SPECIAL ARTICLE

Long-Term Management of the Successful Adult Liver Transplant: 2012 Practice Guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation

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PREAMBLE

This practice guideline has been approved by the American Association for the Study of Liver Diseases and the American Society of Transplantation. These recommendations provide a data-supported approach to management of adult patients who have successfully undergone liver transplantation. They are based on the following: (1) a formal review and analysis of recently published world literature on the topic (via a MEDLINE search); (2) *A Manual for Assessing Health Practices and Designing Practice Guidelines* (American College of Physicians)[1]; (3) guideline policies,[2] including the American Association for the Study of Liver Diseases policy on the development and use of practice guidelines and the American Gastroenterological Association policy statement on guidelines[3]; and (4) the experience of the authors in the specified topic.

Intended for use by physicians and health care providers working with adult recipients of liver transplantation (LT), these recommendations suggest preferred approaches to the diagnostic, therapeutic, and preventive aspects of care. They are intended to be flexible, in contrast to standards of care, which are inflexible policies to be followed in every case. Specific recommendations are based on relevant published information.

Abbreviations: AIH, autoimmune hepatitis; ALD, alcoholic liver disease; BMD, bone mineral density; CKD, chronic kidney disease; CMV, cytomegalovirus; CNI, calcineurin inhibitor; CUC, chronic ulcerative colitis; DM, diabetes mellitus; EBV, Epstein-Barr virus; ESRD, end-stage renal disease; FDA, Food and Drug Administration; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HAART, highly active antiretroviral therapy; HbA1c, hemoglobin A1c; HBIG, hepatitis B immune globulin; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; LT, liver transplantation; mTOR, mammalian target of rapamycin; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NODM, new-onset diabetes mellitus; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; PTLD, posttransplant lymphoproliferative disorder; TB, tuberculosis.

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TABLE 1. GRADE

Strength of Recommendation	Criteria
1. Strong	Factors influencing the strength of the recommendation include the quality of the evidence, the presumed patient-important outcomes, and the cost.
2. Weak	There is variability in the preferences and values or more uncertainty. The recommendation is made with less certainty, or the cost or resource consumption is higher.
Quality of Evidence	**Criteria**
A. High	Further research is unlikely to change confidence in the estimate of the clinical effect.
B. Moderate	Further research may change confidence in the estimate of the clinical effect.
C. Low	Further research is very likely to affect confidence in the estimate of the clinical effect.

To more fully characterize the available evidence supporting the recommendations, the American Association for the Study of Liver Diseases Practice Guidelines Committee has adopted the classification used by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) workgroup with minor modifications (Table 1).[4] In the GRADE system, the strength of a recommendation is classified as (1) strong or (2) weak. The quality of evidence supporting a strong or weak recommendation is designated by 1 of 3 levels: (A) high, (B) moderate, or (C) low.

LT AS A TREATMENT FOR END-STAGE LIVER DISEASE

LT is the treatment of choice for patients with decompensated cirrhosis, acute liver failure, small hepatocellular carcinomas (HCCs), or acute liver failure. The success of LT has meant that there is a growing cohort of LT recipients throughout the world. From 1985 through 2011, approximately 100,000 persons in the United States underwent LT. On December 30, 2011, there were 30,000 LT recipients who were alive and had survived at least 5 years, and there were more than 16,000 recipients with 10 or more years' survival. These long-term survivors are at risk of early death and increased morbidity. The purpose of this guideline is to assist in the management of adult recipients of LT, identify the barriers to maintaining their health, and make recommendations on the ways to best prevent or ameliorate these barriers. This guideline focuses on management beyond the first 90 days after transplantation.

MORTALITY AFTER LT

The greatest proportion of deaths or retransplants after LT occur soon after transplantation. The causes of death and graft loss vary according to the interval from transplantation, with infection and intraoperative and perioperative causes accounting for nearly 60% of deaths and graft losses in the first posttransplant year. After the first year, death due to acute infections declines, whereas malignancies and cardiovascular causes account for a greater proportion of deaths. The recurrence of the pretransplant condition, especially hepatitis C virus (HCV) or autoimmune liver disease, is an increasingly important cause of graft loss the longer the patient survives transplantation for these etiologies. Today, death (or a need for retransplantation) attributable to acute or chronic allograft rejection is uncommon throughout the first 10 years after transplantation.

MORBIDITY AFTER LT

The transplanted liver becomes partially tolerant of immune-mediated injury, so the requirement for immunosuppression declines after the first 90 days. Although some LT recipients may eventually achieve operational tolerance (ie, maintenance without immunosuppressant medications), this is rare. Most patients receive immunosuppression throughout the life of the allograft.[5] The continued use of immunosuppression carries inevitable consequences: an increased risk of bacterial, viral, and fungal infections, which can be recurrent or newly acquired; metabolic complications such as hypertension, diabetes mellitus (DM), hyperlipidemia, obesity, and gout; and hepatobiliary or extrahepatic de novo cancers [including posttransplant lymphoproliferative disorder (PTLD)]. The combination of the complications of immunosuppression and the recurrence of the underlying liver disease translates into a heavy burden of ill heath for many LT recipients. An analysis of a longitudinal US database of 36,847 LT recipients indicated that the prevalence of kidney failure [defined as a glomerular filtration rate of 29 mL/minute/1.73 m^2 of body surface area or less or the development of end-stage renal disease (ESRD)] was 18% at 5 years and 25% at 10 years.[6] LT recipients have at-risk cardiovascular profiles with a high prevalence of hypertension requiring antihypertensive medications, recurrent DM and new-onset diabetes mellitus (NODM), and hyperlipidemia requiring lipid-lowering agents.

Cardiovascular disease and renal failure are the leading nonhepatic causes of morbidity and mortality late after LT (Table 2). The recurrence of the original disease, such as a chronic HCV infection, primary

TABLE 2. Prevalence of Cardiovascular Risk Factors and CKD in LT Recipients Beyond the First Posttransplant Year

	Prevalence Rate
Cardiovascular risk factor	
Metabolic syndrome*	50%-60%
Systemic hypertension	40%-85%
DM	10%-64%
Obesity	24%-64%
Dyslipidemia	40%-66%
Cigarette smoking	10%-40%
CKD (stage 3-4)†	30%-80%
End-stage kidney disease	5%-8%

*Any 3 of the following: hypertension, obesity, dyslipidemia, and DM.
†Estimated glomerular filtration rate = 15 to <60 mL/minute/1.73 m^2.

biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), autoimmune hepatitis (AIH), or HCC, can cause ongoing morbidity and mortality. Many of the patients undergoing LT have a past or present history of addictions, especially to alcohol, cigarettes, or both, which may also persist with harmful effects on patients' health, often by interacting with other risk factors already mentioned.

An assessment of the quality of life after LT has shown that although quality measures improve in LT patients in most domains in comparison with their status before transplantation, LT recipients continue to have many deficits in comparison with age-matched control populations; these are manifested as worsening physical symptoms, fatigue, and a greater sense of being unwell.[7]

Through the reduction of cardiovascular risks, the suppression or eradication of specific infections, improved surveillance for cancer, and the prevention or treatment of recurrent liver diseases, both the quantity and the quality of post-LT life can be improved. In these guidelines, we show how a concentrated effort to moderate immunosuppression, manage recurrent disease, and ameliorate metabolic complications of immunosuppression is required to convert short-term success into sustained success for an extended healthy life.

COMPLICATIONS OF PORTAL HYPERTENSION AFTER LT

Typically, clinical features of liver failure and portal hypertension resolve rapidly after LT, and they are not usual after the first 3 months. The exception is splenomegaly, which may persist for years. Variceal hemorrhage is very unusual unless the patient has an occluded portal vein. The late emergence of hepatic encephalopathy in a patient with a functioning liver allograft suggests the development of clandestine cirrhosis or a persistent portosystemic shunt. Late-onset ascites or peripheral edema may indicate stenosis of the inferior vena cava or portal vein anastomosis. Persistent late ascites in a patient with a recurrent HCV infection is a poor prognostic sign.

TABLE 3. Causes of Liver Test Abnormalities in the Asymptomatic Recipient

- Allograft parenchymal damage
  - Immune-mediated disease (rejection and de novo AIH)
  - Recurrent disease (HCV, HBV, PBC, PSC, AIH, and others)
  - Drug toxicity (including immunosuppressive drugs)
  - Alcohol and other toxins
  - De novo infection (including de novo HBV and HCV)
  - Space-occupying lesion (recurrent cancer)
  - De novo or recurrent NAFLD
- Biliary damage
  - Biliary strictures (anastomotic strictures, hepatic artery thrombosis or stenosis, and others)
  - Biliary stones/cast syndrome
  - Recurrent PSC
- Vascular disease
  - Hepatic artery thrombosis
  - Portal or hepatic vein thrombosis
- Metabolic disease in the allograft
  - Gilbert's syndrome
- Nonhepatic disease mimicking liver disease
  - Hemolysis causing raised indirect bilirubin levels
  - Bone disease causing raised alkaline phosphatase levels
- Nonhepatic disease causing liver abnormalities
  - Celiac disease
  - Diabetes

LIVER TESTS

Liver tests are routinely monitored after LT. When liver tests are elevated for a healthy recipient, the course of action will depend on the severity and type of abnormality (cholestatic, hepatitic, or other). Clinical challenges arise when liver tests are normal in the presence of graft damage or conversely abnormal in an asymptomatic LT recipient. The many causes of liver test abnormalities in the asymptomatic recipient are shown in Table 3. More than 1 cause may coexist in the same patient. When abnormal liver tests are recognized in a healthy, asymptomatic LT recipient, it is reasonable to repeat the tests in 1 to 2 weeks. A decision to investigate further should be based on the persistence and severity of the liver test abnormalities. Investigations should include a thorough history and examination, appropriate laboratory tests, and Doppler ultrasound of the liver. It should not be assumed without appropriate histological confirmation that abnormal liver tests represent immune-mediated damage.

Elevated alkaline phosphatase, total bilirubin, and aminotransferase levels may arise from the late appearance of biliary anastomotic strictures due to

TABLE 4. Major Drug-Drug Interactions Involving Immunosuppressive Agents

Antimicrobials	CNIs	mTOR Inhibitors	Mycophenolate
Fluoroquinolones (primarily ofloxacin > ciprofloxacin)	Increased levels		
Macrolides (erythromycin > clarithromycin > azithromycin)	Markedly increased levels	Markedly increased levels	
Rifamycins (rifampin > rifabutin)	Markedly decreased levels	Markedly decreased levels	
Linezolid		Increased myelosuppression	Increased myelosuppression and platelet decrease
Triazoles (ketoconazole/ voriconazole/posaconazole > itraconazole/fluconazole)	Increased levels	Increased levels (voriconazole contraindicated)	
Ganciclovir/valganciclovir		Increased myelosuppression	Increased myelosuppression

thrombosis or stenosis of the hepatic artery or to recurrent PSC or PBC. Appropriate biliary imaging includes endoscopic retrograde cholangiopancreatography, magnetic resonance cholangiopancreatography, and/or ultrasound. Biliary cast syndrome refers to a severe form of intrahepatic bile duct ischemic injury unique to post-LT patients,[8] and it is associated with hepatic artery thrombosis and the use of a split liver, including partial grafts derived from living donors and, more commonly, from donation after cardiac death donors. Biliary cast syndrome may resolve with repeated clearance of bile duct debris either percutaneously or endoscopically.

Recommendations

1. The frequency of monitoring with liver tests should be individualized by the transplant center according to the time from LT, the complications from LT, the stability of serial test results, and the underlying cause (grade 1, level A).
2. Depending on the pattern of liver tests, magnetic resonance imaging, computed tomography, endoscopic retrograde cholangiopancreatography, and sonography may be appropriate (grade 1, level A).
3. Liver histology should be obtained when parenchymal injury is suspected as the cause of abnormal liver tests (grade 1, level A).

VASCULAR THROMBOSIS

Hepatic artery thrombosis (HAT) or stenosis may present clinically after 3 months, as :

- intrahepatic non-anastomotic strictures and/or sterile or infected fluid collections within the liver, sometimes referred to as bilomas,
- ischemic cholangiopathy or
- biliary cast syndrome.

The combination of hepatic artery thrombosis and biliary complications usually requires retransplantation.[9]

Recommendations

4. Bilomas and biliary cast syndrome should be managed in a center with expertise in LT medicine, radiology, and biliary endoscopy (grade 1, level A).
5. Hepatic artery thrombosis or stenosis is most readily assessed initially by Doppler ultrasound, but angiography is usually required to confirm the diagnosis and plan therapy (grade 1, level B).

IMMUNOSUPPRESSION

The choice of immunosuppression depends on the following:

- Indication for transplantation: the choice of immunosuppression may affect disease recurrence (eg, HCV, malignancy, or autoimmune disease).
- Comorbidities.
- Drug side effects: calcineurin inhibitors (CNIs) may cause renal impairment.
- Likelihood of pregnancy: mycophenolate and mammalian target of rapamycin (mTOR) inhibitors such as sirolimus are potential teratogens.
- History of severe or recurrent rejection.
- Prior experience with the various immunosuppressive agents.
- History of or risk for cancers.
- History of or risk for infections.

There is no reliable marker for determining the effective level of immunosuppression; therefore, the choice of the agent (or agents) and doses given will be determined by the clinical, laboratory, and histological response. The CNI dose is generally determined by the drug level; the target levels after 3 months are 5 to 10 ng/mL for tacrolimus and 100 to 150 ng/mL for cyclosporine (both are whole blood trough levels). The target whole blood trough level for sirolimus is 5 ng/mL. The need for therapeutic drug monitoring for mycophenolate is uncertain. Table 4 describes drug-

TABLE 5. Unwanted Side Effects of Immunosuppressives

Side Effect	Corticosteroids	CNIs	mTOR Inhibitors	Mycophenolate Mofetil
Kidney injury	−	+++	+ (proteinuria)	−
Bone disease	+++	−	−	−
Gastrointestinal	+/−	−	−	+
Bone marrow suppression	−	−	−	+
Pulmonary fibrosis	−	−	+	−
Hypercholesterolemia	+	+	+++	−
Diabetes	++	+ (tacrolimus)	−	−
Hypertension	+	++	+	−

drug interactions involving the commonly used immunosuppressant medications. Common side effects of immunosuppressants are presented in Table 5.

The majority of LT recipients need lifelong immunosuppression to maintain graft function. A very small number of LT recipients develop operational tolerance to the allograft and do not require long-term immunosuppression.[5]

LATE REJECTION

Late rejection is defined as rejection that has its onset more than 90 days after transplantation. Traditionally, 2 forms have been recognized: cellular rejection (also known as acute cellular rejection and late-onset rejection) and ductopenic rejection (also known as vanishing bile duct syndrome). Both forms of rejection are, until the late stages, asymptomatic, and the diagnosis is made through the investigation of abnormal liver tests; the diagnosis can be confirmed only on the basis of histology. For both cellular rejection and ductopenic rejection, the Banff criteria have been adopted to define the nature and severity.[10] Liver tests in patients with late-onset cellular rejection show nonspecific abnormalities with a rise in serum bilirubin and aminotransferases. Histologically, cellular rejection is characterized by the triad of inflammatory bile duct damage, subendothelial inflammation of the portal, central, or perivenular veins, and a predominantly lymphocytic portal inflammatory infiltrate with neutrophils and eosinophils in addition. The focus of inflammation may be portal, central, or both, but the central component is more prominent and frequently occurs as pure centrilobular necroinflammation (isolated central perivenulitis). Late acute rejection differs from early acute cellular rejection by having fewer classic histological features.

Risk factors leading to late-onset cellular rejection include the following:

- Reduction of immunosuppression (whether iatrogenic or due to noncompliance).
- Pre-LT autoimmune liver disease.
- Concurrent administration of interferon (for HCV treatment).

The differential diagnosis includes infection, recurrent and de novo autoimmune disease, and drug toxicity; it may sometimes be difficult to distinguish cellular rejection from HCV infection, and indeed, the two often coexist.

In mild cases of cellular rejection, an increase in maintenance levels of immunosuppression may be sufficient, whereas in histologically moderate or severe cases, the treatment should be a short course of increased immunosuppression (eg, methyl prednisone at 500 mg/day or prednisolone at 200 mg/day for 3 days) followed by an increase in the baseline immunosuppression. A full response (defined as a return to normal liver tests) is seen in only approximately half of patients, with approximately 25% developing a further episode of cellular rejection and 25% developing ductopenic rejection.

Ductopenic rejection is seen most commonly in the first year but may occur at any time. Recent data suggest that humoral alloreactivity mediated by antibodies against donor human leukocyte antigen (HLA) molecules, acting in concert with cellular mechanisms, may play a role in the development of ductopenia (a process known as antibody-mediated rejection).[11] The onset of ductopenia is usually insidious, with a progressive rise in liver tests with a cholestatic picture (a rise in alkaline phosphatase and gamma-glutamyl transpeptidase followed by a progressive rise in serum bilirubin). In late cases, the recipient may complain of pruritus and jaundice. A liver biopsy sample with at least 10 portal tracts is advisable in order to establish with confidence that injury to and loss of bile ducts have occurred. In the early stages of ductopenic rejection, there may be a cellular infiltrate, but more commonly, the characteristic features include the progressive loss of bile ducts from the portal tracts and cholestasis; in late stages, foamy macrophages may be seen.

Risk factors for ductopenic rejection include the following:

- Recurrent and unresponsive cellular rejection.
- Transplantation for autoimmune disease.
- Exposure to interferon.
- Loss of a previous graft to ductopenic rejection.

The differential diagnosis includes recurrent disease (PBC or PSC) and drug toxicity.

The treatment of ductopenic rejection is increased immunosuppression, and an increase in or switch to tacrolimus may be effective in some early cases.

Conversely, especially when fewer than 50% of the portal tracts contain bile ducts, the condition progresses to graft failure.

Recommendations

6. Immunosuppressive drugs for LT recipients should be prescribed and monitored only by those with knowledge and expertise in that area. The choice of agents will depend on many factors, and no one regimen can be recommended for any patient (grade 2, level A).
7. Every patient's immunosuppressive regimen should be reviewed at least every 6 months and modified as required with the goal of minimizing long-term toxicities (grade 1, level B).
8. Rejection can be reliably diagnosed only on the basis of liver histology; a biopsy sample should be taken before treatment initiation and classified according to the Banff criteria (grade 1, level A).
9. Although the long-term withdrawal of all immunosuppression can be achieved in a small number of patients, this should be undertaken only with select recipients and under close supervision (grade 2, level C).

PROMOTING HEALTH AFTER LT

Recommendations

10. Frequent handwashing reduces the risk of infection with pathogens acquired by direct contact, including *Clostridium difficile*, community-acquired viral infections, and pathogens found in soil (grade 1, level A).
11. Shoes, socks, long-sleeve shirts, and long pants should be worn for activities that will involve soil exposure and tick exposure and also to avoid unnecessary sun exposure (grade 1, level A).
12. During periods of maximal immunosuppression, LT recipients should avoid crowds to minimize exposures to respiratory illnesses (grade 1, level A).
13. Work in high-risk areas, such as construction, animal care settings, gardening, landscaping, and farming, should be reviewed with the transplant team to develop appropriate strategies for the prevention of high-risk exposures (grade 2, level A).
14. LT recipients should avoid the consumption of water from lakes and rivers (grade 1, level A).
15. LT recipients should avoid unpasteurized milk products and raw and undercooked eggs and meats (particularly uncooked pork, poultry, fish, and seafood; grade 1, level A).
16. LT recipients should avoid high-risk pets, which include rodents, reptiles, chicks, ducklings, and birds (grade 1, level A).
17. Travel by LT recipients, especially to developing countries, should be reviewed with the transplant team a minimum of 2 months before departure to determine optimal strategies for the reduction of travel-related risks (grade 1, level A).
18. LT recipients should take precautions to prevent vector (including mosquito) -borne diseases. These include avoiding going out during peak mosquito feeding times (dawn and dusk) and using *N,N*-diethyl-*meta*-toluamide–containing insect repellants (grade 1, level A).
19. LT recipients should undertake a thorough review of hobbies to assess potential infectious disease risks, particularly those associated with outdoor hobbies (grade 2, level A).
20. All LT recipients should be educated about the importance of sun avoidance and sun protection through the use of a sun block with a sun protection factor of at least 15 and protective clothing. They should be encouraged to examine their skin on a regular basis and report any suspicious or concerning lesions to their physicians (grade 1, level A).
21. Because of the strong association of lung, head, and neck cancers with smoking, the sustained cessation of smoking is the most important preventative intervention (grade 1, level A).
22. For female LT recipients of a child-bearing age, preconception counseling about contraception and the risks and outcomes of pregnancy should start in the pretransplant period and should be reinforced after transplantation (grade 1, level A).

BONE HEALTH

Bone loss and fracturing are seen with 2 distinct phases after LT. In the first 4 postoperative months, there is accelerated bone loss in almost all liver recipients, regardless of the pretransplant bone mineral density (BMD), that is consistent with the effects of corticosteroids and possibly CNIs.[12] After the first 4 postoperative months with normal allograft function, bone metabolism improves, and in the osteopenic patient, there will be a gain in bone mass over the next postoperative years with a gradual reduction in the incidence of fractures.[12,13] In patients with preexisting osteopenia or pretransplant fracturing, this early, rapid bone loss results in a high susceptibility to fracturing, mainly at sites of trabecular bone (vertebrae and ribs), especially in the first year after LT, but there is a smaller but steady cumulative increase in fracturing.

Table 6 outlines the evaluation of the metabolic bone status of LT recipients with osteopenia. In the early years after LT, BMD should be measured annually in osteopenic patients and every 2 to 3 years in patients with normal BMD. Later screening depends on risk factors.

In order to diminish factors that promote bone loss, glucocorticoids should be reduced or discontinued as soon as possible after LT. Calcium supplements are

TABLE 6. Evaluation of the Metabolic Bone Status of the LT Recipient With Osteopenia

Assessment of bone pain or fractures
Dietary intake of protein and calcium
Serum calcium, phosphorus, and parathormone levels
25-hydroxyvitamin D level
24-hour urinary calcium (200-300 mg/day)*
Gonadal status: free testosterone (males) or menopausal status (females)
Thyroid function
BMD: lumbar spine and hips
Spinal radiographs (thoracolumbar)

*If it is necessary to confirm a positive calcium balance.

recommended for all LT recipients with (or at risk of) osteopenia, and all patients should receive 1000 to 1200 mg of elemental calcium daily to optimize bone remodeling and mineralization. Vitamin D levels should be maintained at a serum level of at least 30 ng/mL, and most LT patients will require supplementation (generally 400-1000 IU/day). The serum levels of 25-hydroxyvitamin D must be checked to assess the adequacy of replacement, even with supplementation, and should be rechecked annually or more frequently if a deficiency is diagnosed. Many issues with regard to bisphosphonate therapy for LT recipients remain to be defined: the optimal duration of therapy, the optimal doses of bisphosphonates, whether oral or intravenous therapy is better, and the LT population most likely to benefit. Despite these caveats, we suggest that bisphosphonate therapy should be considered in the following circumstances:

- T-score less than −2.5 or atraumatic fractures.
- T-score between −1.5 and −2.5 and other risk factors.

Oral alendronate at 70 mg weekly is an appropriate starting point, although other oral agents may, however, be equally efficacious. If oral therapy is not tolerated, intravenous zolendronic acid or ibandronate can be used. The optimal duration of therapy is unknown, although oral alendronate has been given with good effect for 10 years for postmenopausal osteoporosis. Hormone replacement therapy is an alternative in postmenopausal women.

Recommendations

23. In the first 5 years after transplantation, screening by BMD should be done yearly for osteopenic patients and every 2 to 3 years for patients with normal BMD; thereafter, screening depends on the progression of BMD and on risk factors (grade 2, level B).
24. If osteopenic bone disease is confirmed or if atraumatic fractures are present, then patients should be assessed for risk factors for bone loss; in particular, this should include an assessment of calcium intake and 25-hydroxyvitamin D levels, an evaluation of gonadal and thyroid function, a full medication history, and thoracolumbar radiography (grade 1, level A).
25. The osteopenic LT recipient should perform regular weight-bearing exercise and receive calcium and vitamin D supplements (grade 1, level A).
26. Bisphosphonate therapy should be considered in LT recipients with osteoporosis or recent fractures (grade 1, level A).

SYSTEMIC DISEASE

Kidney Disease

The majority of LT recipients who survive the first 6 months develop chronic kidney disease (CKD).[6] Predialysis CKD prevalence rates in this population range from 30% to 80%. The wide range of reported incidences is partly due to the different thresholds used to define CKD and the various durations of posttransplant observation. The cumulative risk of ESRD that requires maintenance dialysis therapy or kidney transplantation is 5% to 8% during the first 10 years after LT.[6,14,15] Furthermore, 1.0% of all kidney transplants currently in the United States are undertaken for LT recipients who subsequently developed ESRD.[16]

The etiology of CKD in the LT population is multifactorial (Table 2) and includes chronic exposure to CNIs, hypertension, DM, obesity, atherosclerosis, hyperlipidemia, chronic HCV infection, pretransplant renal dysfunction, and perioperative acute kidney injury. CKD is associated with a 4.48 relative risk of death more than 1 year after LT in comparison with recipients without CKD.[6,17]

A serum creatinine elevation is a late and insensitive indicator of CKD in this population. An estimating equation that has been shown to have reasonable precision should be routinely used. Both the 4-variable Modification of Diet in Renal Disease equation and the Chronic Kidney Disease Epidemiology Collaboration formula are superior to serum creatinine alone and 24-hour urinary creatinine clearance in estimating renal function.[18,19] Increased proteinuria (spot protein-to-creatinine ratio > 0.3) may be absent even in the presence of advanced CKD because of the antiproteinuric effect of CNIs. Proteinuria is best assessed by the measurement of the concentration ratio of protein to creatinine in a spot urine specimen.[20]

Aggressive blood pressure control and the use of agents that block the renin-angiotensin-aldosterone system are key foundations of CKD treatment in the nontransplant population and would be expected to have beneficial effects in LT recipients. A reduction in the dosage or a complete withdrawal of CNIs several months to years after LT is a common practice aimed at ameliorating the progression of CKD. These renal-sparing maintenance protocols typically rely on

TABLE 7. Factors Associated With the Clinical Features of Metabolic Syndrome

Factor	Corticosteroids	Tacrolimus	Cyclosporine	Sirolimus	Chronic HCV
Abdominal obesity	+	−	−	−	−
Dyslipidemia	+	+	+	+++	−
Systemic hypertension	+	++	++	+	−
Insulin-resistant DM	+++	++	+	−	++

sirolimus or everolimus, often in combination with mycophenolate, to prevent acute rejection; others use steroids and mycophenolate or azathioprine.[21-24] Renal function is more likely to be preserved if CNI withdrawal is instituted when the estimated glomerular filtration rate is between 40 and 50 mL/minute/1.73 m^2.[25] LT recipients with ESRD who subsequently receive a living or deceased kidney transplant have a 44% to 60% reduction in long-term mortality in comparison with their dialysis-treated counterparts.[26,27]

Recommendations

27. Monitoring of renal function in LT recipients for the detection and management of CKD should use an estimating equation to evaluate the glomerular filtration rate (grade 1, level B).
28. Urinary protein quantification using the concentration ratio of protein to creatinine in a spot urine specimen should be evaluated at least once yearly (grade 1, level B).
29. The reduction or withdrawal of CNI-associated immunosuppression is an appropriate response to the development of CKD in LT recipients (grade 1, level A).
30. Kidney transplantation from deceased or living donors is beneficial in improving survival and should be considered the optimal therapy for LT recipients who develop ESRD (grade 1, level A).

Metabolic Syndrome

The clinical features of metabolic syndrome, either alone or in combination, contribute to post-LT morbidity and mortality. The clinical factors related to LT that exacerbate metabolic syndrome are shown in Table 7.

DM

The spectrum of hyperglycemia after LT includes preexisting DM and NODM, some of which is transient in the perioperative period. Insulin-requiring DM that is present at the time of transplantation virtually always persists after LT, and many patients on oral hypoglycemic agents need a conversion to insulin early after LT. In LT recipients followed beyond 1 year, estimates of the prevalence of NODM vary from 5% to 26%. Diabetogenic factors after LT include corticosteroids, CNIs (tacrolimus more than cyclosporine), HCV infection, and metabolic syndrome.[28-33] NODM tends to remit over time, especially as corticosteroids are withdrawn and the tacrolimus dosage is reduced, and patients may go from insulin therapy to oral hypoglycemic agents to diet control only over the years.

Because stringent glycemic control significantly reduces morbidity and mortality in diabetic patients, it seems reasonable to assume that LT recipients would similarly benefit. The goals of the long-term management of diabetes after LT are not substantially different from the goals for nontransplant patients (Table 8). There is controversy regarding the appropriate target level of hemoglobin A1c (HbA1c), and consequently, our recommendation of a threshold of <7.0% rather than <6.0% reflects the view that the more demanding standard may confer no additional advantage. When insulin requirements are low, oral agents may be substituted if allograft function is normal. Metformin or a sulfonylurea may be used in LT recipients with normal renal function, whereas sulfonylureas such as glipizide and glimepiride are preferable if there is any deterioration in renal function. The safety of thiazolidinediones in LT recipients is unproven. Retrospective data sets and a small prospective study suggest that the conversion of immunosuppression from tacrolimus to cyclosporine improves glycemic control in patients with established DM and NODM.[33]

Recommendations

31. The treatment of DM after LT should aim for an HBA1c target goal of <7.0% with a combination of lifestyle modifications and pharmacological agents as appropriate (grade 1, level B).
32. When high-dose corticosteroids are administered, insulin therapy is the most effective and safest agent with which to control hyperglycemia; however, as the interval from LT extends, patients with NODM may experience a decline in insulin requirements, and oral hypoglycemic agents may be appropriate if allograft function is normal (grade 1, level C).
33. Metformin or sulfonylureas may be used in LT recipients with normal renal function, whereas sulfonylureas such as glipizide and glimepiride are preferable if there is any deterioration of renal function (grade 1, level C).
34. Consideration can be given to the conversion of immunosuppression from tacrolimus to cyclosporine in LT recipients with poor glycemic control (grade 2, level B).

TABLE 8. Long-Term Management of DM (New-Onset or Preexisting) After LT

	Intervention	Frequency
Diagnosis	Fasting plasma glucose	Every 3 months in the first year and then annually
Monitoring	Self-monitoring of blood glucose	Review every 3 months
	HbA1c	Every 3 months (intervention at ≥7.0%*)
	Diabetic complications	Annual screening (retinopathy)
	Microalbuminuria	Annual screening
	Tailoring of immunosuppression (especially if there is poor control): discontinuation of steroids and change from tacrolimus to cyclosporine	
	Lipid levels	Annual evaluation
Treatment	For all patients	
	Dietary and lifestyle modification: exercise and weight loss (if the patient is obese)	
	Control of hypertension and dyslipidemia	
	Depending on glycemic control	
	Insulin†	
	Oral agent or agents	
	Insulin ± oral agent (if there is poor control)	

*This should be interpreted with care for patients with anemia or renal impairment.
†Refer patients to an endocrinologist once insulin is started.

Hypertension

Hypertension in LT recipients increases the risk of fatal and nonfatal cardiovascular disease events and CKD.[15] Although there are no clinical trials of antihypertensive therapy in LT recipients, it is prudent to target a blood pressure treatment goal of 130/80 mm Hg in LT recipients with systemic hypertension.[34]

For the management of hypertensive LT recipients, immunosuppression leading to hypertension, such as CNIs and corticosteroids, should be minimized under the direction of the transplant center.[35] Lifestyle modifications, including weight loss in overweight recipients (see the discussion on obesity) and the restriction of dietary salt intake, are appropriate nonpharmacological interventions.[34] Home measurement of blood pressure is encouraged. If lifestyle modification and a reduction of immunosuppression do not achieve the target blood pressure goal, antihypertensive medications should be introduced. Calcium channel blockers such as amlodipine and nifedipine may be more effective in LT recipients because they counteract the vasoconstrictive effect of CNIs.[36] The non-dihydropyridine calcium channel blockers (verapamil and diltiazem) should be used with caution because they may increase the bioavailability of CNIs significantly. Beta-blockers are equally as effective as calcium channel blockers in the treatment of hypertension among LT recipients.[36] Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and direct renin inhibitors should be used as first-line antihypertensive therapy in LT recipients with DM, CKD, and/or significant proteinuria. Monitoring of potassium levels is necessary when these drugs are used in conjunction with CNIs (particularly tacrolimus). Because of the increased risk of electrolyte abnormalities, thiazide or loop diuretics should be used with caution. The combination of diuretics with other classes of antihypertensive medication may be particularly effective in some LT recipients because diuretics tend to mitigate the volume retention associated with CNIs and/or advanced CKD that commonly coexists in hypertensive LT recipients.

Recommendations

35. The treatment of hypertension should aim for a target goal of 130/80 mm Hg with a combination of lifestyle modifications and pharmacological agents as appropriate (grade 1, level A).
36. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and direct renin inhibitors should be used as first-line antihypertensive therapy in LT recipients with DM, CKD, and/or significant proteinuria (grade 1, level A).

Hyperlipidemia

Dyslipidemia occurs in up to 70% of LT recipients (a prevalence much higher than that before transplantation) and is a major risk factor for cardiovascular morbidity and mortality (Table 2).[37,38] Although age, body weight, and genetics have some influence, medications—especially CNIs, mTOR inhibitors, and glucocorticoids—are the major influences on the high prevalence of dyslipidemia in LT recipients. Furthermore, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors and CNIs share metabolic pathways and have significant drug-drug interactions (Table 4). The

TABLE 9. General Plan for the Stepwise Management of Dyslipidemia

Elevated low-density lipoprotein cholesterol level > 100 mg/dL (with or without elevated triglycerides)
1. Therapeutic lifestyle and dietary changes
2. Statins
3. Addition of ezetimibe
Hypertriglyceridemia with normal cholesterol
1. Fish oil at 1000 mg twice daily to 4 g daily if tolerated
2. Fibric acid derivatives
Refractory hyperlipidemia: consider changes in immunosuppression
1. Conversion of cyclosporine to tacrolimus
2. CNI reduction (eg, add mycophenolate mofetil)
3. Discontinuation of sirolimus

measurement of blood lipids after a 14-hour fast is recommended annually for healthy LT recipients. Table 9 shows a plan for the stepwise treatment of dyslipidemia after LT.

Recommendations

37. The measurement of blood lipids after a 14-hour fast is recommended annually for healthy LT recipients. An elevated low-density lipoprotein cholesterol level > 100 mg/dL, with or without hypertriglyceridemia, requires therapy. If therapeutic lifestyle and dietary changes are not enough, statin therapy should be introduced. Suboptimal control with statins can be improved by the addition of ezetimibe (grade 2, level B).
38. Isolated hypertriglyceridemia is first treated with omega-3 fatty acids (up to 4 g daily if tolerated). If this is not sufficient for control, gemfibrozil or fenofibrate can be added, although patients must be followed carefully for side effects, especially with the concomitant use of statins and CNIs (grade 2, level C).

NUTRITION AND OBESITY (BODY MASS INDEX > 30 kg/m^2)

Weight accumulation is common after LT. In American and European cohorts, approximately 20% of lean patients become obese (body mass index > 30 kg/m^2) in the first 2 to 3 years after LT; this phenomenon is driven by the restoration of health and the stimulation of appetite by medicines such as corticosteroids.[39,40]

Recommendations

39. All LT patients require ongoing dietary counseling to avoid obesity (grade 1, level C).
40. Among LT recipients who become severely or morbidly obese and fail behavioral weight-loss programs, bariatric surgery may be considered, although the optimal procedure and its timing with respect to transplantation remain to be defined (grade 1, level C).

TABLE 10. Relative Risks of De Novo Malignancies in LT Recipients Versus a Sex- and Age-Matched Population

Malignancy	Relative Risk
Skin cancers	
Squamous and basal cell carcinoma	20%-70%
Melanoma	2%-5% (estimate)
Lymphoma	10%-30%
Oropharyngeal cancer, including esophageal cancer	3%-14% (as high as 25% if the prior diagnosis was alcoholic cirrhosis)
Lung cancer	1.7%-2.5%
Colorectal cancer	25%-30% if ulcerative colitis is present
Kidney cancer	5%-30%

ONCOLOGY

De Novo Cancer

The incidence of de novo cancer is higher among LT recipients versus an age- and sex-matched nontransplant control population[41] (Table 10). The cumulative incidence of de novo cancer after LT increases from 3% to 5% at 1 to 3 years to 11% to 20% at 10 years after LT.[42,43] Cutaneous malignancies are the most common form of malignancy in recipients of solid organ transplants, but cigarette smokers are at increased risk of developing lung cancer and oropharyngeal cancer, and the rate of colon cancer is increased in patients undergoing transplantation for PSC because of the comorbid risk from inflammatory bowel disease.[42-45] The oncogenic risk due to viral infections [eg, Epstein-Barr virus (EBV) leading to PTLD] is discussed in the section on viral infections. The American Cancer Society guideline on screening for cervical cancer recommends that women who are immunosuppressed on account of solid organ transplantation "may need to be screened more often (than every 3 to 5 years). They should follow the recommendations of their healthcare team."[46] Careful prospective surveillance accompanied by lifestyle modifications to protect the skin and to quit smoking improves outcomes for LT recipients.[43,44]

Recurrent or Persistent Cancer

The proportion of patients undergoing LT for HCC has increased significantly in the past decade. Rates of recurrence at 4 years are 10% for patients with tumors within the Milan criteria and 40% to 60% for patients with tumors outside the Milan criteria.[47] Tumor recurrence reduces long-term survival after LT

for HCC. Accumulating data suggest that once postoperative healing is complete, the substitution of sirolimus for a CNI reduces the risk of recurrence of HCC.[48]

Guidelines for surveillance after LT, including the choice of the surveillance method, the intervals between surveillance tests, and the duration of surveillance, have not been established for patients undergoing transplantation for known HCC or for patients with incidental HCC found in the explanted liver.[47] A reasonable plan is for the patient to undergo abdominal and chest computed tomography every 6 months for 3 years after LT. The serial measurement of alpha-fetoprotein is a useful adjunct for patients who had an elevated alpha-fetoprotein level before transplantation or ablation therapy. Any suspicious lesion discovered on surveillance should be characterized fully, and biopsy should be included when the diagnosis is in doubt. Ablation with radiofrequency is the best treatment for small solitary recurrences.

Recommendations

41. All LT recipients should see a dermatologist after transplantation to assess cutaneous lesions, with at least an annual evaluation by a dermatologist 5 years or more after transplantation (grade 1, level A).
42. Patients with PSC and inflammatory bowel disease or other established risk factors for colorectal cancer should undergo an annual screening colonoscopy with biopsies. Colectomy, including continence-preserving pouch operations, should be considered when colonic biopsy reveals moderate or severe dysplasia (grade 1, level B).
43. For patients without prior HCC who develop recurrent cirrhosis of the allograft, surveillance for de novo HCC should be undertaken with abdominal imaging every 6 to 12 months (grade 1, level A).
44. An immunosuppressant regimen that includes sirolimus (started several weeks after transplantation) should be considered for patients undergoing transplantation for HCC (grade 2, level B).
45. Resection or ablation is usually the treatment of choice for a solitary extrahepatic metastasis or an intrahepatic recurrence of HCC (grade 1, level B).

REPRODUCTIVE HEALTH

Menstruation and probably fertility return by 10 months in 90% of premenopausal females after successful LT and in some patients as early as 1 to 2 months.[49-51] Free testosterone levels increase in males after LT, but the recovery of male gonadal function is often incomplete. LT has limited efficacy for curing pretransplant sexual dysfunction in either men or women.[52] Sildenafil is beneficial and well tolerated by male LT recipients with erectile dysfunction.[53]

TABLE 11. FDA Safety Categories for Drugs Used During Pregnancy

A. Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of risk in later trimesters), and the possibility of fetal harm appears remote.
B. Animal reproduction studies have not demonstrated fetal risk, but there are no controlled studies in pregnant women, OR animal studies have shown an adverse effect that has not been confirmed in controlled studies in women in the first trimester.
C. Animal studies have revealed adverse effects on the fetus, and there are no controlled studies in women, OR studies in women and animals are not available. Give the drug only if the potential benefit justifies the risk.
D. There is positive evidence of human fetal risk, but benefits from use in pregnant women may be acceptable despite the risk.
X. A definitive fetal risk exists, and the drug is contraindicated in women who are or may become pregnant.

Pregnancy in the LT recipient has risks to both the mother and the fetus.[51,54] Although the numbers of pregnancies reported are relatively small, pregnancies completing the first trimester successfully generally proceed to a live birth, although there is a higher incidence of prematurity (29%-50%) and low birth weight (17%-57%).[51,54] Neonatal deaths or birth defects are not more frequent in comparison with the general population (except when the mother is on mTOR inhibitors).[55,56] The maternal risks include hypertension and pre-eclampsia, which occur more commonly in comparison with the general population.[57] Maternal deaths following pregnancy in LT recipients are rare and occur at a rate similar to that in the general population. The National Transplant Pregnancy Registry guidelines[51] recommend the female LT recipients postpone conception until

- At least 1 year after LT.
- Allograft function is stable.
- Medical comorbidities such as diabetes and hypertension are well controlled.
- Immunosuppression is at a low maintenance level.

The choice of immunosuppression should be made before conception. All immunosuppressive drugs cross the placenta and enter the fetal circulation with resulting concerns about teratogenicity and fetal loss. Table 11 shows the Food and Drug Administration (FDA) safety categories for drugs in pregnancy. Generally, CNIs (class C drugs), prednisone (class B), and azathioprine (class D) appear to be safe.[54] The newer agents should be avoided if possible; in the National Transplant Pregnancy Registry,[51] more structural abnormalities have been seen in babies born to

mothers on mTOR inhibitors or mycophenolic acid, especially when they are used in early pregnancy.[55,56] European guidelines for renal recipients advise discontinuing mTOR inhibitors at least 6 weeks before conception.[58]

An early diagnosis of pregnancy is desirable to maximize positive pregnancy outcomes. Immunosuppression should be maintained during pregnancy to avoid rejection, and drug levels of CNIs should be monitored with dose adjustments for the increasing blood volume during the second half of pregnancy.[59] Allograft function and CNI serum levels should be monitored frequently until delivery. Screening the mother for urinary tract infections, the presence of cytomegalovirus (CMV) and toxoplasmosis, hypertension, gestational diabetes, and pre-eclampsia, along with serial assessments of fetal growth, is mandatory.

Allograft dysfunction during pregnancy warrants appropriate investigation, including liver biopsy in selected patients, to assess for rejection. The pregnant patient with acute cellular rejection is treated in the same manner as the nonpregnant patient. There are no contraindications to vaginal delivery.

Allograft function and drug levels should be checked weekly for at least 1 month after birth or until the patient is stable, especially if adjustments were made during the pregnancy or allograft dysfunction arose late in the pregnancy. Although the known benefits of breast feeding probably outweigh the theoretical risks, no definitive recommendations regarding breast feeding can be made. Low levels of immunosuppressive drugs may be found in breast milk. Contraception with whatever method is favored by the LT recipient should start before sexual activity is resumed.

Recommendations

46. Pregnancy in an LT recipient should be managed by a high-risk obstetrician in coordination with the transplant hepatologist (grade 1, level C).
47. Pregnancy should be delayed for 1 year after LT and occur at a time with good, stable allograft function, with maintenance immunosuppression, and with good control of any medical complications such as hypertension and diabetes (grade 1, level B).
48. The ideal immunosuppression for pregnancy is tacrolimus monotherapy, which should be maintained at therapeutic levels throughout pregnancy; cyclosporine, azathioprine, and prednisone may also be used if they are necessary (grade 1, level B).
49. Allograft function and CNI serum levels are monitored every 4 weeks until 32 weeks, then every 2 weeks, and then weekly until delivery (grade 1, level B).
50. Contraception should begin before the resumption of sexual activity, although no particular form of contraception can be recommended over another (grade 2, level B).

INFECTIOUS DISEASE

General Overview

The interval from the third to sixth month after LT is a high-risk period because of the occurrence of infections with opportunistic pathogens: herpes viruses (especially CMV, herpes zoster and simplex, and EBV), fungi (including *Aspergillus* and *Cryptococcus*), and unusual bacterial infections such as *Nocardia*, *Listeria*, and mycobacteria. The implementation of prophylactic antimicrobials, the avoidance of high-risk exposures, and the minimization of immunosuppression may reduce the occurrence of these pathogens.[60] After the sixth posttransplant month, the risk of infection is lower, and this is related to the reduction of immunosuppression. From 3 to 24 months after LT, in the standard-risk LT recipient (ie, no augmented immunosuppression or specific environmental exposures), the most common infections are intra-abdominal or in the lower respiratory tract or infections by community-acquired pathogens such as enteric gram-negative infections, *Streptococcus pneumonia*, and respiratory viruses.[60] Rare infections related to immunosuppression, such as the reactivation of John Cunningham polyomavirus resulting in progressive multifocal leukoencephalopathy, are not reviewed here. Table 12 shows an outline of prophylactic strategies for countering common organisms that affect LT recipients. Table 4 outlines the drug-drug interactions involving anti-infectives and immunosuppressive agents.

Recommendations

51. An assessment for infections following LT should take into account the intensity of immunosuppression, the timing of the presentation, the environmental and donor exposures, the recipient's history of both symptomatic and latent infections, and the utilization of prophylactic antimicrobials and immunizations (grade 1, level A).
52. Attention should be paid to potential drug interactions when new antimicrobial therapies are initiated (grade 1, level A).

CMV

CMV remains the most significant opportunistic pathogen affecting LT recipients and produces diverse clinical manifestations and significant morbidity and mortality.[61,62] The most common clinical syndromes include viremia, bone marrow suppression, and involvement of the gastrointestinal tract and liver.

Risk factors for CMV[61,62] include the following:

- CMV-seropositive donor organ (especially in the absence of prior immunity, ie, a CMV-seronegative recipient).

TABLE 12. Prophylactic Strategies for Common Organisms That Affect LT Recipients

Organism	Agent/Dosage	Duration	Comments
CMV			
Donor-positive/ recipient-negative	Valganciclovir (900 mg/day) or intravenous ganciclovir (5 mg/kg/day)	3-6 months	Valganciclovir is not FDA-approved for LT. Prolonged-duration regimens are effective in kidney transplantation.
Recipient-positive	Valganciclovir (900 mg/day), intravenous ganciclovir, or weekly CMV viral load monitoring and antiviral initiation when viremia is identified	3 months	Valganciclovir is not FDA-approved for LT.
Fungi	Fluconazole (100-400 mg daily), itraconazole (200 mg twice daily), caspofungin (50 mg daily), or liposomal amphotericin (1 mg/kg/day)	4-6 weeks? (optimal duration unknown)	Reserve for high-risk individuals (pretransplant fungal colonization, renal replacement therapy, massive transfusion, choledochojejunostomy, reoperation, retransplantation, or hepatic iron overload).
P. jirovecii (*P. carinii*)	Trimethoprim sulfamethoxazole (single strength daily or double strength 3 times per week), dapsone (100 mg daily), or atovaquone (1500 mg daily)	6-12 months (optimal duration unknown)	A longer duration of therapy should be considered for patients on augmented immunosuppression. Lifelong therapy should be considered for HIV-infected recipients.
TB (latent infection)	Isoniazid (300 mg daily)	9 months	Monitor for hepatotoxicity.

- Augmented immunosuppression (especially with the use of anti-lymphocyte antibodies or high-dose mycophenolate).
- Allograft rejection.
- Coinfection with other immunomodulating viruses (eg, human herpesviruses 6 and 7), bacteria, or fungi.

The diagnosis of CMV includes the detection of the virus in conjunction with the recognition of an associated clinical syndrome.[61,62] Patients who are not receiving prophylactic antivirals and are at increased risk for CMV (because of a CMV-seropositive donor and/or treatment for rejection) may be monitored for evidence of infection with nucleic acid testing (polymerase chain reaction). Typically, CMV occurs in the first 3 months in the absence of prophylaxis. However, because of current standard prophylactic strategies, it now presents later after the cessation of prophylaxis, frequently in the first year or after the augmentation of immunosuppression. Currently, routine screening for CMV is not recommended while patients are receiving prophylaxis. After the completion of prophylaxis, some centers have adopted a hybrid approach using nucleic acid testing to screen for infections in the highest risk patients. However, there is no clear evidence to support the screening of asymptomatic patients at this time. The detection of viremia by either nucleic acid testing (polymerase chain reaction) or the pp65 antigenemia assay is recommended for the diagnosis of an active CMV infection.[61,62] Typically, the viral load correlates with the severity of disease and can be a marker of the response to therapy. Some individuals, especially those with hepatitis or gastrointestinal disease, may exhibit low-level or no viremia despite a symptomatic infection and require tissue biopsy for the diagnosis of CMV disease to be made. Finally, some LT recipients exhibit low-level viremia without symptomatic disease.

The treatment of CMV should be started whenever recipients are symptomatic, have a tissue injury, or have persistent or increasing viremia.[61,63,64] All LT recipients with a symptomatic CMV infection and/or end organ disease should receive antiviral therapy and have their immunosuppression reduced until viremia and all symptoms have resolved. Patients with low-level viremia (this is difficult to define because of laboratory variability) should be assessed for symptoms and, if they are asymptomatic, should have immunosuppression reduction as tolerated and viral load testing repeated. If the viral load rises and/or symptoms develop, treatment should be administered.

Options for antiviral treatment include intravenous ganciclovir (5 mg/kg twice daily adjusted for renal impairment) and oral valganciclovir (900 mg twice

daily adjusted for renal impairment) for mild to moderate disease if no significant gastrointestinal involvement is assumed (note: valganciclovir is not approved for use in LT). For those patients with more severe disease or gastrointestinal involvement, intravenous ganciclovir is preferable. A minimum of 2 weeks of treatment is recommended for those patients with rapid resolution of symptoms, but treatment should be continued until there is complete resolution of both symptoms and viremia. Whenever possible, a reduction in immunosuppression should be combined with antiviral therapy. Ganciclovir resistance is uncommon in solid organ transplant recipients.

Recommendations

53 High-risk recipients (CMV-seronegative recipients of CMV-seropositive donor organs) should receive prophylaxis with ganciclovir or valganciclovir for a minimum of 3 months after transplantation (grade 1, level B).
54. The treatment of LT recipients with CMV should be maintained until viremia and all symptoms have resolved (grade 2, level B).
55. Prophylaxis against CMV should be resumed whenever LT recipients receive anti-lymphocyte therapy for the treatment of rejection and should be continued for 1 to 3 months after the treatment of rejection (grade 2, level B).
56. The treatment of a CMV infection should consist of the following:
    a. Consideration of immunosuppression reduction.
    b. High-dose intravenous ganciclovir or oral valganciclovir in individuals with mild to moderate disease without gastrointestinal involvement or a reduced capacity for absorption.
    c. A minimum of 2 weeks of treatment. Treatment should be continued to complete the resolution of all symptoms and viremia (grade 1, level A).
57. Resistant virus should be suspected in patients with a history of prolonged ganciclovir or valganciclovir exposure who have a persistent or progressive infection despite treatment with high-dose intravenous ganciclovir (grade 1, level A). In such instances, genotypic assays should be performed, and consideration should be given to the initiation of foscarnet with or in substitution for ganciclovir (grade 1, level B).

EBV/PTLD

EBV-associated PTLD is an uncommon but serious complication of LT with an incidence in adults of 0.9% to 2.9%.[64,65] Risk factors include a primary EBV infection, CMV donor-recipient mismatch or CMV disease, and augmented immunosuppression, especially with anti-lymphocyte antibodies.[66] It is uncertain whether the etiology of liver disease influences the development of PTLD.[67,68] The association of PTLD with EBV infection is variable in adult LT recipients; later onset PTLD is less likely to be EBV-associated.[64,67,68] Manifestations of PTLD include lymphadenopathy, cytopenias, unexplained fever, and disturbances of the gastrointestinal tract, lungs, spleen, and central nervous system.

The diagnosis of PTLD requires a high index of suspicion and should be considered in high-risk individuals who present with undiagnosed fever or unexplained lymphadenopathy or cytopenias.[66–69] Radiographic studies can identify sites of involvement, especially when pulmonary or intra-abdominal sites are involved. The detection of EBV viremia with nucleic acid testing is not diagnostic of EBV-associated PTLD.

The initial treatment of PTLD is a reduction of immunosuppression.[65–69] If there is no clinical response within 2 to 4 weeks, additional therapies, including anti-CD20 humanized chimeric monoclonal antibodies (rituximab), surgical therapy, radiation therapy, and cytotoxic chemotherapy, may be required. The addition of antiviral therapy has not been proven to affect outcomes.

Recommendations

58. PTLD should be considered in LT recipients (especially high-risk individuals) who present with unexplained fever, lymphadenopathy, or cytopenias (grade 1, level A).
59. Although EBV may be associated with the development of PTLD, the detection of EBV viremia is not diagnostic for PTLD; a histopathological diagnosis is required (grade 1, level A).

Fungal Infections

Risk factors for fungal infections after LT include preoperative fungal colonization, massive transfusion requirements (>40 U of blood products), choledochojejunostomy, reoperation, retransplantation, hepatic iron overload, renal replacement therapy, and extended intervals of intensive care immediately before LT. The epidemiology of invasive fungal infections in LT recipients has shifted over the past 2 decades, with a decrease in *Candida* infections and an increasing incidence of *Aspergillus* infections.[70] The recognition of an invasive fungal infection after 90 days is challenging. Blood cultures are relatively insensitive for the diagnosis of many fungal infections, including *Candida* species, for which the (1,3)-β-D-glucan test is an inconsistent measure.[71,72] *Aspergillus* is especially difficult to diagnose with noninvasive testing.[70] The sensitivity and specificity of galactomannan in either blood or bronchoalveolar lavage from LT recipients with presumed pulmonary aspergillosis are variable.[72-74] Serum and cerebrospinal cryptococcal antigen testing is a sensitive tool for the rapid diagnosis of cryptococcal infections in organ

TABLE 13. Preferred Antifungal Agents

Organism/Disease	Agent	Comments
Candida	Triazoles (fluconazole, Itraconazole, voriconazole, and posaconazole), echinocandins (eg, caspofungin, micafungin, and anidulafungin), or amphotericin B and analogues	*Candida glabrata* and *Candida krusei* may be resistant to triazoles (especially fluconazole). Differentiate colonization from infection. The duration of therapy varies with the site of infection.
Aspergillus	Triazoles (voriconazole is the drug of choice; itraconazole and posaconazole are also active), caspofungin, or amphotericin B and analogues	The duration of therapy is dependent on the response to therapy.
Cryptococcus	Amphotericin B and analogues in combination with 5-flucytosine for 2 weeks followed by fluconazole (400-800 mg/day) for 8 weeks and then fluconazole (200 mg/day) for 6-12 months	Cautiously reduce immunosuppression. Patients with isolated pulmonary disease may not require amphotericin induction. The duration varies with the response.
Blastomycosis	Itraconazole (200 mg twice daily) for mild to moderate disease and amphotericin B and analogues for severe disease	The standard duration is 6-12 months.
Coccidiomycosis	Fluconazole (400-800 mg daily), itraconazole (200 mg twice daily), or amphotericin B and analogues	Amphotericin should be used for more severe disease and should be considered when there is central nervous system involvement. The standard duration is 6-12 months with chronic suppression thereafter.
Histoplasmosis	Itraconazole (200 mg twice daily) or amphotericin B and analogues for 2 weeks of induction followed by fluconazole	The minimum duration is 12 months.

transplant recipients.[75] The isolation of *Cryptococcus* from a site other than cerebrospinal fluid should prompt lumbar puncture to rule out central nervous system involvement. Urinary histoplasmosis and *Blastomyces* antigens have been useful for the diagnosis of disseminated histoplasmosis and blastomycosis, respectively.[76,77]

The treatment of fungal infections includes antifungal drug therapy as well as a reduction of immunosuppressive therapy. The choice of antifungal agents varies with the pathogen and the site of involvement, as shown in Table 13.

Recommendations

60 The diagnosis of fungal infections may require diagnostic biopsy for pathological and microbiological confirmation (grade 1, level A).
   a. Blood cultures are most helpful for the diagnosis of *Candida* bloodstream infections (class 1, level B) and *Blastomyces* (grade 1, level B).
   b. Cryptococcal antigen testing of cerebrospinal fluid or blood is most helpful for the diagnosis of *Cryptococcus* (grade 1, level B).
   c. Urinary histoplasmosis and *Blastomyces* antigens are useful for the diagnosis of disseminated histoplasmosis and blastomycosis, respectively (grade 1, level B).

61. A cautious reduction of immunosuppression should be initiated to prevent immune reconstitution syndrome, especially for cryptococcal infections (grade 1, level B).

Pneumocystis jirovecii (*Pneumocystis carinii*)

P. jirovecii (formerly called *P. carinii*) is an uncommon pathogen in LT recipients, primarily because of the widespread use of antimicrobial prophylaxis after LT.[78] *Pneumocystis* should be suspected in individuals presenting with respiratory symptoms, hypoxemia (often exacerbated by exercise), and fever.[78] Classic radiographic findings include bilateral interstitial infiltrates. The diagnosis is confirmed by the identification of the organism by a cytological examination of induced sputum or bronchoalveolar lavage fluid. High-dose trimethoprim-sulfamethoxazole (administered orally or intravenously at 15-20 mg/kg/day in divided doses and adjusted for renal dysfunction) is the drug of choice.[78] Corticosteroids (40-60 mg of prednisone or its equivalent) should be used in conjunction with antimicrobial therapy for patients with significant hypoxia (partial pressure of arterial oxygen

< 70 mm Hg on room air). The minimal duration of antimicrobial therapy is 14 days, but more severe infections may merit longer courses of treatment.

Recommendations

62. All LT recipients should receive prophylaxis against *P. jirovecii* with trimethoprim-sulphamethoxazole (single strength daily or double strength 3 times per week) for a minimum of 6 to 12 months after transplantation (grade 1, level A). Atovaquone and dapsone are the preferred alternatives for patients who are intolerant of trimethoprim sulfamethoxazole (grade 1, level B).
63. Trimethoprim-sulphamethoxazole is the drug of choice for the treatment of *P. jirovecii* pneumonia. Intravenous pentamidine is the preferred alternative for patients intolerant of trimethoprim-sulphamethoxazole with more severe infections (grade 1, level A).
64. Patients with clinical signs and symptoms or radiological features suggestive of *P. jirovecii* pneumonia should undergo sputum sampling or bronchoalveolar lavage with a cytological examination using a silver or Giemsa stain, polymerase chain reaction, or a specific antibody stain to identify the organism (grade 1, level A).

Tuberculosis (TB)

Several risk factors for the development of symptomatic TB after LT have been identified: a prior infection with TB; intensified immunosuppression (especially anti–T lymphocyte therapies); DM; and coinfections with CMV, mycoses, *P. jirovecii*, and *Nocardia*.[79] Donor-derived TB is rare. The diagnosis of TB may be confounded by an increased incidence of atypical presentations (especially extrapulmonary infections involving diverse organs and locations).[80,81] Standard antituberculous regimens for drug-susceptible isolates include 2 months of 4-drug therapy with isoniazid, rifampin, ethambutol, and pyrazinamide followed by an additional 4 months of isoniazid and rifampin. Patients with central nervous system involvement, bone and joint disease, or disseminated infections may warrant longer courses of treatment.[80-82] The use of anti-TB agents in LT recipients is complicated by hepatotoxicity and by the significant drug-drug interactions with immunosuppressive agents, which lead to the potential for hepatotoxicity associated with antitubercular chemotherapy. Because of the risk of a marked reduction in CNI and mTOR inhibitor levels with rifampin coadministration, the doses of CNIs will need to be increased 2- to 5-fold at the initiation of treatment.[79] Rifabutin may be substituted for rifampin to reduce the impact on drug levels, or non–rifampin-containing regimens can be considered, although the duration of treatment will need to be extended.

Recommendations

65. The treatment of active TB should include the initiation of a 4-drug regimen using isoniazid, rifampin, pyrazinamide, and ethambutol (under the assumption of susceptible TB) with adjustments in accordance with subsequent culture results. This may be tapered to 2 drugs (isoniazid and rifampin) after 2 months (under the assumption of no resistance) and continued for a minimum of 4 additional months (grade 1, level B).
66. Close monitoring for rejection and hepatotoxicity is imperative while LT recipients receive anti-TB therapy (grade 1, level A).

Human Immunodeficiency Virus (HIV)

HIV-infected patients with well-controlled infections have undergone transplantation with success, although aggressive HCV recurrence has been problematic in LT recipients coinfected with HCV.[83] HIV-infected patients maintained on highly active antiretroviral therapy (HAART) after transplantation do not experience an increase in opportunistic infections. The use of HAART in LT recipients is complicated by significant drug-drug interactions with immunosuppressive agents, which lead to a risk of cyclosporine or tacrolimus toxicity or inadequate immunosuppression.[84] LT recipients with HCV-HIV coinfections have a higher frequency and severity of acute cellular rejection.[85] The CNI doses and the frequency of their administration need to be reduced markedly in LT recipients receiving HAART containing protease inhibitors.[83,84] In contrast, those receiving nonnucleoside reverse transcriptase inhibitors (especially efavirenz) will require higher doses of CNIs.

Recommendations

67. HIV-infected LT recipients receiving HAART require frequent monitoring of CNI levels because of the significant interaction between antiretrovirals and CNIs (grade 1, level A).
68. HIV-infected LT recipients receiving HAART should be followed with scheduled HIV viral loads and T lymphocyte subset counts (grade 1, level A).
69. Standard prophylaxis for CMV is recommended for HIV-infected LT recipients receiving HAART, and lifelong *Pneumocystis* pneumonia prophylaxis is the norm (grade 1, level A).
70. Standard HIV-specific prophylaxis for low CD4 counts should be used (grade 1, level A).

IMMUNIZATIONS

Appropriate advice regarding vaccination after LT has been reviewed by Danzinger-Isakov et al.[86] and is also reviewed in Table 14. LT recipients should avoid live

TABLE 14. Recommended Immunizations for Adult LT Recipients

Before Transplantation	After Transplantation
Influenza	Influenza
Pneumococcus*	Pneumococcus*
Hepatitis A virus†	
HBV†	
Tetanus/diphtheria/ acellular pertussis‡	
Human papilloma virus§	
Varicella virus‖	
Zoster¶	

NOTE: Transplant recipients may also receive the following vaccines safely: the meningococcal vaccine, the inactivated *Salmonella* Typhi vaccine (Typhim Vi intramuscular vaccine), the Japanese encephalitis vaccine, and the *Vibrio cholera* vaccine. Live virus vaccines should be avoided after transplantation.

*The pneumococcal vaccine should be repeated every 3 to 5 years after the initial administration.

†Ideally, hepatitis A virus and HBV immunizations should be administered before transplantation. There are no guidelines regarding posttransplant immunization, although these vaccines are safe after transplantation. HBV antibody levels should be measured annually after transplantation, with boosters considered for waning immunity.

‡The tetanus/diphtheria/acellular pertussis vaccine can also be safely administered after transplantation.

§This vaccine is indicated for females up to the age of 26 years. It can be safely administered after transplantation.

‖This vaccine can be administered safely before transplantation to nonimmune individuals. It should not be administered after transplantation.

¶This vaccine is indicated for individuals who are 60 years old or older. No studies have been conducted in patients with cirrhosis. It should not be administered after transplantation.

virus vaccines because of concerns about the dissemination of infections. Vaccine-related rejection has not been associated with immunization following LT.

Recommendations

71. All LT recipients should receive an annual influenza vaccination (grade 1, level B).
72. All LT recipients should avoid live virus vaccines (grade 1, level A).
73. Re-immunization is indicated for some vaccines, notably the influenza vaccine (annually) and the pneumococcal vaccine (every 3-5 years; no class or level provided). (grade 1, level A).

VIRAL HEPATITIS

Hepatitis B Virus (HBV)

Chronic HBV accounts for less than 10% of transplants performed in the United States and Western Europe, whereas in Asia, it is the most common indication for LT. Importantly, in the last decade, there has been a shift in the primary indication for LT among HBV-infected patients, with HCC more frequent than end-stage liver disease.[87] This trend reflects the efficacy of antiviral therapy in preventing complications of cirrhosis as well as the increased prioritization of HCC for LT.

The survival for patients undergoing transplantation for HBV is excellent, and HBV ranks among the best of all indications for LT. The improvements in patient and graft survival evident over the past 10 to 15 years reflect the advances in therapeutics to prevent and control HBV infections after LT. The combination of hepatitis B immune globulin (HBIG) and nucleos(t)ide analogues can prevent recurrent infections in almost all HBV-infected LT patients.[88-91] The combination of HBIG and nucleos(t)ide analogues is superior to HBIG alone. The individualization of prophylactic combination therapy can be undertaken on the basis of pretransplant clinical and virological characteristics. For example, low-dose intramuscular HBIG is much less expensive and avoids painful side effects associated with intravenous HBIG. The discontinuation of HBIG is generally reserved for patients at low risk for HBV recurrence.[92]

A recurrent infection is manifest with persistently detectable HBV DNA and hepatitis B surface antigen in serum and is usually due to a failure of prophylactic therapy. Liver biopsy is useful for assessing the severity of HBV recurrence and the progression of fibrosis. Fibrosing cholestatic HBV is a unique histological variant observed in LT recipients and is characterized by high intrahepatic levels of HBV DNA, hepatocyte ballooning with cholestasis, and a paucity of inflammatory cells.[93] This represents the most severe presentation of recurrent disease and is rarely seen in the current era of prophylactic therapy.

Recommendations

74. Long-term prophylactic therapy using a combination of antiviral agents and low-dose HBIG on demand or at fixed intervals can effectively prevent HBV recurrence rates in $\geq$90% of transplant recipients (grade 1, level B).
75. In patients with low or undetectable HBV DNA levels before transplantation and an absence of high-risk factors for recurrence, HBIG can be discontinued, and long-term treatment with antivirals (single or in combination) can be used as an alternative prophylactic strategy (grade 2, level B).
76. Lifelong antiviral therapy should be used to treat patients with recurrent HBV infections. Combination antiviral therapy is superior to monotherapy when drugs with a low genetic barrier to resistance are used, whereas the discontinuation of HBIG is generally reserved for patients at low risk for HBV recurrence (grade 1, level B).

77. Retransplantation for recurrent HBV is appropriate when treatment strategies to prevent or treat recurrent HBV disease are available (grade 1, level C).

HCV

Recurrent HCV infection is invariable among patients who are viremic at LT, the majority of whom will have histological evidence of recurrent hepatitis within the first year after LT.[94] Although the progression of fibrosis in HCV-infected LT recipients is highly variable, in the absence of antiviral therapy, the median time to the development of cirrhosis is 8 to 10 years, whereas an estimated 30% will develop cirrhosis within 5 years of LT.[95] The risk of decompensation is 15% to 30% within the first year of the onset of cirrhosis, and the mortality risk is 40% to 55% within 6 to 12 months of the decompensating event. Recurrent HCV cirrhosis is the most frequent cause of graft loss in this population.[96] Patient survival and graft survival are reduced in HCV-infected patients versus HCV-negative patients, with a 5-year patient survival rate of approximately 70%.[97,98]

HCV-infected recipients have higher rates of graft loss when the allograft is from an older donor.[99] There is a higher risk of cirrhosis when HCV-infected LT recipients develop acute rejection that requires treatment or comorbid CMV hepatitis.[100] Although recurrent HCV is more likely the longer the interval from LT, in practice, it is often difficult to distinguish between the histopathological appearances of a recurrent HCV infection and acute cellular rejection. The impact of immunosuppressives on the progression of HCV is poorly understood, although some data suggest that anti-lymphocyte agents promote HCV-associated liver injury. Post-LT diabetes, insulin resistance, and (more inconsistently) steatosis have been associated with a higher risk of rapid progression to advanced fibrosis.

Posttransplant antiviral therapy is generally reserved for those showing evidence of progressive disease, which is manifested by the presence of moderate to severe necroinflammation or mild to moderate fibrosis, although this paradigm will change with more efficacious and less toxic antiviral therapy.[100] The primary goal of post-LT antiviral therapy is the achievement of sustained viral clearance because this virological outcome is associated with fibrosis stabilization or regression and improved graft survival.[101] The initiation of antiviral therapy is recommended when significant histological disease is present, although this paradigm would change with more efficacious and less toxic antiviral therapy. The pooled estimated rate of acute graft rejection occurring in patients receiving peginterferon and ribavirin is 5%, which is not significantly higher than the rate in untreated controls.[102] However, alloimmune or plasma cell hepatitis, characterized histologically by an inflammatory infiltrate with abundant plasma cells in the setting of increased liver enzymes, has been described during antiviral therapy.[103] This is most likely a variant of allograft rejection and responds to the discontinuation of interferon and the amplification of immunosuppression in most cases. With the recent approval of the first-generation protease inhibitors, telaprevir and boceprevir, it is anticipated that triple therapy (peginterferon, ribavirin, and either telaprevir or boceprevir) will evolve into the new standard of care over the next few years for LT recipients infected with genotype 1 virus. Currently, neither protease inhibitor is approved for use in transplant recipients. There are significant drug-drug interactions between HCV protease inhibitors and CNIs and probably mTOR inhibitors as well. The prospect of interferon-free protocols is also of great interest because of the possibility that interferon induces an alloimmune response in some LT recipients.

Recommendations

78. Liver biopsy is useful in monitoring disease severity and progression and in distinguishing recurrent HCV disease from other causes of liver enzyme elevations (grade 1, level C).
79. Prophylactic antiviral therapy has no current role in the management of HCV disease (grade 1, level A).
80. Moderate acute rejection should be treated with increased maintenance immunosuppression and corticosteroid boluses, whereas lymphocyte-depleting drugs should be avoided (grade 1, level B).
81. Antiviral therapy is indicated for significant histological disease: grade 3 or higher inflammatory activity and/or stage 2 or higher fibrosis (on a scale of 4) or cholestatic hepatitis. Peginterferon and ribavirin are the current drugs of choice. The risks and benefits of triple therapy with protease inhibitors are to be determined. The goal of antiviral therapy is the achievement of a sustained virological response, and this confers a survival benefit (grade 1, class B).
82. Retransplantation for recurrent HCV disease should be considered selectively (grade 2, level B).

PBC

PBC is an excellent indication for liver replacement with the one of the highest rates of risk-adjusted outcome.[104] Immunological abnormalities (eg, elevated immunoglobulins and autoantibodies) persist after transplantation. Recipients remain at risk for associated conditions, such as sicca syndrome, osteoporosis, and thyroid disease, so screening should be included in the follow-up.

Recurrent PBC is diagnosed by liver histology: recurrent disease may occur in the presence of normal liver tests, and neither the presence nor the titer of anti-mitochondrial antibodies correlates with the presence or degree of recurrence.[105,106] The reported

incidence of recurrent PBC varies from 4% to 33% (the average is 18%).[104] Although the use of cyclosporine is associated with less severe recurrence and corticosteroids may be associated with less recurrence, there are insufficient data to recommend a preferred immunosuppressive regimen.[106] The impact of the recurrence of PBC on graft function and survival is minimal for the first decade after transplantation, with end-stage disease affecting less than 5%. There is no evidence that routine protocol biopsy in PBC LT recipients will improve outcomes. Ursodeoxycholic acid at a dose of 10 to 15 mg/kg/day is associated with an improvement in liver tests, but there are no data to show benefits in patient or graft survival.[104]

Recommendations

83. PBC LT recipients should be routinely monitored for associated autoimmune diseases (eg, thyroid disease) and bone density (grade 2, level B).
84. For those with histological evidence of recurrent disease, treatment with ursodeoxycholic acid at 10 to 15 mg/kg/day (grade 2, level B) may be considered, and although its use is associated with the improvement of liver tests, no impact on graft survival has been documented (grade 2, level B). There is no indication for offering prophylaxis with ursodeoxycholic acid to patients with normal liver histology (grade 2, level B).

PSC

PSC is an excellent indication for LT with good long-term outcomes. Recipients with a Roux loop are at increased risk for recurrent cholangitis; those few who have a retained native bile duct are at risk for cholangiocarcinoma. In patients with chronic ulcerative colitis (CUC), colitis may improve or deteriorate after transplantation.[107] PSC LT recipients with CUC are at greater risk of developing colonic polyps and cancer and should have an annual colonoscopy. There is no evidence for the optimal screening approach in PSC LT recipients without CUC, but many advocate an annual colonoscopy in this group also.

Recurrent PSC is seen in up to 50% of patients at 5 years, with graft loss due to recurrent PSC occurring in as many as 25% of patients with recurrent PSC.[108] The diagnosis of recurrent PSC is based on a combination of biochemical, radiological, and histological findings in particular, multiple nonanastomotic biliary strictures or characteristic liver histology, and the exclusion of other causes such as infections or ischemia secondary to thrombosis of the hepatic artery. Risk factors for recurrent PSC include male sex, an intact colon before or during transplantation, a history of steroid-resistant or recurrent rejection, active CUC after transplantation, the use of anti-lymphocyte therapy for the treatment of cellular rejection, sex mismatch between the donor and the recipient, CMV infection, and the presence of specific HLA haplotypes (eg, HLA-DRB1*08). In PSC recipients with CUC, prophylactic colectomy does not reduce the risk of recurrent PSC. There is insufficient evidence to support maintaining corticosteroids in patients undergoing transplantation for PSC.

Recommendation

85. Although there are few data on prevention, it is recommended that those patients grafted for PSC in the presence of CUC have an annual colonoscopy with mucosal biopsy (grade 2, level B).

AIH

Outcomes after transplantation for AIH are good. Patients should be closely monitored for evidence of recurrence via liver tests every 6 months.[109] Protocol liver biopsy should be considered at 5 yearly intervals. The reported outcome rates for recurrent AIH are highly variable. Although the majority of patients with putative recurrent AIH will respond clinically, serologically, and histologically to increased immunosuppression, some will progress to end-stage graft failure and may require retransplantation.

Recommendation

86. Although there is no evidence for recommending a particular immunosuppressive regimen in patients undergoing transplantation for AIH, it is prudent to maintain patients on long-term, low-dose corticosteroids in addition to routine immunosuppression (with attention to maintaining bone health; grade 2, level B).

ALCOHOLIC LIVER DISEASE (ALD)

Although ALD patients selected for LT have a survival rate similar to that of recipients without ALD,[110] post-LT mortality is increased in recipients with comorbid ALD and HCV. There is a wide variation in the reported rates of alcohol relapse by ALD patients after LT (10%-90%). The best prospective study showed that 80% of ALD LT recipients either did not drink or consumed only small amounts occasionally in the first 5 years.[111] Conversely, in the remaining 20%, there were various patterns of harmful drinking. Anecdotal reports suggest that patients who relapse to harmful drinking are at risk for alcoholic hepatitis, delirium tremens, alcoholic pancreatitis, and reduced survival.[110] Furthermore, the causes of death for the patients who returned to heavy consumption of alcohol tended to be liver-related, whereas abstinent ALD patients died of cardiovascular disease and malignant tumors. The stratification of cardiovascular deaths and new-onset cancers of the aerodigestive tract in patients undergoing LT for ALD suggests a causal linkage with cigarette smoking.[17]

Recommendations

87. All patients with a prior diagnosis of ALD should be encouraged to remain abstinent from

alcohol (grade 1, level B).
88. Patients should be encouraged to enter therapy or counseling if they relapse into alcohol use (grade 1, level C).
89. All patients with a prior diagnosis of ALD who are users of tobacco should be encouraged to undertake smoking cessation (grade 1, level B).
90. Careful attention should be given to the risk of cardiovascular disease and/or new-onset cancers of the aerodigestive tract, especially in cigarette smokers (grade 1, level A).

NONALCOHOLIC STEATOHEPATITIS (NASH)/NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)

It appears that NASH-associated cirrhosis is the fourth most common cause of liver failure leading to LT in the United States, and it is predicted that by 2020-2030, NASH-associated cirrhosis will become the most common indication for LT.[112] NAFLD and NASH, both recurrent and de novo, are common after LT.[37,113-115] Immunosuppressant agents may contribute to metabolic syndrome: corticosteroids and tacrolimus promote diabetes, sirolimus promotes hyperlipidemia, and cyclosporine and tacrolimus promote systemic hypertension. Risk factors for post-LT NASH/NAFLD are familiar as the hallmarks of metabolic syndrome: body mass index before and after LT, DM, systemic hypertension, hyperlipidemia, and steatosis on an allograft biopsy sample. Among patients who undergo LT on account of NASH-associated or cryptogenic cirrhosis, 50% to 70% will gain excessive weight in 1 year.[115]

New-onset or recurrent NAFLD/NASH may present with elevated liver aminotransferases. Distinguishing NAFLD/NASH from other causes of elevated liver tests in the post-LT patient requires liver biopsy. NAFLD/NASH arising in the liver allograft, whether new-onset or recurrent, may lead to fibrosis.[115] Cirrhosis associated with fat accumulation in the allograft is uncommon in the first 5 years after LT. No effect on patient or graft survival has been observed among LT recipients with new-onset or re-emergent NAFLD/NASH, although most studies have been short in duration. Although there are no good data to support one immunosuppressive regimen over another in patients who undergo transplantation for NASH/cirrhosis or cryptogenic cirrhosis, minimizing corticosteroids appears prudent. Renal impairment is more common in those undergoing transplantation for NAFLD.

Recommendations

91. The confirmation of recurrent or de novo NAFLD, the recognition of fibrosis, and the exclusion of alternate causes of elevated liver chemistry tests require liver biopsy (grade 1, level B).
92. No specific recommendations regarding the prevention or treatment of NAFLD or NASH in LT recipients can be made other than general recommendations to avoid excessive gains in body weight and control hypertension and diabetes (grade 1, level C).

LATE SURGICAL COMPLICATIONS

Hepatic artery stenosis, biliary cast syndrome, and bilomas have already been discussed with respect to abnormal liver tests. Incisional hernia is a common late complication after LT. Postoperative weight gain exacerbates the risk.

Recommendation

93. LT recipients with an incisional hernia should be instructed to recognize incarcerated hernias and advised to seek immediate medical assistance (grade 1, level B).

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