
Liver transplantation

Managing complications in primary care

The number of people surviving liver transplants has increased steadily over the past 3 decades. Immunosuppressive regimens have become more sophisticated, as have strategies for preventing complications.

Mark Dedmon, MPAS, PA-C

In the United States, approximately 3.9 million people—1.8% of the total population—have been infected with the hepatitis C virus (HCV). Of those infected, thousands will develop liver failure and be placed on waiting lists to receive a liver transplant. Also included on those waiting lists are people who have liver failure resulting from autoimmune hepatitis, cryptogenic cirrhosis, primary sclerosing cholangitis, alcohol abuse, and dozens of other conditions. In fact, the waiting list grows larger each year, despite the steadily increasing number of orthotopic liver transplants (OLTs) performed annually. Heightened public awareness has increased the overall number of available livers, but demand has far outpaced supply. This has resulted in an increased need to optimize the outcome for OLT through better graft preservation before transplant, improved surgical techniques during transplant, improved antirejection medications, and the early detection and treatment of infections after transplant.

Liver transplantation has a 1-year survival rate of 85.9% and a 3-year survival rate of 77.5%.¹ However, a number of potentially fatal complications can occur in patients who have undergone transplantation. These complications can be divided into four major categories (see Table 1, page 43):

- Postoperative complications
- Rejection
- Complications of immunosuppressive therapy
- Recurrence of disease.²

Now more than ever, primary care providers must be able to anticipate, diagnose, and treat these poten-

tial complications before they can cause irreparable damage or even death.

Postoperative complications

Hepatic artery thrombosis (HAT), one of the most ominous complications following liver transplantation,³ can cause fulminant hepatic failure with rapid decompensation, altered mental status, bacteremia, biliary strictures and leaks, and obstruction.⁴ Pediatric patients, those who receive donor livers with prolonged ischemia time (greater than 8 hours from time of procurement), or patients who required complex arterial reconstruction are at a higher risk for HAT.⁵ If this condition is suspected, the clinician should request Doppler studies.⁶ Because false-negative results can rarely occur with Doppler studies, dynamic CT, magnetic resonance angiography, or contrast angiography may be warranted. If HAT is diagnosed early in the perioperative period, thrombectomy and arterial reconstruction may salvage the graft; otherwise immediate retransplantation is essential or the patient will not survive.

Hepatic artery stenosis Although not as menacing as HAT, hepatic artery stenosis (HAS) with impaired flow also carries very high morbidity and mortality rates. HAS is seen in as many as 60% of patients with biliary abnormalities.⁷ Arteriography will confirm the diagnosis, and the treatment is similar to that for HAT, with immediate surgical revascularization and possible retransplantation needed.

Portal vein thrombosis Portal vein thrombosis (PVT) occurs in approximately 1% to 3% of transplant recipients.⁸ Its infrequency is attributed to increased surgical expertise, which prevents a redundant portal vein after transplant. Although it is a rare occurrence, PVT can be devastating. Hepatic failure resulting in

Mr. Dedmon is Senior Physician Assistant, Organ Transplantation Division, Department of Surgery, University of Texas Health Science Center at San Antonio. The author has indicated no relationships to disclose related to the content of this article.

encephalopathy and multiple organ failure may arise if PVT occurs within the first month following OLT. If diagnosed after the first month, PVT may still result in less severe ascites, variceal hemorrhage, and encephalopathy. Hepatic failure usually does not occur in these patients, however.

The risk factors for postoperative PVT include a history of PVT before transplant, prior portal vein surgery, hypercoagulable states, or Budd-Chiari syndrome.⁹ Diagnosis is made with Doppler ultrasonography (US) or dual-phase CT. Angiography can be used to evaluate the extent of the thrombosis. Treatment depends on the extent of liver failure, the residual amount of portal flow, and the clinical presentation. If PVT is associated with liver failure and multiple organ dysfunction, immediate revascularization or retransplantation is warranted. However, patients who are fairly stable but show signs of portal hypertension may benefit more from elective decompressive shunt surgery such as a splenorenal shunt, stenting, thrombectomy, or lytic therapy.¹⁰ Other, more rare vascular complications include arteriobiliary fistula, hepatic artery pseudoaneurysm, inferior vena cava stenosis or thrombosis, and hepatic vein occlusion.

Biliary tract complications Approximately 10% to 20% of all liver transplant recipients experience biliary tract complications.¹¹ Most early posttransplant biliary complications are bile leaks and anastomotic strictures. Early bile leaks occurring within the first month after transplants usually result from an anastomotic leak. Late biliary leaks occurring after the first month are usually caused by ischemic injury from HAT or T-tube removal.¹² Patients will typically present with fever, leukocytosis, right upper quadrant pain, and signs of sepsis.

Treatment for biliary leaks depends on the type of surgery the patient had and the size and location of the leak. If HAT or HAS caused a leak, the condition must be corrected before bile duct repair. Choledochocholedochostomy (CDCD, or duct-to-duct surgery) may be dispensed with in favor of endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy and stent placement if the leak is small. This procedure may be performed on an outpatient basis with follow-up ERCP performed every 3 months. If a patient has undergone choledochojejunostomy (CDJ) to a Roux limb, successful ERCP is less likely because the endoscopist cannot see and cannulate the bile duct anastomo-

KEY POINTS in this article

- ▶ Liver transplant has a survival rate of from 85.9% in the first year to 77.5% in the third year posttransplant.
- ▶ Liver transplant complications include postoperative complications, rejection, complications of immunosuppressive therapy, and recurrence of disease.
- ▶ Rejection can be prevented to some extent if it is recognized and treated early.
- ▶ The same medications that avert rejection also enable life-threatening viral, bacterial, and fungal infections to take hold.

sis. This patient would require percutaneous transhepatic directed stenting (PTC) or surgical correction. Likewise, the patient with a very large bile leak would also require surgical correction.

Patients with biliary stricture will often present with many of the same symptoms, such as fever and abdominal pain, as

those with biliary leaks. However, persons with biliary stricture will usually also have jaundice and increasing cholestasis as evidenced by increasing levels of alkaline phosphatase, gamma glutamyl transpeptidase (GGT), and total bilirubin. On the other hand, they can also present with completely asymptomatic cholestasis.¹³

Biliary strictures are divided into nonanastomotic and anastomotic subcategories. Whether the OLT recipient has had a CDCD or a CDJ, generally the hepatic artery provides the sole blood supply for the donor bile duct. Nonanastomotic strictures are usually caused by an inadequate blood supply to the donor biliary tree via the hepatic artery. Fifty percent of patients having a nonanastomotic stricture have HAT. A pretransplant history of primary sclerosing cholangitis, prolonged intraoperative cold ischemic time, and incompatibility among the ABO blood groups are also factors that can lead to a nonanastomotic biliary stricture.¹⁴ Anastomotic strictures, by contrast, are usually caused by scar tissue formation, surgical technique, and local ischemia; they are seen more commonly in patients who underwent CDJ than in those who underwent CDCD.¹⁵

When the patient with an anastomotic stricture has had a CDCD transplant, ERCP with ballooning and stenting repeated every 2 to 3 months is very effective. If several attempts at ERCP do not correct the stricture, the CDCD is converted to a CDJ. Anastomotic strictures following CDJ transplants are treated initially with PTC. If this intervention fails, the patient will require a remake of the CDJ. In both situations, the hepatic vasculature must be confirmed—and corrected if necessary—before surgery is considered. Other very rare biliary complications include Oddi's sphincter dysfunction,¹⁶ posttransplant cholelithiasis,¹⁷ mucocele, cholangitis,¹⁸ and hemobilia.¹⁹

Rejection

One of the biggest fears of patients and health care providers alike is the fear of organ rejection. Although rejection cannot always be avoided, several practices will help to facilitate prevention and early recognition.

In every patient, a CBC with differential, comprehensive metabolic profile, magnesium level, and GGT should be routinely ordered. Schedules vary by transplant program, but a good rule of thumb is to schedule these routine laboratory tests weekly for 4 weeks, biweekly for 2 to 3 months, monthly for 6 months, every 3 months for 2 years, and thereafter every 6 months for life. Medication peak and/or trough levels should be followed in accordance with the drug manufacturer's recommendations. An unexpected rise in the serum bilirubin and/or transaminase levels can be the first sign of acute rejection. Liver biopsy is warranted to confirm any suspicions.

Hyperacute rejection and primary nonfunction Hyperacute rejection is extremely rare in liver transplantation. It was originally thought to occur when the recipient had a fulminant immune reaction due to preformed specific antigenic antibodies on the donor graft. It manifests with profound coagulopathy and acidosis, as well as elevated values from liver function tests. Hepatic coma may follow immediately or even occur during transplant. Doppler imaging will help to establish or rule out suspected vascular thrombus, a possible precipitating factor. The only treatment option for hyperacute rejection is emergent retransplantation. Hyperacute rejection was seen in some of the earliest liver transplants, when recipients received ABO-incompatible grafts, resulting in rapid destruction of the donor organ by the recipient's immune response.²⁰ If urgently needed, livers can sometimes be transplanted across the barriers of the ABO blood system; for instance, a liver from an O Rh-negative donor can be transplanted to a recipient of blood groups A or B. In fact, hyperacute rejection of the vast majority of livers transplanted across the barriers of the ABO system has not occurred. This has led many researchers to dismiss the existence of hyperacute rejection, stating that what is actually occurring is "primary nonfunction" (PNF) or failure of the liver to function after revascularization.²¹

No universally recognized definition for PNF exists.²² PNF is loosely defined as "initial poor hepatic func-

TABLE 1

Complications following liver transplantation

Complications of immunosuppressive therapy

Diabetes mellitus
GI complications
Hyperlipidemia
Hypertension
Infections
Malignancies
Neurologic complications
Obesity
Pulmonary complications
Renal complications

Postoperative complications

Biliary tract complications
Hepatic artery stenosis
Portal vein thrombosis

Recurrence of disease

Hepatitis C
Viral and nonviral hepatitis

Rejection

Acute rejection
Chronic rejection
Hyperacute rejection and primary nonfunction

tion."²³ Some researchers describe it as "immediate graft failure with elevated liver enzymes, little or no bile output, encephalopathy, and coagulopathy."²⁴ Although, researchers do not state a definite time frame, most agree that PNF occurs within the first few hours or days after transplantation. The use of a preservation solution developed at the University of Wisconsin (the UW solution) has extended the available cold ischemic time by preventing cellular swelling and biochemical injury, resulting in a dramatic decrease in the occurrence of PNF.²⁵

Acute rejection Acute cellular rejection (ACR) is the most common form of liver allograft rejection.²⁶ In the past decade, up to 50% of liver allograft recipients experienced some degree of ACR within the first 6 weeks after transplantation. This percentage has decreased with newer immunosuppressive medications and is less than 20% in the author's program.²⁷

ACR has three main categories based on histopathologic findings: mild, moderate, and severe. Most patients are clinically asymptomatic in early or mild acute rejection. However, hepatomegaly, tenderness to palpation of the allograft (thought to be caused by localized peritonitis), and cyanosis can be seen in late or severe acute rejection. Increased intrahepatic pressure leading to ascites may also be present in severe or late acute rejection.²⁸

Elevations in total bilirubin, transaminase (AST and ALT), GGT, and/or alkaline phosphatase levels indicate, but are not specific for, ACR. The clinician should suspect the diagnosis on clinical and routine laboratory examination or when immunosuppressive therapy has been minimized or recently changed. ACR is confirmed by biopsy, and histopathology remains the gold standard for the diagnosis. Rejection can be diagnosed from evidence of portal inflammation, bile duct damage, and venous subendothelial infiltration of inflammatory cells. These features are scored on a scale of 0 (none) to 3 (severe) and are collated to give a final rejection grade.²⁹ In many cases, eosinophils can be a helpful indication of acute rejection.³⁰ Cellular rejection can be difficult to distinguish from recurrent disease, especial-

ly hepatitis C infection; therefore most transplant centers ask that locally acquired liver biopsy slides be sent to the transplant center for evaluation.

ACR is typically treated with increased immunosuppression via corticosteroid bolus therapy and/or an increase in the dosage of immunosuppressant medication (such as tacrolimus) if blood levels are found to be subtherapeutic.³¹ Antilymphocyte therapy such as antithymocyte immunoglobulin (Thymoglobulin) or the monoclonal antibody OKT3 should be considered if there is little to no response to corticosteroid therapy and adjustments to the dosage of immunosuppressant medication.

Chronic rejection Chronic rejection (CR) usually occurs after the first 6 months. Patients with CR can appear clinically asymptomatic but may still show characteristic laboratory abnormalities.

CR may manifest with increased cholestasis, such as a rise in alkaline phosphatase, GGT, and/or total bilirubin levels. On biopsy, the loss of small bile ducts and obliterative angiopathy are apparent as the cause for the cholestasis.³² Depending on a program's immunosuppressive regimen and timing of protocol biopsies, some cases of CR may be seen on histologic examination even before this condition causes elevated serum laboratory findings.

Several risk factors contribute to CR. Almost all affected patients have had at least one episode of acute rejection. Other contributing factors are inadequate immunosuppression in the early postoperative phase, cytomegalovirus (CMV) infection, primary biliary cirrhosis, primary sclerosing cholangitis, or a history of autoimmune hepatitis.³³ The chief predictor of CR is retransplantation for previous graft loss from chronic rejection; CR develops in as many as 90% of patients who undergo retransplantation for this reason.³⁴ Patients in centers that use a more potent immunosuppressant therapy, such as OKT3, or multiple drug immunosuppressant regimens have a lower risk of CR. Rejection is also less likely in elderly patients or in those who had severe liver disease or comorbid conditions before transplant due to an already weakened immune system. Somewhat healthy young patients—who tend to have stronger immune systems—are actually at the highest risk for CR because they are not additionally challenged by comorbid conditions.³⁵ CR can be very difficult to diagnose and manage and, depending on the particular cause for the rejection, it is

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often an indication for possible retransplantation.

The treatment of CR has changed considerably in the past decade. The corticosteroid boluses and antilymphocytic treatment employed for the treatment of acute rejection have little effect in CR. Tacrolimus has proven to be the most effective treatment of CR, especially if the diagnosis was made within 3 months of transplantation.³⁶ CR can be successfully treated (and even prevented to some extent) if the provider is careful to follow a routine of cautious suspicion, early evaluation, and routine biopsies.

Complications of immunosuppressive therapy

Early attempts at immunosuppression, which included whole-body irradiation and irradiation plus corticosteroids, were often more harmful than beneficial to transplant patients and their grafts. In 1963, Hume and colleagues described the use of focused irradiation confined to the transplanted graft, in this case a kidney, which resulted in fewer posttransplant infections and greater graft survival.³⁷ The first cases of immunosuppression using medication without radiation were described in 1963 by Murray's group, who used azathioprine (Imuran) in a canine kidney allograft model. He later presented 13 patients who were using only azathioprine for immunosuppression, although that regimen was found to be inadequate and to have caused adverse effects.³⁸ Based on these findings and the knowledge that prednisone delayed the rejection of skin grafts in rabbits, the combination of azathioprine, prednisone, and local irradiation was initiated. In the early 1960s, Thomas E. Starzl, MD, was the first to report success in controlling rejection using a combination of prednisone and azathioprine in living related kidney transplant patients.³⁹ Not until the 1980s and 1990s did the development of calcineurin inhibitors such as cyclosporine and tacrolimus make it possible to consider the use of a single-drug regimen for the prevention of rejection.

These new drugs are extremely powerful and are not without serious side effects. The clinician must find a balance between the desired therapeutic effects and the deleterious side effects. Even under ideal conditions, immunosuppression has multiple avoidable and unavoidable consequences. It has long been known that corticosteroids are diabetogenic, while cyclosporine and tacrolimus have proven to be nephrotoxic. Hypertension, obesity, and neoplasms are all adverse side effects

seen in the immunosuppressed patient. The individual and combined use of all immunosuppressant drugs can render the OLT patient vulnerable to any number of opportunistic infections, greatly increasing morbidity and mortality. The provider must find a way to avoid, or at least minimize, these adverse side effects.

Infections Perhaps the Achilles' heel of the powerful immunosuppressant medications is the post-OLT infection. The same medications that avert rejection also enable life-threatening fungal, bacterial, and viral infections to take hold. CMV and Epstein-Barr virus (EBV), which usually have relatively low morbidity in the general population, can be extremely virulent in the immunosuppressed patient.⁴⁰

A clinician must always keep in mind that the very nature of the immunosuppressant medications themselves sometimes may prevent the patient from developing and displaying fever and other more overt signs of infection. In other words, sepsis may be well advanced, as demonstrated by CBC or blood cultures, yet the patient may have very few clinical signs of infection. The practitioner should consider early judicious use of laboratory and other diagnostic studies, even if the clinical presentation is not alarming.

Many transplant centers routinely employ antifungal prophylaxis, with fluconazole being the most widely

used agent. Although this practice has greatly reduced the rate of common fungal infections, such as infections caused by *Candida albicans*, studies have shown that it also has increased the number of drug-resistant pathogens, such as *Candida glabrata*. Still, *Candida* species and *Aspergillus* species remain the most common fungal pathogens troubling post-OLT patients.⁴¹

The severe bacterial infections resulting from the increased prevalence of resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) carry a mortality rate that is as high as 86%.⁴² Linezolid-resistant and vancomycin-resistant enterococci have also been observed.

In the immunocompetent patient, viruses, such as CMV, can seem somewhat innocuous. However, for the immunosuppressed transplant patient, CMV infection can be disastrous. Prophylactic treatment is based on the CMV antibody status in the donor and recipient. If the donor tests negative (CMV IgG less than 101) or if the recipient tests positive (CMV IgG of 101 or higher), the recipient is given oral acyclovir, 800 mg three times per day for 6 months. If the donor is CMV positive and the recipient is either CMV negative or low positive, the more potent valganciclovir is given at a dosage of 450 mg orally once daily for 6 months. After the first 3 months of this regimen, these patients can

be switched to acyclovir if treatment with that drug is economically beneficial.

Hypertension Posttransplant hypertension is common in liver transplant patients. A good medical history is important; if a patient had hypertension before end-stage liver disease developed, the hypertension almost certainly will recur following liver transplantation. Some evidence of arterial hypertension is ultimately seen in as many as 80% of patients who have had liver transplants.⁴³ Several factors are believed to be involved, but the leading cause for posttransplant hypertension is thought

to be renal vascular constriction induced by immunosuppressant medications.⁴⁴ The hypertension is usually controlled with a calcium channel blocker (CCB); these agents block vasoconstriction and improve renal hemodynamics.⁴⁵ CCBs alone may be insufficient, and additional agents might be necessary to control hypertension. These pharmaceutical interventions should be coupled, of course, with ongoing efforts to decrease BP through weight loss, salt restriction, and exercise.

Diabetes mellitus Chronic liver disease is an insulin-resistant condition; therefore, the use of some essential medications may result in the onset of diabetes mellitus (DM).⁴⁶ Corticosteroids, cyclosporine, and tacrolimus are all diabetogenic and may precipitate onset of DM or trigger the need for insulin in preexisting diabetes. Although posttransplant DM occurs frequently, it is usually controlled with oral antihyperglycemic agents or insulin.

Hyperlipidemia As many as 30% of liver transplant patients develop hyperlipidemia.⁴⁷ Obesity, poorly controlled diabetes, and immunosuppressant medications such as cyclosporine, sirolimus, and corticosteroids contribute to posttransplant hyperlipidemia. If continued long enough, corticosteroids will increase levels of triglycerides, total cholesterol, and very low-density lipoprotein cholesterol. However, most transplant programs will taper the corticosteroid dosage before the overall nutritional status of the patient has improved to the extent that dyslipidemia can develop. Early withdrawal of corticosteroids after transplant will have the most significant effect on lowering cholesterol levels, although graft function must be closely monitored to prevent graft loss. Again, cyclosporine and sirolimus can cause high levels of posttransplant hyperlipidemia, and their administration should be carefully monitored. Attempts at lipid control should first focus on dietary

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modification, weight loss, and diabetes control. If these methods are found to be ineffective, a lipid-lowering agent should be added to the medication regimen.

Obesity Approximately one out of five patients will develop posttransplant obesity within the first year after transplant, with an estimated average weight gain of 25% to 30%.⁴⁸ Excessive eating, high corticosteroid dosages, and adverse effects of calcineurin inhibitors all contribute to the condition. Before their procedures, most patients suffer from malnutrition and anorexia—a result of chronic liver disease. After transplant, they enjoy im-

proved liver function, which in turn rekindles long-forgotten appetites. Increased appetite, combined with the effects of the immunosuppressant medications, often results in significant weight gain. Close dietary monitoring and a supervised weight-loss and exercise program should be standard procedures for every patient.

Malignancies The relationship between immunosuppression and malignancy is well-known. Lymphoma, Kaposi's sarcoma, skin cancer, and colorectal cancers are seen at a much higher frequency in posttransplant patients than in the general population.⁴⁹ The most common malignancies to occur are those of the skin and lips.⁵⁰ Prophylaxis is essential; therefore the levels of immunosuppression should be kept as low as possible while still maintaining good function in the transplanted liver.⁵¹ In patients who have had kidney transplantation, immunosuppression can be abandoned and the patient returned to dialysis with consideration for possible retransplantation, but this luxury is not available to the liver transplant patient. In fact, immunosuppression is often increased to much higher levels in these patients in an effort to save the graft and life of the patient.

The incidence of *de novo* neoplasms after liver transplant is approximately 6%. Transplant recipients also have 20 times as much skin cancer as the general population; squamous cell carcinoma and melanoma are the lesions found most often in these patients. To lessen risk, OLT recipients should follow strict sun exposure precautions and have regular dermatologic checkups. More ominous neoplasms, such as the rare posttransplant lymphoproliferative disease (PTLD), can develop as well; this condition appears to be due to EBV and is usually treated with either a reduction or withdrawal of immunosuppressive drugs along with chemotherapy.⁵²

Renal complications A mild to severe reduction

in renal function, as demonstrated by decreased creatinine clearance, is common in OLT recipients before, during, or after transplant. Hepatorenal syndrome occurs before transplant and manifests as decreased urine sodium concentration, elevated BUN values, and rising creatinine levels despite normal hydration status. Seen in approximately 10% to 15% of adult patients, this syndrome is fortunately reversed with liver transplant and has not been associated with decreased long-term survival.⁵³ After transplant, adverse effects from cyclosporine or tacrolimus and progression of comorbid conditions such as DM, hypertension, and HCV glomerulonephritis can also significantly decrease renal function.

GI complications Postoperative intra-abdominal bleeding may result from an occult bleed originating from an anastomosis site, an undetected surgical injury, or as a form of diffuse oozing in split-liver transplants. If variceal bleeding occurs after transplantation, it is important to rule out PVT.⁵⁴ The technical difficulty added when freeing intra-abdominal adhesions from a previous surgery increases the risk of developing an intraoperative injury at the time of transplant.

Pulmonary complications Pneumonia is the second most common post-OLT infection,⁵⁵ with a

mortality rate that may be as high as 53%.⁵⁶ A delayed radiographic appearance attributable to high early immunosuppression, coupled with the frequent and expected right-sided pleural effusion and right lower lobe atelectasis, can often lead to a false-negative results from chest radiograph. Always consider chest CT when the radiograph findings are negative and clinical suspicion is high. A prolonged ICU stay and the need for mechanical ventilation are the biggest risk factors for posttransplant bacterial pneumonia in the first month. After discharge, the immunosuppressed liver recipient remains at increased risk not only for community-acquired pneumonia and respiratory viruses, but also for infection with opportunistic pathogens such as *Legionella* species and *Pneumocystis carinii*. The author's center uses a prophylactic regimen of trimethoprim/sulfamethoxazole, one single-strength tablet per day for 1 year. If the patient has an allergy to sulfa drugs, pentamidine, 300 mg, is administered via nebulizer monthly for 6 months.

Neurologic complications The anti-inflammatory effects of immunosuppressant agents can sometimes mask the signs and symptoms of meningitis and other posttransplant CNS infections. Give careful consideration to the patient with unexplained fever and

headache, a condition that warrants an immediate and thorough neurologic examination with a head imaging study using contrast and possible lumbar puncture. Although the majority of focal CNS lesions found in the first 30 days post-OLT are vascular in origin, up to 18% may have an infectious etiology. The most rarely seen, yet most lethal, are the brain abscesses, which have a mortality rate of 86% when diagnosed.⁵⁷

Brachial plexus and peroneal nerve impingement can occasionally occur as a result of positioning of the patient during surgery. Low magnesium levels accompanied by high cyclosporine levels have frequently been associated with seizures, which are usually effectively treated by reducing the cyclosporine level and administering magnesium infusions. Seizures or other neurologic symptoms may occasionally be seen with tacrolimus; these problems respond to a change to another immunosuppressant drug.

Recurrence of disease

Hepatitis C HCV reinfection is a nearly universal occurrence in liver transplant recipients.⁵⁸ In many instances, HCV RNA can be detected in the recipient's serum within days. Within 2 to 3 months, the RNA can rise to levels up to 100 times higher than before transplant.⁵⁹ At times HCV RNA may be seen in tissue biopsy, even in the absence of HCV serum antibodies. For this reason, the clinician should not rely entirely on serum antibody test results. All OLT recipients should also undergo liver biopsy when recurrent disease is suspected.

The severity of recurrent disease can be determined in several ways, such as by questioning the patient about alcohol consumption and ordering blood alcohol tests if needed, and by monitoring HCV genotype, frequency and severity of rejection episodes, and the pre-transplant viral load.⁶⁰ Although ACR usually occurs within the first 6 months, recurrence of HCV infection is typically seen in the intermediate to late posttransplant stages. When ACR is associated with an HCV patient, approximately 90% of the episodes of ACR occur in the first month, when the inflammatory changes of HCV infection are unlikely.

Viral and nonviral hepatitis Approximately 20% to 40% of patients who had a biopsy at least 12 months before transplantation had histologic features of nonviral chronic hepatitis.⁶¹ Factors that contribute to post-transplant chronic hepatitis include viral hepatitis (generally acquired hepatitis B or C), autoimmune disease (recurrent or acquired), or a drug reaction.⁶² When no evidence supports these factors, the possibility of "idiopathic" hepatitis still exists, although this disease is actually thought to represent a form of late modified rejection.⁶³

Conclusion

The number of liver transplants performed worldwide is increasing every year. This has resulted in a greater need for the primary care provider to help manage these challenging patients. Liver transplant complications cannot be totally prevented, but if the primary care provider knows how to avoid, identify, and treat these complications, liver transplant recipients will enjoy longer and more productive lives. □

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