Liver Transplant Workup: Introduction

What is Cirrhosis of the Liver?

Cirrhosis of the liver is the end result of chronic injury to the liver from various causes. A cirrhotic liver is shrunken and fibrosed and thus loses its ability to secrete bilirubin; make various proteins (i.e., coagulation proteins, albumin, immune antibodies), and clear toxins from the blood like ammonia. Many patients with cirrhosis develop portal hypertension, which is elevated pressure in the portal venous system (a major vein that leads into the liver). Portal hypertension leads to additional complications in a patient with cirrhosis including, an enlarged spleen, ascites (fluid accumulation within the abdominal cavity) and life threatening bleeding into intestinal tract and death. In addition, patients with cirrhosis of liver can develop cancer in the liver – hepatocellular carcinoma (HCC).

What are the stages of cirrhosis?

1. Latent phase (well compensated stage)
2. Advanced phase (decompensated stage)

What are the clinical manifestations and complications of decompensated cirrhosis?

The manifestations of decompensated cirrhosis are usually caused by the development of portal hypertension and include:

1) Gastroesophageal varices and bleeding

Eosophageal varices are often managed by sclerotherapy or endoscopic variceal band ligation (EVBL). Gastric varices also cause upper GI bleeding but it is usually difficult to stop them bleeding by endoscopic means. Patients with refractory Gastroesophageal bleeding often require a Transjugular intrahepatic Portosystemic Shunt (TIPS) placement for the control of their bleeding. Patients might also bleed from portal hypertensive gastropathy (PHG), which is diffuse bleeding from the surface of the stomach. TIPS is indicated in these patients as well.
Transjugular intrahepatic portosystemic shunting (TIPS) is indicated in some selected cases not responding to EVBL. TIPS is placed by an interventional radiologist between the hepatic vein and portal vein. In some instances, a shunt may have to be created surgically by a liver transplant surgeon, who also specializes in these types of shunt procedures.

2) Ascites

Ascites is the presence of excess fluid in the abdominal cavity and frequently develops in patients with chronic liver disease. Ascites is sometimes seen in association with collateral venous return (caput medusae) and abdominal wall hernia. The fluid collection in the abdominal and thoracic cavity is usually managed with salt restriction to 2 Grams of Sodium a day and in addition to diuretics. Fluid restriction is especially necessary in patients who develop hyponatremia (low serum Sodium levels).
Large volume paracentesis with albumin infusions are usually effective. TIPS can be considered in selected patients, refractory to the above interventions.

3) Spontaneous Bacterial Peritonitis (SBP)

SBP is often seen in patients with cirrhosis and ascites and refers to bacterial infection of the ascitic fluid without the presence of a surgically treatable cause. Patients with SBP are treated with antibiotics and may require antibiotic prophylaxis to prevent recurrent infections.

4) Encephalopathy

Hepatic Encephalopathy (HE) refers to the state of confusion induced by high serum Ammonia levels. Signs of the buildup of toxins in the brain include neglect of personal appearance, slow in responsiveness, forgetfulness, trouble concentrating or even changes in sleep habits. In advanced stages, hepatic encephalopathy can induce coma (Hepatic Coma - HE). HE is managed by changing the intestinal flora by addition of Lactulose as a stool softener. Antibiotics like Rifaximine can be useful. 1 gram /kg body weight of protein intake is essential in these patients to avoid malnutrition.

5) Hepatorenal Syndrome

Hepatorenal Syndrome (HRS) is decreased renal function as a consequence of cirrhosis and reflects the severity of the liver disease and the urgency for liver transplant consideration.

6) Hepatopulmonary Syndrome

Hepatopulmonary Syndrome (HPS) patients usually present with cyanosis (bluish discoloration of skin) and clubbing (enlargement of the finger tips). Home oxygen therapy is required prior to liver transplant since blood oxygen levels are decreased due to effects of cirrhosis on the lungs. HPS is often reversible following liver transplantation.

7) Porto pulmonary Hypertension

Porto pulmonary Hypertension (PPHTN) is a pulmonary vascular disorder seen in patients with portal hypertension. In mild to moderate cases, urgent liver transplant is required to avoid further cardiopulmonary complications. Patients might be required to be on continuous drip of epoprostenol (prostaglandin) at home, or some other oral medications, in preparation for the liver transplant. Severe cases usually are not offered liver transplantation because of significantly increased morbidity and mortality.

8) Hypersplenism
Enlargement of the spleen due to portal hypertension can cause decreased platelets and white blood cells in the peripheral blood, making the cirrhotic patient prone to easy bleeding and some infections.

Clinical manifestations of cirrhosis unrelated to portal hypertension include:

9) Coagulopathy
This is caused by deficient production of blood coagulation factors by the cirrhotic liver. Patients are usually prone to spontaneous bleeding and easy bruising. The PT/INR is used to follow the hypocoagulable state in a cirrhotic patient.

10) Jaundice
Jaundice is a yellowish discoloration of the skin and eyes that occurs when the diseased liver does not secrete enough bilirubin. This signifies a major secretory dysfunction of the liver and is followed by serum total bilirubin (TB) levels.

11) Itching
Itching usually becomes a significant problem in patients with cholestatic liver diseases i.e., PBC, PSC.

12) Edema
Accumulation of fluid in the arms and legs occurs when the liver loses its ability to make the protein albumin.

13) Hepatocellular Carcinoma
Hepatocellular carcinoma HCC is a primary liver tumor commonly caused by cirrhosis usually in the setting of Hepatitis B and C, although it can occur in cirrhosis from any cause. It has a high mortality rate.

14) Sensitivity to medication
Cirrhosis decreases liver's ability to metabolize medications from the blood. This cause some medications act longer than expected and build up in the body. This causes a person to be more sensitive to medications and their side effects.
Liver Transplant Workup: Anatomy

The liver is the largest organ in the abdominal cavity and the most complex (Figure 7). It consists of a myriad of individual microscopic functional units called lobules. The liver performs a variety of functions including the removal of endogenous and exogenous materials from the blood, complex metabolic processes including bile production, carbohydrate homeostasis, lipid metabolism, urea formation, and immune functions.

The liver is located in the right upper quadrant, between the fifth intercostal space in the midclavicular line down and the right costal margin. It weighs approximately 1800 grams in men and 1400 grams in women. The surfaces of the liver are smooth and convex in the superior, anterior and right lateral regions. indentations from the colon, right kidney, duodenum and stomach are apparent on the posterior surface.

The line between the vena cava and gallbladder divides the liver into right and left lobes. Each lobe has an independent vascular and duct supply. The lobes are divided into eight segments each containing a pedicle of portal vessels, ducts, and hepatic veins.

The portal venous system extends from the intestinal capillaries to the hepatic sinusoids (Figure 8). This system carries blood from the abdominal gastrointestinal tract, the pancreas, the gallbladder and the spleen back to the heart (coursing through the liver). The largest vessel in this system is the portal vein, which is formed by the union of the splenic vein and superior mesenteric veins. The left gastric and right gastric veins and the posterior superior pancreaticoduodenal vein drain directly into the portal vein. The portal vein runs posterior to the pancreas and its extrahepatic length is anywhere from 5 to 9 centimeters. At the porta hepatis, it divides into the right and left portal veins within the liver, and the cystic vein typically drains into the right hepatic branch.

The portal vein supplies 70% of the blood flow to the normal liver, but only 40% of the liver oxygen supply. The remainder of the blood comes from the hepatic artery, and blood from both vessels mixes in the sinusoids.

The liver receives a tremendous volume of blood, on the order of 1.5 liters per minute. This dual blood supply—from the portal vein and hepatic artery—allows the liver to be relatively resistant to hypoxemia. Unlike the systemic vasculature, the hepatic vascular system is less influenced by vasodilation and vasoconstriction. This is due to the fact that sinusoidal pressures remain relatively constant in spite of changes in blood flow. A classic example is hepatic vein occlusion resulting in high sinusoidal pressure and extracellular extravasation of fluid. To maintain a constant inflow of blood, hepatic artery blood flow is inversely related to portal vein flow. This appears to be hormonally mediated rather than neurally mediated, since it persists even in the transplanted liver.
Liver Transplant Workup: Causes

What causes cirrhosis of the liver?

- **Alcoholic Liver Disease**
- **Infections**
  - Chronic Hepatitis B virus infection (with delta hepatitis in some cases)
  - Chronic Hepatitis C virus infection
- **Autoimmune diseases**
  - Autoimmune hepatitis (AIH)
- **Metabolic diseases**
  - Hemochromatosis which is an iron metabolism abnormality leading to iron deposition within the liver.
  - Wilson's Disease which is a copper metabolism abnormality leading to copper deposition within the liver (can also present as acute liver failure)
- **Cholestatic Liver Disease**
  - Primary biliary cirrhosis (PBC)
  - Primary sclerosing cholangitis (PSC)
  - Secondary biliary cirrhosis (extrahepatic biliary obstruction)
  - Biliary atresia (in children)
- **Non Alcoholic Fatty Liver Disease (NAFLD) / Non Alcoholic Steatohepatitis (NASH)**
- **Drugs i.e. Methotrexate and Amiodarone**
- **Vascular disease of the liver e.g. Budd-Chiari Syndrome**
- **Cryptogenic Cirrhosis** (unidentifiable cause but may include several cases of NAFLD)
- **Miscellaneous causes**
  - Alpha 1 antitrypsin deficiency
  - Glycogen Storage Diseases
  - Severe heart failure with congestion of the liver
  - Parasitic infestation like schistosomiasis

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What is Liver Transplantation?
Orthotopic liver transplantation (OLT) has become the definitive treatment for end stage liver disease (ESLD) and its complications as well as acute liver failure (ALF), primary liver cancer (hepatocellular carcinoma-HCC) and some metabolic diseases.

What are the types of liver transplant?
There are two types of liver transplant:
1) Cadaveric: Here the organ is harvested from a brain dead individual who was an organ tissue donor.
2) Live Donor: Here a portion of the liver is taken from the healthy relative of the recipient who had undergone extensive workup for suitability prior to the surgery.

Who allocates organs for liver transplant?
In the United States, cadaveric organs are allocated by the United Network for Organ Sharing (UNOS).

How does UNOS allocate organs?
UNOS allocates organs based on the MELD (Model for End stage Liver Disease) scoring system. MELD is a liver disease severity scoring system that uses three major biochemical parameters of a patient, i.e., Prothrombin Time/INR, Total Bilirubin and Creatinine in a logarithmic formula to predict survival. The MELD score was implemented by UNOS on Feb. 27, 2002 in an effort to prioritize organ allocation, since it is highly predictive of three-month mortality from cirrhosis.

Transplant work up is usually initiated when the MELD score reaches around 15 or a major complication of cirrhosis is encountered. MELD score emphasis is on the acuity of the patient rather than the time spent on the waiting list.
For MELD score calculation please visit www.unos.org.

What are the indications for a liver transplant?
The indications for liver transplantation can be either acute (fulminant) liver failure from medication toxicity (most commonly acetaminophen) or other toxic ingestions. Rarely acute viral hepatitis B cause fulminant hepatic failure necessitating a liver transplant.

Most cases of liver transplants are offered for end stage liver disease from any cause. In the United State, the most common indications for OLT are Cirrhosis from Hepatitis C, Alcohol, NASH, PBC and PSC. Less common causes are cirrhosis from Hepatitis B and metabolic diseases like hemochromatosis and Wilson’s disease.

Patients with Hepatocellular Carcinoma (HCC) are considered for liver transplantation if they meet certain criteria (Milan Criteria) which have been adopted by UNOS. This criteria state that there must be single tumor of less than 5cm or 3 tumors each measuring less than 3 cm.

Rare causes for a liver transplant are Alagille’s Syndrome, amyloidosis, sarcoidosis, polycystic liver disease (with or without simultaneous kidney transplantation), selected cases of neuroendocrine tumors, secondary biliary cirrhosis developing on the basis of previous common bile duct injuries.

What are the contraindications for a liver transplant?

Absolute Contraindications
- Active alcohol and or substance abuse
- Severe cardiopulmonary or other comorbid conditions that would preclude meaningful recovery after transplant
- Active extrahepatic malignancy
- Hepatic malignancy with macrovascular or diffuse tumor invasion and extrahepatic metastasis
- Active and uncontrolled infection outside of the hepatobiliary system
- Technical and/or anatomical barriers: i.e. prior major abdominal surgery
Psychosocial factors that would likely preclude recovery after liver transplantation
- Brain death

Relative Contraindications:
- Advanced Age
- Cholangiocarcinoma (Cholangiocarcinoma developing on the basis of PSC can be considered for transplantation under strict protocols)
- Chronic or refractory infections
- Human immunodeficiency virus infection (with advances in HIV Medications, some patients are considered suitable for liver transplant)
- Previous malignancy
- Portal vein thrombosis
- Active psychiatric illness
- Poor social support

What are the components of a liver transplant workup?
A liver transplant workup is performed by a well trained team of physicians, nurses, social workers, dieticians and also includes consultation with various specialists based on each individual patient’s need, several imaging studies and a battery of laboratory tests. Prior to presentation to the Liver Transplant Selection Committee, all patients are expected to undergo the following procedures:

A) Consultations

Once the transplant hepatologist (Liver Transplant Medical Specialist) identifies a liver transplant candidate patient, work up is initiated in coordination with the liver transplant surgical team. All patients and their immediate family members are interviewed by the transplant social worker. In the absence of psychosocial contraindications, work up is pursued with other essential consultations.

All patients undergo cardiac work, usually with a stress echocardiogram. Also, pulmonary function tests are obtained. Patients with certain risk factors might also be required to be evaluated by a neurologist. Renal, pulmonary, psychiatric consultations are obtained on an as needed basis.

Patients with hepatocellular carcinoma HCC are usually required to be seen in consultation with an oncologist and an interventional radiology specialist, in preparation for pre OLT treatment, i.e., transarterial chemoembolization (TACE) or radiofrequency ablation (RFA).

B) Radiology

All patients undergo radiological evaluation by ultrasound (US) and CT scan of the abdomen. US exam also involves Doppler study of the portal vein, to check for its patency. CT scan with three phasic IV contrast is usually a reliable way of searching for HCC. MRI of the liver can be ordered for further evaluation, if suspicious lesions are identified on CT/US exams. Patients with HCC are also worked up with CT of lungs and brain as well as nuclear bone scans to look for potential metastatic disease. Chest X Ray, sinus X-Ray, and Panorex (X Ray of teeth) are also obtained. Occasionally MR angiography and cholangiography might be needed.

C) Laboratory Studies

- Blood type and antibody screen
- Autoimmune markers as well as iron and copper studies, immune protein electrophoresis
- Cancer markers, i.e. alpha fetoprotein (AFP), CEA, PSA (prostate specific antigen), CA 19-9
- Complete blood count (CBC), complete metabolic panel (CMP) to include magnesium and phosphate
- Cytomegalovirus (CMV) status, varicella titers, cryptococcal antibodies

D) Miscellaneous Procedures and Cancer Screening

1. Esophago-gastro-duodenoscopy (EGD): to screen for esophageal/gastric varices and to determine the extent of portal hypertensive gastropathy (PHG). This is important for bleeding risk stratification while the patient is on the waiting list. Usually the esophageal varices are endoscopically ligated with rubber bands.

2. Colonoscopy: All patients with cirrhosis older than age 40, or younger patients with higher risk (history of colitis or family history of early colon cancer), undergo screening colonoscopy with prostate digital exam being performed in men at the same time. Polyps are identified and endoscopically removed. Patients with precancerous polyps and with history of colitis or PSC, will require further screening colonoscopies every few years following liver transplant.
3. Endoscopic retrograde cholangiopancreatography (ERCP): Patients with PSC or history of colitis will require this procedure to identify the biliary strictures and potential cholangiocarcinoma. Biliary brushings are routinely obtained to rule out malignancy, although the yield is generally low.

These procedures are performed by your transplant hepatologist who also coordinates the rest of the workup.

Liver biopsy is not required for the work up. In rare instances, if it is indicated (i.e., cryptogenic cirrhosis, tumor), it will be performed by your hepatologist or the interventional radiologist. In cases of acute liver failure, transjugular approach (neck vein) can be used to obtain a liver biopsy.

Other tests prior to liver transplant are:
4. Mammogram and pap smear for female patients
5. Nuclear cardiac stress testing or coronary arteriogram, if recommended by the cardiology consultant.

E) Vaccinations:

- Hep A and B vaccination, if there is no evidence of prior immunity.
- Pneumovax (pneumonia vaccine, needs to be repeated every five years).
- Flu vaccination once a year.
- PPD skin test for TB screening is also applied.

After the full preparation period, patient is evaluated by the liver transplant surgeon, before being officially presented to the selection committee.

The selection committee consists of the above mentioned group of physicians and Liver transplant Anesthesiologists, as well as the social workers, pre and post liver transplant nurse practitioners (NP) and nurse coordinators (RN), financial coordinators and a secretary recording the minutes.

For more information, you can also visit the Comprehensive Transplant Center at: www.hopkinsmedicine.org/transplant