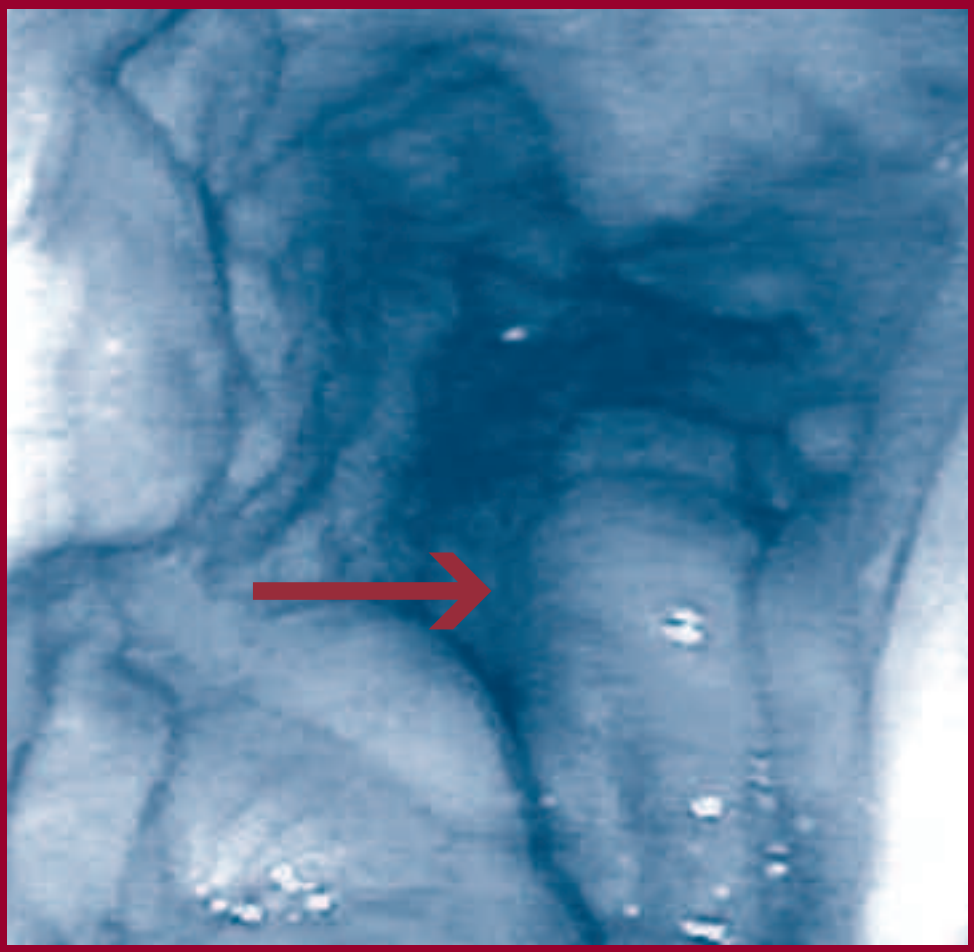

Individuals with chronic liver disease are susceptible to a number of complications, including elevated blood pressure (hypertension) in the portal vein, which drains blood from much of the digestive tract. Portal hypertension causes the walls of the vein to balloon out, and can lead to varices (swollen veins) in the esophagus that can be visualized by endoscopy (arrow). Varices constitute a potentially life-threatening complication if the veins burst (so-called "bleeding varices"). Photo: Dr. Thomas Boyer, University of Arizona.

CHAPTER 13: COMPLICATIONS OF LIVER DISEASE

INTRODUCTION AND BACKGROUND

Chronic liver disease and cirrhosis account for approximately 27,000 deaths in the United States each year. The mortality rate from cirrhosis has been declining for the last 10 years, due in part to the many advances made in treatment and prevention of liver disease. The majority of patients who die of cirrhosis succumb ultimately to a complication of portal hypertension, such as variceal hemorrhage, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatopulmonary syndrome, or hepatorenal syndrome. These complications are also the most common proximal causes of death in patients awaiting liver transplantation. Future improvements in managing these complications could improve the quality of life and survival of patients with chronic liver disease.

Progression of cirrhosis leads to portal hypertension, which can result in esophageal varices, ascites, and renal and pulmonary complications. The most frequent severe complication of portal hypertension is variceal hemorrhage, which, despite many advances in management, remains a significant cause of death in patients with cirrhosis. Among patients who survive a first episode of variceal bleeding and do not receive prophylactic therapy, two thirds have recurrent bleeding and a third die within 1 to 2 years. Reduction of the hepatic venous pressure gradient (HVPG) below 12 mm Hg (normal is <6 mm Hg), either spontaneously or with medical, radiological, or surgical therapy, effectively prevents recurrent bleeding.

Ascites is likewise a common complication of portal hypertension, which eventually occurs in almost all patients with cirrhosis. The standard treatment of ascites is salt restriction and use of diuretics. A proportion of patients, however, develop ascites that is unrelieved by medical therapy. Refractory ascites has a poor prognosis—less than half of patients survive for more than a year. Patients with ascites are also at high risk for the development of spontaneous bacterial peritonitis, hepatic hydrothorax, hyponatremia, and hepatorenal syndrome—complications that also have poor prognoses. The presence of portal-systemic shunts also carries the risk of development of hepatic encephalopathy and hepatopulmonary syndrome. Hepatic encephalopathy can be clinically overt, particularly when precipitated by infection, bleeding, or another known cause. The encephalopathy can also be minimal to the point of being detected only by neuropsychological testing, but, nevertheless, have significant adverse effects on quality of life.

Other complications of liver disease include symptoms such as fatigue, weakness, jaundice, and pruritus (itching). These symptoms are generally mild, but can progress and ultimately be severe enough to warrant liver transplantation. Interestingly, the causes of fatigue and itching in cirrhosis are not known. There are no specific therapies for fatigue, and the treatments for pruritus are only partially effective.

Complications also arise from acute liver disease, the most serious of which is fulminant hepatic failure. Acute liver failure occurs in approximately 1 percent of persons with acute viral hepatitis and a higher proportion of patients with jaundice due to drug-induced liver injury. There are no specific therapies for acute liver failure, and this syndrome currently accounts for 5 to 10 percent of liver transplants performed in the United States each year.

Thus, complications of acute and chronic liver disease are challenging medically and have significant effects on morbidity and mortality. Elucidation of the cause of these complications and development of better approaches to therapy and prevention would substantially improve the survival and quality of life of persons with liver disease.

RECENT RESEARCH ADVANCES

In the past 10 years, there have been major advances in the understanding of the pathogenesis of portal hypertension and its complications.

Understanding Portal Hypertension: Previously, portal hypertension was considered to be a fixed complication of the fibrosis and remodeling of the liver that occurs in cirrhosis. Recent work in experimental models suggests that there is a major dynamic and reversible component to portal hypertension. Endogenous vasoconstrictors such as endothelin, angiotensin, and others can acutely increase portal pressure and may be involved in the chronic portal hypertensive syndrome. Nitric oxide and nitric oxide donors can reduce portal pressure acutely and chronically. Underproduction of intrahepatic nitric oxide appears to be a factor that worsens portal hypertension in cirrhotic animals and in humans. In contrast, overproduction of nitric oxide in the splanchnic and systemic circulation induces vasodilation and may contribute to the hyperdynamic circulation in cirrhotic patients. These findings indicate that there are active and modifiable components to portal hypertension that might be targets of therapy. Furthermore, the optimal targets of therapy may change with progression of portal hypertension and the systemic complications of cirrhosis.

Understanding Complications of Portal Hypertension: Progress has also been made in the understanding of ascites and renal dysfunction associated with portal hypertension in cirrhosis. Vasodilation in portal hypertension is present in both the systemic and splanchnic vasculature, which leads to a decreased functional intravascular volume and perfusion of the kidneys with resultant sodium and water retention and expansion of the plasma volume. The validity of this concept has been shown by the findings that some vasopressors, when given to cirrhotics, cause redistribution of blood flow to the kidneys, leading to an improvement in renal function. Studies of bacterial translocation in cirrhosis have helped to understand the cause not only of infections, but also of vasodilation in cirrhosis. Advances in hepatic encephalopathy (HE) have documented the importance of neurotransmitters in the cerebral complications of liver disease. Nevertheless, management of HE continues to rely upon decreasing the production of ammonia and nitrogenous compounds from colonic bacterial flora by the use of lactulose, antibiotics, and other ammonia-reducing compounds.

Management of Complications of Cirrhosis: Increased understanding of the pathogenesis of portal hypertension and a large number of randomized controlled trials of potential therapies for this condition have led to improvements in the management of complications of cirrhosis. Patients at risk for variceal bleeding can now be identified endoscopically and the risk of bleeding reduced with either pharmacologic or endoscopic therapy. Similarly, once a patient has bled, pharmacologic and/or endoscopic therapy

is effective in reducing the rate of rebleeding. The treatment of acute variceal hemorrhage has improved with the use of endoscopic therapy, short-term antibiotic prophylaxis, and the development of drugs with fewer side effects but similar efficacy to vasopressin. If bleeding cannot be controlled or if it recurs despite pharmacologic or endoscopic therapy, either transjugular intrahepatic portosystemic shunt (TIPS) or surgical shunt is effective and their relative benefits and risks are now being actively studied.

Progress has also been made in the management of ascites, especially ascites that is not controlled by standard diuretic therapy. Controlled trials have helped in defining the value of repetitive large-volume paracentesis vs. TIPS for refractory ascites. Of great potential importance are the recent reports that vasoconstrictors, such as terlipressin, when given in concert with albumin, are an effective therapy for hepatorenal syndrome. Most impressive have been the observations that some patients with hepatorenal syndrome maintained improved renal function after the infusion of the vasoconstrictor was withdrawn. The ability to improve renal function in these patients has an impact not only on their response to diuretics, but also may influence their need for liver transplantation.

RESEARCH GOALS

The major goals of research on complications of chronic liver disease are to identify ways to prevent or ameliorate the complications of portal hypertension, including variceal hemorrhage, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, and hepatorenal and hepatopulmonary syndromes.

Pathophysiology of Portal Hypertension: Central to progress in management of patients with cirrhosis is to better characterize the molecular pathophysiology of portal hypertension.

- *Research Goal:* To more fully define the pathophysiology of portal hypertension (Matrix Cell A3).

Alterations in the intrahepatic and systemic circulations have led to the identification of several important mediators, including nitric oxide and endothelin, the effects of which may either worsen or improve the portal hypertensive state. The sequence of events from increased portal resistance to splanchnic and systemic vasodilation and fluid retention needs to be defined.

Management of Complications of Chronic Liver Disease: Findings on the pathophysiology of portal hypertension should be translated rapidly into clinical medicine. Elucidation of the pathways that control intrahepatic and peripheral vascular resistance would provide targets for therapy of portal hypertension and might provide means for high-throughput screening of small molecules.

- *Research Goal:* To identify small molecule targets that would lead to better therapy for portal hypertension at different stages of disease (Matrix Cell B3).

Variceal hemorrhage resulting from portal hypertension remains an important cause of morbidity and mortality from chronic liver disease. While there are effective means of decreasing the risk of variceal hemorrhage (e.g., use of beta adrenergic blockers, esophageal variceal banding, surgical shunt, and TIPS), none of these therapies are completely effective and without side effects. In particular, medical therapies to reduce portal pressure are limited in efficacy. A large proportion of patients experience no benefit from beta blocker therapy,

and many patients have significant side effects from these drugs.

- *Research Goal:* To develop and evaluate better medications for reducing portal pressure that are more physiologically based upon underlying mechanisms, directed at different stages in the course of portal hypertension, and less likely to cause side effects (Matrix Cell C2).

The primary issue in management of varices at present is determining the optimal approach to patients with both cirrhosis and moderate or large varices which have not bled.

- *Research Goal:* To define the natural history and predictors of the development and growth of varices (Matrix Cell B2).
- *Research Goal:* To elucidate the optimal approach to primary prevention of variceal hemorrhage through a prospective randomized controlled trial of various practical approaches (Matrix Cell C1).

Regarding the latter goal, such a study could also include a careful assessment of whether measurement of portal pressure is clinically useful in managing patients.

From a clinical point of view, an important roadblock to progress in chronic liver disease is the difficulty in measuring portal pressure. Transvenous measurement of wedged hepatic venous pressure (WHVP) with calculation of the HVPG (WHVP-free hepatic venous pressure) is a reliable means of assessing portal pressure, which can predict the likelihood of variceal hemorrhage, as well as survival, and demonstrate whether medical therapies are effective in reducing portal pressure. Current methods of HVPG measurement require venous catheterization, which can be done safely and without major discomfort. Nevertheless, few physicians are trained in performing HVPG measurements, and there is little standardization in technique or in quality control of pressure-recording measurements. Similar criticism can be made of the diagnosis and grading of hepatic encephalopathy and the hepatopulmonary syndrome.

- *Research Goal:* To standardize clinical measures of cirrhosis and portal hypertension, particularly WHVP measurements (Matrix Cell A1).
- *Research Goal:* To define the clinical utility and optimal use of WHVP or portal pressure measurement in management of patients with cirrhosis (Matrix Cell C1).

Most helpful would be an improved and less invasive means of monitoring portal pressure. The ability to measure portal pressure and to assess esophageal and gastric varices without need for catheterization or endoscopy would be helpful in clinical management of patients, as well as in design and conduct of studies relating to the complications of cirrhosis.

- *Research Goals:* To develop a reliable, non- or minimally invasive means of measuring portal pressure and of screening for large varices (Matrix Cells B3 and C3).

Other challenges for future research in complications of cirrhosis include the elucidation of the cause of increased susceptibility to bacterial infections and how infections precipitate variceal hemorrhage, hepatic encephalopathy, and hepatorenal syndrome.

- *Research Goal:* To better characterize the cause of increased susceptibility to bacterial infections in cirrhosis (Matrix Cell A3).

Focused clinical studies on prevention and management of infections and other complications of cirrhosis are warranted. Recent excellent preliminary results using antibiotics for variceal hemorrhage and ascites, vasopressors for hepatorenal syndrome, vasopressin 2 antagonists for hyponatremia and

ascites, probiotics for hepatic encephalopathy, and recombinant coagulation factors for coagulopathy deserve careful prospective evaluation. Prospective studies of the natural history of complications of cirrhosis would also be helpful.

- *Research Goal:* To define optimal nonspecific approaches to management of hepatic encephalopathy, hepatorenal syndrome, refractory ascites, prevention of bacterial infection, and coagulopathy in patients with cirrhosis (Matrix Cell B1).
- *Research Goal:* To define the natural history of hepatopulmonary syndrome and the growth and progression of small esophageal varices (Matrix Cell A2).

Prevention and Therapy of Acute Liver Failure:
In the area of acute liver failure, the primary goals of research should be in developing means to prevent acute liver failure and to ameliorate its course.

- *Research Goals:* To determine whether nonspecific cytoprotective agents such as N-acetylcysteine and hypothermia are beneficial in acute liver failure (Matrix Cells A1 and B2).

Most helpful would be an artificial or bioartificial liver assist device that could be used to sustain patients and serve as a bridge to liver transplantation, which is the only effective therapy that is currently available for fulminant hepatic failure.

- *Research Goal:* To develop a hepatic assist device or bioartificial liver and demonstrate its efficacy in acute liver failure (Matrix Cell C3).

Also, noninvasive means of imaging or measuring hepatic regeneration and reserve in acute liver failure would be valuable for assessing whether spontaneous recovery is possible or whether liver transplantation is necessary.

- *Research Goal:* To develop noninvasive means of assessing liver regeneration and reserve that could be used in management of acute liver failure (Matrix Cell C2; see also Chapter 3, A2 and B2).

In the long run, identifying the causes of acute liver failure and means of prevention, as well as applying those means to public health, should be major research goals.

STEPS TO ACHIEVE RESEARCH GOALS

Progress in elucidating the pathophysiology of portal hypertension would be helped by application of state-of-the-art techniques of cell biology, as well as newer methods, such as gene arrays and proteomics, to help define pathways that occur with the development of cirrhosis. Studies in both animal models and humans with chronic liver disease are warranted. It important that these types of investigations are strongly encouraged with a focus on findings that might be translated into practical clinical therapies.

Progress in standardization and improvement in methods of clinical measurement of cirrhosis and portal hypertension would be helped by a clinical research workshop on this topic. A major focus of the workshop could be techniques of HVPG measurement and reproducibility and reliability of the methods. The workshop could also cover standardization of diagnosis and grading systems for other complications of cirrhosis, such as hepatic encephalopathy, hepatopulmonary syndrome, and hepatorenal syndrome, types I and II. Publication of standards and guidelines for grading systems and measurements would be important.

Progress in clinical research would benefit from a multicenter trial of primary prevention of variceal hemorrhage in patients with cirrhosis and moderate-

to-large varices. Such a trial could also serve to help define the role of HVPG measurements in managing patients with cirrhosis and to establish quality control of techniques for these measures across multiple institutions. Emphasis should also be placed on determining the natural history of patients with cirrhosis who have no or small varices, and on prospectively evaluating the clinical and radiological parameters that predict the presence of large varices. Development of other clinical trials can be promoted through the use of small planning grants (R03s). Studies on acute liver failure will be aided by the Acute Liver Failure Study Group (ALFSG), which has both adult and pediatric components and has been successful in collecting prospective data on acute liver failure and in designing and conducting clinical trials.

Matrix of Research Goals in Complications of Liver Disease

	Short Term (0-3 years)	Intermediate Term (4-6 years)	Long Term (7-10 years)
High Risk	**A3.** More fully elucidate the pathophysiology of portal hypertension. Better characterize the cause of increased susceptibility to bacterial infections in cirrhosis.	**B3.** Identify small molecule targets that would lead to better control of portal hypertension at different stages of disease. Develop a noninvasive means of measuring portal pressure.	**C3.** Develop an artificial or bioartificial hepatic support and demonstrate that it prolongs survival in acute liver failure. Develop noninvasive means to screen for large varices.
Intermediate Risk	**A2.** Better define the natural history of hepatopulmonary syndrome and whether early detection is beneficial.	**B2.** Define whether hypothermia is beneficial in acute liver failure for management of cerebral edema. Define natural history and identify predictors of development and growth of varices.	**C2.** Develop a noninvasive means to assess hepatic regeneration and reserve in liver failure. Develop and evaluate better drugs for portal hypertension.
Low Risk	**A1.** Hold a research workshop on improvement and standardization of clinical measurements of cirrhosis and portal hypertension. Define whether N-acetylcysteine is beneficial in acute liver failure.	**B1.** Define optimal nonspecific approaches to management of hepatic encephalopathy, hepatorenal syndrome, refractory ascites, prevention of bacterial infection, and coagulopathy in patients with cirrhosis.	**C1.** Elucidate the optimal approach to manage patients with varices that have not bled (primary prevention). Define whether monitoring portal pressure (HVPG) improves management of patients with chronic liver disease.