cleared by biliary excretion or undergo non-CYP and CYP 3A4 hepatic transformation. Pravastatin is a substrate of P-gp and OATP1B1/1B3.	Cyclosporine: increased risk of myopathy due to additive toxicity and elevation of statin serum level by competitive inhibition of CYP 3A4, BCRP, OATP1B1/1B3, and/or P-gp. Pravastatin and fluvastatin are less likely than other statins to interact significantly with cyclosporine.	Gastrointestinal intolerance, CK elevations, transaminase elevations, muscle toxicity, rhabdomyolysis (rare). Close monitoring of transaminases may provide early evidence of elevated statin levels and toxicity.
Fluvastatin	20 mg once per day	Approximately 75% undergoes hepatic transformation by CYP 2C9 and 20% by CYP 3A4. Fluvastatin inhibits and can interact with other drugs metabolized by CYP 2C9. Fluvastatin is a substrate of OATP1B1/B3.		
Rosuvastatin	5 or 10 mg once per day. Maximum 5 mg per day with cyclosporine.	Most clearance occurs as unchanged drug. Approximately 10% undergoes CYP 2C9 transformation to a partially active metabolite. Rosuvastatin is a substrate of BCRP and OATP1B1/1B3.		

Atorvastatin	5 or 10 mg once per day. Maximum 10 mg per day with cyclosporine.	Undergoes extensive CYP 3A4 transformation to active metabolites. Atorvastatin is a substrate of P-gp, OATP1B1/1B3, and BCRP.		
Simvastatin	5 or 10 mg once per day. Avoid use with cyclosporine.	Undergoes extensive CYP 3A4 transformation to active and inactive metabolites. Simvastatin is a substrate of OATP1B1/1B3.		
Cholesterol absorption inhibitor				
Ezetimibe	10 mg once per day	Undergoes glucuronide conjugation in small intestine and liver to form active metabolite. Most clearance occurs by enterohepatic recycling and fecal excretion.	Statins: useful for added LDL lowering in combination with a statin or as single agent. Fibrate: increased serum level of ezetimibe; theoretic increased risk of cholelithiasis. Cyclosporine: increased serum level of ezetimibe and possible alteration of cyclosporine level. Ezetimibe 5 mg daily may suffice for LDL lowering effect in combination with cyclosporine.	Gastrointestinal intolerance, headache. In combination with statin, slightly higher incidence of serum aminotransferase elevations than statin monotherapy.
Refractory severe hypertriglyceridemia (≥500 mg/dL [5.6 mmol/L])				
Gemfibrozil	600 mg twice per day	Undergoes non CYP transformation by glucuronide conjugation with small amount of	Statins: increased risks of hepatotoxicity, myopathy, and rhabdomyolysis due	Gastrointestinal intolerance, muscle toxicity, cholelithiasis,

		CYP 3A4 transformation. Gemfibrozil inhibits and can interact with other drugs metabolized by CYP 2C8 or transported by OATP1B1.	to additive toxicity and elevation of statin serum level. Avoid combining gemfibrozil with statins. Cyclosporine: additive risk of nephrotoxicity and altered serum concentration of cyclosporine.	rhabdomyolysis (rare).
Fenofibrate	30 to 67 mg once per day depending on preparation	Hydrolysed to active intermediary by plasma and tissue esterases. Undergoes non CYP metabolism by glucuronide conjugation.	Statins: increased risk of myopathy and rhabdomyolysis due to additive toxicity. If combination with a statin is unavoidable, fenofibrate with fluvastatin or pravastatin may be less likely to interact significantly than gemfibrozil with a statin. Cyclosporine: additive risk of nephrotoxicity and altered serum concentration of cyclosporine. Tacrolimus: additive risk of nephrotoxicity.	
Omega-3-acid ethyl esters◇	1 to 2 grams twice per day	Inadequately defined.	CYP-mediated interactions with immunosuppressive agents, statins, fibrates, or ezetimibe are not expected based on in vitro data.	Dyspepsia, fishy taste, modest increase in LDL-C (5%). Modest increase in bleeding time that is insignificant for patients with functional hemostasis.

CYP: cytochrome P450; OATP1B1: organic anion transporting polypeptide 1B1; P-gp: P-glycoprotein transporter; BCRP: breast cancer resistance protein.

* This table notes usual starting doses for oral administration in adult liver transplant recipients, which may differ from usual starting doses in other patient populations. Post liver transplant patients with compromised kidney function are at elevated risk of adverse effects due to statins and other hypolipidemic drugs. Limited dose titration or dose reduction may be necessary.

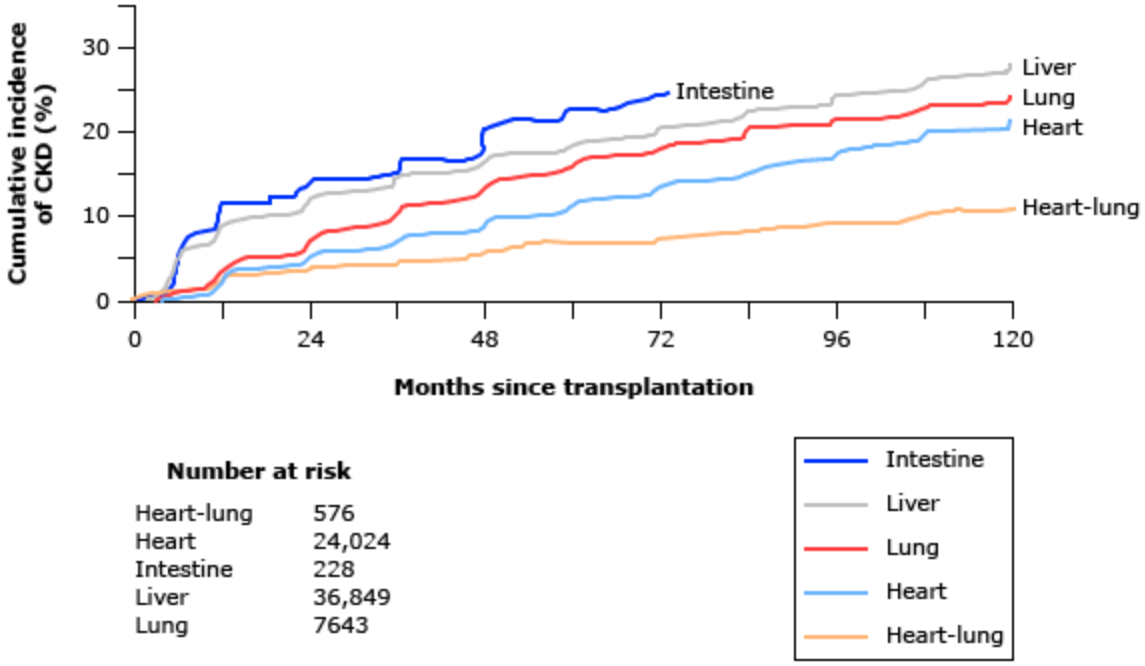
¶ Shows disposition of drug reaching systemic circulation. Statins undergo extensive pre-systemic clearance in gastric mucosa and/or liver. Patients with hepatic insufficiency may have increased systemic exposure.

Δ For additional information, refer to the Lexicomp drug interactions database included with UpToDate.

◇ Potential option. Inadequate data and experience in patients with hepatic insufficiency and/or post liver transplant. If used, a licensed standardized preparation (eg, Lovaza or icosapent ethyl [Vascepa]) appears to be preferable.

Graphic 78053 Version 10.0

Graph showing incidence of chronic kidney disease following nonrenal solid organ transplantation



Number at risk

Heart-lung	576
Heart	24,024
Intestine	228
Liver	36,849
Lung	7643

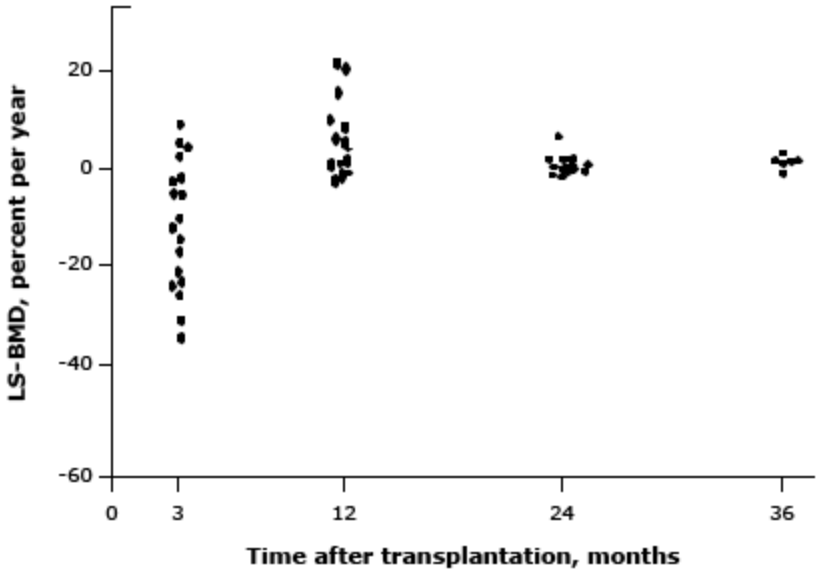
Cumulative incidence of CKD, defined as an estimated glomerular filtration rate ≤29 mL/min/1.73 m^2, among 69,321 people who received nonrenal solid organ transplants in the United States between January 1, 1990 and December 31, 2000. Cyclosporine was given to 60% and tacrolimus to 28%. Measurements of renal function were obtained at six-month intervals during the first year and annually thereafter.

CKD: chronic kidney disease.

Data from Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med 2003; 349:931.

Graphic 54972 Version 4.0

Bone loss after liver transplantation



Rate of change in LS BMD after orthotopic liver transplantation in 105 women with primary biliary cholangitis. Most women had a substantial loss of LS BMD (mean rate 18.1 percent per year) at three months. Measurements at 12, 24, and 36 months showed stable BMD with evidence for recovery of bone loss in some women at 12 months.

BMD: bone mineral density; LS: lumbar spine.

Data from: Eastell R, Dickson ER, Hodgson SF, et al. Hepatology 1996; 14:296.

Graphic 68819 Version 6.0

Contributor Disclosures

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Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

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