Management on the Liver Transplant Waiting List

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Prior to transplantation, the patient must be closely monitored: 1) to provide prophylaxis for complications of liver disease, 2) to detect new problems, and 3) the ensure patient fitness in order to maximize the outcome transplantation. Complications of end-stage liver disease must be prevented: variceal hemorrhage, spontaneous bacterial peritonitis, renal dysfunction, and hepatocellular cancer. Patients must be current on vaccinations for tetanus-diphtheria, poliomyelitis, influenza, hepatitis B, Hepatitis A, pneumococcus, H. influenzae type b, varicella, and mumps-measles-rubella (MMR). Patients are suspended from the waiting list for intercurrent infections, variceal bleeding, and alcohol use by alcoholics. They are reinstated when these problems are corrected.

Keywords: liver transplantation; transinusoidal pressure gradient; spontaneous bacterial peritonitis

TRANSINUSOIDAL PRESSURE GRADIENT

Portal pressure less inferior vena caval pressure

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Introduction

While awaiting liver transplantation, the patient should be closely monitored for several reasons:

- To ensure that the patient is receiving prophylaxis for complications of the liver disease
- To detect any new problems that may affect the success of the transplant
- To ensure the patient is as fit as possible for the procedure

Prevention of Complications of End-Stage Liver Disease

The patient awaiting liver transplantation, like any other patient with end-stage cirrhosis, is at risk of complications, which may affect survival or the successful outcome after transplantation (Table 1).

Variceal Hemorrhage

In portal hypertension due to cirrhosis, the threshold of portal hypertension necessary for variceal hemorrhage is a transinusoidal gradient (portal pressure less inferior vena caval pressure) of 12 mm Hg. The likelihood of a variceal hemorrhage is predicted by

- The degree of portal hypertension
- Severity of liver disease
- Endoscopic appearances: size of varices, presence of red spots
- History of previous variceal hemorrhage

The probability of bleeding or re-bleeding from esophageal varices can be reduced by pharmacological or physical means. Prophylaxis is indicated in those patients with cirrhosis who

- have had a previous variceal bleed
- are at high risk (varices in a patient who is Child's class B or C or has large varices)

The initial choice is with a noncardioselective beta-receptor antagonist such as propranolol or nadalol. This effect of beta-blockade may be assessed either by

- pulse, either a reduction of resting pulse by 25% or to 60 bpm. These are indirect meas-

Table 1 | **Potential Complications in Patients with Cirrhosis Awaiting Liver Transplantation**

Variceal hemorrhage
Development of hepatocellular carcinoma
Development of portal vein thrombosis
Renal failure and electrolyte disturbance
Spontaneous bacterial peritonitis
Encephalopathy
Malnutrition
Sepsis
Osteopenia

SPONTANEOUS BACTERIAL PERITONITIS (SBP)

Associated with ascites

HEPATORENAL FAILURE

Renal failure associated with end-stage liver disease

ures of changes in portal pressure gradient and may overestimate the decline in pressure.

- reduction in measured portal pressure to either less than 12 mm Hg or 25%-50% below the initial portal pressure

About 30% of patients are unable to tolerate beta-blockade in sufficient doses, so mechanical methods should be considered.

Long acting nitrates given in conjunction with nonselective beta receptor antagonists may have some additional efficacy.

- Prophylactic sclerotherapy
- Prophylactic band ligation
- Transjugular intrahepatic porto-systemic shunt (TIPS)

Band ligation is preferable to sclerotherapy, as the latter is more likely to cause esophageal ulceration or peri-esophageal abscess in the postoperative period. TIPS is effective in reducing portal pressure and preventing variceal hemorrhage. However, there are potential problems:

- The presence of the stent may complicate transplant surgery
- Stent thrombosis and narrowing may occur. The benefits of long-term anticoagulation as a means of preventing stent occlusion are uncertain
- TIPS is associated with deterioration in hepatic function when attempted in patients with severely compromised hepatic function (elevated serum bilirubin, renal failure, or marked coagulopathy)

Spontaneous Bacterial Peritonitis

Patients with ascites, which results from portal hypertension, are at risk of spontaneous bacterial peritonitis (SBP). The predictive factors for SBP are

- a previous episode of SBP
- ascitic protein < 1 mg/dl

Antimicrobial therapy has been shown to be effective in reducing the probability of developing SBP from Gram-negative organisms but has no impact on the rarer instances of SBP from Gram-positive organisms. Furthermore, prophylaxis has not been shown to affect mortality among patients with a history of SBP or who have "high-risk" indicators for a first episode. There are many regimens for prophylaxis against SBP:

- Norfloxacin 400 mg/day
- Ciprofloxacin 250 mg/day or 500 mg once per week
- Co-amoxyclav one tablet/day
- Trimethoprim/cotrimoxazole one tablet/day

Renal Function and Electrolyte Balance

Patients with end-stage liver failure are at risk of renal failure, occurring spontaneously (hepatorenal failure) or due to iatrogenic intervention. Patients with ascites are at greatest risk, because the factors leading to ascites development (portal hypertension, splanchnic vasodilation, and peripheral vasodilatation) are also the factors promoting renal impairment through the development of intrarenal vasoconstriction and renal sodium retention.

Renal function should be monitored carefully, and any episode of renal impairment should be investigated fully.

Care must be taken to avoid precipitating renal impairment by

- Avoidance of nephrotoxic drugs (such as gentamicin)
- Avoidance of nonsteroidal anti-inflammatory agents
- Avoidance of intravenous contrast material
- Monitoring the use of diuretics very closely and discontinue if serum urea > 8 μmol/L, serum creatinine > 150 μmol/L or serum sodium < 120 μmol/L
- Avoidance of hypovolemia: in particular, reduce diuretics when patient is likely to become dehydrated (as in hot weather)

Hyponatremia, due to impaired free water clearance, often exacerbated by diuretics, is common in end-stage liver failure. When the serum sodium concentration is less than 120 mmol/L, there is a high risk of central pontine myelinolysis during or soon after liver transplantation. Treatment of hyponatremia includes withdrawal of diuretics, restriction of water intake, and in rare cases dialysis. Many programs will attempt to restore the serum sodium concentration to greater than 120 mmol/L before starting the procedure.

Cancer Development

Hepatocellular Carcinoma (HCC)

HCC may be the indication for liver transplant or may develop during the waiting period. Follow-up of transplant candidates will differ.

Follow-up of Patients with Known HCC

In patients known to have HCC, it is important to monitor the growth of the tumor since during this time transplantation may no longer be indicated. Features indicating transplantation may no longer be appropriate include

- More than three detectable nodules
- Tumor diameter greater than 5 cm
- Spread of tumor outside the liver
- Invasion of the portal vein or hepatic artery by tumor. This may be recognized as clot formation and a presumption drawn that the clot is malignant.

The serum alpha-fetoprotein (AFP) level is a poor guide to the size of the cancer, but the rate of rise is a reasonable guide to the rate of growth. The frequency of repeat imaging of the tumor will depend on the size and location of the tumor: for example, a large tumor close to the margin of the liver will require more frequent monitoring than a small 1 cm tumor in the right lobe. As an approximate guide, we suggest the following follow-up schedule:

- Serum AFP every month
- Liver ultrasound or CT every 3 months
- Chest x-ray every 6 months

The role of ablative therapy (radiofrequency ablation, cryotherapy, chemoembolization, alcohol injection) in this situation is uncertain.

Follow-up of Patients without a Known HCC (the "At-Risk" Group)

The main risk factors for the development of HCC include the presence and duration of cirrhosis, male sex, and chronic viral infection. There are no established guidelines regarding the best screening protocol for at-risk patients.

- Serum AFP measurement: There are many causes of an elevated serum AFP. Elevations of serum AFP, often in the range of 100-500 ng/ml, are particularly common among patients infected by HCV. Sustained, progressively rising serum AFP levels demand a full assessment for HCC. In the absence of rising levels, repeat levels every 3-6 months are appropriate for cirrhotic patients awaiting liver transplantation.
- Imaging of the abdomen (sonography or CT scanning) should be done every 6 months while awaiting a liver transplant.

Cholangiocarcinoma

In general, the known presence of cholangiocarcinoma is a contraindication for liver transplantation. However, such cancers are very difficult to detect using either serological tests (such as CA19-9 or CEA) or imaging techniques (such as ultra-

Table 2 | **Immunizations in Adults Awaiting Liver Transplantation**

Vaccine	Type of Vaccine	Dose Regimen	Comment
Tetanus-diphtheria	Toxoid vaccine	Three doses in naive patients at 0, 4 weeks, and 6-12 months	Persistent immunity up to 10 years
Poliomyelitis	Trivalent inactivated whole virus vaccine (IPV)	Naive: Three doses at 0, 4 weeks, and 6-12 months	Booster every 10 years
Influenza	Trivalent split or subunit vaccine	One dose	Annual booster prior to "flu season"
Hepatitis B	Recombinant or plasma-derived subunit vaccine	Three doses at 0, 4 weeks, and 6 months	Monitor anti-HBs; if < 10 IU/L, repeat booster dose
Hepatitis A	Inactivated whole- virus vaccine	Two doses at 0 and 3-6 months	Persistent immunity up to 10 years
Pneumococcus	23-valent polysaccharide vaccine	One dose	Persistent immunity up to 6 years
H influenzae type b	Polysaccharide conjugate vaccine	One dose	Complete immunization 6 weeks prior to Tpx
Varicella	Live-attenuated vaccine	Two doses 6 weeks apart	Complete immunization 4 weeks prior to Tpx
Mumps-measles-rubella (MMR)	Live-attenuated vaccine	One dose	Complete rubella immunization 4 weeks prior to Tpx

Adapted from Stark K, Gunther M, Schonfeld, Tullius SG, Bienzle U. Immunizations in solid-organ transplant recipients. Lancet 2002;359:957-65.
Tpx indicates transplantation.

sound, CT, or MRI scanning). There is little evidence to suggest that assessment by serological or imaging is of value, although the development of progressively dilated bile ducts may herald the onset of a cholangiocarcinoma.

Other Cancers

Patients awaiting liver transplantation are susceptible to the development of extra-hepatic malignancy. It remains uncertain whether the presence of cirrhosis or which of the diseases predisposing to cirrhosis are associated with a greater probability of developing cancer. The most common extrahepatic cancers to bear in mind are colon cancer in patients with ulcerative colitis. These patients should have full colonoscopy every year while awaiting liver transplantation. Annual mammography and cervical screening ("Pap smears") should be maintained in women of 40 years or more who are awaiting transplantation. Annual prostatic specific antigen (PSA) levels should be measured in men over 45 years who are on the waiting list for liver transplantation.

Vaccinations

Most candidates for liver transplantation will have been vaccinated against or exposed to many of the viral pathogens that might prove harmful after liver transplantation. It is appropriate therefore to assess the immunity to potential viral pathogens as part of the transplant evaluation. Serologic markers to CMV, EBV, HSV, varicella, HBV, HCV, and HAV are checked as a routine measure. Patients without immunity to the viruses listed in Table 2 should be vaccinated if time permits. Candidates for liver transplantation should receive annual influenza immunization.

Progression of Medical Complaints

Hypertension

Patients with systemic hypertension will need monitoring to ensure that the blood pressure is optimally controlled. If there is any cardiac abnormality on screening, then it may be helpful to repeat the ECG and echocardiograph at 6 monthly intervals.

Diabetes Mellitus

Patients with established diabetes mellitus will need careful monitoring to ensure that the blood sugar is within acceptable limits; when normoglycemia cannot be maintained by dietary methods or with oral hypoglycemic agents, then insulin should be instituted.

Alcoholism and Other Addictions

Alcohol-addicted persons should have their alcohol use monitored while awaiting transplantation. This can be achieved by asking the patient and his or her family about drinking relapses and by random checks of blood and urine screens. Smoking cessation: patients are advised to stop smoking, and formal smoking cessation programs are worth attempting.

Temporary Suspension Pfrom the Waiting List

Patients may be suspended from the waiting list for several reasons and returned to the active list when the temporary problem is resolved. Temporary events leading to suspension from the list include

- Intercurrent infections
- Variceal bleeding
- Alcohol use by alcoholics

Suggested Reading

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