

In one report, the clinical improvement in patients with fulminant hepatic failure paralleled improvement of cytochrome P450-related liver function as measured by aminopyrine and caffeine clearance tests. In patients treated for cirrhosis with hepatocyte transplantation, improvement in ascites, recurrent portosystemic encephalopathy and anuria has been reported. Additionally, hepatocyte transplantation has also been successful in treating metabolic diseases such as ornithine transcarbamoylase deficiency, alpha-1-antitrypsin deficiency and Crigler-Najjar syndrome type I.

In the case of Crigler-Najjar syndrome, total serum bilirubin was shown to decrease more than 60 percent and bilirubin-UDP-glucuronosyltransferase enzyme activity was found to be normal at two-year follow-up. In addition to treating metabolic, acute and chronic liver disease, hepatocytes genetically manipulated ex-vivo have been proposed as vehicles for gene transfer. In one study, four patients with familial hypercholesterolemia treated with phenotypically corrected hepatocytes have resulted in reduction of plasma cholesterol level and persistence of transgene function in the long-term followup.

Presently, the major source of hepatocytes is the cadaver donor livers that are not used for the whole organ transplantation. Aborted fetuses and surgically excised liver specimens have also been successfully used to isolate the hepatocytes. Steatosis and cold ischemia times over 18 to 24 hours seem to have a negative impact on the hepatocyte viability and cryopreservation.

In the majority of the reported cases, the isolated hepatocytes are infused via a percutaneously placed catheter

in the portal vein, splenic artery or the peritoneal cavity. Hepatocytes appear to function best when engrafted in the liver and infused via the portal vein. Engraftment of approximately 5-10 percent of the liver mass appears to be necessary to provide significant therapeutic benefit. The liver of a 70-kilogram adult contains approximately  $3 \times 10^{11}$  hepatocytes and reconstitution of 10 percent of the normal host hepatocyte mass requires transplantation of  $6 \times 10^{10}$  hepatocytes. Using current approach, only 30-40% of hepatocytes appear to engraft after each infusion thus necessitating repeat procedures for optimal outcome. Overall, survival of engrafted hepatocytes has been shown to vary from a few days to 20 months and in some cases the lifetime of the host.

A significant advantage of hepatocyte transplantation over conventional whole or partial organ transplantation is that the procedure can be performed in the outpatient setting with very little morbidity. The estimated cost of hepatocyte transplantation is proposed to be 10 percent of orthotopic liver transplantation. Shortage of donor organs for hepatocyte isolation and the need for immunosuppression to prevent rejection are two major hurdles for widespread use of this procedure. Currently, techniques are lacking to expand a small number of hepatocytes in culture to quantities adequate for therapeutic use. Research is underway for generating nontumorigenic immortalized hepatocytes that have the advantage of uniformity and unlimited supply. This approach should allow for a wider application of hepatocyte transplantation in the future.

### *Suggested Reading*

Fox IJ, RoyChowdhury J. *Hepatocyte transplantation*. In: Maddrey WC, Schiff E, Sorrell M (Ed). *Transplantation of the liver*. 3rd Ed. Lippincott William & Wilkins, 2001: 455-464

Strom SC, RoyChowdhury J, Fox IJ. *Hepatocyte transplantation for the treatment of human disease*. *Seminars in Liver Disease* 1999; 19(1): 39-48

---

Inova Health System is a not-for-profit health care system in Northern Virginia that consists of hospitals and other health services including home care, nursing homes, mental health services, physician practices, wellness classes, and freestanding emergency and urgent care centers. Governed by a voluntary board of community members, Inova's mission is to provide quality care and to improve the health of the diverse communities we serve.

[www.inova.org](http://www.inova.org)

*Liver Update* is published by the  
Inova Transplant Center,  
3300 Gallows Road,  
Falls Church, VA 22042-3300

Managing Editor  
Denise Tatu  
703-321-2912

*Inova Transplant Center  
Inova Fairfax Hospital  
3300 Gallows Road  
Falls Church, VA 22042-3300*



FIRST CLASS  
U.S. POSTAGE  
PAID  
Falls Church, VA  
PERMIT #118

# Liver Update

*A publication of the Center for Liver Diseases and the Inova Transplant Center*

## Hepatocyte Transplantation

Khavir A. Sharieff, DO

*Transplant Surgeon, Inova Fairfax Hospital*

The feasibility of hepatocyte transplantation has been established in the last two decades. Transplantation of isolated hepatocytes into spleen, liver or peritoneal cavity of animals has shown that the transplanted hepatocytes display normal architecture, integrate and survive at the transplantation site and function fully as differentiated hepatocytes. Additionally, transplanted hepatocytes have been shown to participate in the normal regenerative processes and support various liver-specific functions such as albumin synthesis, ammonia metabolism, glycogen storage and glycolysis, bilirubin conjugation and cytochrome P450 gene expression.

In animal models of metabolic diseases, transplantation of hepatocytes has been successfully used to correct enzyme deficiency in bilirubin metabolism and reduction of cholesterol in low-density lipoprotein deficiency states. In albuminemic rats, plasma level of albumin has been shown to significantly increase following hepatocyte transplantation. Furthermore, in animals with chemical or surgically induced acute liver failure, hepatocyte transplantation has been shown to improve survival, reverse encephalopathy and prevent intracranial hypertension.

The experience with hepatocyte transplantation in humans is limited and less than 50 hepatocyte transplantation cases have been reported in the literature. Hepatocyte transplantation has been attempted in the management of patients with acute and chronic liver failure and in the treatment of liver-specific metabolic disease.

In acute liver failure, hepatocyte transplantation has been useful in bridging patients awaiting orthotopic liver transplantation, and in few cases, the transplanted hepatocytes have been shown to provide synthetic function and metabolic support to allow enough time for the injured liver to fully recover, thus obviating the need for whole organ transplantation. In one reported study of patients with fulminant hepatic failure, transplantation of fetal hepatocyte was shown to improve survival, especially in patients with grade III and IV hepatic encephalopathy. In other studies there has been a lack of improvement in survival, but significant changes in clinical parameters have been documented. These changes include a decrease in the ammonia level, improvement in the cerebral blood flow, reduction in the intracranial pressure, improvement in the hepatic encephalopathy grade and the level of prothrombin time.

*see Sharieff, page 5*

*Director, Center for Liver Diseases  
Medical Director,  
Liver Transplant Program  
Zobair M. Younossi, MD, MPH,  
FACP, FACG*

*Acting Surgical Director,  
Liver Transplant Program  
Johann Jonsson, MD*

*Transplant Surgeons  
Dympna Kelly, MD  
Khavir Sharieff, DO*

*Hepatologists  
Ronald Barkin, MD  
R. Allen Blosser, MD  
James Cooper, MD  
Gabriel Herman, MD  
Martin Prosky, MD  
Peter Scudera, MD  
Rakesh Vinayek, MD*

*Director, Inova Transplant Center  
Susan Humphreys, RN, MS*

*Transplant Coordinators  
Bonnie Erickson, RN, CCTC  
Marion Stewart, RN, CCTC*

*Center for Liver Diseases Staff  
Harpreet Gujral, RN, MSN  
Nurse Practitioner  
Peggy Kraft, RN  
Research Coordinator  
Manirath Srishord, RN,  
Clinical Nurse Coordinator*

---

# Endoscopic and Medical Management of Variceal Bleeding

Peter L. Scudera, MD

Zobair M. Younossi, MD, MPH, FACP

Titles?

## BACKGROUND

Chronic liver disease and cirrhosis are major causes of morbidity and the ninth leading cause of mortality in the United States. Portal hypertensive bleeding is a common cause of upper GI bleeding and is associated with enormous utilization of health care resources. The estimated total economic burden of liver disease and cirrhosis can be enormous. Esophageal variceal bleeding alone accounted for 62,000 hospital days and an average daily hospitalization cost of \$1,091 in 1985.

In addition to significant impact on patient survival and health care costs, cirrhosis and its associated portal hypertension are also associated with significant impact on patients' health related quality of life and other intangible costs. Similar to other chronic diseases, the clinical impact of variceal bleeding relates to its prevalence, incidence, and natural history. Some of these issues are summarized below:

- Typically, bleeding varices occur when significant portal hypertension has developed [Portosystemic gradient (PHVG) > 12 mmHg]
- Prevalence of medium to large varices in about 20 percent of patients with cirrhosis.
- The risk of developing new varices for patients with cirrhosis is about four to 12 percent each year.
- Once present, the risk of varices to enlarge is about four to 10 percent each year.
- The average rate of bleeding from varices not treated medically is about 29.6 percent in the year following diagnosis.
- Mortality from an acute episode

of variceal bleeding is 30 to 50 percent.

- Risk factors associated with variceal bleeding include high Child-Pugh scores, degree of portal hypertension, variceal size, and endoscopic finding of red wale or cherry red spots on the varices.

The role of endoscopy in the management of patients with cirrhosis ranges from identification of patients with large varices who are at risk for active variceal bleeding to endoscopic therapy. Additionally, endoscopic treatment (endoscopic sclerotherapy or esophageal band ligation) plays an important role in preventing recurrent episodes of variceal bleeds by eradicating them. Treatment of esophageal varices can be divided in the following three different areas:

## PRIMARY PROPHYLAXIS

Given that 25 to 30 percent of varices can bleed within one year of diagnosis, and that each episode of bleeding is associated with 30 to 50 percent mortality, prevention of the first bleed has become an important issue. Medical therapy with non-selective beta-blockers (Propranolol, Nadolol) or long acting nitrates (Isosorbide-5-Mononitrates) has been evaluated in prospective randomized clinical trials. Multiple trials and a recent meta-analysis have shown a reduction in the risk of variceal bleeding with beta-blockers and a trend in reduction in the rate of mortality. Additionally, sequential hemodynamic studies have shown that reduction of portal hypertension to a PHVG < 12 mm Hg provides protection against variceal hemorrhage. In addition to non-selective beta-blockers, long acting nitrates such as Isosorbide-5-Mononitrate may be effective, and preliminary data from a few recently reported studies suggest that combining beta-blockers and long acting nitrates may be even

more efficacious in lowering PHVG and preventing variceal bleeding. This added benefit of combination therapy should be weighed against potentiation of its side effects and the resultant lower compliance.

The role of endoscopic therapy for prevention of the first variceal bleed remains controversial. Although endoscopic sclerotherapy has shown no benefit, recent trials of endoscopic band ligation (EBL) have been encouraging. The initial two trials of EBL suggested superior efficacy in preventing the first variceal hemorrhage. In a recent study comparing EBL to Propranolol, actuarial probability of hemorrhage in the EBL group was 15 percent, as compared to 43 percent in the Propranolol treated group (p=0.04). These data increasingly support the role of EBL in preventing the first variceal hemorrhage in high-risk cirrhotics. This option may be especially important if medical therapy is contraindicated or cannot be tolerated.

Finally, the current published literature does not support the use of TIPS or surgical shunts in preventing the first variceal hemorrhage.

## CONTROLLING ACTIVE VARICEAL BLEEDING

Initial management of acute variceal bleeding includes resuscitation, airway protection, and hemodynamic stabilization with fluids and blood products. Pharmacologic agents available for the treatment of acute variceal bleeding include Octreotide or Vasopressin plus Nitroglycerine (as an alternative). Even though Vasopressin alone can successfully control acute variceal bleeding, it is associated with significant side effects, including myocardial ischemia, peripheral ischemia, bradycardia, hypotension, and fluid retention. The addition of Nitroglycerin,

---

either as a patch or intravenously, maintains the efficacy of this drug with a lower side effect profile.

Because of these significant hemodynamic effects, Octreotide has become the most commonly used medical regimen for acute variceal bleeding.

Randomized clinical trials of Somatostatin (Octreotide is an analogue of Somatostatin) have confirmed its superiority as compared to placebo in controlling acute variceal hemorrhage. Octreotide is started at a bolus of 50–100 microgram and a drip of 50 microgram per hour for a total of three to five days.

Once the patient is stabilized, endoscopy not only can confirm the source of bleeding, but also provides a potential therapeutic modality (sclerotherapy or band ligation). Both sclerotherapy and esophageal band ligation can adequately control esophageal variceal bleeding, with success rates ranging between 85 and 95 percent. Multi-band ligators are the current preferred method of choice for endoscopic therapy. Sclerotherapy can be used as an alternative if expertise in the use of band ligation is not available. The rate of complication is lower with EBL and the number of sessions required to obliterate the varices with EBL is lower.

Endoscopic treatment of actively bleeding gastric fundal varices has not been extensively investigated. Cases of successful treatment of these varices with sclerotherapy and band ligation have been reported. Cyanoacrylate glue injection appears to be very effective for control of actively bleeding gastric varices. This technique requires special injection techniques to avoid damaging endoscopic equipment. Additionally, this treatment may be associated with embolic phenomena and other major complications. Cyanoacrylate glue for

this use is currently not available in the United States.

Several trials have examined the value of Octreotide in combination with endoscopic sclerotherapy in patients with active bleeding from esophageal varices. Data from these trials suggest some benefit (e.g. reduced transfusion needs, lower incidence of recurrent hemorrhage) from combining these treatments and extending the drug treatment from two to five days after endoscopic control is achieved.

In patients with active variceal bleeding that cannot be controlled by endoscopic and medical therapy, decompressive interventions with radiologically (TIPS) or surgically placed shunts should be considered. In this setting, it is important that the patient is intubated (for airway protection) and that a compression balloon (Minnesota tube, etc) is considered. These balloons provide temporary control of active variceal bleeding until a more definitive treatment (decompression) is provided. Given the high rate of potential complications with these balloons, it is important that they are inserted by individuals familiar and experienced with their use.

#### PREVENTION OF RECURRENT VARICEAL BLEEDING

At the time of the first variceal bleed, a management plan to prevent subsequent bleeding needs to be drawn. This plan should include not only medical therapy with nonselective beta-blockers and/or nitrates, but also sessions of endoscopic eradication of esophageal varices. The two modalities available for this purpose are again esophageal sclerotherapy or band ligations (EBL). A recent meta-analysis concluded that both means of endoscopic therapy can equally eradicate varices. However, the num-

ber of sessions and complication rates were lower with esophageal band ligation.

Trials of combined endoscopic ligation and sclerotherapy to prevent variceal rebleeding have recently been carried out. In these trials, the combined treatment required more treatment sessions to eradicate varices, with a higher rate of complications. At the moment, there appears to be no advantage to using these two endoscopic treatment modalities in combination.

The addition of Sucralfate after endoscopic therapy may also be beneficial in reducing post procedure complications. In a recent trial, EBL alone was compared to a combination of EBL, Nadolol and Sucralfate. Patients in the latter group experienced a significant reduction in their rate of recurrent variceal bleeding and a trend towards improved survival.

Finally, the role of TIPS in this setting has been evaluated in clinical trials. In these trials, TIPS consistently reduced the incidence of recurrent bleeding. Unfortunately, there was an associated increase in the incidence of encephalopathy and no improvement in patients' survival. Because of the high rate of stenosis with the currently available stents, the role of TIPS in this setting remains controversial. If used in long term management, at least biannual duplex ultrasound of the TIPS is needed. If stenosis is found, dilation or placement of a new TIPS by the interventional radiologist may be required.

For patients who continue to bleed despite endoscopic and medical therapy, a surgical approach may be indicated. These include surgical shunt and liver transplantation. In patients with advanced liver disease, liver transplantation (OLT) should be con-

sidered, and TIPS may serve as an appropriate bridge to OLT. In those with well-preserved liver function, surgical shunts (most likely a selective shunt, such as distal splenorenal shunt) can provide a good long-term alternative.

## CONCLUSION

In this era of technological breakthroughs for treatment of portal hypertension, clinicians are increasingly faced with a variety of therapeutic modalities at their disposal to manage these patients. These modalities include pharmacologic, endoscopic, radiologic, and surgical options. Development of a multidisciplinary team to efficiently manage these patients is crucial. This team should include not only the gastroenterologist/hepatologist but also the intensivist, interventional radiologist, and a surgeon familiar with the surgical decompressive techniques.

It is also important that the intensivist is involved not only in providing the airway protection and assuring hemodynamic stability of these patients, but also in the initiation of appropriate medical therapy (Octreotide) promptly. Endoscopy should be performed once the patient is stabilized, for both its diagnostic and therapeutic value. For those who fail endoscopic and medical therapy, options of surgical or radiologically placed shunts should be considered. This systematic and multidisciplinary approach to variceal bleeding should not only improve patients' health outcomes (mortality and morbidity), but also their health-related quality of life and cost of care.

## Center for Liver Diseases Receives Hepatology Fellowship

The Center for Liver Diseases has been granted a \$50,000 fellowship from the American Association for the Study of Liver Diseases. Janus Ong, MD, of the Liver Diseases Section, National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK), National Institutes of Health, is the recipient of this award and has been named the center's first Advanced Hepatology Fellow.

The grants are awarded to recipients focusing on formal training in advanced hepatology, liver disease or related disciplines. Dr. Ong's award was one of 29 granted to and accepted by educational and training institutions in the United States and Canada.

He will assist the Center's hepatologist in developing and carrying out investigator-initiated research protocols and gain experience in transplant and non-transplant hepatology.

Dr. Ong holds a bachelor's degree in biology from the University of the Philippines, where he also attended medical school. He served his internship and residency with the Yale Primary Care Internal Medicine Residency Program and later received a fellowship in gastroenterology at the Cleveland Clinic Foundation. Since July 2000, he has been a medical staff fellow in Hepatology at the NIDDK/NIH.

Dr. Ong is certified in internal medicine and gastroenterology by the American Board of Internal Medicine. He was the recipient of the Young Researcher award at the 10th International Symposium on Hepatic Encephalopathy and Nitrogen Metabolism, held in 1999 in Istanbul, Turkey and received the Gary Vernon Ralph Humanism in Medicine Award, Yale Primary Care Internal Medicine Residency Program, in 1995. He has authored multiple articles on various areas of liver disease, including hepatic encephalopathy, hepatitis C and non-alcoholic fatty liver disease.

Dr. Ong is a member of the American College of Gastroenterology and American Gastroenterological Association and a life member of the Phi Kappa Phi Honor Society. He can be reached at **703-698-3182**.