**APPLIED EVIDENCE**

New research findings that are changing clinical practice

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**The liver transplant recipient: What you need to know for long-term care**

Anticipate known complications and your response in concert with the transplant center

**Practice recommendations**

- In general, long-term treatment of hypertension, diabetes, and obesity after liver transplantation is similar to that for the general population (C).

- Measure bone density within the first year after transplantation. Treat osteoporosis with standard agents. Joint replacement surgery appears safe in this group of patients (B).

- Resume standard screening for malignancy 2 to 3 years after transplantation, and repeat at intervals similar to that used with the general population. Given the high risk of skin cancer, transplant recipients should wear sunblock (SPF >40) and have routine dermatologic examinations (B).

- Patients should wait at least 2 years before considering pregnancy and use barrier-type methods in this period (C).

- Vaccinate patients against hepatitis A and B, influenza, and pneumococcus. Avoid live vaccines (C).

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Orthotopic liver transplantation (OLT) is the replacement of a whole diseased liver with a healthy donor liver. The number of persons receiving OLT is increasing. Though it is unlikely you will be involved in the care of a patient immediately after OLT, you’ll need to know about the complications that occur in this period as they may impact the long-term care of the patient.

Long-term issues—such as cardiovascular disease, bone disease, malignancy, anemia, psychiatric disorders, and financial stressors—put these patients at higher risk for problems more than the average patient. Perhaps the most important task is for you to keep in contact with the transplant center when questions or concerns arise. Over time, you will once again become the primary physician and advocate for these patients.

**Complications after transplant (less than 1 year)**

Within 1 month post-OLT, the most frequent complications are acute graft rejection, vascular thrombosis, biliary leak or stricture, and infection. Between 1 and 3 months, acute and chronic graft rejection can occur, but medication toxicity and opportunistic infections become more common (TABLE 1). A broad range of infections may develop, including cytomegalovirus, Epstein-Barr virus, herpes simplex virus, varicella zoster virus, adenovirus, tuberculosis,
Pneumocystis, toxoplasmosis, *Listeria* spp, *Candida* spp, *Aspergillus* spp, and *Cryptococcus* spp. During this time, doses of immunosuppressive agents are lowered and corticosteroids are discontinued in many patients.

Once patients are considered stable after OLT, they will likely come under your supervision again. While opportunistic infections, surgical issues, and acute rejection become less common between 3 and 12 months, other complications related to OLT may occur.

Graft reinfection with hepatitis C virus (HCV) is universal, and 50% to 80% patients will develop biopsy-proven hepatitis. Many will require treatment for recurrent HCV to avoid progression to cirrhosis.

Recurrent hepatitis B infection is much less common due to prophylactic therapy with hepatitis B immunoglobulin and antiviral medications, although 10% of transplant recipients will develop hepatitis despite prophylaxis.

### TABLE 1

<table>
<thead>
<tr>
<th>COMPLICATION</th>
<th>SIGNS/SYMPTOMS</th>
<th>LABORATORY TESTS</th>
<th>INITIAL MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute rejection</td>
<td>Usually nonspecific or asymptomatic; low-grade fever, malaise, RUQ pain</td>
<td><em>Early</em>: high AP, GGT; mild AST/ALT</td>
<td>1) Doppler U/S: exclude HAT, biliary obstruction 2) Liver biopsy</td>
</tr>
<tr>
<td>Biliary obstruction or leak</td>
<td>Nonspecific to cholangitis (high fever, jaundice, sepsis); often no abdominal pain</td>
<td>High TB, AP, GGT</td>
<td>1) Doppler U/S: exclude HAT, evaluate bile duct dilation 2) T-tube cholangiogram 3) ERCP or PTC; surgical revision if failure</td>
</tr>
<tr>
<td>Hepatic artery thrombosis (HAT)</td>
<td>High fever, RUQ pain, jaundice; may progress to liver failure rapidly</td>
<td>High AST/ALT, TB</td>
<td>1) Doppler U/S: evaluate artery flow, bile ducts, liver abscess, infarction; if HAT, urgent revascularization 2) Equivocal presentation: arteriography</td>
</tr>
<tr>
<td>Hepatic vein or inferior vena cava obstruction</td>
<td>Hepatomegaly, ascites, lower extremity edema</td>
<td>Nonspecific liver test abnormalities</td>
<td>1) If positive or negative + high suspicion, contrast venogram; dilation/stent procedure if stenosis or thrombosis</td>
</tr>
<tr>
<td>Portal vein thrombosis</td>
<td>Hematemesis (variceal bleed), abdominal pain ± ascites</td>
<td>Nonspecific liver test abnormalities; rarely high liver enzymes</td>
<td>1) Doppler U/S 2) If positive or negative + high suspicion: arteriography with portal venous phase; treat with shunt or retransplantation</td>
</tr>
<tr>
<td>Calcineurin-inhibitor toxicity</td>
<td>Tremor, headache, seizure, gastrointestinal</td>
<td>Elevated creatinine, Hyperkalemia, Hypomagnesemia, Anemia</td>
<td>1) Drug level and hold if high 2) Replete electrolytes/fluids 3) Review other medications for interactions (TABLE 2)</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; ERCP, endoscopic retrograde cholangiopancreatography; GGT, gamma glutamyl-transferase; HAT, hepatic artery thrombosis; INR, international normalized ratio; PTC, percutaneous transhepatic cholangiography, RUQ, right upper quadrant; TB, total bilirubin; U/S, ultrasound
Other causes of recurrent liver disease post-OLT include liver injury due to recurrent drug or alcohol abuse, non-alcoholic steatohepatitis, cholestatic and autoimmune liver disease, and liver cancer.

Toxicity due to immunosuppressive medications is also common in this time frame (TABLE 2). Be alert to the potential for hepatotoxicity and drug interactions with any new pharmacologic agent. Other drugs (eg, lipid-lowering agents, antibiotics, antifungals) may cause liver injury on their own and need to be closely monitored.

Lastly, even though patients are at increased risk for such common infections as influenza, pneumonia, and urinary tract infections, opportunistic infections are uncommon in this period. Keep in mind that patients usually develop infections that are community-acquired and not opportunistic, particularly as time goes on.

### Long-term complications

#### Cardiovascular disease

Up to 20% of late deaths after OLT are caused by cardiovascular disease. Uncontrollable factors, such as preexisting cardiac disease, male sex, family history of cardiac disease, and advanced age contribute to the incidence of cardiovascular disease. However, a number of potentially controllable factors, such as hypertension, hyperlipidemia, obesity, and diabetes are common after OLT and should be addressed.

#### Hypertension

Hypertension occurs in 40% to 75% of OLT patients. Causes include calcineurin-inhibitor (cyclosporine, tacrolimus) therapy, high-dose corticosteroids, and renal insufficiency. Calcineurin inhibitors cause renal vasoconstriction, leading to sodium retention and hypertension. Reducing the doses of

### TABLE 2

**Immunosuppressive medications and interactions after liver transplantation**

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>SIDE EFFECTS</th>
<th>MONITORING</th>
<th>COMMON DRUG INTERACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Weight gain, diabetes, hypertension, high lipids, neurotoxic, cataracts, osteoporosis</td>
<td>Glucose, Blood pressure, Lipids</td>
<td>Increased levels with azole antifungals, macrolide antibiotics, diltiazem, verapamil, danazol, metoclopramide Decreased levels with rifampicin, phenobarbital, phenytoin, carbamazepine, St. John’s wort</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Diabetes, hypertension, high lipids, nephrotic, neurotoxic, gastrointestinal, high potassium, low magnesium</td>
<td>As above, Drug levels, Renal function, Electrolytes</td>
<td>As tacrolimus; increased levels with grapefruit juice and sirolimus</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Same as tacrolimus + gingival hyperplasia, hirsutism, rare hepatotoxicity</td>
<td>As tacrolimus</td>
<td>May increase acyclovir levels, Antacids, cholestyramine: lower absorption</td>
</tr>
<tr>
<td>Mycophenylate mofetil</td>
<td>Anemia, leukopenia, thrombocytopenia, gastrointestinal</td>
<td>CBC</td>
<td>Allopurinol, ACE inhibitors, sirolimus: may potentiate marrow toxicity May lower anticoagulation effect of warfarin</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Same as mycophenylate + pancreatitis, hepatotoxicity</td>
<td>CBC, Liver function tests</td>
<td></td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Same as mycophenylate + hyperlipidemia, hypertension, hypokalemia, diarrhea</td>
<td>CBC, Lipids</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** ACE, angiotensin-converting enzyme; CBC, complete blood count.
these medications by the transplant center typically improves blood pressure control.

Treatment of choice for hypertension depends on how recently the transplant was performed. In the first 6 months following the procedure, dihydropyridine calcium-channel blockers (eg, amlodipine) and alpha-blockers are the mainstay of therapy, although peripheral edema and orthostatic hypotension may affect their tolerability. Diuretics can also be used in volume-overloaded patients.

After 6 months, other pharmacologic agents, such as angiotensin-converting enzyme (ACE) inhibitors and beta-blockers, can be administered to patients with stable renal function and without other contraindications (strength of recommendation [SOR]: C). Long-term management of hypertension does not differ significantly from that in non-transplant patients.

**Hyperlipidemia/obesity.** Obesity and hyperlipidemia may affect up to half of OLT patients. Factors that contribute to both disorders include immunosuppressive drugs, increased appetite, diabetes, pretransplant hyperlipidemia, and history of cholestatic liver disease.

For hyperlipidemia, lifestyle modifications, such as diet and exercise, are recommended. If these measures are ineffective, statins are first-line agents. Avoid bile acid binding resins, which may interfere with the absorption of all medications. For refractory cases, switching from cyclosporine to tacrolimus under the direction of the transplant center might be indicated.

Treatment of obesity following OLT should also focus on lifestyle changes, as the safety of pharmacotherapy and surgery for obesity is uncertain in these patients.

**Glucose intolerance and diabetes.** Many patients will have glucose intolerance that resolves after steroid withdrawal. Main risk factors are pre-OLT diabetes, episodes of steroid-resistant rejection, and obesity. Post-OLT onset of diabetes will persist for only a small percentage of patients.

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**Overview of liver transplantation**

**More than 56,000 liver transplants** have been performed since the United Network for Organ Sharing created a national database for liver transplantation in 1988. In 2002, more than 5000 liver transplants were performed and more than 17,000 patients were on the waiting list for transplantation. Approximately 70% to 80% of these patients will survive to 5 years after transplantation and sustain a high quality of life long-term.

The most common indications for OLT in the US are shown in the **FIGURE**. Cirrhosis due to hepatitis C, chronic alcohol use, and idiopathic/autoimmune causes comprise almost 60% of the indications. Patients who meet minimal listing criteria may be placed on the waiting list for liver transplantation.

On February 27, 2002, a new nationwide system called MELD (Model for End-Stage Liver Disease) was adopted to rank patients on the waiting list based on the severity of liver disease and remove the subjectivity associated with the previous ranking system. The MELD score, which ranges from 6 to 40, is a mathematical computation based on the patient’s bilirubin, creatinine, and international normalized ratio (INR). Although early in use, the MELD system appears to be a good predictor of the need for transplantation and posttransplantation outcome.

**FIGURE** Indications for liver transplantation in the US

- **Hepatitis C virus** (30%)
- **Hepatitis B virus** (12%)
- **Acute liver failure** (7%)
- **Primary biliary cirrhosis** (10%)
- **Primary sclerosing cholangitis** (8%)
- **Idiopathic/Autoimmune** (12%)
- **Alcoholic liver disease** (18%)
- **Other** (13%)
- **Cancer** (9%)
- **Idiopathic** (5%)
- **Metabolic** (6%)

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Treatment of post-transplant diabetes is similar to that for any patient. Insulin is often required initially, but with reduction in immunosuppression and corticosteroids, patients can usually be switched to oral agents. Though there is no absolute contraindication to using any antidiabetes medications, most physicians try to avoid those with potential hepatotoxicity, such as the thiazolidinediones (SOR: C).

Weight loss is critical and often improves glucose tolerance. Transplant centers may switch patients from tacrolimus to cyclosporine to control hyperglycemia. Long-term screening for end organ complications (retinopathy, nephropathy, neuropathy) is as important for this population as it is for non-transplant diabetics.

Bone disease
Osteoporosis should be screened for and identified before OLT. Contributing factors for bone disease after transplant include preexisting osteoporosis, immobility, vitamin D deficiency, corticosteroid use, and hypogonadism. In the first 6 months after transplant, bone mineral density (BMD) significantly declines, often accelerated by immunosuppressive medications, corticosteroids, and immobility. After 6 months, BMD increases rapidly and, by 12 months, approaches pre-OLT values. All patients should have bone densitometry performed before OLT or before hospital discharge and receive calcium (1500 mg/d) and vitamin D (800 IU/d) supplementation (SOR: C).

Unless significant risk factors for osteoporosis are present (eg, continued use of corticosteroids, history of bone loss, fracture, or cholestatic liver disease), it is unclear whether low-risk patients should have serial bone densitometry tests performed in the years following OLT. Patients with T-scores ≥ 2 standard deviations below mean should be considered for antiresorptive therapy. Given the recent concerns regarding estrogen use and cardiovascular disease, bisphosphonates and calcitonin are preferred. For patients who develop fractures or avascular necrosis from corticosteroids, joint replacement surgery appears to be safe and effective post-OLT (SOR: B).

Malignancy
Of all of the complications following OLT, malignancy causes the highest morbidity and mortality. The overall incidence of malignancy is between 2.3% and 12.9% and may be up to 5 times higher than in the general population. The most common malignancies are post-transplant lymphoproliferative disorder (1%–4.4%) and nonmelanoma skin cancer (0.5%–4.3%); less common are gastrointestinal (0.4%–1.0%), genitourinary (0.2%–2.2%), lung (0.2%–0.8%), and oropharyngeal (0.4%–0.8%) malignancies. Many patients with small liver cancers (1 lesion...
Anemia

The prevalence of anemia after OLT reportedly is between 4.3% and 28.2%, depending on the population studied and time after transplantation. Blood loss, sepsis, medications, renal dysfunction, or hypersplenism can contribute to immediate postoperative anemia. Beyond the immediate postoperative period, anemia may be related to different causes (TABLE 3). Medication-induced anemia is usually related to bone marrow suppression, although calcineurin inhibitors may cause microangiopathic hemolysis, hemolytic-uremic syndrome, or pure red-cell aplasia.

Viral infections often cause anemia in the first 12 weeks after transplantation. Aplastic anemia may be related to parvovirus B19 infection, although it is more commonly seen in patients who undergo liver transplantation for acute liver failure. Posttransplant lymphoproliferative disorder ranges from polyclonal B-cell hyperplasia (related to Epstein-Barr virus) that responds to reduction in immunosuppression to aggressive lymphoma treated with high dose chemotherapy.

Graft-versus-host disease is a rare but important cause of pancytopenia after OLT and is diagnosed by establishing chimerism, donor and recipient lymphocytes, in the blood and bone marrow; mortality is high.

Lastly, renal failure and iron deficiency are other common causes of anemia after OLT that warrant investigation. Despite complete evaluation, half of adult patients do not have an identifiable cause of anemia and may respond to a therapeutic trial of erythropoietin (SOR: C).

Psychosocial and socioeconomic concerns

Liver transplantation is a tremendously stressful and life-altering procedure affecting patients and their families. In the initial postoperative period, the stress of the operation and other factors (immunosuppression, infection, prolonged hospital stay) can lead to a variety of psychiatric disorders, such as delirium, anxiety, depression, mania, and psychosis. A multidisciplinary approach, including psychiatry, social work, and nursing care, is required to help the patients and families through this period, as expectations for full recovery may be delayed by psychiatric conditions.
A multidisciplinary approach—including social work, psychiatry, and nursing care—is needed to help patients and their families cope with psychiatric problems. Many transplant recipients have long-term psychiatric problems. Depression and anxiety diminish quality of life, particularly for patients whose transplant was for hepatitis C and those with post-transplant viral recurrence.29,30 Most patients will respond to antidepressants and ongoing psychiatric care. The side-effect profile should be individualized for each patient, keeping in mind the potential interactions with the current medications.

Mania and hypomania, while less common than depression, are often related to higher doses of immunosuppression (e.g., corticosteroids). Cyclosporine may increase lithium levels, leading to toxicity.31 Treatment with anticonvulsant medications, such as carbamazepine, may decrease calcineurin-inhibitor levels and should be monitored in coordination with the transplant team. Finally, some patients with encephalopathy prior to OLT have persistent cognitive deficits long after OLT.32

Drug and alcohol recidivism are common post-OLT and typically occurs in about 20% of patients. It is important that active steps are taken to avoid recidivism immediately after OLT. Long-term psychiatric care and continued attendance at support groups help maintain sobriety. The important contributions you can make are maintaining a heightened awareness for recidivism, communicating with patients regularly about drug and alcohol abuse, and providing support and referral services.

### Evaluation of anemia after liver transplantation

<table>
<thead>
<tr>
<th>CAUSE</th>
<th>TIME AFTER TRANSPLANT*</th>
<th>EVALUATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common: mycophenylate mofetil,</td>
<td>&gt;2 weeks</td>
<td>Alter immunosuppression, discontinue drug</td>
</tr>
<tr>
<td>azathioprine, sirolimus, tacrolimus,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cyclosporine, interferon, ganciclovir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infrequent: dapsone, furosemide,</td>
<td></td>
<td>Discontinue drug</td>
</tr>
<tr>
<td>trimethoprim/sulfamethoxazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Viral Infection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parvoviruses B19</td>
<td>2–6 weeks</td>
<td>IgM titer, B19 DNA</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>4–12 weeks</td>
<td>Rapid antigen, DNA</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>4–12 weeks</td>
<td>IgM titer, DNA</td>
</tr>
<tr>
<td><strong>Aplastic anemia</strong></td>
<td>2–6 weeks</td>
<td>Bone marrow biopsy</td>
</tr>
<tr>
<td><strong>Post-transplant</strong></td>
<td>&gt;6 weeks</td>
<td>Hemolysis indices (indirect bilirubin, haptoglobin, Coomb's test), bone marrow biopsy</td>
</tr>
<tr>
<td><strong>lymphoproliferative disorder</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Graft-versus-host disease</strong></td>
<td>2–6 weeks</td>
<td>Demonstrate chimerism</td>
</tr>
<tr>
<td><strong>Renal insufficiency</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common: tacrolimus, cyclosporine,</td>
<td>&gt;2 weeks</td>
<td>Alter immunosuppression, treat diabetes/hypertension</td>
</tr>
<tr>
<td>diabetes, hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infrequent: HBV/HCV-related glomerulonephritis or cryoglobulinemia</td>
<td></td>
<td>Urinalysis, HBV DNA, HCV RNA, renal ultrasound/biopsy</td>
</tr>
<tr>
<td><strong>Iron-deficiency</strong></td>
<td>&gt;6 weeks</td>
<td>Iron studies, evaluate for chronic blood loss (GI, GU)</td>
</tr>
<tr>
<td><strong>Unknown cause</strong></td>
<td>&gt;6 weeks</td>
<td>EPO trial</td>
</tr>
</tbody>
</table>

* These values represent the typical interval after transplantation. EPO, erythropoietin; GI, gastrointestinal; GU, genitourinary; HBV, hepatitis B virus; HCV, hepatitis C virus; IgM, immunoglobulin M.
Socioeconomic problems
While most transplant recipients maintain a good quality of life, some have long-term socioeconomic problems. One study showed that only one third of OLT recipients returned successfully to work, just slightly higher than the percentage working before OLT. The economic situation improved in 11.9% of the recipients, worsened in 33.9%, and stayed the same in 54.2%. Concurrent illness, prolonged inactivity, psychiatric disorders, and the level of physical requirements at work are the main contributing factors to unemployment.

Another major stressor is medical cost. The average cost of immunosuppressive medications alone is $10,000 to $20,000 per year. Most of the charges are reimbursable, although this depends on the payer and time from transplantation. Medicare pays for immunosuppressive medications for only 36 months. Beyond that point, patients will require secondary insurance or other assistance. This expenditure is exacerbated by the cost of other medications, clinic visits with the transplant center, family physicians, and specialists, and time away from work.

Although patients are usually well informed of these concerns before OLT, they often do not appreciate the financial magnitude until after OLT. Encourage patients to return to work, stay active physically and mentally, and prepare for these financial considerations.

Sexual issues
Some patients have persistent sexual dysfunction that may have an organic basis (cardiovascular, renal, liver, endocrine) requiring investigation. The safety and efficacy of sildenafil (Viagra) in OLT recipients has not been investigated to date.

However, other patients regain their libido and gonadal function immediately after OLT; pregnancy may occur in this period. Advise patients to wait at least 2 years post-OLT before considering pregnancy (SOR: C). Contraception, preferably barrier-type, should be used during sexual intercourse. Hormonal contraceptives are not contraindicated but should probably not be administered until the patient’s transplant status is stable.

If pregnancy does occur, apprise the patient of potential complications and adverse outcomes. Hypertension and preeclampsia are more common in pregnant OLT recipients; life-threatening infections and acute rejection are rare. Fortunately, most patients deliver healthy babies; miscarriages, stillbirths, and malformations are uncommon. An obstetrician specializing in high-risk pregnancy should follow all pregnant OLT recipients.

Vaccination
Vaccination after OLT is controversial. Live vaccines are generally contraindicated post-OLT and their safety in patients with stable graft function and on low levels of immunosuppression is unclear (SOR: C). Patients should receive pneumococcal vaccination, hepatitis A and B vaccination if not already immune, and yearly influenza vaccination (SOR: C). For travel outside of the US or in uncertain situations or exposures, the best reference is the Centers for Disease Control web site: www.cdc.org.

Communication with the transplant center
Direct communication with the patient’s transplant center is extremely important. You and the transplant center should determine the most effective way (phone, fax or e-mail) to communicate.

When should you contact the transplant center? First, obtain the center’s approval for any new medications that may be used long-term or have the potential for nephrotoxicity, hepatotoxicity, or immunosuppression. Second, notify the transplant center in the event of new signs or symptoms, such as fever, weight loss, abdominal pain, or jaundice. Being cautious by communicating early is often the most prudent course. Third, alert the transplant center of any hospitalizations.
Transfer to the transplant center for any transplant-related problem or prolonged hospitalization usually provides the best outcome for the patient.

On the flip side, you are the primary caretaker, and the transplant center should regularly communicate with you regarding general medical concerns and any new diagnoses, interventions, or treatments. The transplant center should also regularly communicate with you regarding general medical concerns and any new diagnoses, interventions, or treatments. A strong, mutual relationship between you and the transplant center will have great impact on the recipient’s long-term care.

REFERENCES