2023

Clinical Guidelines for Liver Transplantation

Continuum of Patient Care from Pre-Transplant to Post-transplant/Out-patient

BC TRANSPLANT
Provincial Health Services Authority

Vancouver Coastal Health
Promoting wellness. Ensuring care.

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Guideline Note:

These clinical guidelines have been developed to inform health care workers, including physicians, surgeons, nurse practitioners, and allied health care staff, on the indications for liver transplant, process of evaluation, listing, and post-operative care for the transplant recipient as recommended by the Liver Transplant program of British Columbia. These guidelines are not intended to replace clinical judgement of health care providers. Any clinician seeking to apply or consult the Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment.

While these guidelines are based on available evidence, considerations and expert opinions at the time of development, they will be updated regularly as needed based on evolving liver transplantation evidence and practice and constructive feedback received.

We aim to serve our patients with expert and exceptional care regardless of age, ethnicity, gender, race, religion, sexual orientation, gender identity or socioeconomic background and strive to embrace diversity, equity, belonging and inclusive excellence through our actions, policies and culture.

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List of Abbreviations

AASLD	American Association for the Study of Liver Diseases
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BCT	BC Transplant
CBC	Complete blood count
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor
CT	Computerized tomography
DCD	Donation after circulatory death
EBV	Epstein-Barr virus
ERCP	Endoscopic retrograde cholangiopancreatography
GI	Gastrointestinal
HBcAb	Hepatitis B core antibody
HBIG	Hepatitis B immune globulin
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
HDV	Hepatitis D virus
HE	Hepatic encephalopathy
HIV	Human immunodeficiency virus
HIV Ab	Human immunodeficiency virus antibody
ICU	Intensive care unit
IgG	Immunoglobin G
IM	Intramuscular
INR	International normalized ratio
IV	Intravenous
MELD	Model for End-stage Liver Disease
MELD-Na	Sodium Model for End-stage Liver Disease
MIBI	Myocardial perfusion imaging
MRI	Magnetic resonance imaging
NP	Nurse Practitioner
OR	Operating room
PNF	Primary non-function
PO	Once orally
PO BID	Once orally twice per day
PTN	Patient Transfer Network
TB	Tuberculosis
VGH	Vancouver General Hospital

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Note: 2.4 Updated Jan 2023

1. Introduction

Liver transplantation is a suitable therapy for patients with end-stage liver failure. The outcomes of liver transplantation have improved significantly in recent years, due to improvements in surgical techniques, anesthesia, and immunosuppressive therapies. One- and 5-year survival rates are above 90% and 75%, respectively. Most people return to a normally functioning life, although lifelong monitoring and immunosuppressive therapy is required.

Since the first liver transplantation was performed in British Columbia (B.C.) in 1989, the demand for the therapy has gradually increased. Initially, this demand was driven by the high prevalence of hepatitis B and C infections. While the number of transplants performed for patients with hepatitis B infection has remained stable, recent improvements in medical therapies for hepatitis C have resulted in a dramatic decline in the number of transplants performed for patients with this infection. Over the past 10 years, we have seen an increase in the number of transplants for non-alcoholic fatty liver disease (NAFLD), which will soon become the first indication for liver transplantation in North America. At present, at least 80 adults undergo liver transplantation annually in B.C.

The long wait time for a liver transplant and the progressive liver dysfunction that occurs during the waiting period have motivated many families to consider living donation.

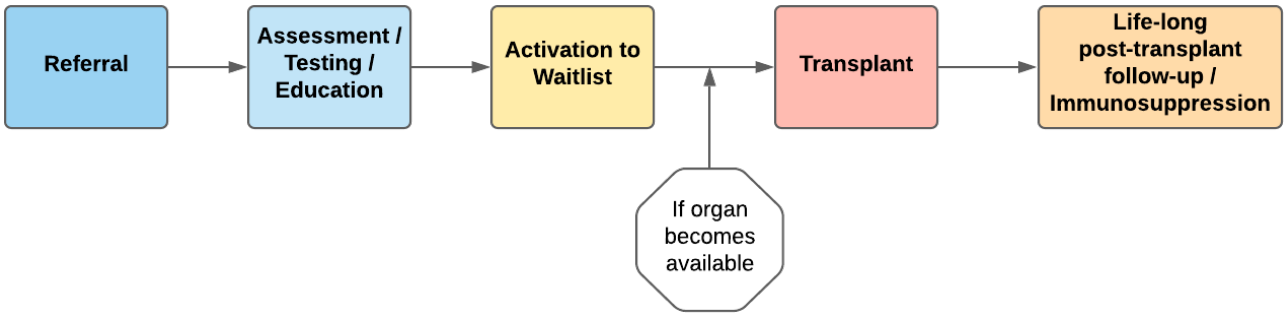
Purpose

These clinical guidelines have been developed to inform health care workers, including physicians, surgeons, nurse practitioners, and allied health care staff, on the indications for liver transplant, process of evaluation, listing, and post-operative care for the transplant recipient as recommended by the Liver Transplant program of B.C. These guidelines are not intended to replace clinical judgment of health care providers but rather delineate a consistent and transparent decision making process to ensure equity in access to liver transplantation in B.C.

Resource utilization, impacts on staff, and program or system issues are not considerations in decision-making for individual patients.

Care must be taken to be cognizant of personal biases that may arise both negatively (e.g., patient criminal history, developmental disability, racist patient attitudes) and positively (e.g., patient likeability, expressions of remorse, age, verbal skills, parenting status). As stated by the International Society for Heart and Lung, "*Care must be taken to ensure that psychosocial factors predictive of outcome are not confused with judgments of an individual's social worth*".

Figure 1. Steps in liver transplantation



Methods

This guidelines document was developed after reviewing the most up-to-date evidence available. The following guidelines were reviewed from the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL), and the International Liver Transplantation Society (ILTS):

- AASLD Position Paper: The Management of Acute Liver Failure – Update 2011
- AASLD Diagnosis and Treatment of Alcohol-associated Liver Disease – 2019 Practice Guidance
- AASLD Diagnosing, Staging and Management of Hepatocellular Carcinoma – 2018 Practice Guidance
- AASLD Therapies for Patients with Hepatocellular Carcinoma Awaiting Liver Transplantation: A Systematic Review and Meta-analysis, 2018
- AASLD Evaluation for Liver Transplantation in Adults - 2013 Practice Guideline
- AASLD Long-Term Management of the Successful Adult Liver Transplant – 2012 Practical Guideline
- AASLD Revised Practice Guideline – Management of Adult Patient with Ascites due to Cirrhosis, 2012
- AASLD Portal Hypertensive Bleeding in Cirrhosis: Risk stratification, Diagnosis and Management - 2016 Practice Guidance
- AASLD/EASL Hepatic Encephalopathy in Chronic Liver Disease – 2014 Practice Guideline
- EASL Clinical Practice Guidelines: Management of Alcohol-Related Liver Disease, 2018
- EASL Clinical Practice Guidelines: Management of Hepatocellular Carcinoma, 2018
- EASL Clinical Practice Guidelines: Management of Decompensated Cirrhosis, 2018
- EASL Clinical Practice Guidelines: Management of Acute (Fulminant) Liver Failure, 2017
- EASL Clinical Practice Guidelines: Liver Transplantation, 2015
- EASL Clinical Practice Guidelines on Nutrition and Chronic Liver disease, 2019
- ILTS Practice Guidance: Diagnosis and Management of Hepatopulmonary Syndrome and Portopulmonary Hypertension, 2016
- ILTS Consensus Statement on Immunosuppression in Liver Transplantation, 2018

Commitment to Culturally Safe & Equitable Health Care

The In Plain Sight report, released in November 2020, calls for action toward the elimination of anti-Indigenous racism in health care. All of the report's findings and recommendations were accepted and supported by the province's health authorities, who also collectively apologized to patients, families and staff in the health care system.

Racism exists, and much work is needed to eliminate racism in our health care system. Anti-Indigenous racism in particular, has significant consequences for Indigenous peoples accessing and receiving health care services. Anti-Indigenous racism negatively affects Indigenous patients and families access to care, their feelings of safety during health-care interactions, and the quality of their care outcomes.

The VGH liver transplant program and BC Transplant is committed to providing culturally safe and equitable organ transplant care in alignment with the Vancouver Coastal Health Authority and Provincial Health Service Authority's (PHSA) Service Plans.

All health care professionals are accountable to provide care according to the principles of anti-racism, cultural safety, and trauma informed care. We urge all providers across the continuum of transplant care (i.e., those who refer patients for transplant, and those who provide care during and after transplant) to personally consider and examine how existing structures and practices may be perpetuating health inequities and racism.

All providers are expected to increase their knowledge in addressing anti-Indigenous racism and practicing cultural safety and humility. Health authority educational resources are available through:

San'Yas: Anti-Racism Indigenous Cultural Safety Program
PHSA: Indigenous Health
Providence Health: Indigenous Cultural Safety at PHC
Coastal Health: Aboriginal Health Programs and Initiatives
Northern Health: Indigenous Health
Interior Health: Aboriginal Health and Wellness
Fraser Health: Cultural Safety and Humility
Island Health: Indigenous Health Cultural Safety

If patients are experiencing care that is not following the principles of anti-racism, cultural safety, and trauma informed care, they can confidentially contact the Patient Care and Quality Office (PCQO) at Vancouver Coastal Health or the PHSA. The up to date contact information for the PCQO can be found at the websites for the health authorities.

PHSA: email, pcqo@phsa.ca Phone (toll-free): 1-888-875-3256

Vancouver Coastal: email, pcqo@vch.ca Phone: 1-877-993-9199

Also see Definitions

Definitions

Definitions	
Anti-Racism	*is the practice of actively identifying, challenging, preventing, eliminating and changing the values, structures, policies, programs, practices and behaviours that perpetuate racism. It is more than just being "not racist" but involves taking action to create conditions of greater inclusion, equality and justice.*[1]
Cultural Humility	*is a process of self-reflection to understand personal and systemic biases and to develop and maintain respectful processes and relationships based on mutual trust. Cultural humility involves humbly acknowledging oneself as a learner when it comes to understanding another's experience.*[2]
Cultural Safety	*is an outcome based on respectful engagement that recognizes and strives to address power imbalances inherent in the health care system. It results in an environment free of racism and discrimination, where people feel safe when receiving health care*[2]*.*
Culturally Safe Environment	*this is the desired outcome and can only be defined by the Indigenous person receiving care in a manner that is safe and does not profile or discriminate against the person but is experienced as respectful, safe and allows meaningful communication and service. It is a physically, socially, emotionally and spiritually safe environment, without challenge, ignorance or denial of an individual's identity. To be culturally safe requires positive anti-racism stances, tools and approaches and the continuous practice of cultural humility.*[1]
Discrimination	*is treating someone differently because of their membership in the group*[3]
Indigenous	*Indigenous is a term which includes all those who are descendants of the original people of this nation called Canada*[3]
Anti-Indigenous Racism	*refers to the unique nature of stereotyping, bias and prejudice about Indigenous peoples in Canada that is rooted in the history of settler colonialism. It is the ongoing race-based discrimination, negative stereotyping and injustice experienced by Indigenous peoples that perpetuates power imbalances, systemic discrimination and inequitable outcomes stemming from the colonial policies and practices.*[1]

Racism	*is the belief that a group of people are inferior based on the colour of their skin or due to the inferiority of their culture or spirituality. It leads to discriminatory behaviours and policies that oppress, ignore or treat racialized groups as 'less than' non-racialized groups.*[1]
Trauma and Violence Informed Care	*Refer to Trauma and Violence Informed Care: A Tool for Health and Social Service Organizations and Providers 2021*

References:

[1] *In Plain Sight: Addressing Indigenous-specific Racism and Discrimination in B.C. Health Care*

[2] *Creating a Climate for Change* FNHA booklet.

[3] San'yas Anti-Racism Indigenous Cultural Safety Training Program

ADDITIONAL RESOURCES

- San'Yas Anti-Racism Indigenous Cultural Safety Training Program
- Indigenous Cultural Safety Collaborative National Indigenous Cultural Safety Webinar Videos: https://www.icscollaborative.com/webinars

2. Pre-transplant

2.1 Indications for transplant

Liver transplantation should be considered for patients with decompensated chronic liver disease when all other therapeutic options have been exhausted. Patients with compensated liver disease can have a median survival of 12 years, while those with decompensated liver disease have a median survival of 2 years. The Child-Pugh and MELD scores can be used as guides to assess when a patient has reached a level of decompensation. Typically, patients with a Child-Pugh score ≥8 or MELD score ≥14 should be referred for liver transplantation. Other indications for transplant include:

- Hepatic encephalopathy (recurrent, persistent, or refractory to medical treatment);
- Intractable or diuretic resistant ascites;
- Hepatorenal syndrome;
- Variceal bleeding;
- Hepatocellular carcinoma (within Milan criteria); and
- Cholangiocarcinoma (selected cases with low tumour burden).

It is important to consider alternative methods outside of transplantation that can be used for some patients with decompensated liver disease or liver cancer.

2.1.1 Hepatic encephalopathy

Hepatic encephalopathy (HE) is a common complication of advanced liver disease associated with liver dysfunction and with increased portal hypertension. It is an acute and usually reversible complication precipitated by active medical events, such as gastrointestinal bleeding, infections, electrolyte imbalances, dehydration, acute kidney injury, or overuse of sedatives. However, in more advanced cases it can be spontaneous or refractory to medical treatment. Severity of HE can be graded using the West Haven criteria (**Table 1**).

Although elevated ammonia levels are associated with its development, other mechanisms can lead to HE. As such, ammonia levels should not be used to diagnose, monitor, or direct therapy of HE. Lactulose is the first-line therapy for HE, and rifaximin can be used as a second-line agent in patients who have recurrent symptoms despite lactulose or who are lactulose intolerant. In B.C., rifaximin needs a special authority approval. Referral for transplant should be considered in patients with recurrent spontaneous episodes or who are non-responders to lactulose therapy.

Table 1: West Haven classification of hepatic encephalopathy

Grade	Description
Grade 0	No abnormality detected
Minimal HE	Abnormal psychometric test performance
Grade 1	Trivial lack of awareness, euphoria, short attention span, impairment of addition or subtraction
Grade 2	Lethargy, disorientation in time
Grade 3	Somnolence, responsive to stimuli, confused
Grade 4	Coma

HE, hepatic encephalopathy

2.1.2 Intractable or diuretic-resistant ascites

Development of ascites is associated with a poor prognosis. Initially, ascites may be mild and only detectable with ultrasound and can be controlled with small doses of diuretics and sodium restriction. Patients who develop ascites should be followed closely as they may require referral for transplantation. Patients with moderate or severe ascites should be considered for referral, particularly those with intractable or diuretic-resistant ascites. Diuretic-resistant ascites is defined as an ascites that cannot be mobilized or that recurs early due to a lack of response to sodium restriction or to diuretic treatment. Intractable ascites cannot be mobilized due to complications of diuretic treatment (i.e., encephalopathy, acute kidney injury, hyponatremia, hyperkalemia). Although serial large volume paracentesis (LVP) can be effective in managing ascites, it can lead to complications, such as muscle wasting, protein loss, and acute kidney injury. Patients requiring LVP more than once a month should be evaluated for adequate sodium restriction. If the ascites is truly intractable, the patient should be considered for therapies such as transhepatic portosystemic shunts (TIPS) or transplantation. Patients who are diagnosed with spontaneous bacterial peritonitis should also be referred for transplant.

2.1.3 Hepatorenal syndrome

Hepatorenal syndrome (HRS) is a form of rapidly progressive acute kidney injury that is associated with the presence of portal hypertension and ascites. It can sometimes be precipitated by an infectious process or large-volume paracentesis. Sometimes, it can be difficult to differentiate HRS from acute tubular necrosis. Initial management includes discontinuation of all potential nephrotoxic medications (including diuretics), volume repletion with albumin, and a combination of midodrine and octreotide. If HRS continues to progress, it can require intermittent

hemodialysis. HRS can be fully reversible with liver transplantation. As such, patients with HRS should be referred for transplant evaluation.

2.1.4 Variceal bleeding

Bleeding from varices (e.g., gastroesophageal or ectopic varices) can be initially managed with endoscopic treatment and beta blockers. When endoscopic therapies fail, salvage therapies such as TIPS should be considered. Patients with advanced liver disease (Child-Pugh score ≥8), particularly those who have suffered recurrent bleeding despite endoscopic and medical therapy, should be referred for transplant evaluation.

Some patients may not present with acute bleeding but may develop transfusion-dependent iron deficiency anemia from portal hypertensive enteropathy (more commonly in the stomach) or gastric antral vascular ectasias (GAVE). Endoscopic therapies have limited efficacy in managing these conditions, and transplantation referral should be considered.

2.2 Special Considerations

2.2.1 Hepatitis C virus

Hepatitis C virus (HCV) was the most common indication for liver transplantation in most programs in North America. Due to the recent development of direct antiviral agents (DAA), hepatitis C can now be cured in most cases, even in patients with decompensated liver disease. Depending on the severity of the liver disease, patients may have their HCV treated before or after transplant. If a patient has active hepatitis C (i.e., HCV RNA positive) before transplant, there is a risk of recurrent hepatitis C in the new liver. However, with rapid initiation of DAA therapy after transplant, the infection can be cleared and development of significant damage in the liver allograft can be avoided.

Due to the high efficacy levels of DAA, it is possible to accept an organ from a donor with an active HCV infection, as long as the organ has no fibrosis. DAA therapies can be initiated immediately after surgery, and HCV can thus be eradicated. This option can lead to a non-negligible increase in the number of organs that can be accepted for donation.

Patients are required to complete an Informed Consent Form: Willing to Accept a Donor Offer from HCV NAT - Positive Donors. Also refer to Patient Handbook: Accepting an Organ from a Donor with Hepatitis C Infection (on *BCT Website*).

2.2.2 Hepatitis B virus

With the advent of effective strategies for preventing allograft reinfection with hepatitis B virus (HBV), patients with HBV have successful outcomes after liver transplantation. Patients' HBV DNA level must be as low as possible before transplant although this may not be possible in those presenting with acute liver failure. Patients who are on treatment with lamivudine before transplant and have an undetectable viral load can continue with this medication. Patients who show a viral breakthrough with lamivudine or who have liver dysfunction with a detectable viral load and are treatment naïve should receive therapy with tenofovir or entecavir.

For long-term prophylaxis, tenofovir or entecavir combined with low-dose hepatitis B immune globulin (HBIG) is used for the first year after transplantation. For information on lamivudine, entecavir, and tenofovir, refer to **Chapter 7. Hepatitis B Antiviral Agent** of the *BC Transplant Clinical Guidelines for Transplant Medications*.

2.2.3 Alcohol-associated liver disease

Patients with liver disease caused by alcohol consumption can be considered for liver transplantation if there is a lack of spontaneous improvement after a period of clinical observation following abstinence from alcohol use. Patients with acute alcohol-associated hepatitis (previously known as alcoholic hepatitis) can also be considered for liver transplant if they show no response to treatment with steroids and if there is no previous history of documented alcohol-related disease. ***There is no longer a minimum period of abstinence that is required (i.e., the 6-month rule) to accept a referral.*** Patients for whom the reason for decompensation or lack of improvement is ongoing alcohol use, despite previous recommendations for abstinence, will not be considered for transplantation. Patients are still required to read and sign an Informed Consent Form (see **Appendix B**), as well as receiving a satisfactory report from an independent alcohol and drug counsellor (see **Appendix C** for the request form for addiction counselling) and favourable assessments from the transplant program staff members who have expertise in the evaluation of patients with history of substance use (see **Appendix E** for sample information for patients about alcohol and drug relapse prevention counselling).

Given the complexity of this situation, a specific guideline for transplantation in alcohol-associated liver disease (ALD) is available for consultation (Refer to Appendix I, Supplement - Clinical Guidelines in Patients with Alcohol Use).

2.2.4 Metabolic diseases

Liver transplantation is occasionally offered as therapy for patients with genetic disorders that can be corrected by liver transplantation. Examples include familial amyloidosis and metabolic conditions, such as oxaluria, glycogen storage disease, and urea cycle defects.

2.2.5 Human immunodeficiency virus

Eligibility criteria for patients with human immunodeficiency virus (HIV) to be considered for liver transplantation are:

- Undetectable HIV viral load and CD4+ cell count greater than 200 cells/mL (CD4+ cell count less than 200 cells/mL may be considered on a case-by-case basis);
- HIV antiretroviral medications while on wait list (no minimum duration of treatment required; HIV medications may be changed by HIV specialist at any time as long as treatment is uninterrupted); and
- No active opportunistic infections or history of previously untreatable opportunistic infection (e.g., progressive multifocal leukoencephalopathy).

Each case is assessed individually. HIV guidelines are dynamic in nature and are subject to change based on emerging research findings. The BC Liver Transplant Program has an on-going dialogue with the BC Centre for Excellence in HIV/AIDS on these issues.

2.2.6 Age

Although there is no absolute age limitation for transplantation, post-operative complications are more common and long-term outcomes are often below expectations in patients over 70 years of age. Candidates older than 70 years of age are screened carefully for concomitant diseases, and some individuals will not be suitable for transplantation due to comorbid conditions or frailty that would impact negatively the short-term (85% at 1 year) or long-term (60% at 5 years) probability of survival.

2.2.7 General health

Although secondary organ dysfunction may be present, it is not necessarily a contraindication if the condition is expected to improve after transplantation. Medical conditions that are not expected to improve and that can impact short-term (85% at 1 year) or long-term (60% at 5 years) probability of survival after transplantation could be considered as contraindication. Patients

should be advised against smoking before transplant in order to avoid an undesirable effect in the vascular anastomosis that can lead to serious and potentially fatal outcomes.

2.2.8 Ability and willingness to follow pre- and post-transplant regimen

Patients should be assessed for their ability to follow a complex medical regimen. Those with an ongoing history of non-compliance cannot be accepted.

2.2.9 *Psychosocial Factors*

At the VGH Liver Transplant Program, patients meet with a mental health interdisciplinary team, which can consist of social work, psychology, concurrent disorder clinician, psychiatry, or addiction medicine, for assessment of psychosocial factors pertaining to transplant suitability. Psychosocial assessment, psychological evaluation, and substance use support may be needed depending on patients' unique circumstances. The purpose of meeting with the interdisciplinary team is to identity any psychosocial factors affecting transplant suitability and to determine what recommendations, interventions, or support is required to help mitigate these factors for transplant candidacy. It should be recognized that medical and psychosocial issues may change over time. Thus, reassessment may be needed once psychosocial recommendations are fulfilled and/or if there are marked changes in the patient's circumstances. Pre- and post-transplant patients receive transplant related care both in-person and virtually, and in consultation with their community based healthcare providers. However, transplant recipients should be aware that they may be asked to travel to Vancouver for tests and appointments at any time. Some patients are eligible for travel benefits through The Ministry of Social Development and Poverty Reduction, First Nation Health Authority, Indigenous community or Nation, extended health plans, or other community or governmental programs.

Psychosocial Assessment

Transplant social workers meet with transplant candidates to conduct the psychosocial assessment. This assessment includes exploration of each patient's social determinants of health (i.e., finances, housing, vocational, social support, etc.), knowledge of the transplant process, cultural identity, diversity, and adjustment to illness. Information gathered helps determine resources that are already in place and what further factors need to be addressed in order to enable a patient to become a candidate. The Stanford Integrated Psychosocial Assessment for Transplant (SIPAT) is completed by the transplant social worker to adjunct the psychosocial assessment.

Psychological Evaluation

The Solid Organ Transplant (SOT) multidisciplinary team identifies some patients as needing psychological evaluation as part of the assessment for liver transplant consideration. Psychological evaluation for transplant candidacy can include an assessment of one's psychological functioning, psychiatric history, coping abilities or personal resources, understanding of the transplant process, motivation for surgery, treatment adherence factors, neurocognitive functioning, and history of substance abuse/misuse. This evaluation can include brief screening of health literacy, cognition, and psychiatric symptoms with objective and self-report measures. The psychological evaluation yields clinical recommendations on how to improve a patient's psychiatric stability, referrals to other services, and guidance on how to mitigate any concerning psychological variables or risk factors. Additionally, the transplant psychologist provides re-assessment, follow-up, and brief intervention to patients pre- and post-transplant as well as coordination of care with community partners.

Substance Use Supports

Patients identified as having complex substance use histories or concerns for relapse may be referred to the integrated providers on the SOT team, including an addiction medicine physician or concurrent disorder clinician. These providers collaborate with the patient to identify substance use challenges and to determine what interventions or supports might be beneficial to move the patient towards transplant candidacy. Patients can be supported through pharmacological treatment, individual counselling or group counselling, or other programming in **their community**. Moreover, this support is available to both pre- and post-transplant patients. Although the SOT clinic will try to support patients with these problems, it is not within its scope to treat or manage substance use disorder. Furthermore, an uncontrolled substance use disorder is a contra-indication for transplantation as it predicts non-compliance to medical directives after organ transplantation.

Required Documentation

The social support agreement (Appendix D) is discussed with and completed by all transplant candidates and their social support network. The Informed Consent Form (Appendix B) is also included when clinically indicated for support with relapse prevention.

2.2.10 *Social Support*

Having support in place for both the pre and post-transplant period yields successful transplant outcomes and is a requirement for transplant candidacy. Therefore, it is required that patients in collaboration with the transplant social worker identify caregivers or a social support network. The support network offers instrumental, informational, and emotional support. A social support network can be one individual and/or any combination of individuals who are able and willing to assist pre and post-transplant. Social support is required for an approximate period of three months post-transplant. With consent from the transplant candidate, the transplant social worker will liaise with the identified supports to ensure understanding of the role and to discuss the community, government, and financial supports available.

2.2.11 Post-transplant Requirements

Patients in collaboration with the transplant social worker arrange accommodations in the Greater Vancouver Area, defined as Chilliwack to Lions Bay, for an approximate period of three months post-transplant for themselves and their identified social support network. When indicated, third party funding options are explored to assist with costs. As part of the requirement to be in the Vancouver area, patients and their social support network will have required multidisciplinary post-transplant follow up appointments at the VGH Solid Organ Transplant (SOT) Clinic. Once deemed medically stable, a patient is able to return to their home community. Post-liver transplant patients are followed by the multidisciplinary team in the SOT clinic on an ongoing basis; the level of intervention and frequency of interactions with the team will fluctuate depending on a patient's medical and psychosocial status.

2.2.12 Transparency, expectations setting, and informed consent

Patients should be informed about what is involved in transplantation, including assessments by numerous members of the transplant team to determine if transplantation is a feasible treatment option. Patients should be informed that the decision regarding the appropriateness of transplantation is not made until after all assessments are completed. Patients should be advised that, in some cases, transplantation can lead to medical complications that can negatively impact their quality of life, overall wellness, and longevity.

2.2.13 Physician support

After consultation, patients are returned to the care of their referring specialist and family physician. The referring physician should be prepared to assist in arranging investigations required for the transplant assessment. Throughout the assessment process, the clinical coordinator communicates with the referring physician, the patient, and the transplant physicians regarding the assessment process and the patient's clinical condition.

After transplantation, patients are seen by the transplant team at the VGH Transplant Outpatient Clinic and then followed by the referring physician and their regular family physician. **The role of the transplant team in post-transplant care is limited to monitoring graft function, prescribing immunosuppressive agents, and assisting with management of transplant-related complications**. The family physician should be prepared to provide non-transplant-related care. In patients who redevelop cirrhosis in their graft, the referring physician should be ready to take over in the patients' care and assist in the management of liver decompensation.

2.2.14 Contraindications

The following are generally considered to be contraindications to liver transplantation as they are associated with high risk of immediate post-operative mortality or decreased short-term and long-term graft or overall survival:

- Active or chronic infection outside the biliary tree;
- Extra hepatic malignancy;
- Systemic disease that significantly limits life expectancy or quality;
- Refusal of all blood transfusions/blood products*;
- Ongoing or recurrent alcohol or substance use; and
- Inability or lack of support to follow a complex medical regimen.

*In some situations, it is possible, in consultation with the anesthesia and hematology teams, to optimize a patient's condition to avoid the use of blood products. However, some anomalies may not be correctable and will require transfusion of blood products.

2.2.15 Ethnicity Considerations

In October 2021, BC researchers published a cohort study: End stage liver disease etiology & transplantation referral outcomes of major ethnic groups in British Columbia, Canada. The research reviewed all referrals to the BC liver transplant program for patients with documented ethnicity from 1984 to 2019 and found that liver disease etiology and transplantation outcomes may vary by ethnicity.

Some study finding highlights included:

- confirmed known epidemiologic patterns for certain ethnicities such as hepatitis B in Asian patients with evolving trends such as alcohol related liver disease and primary sclerosing cholangitis (PSC) within the South Asian population.
- confirmed that First Nations patients have an increased predisposition to autoimmune liver disease, specifically primary biliary cholangitis (PBC) and autoimmune hepatitis (AIH) but not PSC, and may have lower transplantation rates.
- discovered that South Asian patients may be deemed ineligible for transplantation at an earlier stage of assessment.

More work is needed to fully understand the results so preventative and management strategies can be designed, as well as public and health care professional education, tailored towards specific ethnic communities.

2.3 Acute liver failure

Acute liver failure (ALF) is defined as the development of hepatic dysfunction (i.e., coagulopathy, jaundice, altered mentation) in a patient without a prior history of hepatic disease, with the exception of non-cirrhotic Budd-Chiari, Wilson's disease, or autoimmune hepatitis. The time period between the onset of jaundice and the development of hepatic encephalopathy (HE) can range from 10 days to 24 weeks. The most common etiologies of ALF are viral (i.e., hepatitis B and E), drugs/toxins (acetaminophen), and vascular causes. Although some patients with ALF survive without the need for transplant, anywhere from 20 to 60% of patients with ALF require a liver transplant. Currently, ALF accounts for 10% of all transplants.

2.3.1 Candidacy for transplant

Criteria for evaluation is based upon the King's College criteria (**Table 2**), which identify patients at high risk for need for transplant, where laboratory parameters are separated by ALF etiology (paracetamol or acetaminophen vs. non-acetaminophen).

Table 2: King's College criteria for liver transplantation in acute liver failure

Acetaminophen	Non-Acetaminophen
pH<7.3* or Arterial lactate >3.5mmol at 4h or Arterial lactate >3.0mmol at 12h* or PT>100s (INR>6.5) Serum creatinine >300 mmol/L (3.4mg/dL) Grade 3 or 4 encephalopathy	Prothrombin time greater than 100 s (INR>6.5) (irrespective of grade of encephalopathy) or any three of the following: 1. Age less than 11 years or greater than 40 years 2. Etiology of non-A/non-B hepatitis, halothane hepatitis, or idiosyncratic drug reactions 3. Duration of jaundice of more than 7 days before onset of encephalopathy 4. Prothrombin time greater than 50s (INR>3.5) 5. Serum bilirubin level greater than 17mg/dL (300µmol/L)

*After fluid resuscitation. PT, prothrombin time

2.3.2 Pre-transplant testing

Prior to being placed on the transplant list, patients should have had assessments completed to rule out pre-existing cirrhosis, as well as ALD, keeping in mind that patients with subacute ALF (i.e., 5 to 24 weeks between the development of jaundice and HE) can often present with a shrunken nodular liver, splenomegaly, and ascites. Thus, a thorough history from either the patient or from family members is crucial. Liver biopsy can be performed to assess for chronic fibrosis, but most often a liver biopsy demonstrates only massive or submassive necrosis. However, a liver biopsy can help exclude malignant infiltration and is recommended in patients with a history of malignancies, especially if no other etiology has been identified as a cause of the ALF. An etiology for the ALF should be sought, including infectious (hepatitis A, B, C, and E), hereditary (autoimmune hepatitis, Wilson's), vascular (Budd-Chiari), or toxic causes using both bloodwork and imaging, and all patients should have a baseline toxicology screen done on admission, including acetaminophen (Tylenol®) level.

2.3.3 Pre-transplant management

The leading causes of mortality in patients with ALF are infections, cerebral edema, and multi-organ failure. Currently, management is geared towards treatment of the underlying etiology as well as screening for and preventing infection and cerebral edema. All patients should be closely monitored for potential cerebral edema by assessing for any changes in their mentation or level of consciousness. We recommend referring to the American Association for the Study of Liver

Diseases (AASLD) and the European Association for the Study of the Liver (EASL) clinical guidelines for the management of ALF for more details.

2.4 Hepatocellular carcinoma (REVISED JAN 2023)

Liver transplantation is the optimal treatment strategy for patients with early-stage hepatocellular carcinoma (HCC) who are not candidates for surgical resection or locoregional therapies. It provides the best oncologic resection, replaces the diseased liver, and restores normal hepatic function. For patients with HCC exceeding the Milan criteria (i.e., one lesion ≤5cm, or 2 or 3 lesions ≤3cm), survival after transplantation incrementally decreases with increasing tumour size and number. However, it was felt that the Milan Criteria was too restrictive and that it would still be possible to achieve excellent outcomes with a more permissive criteria.

Selection criteria for liver transplantation are aimed at improving patient's quality of life and survival. They consider tumour biology, tumour size and number, probability of survival, transplant benefit, organ availability, wait list composition, and allocation priorities.

2.4.1 Current size criteria

In the VGH Liver Transplant Program, liver transplantation is offered as an option for patients with HCC who are not candidates for locoregional therapy of who have persistent or recurrent tumors despite treatment and who fall within the following criteria:

- Total Tumor volume $\leq$145 cm^3 AND Alfa-fetoprotein level < 1000 ug/L (TTV criteria)
- No angioinvasion, ruptured HCC, or evidence of extrahepatic disease

The TTV is calculated by summing the volumes of each visible tumor (LR-5 lesion). The radius should be the half of the longest axis measured in a lesion.

2.4.2 Role of downstaging and bridging treatments

There is limited evidence supporting the use of locoregional therapy (LRT) to reduce the risk of wait list drop-out and to serve as a "bridge" to liver transplantation. However, LRT is justified when the wait time for transplantation is expected to exceed 6 months. The goal is to prevent tumor progression beyond transplant criteria. In addition, response to LRT is a marker of tumour biology and can aid in more a refined selection of patients who have lower risk of recurrence and better success with liver transplant.

The BC Liver Transplant Program uses LRT as a way to reduce tumour size to acceptable liver transplant criteria. Given that patients who were downstaged to Milan have similar outcomes to those who were within criteria at the start, this approach was justified. However, there is less

evidence for long-term outcomes of patients who are downstaged to a TTV criteria. We have not yet defined the entry criteria for downstaging therapy, although most common practice is to exclude those with a large burden of disease, extrahepatic disease, and angioinvasion. Exclusion criteria to LRT include inadequate hepatic function defined as Child Pugh B/C status. Locoregional therapy used includes transarterial chemoembolization (TACE), radioembolization (Y90), stereotactic radiation therapy, and thermal ablation.

Patients with HCC should have abdominal imaging every 3 months while waiting for a liver transplant, and the images are reviewed by a multidisciplinary team at a liver tumour board. **It is the responsibility of the referring physician to ensure that recommendations for imaging and treatment are followed.** Patients are removed from the transplant waitlist if tumours increase and are outside the TTV criteria. Patients with HCC are assigned a MELD equivalent to the Median MELD score at the time of transplant plus 3 (MMaT+3) if they have at least one viable lesion larger than 2 cm in diameter. If their natural MELD (i.e., MELD score that reflects their liver disease) exceeds the HCC-MELD score, their place on the waiting list is based on their natural MELD. That means that patients will always receive the score that will increase their priority on the waiting list.

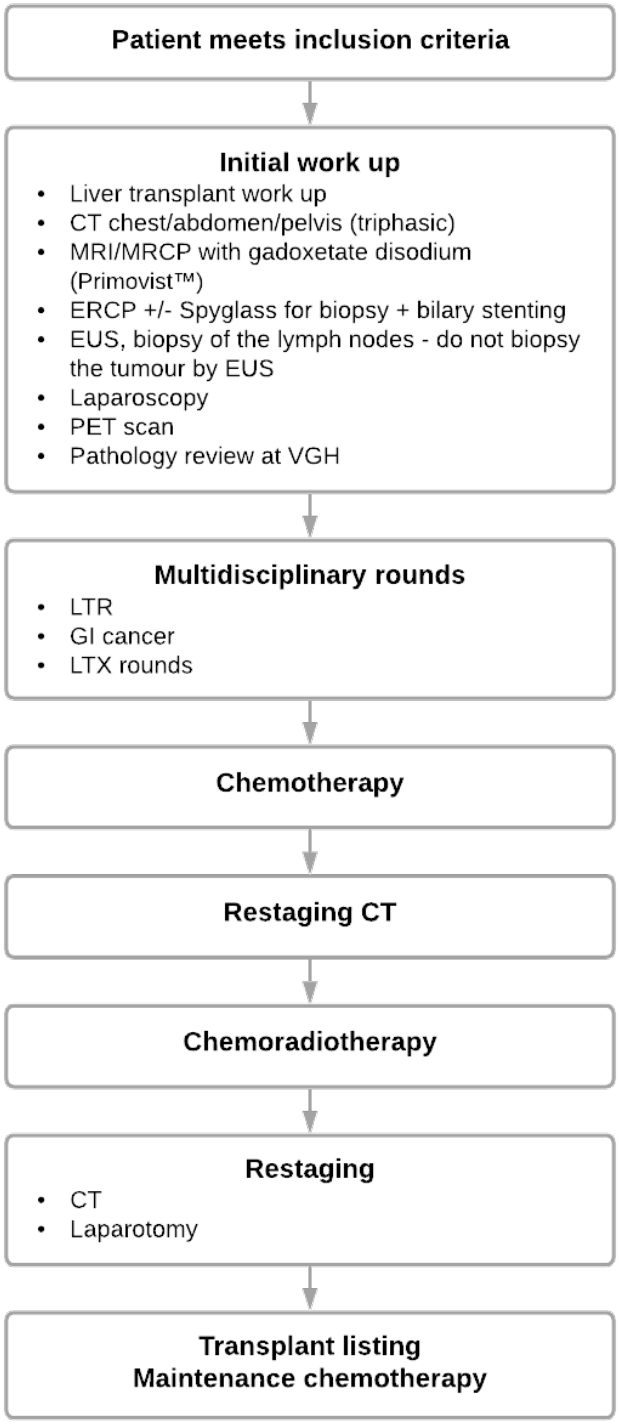
2.5 Hilar cholangiocarcinoma

Table 3. Inclusion and exclusion criteria for liver transplant in hilar cholangiocarcinoma

Inclusion criteria	Exclusion criteria
Unresectable HCC (cases should be presented at liver tumour rounds)	Metastatic disease (intrahepatic metastases, extrahepatic metastases)
Size ≤3cm	Age >65 years (relative)
Cancer at or above cystic duct insertion on the common hepatic duct	Poor candidate for chemotherapy
Absence of involvement of portal lymph nodes (retroduodenal and hepatic artery lymph node) by EUS	ECOG ≥2
Serum creatinine >300 mmol/l (3.4mg/dl)	Prior attempt at resection or percutaneous biopsy of the tumour
Grade 3 or 4 encephalopathy	

HCC, hilar cholangiocarcinoma; EUS, endoscopic ultrasound; ECOG, Eastern Cooperative Oncology Group Performance Status.

Figure 2. Protocol for clinical management of hilar cholangiocarcinoma



2.6 Neuroendocrine tumours

Neuroendocrine tumours (NET) occur at the rate of 5 per 100,000. NET can arise from different parts of the neuroendocrine system, and the heterogeneity of their presentation makes the management and analysis of outcomes difficult. The diagnosis is often delayed, and often the tumours are not identified until liver metastases are present. Liver metastases are the leading cause of death in NET patients, and effective management of liver metastases is important in the patient's overall care.

The results of retrospective studies examining liver transplantation for NET-related liver metastases have been variable, and the interpretation of these studies is difficult due to selection biases and heterogeneity of patients (**Table 4**). Randomized controlled trials for NET are considered unfeasible due to many unknowns regarding selection criteria and questionable outcomes.

Table 4: Summary of retrospective studies examining liver transplantation for NET-related liver metastases

Lead author, year	N	5-year survival after liver transplant	5-year DFS	5-year survival after diagnosis of metastases
Le Treut, 2013	213	52%	30%	73%
Olausson, 2007	10	90%	--	--
Frilling, 2006	15	67.2%	48.3%	--
Gedaly, 2011	150	49%	--	--
Máthé, 2011	89	44%	47%	--

NET, neuroendocrine tumours; DFS, disease-free survival

Criteria for liver transplantation for NET:

- Age <60 years (relative)
- Confirmed low grade (G1-G2)
- Primary tumour drained by the portal system and removed, and all extrahepatic disease removed
- Metastases disease to <50% of liver volume
- Stable disease and response to therapy for at least 6 months prior to transplant consideration

Table 5. Protocols for liver transplantation for NET-related liver metastases

Stage	
Initial referral	Consultation • Medical oncology consultation • Surgical consultation • Hepatologist consultation
	Staging • MRI of the liver • CT chest and pelvis with IV/PO contrast • CT abdomen pancreas protocol (if vascular anatomy to the liver not adequately visible on MRI) • Ga scan, PET-CT scan
	Labs • Chromogranin A • If serotonin secreting tumour suspected, 24-hour urine for 5-HIAA
Determination of Resectability	Surgical consult to determine resection vs. transplant Discussion at the liver tumour rounds
Liver transplant evaluation (to start 6 months after initial referral after disease stability)	Standard liver transplant evaluation
	Medical clearance
	Echocardiogram
	Transplant surgeon consult • Specifically ask about high risk organs (CDC high risk, DCD) • Assess for suitability for a split liver graft
	Hepatologist consult
	Social worker consult

2.7 Hepatopulmonary syndrome

Hepatopulmonary syndrome (HPS) is defined as hypoxemia resulting from the presence of intrapulmonary vascular dilatations in a patient with portal hypertension. The prevalence of HPS in patients with cirrhosis ranges anywhere from 5 to 32%, with a wide variability in severity of the condition. Patients often present with hypoxia, orthodeoxia, and platypnea. In HPS, the arterial-alveolar oxygen gradient ($AaPO_2$) is greater than 15mmHg.

2.7.1 Initial testing

Initial screening for HPS is completed with pulse oximetry, and if a patient shows evidence of decreased oxygen saturation, then further testing is initiated. Often, the first-line for HPS is a contrast (i.e., bubble) transthoracic echocardiogram: bubbles appearing in the left atrium after three or more cycles indicate a positive result for HPS. Other options for imaging are an arterial blood gas (ABG), a microaggregate albumin scan (MAA), or a lung perfusion scan.

If HPS is identified, the patient is referred to the pulmonary specialist to determine severity (**Table 6**) and whether treatment (i.e., supplemental oxygen or other therapeutic measures such as coil embolization) need to be undertaken. The severity of the patient's disease can be assessed based on the PaO_2. Anesthesiology evaluation is an essential part of the transplant evaluation, as peri-operative management in these patients to prevent possible air embolization is crucial.

Table 6. Hepatopulmonary syndrome severity index

HPS Stage	PaO_2 (mmHg)
Mild	≥80
Moderate	60 to <80
Severe	50 to <60
Very Severe	<50

HPS, Hepatopulmonary syndrome

2.7.2 Management

In patients who have had desaturation and hypoxia affecting their ability to function, supplemental oxygen should be the first step for treatment if they meet the criteria to receive it at home. Supplemental oxygen results in improvement in the majority of patients.

2.7.3 Transplant

American Association for the Study of Liver Diseases (AASLD) guidelines recommend that patients with severe hepatopulmonary syndrome (HPS; PaO_2 <60mmHg), who also have features of portal hypertension (i.e., ascites, varices, splenomegaly, or thrombocytopenia), positive bubble echo, and no clinically significant pulmonary disease should be listed with exceptional MELD points. Attribution of exceptional MELD points is discussed on a case-by-case basis.

2.8 Polycystic liver disease

Polycystic liver disease (PLD) occurs in the setting of two distinct hereditary conditions: (1) autosomal dominant PLD or (2) in association with autosomal dominant polycystic kidney disease (ADPKD). The extent of cysts within the liver may be defined as either >10 or >20 liver cysts. The classification is based upon the severity of disease assessing the number and size of cysts as well as the extent of liver parenchyma involved. The Gigot classification is a radiological assessment but does not take clinical symptoms into consideration. Assessment of the liver parenchyma involves calculating height-adjusted total liver volume (htTLV) which provides a more detailed picture of the extent of the cysts. There is a good correlation between the htTLV, defined as mild, moderate, or severe phenotype, and the risk of complications.

2.8.1 Complications

Complications of PLD include:

- Impact on Quality of Life (QoL). This can objectively be defined by the Polycystic Liver Disease Questionnaire (PLD-Q) score which is a PLD-specific questionnaire incorporating, for example, abdominal pain, anorexia, early satiety, and nausea. A higher score indicates higher disease burden.
- Cyst hemorrhage
- Cyst infection
- Cyst rupture
- Volume-related complications from mass effect
    - Sarcopenia from gastric compression
    - Obstructive jaundice
    - Portal hypertension (ascites, varices)
    - Edema

2.8.2 Management

Interventions for PLD may include somatostatin analogues for preventing further liver growth, diuretics for ascites and edema, cyst aspiration +/- alcohol injection, cyst fenestration, cyst resection, or liver resection.

2.8.3 Role of liver transplantation

Liver transplantation is reserved for complications refractory to other therapeutic interventions such as severe malnutrition associated with hypoalbuminemia and sarcopenia or portal

hypertension. Liver transplantation may also be a consideration combined with renal transplantation in patients with ADPKD. Further, subjective assessment of deterioration in quality of life assessed by the PLD-Q score may also be a consideration for liver transplantation. It should be noted that prior liver resection results in an increase in morbidity and mortality following liver transplantation.

2.9 Frailty

Malnutrition affects a large proportion of patients with cirrhosis, often increasing in severity as the liver disease progresses. While approximately 20% of patients with compensated cirrhosis are malnourished, the rate of malnutrition is greater than 50% in patients with decompensated disease. **Table 7** illustrates different nutritional deficiencies.

Sarcopenia, defined as the presence of malnutrition in the setting of loss of muscle mass and near the severe end of the spectrum of malnutrition, is associated with higher morbidity and mortality. Patients with sarcopenia have higher rates of infections, higher rates of hospitalizations from fluid overload, and hepatic encephalopathy, as well as increased mortality overall and increased mortality in the peri-operative phase post-transplant. As most patients with decompensated cirrhosis are on a sodium restricted diet, and the presence of ascites often results in anorexia, patients awaiting transplant often require specialized dietetic care in order to address these needs.

Table 7. Definitions of nutritional deficiencies

Term	Definition
Malnutrition/ Undernutrition	Nutrition-related disorder arising from decreased intake or absorption of nutrition, leading to decreased mental and physical ability and impaired clinical outcome from disease.
Muscle Wasting	Ongoing, progressive loss of muscle mass; can lead to muscle atrophy.
Sarcopenia	Generalized decrease in overall muscle mass and function.
Frailty	Loss of reserve (physiologic, cognitive, and functional) leading to decreased ability to perform activities of daily living.
Immunonutrition	Use of specific nutrients in an attempt to modulate the immune system and to improve overall health (such as using various amino acids, nucleotides, and fatty acids).
Deconditioning	Declining capacity of muscle function, usually due to immobility or debilitating disease.

2.9.1 Monitoring

Currently, all transplant patients are seen by the transplant dietician at the initial visit, periodically throughout admission, and during followed-up in clinic after hospital discharge. Outpatients identified by the transplant clinic physician as being at risk for malnutrition (e.g., weight loss, loss of muscle mass, endorsed anorexia, or refractory ascites requiring serial paracenteses) are referred to the transplant dietician. The patient is then followed by the dietician at regular intervals (every 1 to 6 months) as needed until any nutritional concerns have resolved. It is recommended that patients at increased risk for malnutrition or patients with sarcopenia should be placed on a high protein diet (i.e., 1.5g per kilogram of patient weight per day).

2.9.2 Assessment

There are many scores to assess frailty that can be done in the clinic. The first and foremost test is a detailed nutritional assessment, taken by a transplant registered dietician or a nutritional expert. Sarcopenia can often be identified via an assessment of skeletal muscle on cross-sectional imaging. Muscle mass at the L3 vertebrae can be measured via the standard index CT abdomen administered on all liver transplant patients). This assessment, along with measurements of mass loss of the psoas, paraspinal, and abdominal wall muscles, is recognized by many nutritional and transplant societies as a reliable method to quantify loss of muscle mass. Image analysis software can be used to calculate the total area of muscle at L3, which is then normalized to height to obtain the skeletal muscle index. Although routine CT imaging surveillance is not feasible in all patients awaiting transplant, this may be possible in patients with malignancy undergoing surveillance imaging.

In patients who have decompensated cirrhosis with fluid overload, weight alone is a misleading indicator of body mass assessment. Currently, the dietician at the VGH Liver Transplant Clinic can assess patients for sarcopenia by measuring mid-arm muscle circumference (MAMC), triceps skinfold thickness (TSF), and midarm muscular area (MAMA). All of these assessments are simple, low cost, and easily done in clinic. MAMC and TSF have been shown to be reliable prognostic markers for mortality in patients with chronic liver disease.

3. Patient referrals

3.1 Outpatient referral

To refer a patient to the outpatient liver transplant program, the referring doctor must be a specialist, such as a hepatologist, surgeon, internal medicine specialist, or gastroenterologist. Referrals from family doctors are generally not accepted. To ensure that patients are booked in an appropriate time frame, the following information should be provided with the referral:

- VGH Pre-Transplant Assessment referral form (see Appendix A)
- Recent blood work to calculate MELD and MELD-Na scores, including INR, total bilirubin, creatinine, sodium, electrolytes, CBC, AST, ALT, gama-glutamyl transferase (GGT), alkaline phosphatase
- Abdominal diagnostic imaging report(s) (CT scan abdomen triple phase/MRI with contrast) within the past 3 months
- Echocardiogram done within the past year and coronary CT angiogram (CTCA) if necessary (i.e., patient older than 60 years of age, NASH cirrhosis, history of diabetes or coronary artery disease, family history of premature coronary artery disease, smoking.) Myocardial perfusion imaging (MIBI) scan is acceptable if CTCA is not possible or available.
- Electrocardiogram and chest X-ray
- Gastroscopy for screening of esophageal varices done within the past year
- Documentation of adequate colorectal and breast cancer screening according to guidelines
- Relevant health history or clinical note
- Abstinence period from alcohol and/or drugs as well as smoking (cigarettes, e-cigarettes, marijuana) if there is a previous history of use

The Social Support Form (Appendix D) is sent to all patients at the time of referral processing. Appendix C would be sent to the Addictions Specialist if they were seeing a patient with a substance use disorder. Appendix E would be sent to a patient who is advised to follow A & D counselling based on past medical history.

A minimum period of alcohol abstinence is no longer an absolute requirement. Refer to Supplement – Appendix I.

Contact information at Vancouver General Hospital:

	Address:	**Contact**:
Pre-Liver Clinical Coordinator **Solid Organ Transplant Clinic** **Pre-Transplant Assessment**	Gordon and Leslie Diamond Center 5th Floor 2775 Laurel Street, Vancouver, B.C. V5Z 1M9	*Phone*: 604-875-5182 *Toll-free*: 1-855-875-5182 *Fax*: 604-875-5236

3.2 Inpatient referral

If a hospitalized patient requires an urgent liver transplant assessment, please contact the liver transplant gastroenterologist on call via the VGH switchboard (604-875-4111).

Patients in hospitals outside VGH should be in a stable condition to tolerate an interhospital transfer. As a general rule, a patient should be in a condition to be moved to a general medicine ward. Patients who are in an intensive care unit (ICU), on mechanical ventilation, or requiring continuous use for vasopressors need to improve sufficiently to be transferred to a general medical ward before a transfer to VGH is possible. For inpatients with a diagnosis of acute liver failure requiring ICU care, transfers to VGH are accepted from ICU to ICU.

Sometimes patients require transfer from a small community hospital with limited resources for testing and management. In these cases, transfer to a larger centre within the patient's health authority should be considered first for stabilization.

Patients should be evaluated for possible contraindications to transplantation within their home centre. The following investigations should be done before a transfer is accepted:

- CT scan triple phase/MRI abdomen with contrast
- Echocardiogram
- CTCA or MIBI scan if CTCA not possible or available (refer to **Section 3.1** for risk factors);
- CT chest (if the patient is a smoker)
- Pulmonary function tests (if the patient is a smoker or has a history of obstructive or restrictive lung disease)
- TB skin test or QuantiFERON®
- Gastroscopy to exclude high risk gastroesophageal varices

In patients with acute liver failure, a transfer can be accepted without completion of the above investigations, given the urgency of the situation.

Once the case is discussed with the on-call hepatologists and no obvious contraindications are identified, a three-way discussion should be immediately arranged via the Patient Transfer Network (PTN). This call should include the referring physician, the hepatologist on-call, and the accepting physician (i.e., internal medicine, ICU, or gastroenterology). The goal of the discussion is to delineate the patient's needs, the suitability and stability of the patient, and the goal of the transfer. The patient should be transferred with all the relevant information that must include a dictated transfer report, results of all the imaging and cardiology tests, medications list, and consult notes of relevant specialists.

A checklist was created to guide referring physicians and it is available on BC Transplant website. This checklist should be completed and sent alongside the transfer notes.

After the transplant evaluation is completed, the patient is transferred back to their original hospital or to a centre within their health authority that can offer the level of care that is required by their condition.

3.3 Assessment

Patients are usually seen on an outpatient basis at the Pre-Transplant Assessment Clinic at VGH Diamond Centre unless they are too ill and need to be hospitalized. Critically ill patients may be transferred to VGH for assessment and then transferred back to their referring physician whenever possible for ongoing management.

At the time of the initial assessment, patients are seen by the clinical coordinator, a transplant hepatologist, a surgeon, and an anaesthetist, as well as by the team's psychologist, social worker, and dietician. All referred patients are discussed at a weekly meeting of the liver transplant team. At that time, a recommendation is made about the most appropriate management of the patient's liver disease and further investigations may be arranged for patients deemed to require transplantation. In some cases, consultation with other specialists may also be sought.

Patients referred to VGH Pre-Transplant Assessment often come to clinic and assume that he/she/they is on the "list for transplant." It is important to clarify with patients and families during their initial clinical visit the difference between pre-assessment list and active list.

3.3.1 Testing

Table 8 outlines the routine pre-liver transplant investigations that are typically completed during the assessment stage.

Table 8. Routine pre-liver transplant investigations

Type	Test
Laboratory	ABO Complete blood count Electrolytes, urea, creatinine, glucose Total protein Liver tumour markers PTT, INR Liver function tests BNP levels FIT test Where indicated: iron studies, ceruloplasmin, alpha-1 antitrypsin, autoimmune panel (antinuclear antibody, anti-smooth muscle, anti-LKM, antimitochondrial antibodies, immunoglobulins) HCV RNA, HCV genotype, Hepatitis D Antibody
Urine	Urinalysis Urine drug testing (if history of alcohol, drug or cigarette use)
Microbiology/ Serology	Testing for tuberculosis (TB skin test or IGRA) Hepatitis B, Hepatitis C, CMV, EBV, Hepatitis A, HSV, VSV, HIV, mumps, measles, rubella Additional screening as necessary based on country of origin/travel (e.g., Strongyloides)
Radiology Studies	Chest X-ray Electrocardiogram Echocardiogram Ultrasound Doppler of liver Mammogram for females (40 years or older) Triphasic abdominal CT scan/contrast enhanced MRI of liver Persantine MIBI (if 60 years or older or if cardiac risk factors) CT chest (if significant smoking history or liver tumours)
Other	Selected patients may require gastroscopy, ERCP, colonoscopy Dental exam Anesthetic consult Oxygen saturation

ABO, blood type test; PTT, partial thromboplastin test; INR, International ratio; BNP, B-type natriuretic peptide; FIT, fecal immunochemical test; HCV, hepatitis C virus; IGRA, interferon-gamma release assay; CMV, cytomegalovirus; EBV, Epstein-Barr test; HSV, herpes simplex virus; VZV, varicella zoster virus; HIV, human immunodeficiency virus; LKM, liver-kidney microsomal antibody; MIBI, myocardial perfusion imaging; ERCP, endoscopic retrograde cholangiopancreatography.

3.3.2 Education of patients

During assessment, patients and families receive written information about transplantation that outlines:

- Transplant process
- Program options
- Risks and benefits (both live donor and deceased donor transplants)
- Medication regimen
- Lifestyle adjustments
- Effect of transplantation on existing medical conditions
- Short- and long-term outcomes

Communication with the patient should be clear and respectful and avoid false hope. In conjunction with the patient, assessment will focus on whether transplantation is the best option given the patient's full medical, lifestyle, and psychosocial situation.

Organ donor risk factors and exceptional distribution: Also see Section 5.4 Risk of Donor Disease Transmission

Human cells, tissues, and organs that are to be used in transplantation are regulated by Health Canada's Safety of Human Cells, Tissues and Organs for Transplantation Regulations (CTO Regulations). The purpose of the CTO Regulations is to minimize the potential health risks to Canadian recipients of human CTO by addressing the safety in the processing and handling of these products.

The regulations establish the required safety measures that need to be met for every donor. They include requirements for a detailed medical-social donor history, mandatory serological screening for infections (e.g., hepatitis, HIV, syphilis) and an authorization by the Medical Director of the Organ Donation Organization (ODO) that the organ(s) for transplant have been deemed safe to transplant.

As organs are a scarce resource, the mandatory safety criteria as directed by Health Canada have a negative impact on organ availability for life-saving transplants. However, Health Canada also provides a mechanism in which organs from increased risk donors (i.e., donors who carry an increased risk for inadvertent disease transmission to the transplant recipient, including HIV, HBV, and HCV) or with other contraindications can be transplanted. This mechanism is called *exceptional distribution*. The transplant physician must authorize the use of exceptional distribution organs based on their clinical assessment of the risks and benefits to an individual patient and obtain informed consent from the recipient.

How to discuss risks and benefits with patients:

Information on the use of organs from exceptional distribution donors (including increased risk donors) is provided to potential recipients at the time of assessment for transplant candidacy and again at the time of offer. The discussion should include the transplant physician or surgeon, although other members of the team (e.g., transplant coordinators) may also be involved. The goal of the discussion is to ensure the patient is given the information, support, and time needed to understand the option to accept an exceptional distribution organ so that they can make an informed decision that best reflects the their wishes.

Education of the recipient on donor risk factors and exceptional distribution needs to begin during assessment for transplant candidacy.

The information provided to patients should be accurate and unbiased. The risk should be contextualized in a clear and logical manner. In the discussion, the transplant physician should ensure, at a minimum, that the patient understands:

- Benefits of accepting an exceptional distribution organ vs. waiting for a standard organ
- Risk of acquiring an infectious disease (e.g., tuberculosis)
- Support available throughout and after the transplant
- Post-transplant monitoring and treatment requirements, if any
- Lack of impact to wait list status if the organ is declined

To support the transplant team in providing their patient with accurate and timely information at the time of consent, a Frequently Asked Questions (FAQ) document, *Risk of Disease Transmission from Organ Donors – Patient Information Guide*, has been developed. The information in the FAQ provides an overview of the risk and benefits of utilizing exceptional distribution organs. In addition, a patient informed consent form, which verifies that disclosure of risk of disease transmission has occurred, is to be completed (See Appendix F).

Also refer to Patient Handbook: "*Accepting an Organ from a Donor with Hepatitis C Infection*" (on *BCT Website*).

3.3.3 Domino liver transplants

A patient may undergo a liver transplant and at the same time donate their liver—also known as domino transplant. Commonly, this is performed as a result of the patient having a disorder such as familial amyloidotic polyneuropathy (FAP). Those patients who are being considered for a domino liver transplant must be assessed using the same criteria as living donors.

How the process starts:

Patients are to discuss the option of a domino transplant with the surgeon at one of the pre-liver transplant recipient clinic visits and consent to evaluation. The surgeon (or authorized designate) performs a physical exam. Transient elastography (FibroScan^{TM}) is used to ensure that there is no fibrosis. If the score is F1, then the surgeon discusses with the patient about continuing with the process. A liver biopsy is also required.

If the liver is acceptable by FibroScan^{TM} and the liver biopsy, then all remaining donor assessment tests are performed, including the medical-social questionnaire and social worker/psychologist review.

Final pre-operative testing (Exceptional Distribution requirement):

Health Canada requires all final serological testing to be performed within 30 days of OR date. In addition, the *Living Donor 30 Day Medical-Social Questionnaire* must be completed within 1 month of donation. As a domino liver transplant requires a deceased donor, the actual OR date cannot be planned ahead of time. Thus, it is recommended that an exceptional distribution is preceded by physician/surgeon approval indicating that these requirements may not be met.

3.3.4 Completing the pre-liver transplant assessment

The liver pre-transplant assessment team creates a plan to complete the assessment as the patient nears medical urgency for a transplant (i.e., assess for increasing MELD, increasing signs of liver decompensation, failure of hepatocellular carcinoma [HCC] treatments). The team provides advice during clinic and rounds regarding the timing of completing the assessment and patient-specific tests and consults that are required.

Patients in the pre-assessment liver transplant program are either on the "pre-assessment" or "active" list. Pre-assessment list means patients are not on the active list for transplant but are being followed by VGH Pre-Transplant Assessment. **Ongoing management of liver disease in the pre-assessment phase and while patient is on the waiting list is the responsibility of the referring specialist doctors** (hepatology, internal medicine, or gastroenterology).

3.3.5 Patients deemed unsuitable for transplantation

When a patient is considered unsuitable for transplantation after the liver pre-transplant assessments, they are informed of the reason and discharged from the transplant program by the clinical coordinator. The director of the BC Liver Transplant Program writes a letter to the referring physician and the patient's primary care physician informing them of the decision.

3.4 Activation to transplant wait list

Once a patient has completed all the required pre-liver transplant investigations, the patient's activation to the liver transplant waitlist is discussed during weekly multidisciplinary liver transplant rounds, which includes representation from transplant hepatology, surgery, anesthesia, nursing, nutrition, pharmacy, psychology, and social work.

When a patient is ready for activation, a recipient activation form is completed. Indication for liver transplantation is documented in the physician and surgeon consult notes and in the coordinator's progress notes. A letter is sent to the referring specialist, with copies sent to the family doctor and the patient informing them of the activation.

Patients accepted for transplantation are given instructions to communicate any change in their location or health status to the transplant clinic coordinator. Patients are required to have a cellular phone or other mechanism by which they can be readily contacted so that the transplant team can reach them quickly if a suitable organ becomes available.

The activated patients are re-assessed every 4 months by VGH Pre-Transplant Clinic. These patients or their social supports are advised to update the clinical coordinator if the patient deteriorates and/or if they are admitted to a hospital or travelling outside of B.C. (Note: Activated patients are put on status 0 [i.e., on hold] if travelling outside of B.C.)

Critical recipient-specific listing items are documented in the VGH chart as well as on the Active Liver List. The List is updated as necessary with changes in patients' status, weight, etc. The List is discussed and reviewed at the weekly Liver Team rounds. Any changes to the List are made under the direction of the transplant physician and/or surgeon on call.

Each member of the Liver Transplant team receives an updated Active Liver List at weekly Liver Team meetings. An updated list is distributed to the on-call transplant physician, transplant surgeon, and clinical coordinator as changes occur.

3.4.1 Continued evaluation and assessment of patients on waitlist

Every week during liver rounds, the Active Liver List is re-evaluated based on patients' health condition. The ranking of the List is based primarily on medical status (**Table 9**), MELD/MELD-Na and Child-Pugh scores, and symptoms, with the exception of patients with hepatocellular carcinoma (HCC). HCC patients are noted with an asterisk (*) next to their status.

Table 9. Waitlist activation status of liver patients

Status	Clinical Scenario
1	At home
2	In hospital
3	In ICU
3F	In ICU, fulminant failure
4	In ICU, intubated
4F	In ICU, intubated, fulminant failure
0	On hold

Note: * is used for status 1 and status 2 patients if they have HCC greater than 2cm

Priority is given to patients with higher status and fulminant (F) level. Patients with status 4 are usually too unstable to proceed to transplantation and need to improve (i.e., drop to a lower status level) to be considered for transplant.

Active patients are grouped according to blood type. Recipients are matched to potential donors in terms of body size and blood type. Liver size is estimated on the basis of patients' height and weight.

The clinical coordinator must ensure each day that all incoming information related to the activated patients is promptly entered and saved into the Patient Records and Outcomes Management Information System (PROMIS®). Specifically:

- MELD/MELD-Na score
- Child-Pugh score
- Amount of ascites
- Relevant clinical information added to comments (i.e., methicillin-resistant Staphylococcus aureus [MRSA] or vancomycin-resistant enterococci [VRE] infections, other medical diagnosis, etc.)
- Activation status

4. Transplant

4.1 Liver allocation and recipient selection

In Canada, the demand for liver transplantation greatly exceeds the supply of deceased donor livers, leading to a high number of deaths on the wait list. In an attempt to reduce mortality, livers from deceased donors are offered first to patients at the highest risk of death or drop-out (the latter due to the cause for which the patients are currently active on the waiting list). Historically in Canada, donor allocation has been done according to a location-based algorithm (i.e., canWAIT) with patients in the ICU having priority over patients in hospital and at home. A national organ sharing system is in place for patients with acute liver failure (ALF in ICU on ventilator is defined as status 4F with mandatory sharing and ALF in ICU not requiring mechanical ventilation is defined as 3F with mandatory discussion), urgent repeat transplantation for primary non-function (PNF), or hepatic artery thrombosis.

The sodium modification of the MELD, or the MELD-Na scoring system, was adopted in Canada on January 1, 2015 for liver allocation for adults. The score is based on objective laboratory variables (i.e., bilirubin, INR, creatinine, and sodium levels). All non-urgent status patients who are 18 years or older should be ranked locally according to the MELD-Na score and their score should be captured routinely (see **Table 10**). The minimum acceptable estimated 5-year patient survival rate for allocating a deceased donor liver for transplantation is 60%.

Table 10. Laboratory capture schedule for transplant recipients

Patient MELD-Na score	Minimum frequency of laboratory capture*
>30	Every 7 days
21 to 29	Every 30 days
<20	Every 90 days

* Exceptions can be granted for certain patients with hepatocellular carcinoma.

In order to expand the donor pool, extended criteria donors may be used. There is no universal definition, but extended criteria donors usually include donors with advanced age, steatosis, hypernatremia, or donor after circulatory death (DCD) grafts. To ensure favorable outcomes, it is important to match recipients and donors appropriately.

4.1.1 Neurologically deceased organ donors

Neurological determination of death (NDD, also referred to as ''brain death") means the brain has permanently lost all function, and a diagnosis of death using neurological criteria has been determined. The guidelines for the neurological determination of death follows a standardized national protocol. Standard graft consists of a graft from a neurologically deceased donor. Discussion of the criteria used for determination of neurological death is outside the scope of these transplant guidelines.

4.1.2 Donation after circulatory death

Donation after circulatory death (DCD) refers to graft donation from a donor who has suffered an irreversible cardio-circulatory arrest. Controlled DCD donors have often suffered a catastrophic brain injury and are deemed incompatible with any meaningful recovery but do not meet all criteria of neurological death. The withdrawal of life support is planned by the medical team treating the patient, in agreement with wishes of the patient and their family, and is independent from the decision to proceed with organ donation. If organ donation is considered according to the wishes of the patient or their family, withdrawal of care occurs in the ICU or the OR in the presence of an organ procurement team to limit ischemic injury associated with death.

Historically, the use of grafts from DCD donor was associated with inferior outcomes, mainly related to biliary complication. Appropriate donor and recipient selection in high volume centres has yielded improved outcomes and led to the expansion of the available donor pool.

4.1.3 Partial graft transplantation and split liver transplant

In exceptional cases, a liver graft from a neurological death donor may be split into two grafts and used in a recipient who would otherwise require a small sized graft.

4.2 Pre-operative protocol

Patients on the waiting list are discussed by the transplant team at the weekly activation rounds. This discussion includes any changes in status in accordance with the accepted Canadian Society of Transplantation (CST) guidelines.

If an organ becomes available, patients who are assigned a higher priority status are given preference for transplantation compared to patients who have lower CST priority status listing. Status 4 patients may be considered too unstable for transplant surgery and require frequent review by the transplant physicians prior to transplant.

Patients living outside the Vancouver Lower Mainland have urgent transportation to Vancouver arranged by the transplant coordinator when a donor organ is available. The cost of travelling to VGH on the day of transplant is the responsibility of the patient as transportation costs are not covered by Medical Services Plan or by BC Transplant.

Once an appropriate donor is identified, the transplant surgeon on call and transplant hepatologist review the list of activated patients with compatible blood type to the donor and select the recipient based on medical urgency, size compatibility, and waiting time on the list. The recipient is contacted and admitted to VGH. The recipient is assessed by the transplant hepatologist and the transplant surgeon on call to ensure that there is no contraindication to proceed with the liver transplant. Updated laboratory works are drawn. Once the transplant surgeon obtains confirmation of the organ quality by the donor surgeon, the recipient is brought to the OR to be anesthetized.

4.2.1 Surgical consent

Surgical consent forms are signed in accordance with Vancouver Coastal Health's Policies and Procedures.

4.2.2 Back-up recipient

Occasionally a second potential recipient is prepared for transplant in the event the first recipient is found to be unsuitable. If the liver is used for the primary recipient, the back-up recipient is discharged and remains on the list.

4.3 Transplant surgery

Conventional liver transplantation:

A liver transplant is performed depending on patient anatomy and surgeon assessment of the clinical situation. Orthotopic liver transplant can be performed by replacing the recipient inferior vena cava (IVC) by the donor IVC (classic technique) or by preserving the recipient IVC and performing an anastomosis between the donor IVC and the recipient hepatic vein (i.e., Piggyback technique). Neither surgical technique of IVC management has been shown to be superior to the other. Both techniques can be performed without the use of a venovenous bypass.

The donor gallbladder is removed prior to performing biliary anastomosis. Biliary anastomosis is generally performed in a duct-to-duct fashion. If the recipient bile duct cannot be used, a Roux-en-Y hepaticojejunostomy is performed.

5. Post-transplant

5.1 In-hospital care

Following liver transplant, patients are transferred to the ICU. The majority of recipients are transferred intubated to the ICU and placed on a ventilator for a short period of time after the transplant. Occasionally, patients with serious complications or respiratory problems may have a more prolonged ICU stay.

Upon arrival at the ICU, the liver allograft function is assessed, and liver enzymes and other laboratory values are monitored periodically. A peak in the transaminases (i.e., AST & ALT) is expected during the first 2 days after transplant, followed by a decline and normalization of these enzyme levels.

A duplex ultrasonography (DUS) may be obtained in the post-operative period to assess the hepatic artery, portal vein, and hepatic vein flow. Once patients are extubated and weaned from all vasopressor medications, they are transferred to the transplant ward to continue their recovery. Patients learn about their immunosuppression regimen (see **section 5.3**) and are monitored for complications. Patients are discharged once they meet the discharge criteria. The median length of stay after liver transplant at the VGH Clinic was 11 days in 2020.

Post-operative care for patients involves standard surgical nursing care, nutritional support, mobilization, medical and immunosuppressive therapy, monitoring for rejection, sepsis, or biliary tract complications, and education for patients and their families. Psychological interventions are available to assist patients in coping with inevitable stresses and for the management of anxiety, mood, and pain.

5.2 Early complications

5.2.1 Early complications from surgery

Complications from surgery following liver transplant have a major impact on the post-transplant course. Most common post-transplant complications related to the surgery include, but are not limited to, the following:

Primary non-function:

Primary non-function (PNF) refers to inadequate function of the liver after transplantation, which may be due to multiple factors related to the patient and graft. Complete primary non-function is life threatening and occurs in only 2% of transplants. The only option is re-transplantation on an urgent basis.

Bleeding:

Post-operative bleeding can be life-threatening and requires reoperation in 10 to 15% of patients for hemorrhage control or hematoma evacuation. In 80% of patients, no obvious cause will be found at time of re-exploration.

Arterial complications:

The incidence of hepatic artery thrombosis following adult cadaveric liver transplant is between 3 and 10%. The most common presentation of early hepatic artery thrombosis is graft dysfunction. Patients can sometimes be treated with revascularization in the OR or by radiology but may require re-transplantation. The most serious complication related to arterial complication is ischemic biliary lesion that can lead to re-transplantation. Hepatic artery stenosis has an incidence of 5 to 11% and is defined as 50% reduction in caliber of the lumen of the artery seen on angiography. It can also be associated with biliary complication and is most often treated with balloon angioplasty.

Venous complications:

Outflow obstruction at the level of the inferior vena cava (IVC) anastomosis is a rare but serious complication with an incidence of 1 to 6%. Patients usually present with liver dysfunction, ascites, lower extremities edema, or impaired renal function. Endovascular dilation or stent insertion is the usual treatment.

Patients with portal vein thrombosis before transplant are often placed on anticoagulation following the transplant to prevent re-thrombosis. Portal vein thrombosis following liver transplant is rare and often present with acute graft dysfunction, ascites, or variceal bleed. Treatment includes revascularisation, bypass, or re-transplantation.

Biliary tract complications:

Biliary tract complications are an important cause of morbidity and mortality in liver transplantation recipients. The incidence of these complications ranges between 10 and 25% in various reports.

Early-onset complications: Bile leak following transplant can occur in up to 8% of liver transplant recipients of deceased donor graft. Symptoms may include elevation of liver enzymes or non-specific symptoms, such as fever, right upper quadrant pain, jaundice, and bilious ascites. Treatment may include endoscopic retrograde cholangiopancreatography (ERCP), stent and drain, or re-operation and revision of the biliary anastomosis with reconstruction with a Roux-en-Y gastric bypass. Early biliary stricture affects 12.8% of liver transplant recipients. Most anastomotic strictures present within the first year after transplant, with a mean interval of 5 to 8 months. Treatment includes ERCP and stent or balloon dilation, percutaneous cholangiography when the bile duct cannot be accessed by ERCP, or revision of the anastomosis. Most anastomotic strictures identified within 6 months after liver transplant respond well to stenting, but patients require long-term surveillance due to a recurrence rate of 20 to 30%.

Late-onset complications: Non-anastomotic strictures and ischemic bile duct injury can happen after hepatic artery thrombosis or stenosis and is sometimes associated with graft from donors after circulatory death (DCD). Recurrence of primary sclerosing cholangitis (PSC), which happens in up to 20 to 30% of patients, can present a similar clinical picture. The outcomes of non-anastomotic strictures are not as favorable as anastomotic strictures. Re-transplant may be considered for patients who develop non-anastomotic strictures.

5.2.2 Re-transplantation

Re-transplantation remains the only option for patients with allograft failure. From a technical standpoint, the development of adhesion may add some difficulty and length to the graft hepatectomy. The need for appropriate vascular inflow should be assessed prior to proceeding with re-transplantation. In the literature, recipients of a second or third graft tend to have lower patient and graft survival than recipients undergoing their first transplant. Re-transplantation indications can be divided into early and late re-transplantation.

The most common causes of early graft loss (i.e., within 7 to 30 days after transplant) are primary non-function (PNF) and hepatic artery thrombosis (HAT).

Indications for late re-transplantation include recurrent disease and chronic rejection. Prior to being re-listed for re-transplantation, recipients undergo a full evaluation of their candidacy.

5.2.3 Early medical complications

Acute kidney injury:

Acute kidney injury (AKI) following liver transplantation is common with a reported range between 17 to 95%. The definition of AKI varies widely, explaining the wide range of incidence found after liver transplant. Furthermore, up to one fifth of liver transplant recipients require transient kidney replacement therapy. AKI following transplant is usually due to a combination of recipient, donor, and surgical factors. The presence of AKI following liver transplant has a significant impact on patient outcome.

Infections:

Early post-transplant infections are more commonly bacterial. Risk factors for bacterial infection include longer operating time, high pre-transplant bilirubin level, increased duration of antibiotic therapy, and increased transfusion. Bacteremia has been observed in up to 27% of transplant recipients and is associated with mortality rate between 13 to 36%. In one third of patients with bacteremia, no apparent source is identified. Fungal infection occurs in 10% of liver transplant recipients with mortality rate between 25 to 69%. Most fungal infections occur within the first 2 months following a liver transplant. Viral infection after liver transplant usually occurs between the first and sixth months following the transplant. Viral infections can also occur later if the patient's overall immunosuppression state changes, such as during treatment for rejection.

Rejection:

Acute cellular rejection (ACR) occurs in approximately 20% of patients within the first month of transplantation. The cumulative incidence of ACR during the first year after transplantation is approximately 30%.

ACR is usually suspected by an increase in liver enzymes. A liver biopsy is performed to confirm the diagnosis. Treatment usually consists of the following:

- Methylprednisolone (SoluMedrol®) is administered 10mg/kg per day for 3 days, followed by oral prednisone (approximately 0.3mg/kg/day) which is tapered over 3 to 4 months
- Additionally, reassessment and escalation of baseline immunosuppressive regimen is considered
- Anti-thymocyte globulins (ATG) may be utilized in patients with steroid refractory rejection

5.3 Anti-rejection protocols and target levels

Liver is the most tolerogenic organ. In liver transplantation, immunosuppression is individualized based on patients' propensity for alloreactivity and tolerance. We aim to balance the risk of rejection with immunosuppressive adverse events, taking into account patients' age, indication for transplantation, history of rejection, other medical comorbidities, and time since transplantation.

Early standard immunosuppressive regimen after liver transplantation consists of corticosteroids (methylprednisolone/prednisone), tacrolimus, and mycophenolate mofetil. In select patients, induction immunosuppression with basiliximab is also utilized.

Other second-line immunosuppressive medications (e.g., cyclosporine, azathioprine, sirolimus) are used in select patients who are intolerant to the first-line agents. Sirolimus-based therapy is also used in patients with a history of hepatocellular carcinoma.

Immunosuppression reduction can be considered in select patients who fulfill a strict list of criteria. This usually includes patients who are transplanted for non-immune mediated liver disease, who are older than 60 years of age and have been transplanted for more than one year with stable graft function and no history of recent rejection.

If you are caring for a liver transplant patient, please contact the transplant clinic to confirm and/or adjust the patient's immunosuppressive regimen when needed.

For detailed immunosuppressive pharmacology, adverse drug reactions, and drug-drug interactions, please see BCT Clinical Guidelines for Transplant Medications.

5.3.1 Calcineurin inhibitors

Calcineurin inhibitors (CNIs), tacrolimus and cyclosporine, are the backbone of immunosuppression in liver transplantation. Due to its superior efficacy and improved toxicity profile, tacrolimus has replaced cyclosporine as the first-line immunosuppressive agent in almost all early immunosuppressive protocols (see **Table 11** for tacrolimus dosage and formulations).

Table 11. Tacrolimus dosage and formulations

Formulations	Brand names	Strengths	Initial dosage	Conversion factor
Immediate release (IR-TAC)	Prograf® Generic: Sandoz	Capsules: 0.5mg, 1mg, 5mg Intravenous: 5mg/mL	Oral: 0.03-0.05mg/kg PO BID	IR-TAC to IV - use 25% of PO dosage (4:1 conversion)
Extended release (ER-TAC)	Advagraf®	Capsules: 0.5mg, 1mg, 3mg, 5mg	0.1-0.2mg/kg/day	IR-TAC to ER-TAC 1:1 or 1: 1.1
Extended release (LCPT)	Envarsus PA®	Tablets: 0.75mg, 1mg, 4mg	0.07-0.1mg/kg/day	IR-TAC: LCPT(2) 1: 0.7 ER-TAC: LCPT(2) 1: 0.7 or 1: 0.65

Tacrolimus extended-release formulations, Advagraf® and Enversus®, are administered once daily in the morning. The once daily formulations may be considered on a case-by-case basis in patients receiving stable immunosuppression in whom once daily administration would offer convenience and aid in patient adherence. In kidney transplant population, Enversus® has been shown to be associated with fewer tremors, and therefore it may offer an alternative in patients with tacrolimus induced neurotoxicity, such as headaches and tremors.

Target tacrolimus trough concentrations:

In the early post-operative course, tacrolimus dosage strategy is determined by the magnitude of alloimmune activation and patients' underlying kidney function. In patients with impaired kidney function or with risk factors for acute kidney injury (e.g., older age, high MELD score, high intraoperative transfusions, early allograft dysfunction, severe post reperfusion syndrome), lower target tacrolimus strategy, in addition to induction with basiliximab, is utilized. Subsequent

dosing is based on kidney recovery and risk of allograft rejection. **Table 12** summarize the general approach to tacrolimus dosing and target trough concentrations. However, tacrolimus concentration targets may very between patients and even within the same patient based on medical comorbidities, acute illnesses, and history of rejection.

Table 12. Tacrolimus dosing and target trough concentration

	Standard dosing	**Low target/kidney sparing**
Dosing	0.05mg/kg PO BID	0.03mg/kg PO BID in combination with basiliximab induction
Time post-transplant (months)	**Tacrolimus trough blood concentration (ng/mL) 12 hours post-dose tandem mass spectrometry assay**	
	Normal kidney function	**Abnormal kidney function**
Less than 1	8-10	6-8
1 to 3	7-9	6
3 to 12	6-8	4-6
Greater than 12	4-6	3-5

After 5 years, tacrolimus (and cyclosporine) levels are less important if allograft function is stable. Lower CNI levels of just above the lower limit of detection can be accepted if patient has normal liver biochemistry.

Cyclosporine:

Cyclosporine (CSA) can be considered in patients who are intolerant to tacrolimus (see **Tables 13 and 14** for CSA dosage and trough concentrations). The most common indication for switching from tacrolimus to cyclosporine is the development of severe tacrolimus-induced neurotoxicities, such as posterior reversible encephalopathy syndrome (PRES) and tremors. Cyclosporine is, however, associated with higher risk of rejection, kidney dysfunction, and cardiovascular disease. Due to tacrolimus-induced neurotoxicites early post-transplantation, patients who are switched to cyclosporine may be re-challenged with tacrolimus if there is a strong indication for tacrolimus re-initiation, such as the development of chronic rejection or multiple episodes of acute cellular rejection.

Table 13. Cyclosporine dosing

Formulations	Brand names	Strengths	Initial dosage	Conversion factor
Capsules **Oral liquid** **IV**	Neoral® Sandimmune IV®	Capsules: 10mg, 25mg, 50mg, 100mg Oral liquid: 100mg/mL, Intravenous: 50mg/mL	Oral: 3-5mg/kg PO BID	PO to IV - use one third of PO dosage (1:⅓)

Table 14. Cyclosporine target trough concentrations

Time post-transplant (months)	Cyclosporine trough concentration (ng/mL)(3) mass spectrometry assay
0 to 3	200-250
3 to 12	150-200
Greater than 12	100-125

5.3.2 Antimetabolites

Antimetabolites are commonly added to CNIs and short-term steroids as part of the standard maintenance immunosuppression protocol after liver transplantation. Mycophenolate mofetil has replaced azathioprine as the first-line antimetabolite due to its superior immunosuppressive efficacy (as demonstrated in kidney transplant population) and less bone marrow toxicity.

Mycophenolic acids – mycophenolate mofetil and mycophenolate sodium:

Mycophenolate mofetil (MMF) is initiated at 1g PO BID at the time of transplantation (see **Table 15** for dosing details). MMF dosage may be reduced at 1-year post-transplantation with a view to discontinue over 6 to 12 months in select patients who fulfill the criteria for immune suppression reduction and conversion to monotherapy.

Mycophenolate sodium may be considered in patients with a history severe GI side effects to MMF, although the current available evidence does not indicate significant improvements in GI side effects with mycophenolate sodium (see **Table 15** for dosing details).

Mycophenolate mofetil capsule and tablets are contained in a blister pack which should not be opened until the dose is to be administered. MMF has demonstrated teratogenic effects and therefore tablets and capsule should not be opened or crushed. MMF should not be re-blister packed with other medications. Patients of childbearing potential who are receiving MMF should use two reliable types of contraception during therapy with MMF and for 6 weeks following discontinuation of MMF. If pregnancy is planned, MMF should be discontinued and alternative immunosuppressive medications, such as azathioprine, should be considered.

Table 15. Mycophenolic acid dosage for liver transplantation

Formulations	Brand names	Strengths	Initial dosage	Conversion factor
Mycophenolate mofetil	CellCept® Generics	250mg capsules, 500mg tablets, Powder for oral suspension: 200mg/mL, Intravenous: 50mg/mL	1g PO BID	PO to IV 1:1
Mycophenolate sodium - EC	Myfortic®	EC tablets 180 and 360mg	720mg PO BID	MMF to Myfortic® 250mg = 180mg

5.3.3 Azathioprine

Azathioprine is considered second-line antimetabolite immunosuppressant which is primarily used in patients who are intolerant to mycophenolate, in patients with increased incidence of infection while on MMF, or in transplant recipients who are considering pregnancy.

The initial adult dosage of azathioprine is 1 mg/kg/day PO given once daily. In the absence of thiopurine methyltransferase (TPMT) testing, lower starting dosage should be considered with careful up-titration and monitoring of WBC. If tolerated, azathioprine can be titrated up to a maximum daily dosage of 2.5mg/kg/day.

5.3.4 Methylprednisolone/prednisone

The initial liver transplant immunosuppressive protocol includes high-dose methylprednisolone administered immediately post allograft reperfusion and tapered gradually over 5 days, with conversion to oral prednisone which is tapered over 4 months (see **Table 16**).

Table 16. Corticosteroid dosage post-transplant

Post-operative day	Corticosteroid regimen
Day 0	Methylprednisolone 500 mg IV X1
Day 1	Methylprednisolone 200 mg IV X1
Day 2	Methylprednisolone 160 mg IV X1
Day 3	Methylprednisolone 120 mg IV X1
Day 4	Methylprednisolone 80 mg IV X1
Day 5	Methylprednisolone 40 mg IV X1
Day 6	Prednisone 20mg (0.3 mg/kg) PO daily
Day 30	Prednisone 15mg PO daily (or decrease dosage by 5mg)
Month 2	Prednisone 10mg PO daily (or decrease dosage by 5mg)
Month 3	Prednisone 5mg PO daily (or decrease dosage by 5mg)
Month 4	Stop prednisone

The initial high dose intravenous steroids protect against allograft ischemia reperfusion injury in addition to providing broad-spectrum immunosuppression. In select patients at high risk of steroids-related infections or metabolic complications, individualized steroid minimization strategies may be utilized.

Prednisone is available as 1mg, 5mg, and 50mg tablets.

Following episodes of acute cellular rejection treated with pulse methylprednisolone, prednisone regimen is usually re-initiated at 0.3 mg/kg with subsequent taper over 3 to 4 months. In patients who require steroids re-initiation, pneumocystis pneumonia (PJP), viral, and GI prophylaxes should be considered. Frequent monitoring of blood pressure and blood glucose levels are also recommended.

5.3.5 IL-2 receptor blockers: basiliximab

Basiliximab (Simulect®) induction is indicated in patients with a history of kidney impairment or in those at high risk of developing acute kidney injury (e.g., older age, high MELD score, high intraoperative transfusions, early allograft dysfunction, severe post reperfusion syndrome). Basiliximab induction and delayed calcineurin inhibitor (CNI) initiation allows for kidney recovery prior to the introduction of potentially nephrotoxic CNIs, resulting in improved long-term kidney function. Basiliximab can also be considered in patients at high risk of rejection post-transplantation, such as young patients with immune-mediated liver disease.

Basiliximab is administered at 20mg IV immediately post-operation and repeated on post-operative day 4. Tacrolimus initiation can be delayed for 5 to 7 days to aid kidney recovery.

5.3.6 m-TOR inhibitors: sirolimus

Sirolimus (Rapamune®) is a second-line immunosuppressive medication that is commonly used in patients with a history of hepatocellular carcinoma (HCC) or in patients with severe intolerance to CNIs. Its advantage over CNIs include relative lack of nephrotoxicity and neurotoxicity, in addition to antineoplastic properties against certain types of cancers. Unfortunately, sirolimus has an extensive side effect profile limiting its use in clinical practice. Sirolimus is usually not used within the first month after transplantation as it has a black box warning due to increased risk of hepatic artery thrombosis when used as de novo immunosuppression. However, earlier sirolimus initiation can be attempted in rare cases when tacrolimus or cyclosporine are a not viable option.

Sirolimus is usually initiated at 1 to 2mg PO daily and up-titrate at 1- to 2-week intervals with weekly trough concentration monitoring. Sirolimus has a long half-life of approximately 72 hours; therefore, it takes 2 to 4 weeks to reach target therapeutic levels. Sirolimus should be used with another agent until therapeutic levels are obtained.

Table 17. Sirolimus trough concentrations

Time post-transplant (months)	Sirolimus trough concentration (ng/mL) when combined with other IS	Sirolimus trough concentration (ng/mL) when used as monotherapy
1 to 3	8 to 12	10 to 15
Greater than 3	5 to 10	8 to 12

IS, immunosuppressant

Indications for sirolimus are the following:

- Patients with a history of HCC should be ultimately converted to single agent sirolimus if tolerated. For patients at high risk of rejection, sirolimus should be combined with tacrolimus.
- Patients with kidney dysfunction may be considered for sirolimus based therapy if there is no proteinuria. Conversion to sirolimus should take place within 6 months after transplantation to maximize renal sparing effects of sirolimus. Mycophenolate might be combined with sirolimus to provide additional immunosuppression in patients at high risk of rejection. These patients should be monitored for development of cytopenias closely.
- Patients with recurrent squamous cell carcinoma can be switched to sirolimus-based immunosuppression.
- Patients who experience rejection despite optimized tacrolimus and mycophenolate dosage may benefit from the addition of sirolimus to their baseline immunosuppression regimen.
- Combination of sirolimus and cyclosporine should be avoided if possible due to increased risk of nephrotoxicity and dyslipidemia. Ensure separation between sirolimus and cyclosporine administration by at least 4 hours in order to minimize the risk of nephrotoxicity.

5.4 Risk of donor disease transmission (Exceptional Distribution)

It is recognized that in exceptional circumstances and due to compassionate reasons a liver may be transplanted even when there is a contraindication during donor assessment (e.g., incomplete donor screening). If such cases, an organ may be released for transplant under exceptional distribution as per Health Canada requirements. The process is documented on an exceptional distribution form by the BCT Organ Donation Coordinator. The transplanting physician must authorize the exceptional distribution, including obtaining informed consent of the recipient. Copies of the exceptional distribution form are to be included in the recipient's chart.

It is important that in all cases, appropriate follow-up of recipients is performed by the post-transplant medical care team. Each exceptional distribution is to be reviewed and assessed by the team for any follow-up treatment and diagnosis.

5.4.1 Risk for viral mediated disease transmission

In exceptional distribution cases involving risk for viral mediated disease transmission, the following is sent from BCT Quality Assurance to the transplant hospital or outpatient location:

- Copy of the "Exceptional Distribution Form" with description of risks.
- Recommended follow-up testing for recipients transplanted under exceptional distribution (See Appendix G)

The post-transplant nurse at VGH ensures the above documents are reviewed by the post-transplant medical care team and the recommended follow-up is performed at the required intervals.

5.4.2 Risk for tuberculosis

For recipients transplanted under risk for donor TB transmission, the applicable Monitoring or Treatment follow-up protocol (Appendix H) is sent from BCT Quality Assurance to the transplant hospital or outpatient location.

5.4.3 Adverse events

For any suspected recipient errors, accidents, or adverse reactions that may be a result of donor disease transmission, the event is immediately communicated to the program manager, Liver Medical Director, and the Department Manager of ODHD (Organ Donation and Hospital Development) at BC Transplant.

The event is documented using the Patient Safety Learning System (PSLS). All adverse events and incidents are fully reviewed, investigated, and followed up, and all hospital and Health Canada regulatory requirements are met.

6. Outpatient follow-up

6.1 Ambulatory care phase

Patients typically remain in the hospital for less than 2 weeks (median length of stay in 2020 was 11 days). After discharge from hospital, patients are usually seen in the VGH Post-Transplant Clinic. In rare cases, patients are discharged with abdominal drains which are removed during a follow-up visit. The incisional staples are removed after 3 weeks. For patients with no major complications, frequency of visits is gradually reduced to:

1. monthly for the first 4 months
2. every 2 to 3 months for the remaining part of the first year
3. every 4 months for the second year
4. gradually reduced to every 6 months and then annually

Psychological services are available to assist patients with their emotional adjustment issues.

Blood tests are done twice weekly for the first few months and, if stable, biweekly and then monthly by the end of the first year. The blood tests monitor liver and renal function, blood counts, and blood levels of immunosuppressive medication and screen for opportunistic infections, such as cytomegalovirus (CMV) reactivation/disease. Patients who had a liver cancer are also monitored for alpha-fetoprotein levels and receive liver MRI or CT scans.

At 6 months, 12 months, and every year thereafter, patients have more extensive investigations, which include hepatitis serology, cholesterol, hemoglobin A1C, and ultrasound of the abdomen. The purpose of these tests is to monitor for possible side effects of immunosuppressive medications and screen for new or recurrent viral infection.

Patients develop a close relationship with the transplant team and have an understandable tendency to call on the transplant team for all their health concerns. However, the transplant physicians and nurses are neither able to nor are necessarily the best qualified persons to advise on general health concerns or routine follow-up. **It is expected that the family physician and referring specialist continue to take primary responsibility for the patient's general medical care**.

6.2 Bloodwork standing orders

Patients receive a set of standing orders for bloodwork monitoring as outpatients (see **Table 18**). The interval of blood work monitoring is decided by the transplant physician and depends on the length of time from transplant and the presence of medical issues requiring more frequent monitoring. An annual bloodwork is completed before clinic visit at every anniversary of the transplant (see **Table 19**).

Table 18. Standing bloodwork monitoring for outpatient follow-up

Full bloodwork
CBC with differential
PTT, INR, K, Na, Cl
BUN, Cr, glucose (fasting)
Total/direct bilirubin, ALP, GGT, AST, ALT
Albumin
Tacrolimus level, sirolimus level or cyclosporine level
CMV PCR for 3 to 6 months
Time Specific Testing:
HbA1C q3months
Cholesterol/lipids x 1 at 6 months
Urine ACR q3months

CBC, complete blood count; PTT, partial thromboplastin time; INR, international normalized ratio; BUN, blood urea nitrogen; Cr, creatinine; ALP, alkaline phosphatase; GGT, gama-glutamyl transferase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CMV PCR, cytomegalovirus polymerase chain reaction.

Table 19. Annual bloodwork monitoring for outpatient follow-up

Test	**Schedule**
HgA1c	Completed at 3 months post-transplant. If the values are abnormal and/or in diabetic patients, repeat every 3 months and consult doctor. If the values are normal, then annually thereafter.
Lipid studies (cholesterol, triglycerides, HDL, LDL)	Completed at 6 months and annually thereafter. If the values are elevated, follow levels and consult doctor.
Hepatitis Screening	Completed 1-year post-transplant and as ordered thereafter. Hepatitis B positive patient/or donor: HBV DNA, HCV Ab *HBV DNA annually thereafter. Hepatitis C positive patient: HBsAg, HBc Ab (total) Non Hep B & Hep C: HBsAg, HBc Ab (total), HCV Ab
AFP test	Every 6 months x 3 years and annually thereafter patients who had a history of cancer related transplant
CA19-9	Every 6 months x 3 years and annually thereafter for patients who had a history of cancer related transplant
CEA	Every 6 months x 3 years and annually thereafter for patients who had a history of cancer related transplant

HbA1c, hemoglobin A1C; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein; CA19-9, carbohydrate antigen 19-9.

6.3 Protocol for hepatitis B liver transplant recipients

Transplant recipients with hepatitis B receive:

- Entecavir 0.5mg PO daily or tenofovir disoproxil fumarate (TDF) 300mg PO daily; and
- Hepatitis B immune globulin (HBIG) for 12 months post-transplant (if patient satisfies HBIG withdrawal criteria). HBIG is available as:

Brand Name	**Formulation**	**Vial size**	**Dose**	**Route**	***Administration***
HepaGam B®	SC	1560 units per 5mL	10mL (3120 units)	SC	4 x 2.5mL SC As 2 injections into each upper arm

IM formulation may be substituted with HBIG SC dosing (IV formulation) for patients with contraindications to IM injections, for patients previously enrolled in a clinical study, or at physician discretion.

6.3.1 Induction phase (intra-operatively)

Inject HBIG 10mL IV during the anhepatic phase.

6.3.2 HBIG protocol for week 1 to week 52

1. Post-operative inpatient administration:
   - HBIG 10mL IV daily until anti-HBs titer is >1000 IU/L .
   - Then, HBIG 10mL IV twice weekly (every Mon, Thurs). Reduce titer frequency to every Mon, Thurs; ensure trough anti-HBs titre remains >500 IU/L.

2. Post-operative outpatient administration
   - HBIG 10mL SC as needed to reach HBIG titers according to HBIG protocol

6.3.3 HBIG protocol for >1 year post-transplant

One year after transplant, patients receive HBIG 10mL. Patients go to a local lab (near their place of residence or a location of their choice) to complete anti-HBs titer 4 weeks after each injection. Then, the frequency of administration of HBIG is to be adjusted based on anti-HBs (see **Table 20**).

Table 20. Hepatitis B immune globulin administration based on hepatitis B antibody titre

Hep B Ab titer (IU/L)	Action
>300	Level in 2 weeks
200-300	Injection in 3 weeks
150 - 200	Injection in 2 weeks
100-150	Injection in 1 week
<100	Injection ASAP

Stable patients who are receiving HBIG injections at regular intervals may be converted to a routine dosing interval regardless of titer.

Trough anti-HBs titer is completed every 4 months at minimum to ensure maintenance >100 IU/L.

6.3.4 Discontinuation of HBIG 6 months post-transplant

The following inclusion/exclusion criteria may be followed to discontinue HBIG after 6 months from the date of transplantation:

Inclusion:

- More than 6 months post-transplantation in the context of chronic hepatitis B
- HBV DNA undetectable prior to HBIG withdrawal at 6 months post-transplantation

Exclusion:

- Hepatitis D coinfection
- Drug-resistant HBV (e.g., HIV coinfection, patient exposure to other heavy nucleoside/nucleotide analogue)
- Risk of non-adherence to HBIG or antivirals against HBV

The protocols for HBIG discontinuation are the following:

1. **Medications:**
    - For patient receiving entecavir, tenofovir, or lamivudine + adefovir, discontinue HBIG and initiate HBV monitoring bloodwork (see below).
    - For patients receiving lamivudine:
        - If more than 5 years post-transplant, no change in antiviral therapy required, or

- If less than 5 years post-transplant, switch patient to entecavir or tenofovir (hepatologist to determine medication regimen).

2. **Bloodwork:**
   - Hepatitis B surface antigen (HBsAg), anti-HBs, and HBV DNA are tested:
     - At the time of HBIG withdrawal, and
     - Post HBIG withdrawal every 3 months for 1 year, then every 6 months for 1 year and annually thereafter.

6.4 Hepatocellular cancer surveillance protocol

Patients with a diagnosis of hepatocellular carcinoma are monitored for recurrence post-transplant with the following abdominal imaging protocol:

- MRI at 6 months post-op and every 6 months thereafter until third anniversary
- Then annual MRI for 3 years to coincide with annual visit
- Then routine annual abdominal ultrasound with Doppler
- Tumor markers (AFP, CA 19-9, CEA) to be done with each MRI and ultrasound

6.5 Immunization

The following are the general principles for immunization of the immunocompromised:

1. **Maximize benefit while minimizing harm.** There is potential for serious illness and death in the under-immunization of immunocompromised people and every effort should be made to ensure adequate protection through immunization.

2. **Make no assumptions about susceptibility or protection.** A history of childhood infection or previous vaccination may be irrelevant.

3. **Vaccinate at the time when maximum immune response can be anticipated.**
   - The best time to vaccinate is before the transplant. Vaccinations can resume 3 months post-transplant for all inactivated vaccines.
   - Vaccines may be less effective when administered during the period of altered immunocompetence.
   - Vaccinate early when immunologic decline is predictable.
   - Delay vaccination if the immunodeficiency is transient (if this can be done safely).
   - Individuals who are fully immunized may remain at risk for vaccine-preventable diseases.

- Primary health care provider in consultation with the transplant team may decide to stop or reduce immunosuppressive therapy temporarily to permit better vaccine response (if this is appropriate).

4. **Consider the immunization environment broadly.** Vaccinate family and care givers when individuals need protection (i.e., against influenza).

5. **Avoid live vaccines unless**:
   - Data are available to support their use; and
   - The risk of natural infection is greater than the risk of vaccination.

6. **Administer routine boosters as indicated.** The degree and duration of vaccine-induced immunity are often reduced in immune compromised individuals.

7. **Consider the use of passive immunizing agents for patients post-exposure.** These include:
   a. Intravenous immune globulin (IVIG)
   b. The several "pathogen-specific" Ig preparations that are available (i.e., varicella zoster immunoglobulin (Varizig®), tetanus immunoglobulin (HyperTET® S/D).

It is the responsibility of Immunization Program users to ensure that they are consulting the most up-to-date version of the BC Centre for Disease Control (BCCDC) Immunization Manual. This can be accomplished by checking the online Administrative Circulars listing on BCCDC website (http://www.bccdc.ca/)

6.5.1 Solid organ transplant recipients

There is potential for serious illness or death in the under-immunization or over-immunization of solid organ transplant recipients. Immunization of those with significant immunodeficiency should be performed only in consultation with experts.

Table 21. Immunization requirements of solid organ transplant recipients

Organ	Tdap /Td	IPV	HAV	HBV	Men-C-ACWY	PPSV23	Hib	Influenza
Kidney	✓	✓		✓	✓	✓	✓	✓
Liver	✓*	✓	✓	✓	✓	✓	✓	✓
Pancreas	✓	✓			✓	✓	✓	✓
Lung	✓	✓			✓	✓	✓	✓
Heart	✓	✓			✓	✓	✓	✓

* Booster d

Tdap, tetanus, diphtheria, pertussis; Td, tetanus and diphtheria; IPV, inactivated polio vaccine; HAV, hepatitis A; HBV, hepatitis B; Men-C-ACWY, meningococcal quadrivalent conjugate; PPSV23, pneumococcal polysaccharide; Hib, haemophilius influenzae type b

Booster doses:

- Td: every 10 years for life
- Influenza: every year for life
- Pneumococcocal: once-only revaccination after 5 years

All live vaccines (such as MMR, varicella, and zoster/shingles) are contraindicated after solid organ transplantation

Refer to current version of *BCCDC Immunization Manual* for disease-specific immunization protocols and schedules.

6.6 Dental protocol

There are a variety of considerations when providing dental care to patients with liver disease. Not only do these patients have lower platelet counts, but their function is also diminished. They also have anomalies in the clotting cascade and can be prone to bleeding. Hepatic encephalopathy can occur if a patient swallows an excessive amount of blood. These patients also have ascites and can be prone to episodes of spontaneous bacterial peritonitis.

There is no substantiated evidence that patients with ascites can develop bacterial peritonitis with dental procedures. There is also no evidence that patients with cirrhosis are at higher risk of infective endocarditis from dental procedures. In post liver transplant recipients, evidence is also lacking to demonstrate an increased risk of systemic infections or infective endocarditis following dental procedures and whether that risk is reduced with prophylactic antibiotics.

The American Heart Association recommends antibiotic prophylaxis before dental procedures only for patients who have a history of previous infective endocarditis or who have had cardiac valve replacement, surgically constructed pulmonary shunts, or conduits.

Prophylactic antibiotic coverage for dental procedures is recommended only for transplant recipients who have any of the following:

- Prosthetic cardiac valve
- Previous infective endocarditis
- Congenital heart disease (CHD), including:
  - Unrepaired cyanotic CHD
  - Repaired CHD with any prosthetic material or device within less than a year prior to transplant
  - Repaired CHD with residual defects
- Developed cardiac valvulopathy after receiving cardiac transplant

We suggest avoiding any non-urgent dental work within the first 6 weeks after transplant. See **Table 22** for recommended prophylactic antibiotic regimens for dental procedures in patients who meet the above criteria.

Table 22. Antibiotic regimens for dental procedure*

Situation	Antibiotic, regimen (single dose 30 to 60 min prior to procedure)
Standard therapy	**amoxicillin** 2g PO
If unable to take oral medication	**ampicillin** 2g IV or IM **or** **cefazolin† or ceftriaxone‡** 1g IV or IM
If true allergy to penicillin	**cephalexin†** 2g PO **or** **clindamycin** 600mg PO **or** **azithromycin or clarithromycin** 500mg PO
If true allergy to penicillin and unable to take oral medication	**cefazolin or ceftriaxone‡** 1g IV or IM or **clindamycin** 600mg IV or IM

* Adapted from American Heart Association.

† Or other first or second generation oral cephalosporin in equivalent adult or pediatric dosage.

‡ Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillin or ampicillin.

6.7 Late complications

6.7.1 Rejection

Rejection of the donor organ is less common after 9 months, although acute rejection can occur at any time after transplantation. Rejection is almost always confirmed by liver biopsy before treatment is instituted. Patients are then treated the same way as they are in the immediate perioperative period with methylprednisolone (SoluMedrol®) approximately 10 mg/kg IV daily for 3 days. Patients with severe rejection or steroid-resistant rejection may require treatment with polyclonal antibody (ATG) IV for 7 to 10 days. In addition, they may have their maintenance immunosuppressive treatment intensified.

6.7.2 Cytomegalovirus infection

Cytomegalovirus (CMV) infection is common 3 weeks to 6 months after transplantation. Typically, this infection occurs in patients who are already CMV-positive by CMV PCR testing, as immunosuppression decreases the body's immune surveillance of the virus. Patients may develop generalized malaise, low-grade fever, and, often, upper GI complaints. To ensure prompt initiation of therapy, perform CMV PCR tests routinely. See **Table 23** for CMV prophylaxis and treatment regimens for liver transplant recipients.

CMV PCR tests are not 100% reliable and diagnosis may have to be confirmed by upper GI endoscopy or some other method of demonstrating tissue invasion. Patients who are a CMV-mismatch (i.e., the donor is CMV-positive and the recipient is CMV-negative) are at very high risk of CMV disease.

6.7.3 Herpes simplex virus infection

Herpes simplex virus (HSV) infection and reactivation can occur in the first few months after transplant and at any time thereafter. Patients who are not receiving CMV prophylaxis with valganciclovir receive prophylactic therapy with valacyclovir for HSV in the first 4 months after transplant. See **Table 24** on p. 67 for HSV treatment regimen.

Table 23. Cytomegalovirus prophylaxis and treatment regimen for liver transplant patients

DONOR	RECIP	PROPHYLAXIS	PRE-EMPTIVE TREATMENT asymptomatic	DISEASE TREATMENT symptomatic
Neg	Neg	No prophylaxis with valganciclovir If ATG is used for rejection, obtain CMV IgG prior to starting ATG. □ CMV DNA viral load weekly for 3 months post-transplant and for an additional 3 months following any antiviral treatment	CMV DNA viral load weekly: CMV DNA viral load less than 35 IU/mL - no treatment CMV DNA viral load 35 to 1000 IU/mL; repeat CMV DNA viral load in 1 week CMV DNA viral load greater than 1000 IU/mL; start treatment: valganciclovir 900 mg PO BID. Dose adjust for renal function.^ □ CMV DNA viral load and CBC with diff weekly while on treatment dose If CMV DNA viral load is increasing or patient becomes symptomatic, reduce immunosuppression and consider change to IV ganciclovir. If patient is clinically stable, treat until CMV DNA viral load is less than 35 IU/mL for 2 consecutive readings, then discontinue. Secondary Prophylaxis: may be considered for high risk patients* valganciclovir 900 mg PO daily for 2 month. Dose adjust for renal function.^ □ CMV DNA viral load and CBC with diff q2wk (minimum) while on reduced therapy. Following valganciclovir therapy: □ CMV DNA viral load weekly for 3 months □ Check for CMV IgG seroconversion after FIRST CMV episode. If the patient is CMV seropositive, follow the CMV Recipient Positive pathway guidelines for subsequent episodes	Any level of CMV DNA viral load start treatment: valganciclovir 900 mg PO bid or ganciclovir 5 mg/kg/dose IV q12h. Dose adjust for renal function.^ □ CMV DNA viral load and CBC with diff weekly while on treatment dose If patient is clinically stable, treat until CMV DNA PCR is less than 35 IU/mL for 2 consecutive readings (minimum 1 month), stop therapy. Secondary Prophylaxis: may be considered for high risk patients* valganciclovir 900 mg PO daily for 2 month. Dose adjust for renal function.^ □ CMV DNA viral load and CBC with diff q2wk (minimum) while on reduced therapy. Following valganciclovir therapy: □ CMV DNA viral load weekly for 3 months □ Check for CMV IgG seroconversion after FIRST CMV episode. If the patient is CMV seropositive, follow the CMV Recipient Positive pathway guidelines for subsequent episodes
Pos	Neg	Adult Prophylaxis: valganciclovir 900 mg PO daily for 3 months. Dose adjust for renal function^	Same as above	Same as above
(Mismatch)		Lymphocyte Depleting Therapies for Acute Rejection: valganciclovir 900mg PO daily or ganciclovir 5 mg/kg/dose IV q24h for 3 months Dose adjust for renal function.^ Steroid Therapy for Acute Rejection: valganciclovir 900 mg PO daily for 1 month. Dose adjust for renal function.^ □ No CMV DNA viral load testing required during prophylaxis □ CBC with diff weekly while on therapy Following valganciclovir therapy: □ CMV DNA viral load weekly for 3 months post CMV prophylaxis and for additional 3 months following any antiviral treatment.		

DONOR	RECIP	PROPHYLAXIS	PRE-EMPTIVE TREATMENT asymptomatic	DISEASE TREATMENT symptomatic
Pos OR Neg	Pos	**Adults: No prophylaxis** **Lymphocyte Depleting Therapies for Acute Rejection:** **valganciclovir 900mg PO daily or ganciclovir 5mg/kg/dose IV q24h for 1 to 3 months. Dose adjust for renal function.^** **Steroid Therapy for Acute Rejection:** **valganciclovir 900 mg PO daily for 1 month. Dose adjust for renal function.^** ☐ No CMV DNA viral load testing required during prophylaxis ☐ CBC with diff weekly while on therapy Following valganciclovir therapy: ☐ CMV DNA viral load weekly for 3 months post CMV prophylaxis and for additional 3 months following any antiviral treatment.	CMV DNA viral load less than 35 IU/mL or 35-1000 IU/mL - no treatment. Repeat CMV DNA viral load as per protocol. CMV DNA viral load greater than 5000 IU/mL on a single reading or patient with rising viral load on 2 consecutive measurements greater than 1000 IU/mL; start treatment: valganciclovir 900 mg PO BID. Dose adjust for renal function.^ ☐ CMV DNA viral load and CBC with diff weekly while on therapy. If CMV DNA viral load is increasing or patient becomes symptomatic, reduce immunosuppression and consider change to IV ganciclovir. If patient is stable, treat until CMV DNA viral load is less than 35 IU/mL for 2 consecutive readings, then discontinue. Following valganciclovir therapy: ☐ CMV DNA viral load weekly for 3 months	Same as above

^Dose adjustment for valganciclovir/ganciclovir for patients with impaired renal function. Click here. (put in hyper link to this section in guidelines

If leukopenia is thought to be due to valganciclovir and patient has been receiving prophylaxis for 4-6 months, stop valganciclovir and start weekly CMV DNA viral loads and CBC with diff. If patient is neutropenic (ANC<0.5) or has declining WBC counts on therapeutic valganciclovir, may need to start filgrastim 300mcg SC daily x 3 doses to increase the count and continue with valganciclovir for treatment. Do not dose reduce valganciclovir or ganciclovir for leukopenia. See BCT Filgrastim Neutropenia guideline here

CMV DNA Viral Load = number of International Units (IU) of CMV DNA virus per millilitre

***Secondary prophylaxis**
is defined as prolonged therapy with standard prophylaxis doses (e.g., once daily) after a successful treatment course. Use and duration should reflect the likelihood of recurrent CMV infection.
High risk patients:
Serious tissue-invasive disease without viremia
Multi-organ disease
Gastrointestinal tissue-invasive disease
Primary CMV infection
High initial viral load
Slow reduction in viral load on treatment
Recurrent CMV disease
Treatment of rejection during treatment for CMV disease
High net state of immunosuppression

6.7.4 Other infections

Fungus infection, such as *Candida*, is common in the post-transplant setting. Patients who are at an increased risk of fungal infection are treated with fluconazole 400mg daily for 10 days.

In rare cases, patients may develop cryptococcal meningitis, which manifests as subtle neurological complaints, variable physical findings, and mild fever. These patients need to be aggressively assessed and treated.

Pneumocystis jiroveci is a micro-organism, which occasionally causes pneumonia and occurs in approximately 2 to 3% of liver transplant patients. Cotrimoxazole is used as prophylaxis against pneumocystis pneumonia (PCP) (see **Table 24**).

Table 24. Treatment for other opportunistic infections in liver transplant recipients.

Organism	Site of infection	Drug of choice
Herpes Simplex Virus (HSV)	Mucocutaneous (mild to moderate)	Acyclovir 800 mg PO QID for 7 days OR Valacyclovir 1000 mg PO BID for 7 to 10 days
	Mucocutaneous (severe)	Acyclovir 5 mg/kg/dose IV q 8h for 7 days
	Respiratory	Acyclovir 10 mg/kg/dose IV q 8h for 10 days
	Encephalitis	Acyclovir 10 mg/kg/dose IV q 8h for 10 days
	Post-Transplant Prophylaxis	Valacyclovir 500mg PO BID for 3 months after transplant (if not on CMV prophylaxis)
Varicella-Zoster Virus (VZV)	Mild	Acyclovir 800 mg PO for 4 to 5 times daily for 7 to 10 days OR Valacyclovir 1 g PO TID x 7 to 10 day
	Severe	Acyclovir 10 to 12 mg/kg /dose IV q 8h for 7 to 14 days
Pneumocystis jiroveci	Prophylaxis	Single strength tablet (400/80) PO once daily for 1 year
	Treatment	TMP-SMX 5 mg/kg IV (based on TMP component) q6h for 21 days Sulfa allergy: pentamidine 4 mg/kg/day IV for 21 days

6.7.5 Renal dysfunction

Renal dysfunction is one of the most common complications of long-term immunosuppression. It is typically associated with calcineurin inhibitors (i.e., cyclosporine and tacrolimus). Patients with decreased renal function may need to have their immunosuppressive regime modified (see **Tables 25 to 27**). Patients whose serum creatinine continues to rise are referred to a nephrologist. Some patients may eventually require dialysis.

Table 25. Ganciclovir IV dose for adult patients with impaired renal function

Creatinine clearance (mL/min)	Ganciclovir IV dosage (mg/kg) PRE-EMPTIVE OR TREATMENT	Ganciclovir IV dosage (mg/kg) PROPHYLAXIS
Greater and equal to 70	5 mg/kg/dose q12h	5 mg/kg/dose q24h
50 to 69	5 mg/kg/dose q24h OR 2.5 mg/kg/dose q12h	2.5 mg/kg/dose q24h
25 to 49	2.5 mg/kg/dose q24h	1.25 mg/kg/dose q24h
10 to 24	1.25 mg/kg/dose q24h	0.625 mg/kg/dose q24h
Less than 10	1.25 mg/kg/dose three times weekly post dialysis	0.625 mg/kg/dose three times weekly post dialysis

Table 26. Valganciclovir oral tablet dose for adult and adolescent patients greater than 16 years of age with impaired renal function

Creatinine clearance (mL/min)	Valganciclovir tablets PO PRE-EMPTIVE OR TREATMENT dosage	Valganciclovir tablets PO PROPHYLACTIC
Greater and equal to 60	900 mg PO BID	900 mg PO daily
40 to 59	450 mg PO BID	450 mg PO daily
25 to 39	450 mg PO daily	450 mg PO every 2 days
10 to 24	450 mg PO every 2 days	450 mg PO twice weekly

Table 27. Valganciclovir oral solution dose for adult and adolescent patients greater than 16 years of age with impaired renal function

Creatinine clearance (mL/min)	Valganciclovir solution PO PRE-EMPTIVE OR TREATMENT dosage	Valganciclovir solution PO PROPHYLACTIC
Greater and equal to 60	900 mg PO BID	900 mg PO daily
40 to 59	450 mg PO BID	450 mg PO daily
25 to 39	450 mg PO daily	225 mg PO daily
10 to 24	225 mg PO daily	125 mg PO daily
Less than 10	200 mg three times a week post dialysis	100 mg PO three times a week post dialysis

6.7.6 Hypertension

Hypertension is common after transplantation and may be related in part to unmasking of essential hypertension. However, cyclosporine and tacrolimus can cause hypertension, partly through direct effects on blood flow in the kidney. There is a view that calcium channel blockers may be of benefit, as they cause vasodilatation and preserve renal function. In general, hypertension in these patients should be treated similarly to patients in non-transplant settings.

6.7.7 Bile duct disease

Bile duct disease is a common complication of liver transplantation, occurring in up to 15% of patients. This is typically related to ischemic injury but may be associated with strictures occurring at the area of anastomosis. Usually, patients are asymptomatic, and these problems are detected only on the basis of increasing liver enzymes. However, patients may also present with jaundice or episodes of cholangitis. Rapid identification of the problem is paramount. Patients require immediate assessment with blood tests, blood cultures, and ultrasound. They often require an endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiogram (PTC). Patients with evidence of biliary tract stenosis may require stenting at the time of the ERCP or placement of a percutaneous catheter at the time of their PTC. These stents are typically left in place for a few months and exchanged.

Some patients benefit from ERCP or PTC and require no further therapy after their stents are eventually removed 6 months later. In other cases, patients ultimately require revision of their anastomosis or conversion to Roux-en-Y hepaticojejunostomy. Patients with significant intrahepatic strictures who continue to develop recurrent cholangitis may eventually require re-transplantation. Initial treatment of patients who develop cholangitis usually consists of a combination of broad-spectrum antibiotics and gram-negative enterococcal coverage. The

antibiotics are adjusted when culture and sensitivity results are available. If the patient develops cholangitis and is treated for cholangitis at a hospital other than VGH, it is important that the transplant team be notified.

6.7.8 Diabetes

Approximately 10% of patients present with diabetes prior to liver transplantation, which is further worsened with the use of prednisone and calcineurin inhibitors (i.e., tacrolimus/cyclosporine) in the post-transplant period. While in hospital, patients may require insulin, although insulin-dependent diabetes typically presents several weeks after transplantation. This is particularly true in patients who receive tacrolimus. Ten to 20% of patients may develop de novo diabetes post-transplant secondary to steroids and calcineurin inhibitors.

6.7.9 Hyperlipidemia

Hyperlipidemia is a long-term complication that can be detected by examining lipid profiles at the time of annual post-transplant assessments. Sirolimus is associated with an increased risk of dyslipidemia.

6.7.10 Hyperkalemia

Hyperkalemia is another common side effect of cyclosporine and tacrolimus. In general, it is readily treated with a potassium exchange resin, such as sodium polystyrene (Kayexalate®) 15g orally 2 to 3 times a day. Patients with peripheral edema are also treated with furosemide. It should be noted that patients who are also receiving sulfa/trimethoprim (Septra®) are at an increased risk of hyperkalemia, as trimethoprim has an amiloride-like effect.

6.7.11 Osteoporosis

Osteoporosis is another important metabolic complication of transplantation. Supplemental calcium and vitamin D are part of the standard protocol. High-risk patients are evaluated further with bone densities and, if abnormal, are referred to an endocrinologist and bisphosphonates may be recommended.

6.7.12 Complications in pregnancy

Plans for pregnancy should be discussed with the transplant team on an ongoing basis and the risks carefully explained. Factors associated with good outcomes for both the transplant recipient and the fetus include time post-transplant, good kidney function, absence of proteinuria, and well controlled blood pressure.

Mycophenolate has been associated with higher risk of birth defects. Recipients who wish to become pregnant should be switched from mycophenolate to azathioprine 3 months before attempting pregnancy.

Pregnant transplant patients require close monitoring. All transplant pregnancies should be viewed as high risk, so the pregnant transplant recipient should be referred to an obstetrician who specializes in high-risk pregnancies. A working relationship between the transplant team and the obstetrician should be established. Transplant patients should be seen at frequent intervals during the third trimester (i.e., once per week).

Blood pressure should be well-controlled and transplant recipients should be off drugs (e.g., ACE inhibitors) which can cause fetal abnormalities. The safest antihypertensive drugs are methyldopa and beta blockers and calcium channel blockers.

The following are potential risks for the pregnant liver transplant recipient. Data is from the National Transplantation Pregnancy Registry on 281 recipients and 575 pregnancies between 1991 and 2006.

- Hypertension: Incidence of hypertension for liver recipients is 20%. A fall in blood pressure during pregnancy may be seen as well.
- Spontaneous abortions: Incidence of spontaneous abortion is approximately 23%, depending on immunosuppressive regimens.
- Higher incidence of a pre-eclamptic-like syndrome characterized by hypertension, edema, and proteinuria developing in the third trimester. Pre-eclampsia should be aggressively treated with hospitalization and urgent delivery if patients do not respond to more conservative means. Pre-eclampsia occurred in approximately 24%.
- Increase in incidence of premature births (39%) and low birth weight infants (30%).
- Acute rejection occurred in 4.5%.
- Diabetes during pregnancy occurred in 8%.

Following pregnancy, the transplant recipient may wish to breastfeed. Anti-rejection drugs including tacrolimus and cyclosporine are found in breast milk, but it is not known if these small quantities are harmful to the infant.

6.7.13 Recurrence of liver disease

Hepatitis B reinfection was universal, but nowadays the risk is minimized with HBIG therapy and long-term use of highly potent antiviral agents. Hepatitis C (HCV) also recurs after transplant if there was a positive viral load before the surgery. To prevent this outcome, the HCV infection should be treated whenever possible before transplant with documentation of sustained viral response. Pre-transplant therapy can be done with the guidance of transplant physicians. In cases where HCV was still active at the time of transplant, it is now possible to effectively treat it with extremely high success rates using direct antiviral agents. Once a grim consequence of HCV graft reinfection, fibrosing cholestatic hepatitis is now rarely encountered.

Autoimmune hepatitis, primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC) can all recur after transplant. Given the immunological nature of these diseases, recurrence prevention is managed with higher level of immunosuppression. Patients with these conditions are rarely candidates for immunotherapy minimization or withdrawal. Patients with PBC can be treated with ursodeoxycholic acid (UDCA). The effect of UDCA post-transplant in patients with PSC is still debated, but given its good tolerability and safety profile, we recommend its use.

6.7.14 Alcohol use-related complications

Alcohol can injure the graft, and cirrhosis can develop within a few years of sustained alcohol use. Occasional use of alcohol can be tolerated in patients with normal graft function, with the exception of patients transplanted for alcohol-related liver disease in whom complete abstinence is required. Approximately one third of patients with alcohol-related liver disease who received a transplant will experience a severe alcohol relapse and this is associated with high risk of graft loss. For this reason, prevention of alcohol relapse after liver transplant is of high importance and abstinence is recommended.

6.7.15 Non-alcoholic hepatitis

Non-alcoholic hepatitis (NASH) can recur or develop de novo in patients after transplant. Unfortunately, metabolic syndrome with dyslipidemia, diabetes, hypertension, and weight gain is a frequent complication of the medications used in transplantations (i.e., tacrolimus, cyclosporine, sirolimus, prednisone). These complications can lead to fat accumulation in the liver, steatohepatitis, and cirrhosis. For this reason, it is essential that patients are properly followed by their primary care physician or specialist and that they receive adequate treatments.

6.7.16 Cancer

Liver cancers can also recur after transplant, although the risk is minimized by following adequate screening and surveillance. In patients with a history of liver cancer, the type and level of immunosuppression is adjusted, and proper surveillance is performed to detect early recurrence.

Table 28. Cancer screening recommendations

Cancer type	Recommendations
Breast	Mammography every 1-2 years
Cervical	Pap cytology and pelvic exam every 3 years
Colorectal	Colonoscopy annually in PSC/IBD patients Average risk patient aged 50-74: FIT every 2 years Family or personal history of adenomas: colonoscopy every 5 years MSM (or anyone engaging in receptive anal intercourse): anal Pap annually
Oropharyngeal	Regular dental screening
Prostate	Ages 50 and above: PSA and DRE annually
Skin	Skin surveillance annually
Thyroid	All patients: annual physical exam Patients who smoke or transplanted for alcohol: Ultrasound of thyroid every 2-3 years

PSC, primary sclerosing cholangitis; IBD, inflammatory bowel disease; MSM, men who have sex with men; PSA, prostate-specific antigen; DRE, digital rectal exam

6.7.17 Other diseases

Budd-Chiari syndrome can also recur after transplant, particularly in patients with an underlying thrombophilic disorder who require life-long anticoagulation therapy.

Patients with Wilson disease, hemochromatosis, or alpha-1-antitrypsin deficiency should not have recurrence of their liver disease, as the defect is corrected with the new liver.

6.7.18 Psychiatric complications

In the majority of cases, post-transplant psychiatric conditions are due to the worsening of pre-existing conditions as a result of steroids and the stress of the post-operative course. It is expected that psychiatric issues caused by steroids improve with minimization and discontinuation of the medication. The risk of psychiatric complications is evaluated during the pre-transplant assessment, and we attempt to build a management plan with the help of specialists and primary care physicians.

6.7.19 Hepatic encephalopathy

Hepatic encephalopathy (HE) can persist several months after the transplant. Patients with severe or frequent symptoms of HE or older or frail individuals can be at particularly higher risk. Similarly, patients with prolonged history of refractory ascites may continue to accumulate ascites for some time after the operation.

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Appendices

Appendix A.

Vancouver CoastalHealth

Solid Organ Transplant Clinic
Gordon & Leslie Diamond Health Center
5th Floor, 2775 Laurel Street, Vancouver BC V5Z1M9

Fax: 604.875.5236
Tel: 604.875.5182

Liver Transplant Referral Form (Outpatient)

Referral Date: (DD/MM/YYYY): _____

Referral must be submitted by specialists. **INCOMPLETE REFERRALS WILL NOT BE ACCEPTED.**

PATIENT CONTACT INFORMATION

Last Name: *First Name:*		*Address:*
BirthDate (DD/MM/YYYY): _____ ❒ *Male* ❒ *Female*		*City:* *Province:* *Postal Code:*
BC PHN: *Other PHN:*		*Home Phone:* *Cell Phone:*
Height: _____ *cm* *Weight:* _____ *kg*		***Email:***
❒ *English Speaker:* ❒ *Other Language:* _____		❒ *Translator Needed:*
CAREGIVER/SUPPORT PERSON	*Name:*	*Home Phone:*
Relationship to Patient:		*Cell Phone:*
REFERRING SPECIALIST MSP #:		**FAMILY PHYSICIAN** MSP #:
Last Name: *First Name:*		*Last Name:* *First Name:*
Phone: *Fax:*		*Phone:* *Fax:*
Nurse Practitioner *(Note: Not for specific referrals to program)*		
Last Name: *First Name:*		
Phone: *Fax:*		

Indication for Liver Transplant Assessment (12 years of age and older)
❒ Cirrhosis ❒ Liver Cancer ❒ Other _____

in the context of
❒ HCV ❒ HBV ❒ Alcohol & Abstinence Demonstration
❒ NASH ❒ PSC ❒ PBC ❒ AIH ❒ Other _____

complicated by
❒ Ascites ❒ controlled by diuretics ❒ require regular paracentesis
❒ SBP last episode (MM/YYYY) _____
❒ Variceal bleed last episode (MM/YYYY) _____
❒ Encephalopathy last episode (MM/YYYY) _____
❒ Other _____

Cardiac Risk Factors
❒ Hyper-tension ❒ Diabetes ❒ Hyper-lipidemia ❒ Personal History CAD ❒ Family History CAD

	Smoking	Excessive Alcohol	Non- therapeutic Drugs
Current user?	❒ Yes ❒ No	❒ Yes ❒ No	❒ Yes ❒ No
Previous user?	❒ Yes ❒ No	❒ Yes ❒ No	❒ Yes ❒ No
Date of Last use: (DD/MM/YYYY)	_____	_____	_____
Attended rehab or counselling in the last 2 years?		❒ Yes ❒ No	❒ Yes ❒ No

❒ **If YES, please provide us with supporting documents**

TO BE SUBMITTED WITH REFERRAL FORM

MANDATORY REPORTS

- ❒ Relevant consult notes that include Medication list and Allergies
- ❒ **Bloodwork within last 2 months including CBC, INR/PTT, Lytes, Urea, Creatinine, LFT's, Albumin. For HCC including tumor markers AFP, CEA, Ca 19-9**
- ❒ **FIT (over 50 yrs old)**
- ❒ **Abdominal Imaging within 2-3 months including Contrast CT Abdo/MRI OR Abdo U/S if contraindicated due to low GFR**
- ❒ **CXR**
- ❒ **ECG**
- ❒ **ECHO (TTE)**
- ❒ **MIBI (for Diabetic and/or over 60 years old)**
- ❒ **CT chest non contrast (long time ex-smoker or recently quit smoking)**
- ❒ **Gastroscopy in the last year if history of portal hypertension**

CONDITION-SPECIFIC REPORTS

- ❒ HCV: Hepatitis C genotype report
- ❒ HCC: Dynamic phase imaging either contrast enhanced MRI or 4 phase abdominal CT scan within last 3 months
- ❒ HIV positive: HIV viral load and CD4 count
- ❒ FAP: Neurology consult notes

If available, please provide the following

- ❒ **Colonoscopy report(s)**
- ❒ Liver biopsy report
- ❒ All abdominal imaging for previous 2 years

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Office Use Only			
❒ Referral Package Complete Date _____		❒ Referral Criteria Met ❒ Yes ❍Emergent ❍Urgent Na MELD_____Child-Pugh_____ ❒ No; advised referring specialist	
Reviewed by	Doctor	RN	SW
Review date	____/____/_____	____/____/____	____/____/____
Appt Date (DD/MM/YYYY) ____/____/_____		❒ Arranged for Translation Services	

Indications

At least one of the following:

1. Decompensated liver disease with a minimum Na MELD score greater than 12 (based on labwork within 2 months) and/or a minimum Child-Pugh score of 9
2. Severe hepatic encephalopathy
3. Refractory ascites
4. Spontaneous bacterial peritonitis
5. Refractory variceal hemorrhage
6. Severe pruritis, refractory to medical management
7. Worsening renal function (hepatorenal syndrome) under nephrologist's care
8. Hepatocellular carcinoma (HCC)
   - Within Milan / San Francisco criteria
   - No further local regional options
9. Hepatopulmonary syndrome with positive bubble echocardiogram
10. Metabolic disorder that would be cured by liver transplant
11. Familial Amyloidoisis Polyneuropathy (FAP) with neurological symptoms

Exclusion Criteria

1. Non-compliance with medical management
2. Use of illicit drugs and/or excessive use of therapeutic drugs within the last six months
3. Ongoing smoker (cigarettes, e-cigarettes, marijuana) and unwilling to quit
4. Absence of 24/7 social support for recovery period after transplant
5. Unable or not committed to adhere to medical treatment
6. Refusal of **all** blood products and blood components transfusions
7. Unmanaged psychiatric disorder
   - Recent suicide attempt
   - Ongoing dementia
8. Any disease or illness with a predicted 5 year survival rate less than 50%
9. Pulmonary arterial systolic hypertension greater than 50mm Hg and pulmonary vascular resistance greater than 240 dynes in right heart catheterization
10. Right heart failure
11. Advanced cardiac disease
12. HIV viral load detectable on HAART therapy and/or CD4 count less than 200
13. Persistent extrahepatic infection despite medical management
14. BMI greater than 40 or less than 15; with serious co-morbidity risk(s)
15. Advanced debilitation with poor functional status and limited mobility
16. Chronic kidney disease on dialysis unless undergoing concurrent kidney transplant assessment
17. Na MELD greater than 40

For urgent inpatient liver transplant referrals, please discuss with VGH Liver Transplant Gastroenterologist on call via VGH Switchboard 604.875.4111

Appendix B.

Pre-Assessment Solid Organ Transplant Clinic
Gordon and Leslie Diamond Health Care Centre
2775 Laurel Street – 5th Floor
Vancouver, BC V5Z 1M9
Phone: 604-875-5182
Fax: 604-875-5236

INFORMED CONSENT FOR SOLID ORGAN TRANSPLANT (LIVER)

Introduction

The goal of the Solid Organ Transplant Program is to maximize both patient health outcomes and the health of the transplanted liver following surgery. **These terms of consent below are set solely for these purposes.**

In order to do this, the Solid Organ Transplant Program conducts assessments of client substance use to ensure they are stable prior to proceeding with liver transplantation. The ability to demonstrate a commitment to future abstinence from alcohol and other mood altering substances (including recreational drugs, smoked tobacco and marijuana) is an important part of this assessment.

Consent

I understand that substance use disorder includes a risk of relapse to compulsive alcohol or drug taking. I may therefore be asked to begin an alcohol and drug (A&D) treatment program for relapse prevention and I will be asked to follow the recommendations of the A&D counselor. The A&D program and counselor will inform the Transplantation team of my participation in the program. In addition, I may be asked to undergo random testing of my blood, breath, and urine to provide evidence of my abstinence. I give permission to have family members, significant others, and relevant health care providers be contacted to help verify my continuing abstinence and for purposes of ongoing transplant assessment.

I understand that lifelong abstinence from all mood altering substances (including alcohol, recreational drugs, smoked tobacco and marijuana) is an important part of my ability to maintain my health and the health of the transplanted liver following surgery.

I understand that ongoing substance use may result in discharge from the transplant assessment program until such a time that I am able to follow the A&D treatment program. Resuming substance use any time following acceptance into the transplant program may result in my being removed from the transplant waiting list until such a time that I am able to follow the A&D treatment program.

In the event of relapse after transplantation, I agree to enter substance use disorder treatment including traditional or culturally safe treatment programs, as recommended for me by the Transplant Team**. I also understand that if I relapse to substance use following transplantation, I will not be offered a second transplant should one become necessary.**

I have read the above and agree to the conditions set forth and I have a copy of this informed consent document for my records.

_____	_____
Patient Signature	Signature of Witness
_____	_____
Date and Place	Print Name and Relationship to Patient

Appendix C.

Pre-Assessment Solid Organ Transplant Clinic
Gordon and Leslie Diamond Health Care Centre
2775 Laurel Street – 5th Floor
Vancouver, BC V5Z 1M9
Phone: 604-875-5182
Fax: 604-875-5236

Date: _____

RE: **DOB:**

To Whom It May Concern:

Re: Request for addiction counseling

This patient has end-stage liver disease and wishes to be considered for a liver transplant by the Solid Organ Transplant (SOT) clinic. All patients being considered for a liver transplant at the SOT clinic **must demonstrate the ability to sustain remission from alcohol or other substances.** We also require that all patients with a drug and alcohol history obtain addiction counseling.

In order to avoid irreparable damage to transplanted liver(s), it is important that this individual acquire all the relapse prevention tools possible, including knowledge of the resources that are available to support continued abstinence if needed. The goal is to increase the probability of remaining abstinent from substances in the face of post-transplant stressors. The number of sessions and type of counselling required we leave to your discretion as an addiction specialist. We have asked our client to contact you to initiate this referral.

Please note this patient must attend in order to be eligible for transplantation.

The liver transplant team requires documentation of successful completion of counseling. A brief report outlining: **assessment, dates of sessions, types of services provided, patient's response to treatment, and any future interventions planned.**

When conducting your assessment and treatment of this patient, consideration of the following risk factors for relapse to substance use in liver transplant patients may be useful:

- Cessation of substance use due primarily to a medical event without patient addressing the underlying addiction-related issues
- Limited alternate (substance-free) coping strategies
- Limited understanding of health impact of substance misuse
- Limited sense of responsibility for substance misuse
- Polysubstance use (previous or current)

- Social circle reinforcing substance misuse
- Continued exposure to high-risk situations
- Family history of alcohol misuse
- Ongoing significant psychosocial or biomedical stressors
- Previous repeated treatment failures
- Limited understanding of factors leading to previous relapses
- Social instability (poor quality of existing personal relationships
- Social isolation
- Limited social support
- Previous history of medical treatment non-adherence
- Co-existing mental health disorders

Thank you for your assistance and please do not hesitate to contact me if you need any further information.

Sincerely,

Transplant Psychologist

Revised Feb 2022

Appendix D.

Pre-Assessment Solid Organ Transplant Clinic
Gordon and Leslie Diamond Health Care Centre
2775 Laurel Street – 5th Floor
Vancouver, BC V5Z 1M9
Phone: 604-875-5182
Fax: 604-875-5236

SOCIAL SUPPORT FOR TRANSPLANTATION
RE: _____

Liver transplantation is a complex medical procedure that requires the recipient to engage in numerous health care behaviors to help ensure a successful outcome to transplantation.

In order to help the patient adhere to the complicated medication schedule and other treatment requirements, a support person must be available during the various phases of transplantation. In the event that it is not feasible for one person to be consistently available for the patient, a social support network may be acceptable. Details of the plan will need to be made available to the transplant team.

The support person(s) needs to be present during the pre-transplant waiting period (attending all pre-transplant clinic appointments), during the in-hospital post-operative stay, and following hospital discharge for a minimum of three (3) months in the Vancouver area.

The support person will offer both instrumental and emotional support. Instrumental support means that the support person will be available to offer assistance with personal care. The support person will accompany the patient to and from treatment appointments. To help ensure that medication requirements are accurately followed, the support person will assist in medication scheduling by prompting at appropriate intervals. Other responsibilities can include providing assistance with groceries, laundry, meal preparation, and other activities necessary for a safe and comfortable postoperative recovery.

Emotional support implies that the support person will be available to encourage and generally foster an environment of hopeful optimism to promote healing and recovery. A part of creating this healthy atmosphere is to ensure that the patient is not exposed to high risks associated with substance abuse.

I have read the above and agree to the conditions set forth.

I agree to provide social support for the:

☐ Pre-Transplant Period ☐ Post-Transplant Period

----------	----------
Support Person Signature	Signature of Witness
----------	----------
Print Name, Relationship to Client & Contact info	Name &Title
----------	----------
Date & Place	Date & Place

Promoting wellness. Ensuring care. Vancouver Coastal Health Authority

Appendix E.

Pre-Assessment Solid Organ Transplant Clinic
Gordon and Leslie Diamond Health Care Centre
2775 Laurel Street – 5th Floor
Vancouver, BC V5Z 1M9
Phone: 604-875-5182
Fax: 604-875-5236

Information for patients about Alcohol and Drug Relapse Prevention Counseling before referral for a liver transplant assessment

As part of your doctor's assessment, it has been identified that you have a history of alcohol and/or drug use. The Liver Transplant Team requires that you attend addiction counseling focusing specifically on relapse prevention in order to be eligible for a possible liver transplant. If you have been abstinent for an extended period, an assessment by the addiction counselor may determine that no additional counseling is required. Nonetheless, the Team would like you to have that discussion with the counselor and also be informed of any services that may be available to you, now or in the future, to support your continuing abstinence.

Why am I asked to attend counseling?
One of the goals of the Liver Transplant Team is to help ensure that you maintain your health before and after a potential liver transplant. Sometimes, after transplant, when you are feeling well again, it can be a struggle to maintain a healthy lifestyle. Normal daily routines can stimulate old behaviours which can be very damaging to your new liver as well as your overall health.

A focus on relapse prevention is useful in developing new ways to cope with life stresses and reduce the likelihood of returning to alcohol or drugs. Learning to become aware of triggers for alcohol or drug use and developing new ways of coping with those triggers will not only protect you from the possibility of relapse, but also help you to live a more satisfying life.

How do I find a counselor?
You will need to contact the *BC Alcohol and Drug Information and Referral Service* at **604-660-9382 or BC Toll Free 1-800-663-1441**. Please call and they will help you find a service, such as a counselor in your community. If you are already aware of a service in your community, you can contact them directly.

In addition, please take the accompanying document to your first appointment and give it to your counselor. The information will help highlight to the counselor the reasons why you are asked to attend alcohol and drug counseling.

Sincerely,
The Liver Transplant Team

Appendix F.

INFORMED CONSENT FORM
DISCLOSURE OF RISK OF DISEASE TRANSMISSION

Patient Label

1. I understand that receiving an organ carries a risk of disease including but not limited to bacterial or viral infection (e.g. hepatitis C) and cancer. Some organ donors have a higher risk of transmitting infectious diseases than other donors. These donors are called increased risk donors.

2. I understand that testing of donors for diseases has limitations. I understand that some of these diseases may not be identified until after my transplant has occurred (e.g. the donor had an unrecognized bloodstream infection). I may need to be monitored after my transplant as a result. If appropriate, I may be offered treatment or see specialists about this.

3. I understand that I may be offered an organ from an increased risk donor. This will be because my transplant doctor feels the benefit of accepting this organ outweighs the risk. The specific benefits and risks of taking this organ will be explained to me at the time of transplantation. I can refuse the organ and my status on the waiting list will not be affected.

4. I have been provided with a copy of the Patient Info Guide – *"FAQ on Risk of Disease Transmission from Organ Donors"*. I understand that I can ask a transplant nurse or physician about any questions that I may have on infectious disease from donors at any time to assist me in making an informed decision.

I understand and accept the risks described above.

Name: (Mr., Mrs., Ms.) _____
SURNAME GIVEN NAMES

SIGNATURE: _____ _____
(PATIENT OR GUARDIAN) (PRINT NAME IF NOT THE PATIENT)

_____ DATE:_____
(Relationship to Patient if not the Patient)

WITNESS:_____ _____
(SIGN) (PRINT NAME)

DATE:_____

STATEMENT BY PROFESSIONAL INTERPRETER
COMPLETE **ONLY** IF A PROFESSIONAL INTERPRETER IS USED TO OBTAIN CONSENT.
I have translated the above information to the: _____Patient/Client ____parent ___legal guardian or representative and I have interpreted their responses to the health care provider.

_____ _____ _____
SIGNATURE OF INTERPRETER PRINT NAME DATE SIGNED

Appendix G.

Recommended Follow-up Testing for Recipients Transplanted under EXCEPTIONAL DISTRIBUTION

NOTICE TO TRANSPLANT RECIPIENT MEDICAL TEAM

For Recipient:_____

You are receiving this notice because the donor for this recipient has evidence of: (✓)

- ☐ High Risk Behavior for Increased Risk of HIV, Hep B, Hep C
- ☐ Positive Hepatitis C Antibody Test with Negative RNA (NAT)
- ☐ Unknown Medical-Social History
- ☐ Other_____

IT IS RECOMMENDED THAT RECIPIENTS ARE TESTED FOR HIV, HEPATITIS B and HEPATITIS C AT:

4 weeks
3 months
1 year

Recommended Test Methods:
HIV serology (fourth generation Ag/Ab test)[1]
HBV – HBV DNA (NAT), HBs Ag and anti-HBV core total antibody[2]
HCV – HCV Quantitative RNA (NAT)[2]**

NOTES:

1. *If there is still concern for HIV despite a negative test, please consult medical microbiology about ordering an HIV NAT test.*
2. *Antibody testing is unreliable early post-transplant. It may be positive in the recipient for three to twelve months after transplant due to passive transfer of antibody with the transplanted organ. In addition, if the recipient has received cytomegalovirus immune globulin (CytoGam) or IVIG within the last 3 months, then PCR testing must be used over serology for HBV testing because of the risk of false positives.*
3. *Recipients with symptoms or laboratory evidence of reactivation (e.g. elevated liver enzymes) should be tested more frequently.*

For further information on these protocols, please contact Transplant Infectious Diseases Specialist

Appendix H.

BC TRANSPLANT An agency of the Provincial Health Services Authority	**Recommended Follow-up MONITORING for Recipients Transplanted under Risk for Tuberculosis**

NOTICE TO TRANSPLANT RECIPIENT MEDICAL TEAM:

For Recipient:_____

You are receiving this notice because the donor for this recipient has risk factors for exposure to TB[1]. Although the donor did not have chest imaging with TB concerns or a history of a positive TST/IGRA at the time of transplant, there is still a small risk for TB.

The recipient of this organ should be **monitored** in the future for signs or symptoms of reactivation TB.

Symptoms

These include persistent unexplained fever, night sweats, fatigue, and weight loss. Patients may also experience pulmonary symptoms (cough and shortness of breath) or graft dysfunction. Any of these should prompt an evaluation for TB.

Suggested Investigation/Evaluation

Investigation could include a CXR and sputum samples as well as samples from any organ or tissue of concern found by history, physical or imaging. A repeat TST/IGRA may be helpful if the patient was negative prior to transplant; however false negatives in the setting of active TB can occur and therefore a negative result does not rule out TB.

References:

[1]WHO Global Tuberculosis Report - Current Edition

Appendix H (Con't)

BC TRANSPLANT An agency of the Provincial Health Services Authority	**Recommended Follow-up TREATMENT for Recipients Transplanted under Risk for Tuberculosis**

NOTICE TO TRANSPLANT RECIPIENT MEDICAL TEAM:

For Recipient:_____

You are receiving this notice because the donor for this recipient has evidence of untreated latent TB infection including:

(✓)

☐ Abnormal Chest Imaging

☐ Positive IGRA

☐ Positive TST

Recipients of these donors should be given treatment for latent TB. Nine months of isoniazid (INH) plus pyridoxine (vitamin B6) is the gold standard barring contraindications. Patients should start therapy as soon as feasible and ideally within one month of transplant as 95% of patients reactivate within the first post-transplant year[1]. This can be started in hospital or at the time of discharge if the patient recovers quickly. Patients with contraindications to therapy should be very closely monitored.

Please refer to TB Services at BCCDC on discharge for follow-up (see attached referral form).

References:

[1] J. Torre-Cisneros et al. Tuberculosis after solid organ transplant: Incidence, risk factors, and clinical characteristics in the RESITRA (Spanish Network of Infection in Transplantation) Cohort. Clinical Infectious Diseases 2009; 48:1657-65.

SUPPLEMENTAL

APPENDIX I.

Clinical Guidelines in Patients with Alcohol Use

SUPPLEMENTAL INFORMATION TO CLINICAL GUIDELINES FOR LIVER TRANSPLANTATION

Prepared by the BC Liver Transplant Program VGH

NOTE: These guidelines are intended to supplement existing Liver Transplant Clinical Guidelines and as such should not be considered on their own. The content of these guidelines may be updated later for consistency and organization and to reflect any new evidence and considerations.

Background

Alcohol-associated liver disease (ALD) is among the top three indications for liver transplantation in British Columbia. The purpose of this exceptional pathway is to offer a decision-making framework which carefully considers the ethical, practical, and other relevant dimensions of resource allocation decisions in a setting of limited availability of organs for transplantation.

I. Criteria for liver transplantation in patients with alcohol-associated acute hepatitis

This is a condition where a patient with no pre-identified underlying chronic liver disease presents with acute inflammation of the liver from alcohol consumption leading to liver failure. If the diagnosis is in doubt, a liver biopsy may be necessary to confirm the diagnosis.

Absolute criteria for liver transplantation:

1. Acute alcohol-related hepatitis with the absence of the following:
    a. Pre-existing known liver disease secondary to alcohol consumption.
    b. Previous diagnosis or admissions for alcohol-related hepatitis.
    c. Advanced chronic liver disease secondary to other condition for which the patient was asked to reduce alcohol consumption.
    d. Other medical condition caused by alcohol consumption for which the patient was asked to reduce or stop alcohol consumption (e.g., pancreatitis, alcohol withdrawal).
2. Patient has severe alcohol-related hepatitis with a Maddrey score ≥32 or a Glasgow Alcoholic Hepatitis Score ≥9. (See Appendix 1, #4.)
3. Patient has not shown favourable response to medical treatment with prednisone 40 mg daily or prednisolone 40 mg daily. A Lille score ≥0.45 one week after initiation of therapy is indicative of lack of response. (See Appendix 1, #6.)
4. Patient acknowledges the contribution of alcohol to his/her disease.
5. Presence of strong social support by family or friends and stable financial condition (personal or with third party funding) as required for other indications for liver transplantation.
6. Assessment of risk factors for alcohol relapse and psychosocial suitability using the Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT)[7, 8] whenever possible.

7. Assessment of risk factors for alcohol relapse by an addiction specialist whenever possible.
8. Absence of significant medical comorbidities (e.g., congestive heart failure, pulmonary hypertension, untreated malignancy).
9. Commitment to a lifelong adherence to alcohol abstinence and willingness to sign an informed consent form to comply with post-transplant care.[2]
10. Absence of evidence of intractable inability to cease drinking.

Non-absolute criteria liver transplantation:

11. Absence of current or historical polysubstance use and/or addiction or unstable or uncontrolled psychiatric disease (including personality disorders) that can impact the ability to follow medical directives or increase the risk of alcohol relapse and affect graft function.[3]
12. Absence of significant legal problems related to alcohol misuse.
13. Alcohol consumption estimated at 10 units or more per day. (See Appendix 1, #7.)

A patient who does not fulfill one or more non-absolute criteria but has other strong protective factors may still be suitable for transplant. A patient not fulfilling the majority of the non-absolute criteria may not be considered suitable. The decision to list a patient will be reached after discussion with the transplant team.

II. Criteria for decompensated or acute-on-chronic liver failure in patients with alcohol associated cirrhosis

The purpose of this pathway is to consider patients who have been diagnosed with advanced liver disease and have started the process of abstinence but have developed a severe decompensating event associated with high mortality. It is estimated that these patients will be unlikely to survive a period of abstinence to allow for liver healing. In this context, the criteria of "entry into disease" (as for acute alcohol-related hepatitis) does not necessarily apply.

Absolute criteria for liver transplantation:

1. Based on clinical presentation, patient is an **inpatient** with any of the following:
    a. MELD score equal or superior to 30 (See Appendix 1, #3.)
    b. ACLF score Grade 3[11] (See Appendix 1, #1.)
    c. CLIF-AD score equal or superior to 60 (See Appendix 1, #2.)
    d. Hepatorenal syndrome (on hemodialysis)

    Note: In cases outside VGH, the patient must be in a stable condition to tolerate an inter-hospital transfer. Patients in an intensive care unity should have improved sufficiently to be transferred to a regular medical ward.

2. Patient acknowledges the contribution of alcohol to his/her disease.

3. Patient did not continue consuming alcohol after the diagnosis of cirrhosis. He/she must have started alcohol & drug counselling unless:
    a. There was not enough time between diagnosis and decompensating episode.
    b. Patient did not receive instructions to do so by ANY of his/her treating physicians.
    c. The patient made other reasonable steps to cease alcohol use (doing it "on my own" is not sufficient)

    Note: Transplant referrals for individuals for whom the reason for the severe decompensation or failure is persistent alcohol consumption will not be accepted.
4. Presence of strong social support by family or friends and stable financial condition (personal or with third party funding) as required for other indications for liver transplantation.
5. Assessment of risk factors for alcohol relapse and psychosocial suitability using the Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT)[7, 8] whenever possible.
6. Assessment of risk factors for alcohol relapse by an addiction specialist whenever possible.
7. Absence of significant medical comorbidities (e.g., congestive heart failure, pulmonary hypertension, untreated malignancy).
8. Commitment to a lifelong adherence to alcohol abstinence and willingness to sign an informed consent to comply with post-transplant care.[2]
9. Absence of evidence of intractable inability to cease drinking.

Non-absolute criteria for liver transplantation:

See non-absolute criteria above for liver transplantation in patients with alcohol-related acute liver hepatitis.

III. Patients without severe decompensation

It is recognized that patients can have a significant improvement of their liver function with alcohol abstinence. Indeed, abstinence is the treatment of alcohol-related liver disease. Patients with decompensated liver disease can completely normalize their liver function after a few months. It is estimated that most of the improvement can occur within the first 6-12 months of abstinence. As such, these patients should be carefully monitored by their physician/nurse practitioners before being referred to the transplant clinic. These include patients with:

1. MELD ≤20
2. Ascites managed with diuretics
3. Hepatic encephalopathy responsive to treatment with lactulose

4. Episode of variceal bleed that is responding to endoscopic therapy
5. Single episode of spontaneous bacterial peritonitis responding to medical therapy
6. Inpatients for which a discharge is imminent

The patient is expected to address the substance use disorder during the period of observation, in keeping with his/her value system and with active participation from the referring physician and the family doctor (or nurse practitioner). If during this time the patient's condition deteriorates, a referral can be made with documentation that the patient has engaged in a substance use treatment program and has ceased alcohol use. A patient who has not engaged in alcohol and drug counselling or has not made sufficient steps to stop alcohol use may not be given an appointment until initiation of some form of counselling. Once referral has been accepted, acute-on-chronic liver failure (ACLF) criteria will be used.

IV. Patients with severe decompensation but not meeting criteria for exceptional pathway

Some patients may continue to deteriorate or have severe clinical presentation despite a period of abstinence from alcohol but do not meet the criteria of ACLF or alcohol related acute hepatitis. These patients may have the following:

1. MELD more than 20, but less than 30
2. Refractory or diuretic resistant ascites
3. Refractory spontaneous hepatic encephalopathy despite lactulose AND rifaximin
4. Severe hepatopulmonary syndrome
5. Portopulmonary syndrome
6. Recurrent variceal bleeding, bleeding from GAVE, or portal hypertensive enteropathy despite endoscopic therapy
7. Repetitive episodes of spontaneous bacterial peritonitis

A referral can be made for an outpatient or inpatient assessment depending on the severity of the condition. A discussion of the case with a hepatologist is recommended to explore other therapies or suitable options. The patient is expected to initiate alcohol and drug counselling or other services during the waiting period. Once referral has been accepted, ACLF criteria will be used.

Directives to patients and caregivers after transplant

Patients must comply to lifelong adherence to alcohol abstinence and follow an alcohol and drug program, publicly or privately funded, after transplant. Failure to comply with these directives and to directives of care after transplant (e.g., blood work, treatments, procedures, and visits) will exclude them from being considered for re-transplantation in cases of graft failure. Similarly, if clinical evidence shows that the reason for a graft failure is due to alcohol use relapse, re-transplantation will not be offered. Random testing for alcohol levels may be requested pre- or

post-transplant. Failure to comply (within 24 hours) without a valid reason will affect the decision for future transplantation.

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Appendix 1. Definition of terms used

1. ACLF: Acute-on-chronic liver failure is a syndrome characterized by an acute decompensation of chronic liver disease associated with organ failures and high short-term mortality. An excessive systemic inflammatory response seems play an essential role in its development.

Examples of definitions of organ failures in Patients with cirrhosis		
Failing Organ	EASL-CLIF[11]	NACSELD[14]
Liver	Bilirubin level > 200 umol/L	-
Kidney	Creatinine > 177 umol/L or renal replacement	Need for dialysis or other forms of renal replacement therapy
Brain	West-Haven hepatic encephalopathy grade 3-4	West-Haven hepatic encephalopathy grade 3-4
Coagulation	INR $\geq$ 2.5	-
Circulation	Use of vasopressors (terlipressin or catecholamines)	Presence of shock defined by MAP <60 mmHg or a reduction of 40 mmHg in systolic blood pressure from baseline despite adequate fluid resuscitation and cardiac output
Respiration	$PaO_2/FIO_2 \leq 200$ or SPO_2/FIO_2 of $\leq$ 214 or need of mechanical ventilation	Need for mechanical ventilation

An ACLF grade 3 will signify that 3 or more organs have failed according to the EASL-CLIF criteria. Please refer to this calculator: https://www.clifresearch.com/ToolsCalculators.aspx

2. CLIF-AD score: Acute decompensation score that can be used for patients who do not have ACLF but have severe decompensation.

Please refer to this calculator: https://www.clifresearch.com/ToolsCalculators.aspx

3. MELD score: Model for End-stage Liver Disease is calculated according to the following formula: MELD = 3.78×ln[serum bilirubin (mg/dL)] + 11.2×ln[INR] + 9.57×ln[serum creatinine (mg/dL)] + 6.43

Please refer to any of several online calculators.

4. Maddrey score: Maddrey discriminant function (DF) is the traditional model for evaluating the severity and prognosis in alcoholic hepatitis and evaluates the efficacy of using alcoholic hepatitis steroid treatment. It is calculated using the patient's PT and total bilirubin.

Please refer to this calculator: http://www.alchepscores.com

5. Glasgow score: Glasgow Alcoholic Hepatitis Score is an alternative model that can be used to assess severity of an episode of alcohol-related acute hepatitis and indication for steroid treatment.[15]

The Glasgow Alcoholic Hepatitis Score			
	Score Given		
Criteria	1	2	3
Age	< 50	≥ 50	-
WBC (10^9/L)	< 15	≥15	-
Urea (mmol/L)	<5	≥5	-
INR	<1.5	1.5-2	>2
Bilirubin (umol/L)	< 125	125-250	>250

Please refer to this calculator: http://www.alchepscores.com

6. Lille Score was validated to describe patients who are responding to therapy with steroids and for whom therapy should be continued versus non-responders for whom therapy should be stopped. It is typically evaluated by comparing the changes in bilirubin levels at day-7 after initiation of therapy.[16]

Please refer to this calculator: http://www.alchepscores.com

7. Volume of alcohol estimates:

A bottle of wine is the equivalent of 5 units.

A "Mickey" of strong liquor is the equivalent of 8 units.

A regular size bottle (26oz) of strong liquor is the equivalent of 16 units.