

**STANDARD TREATMENT
GUIDELINES**

ORGAN TRANSPLANT: LIVER

Ministry of Health & Family Welfare
Govt. of India

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Treatment Guidelines for liver diseases and transplantation

1. Diagnosis of chronic liver disease

Algorithm for management of icterus:

1. Patients presenting first time with jaundice from a liver disease should have the following tests:
 - a)Liver function tests,
 - b)INR
 - c)CBC
 - d) Ultrasound of the abdomen.
2. Raised INR over 1.7 has ominous portents and will require referral to a higher centre
3. Patients should then be separated in to obstructive (SOJ) or medical jaundice.
4. Patients with SOJ should be referred to gastroenterologist/GI surgeon.
5. Patients with medical jaundice should be then further divided in to acute hepatitis or chronic liver disease. Additional tests such as HBsAg, anti HCV, and anti Hep E IgM may be conducted to define this further.
6. Patients with chronic liver disease should then undergo testing in a tertiary centre to see if they have a treatable liver condition such as HVOO (Budd Chiari Syndrome), autoimmune hepatitis or Wilson's disease.
7. Patients with advanced chronic liver disease should then be categorized in to Child's A, B or C disease. Those with Child's C disease should be referred to a transplant centre. Patients with Child's A and B cirrhosis should be advised to see a transplant hepatologist at some point to discuss future treatment possibilities.

2) Guidelines for management of Liver disease:

a) Alcoholic liver disease:

The mainstay of treatment is alcohol abstinence. May require help from a psychiatrist. However it may not be clear whether alcohol has caused liver damage or there has been another associated factor such as NASH, hepatitis C or hemachromatosis or diabetes. Management principles are in accordance with general measures to manage chronic liver disease.

Patients presenting with acute **severe alcoholic steatohepatitis** are usually not considered for transplant especially in a predominant cadaver program. The treatment of these patients is with intensive care including dialysis and ventilatory support.

Nutrition is an important component.

It poses an ethical issue whether these patients should have the option of LRLT. The treating clinicians are under immense pressure from the family for this treatment option. At this moment, till a consensus is reached, a case-by-case decision should be taken after counseling the family and the potential donor and after an opinion from a psychiatrist.

b) Hepatitis B

1) Evaluation of patients newly diagnosed with chronic HBV infection should include history, physical examination and laboratory testing as outlined below:

- History and physical examination
- Complete blood counts with platelets, liver function tests and prothrombin time/INR
- Tests for HBV replication—HBeAg/anti-HBe, HBV DNA
- Tests to rule out viral co-infections—anti-HCV, and anti-HIV in those at risk
- Ultrasound upper abdomen
- Upper gastrointestinal endoscopy
- Tests to screen for HCC—AFP and ultrasound
- Liver biopsy in those with suspected chronic hepatitis

2) Patients are classified in the following groups for treatment purpose: inactive carrier state, chronic hepatitis B (HBeAg positive or HBeAg negative groups) and cirrhosis. Once cirrhosis is diagnosed, all attempts should be made to identify its complications such as ascites, GI bleed, hepatic encephalopathy, renal dysfunction, spontaneous bacterial peritonitis, and hepatocellular carcinoma.

3) HBeAg-positive patients:

HBeAg-positive patients with persistently normal ALT should be tested for ALT at 3-6 month intervals. ALT along with HBV DNA should be tested more often when ALT levels become elevated. HBeAg status should be checked every 6-12 months.

4) HBeAg-negative patients:

- a) HBeAg-negative patients with normal ALT and HBV DNA <2,000 IU/ml should be tested for ALT every 3 months during the first year to verify that they are truly in the “inactive carrier state” and then every 6-12 months.
- b) Use of interferon for hepatitis B should be limited to higher centres with extensive experience.

5) In those who need treatment, options include oral antivirals such as entecavir, tenofovir, telbivudine or pegylated interferon in selected subgroup of patients.

6) Patients with decompensated cirrhosis: treatment should be initiated with an oral antiviral agent, which has high viral suppression and low risk of resistance.

- a. Entecavir or tenofovir would be an appropriate treatment in this setting.
- b. IFN should not be used in patients with decompensated cirrhosis.
- c. Treatment is indicated even if HBV DNA level is low.

7) Treatment of patients awaiting Liver Transplantation.

- a. In those who are being considered for liver transplantation, aim is to make the patient HBV DNA negative or achieve at least 2 log reduction in HBV DNA load prior to transplantation.
- b. Treatment of patients with advanced liver disease is advised in order to reduce the risk of HBV recurrence in graft in those who undergo liver transplantation.

8) Patients with hepatitis B related cirrhosis with complications should be referred to a liver transplant centre.

c) Hepatitis C:

The hepatitis C virus (HCV) has a prevalence of 1 to 2% in India.

1. 55% to 85% of individuals who develop acute hepatitis C infection will develop chronic hepatitis.
2. The risk of developing cirrhosis in them is up to 25% over periods of 25 years.
3. The diagnosis of acute or chronic HCV infection generally requires testing of serum for both antibody to HCV (anti-HCV) and for HCV RNA.

Treatment

- Treatment decisions should be individualized based on 1) the severity of liver disease, 2) the potential for serious side effects, 3) the likelihood of treatment response and 4) the presence of comorbid conditions.
- Treatment decisions are often based on liver biopsy findings.
- HCV RNA should be tested (quantitative assay) at the initiation of treatment and at regular intervals thereafter.
- The optimal therapy for chronic HCV infection is the combination of peginterferon and ribavirin.
- For genotype 1 and 4, treatment with peginterferon plus ribavirin should be administered for 48 weeks.
- For genotypes 2 and 3, treatment with peginterferon plus ribavirin should be administered for 24 weeks.
- 50% of patients with genotype 1 and 4 and 80% with genotype 2 and 3 remain persistently HCV RNA negative after stopping therapy.
- The most common adverse events are influenza like side effects (fatigue, headache, fever and rigors), psychiatric symptoms (depression, anxiety), anemia and neutropenia.
- Patients with HCV-related compensated cirrhosis (CTP class A) can be treated with the standard regimen of pegylated interferon and ribavirin but will require close monitoring for adverse events.
- Patients with HCV-related decompensated cirrhosis should be referred for consideration of liver transplantation.

- Interferon-based therapy may be initiated at a lower dose in patients with decompensated cirrhosis (CTP class B and C), as long as experienced clinicians administer treatment with vigilant monitoring for adverse events.
- Treatment can be initiated with half doses that are increased incrementally as tolerated at 2-week intervals (referred to as a LADR, low accelerating dose regimen), supplemented with growth factors if required.

d) Wilson's Disease

Patients with cirrhosis with neuro-psychiatric manifestations should be evaluated for Wilson's disease. However, the type of the liver disease can be highly variable, ranging from asymptomatic with only biochemical abnormalities to acute liver failure.

It should be suspected in any patient presenting with acute hepatic failure with Coombs-negative intravascular hemolysis, modest elevations in serum aminotransferases, or low serum alkaline phosphatase and ratio of alkaline phosphatase to bilirubin of <2.

If Wilson's disease is suspected, patients should undergo Kayser-Fleischer ring examination by slit-lamp. Other tests include estimation of serum ceruloplasmin and basal 24 hrs urinary excretion of copper.

An extremely low serum ceruloplasmin level (<50 mg/L or <5 mg/dL) should be taken as strong evidence for the diagnosis of Wilson's disease.

Penicillamine challenge studies may be performed for the diagnosis of Wilson's disease in selected cases.

In occasional cases, estimation of hepatic parenchymal copper content by liver biopsy may be necessary.

The drugs used for its treatment include D-penicillamine, Trientine and Zinc.

Patients with acute liver failure due to Wilson's disease should be referred for liver transplantation urgently as without transplant, mortality is very high.

e) Hemochromatosis

As this is a genetic disease and progression to cirrhosis can be prevented, screening of target population is important.

i) Symptomatic patients

Unexplained manifestations of liver disease or a presumably known cause of liver disease with abnormality of one or more indirect serum iron markers
 Type 2 diabetes mellitus, particularly with hepatomegaly, elevated liver enzymes, atypical cardiac disease or early-onset sexual dysfunction
 Early-onset atypical arthropathy, cardiac disease, and male sexual dysfunction

ii) Asymptomatic patients

First-degree relatives of a confirmed case of hemochromatosis
 Individuals with abnormal serum iron markers discovered during routine testing

Individuals with unexplained elevation of liver enzymes or the serendipitous finding of asymptomatic hepatomegaly or radiologic detection of enhanced computed tomography attenuation of the liver

Investigations

Serum iron
Total iron binding capacity
% saturation
Serum ferritin

Percent saturation greater than 45% and serum ferritin greater than 150ng/ml suggests hereditary hemochromatosis / iron overload states, and patient should be evaluated further.

Patients should undergo genetic testing for HFE mutations (C282Y and H63D).

Sometimes, liver biopsy may be necessary to evaluate for cirrhosis and iron overload.

Patients with proven hemochromatosis should undergo therapeutic phlebotomy. For those with advanced liver disease, therapeutic phlebotomy should be stopped as liver transplantation will offer definitive treatment

f) Autoimmune Hepatitis

- Autoimmune hepatitis (AIH) is an unresolving inflammation of the liver of unknown cause affecting women more frequently.
- An acute onset of illness is common (40%), and a fulminant presentation, characterized by hepatic encephalopathy within 8 weeks of disease onset, is possible.

Diagnostic Criteria

- Diagnosis of Autoimmune Hepatitis (AIH) often represents a clinical challenge
- Interface hepatitis is the histologic hallmark of the syndrome,² and portal plasma cell infiltration typifies the disorder.
- Neither histologic finding is disease specific, and the absence of portal plasma cells does not preclude the diagnosis
- Liver biopsy examination is essential to establish the diagnosis and evaluate disease severity to determine the need for treatment.
- A scoring system has been proposed to assess the strength of the diagnosis

Diagnostic Scoring System

	1 point	2 points
1. IgG	>16 g/l	>18 g/l
2. ANA, SMA	>1 : 40	>1 : 80 or SLA/LP+
3. Histology	compatible with	typical for AIH
4. Viral markers		negative

- A value of 6 or more points makes the diagnosis of AIH very likely, a value of 7 or 8 points demonstrates definite AIH

Sub-classifications

- Three types of AIH have been proposed based on differences in their immunoserologic markers
- They do not have distinctive etiologies or responses to corticosteroid therapy

Treatment Indications:

- Treatment may not be indicated in patients with inactive cirrhosis, preexistent comorbid conditions, or drug intolerances
- The indications for treatment are shown in Table 2

Absolute	Relative
Serum AST \geq 10-fold upper limit of normal	Symptoms (fatigue, arthralgia, jaundice)
Serum AST \geq 5-fold upper limit of normal and γ -globulin level \geq twice normal	Serum AST and/or γ -globulin less than absolute criteria
Bridging necrosis or multiacinar necrosis on histologic examination	Interface hepatitis

Treatment Regimens:

- Two treatment regimens are comparable with each other and superior to nonsteroidal therapies in the management of severe AIH in adults (Table 3)
- Prednisone in combination with azathioprine or a higher dose of prednisone alone is the appropriate treatment for severe AIH in adults
- Sixty-five percent of patients enter remission within 18 months, and 80% achieve remission within 3 years (mean duration of treatment to remission, 22 months)

	Combination		
	Prednisone Only (mg/d)	Prednisone (mg/d)	Azathioprine (mg/d)
Week 1	60	30	50
Week 2	40	20	50
Week 3	30	15	50
Week 4	30	15	50
Maintenance until end point	20	10	50

Liver biopsy assessment prior to termination of treatment is preferred and recommended, but not essential, in the management of patients who satisfy clinical and laboratory criteria for remission

g) HCC;

HCC often coexists with cirrhosis and with hepatitis B liver disease. Screening interval should be 6 months using ultrasound.

Nodules < less than 1 cm, follow up scans every 3 months for 2 years, if no growth, revert to 6 months

Nodules greater than 1 cm, CT/MRI, typical features, treat like HCC, atypical second contrast scan, biopsy if not clear

Management recommendations

- Single lesion, resection if good liver function, HVPG <10 mmHg. No pre or post adjuvant therapy.
- Liver Transplant if within UCSF criteria
- Preoperative therapy if wait list is likely to exceed 6 months
- Local ablation if resection/transplant can not be done.
- Alcohol injection for HCC less than 2 cm, otherwise RFA
- TACE is recommended as first line non curative therapy for non surgical patients with large multifocal HCC without vascular or extrahepatic spread.
- Sorafenib for those who can not have surgery, TACE, local ablation and still have preserved liver function.
- Radioactive particles may be useful but enough data has not accrued to give guidelines.

h) Pregnancy & Jaundice

Jaundice in pregnancy can either be due to

- a. Exacerbation of a preexisting liver disease,
- b. Coincidental liver disease acquired during pregnancy or
- c. Pregnancy related liver disorder.

A preexisting liver disease as well as coincidental liver disease acquired/detected during pregnancy should be managed as in a non pregnant state, the choice of medications are dictated by the safety profile for the fetus.

Interferon is not to be used in pregnancy.

A pregnant female on therapy for Chronic Hepatitis B should be continued on the medication she is on Lamivudine and tenofovir have the best safety profile in pregnancy with emerging evidence for entecavir as well.

Hepatitis E in pregnancy

This can run a very fulminant course, with a higher risk of developing acute liver failure compared to non-pregnant population as well as higher risk of death if ALF develops. There is no evidence that termination of pregnancy decreases incidence of acute liver failure or mortality in patients with acute viral hepatitis. Termination of pregnancy after development

of ALF has also not shown to decrease mortality. Management of the patient with acute viral hepatitis is supportive, and viral hepatitis is not an indication for termination of pregnancy, caesarean section, or discouragement for breastfeeding.

Chronic liver disease and pregnancy

Chronic liver disease like autoimmune hepatitis (AIH) and Wilson's disease may flare up during pregnancy. These patients should be maintained on the medications they were on before pregnancy, with flares being treated with steroids in AIH.

Gallstones and biliary disease is treated in the same way as in without pregnancy. Surgery is avoided if possible in 1st and 3rd trimester, for increased risk of abortion and premature labor, respectively. Choledocholithiasis is treated with ERCP and papillotomy/stone extraction irrespective of the trimester.

Pregnancy related liver disease

For pregnancy related liver disorders, evaluation of jaundice in pregnancy depends on the type of symptoms and the time of onset of symptoms in relation to the week of gestation.

a) Hyperemesis gravidarum

Severe nausea and vomiting are the key features of *hyperemesis gravidarum*, which occurs predominantly in the first trimester. It occurs most often in women less than 25 years of age who are overweight, multiparous, and with multiple births. Treatment is symptomatic.

If nausea and vomiting is accompanied by headache and peripheral edema, it may indicate preeclampsia and, if accompanied by abdominal pain with or without hypotension in late pregnancy, may indicate hepatic rupture.

b) Preeclampsia and HELLP syndrome usually occurs after 20 weeks of gestation and is characterized by hypertension, proteinuria, and edema. It is generally a disease of primigravidas. Jaundice is usually not a feature of preeclampsia, but is seen with *HELLP syndrome* (Hemolysis, elevated liver enzymes and low platelets) as well as hepatic rupture. Both these conditions are associated with preeclampsia. Treatment for all three conditions is delivery after stabilization of the mother.

c) Pruritus is the characteristic feature of intrahepatic cholestasis of pregnancy. It typically involves the palms of the hands and soles of the feet initially and then affects the rest of the body. Jaundice typically follows the pruritus. It is most common in third trimester of pregnancy but may occur in second and rarely in first also. Maternal outcome is benign, pruritus resolves quickly after delivery. In the fetus, maternal intrahepatic cholestasis has been associated with an increased incidence of prematurity, perinatal deaths, fetal distress, and meconium staining of amniotic fluid. Treatment is symptomatic. Antihistaminics are not of much help. Cholestyramine and UDCA have been used with some success.

d) Acute fatty liver of pregnancy (AFLP) is a rare and potentially fatal disease that generally occurs in the last trimester of pregnancy. AFLP occurs more commonly during first pregnancies, with multiple gestations, and with male fetuses. They present with prodromal symptoms of abdominal pain and then jaundice. More severe manifestations include progressive liver failure, coagulopathy, encephalopathy and renal dysfunction with oliguria or uremia.

AFLP has a very poor prognosis for both mother and fetus unless early diagnosis and prompt termination of pregnancy is done. Early delivery is the mainstay of therapy.

Orthotopic liver transplantation may be required in patients with AFLP and fulminant hepatic failure who do not improve despite delivery and intensive supportive care

2) Management of complications of cirrhosis:

Frequency of blood tests in Chronic liver disease

Patients with chronic liver disease need to be monitored so that they can be transplanted before they deteriorate. Further organ availability may not be immediate.

MELD score	Status rectification	Lab values not older than
>25	Every week	48 h
18 to 24	Every month	7 days
11 to 18	Every 3 months	14 days
0 to 10	Every 12 months	30 days

i) Gastrointestinal bleeding

Endoscopy: Patients with upper GI bleed should have an endoscopy done within 8 hours of presentation. The initial management is with somatostatin infusion. If on Endoscopy, varices are identified, they should be placed on regular endoscopic band ligation.

Endoscopic management is the mainstay and failure of endoscopic management should lead to consideration of TIPS procedure. Surgical shunts are generally not indicated in cirrhotics. If shunt surgery is to be done, a Mesocaval shunt is the shunt of choice.

Recommendations for Endoscopy

- a) At the time the diagnosis of cirrhosis is made.
- b) Repeat every 2 years if no varices at initial screening and no decompensation, if decompensation, at time of decompensation and every year.
- c) Small varices which have not bled, EGD every 1 year or put them on beta blockers and no follow up EGD.
- d) Patients on beta-blockers, adjust dose to the maximal tolerated dose, if treated with EVL, repeat every 1 -2 weeks till obliteration and then surveillance EGD at 1-3 months later and then every 6-12 months for recurrence.

ii) Ascites:

Salt and fluid restriction

Bed rest

Daily weight record

Diuretics to be started; however if there is development of renal impairment, hyponatremia or encephalopathy, patient should be advised liver transplantation.

Large volume paracentesis should be advised if the patient is not a fit candidate for transplant.

TIPS may be considered if the liver function is good.

There is no role for peritoneovenous shunt because of the high occlusion rate and LIMITED EFFICACY.

Indications for TIPS

- Refractory variceal bleeding
- Ascites intolerant to LVP
- Hepatic hydrothorax
- Hepatorenal syndrome
- Budd Chiari Syndrome

TIPS not indicated for GAVE

iii) SBP

- a) hospital admission
- b) ascitic tap and cell count
- c) Injection albumin
- d) I/v antibiotics
- e) observe renal function
- f) prophylaxis with quinolones

iv) Hepatic Hydrothorax

Defined as a significant pleural effusion, usually >500 mL, in a patient with cirrhosis of liver but no primary cardiac or pulmonary disease

- Occurs usually with alcoholic cirrhosis
- Develops in roughly 4% to 10% of ESLD patients
- HH can occur even in the absence of ascites
- Liver transplantation is the most definitive cure
- Uncommon presentation of HH is spontaneous bacterial empyema (SBEM)

Conservative Management Protocol

- restrict daily sodium intake to 90 mEq

- a trial of diuretics (spironolactone and furosemide)
 - Increase doses until the pleural effusion is controlled or side effects preclude greater doses
- No more than 1.5 liters of fluid should be aspirated during therapeutic thoracentesis
 - risk of unilateral pulmonary edema or hypotension

Send the fluid for

- SAAG
- Cytology for malignant cells
- Biochemistry
- ADA
- PCR for TB

After aspiration, confirm lung expansion with an X-ray lung. If there is no expansion even after tapping to dryness, then obtain a CT scan of the chest to rule out any underlying lung fibrosis.

Hepatic hydrothorax and liver transplantation

In patients with cirrhosis and hydrothorax who are planned for liver transplantation, it is essential demonstrate lung expansion prior to the transplantation. If there is no reason for the lungs not to expand other than re-accumulating intrapleural fluid or the patient needs multiple aspirations to prevent re-accumulation, then temporarily place an ICD prior to planned date of operation

v) Renal impairment in cirrhotics

- a) Judicious use of nephrotoxic drugs, avoid when possible
- b) Avoid IV contrast during pre-transplant imaging, however it may be essential to image the portal vein prior to a high risk LRLT
- c) Optimization of extracellular fluid volume and vasoconstriction: Albumin /
- d) Terlipressin/noradrenaline/octreotide and midodrine
- e) Treat sepsis, such as SBP,
- f) If albumin is indicated, then reassess the need for albumin every 48 hrs

vi) Encephalopathy:

Hepatic encephalopathy (HE) is a common manifestation seen in both acute and chronic liver failure. Several factors influence its outcome such as infection, hypoxemia, GI hemorrhage, or electrolyte disturbances. It is classified into following clinical stages:

- Grade 1. Trivial lack of awareness. Shortened attention span. Hypersomnia, insomnia, or inversion of sleep pattern. Asterixis can be detected.
- Grade 2. Lethargy or apathy. Disorientation. Inappropriate behavior. Slurred speech. Obvious asterixis.
- Grade 3. Gross disorientation. Bizarre behavior. Semistupor to stupor. Asterixis generally absent.
- Grade 4. Coma.

Several precipitating factors for HE have been identified such as: GI hemorrhage, infections, electrolyte disturbances, use of sedatives, constipation, and excessive dietary protein.

Treatment guidelines:

Avoidance and prevention of precipitating factors

Nutrition. Improve protein intake by feeding dairy products and vegetable-based diets.

Lactulose. Dosing aims at two to three soft bowel movements per day.

Use of antibiotics such as metronidazole, ampicillin or rifaximin

Refer for liver transplantation in appropriate candidates.

Patients in deeper stages of HE may need prophylactic tracheal intubation. A nasogastric tube is placed for patients in deep encephalopathy. Avoid sedatives whenever possible.

Lactulose can be administered via enema or nasogastric tube in deep encephalopathy. Dosing every hour until stool evacuation appears optimizes oral dosing.

vii) Hepatopulmonary Syndrome (HPS)

Patients with chronic liver disease should be evaluated for Hepatopulmonary syndrome if they have dyspnoea, cyanosis or clubbing, and arterial blood gases show low PaO₂ (<80mmHg). Patients may complain of platypnea and have orthodeoxia. HPS may be present with minimal symptoms of chronic liver disease.

HPS is defined by the triad of liver disease, increased alveolar-arterial oxygen gradient ≥15mmHg while breathing room air, and intrapulmonary vascular dilatations.

The diagnosis is usually based on positive bubble contrast echocardiography and ^{99m}Tc labeled macroaggregated albumin scan (MAA scan).

It is important that other cardio-pulmonary causes should be excluded before labelling a patient as having HPS.

Mainstay of therapy is supplemental oxygen.

Patients with troublesome HPS should be referred to a liver transplant centre as HPS may regress completely following liver transplantation.

viii) Porto-pulmonary hypertension (PPH)

Portopulmonary hypertension should be looked for in patients with liver disease who complain of exertional dyspnoea.

Based on degree of elevation in mPAP, it can be classified as mild (mPAP = 25 to 35 mm Hg), moderate (mPAP = 35 to 50 mm Hg) and severe (mPAP > 50 mm Hg).

Transthoracic echocardiography and, sometimes, right heart catheterization are needed to establish the diagnosis of PPH.

Prostacyclin (epoprostenol) is a potent vasodilator and platelet aggregation inhibitor that results in clinical improvement in PPH. Bosentan and Sildenafil are orally available drugs that improve pulmonary hemodynamics in primary pulmonary hypertension.

Moderate to severe PPH (mean pulmonary artery pressure >50 mm Hg) is a contraindication to liver transplantation because of perioperative mortality of approximately 40% and lack of reversibility of pulmonary hypertension.

Non transplant surgery in cirrhosis:

In general surgery is poorly tolerated in patients with advanced cirrhosis and therefore should be taken up for surgery with caution. They often present with hernias and this should be managed by controlling ascites first.

Cholelithiasis and cirrhosis:

In patients with cirrhosis, category Child's B and C, elective surgery should be avoided, as risk of decompensation is very high with consequent mortality.

Safe medicines in cirrhosis:

NSAIDs should not be given as it may cause GI bleeding.

Anti TB drugs should be prescribed with caution and with regular monitoring of liver function tests every 2 weeks.

Aminoglycosides to be avoided as they may cause nephrotoxicity when used with diuretics.

Diabetes in decompensated cirrhosis should be treated with Insulin rather than with OHAs.

The antiepileptic valproate should be avoided.

In general caution must be exercised in prescribing medicines in patients with chronic liver disease as quite often these medicines are metabolized in the liver. Indigenous medicines and in particular Ayurvedic medicines should be avoided.

Liver Transplantation

1. Indication for transplantation

a) Chronic liver disease

i) *Child's C cirrhosis*

ii) *Child's B cirrhosis* with an episode of life threatening decompensation such as SBP, renal dysfunction, refractory ascites, recurrent GI bleeding refractory to endoscopic management or recurrent HE.

iii) *Cholestatic liver disease*: impairing quality of life such as severe itching, osteoporosis and recurrent cholangitis, presence of a dominant stricture without evidence of cholangiocarcinoma

b) Tumours:

i) *HCC*

a. If within UCSF criteria

(UCSF criteria is a. Single nodule less than 6.5 cm in size,

b. not more than 3 nodules with cumulative diameter less than 8 cms)

ii) *Neuroendocrine tumours*

To be considered for transplantation under exceptional circumstances such as no evidence of extrahepatic disease, and evidence of slow progression of disease. A period of waiting to assess biological behaviour of tumour would be desirable.

iii) *Cholangiocarcinoma*

Although the Mayo group has successfully transplanted patients with cholangiocarcinoma, in general they should not be considered for transplantation, as the results are poor.

iv) *Pediatric tumours*

a. Hepatoblastoma post three cycles of chemotherapy if not resectable and absence of extrahepatic disease with the exception of stable pulmonary metastasis

b. HCC in children can be transplanted beyond UCSF criteria provided they are Hep B and C negative.

c. Indication in acute liver failure:

Pediatrics:

In general, patients for ALF in this age group have been selected for transplant based on Kings College criteria.

However the current evidence from King's College group suggests that patients should be considered for transplant, once the INR is greater than 4 with or without encephalopathy.

It is also realised that symptoms of encephalopathy can be easily missed in an irritable child.

Outcome of transplant in children with grade III or IV coma is not good and therefore these children should be transplanted only in exceptional circumstances.

Adults:

The King's College criteria are a good guide. However large volumes centres have accumulated enough experience to decide on their own the indication for transplant in a particular patient.

i) Listing for transplant as is prevalent in the West has little meaning in India where organ harvesting and allocation is not yet a regular feature.

ii) Patients with non hyperacute liver failure in Grade III or IV coma should be

- transplanted early as without transplant the outcome is dismal.
- iii) INR should be monitored without FFP support, as the use of FFP has not been shown to improve survival.
- iv) A progressive worsening INR or deterioration in sensorium are good indicators for need of transplant.
- v) Patients of ALF in renal or multiorgan failure such as requirement for high FiO₂ do not do well after transplant and therefore should only be considered for transplant under exceptional conditions. Paracetamol overdose could be one exception as renal failure can be an early feature.

2. Management of ALF:

- a) Nurse in a quiet room with head elevation.
- b) I/v fluids and measures to reduce cerebral edema such as i/v Mannitol, 3% hypertonic saline and hypothermia.
- c) Watch for hypoglycemia
- d) Renal support; Institute dialysis early, role of MARS is controversial
- e) Antibiotics and antifungal prophylaxis should be started.
- f) Elective ventilation should be done if the patient is Grade III or more of coma
- g) No FFP should be given, unless an invasive procedure is planned.
- h) Should be referred to a transplant centre if the INR > 2.5. All patients of ALF should be managed in consultation with a Liver Transplant centre so that smooth transfer can be organized if the patient is not recovering.
- i) Intracranial pressure measurement is generally not practiced in India because unequivocal advantages of this has not been shown

3. Acute on chronic liver disease:

- a. These patients should be referred for transplant as soon as the diagnosis is made, as the prognosis is dismal otherwise. Those with encephalopathy should be transplanted early.
- b. Alcoholic steatohepatitis is usually acute on chronic liver disease and alcohol abstinence may improve prognosis. This situation is different from other causes of ACLF**

4 Renal Dysfunction and Liver Transplantation

- i) High Risk Groups who need renal protection during Liver Transplantation**

Creatinine > 1.5 at the time of transplant
Duration of renal failure (Cr. > 1.5) > 2 weeks in the preceding 6 months
GFR < 40 ml/min
Renal dysfunction requiring dialysis in the preceding 6 months
Pre-Transplant renal dysfunction: medical renal disease with proteinuria >500 mg/24 hours indicative of nephropathy

ii). Indications for combined liver and kidney transplant

Serum creatinine > 2 mg/dL in patients who also have chronic renal disease
Dialysis > 8 weeks
GFR < 30 mL/minute
Kidney biopsy: (usually not possible because of low platelet and deranged INR)
> 30% glomerulosclerosis
> 30% interstitial fibrosis, or both
Irreversible kidney damage
Primary Hyperoxaluria

iii). Contra indications and delisting criteria for liver transplantation

Absolute Contraindications:

- a) Extrahepatic malignancy (unless patients meet standard oncologic criteria for cure – as in certain neuro-endocrine malignancies metastatic to the liver with proof of treatment of primary disease).
- b) Hepatocellular cancers known to be radiologically / macroscopically involving a major intra-hepatic vascular structure.
- c) Primary severe pulmonary artery hypertension
- d) Sepsis unresponsive to treatment.
- e) Coma with evidence of irreversible brain injury (particularly relevant in patients with acute liver failure and may also be relevant to a select few patients with chronic liver disease).
- f) Severe, uncorrectable congenital anomalies
- g) Major disease in other organ system (diffuse coronary artery disease that is uncorrectable, endstage COPD, etc)
- h) Current substance abuse (narcotics).

Relative Contraindications

(if ameliorated before transplantation, the transplant operation can proceed)

- a) Cholangiocarcinoma
- b) Age: Generally > 70 years preclude the benefits of transplantation. However, chronologic age is not uniformly indicative of the status of health and marginal exceptions can be made on a case by case basis keeping in view the overall state

of health and possibilities of being able to lead a fruitful & satisfactory life subsequent to transplant.

- c) Respiratory failure requiring > 50% O₂
- d) Advanced malnutrition
- e) Inability to understand or adhere to post-operative regimen
- f) Alcoholics in recovery and other prior substance abusers who have documented abstinence for a minimum of three months and have undergone a thorough multidisciplinary assessment (including social and psychiatric evaluation) may be considered for liver transplantation if they possess appropriate psychosocial support systems so that they can comply with lifelong immunosuppressive therapy and be expected to maintain permanent abstinence from all addictive substances.
- g) Individuals with alcohol consumption where reasonable doubt exists regarding its contribution to the genesis of end stage liver disease or those individuals with alcoholism who were unaware of their chronic liver disease presenting with an acute or chronic liver disease unlikely to survive the minimum abstinence period, can be considered on a case by case basis for transplantation if appropriate psycho-social support and motivation and insight for abstinence is certified by the psychiatrist designated for the transplant program.
- h) HIV infection may not be a contraindication if the viral load is negative and CD4+ T cell counts are >250 cells/dl and the patient does not suffer from opportunistic infections. The history of Pneumocystis Carinii pneumonia is not a contraindication for transplantation.

2. Live liver donor selection:

18-55, blood group compatible, BMI < 33
1st or 2nd degree relatives, Govt. Auth Committee in case the donor is not a near relative
Healthy, no addictions,
Detailed systemic work up
HBsAg, HCV, HIV negative
Triphasic CT scan of abdomen, for Liver Attenuation index (steatosis),
volumetry, vascular map
MRCP, for mapping biliary tree
Ideal GRWR 0.8, remnant 30%

Contraindications

Steatosis > 30%
Abnormal LFT (transaminases x 2)
Inadequate graft or remnant volume
Abnormal anatomy
Systemic disease

3. Immunosuppression

The standard immunosuppression in liver transplant is a triple drug regimen begun within 24 hours of transplantation.

In patients with renal failure, IL2 receptor antagonists may be used based on centre's preference. Low dose CNI could be another alternative.

At the moment, there is no strong evidence for tailoring immunosuppression based on etiology of the liver disease except that steroid boluses should be avoided in patients transplanted for hepatitis C.

Cyclosporine may increase SVR in transplanted patients who are given treatment with IFN. Sirolimus may have a role in patients undergoing transplant for HCC.

Most centres taper steroids between 3 to 6 months post transplant. However in some patients, renal impairment may be an issue and these patients may be given long term steroids together with either MMF or azathioprine.

The standard regimen is as follows:

a) *CNI, either Tacrolimus or Cyclosporine*

Tacrolimus trough levels in first month should be between 5 to 10 ng/ml and later maintained between 5 to 8 ng/ml.

Cyclosporine trough level in the first month should be between 200 to 300 ng/ml and later reduced to 100 to 200 ng/ml. Centres may choose to adjust dose based on C2 level as well.

b) *MMF or azathioprine:*

MMF is given in the dose 500 mg twice a day or the equivalent Myfortic 360 mg twice a day. In selected patients except those with AIH, PSC, PBC, MMF can be discontinued after 1 year

Azathioprine should be given in dose 1 mg/kg body weight once a day. TLC should be monitored frequently and the drugs stopped if the TLC is less than 3500.

c) *Steroids:*

Steroids are given at the time of transplantation during the anhepatic phase in the dose of 500 mg and then gradually tapered in the next few days to 20 mg per day. In the next few months the steroids are gradually tapered off unless the preoperative diagnosis was an autoimmune condition

d) *Renal sparing protocol:*

MMF + steroids + delayed CNI, may consider IL2 receptor blockade,
May also be used in those with neurological toxicity

e) Treatment of Acute rejection:

Steroid boluses usually 500 mg of methyl prednisolone for three days is given preferably after a liver biopsy.

Steroid resistant rejection should be confirmed by a review of liver biopsy slides and by ruling out biliary, vascular and infective issues. ATG/Thymoglobulin is the standard drug to be used for steroid resistant rejection in the dose of? 5-15 mg / kg/day, (ATG) or Thymoglobulin 0.5 to 2 mg/kg/day infused over 4 to 6 hours after premedication for 7 to 14

days depending on the response.

f) Monitoring adverse effects:

Renal function should be monitored closely in patients receiving CNIs. It may lead to either dose reduction or even stopping altogether in case of significant renal impairment. The options at this stage can be MMF monotherapy, Azathioprine with steroids, MMF with steroids or Sirolimus alone or with steroids.

Sirolimus: in case of CNI intolerance, not to be used in the first 4 weeks as may impair healing and result in hepatic artery thrombosis.

The use of Sirolimus will require monitoring of proteinuria and lipid profile. When used with Tacrolimus, the combined level should be kept below 15 ng/ml.

In general all patients on immunosuppression will require monitoring of their metabolic status such as diabetes, lipid profile and atherosclerosis.

Currently there is no recommendation for screening for development of malignancy. However as it is known that there is a higher incidence of malignancy, clinicians should be alert to this possibility.

No guidelines can be given for stopping immunosuppression as the goal of tolerance is yet to be achieved.

Post transplant surveillance

blood tests: for rejection, nephrotoxicity, atherosclerosis, diabetes, leucopenia

In the first few months post transplant, blood tests (CBC, LFT, Renal, CNI level) should be done every 1 to 2 weeks.

When on stable dose of immunosuppression every 2 months and within 1 week post change in dose of medication.

Monitor hepatitis C post transplant by blood tests and liver biopsy every 6 months.

Hep B recurrence by DNA measurement every 3 months.

HCC recurrence by AFP and ultrasound every 3 months for the first two years and then every 6 months for 5 years.

Alogorithm for management of graft dysfunction:

Ultrasound, doppler, CNI level and relevant microbiology first

Liver biopsy if answer is not clear.

Biliary obstruction is difficult to diagnose in the transplanted liver, as IHBR dilatation may not be present. MRCP/ERCP/HIDA should be carried out to define this further.

Monitoring disease recurrence post transplant:

HCC: No adjuvant treatment is recommended for HCC post transplant to prevent recurrence. It should be monitored with 6 monthly AFP levels and ultrasound of the liver.

Hep C: Post transplant liver biopsy should be done every 6 to 12 months post transplant and treated with interferon if there is any evidence of disease recurrence.

Hep B: Disease recurrence can be prevented by use of a combination of HBIG and antiviral medications. However it may be appropriate to use antiviral medicines alone in patients who have been negative for hepatitis B DNA.

Alcoholic liver disease: Drinking and smoking should not be permitted post transplant.

NASH: Weight gain should be curbed. Diabetes should be managed with exercise and metformin/insulin.

6. Monitoring donor complications

- i). Right lobe adult-to-adult liver transplantation is a very complex surgery with requirement for excellent surgical skills and teamwork. Donor deaths have been reported.
- ii). At the time of inspection for grant of license for transplant to a particular hospital, the team must satisfy itself that standards for donor safety are met prior to granting license for conducting right lobe adult to adult transplantation. Consideration for licensing should include evaluation of infrastructure for cadaveric donation and transplantation.
- iii) All donors must be followed up and complications should be documented.
- iv) It may be advisable to have a national donor registry to monitor complications

Nutrition:

- a)`Patients with cirrhosis are usually advised bland, low protein non fatty diet. This is a myth and harmful to the patient. Apart from salt and fluid restriction, diet should have sufficient proteins and fat in much the same way as in the diet of healthy people.
- b) Post transplant diet should be directed to reduce weight gain and atherosclerosis. Uncooked sea food is not allowed. Fruits should be washed and peeled prior to eating. Timing of medication with food should be such that bioavailability is there.

PRETRANSPLANT

For ESLD patients, highly individualized, aggressive nutrition support is usually necessary to minimize catabolism and slow the deterioration of nutritional status while awaiting a donor organ, preferably with the guidance of an experienced dietitian

S.NO	NUTRIENTS
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1	Calories	120 – 140% of BEE
2	Protein	1– 1.5g / kg / day, For patients with hepatic encephalopathy - 0.6 – 1 g/kg/day
3	Carbohydrate	50 – 70% of calories
4	Fat	30% of calories
5	Sodium (salt)	1-2g/day or less
6	Vitamins& Minerals	According to RDA levels

Small, frequent feedings, including high calorie, high-protein supplements, are often necessary to ensure adequate nutrients orally. If oral intake is inadequate then nasoenteric tube feeding is suggested either nocturnally or over 24hours according to the oral intake. Daily calorie counts are useful in assessing readiness to wean from supplemental nutrition support.

POST TRANSPLANT

NUTRIENTS	SHORT TERM	LONG TERM
Calories	120 – 130% of BEE	Maintenance: 120 – 130% BEE
Protein	1.3 – 2g / kg / day	Based on activity level
Carbohydrate	50 – 70% of calories	50 – 70% of calories
Fat	30% of calories	<30% of total calories
Calcium	1200mg / day	1500mg / day
Vitamins & Minerals	According to RDA levels	According to RDA levels

- Estimated energy requirements in the immediate post operative stage are similar to those preoperatively, and the same guidelines may be used. Avoid over feeding.
- Protein catabolism is increased after liver transplantation and positive nitrogen balance may be difficult to achieve in the first week or longer post operatively. Administration of 1.3 to 2g / kg / day is suggested as an initial estimate in patients without significant azotemia.
- Fluid administration must be individualized.
- Ideally, patients would move quickly to an oral diet after transplant. Nasoenteric tube feeding is recommended as soon as the patient is hemodynamically stable.

- TPN is considered only when enteral route cannot be used. This is usually possible within the first 18 to 24 hours post operatively.
- An oral diet is resumed when the patient's mental and physical state allows. A liquid to solid diet progression is implemented according to patient tolerance.

Small, frequent feedings, including high calorie, high-protein supplements, are often necessary until the patient is reliably able to consume adequate nutrients orally. Daily calorie counts are useful in assessing readiness to wean from supplemental nutrition support.

Advice on discharge

Discharge diet instruction may include education involving:

- therapeutic or modified diets
- food- drug interactions
- nutritional care for certain diagnoses/conditions
- post liver transplant diet protocol

Brain death Identification

As per THOA 1994.

Multiorgan retrieval:

All hospitals, which have a neurosurgery department and a trauma centre, should have provision for organ retrieval.

At the current moment, organ retrieval can only be conducted in hospitals, which are licensed for transplantation.

1. Each hospital doing organ or tissue transplantation should draw up an SOP and deposit with Organ Coordinating agency to facilitate organ retrieval.
2. Each hospital should also ensure ready availability of organ retrieval personnel, items, drugs/storage fluids, containers for organ transport and blood sampling to start at short notice.
3. Each hospital should examine the donor patient /records available and satisfy themselves on the organ acceptance criteria.
4. Each hospital to inform Organ coordinating agency on priority if organ is not being utilized/unfit for utilization.
5. Each hospital will be responsible for retrieving and storage of the organ concerned ensuring optimal utilization.

Role of the coordinator:

- a) Will liaise with the donor and recipient team and will be the communication conduit with Organ Facilitating Agency
 - b) Medico legal clearance if necessary
 - c) Arrangement of post mortem if required
 - d) Responsible for overseeing documentation of the case.
 - e) Responsible winding up after donor team leaves with organs.
- f) Will be responsible for ensuring that all donors are tested for HIV Ab, HBsAg, HBcAb, HCV Ab, CMV Ab, Toxoplasma Ab, VDRL.

Team leader:

- a) Check risk of transfer of infection malignancy
- b) brain death diagnosis in accordance with THOA,
- c) cause of death
- d) Consent in accordance with THOA

A proposal is underway for a team to move from a licensed hospital to another hospital for retrieval.

As yet, no major progress has been made.

Till a government proposal does not materialize frequent multi organ retrieval will not become a reality.

The order of retrieval of organs will be as follows:

- a) Heart, heart/lung
- b) liver
- c) pancreas
- d) kidneys
- e) corneas

ICU management of prospective donor

- a) Consent
- b) Maintenance of therapy, as standard medical therapy
- c) Liaise with Local Transplant Coordinator
- d) Change of therapy from the aim of preserving brain function to optimizing transplantable organ function, mainly correcting hypovolemia

Supporting the donor:

- a) Goals:

MAP 60 to 80 mmHg
Preload CVP, 4-10 mmHg, PA occlusion pressure, 10-15 mmHg
Heart rate 60 to 100 beats/min
Rhythm sinus rhythm
Cardiac output CI > 2.1 l/min/m
Inotropes: high dose adrenaline may cause detrimental vasoconstriction
Dobutamine may cause vasodilatation and lead to undesirable hypotension and tachycardia
Vasopressin less likely to cause metabolic acidosis or pulmonary hypertension and may be more appropriate than noradrenaline for the cardiovascular collapse phase

Endocrine support

Diabetes insipidus Maintain Na⁺ = 155 mmol/l with 5% dextrose, Urine output to be maintained 1-2 ml/kg/hr with vasopressin 1 U bolus and 0.5 – 4.0 U/h infusion. If vasopressin fails to control diuresis, intermittent desmopressin (DDAVP) may be required

Hyperglycemia Insulin infusion to maintain plasma glucose 4-9 mmol/l, maintain K >4.0 mmol/l

Hypothyroidism T3 4 mcg bolus and then infusion at 3 mcg/h, debate over its necessity, however most units use it

High dose methylprednisolone as part of the hormone package

Respiratory support:

- a) Fio₂ to be kept below 0.4
- b) Peep <5 cmH₂O
- c) Physiotherapy, gentle inflation of lungs every hour and side to side turning every 2 hours

Mode of ventilation:

- i) pressure control
- ii) SMV not possible

iii) very sensitive triggers may allow cardiac cycle induced pressure changes to trigger ventilation leading to erroneous diagnosis of spontaneous breathing

Renal support:

Donor preconditioning with dopamine may help kidney function post transplant

Hematology:

Keep Hb over 9 g/dl, deranged coagulation should be treated with FFP/platelets

Antifibrinolytics should be avoided.

Temp support: Avoid hypothermia

Nursing

Keep family members well informed and demonstrate good nursing skills

Nurses:

Must have knowledge of donation, transplantation and ethical issues

Diagnosis of death by brain stem testing and its certification

Continued clinical management of potential donor

Communication skills

Ability to support families during a stressful time

Awareness of religious and cultural issues

Role of donor transplant coordinator.

Splitting of liver

This technique should be encouraged as one liver can save two persons. All liver cannot be split as it may compromise graft function

Ideal liver donors from young patients and those who are not on major inotropic support and with a short ICU stay should be split.

Ethical issues in split liver transplantation

- a) The transplant team has an ethical obligation to maximize the number of patients transplanted
- b) Patients have the clear and unequivocal right to refuse an offered organ including a liver segment
- c) The transplant physician must inform potential recipient of current practices of their program regarding split liver transplant.

- d) All parties involved in the transplant process must understand that there is no claim of ownership of an organ by a potential recipient, transplant centre or transplant surgeon. Each individual involved in the process is a guardian than owner of that organ.
- e) The team conducting the split should have the right to both split organs. This will provide an impetus for splitting and may justify the added risk of split organ transplant.

Allocation and sharing of donor organs

Cadaver transplant is in infancy in this country, though a major advance has been made in Tamil Nadu and in AP.

The MELD scoring system has been used in North America for organ allocation. Currently the system in place in the two southern states is as follows:

Patients need to be registered in the city where transplant is going to be done and they then come in the waiting list. The centre maintains its list of recipients and decides who should get the organ. If it does not have a suitable recipient, the organ is offered to another hospital in the state. If there are no suitable recipients in the state, the organ is offered outside.

Only when no suitable Indian recipient is available, can the organ be used for a foreign recipient.