Care of the liver transplant patient

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OBJECTIVE: To provide an approach to the care of liver transplant (LT) patients, a growing patient population with unique needs.

METHODS: A literature search of PubMed for guidelines and review articles using the keywords “liver transplantation”, “long term complications” and “medical management” was conducted, resulting in 77 articles.

RESULTS: As a result of being on immunosuppression, LT recipients are at increased risk of infections and must be screened regularly for metabolic complications and malignancies.

DISCUSSION: Although immunosuppression is key to maintaining allograft health after transplantation, it comes with its own set of medical issues to follow. Physicians following LT recipients must be aware of the greater risk for hypertension, diabetes, dyslipidemia, renal failure, metabolic bone disease and malignancies in these patients, all of whom require regular monitoring and screening. Vaccination, quality of life, sexual function and pregnancy must be specifically addressed in transplant patients.

Key Words: Liver transplant; Long-term complications; Medical management

Since the 1960s, LT has offered a new lease on life to many patients with end-stage liver disease (ESLD) and acute liver failure (1). Survival after transplantation has continued to improve over time, with fine-tuned immunosuppression, postoperative care and management of infections. In 2011, 485 LTs were performed in Canada, with 4419 performed over the 10-year period between 2002 and 2011 (2). The one-year survival rate is as high as 85%, while 10-year survival rates approach 65% (3). The longer-term survival of LT recipients means that gastroenterologists and primary care physicians are caring for these patients concurrently with transplant specialists. The management of this patient population is both unique and complex. The gastroenterologist must be aware of the specialized needs of LT recipients, and be able to recognize and optimally manage key complications. In the present article, we provide an overview of issues pertinent to the management of LT recipients, principally based on consensus recommendations in the literature.

INFORMATION SOURCES

The PubMed database was searched using the keywords “liver transplantation”, “long term complications” and “medical management”, resulting in 77 review articles and guidelines. The Canadian Organ Replacement Register report was a source of information for LT in the Canadian context (2). The Cochrane collaboration website was consulted using the search term “liver transplantation”. There were systematic reviews on infectious prophylaxis and quality of life after LT (Level 1 evidence). The recommendations in the present review are, therefore, based on data from retrospective studies, case series (Level II) or expert consensus guidelines (Level III).

ESLD is the indication for 92% of LTs, with hepatitis C and alcoholic cirrhosis being the most common etiologies. Fulminant liver failure, mostly due to acetaminophen poisoning, autoimmune hepatitis or viral etiologies, was the indication for 4% of LTs. LT can be curative for hepatocellular carcinoma (HCC), and was the indication for 15.3% of LTs between 2002 and 2011 in Canada (2). Advanced, uncorrectable cardiopulmonary disease is an absolute contraindication to transplantation, while age, per se, is not.

IMMUNOSUPPRESSION

Following LT, immunosuppressants are started and the recipient is monitored closely to prevent organ rejection. Calcineurin inhibitors (CNIs), antimitabolites and corticosteroids are the main categories of available immunosuppressants (Table 1). Most LT centres in Canada choose to administer a combination of low-dose tacrolimus and mycophenolate mofetil (MMF) with or without concomitant glucocorticoids (4). Satisfactory immunosuppression can be achieved with monotherapy in many patients beyond six to 12 months post-transplantation, usually with a CNI alone.

EARLY COMPLICATIONS

Liver graft dysfunction is a serious complication that can result in loss of the donor organ. The most common presentation is an asymptomatic elevation of liver enzyme levels (Figures 1 and 2). Causes of early
TABLE 1
Liver transplant medications, adverse effects and monitoring parameters

| Immunosuppressant    | Mechanism of action                                      | Adverse effects                                      | Monitoring parameters                                      |
|----------------------|----------------------------------------------------------|------------------------------------------------------|------------------------------------------------------------|
| Prednisone           | Inhibits leukocyte, macrophage and T cell activity        | Hyperglycemia, hypertension, dyslipidemia, infectious risk, osteoporosis | Blood pressure measurement                                 |
|                      | Decrease cytokines, prostaglandins and leukotrienes      |                                                      | Monitor glucose, lipids profiles, regular bone mineral density scan |
| Tacrolimus           | Calcineurin inhibitor, prevents T cell activation         | Renal failure, diabetes, hypertension, neuropathy, dyslipidemia | Blood pressure measurement, monitor glucose, blood pressure, renal function, magnesium level, drug level |
| Cyclosporine         | Calcineurin inhibitor, prevents T cell activation         | Renal failure, diabetes, hypertension, neuropathy, dyslipidemia, hirsutism | Blood pressure measurement, monitor glucose, blood pressure, renal function, magnesium level, drug level |
| Mycophenolate mofetil| Inhibits T cell and B cell proliferation                  | Bone marrow suppression with cytopenias, gastrointestinal side effects | CBC, liver and renal profile, contraindicated in pregnancy (fetal malformations, first trimester fetal loss) |
| Azathioprine         | Purine analogue, impedes DNA and RNA synthesis           | Bone marrow suppression with cytopenias, pancreatitis | CBC, thiopurine methyltransferase, liver profile |
| Sirolimus (rapamycin)| mTOR inhibitor                                            | Hepatic artery thrombosis, impair wound healing, interstitial lung disease, edema, cytopenias, hyperlipidemia, proteinuria | CBC, lipid profile, liver profile, contraindicated in pregnancy due to teratogenicity |

**CBC** Complete blood count; **mTOR** Mammalian target of rapamycin

Figure 1) Differential diagnosis of high liver enzyme levels in patients with liver transplant (darker circles indicate early post-liver transplant complications). NAFLD Nonalcoholic fatty liver disease

Figure 2) Suggested diagnostic algorithm for liver transplant recipients with high liver enzyme levels. Angio Angiography; CT Computed tomography; ERCP Endoscopic retrograde cholangiopancreatography; MRCP Magnetic resonance cholangiopancreatography; MRI Magnetic resonance imaging; NAFLD Nonalcoholic fatty liver disease; PTC Percutaneous transhepatic cholangiography; UDCA Ursodeoxycholic acid

Liver allograft dysfunction are listed in Table 2, with acute cellular rejection being the most common. Salvage of the organ depends on accurate diagnosis and prompt treatment.

Post-transplant infections may develop in up to 20% of LT recipients during the first month after transplantation. Prophylaxis against infections is, therefore, routinely given to patients for at least six months after LT. A Cochrane review has proven the benefit of fluconazole as an antifungal agent in LT (5), and that of antivirals to prevent cytomegalovirus infection in all organ transplants (6). Trametoprim-sulfamethoxazole is also given to prevent *Pneumocystis jirovecii* infection.

Recurrent disease following LT

Recurrent disease after LT is a concern, particularly when the indication for transplant was hepatitis C virus (HCV) infection or liver malignancies. Details regarding incidence, diagnosis and management are presented in Table 3. HCV infection recurs in virtually all patients in the long term, with development of cirrhosis in 30% of patients over five years after LT (7). Protease inhibitors, such as boceprevir or telaprevir, have been used in combination with pegylated interferon and ribavirin in recent years, with sustained virological response of up to 51% at 12 weeks in the LT population with genotype 1 HCV infection (8). Next-generation protease inhibitors promise to improve on these outcomes even further (9). However, this has required a difficult balancing act with CNIs, given that they are all metabolized by the same cytochrome p450 3A4 enzyme. With the advent of polymerase inhibitors, such as sofosbuvir, with excellent cure rates and no drug-drug interactions with CNIs, treatment of HCV infection in the future will be significantly more easily managed both pre- and post-LT (10).

In the early years of LT, transplantation for hepatitis B virus (HBV) infection was regarded with trepidation. However, since the advent of hepatitis B immunoglobulin and nucleoside/nucleotide analogues, recurrence of disease has not been an issue (11). Future developments are likely to include the incorporation of more effective nucleoside/nucleotide analogues as prophylaxis against recurrence. This will enable us to forego the use of hepatitis B immunoglobulin, especially given that it is a pooled product that carries risk of virus transmission.

With HCC and cholangiocarcinoma, there are concerns for recurrent disease, especially if bulky disease is present on the explant (12). Furthermore, many groups are 'pushing the envelope' with acceptance of HCCs beyond the Milan criteria. Reducing recurrence may include switching to mammalian target of rapamycin (mTOR) inhibitor-based (ie, sirolimus) (13) or neoadjuvant therapies such as sorafenib (14).
TABLE 2
Causes of early liver allograft dysfunction: Incidence, risk factors, diagnosis and management

| Cause                        | Incidence | Risk factors                                                                 | Diagnosis                                                                 | Management                  |
|------------------------------|-----------|------------------------------------------------------------------------------|---------------------------------------------------------------------------|-----------------------------|
| Primary nonfunction          | 5.8%      | Donor age, severity of illness in recipient                                  | Focal loss, death within first 14 days after LT                             | Retransplantation           |
| Acute cellular rejection     | 30% to 50% of LT recipients | Inadequate immunosuppression, Treatment with immune-activating drugs (eg, interferon in HCV infection) | Liver biopsy                                                               | Steroid bolus               |
| Chronic rejection            | 15% with cyclosporine and 5% with tacrolimus based regimens                   | LT for primary sclerosing cholangitis or primary biliary cirrhosis and CMV infection | Liver biopsy                 | Increase CNI levels or sirolimus; Retransplantation (approximately 15%) |
| HAT and stenosis             | 5% to 10% of LT recipients                                                  | Technical difficulties                                                      | Doppler ultrasound MRI or CT angiography                                  | Thrombectomy, surgical repair; retransplantation in the case of HAT, stenting or balloon dilation of the artery for hepatic artery stenosis |
| Biliary complications (bile leaks and strictures) | 5% to 15% (15% to 30%), in living donor LT | Prolonged organ ischemia, HAT, donor organs obtained after cardiac death, CMV infection, immunological rejection, and recurrence of primary sclerosing cholangitis | Ultrasound, MRCP, ERCP, liver biopsy                                      | Percutaneous drainage, percutaneous transhepatic cholangiogram, biliary endoscopy, surgery or retransplantation |
| CMV infection                | 25% to 85%, typically occurs 1 to 4 months post-LT                          | Donor or recipient is CMV positive before LT                               | CMV PCR and/or CMV antigenemia or tissue samples (intestines or liver)    | Prophylaxis with valganciclovir and treatment with ganciclovir |

Adapted from references 54 and 55. CMV Cytomegalovirus; CNI Calcineurin inhibitor; CT Computed tomography; ERCP Endoscopic retrograde cholangiopancreatography; HAT Hepatic artery thrombosis; HCV Hepatitis C virus; LT Liver transplantation; MRCP Magnetic resonance cholangiopancreatography; MRI Magnetic resonance imaging; PCR Polymerase chain reaction

TABLE 3
Diagnosis, prevention and management of recurrent liver diseases post-liver transplantation (LT)

| Disease                      | Probability of recurrence (reference) | Diagnosis                                                                 | Prevention, Management                                                   |
|------------------------------|---------------------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|
| HCV infection                | 60% to 90% (3)                        | HCV PCR; liver biopsy                                                     | Pre-LT ribavirin + peginterferon + protease inhibitors; pre-LT polymerase inhibitor + ribavirin Ibuprofen; pre-LT retransplantation |
| HBV infection                | <10% (4)                              | HBsAg and HBV DNA PCR; liver biopsy                                       | HBlg plus Nucleoside or nucleotide analogues; Nucleoside or nucleotide analogues; retransplantation rare |
| Nonalcoholic fatty liver disease | 4% to 33% (5)                        | Ultrasound; liver biopsy                                                  | Lifestyle modifications; treatment of risk factors; Steroid-free immunosuppression | Lifestyle modifications; treatment of risk factors; retransplantation |
| Alcoholic liver disease      | <5% (6)                               | History; measurement of ethanol level                                     | Six months of abstinence before LT; assessment by addiction psychiatry; support group | Hospitalization (detoxification, withdrawal) |
| Hemochromatosis              | 0% (7)                                | Measurement of ferritin levels and transferrin saturation; liver biopsy    | Regular phlebotomy                                                        | Regular phlebotomy          |
| Hepatocellular carcinoma     | Up to 12.9% with sirolimus, up to 38.7% with CNI (9) | Ultrasound every 6 months                                                 | Sirolimus for high-risk lesions (retrospective data) (8) | Resection; locoregional therapy (eg, TACE and RFA, sorafenib) |
| Cholangiocarcinoma           | Five-year recurrence-free survival 70% (9) | Ultrasound and/or CT and/or MRCP/MRI                                      | Possibly mTOR inhibitors (no evidence for this)                           | Resection, radiation, chemotherapy |
| Autoimmune hepatitis         | 20% to 42% (10)                       | Liver biopsy                                                              | Consider dual immunosuppression –                                    | Glucocorticoids ± azathioprine or MMF UDCA; retransplantation |
| Primary biliary cirrhosis    | 16% (11)                              | GGT, AP and bilirubin levels; liver biopsy                                | –                                                                      | –                            |
| Primary sclerosing cholangitis | 17% (11)                             | GGT, AP and bilirubin levels; MRCP and/or ERCP and/or PTC; liver biopsy   | –                                                                      | Bile duct dilation; retransplantation |

Data adapted from reference 54. AFP Alpha-fetoprotein; AP Alkaline phosphatase; CNI Calcineurin inhibitors; CT Computed tomography; ERCP Endoscopic retrograde cholangiopancreatography; GGT Gamma glutamyl transferase; HBlg Hepatitis B immunoglobulin; HBsAg Hepatitis B surface antigen; HCV Hepatitis C virus; MMF Mycophenolate mofetil; MRCP Magnetic resonance cholangiopancreatography; MRI Magnetic resonance imaging; mTOR Mammalian target of rapamycin; PCR Polymerase chain reaction; PTC Percutaneous transhepatic cholangiography; RFA Radiofrequency ablation; TACE Transarterial chemoembolization; TIPS Transjugular intrahepatic portosystemic shunt; UDCA Ursodeoxycholic acid

Over the years, it has come to be recognized that cryptogenic cirrhosis represents burnt-out nonalcoholic steatohepatitis (NASH). The incidence of NASH following LT is on the rise, and can be compounded by the metabolic syndrome to which LT recipients are susceptible (15). Recurrent NASH should be managed by treating the underlying metabolic syndrome.
CENTRALLY ACTING ALPHA-2-AGONISTS (EG, CLONIDINE) DECREASES CNI-INDUCED RENAL VASOCONSTRICTION

SEDATION AND DEPRESSION

IT IS ASSOCIATED WITH INCREASED CARDIOVASCULAR MORBIDITY AND MORTALITY, TO ONE-HALF OF HCV-POSITIVE LT RECIPIENTS DEVELOPING NODAT (21). BETWEEN 26% OF PATIENTS AT ONE YEAR (20). THERE IS A STRONG ASSOCIATION WITH WEIGHT LOSS, AND INITIATION OF PHARMACOLOGICAL AGENTS FOR TREATMENT OF DIABETES (Table 5) (23). IN ADDITION TO STEROID WITHDRAWAL AND REDUCING CNI DOSE, SWITCHING FROM TACROLISMOUS TO CYCLOSPORINE (A LESS DIABETOGENIC AGENT) IS OFTEN EFFECTIVE (24).

DYSPLIPIDEMIA AFFECTS UP TO 43% OF PATIENTS AFTER LT, AND OCCURS PARTICULARLY DUE TO CNI USE. STORILISMOUS IS ASSOCIATED WITH AN EVEN HIGHER RISK OF DYSPLIPIDEMIA THAN CNIs, ALTHOUGH THIS HAS NOT TRANSLATED INTO AN INCREASED INCIDENCE OF CARDIOVASCULAR EVENTS (25). LIPID PROFILE SCREENING EVERY SIX MONTHS IS RECOMMENDED. STATINS ARE SAFE AND EFFECTIVE IN CONTROLLING HYPERLIPIDEMIA WITHOUT IMPACTING CNI LEVELS (26). CONCERN REGARDING HEPATOTOXICITY SHOULD NOT PREVENT THEIR USE, AND ROUTINE MONITORING SHOULD BE OBSERVED. STORILISMOUS INDUCED MYALGIA OR MYOPATHY WAS SHOWN TO AFFECT 8.6% OF PATIENTS IN A RETROSPECTIVE STUDY (27), ALTHOUGH IT WAS MILD AND DISAPPEARED WITH DISCONTINUATION OF THE STORILISMOUS.

TABLE 4: ANTHYPERTENSIVE AGENTS USED IN LIVER TRANSPLANTATION

| Antihypertensive agent | Benefits | Adverse effects |
|------------------------|----------|----------------|
| Calcium channel blockers, dihydropyridine class (eg, nifedipine) (first-line) | Decrease CNI-induced vasoconstriction | Headache, reflex tachycardia, edema, interact with CNIs |
| Beta-blockers | Decrease CNI-induced headache, decreased left ventricular hypertrophy | Impotence, bronchospasm, interact with CNIs |
| Angiotensin converting enzyme inhibitors and Angiotensin receptor blockers | Renal-sparing effects in diabetics, decreased CNI-induced vasoconstriction | Renal insufficiency and hyperkalemia (more with combination with CNIs) |
| Centrally acting alpha-2-agonists (eg. clonidine) | Decreases CNI-induced renal vasoconstriction | Sedation and depression |

CNI: Calcineurin inhibitor

TABLE 5: HYPOGLYCEMIC AGENTS USED IN LIVER TRANSPLANTATION

| Hypoglycemic agent | Target population | Advantage(s) | Disadvantages |
|--------------------|------------------|--------------|---------------|
| Sulfonylureas | Recent-onset NODAT | Low cost, rapid onset of action | Weight gain, hypoglycemia |
| Metformin | Metabolic syndrome | No weight gain, lower risk of hypoglycemia | GI side effects, lactic acidosis (in CKD) |
| Thiazolidinediones | Metabolic syndrome | Lower risk of hypoglycemia | Weight gain, liver toxicity (rare) |

Adapted from reference 23. CKD: Chronic kidney disease; GI: Gastrointestinal; NODAT: New-onset diabetes after transplantation

TABLE 6: RISK FACTORS FOR THE DEVELOPMENT OF RENAL DYSFUNCTION IN LIVER TRANSPLANTATION

| Pretransplant factors | Post-transplant factors |
|-----------------------|-------------------------|
| Female sex | Postoperative acute kidney injury and liver allograft dysfunction |
| Older age at transplant | Nephrotic drugs including calcineurin inhibitors |
| Pre-existing chronic kidney disease | Hypertension |
| Hypertension | Diabetes |
| Diabetes | Coronary artery disease |
| Hepatitis C virus infection | Diabetes |

Adapted from reference 60

Recurrent alcoholism has been reported in up to 20% of patients transplanted for alcoholic liver disease, with resultant decrease in long-term survival (16). However, the lower risk of recurrent disease is prompting an ethical discussion of appropriate selection of patients for LT. Many factors come into play such as the shortage of organs, optimal organ utilization and ensuring the best possible outcome for recipients. Currently, there is interest in studying and formalizing the indications for LT across Canada.

Metabolic complications following LT

Hypertension occurs in up to 70% of patients within the first year post-transplant secondary to CNI and corticosteroid use (17). Evidence-based information regarding optimal antihypertensive pharmacotherapy in LT is limited, although the effect of hypertension on renal function is particularly important. Based on expert opinion, the goal of antihypertensive therapy should be a blood pressure of 140/90 mmHg, or 130/80 mmHg in individuals with additional risk factors for atherosclerotic cardiovascular disease (18). The dihydropyridine class of long-acting calcium channel blockers, including nifedipine and amldipine, are the first-line antihypertensives because they minimally interact with CNIs (Table 4). Beyond one year after LT, patients may benefit from the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, particularly those who are diabetic or have proteinuria (19).

New-onset diabetes after transplantation (NODAT) occurs in up to 26% of patients at one year (20). There is a strong association between insulin resistance and diabetes with HCV infection, with up to one-half of HCV-positive LT recipients developing NODAT (21). It is associated with increased cardiovascular morbidity and mortality, development of renal dysfunction, a higher incidence of fatal infections, more rejections and impaired graft survival (22). Screening for NODAT should begin in the immediate post-LT period with regular fasting blood glucose monitoring. As discussed above, treatment goals are similar to those of diabetes in general: prevention of complications such as renal failure, neuropathy, retinopathy, cardiovascular and cerebrovascular disease.

Treatment includes limiting caloric intake, appropriate diet/exercise with weight loss, and initiation of pharmacological agents for treatment of diabetes (Table 5) (23). In addition to steroid withdrawal and reducing CNI dose, switching from tacrolimus to cyclosporine (a less diabetogenic agent) is often effective (24).

Dyslipidemia affects up to 43% of patients after LT, and occurs particularly due to CNI use. Storilismoous is associated with an even higher risk of dyslipidemia than CNIs, although this has not translated into an increased incidence of cardiovascular events (25). Lipid profile screening every six months is recommended. Statins are safe and effective in controlling hyperlipidemia without impacting CNI levels (26). Concern regarding hepatotoxicity should not prevent their use, and routine monitoring should be observed. Storilismoous induced myalgia or myopathy was shown to affect 8.6% of patients in a retrospective study (27), although it was mild and disappeared with discontinuation of the stornilismoous.

Nutritional status is often compromised in patients with ESLD. Following LT, an improved sense of well-being, along with prednisone treatment, contributes to overeating and development of obesity. One cohort study showed that approximately 20% of nonobese transplant recipients became obese over a two-year follow-up period (28-29). Patients transplanted for NASH tend to develop recurrent hepatic steatosis after LT with weight gain (30). Treatment of obesity involves a balanced diet, aerobic exercise and considering altering immunosuppressive medications, including steroid withdrawal.

Low bone mineral density occurs in up to 70% of patients with liver disease (31). The use of steroids and CNIs can further precipitate decline in bone mass after LT, reaching a plateau six months postoperatively. Transplant recipients should be screened for metabolic bone disease with dual energy x-ray absorptiometry scan every two years. Preventive strategies, such as physical activity and smoking cessation, should be encouraged. Daily supplementation with 1500 mg of calcium and 800 IU of vitamin D should be given to all patients, along with bisphosphonates and testosterone replacement in hypopandrojenic states as needed.

Renal complications after LT

Chronic kidney disease (CKD), defined as a glomerular filtration rate (GFR) < 60 mL/min/1.73 m² body surface area, occurs in up to 90% of LT recipients and is multifactorial in etiology (Table 6) (32). The incidence of renal dysfunction has specially increased with the...
TABLE 7

Recommended screening intervals for malignancies for liver transplant patients

| Malignancy           | Recommended examination (screening interval, if applicable) |
|----------------------|------------------------------------------------------------|
| Breast cancer        | Annual mammography starting at 50 years of age (similar to general population) |
| Cervical cancer      | Pelvic examination and Pap smear (similar to general population) |
| Colon cancer         | Colonoscopy every 5 to 10 years if no history of colonic neoplasia, every 3 to 5 years with history of neoplasia, yearly in ulcerative colitis patients |
| Esophageal cancer    | EGD in patients with Barrett’s esophagus and those at high risk for esophageal cancer (smokers and those transplanted for EtOH cirrhosis) |
| Lung cancer          | Chest x-ray every 1 to 2 years in smokers and those transplanted for EtOH cirrhosis |
| Oropharyngeal cancer | Otolaryngological examination every 1 to 3 years in smokers and those transplanted for EtOH cirrhosis |
| Prostate cancer      | Digital rectal examination and prostate-specific antigen |
| Skin cancer          | Annual skin examination |

EGD Esophagogastroduodenoscopy; EtOH Ethanol

adoption of the Model for End-stage Liver Disease score to prioritize patients for LT, with a 15% higher risk of post-LT end-stage renal disease (33,34). Based on prospective cohort data, CKD is associated with a 4.5 times greater probability of death versus patients with normal renal function, and a 2% to 5% per year risk of requiring dialysis (35). CNIs cause vasoconstriction of the renal afferent arterioles, resulting in decreased renal perfusion. Renal failure due to CNIs may be reversible with dose reduction or medication withdrawal (10,11).

Patients may be switched to the mTOR inhibitors sirolimus and everolimus for immunosuppression to preserve kidney function in the long term after LT. These patients should be screened for development of proteinuria, although its long-term impact on renal function is unclear (36).

Biliary complications

Biliary complications after LT usually occur as a result of impaired vascular supply at some time point during the patient’s postoperative course (37). Bile leaks are the most common, affecting up to 30% of LT recipients in the early postoperative period. Strictures at the biliary anastomosis may occur in the long term, which can be reversed with dilation and stenting via endoscopic retrograde cholangiopancre- atography (ERCP). In patients who develop hepatic artery thrombosis or have other risk factors with a significant impact on hepatic arterial flow, ischemic cholangiopathy may result in the long term. This condition is often complicated by recurrent cholangitis, and can be treated with antibiotics and stenting, although retransplantation is often indicated. Some patients may have Roux-en-Y anatomy following LT, especially those transplanted for primary sclerosing cholangitis, which will render ERCP more technically challenging (this technical difficulty is due to the length of the Roux limb, which may be circumvented by performing ERCP assisted by double-balloon technique at certain Canadian centres with this expertise).

SCREENING FOR MALIGNANCIES AFTER TRANSPLANT

Transplant patients are at higher risk for developing malignancies because immunosuppression curtails the cancer-sensing function of the immune system (38). Improving patient survival has resulted in exposure to immunosuppression for an extended period; consequently, nonskin malignancies arise in up to 16% of recipients and represent a common cause of late deaths. This is especially true in patients with concurrent smoking and alcohol use, who should undergo annual endoscopy, laryngoscopy and chest-x-ray, as described in Table 7. Skin cancers are up to 100 times more common among LT recipients compared with the general population (25). Transplant recipients should avoid excessive sun exposure, apply sunscreen regularly and undergo a thorough dermatological examination annually. Post-transplant lymphoproliferative disorder (PTLD) is associated with Epstein-Barr virus infection in 90% of cases and occurs in up to 2% of LT patients within the first year (39). Overall, PTLD has been known to affect up to 2.8% of adult and up to 15% of pediatric LT recipients (40). This generally presents as fevers, night sweats, weight loss and malaise, with or without lymphadenopathy. PTLD is managed through reduction of immunosuppression, rituximab or chemotherapy. Colonoscopy for colorectal cancer screening should be performed every five years, and annually if patient has a diagnosis of primary sclerosing cholangitis with ulcerative colitis. All other malignancies are screened as per recommendations for the general population.

PREVENTIVE CARE, QUALITY OF LIFE, SEXUALITY AND PREGNANCY

Potential LT recipients should ideally receive all necessary vaccinations before transplant because immunosuppressants significantly suppress T cell function and increase risk for infection (41). Live-attenuated vaccines carry a potential risk of shedding live virus, although studies have confirmed that these can be safely given to transplant patients (42,43). Any administration of live-attenuated vaccines such as varicella, Bacillus Calmette-Guérin, measles-mumps-rubella, polio, typhoid, yellow fever and rotavirus, should be performed only in consultation with the transplant centre. Only the following vaccines may be safely administered to both LT recipients and their household contacts: hepatitis A, hepatitis B, inactivated influenza, meningococcal, pneumococcal, tetanus, diphtheria, Haemophilus influ- enzae type b, pertussis and human papilloma virus.

Transplant recipients who smoke should be counselled regarding smoking cessation because the adverse effects of tobacco are possibly heightened. Studies have shown that LT recipients who smoke are at increased risk for all-cause mortality and vascular events (coronary artery disease, stroke and hepatic artery thrombosis, which can lead to graft loss). Nicotine replacement therapy and medications, such as bupropion, can safely be offered. Cannabis should be discouraged because it is known to worsen hepatic steatosis and fibrosis in chronic liver disease patients (44,45). Proper dental hygiene and regular check-ups are essential because excess oral bacteria in the presence of immunosuppression can lead to development of serious infections such as infective endocarditis. Antibiotic prophylaxis is not required in the transplant patient population, even in the context of dental procedures, unless an underlying cardiac condition predisposing to endocarditis is present.

ESLD causes significant disability, to the point of being unable to perform activities of daily living. LT enables the return of most patients to the workforce, which greatly enhances daily activities, physical health, health-related quality of life, sexual function and psychosocial well-being (46). Recipients may not have a health-related quality of life equivalent to that of the general population because many are readmitted to hospital for complications such as impaired wound healing and infections. However, resources, such as a dedicated transplant nurse, an exercise program and psychosocial support, can help improve perception of health and quality of life (47).

The availability of psychological support is important because reactive depression can occur due to difficulty coping with post-transplant life. Occupational counselling should be offered if a patient is experiencing difficulties in returning to the workforce. A Canadian transplant centre determined that 57% of their patients surviving a minimum of nine months had returned to employment (48).

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A majority of patients with ESLD lose sexual function and fertility (49). With LT, sexual function returns to normal in >90% of recipients (50). Erectile dysfunction may be treated with standard medications. Fertility could return at any time after transplantation; therefore, contraception should be used on surveillance of sexual activity. Ideally, pregnancy should be delayed beyond the one-year mark after LT. The use of MMF in pregnant mothers has been associated with birth defects and miscarriages. MMF should either be avoided among women of reproductive age or should be discontinued at least six weeks before a planned conception. A live birth rate >70% with favourable maternal and fetal outcomes has been documented in the American National Transplantation Pregnancy Registry (51). During pregnancy, hypertension is a complication encountered in up to 45% of transplant recipients (49). An increase in plasma protein levels that bind cyclosporine and tacrolimus can lead to subtherapeutic levels. Pregnancy is, therefore, associated with a 10% risk of organ rejection and requires more frequent monitoring of immunosuppressant levels to maintain the therapeutic range (52). Prematurity and low birth weight are the most common fetal complications, occurring in 10% to 55% of pregnancies (53). Overall, the long-term outcomes of most babies exposed to immunosuppressants in utero is favourable, with normal development (51).

CONCLUSION
The care of LT recipients has evolved, with excellent survival rates following LT. Gastroenterologists and primary care physicians in the community often follow LT recipients in conjunction with the LT physician, and it is important to be aware of the unique medical needs and complications associated with long-term immunosuppression. Such comprehensive care will ensure that the LT recipient benefits from optimal health and quality of life.

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