

Liver Update

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

Hepatorenal Syndrome — Update 2001

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Hepatorenal Syndrome (HRS) has recently been defined as a clinical condition presenting in patients with chronic liver disease, advanced hepatic failure and portal hypertension. Its hallmarks are evidence of impaired renal function with marked abnormalities in the arterial circulation in the setting of increased activity of the endogenous vasoactive system. These features result in marked renal vasoconstriction with arterial vasodilation in the peripheral circulation, leading to reduced systemic vascular resistance and resultant arterial hypotension.

The seminal observations of the development of oliguria in chronic liver disease in the absence of proteinuria and with normal renal histology were in the 1800's by Frerichs and Flint. Although they were able to link the abnormalities in renal function to the disturbances present in the systemic circulation, a detailed clinical description of HRS did not appear until the 1950s.

Sherlock, Papper and Vessin emphasized the functional nature of the renal failure coexistent abnormalities in the systemic circulation and the poor prognosis of the syndrome. During the 1960's and 1970's, Epstein and others demonstrated that renal failure in HRS is due to extreme renal vasoconstriction, setting the stage for subsequent investigations exploring the role of endogenous vasoactive systems. A key contribution has been the description of the arterial vasodilation hypothesis of arterial underfilling and ascites formation. More recent important observations include the association between spontaneous bacterial peritonitis and the development of HRS and the use of vasopressin analogues in the management of HRS.

Ascites is the most common complication of cirrhosis, which is the most common cause of ascites in the United States. Theories of ascites formation have included underfill, where renal retention of sodium is a secondary event; overfill, where renal retention of sodium is a primary event; and the current arterial vasodilation, or revised underfill theory. This theory proposes that the decreased renal function in HRS is the extreme manifestation of underfilling of the arterial circulation due to marked vasodilation of the splanchnic circulation, leading to a rise in cardiac output and a progressive fall in systemic vascular resistance with resultant hypotension.

The resultant baroreceptor mediated stimulation of vasoconstrictor systems to include the renin-angiotensin system and the sympathetic nervous system eventually leads to decreased GFR. It has been suggested that the renal circulation is affected by an increase in the ratio of vasoconstrictor thromboxanes to vasodilator prostaglandins. It is now felt that nitric oxide is the primary mediator of splanchnic vasodilation in cirrhosis. There is stimulation of nitric

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oxide production via absorbed endotoxin, which is less efficiently cleared due to portal-systemic shunting and decreased reticuloendothelial cell function.

HRS is characterized by a combination of renal failure, circulatory failure and hepatic failure. The renal failure may be of rapid or insidious onset. The degree of marked sodium retention has been inversely correlated with survival, as has the severity of hyponatremia due to water retention from increased secretion of antidiuretic hormone.

In general, the serum creatinine is a poor indicator of the degree of renal function due to marked muscle wasting. A prospective study of 229 nonazotemic patients with cirrhosis and ascites has suggested that the incidence of HRS was 18 percent at one year, and 39 percent at five years. HRS has been classified as type 1 when there is rapid progression of oligoanuric renal failure, advanced liver failure and a median survival of only two weeks; whereas type 2 is typically diuretic resistant ascites.

Major diagnostic criteria for the HRS include a low GFR, absence of proteinuria and normal renal sonography, with the absence of shock, bacterial infection, fluid loss or nephrotoxic drugs. In addition, there has to be no sustained improvement in renal function following withdrawal of diuretics and expansion of plasma volume. Additional criteria can also include oliguria, a low urinary sodium (<10 mEq/L), a urinary osmolarity > plasma osmolarity and hyponatremia (<130 mEq/L).

Treatment options for HRS, other than orthotopic liver transplantation, include medical therapy and use of the transjugular portosystemic shunt (TIPS) and renal replacement therapy (RRT) as bridges to transplantation. Options for medical therapy are

RESEARCH PROTOCOLS

The following protocols are ongoing at the Center for Liver Diseases:

- Pegylated Interferon alfa 2b and Ribavirin for chronic hepatitis C, previous treatment failures.
- Triple regimen of Pegylated Interferon alfa 2b, Ribavirin and Amantadine for treatment of chronic hepatitis C; treatment failures or naïve.
- Adefovir dipivoxil for the treatment of hepatitis B; untreated or with YMDD variant.
- Pegylated Interferon alfa 2a (PEGASYS) alone or in combination with Ribavirin for chronic hepatitis C; treatment failure or naïve. Immunomatrix Evaluation of a rapid one step immunoassay for HCV.
- Adefovir Dipivoxil for treatment of hepatitis B with Lamivudine resistance in pre- and post-liver transplant patients.
- Epidemiology of hepatitis B in the United States.
- Emtricitabine for chronic hepatitis B for Nucleoside naïve patients.
- Procrit for hepatitis C patients on Ribavirin/IFN or Ribavirin/PEG-IFN.

For patient screening or additional information, call the Center for Liver Diseases, 703-698-3182.

directed at increasing vasoconstriction in the splanchnic circulation and include vasopressin analogs, which have been used with albumin and dopamine with variable success but a risk of inducing intestinal ischemia.

Although a preliminary report suggested that the prostaglandin analog Misoprostol, when used with albumin in four patients with HRS, was successful in increasing urine output and serum sodium while decreasing creatinine, this was not confirmed in subsequent investigations. An encouraging trial was conducted with the antioxidant, N-acetylcysteine, in 12 patients with HRS. Significant changes were seen in the serum creatinine, creatinine clearance and urine output, with a 67 percent survival at one month and 58 percent at three months, including two successful OLT after improvement in renal function.

Another recent encouraging trial using midodrine, a selective alpha-1 adrenergic antagonist, and octreotide, a somatostatin analog, took advantage of their respective properties as a systemic vasoconstrictor and an inhibitor of endogenous vasodilator release. Of the five patients treated with midodrine, octreotide and

albumin, 60 percent survived with receiving successful OLT. A control group receiving dopamine and albumin had an 87 percent mortality in the first 12 days.

TIPS has been advocated as a possible bridge to OLT. A small study examining seven patients with HRS did demonstrate a gradual increase in the creatinine clearance with a decrease in the serum creatinine and plasma renin activity. Average survival was five months. There are substantial risks to this procedure in these patients.

RRT has a role as a bridge to OLT and the improvements in continuous renal replacement therapy have many potential advantages to intermittent hemodialysis in the support of these patients. Continuous dialysis avoids rapid fluid and electrolyte shifts, and thereby minimizes increases in intracranial pressure with better preservation of cerebral perfusion pressure. The possibility of real time base adjustment exists with more hemodynamic stability due to a slower rate of fluid removal and cooling of core temperature. Overall metabolic control is better due to the ability to combine diffusive and convective transport.

Treatment Approaches to Hepatic Malignancies

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Each year in the United States, approximately 145,000 new cases of colorectal cancer (CRC) and 8,000 cases of hepatocellular carcinoma (HCC) are diagnosed. Over half the patients with colorectal cancer will eventually develop liver metastases. Overall, only about 10 to 15 percent of patients with CRC or HCC are candidates for curative surgical resection.

Surgery remains the gold standard for treatment of hepatic malignancies, with five-year survival rates of 25 to 40 percent, following resection for colorectal metastases. Transplantation offers the best long-term survival for hepatocellular carcinoma. Unfortunately, only about 10 to 15 percent of patients with metastatic CRC or HCC are candidates for surgery.

A host of palliative treatments have been tried for HCC and CRC. Hepatic malignancies are generally radioresistant, and chemotherapy is just beginning to show survival advantages with three drug regimens and /or the use of chemoinfusion pumps for patients with metastatic colorectal cancer. No effective chemotherapy has been found for HCC.

Radiofrequency ablation (RFA) is a method of local control of hepatic malignancies through thermal tissue ablation. RFA, which employs the principles of electrocautery, was first used clinically in hepatic tumors in the early 1990's. Since then, it has gained acceptance as an effective, minimally invasive therapy for patients who are not candidates for curative surgical resection. RFA has also shown promise as a bridge to transplantation and as a treatment that can help convert patients with multifocal disease to surgical candidates.

RFA is a local therapy in which only a tumor nodule and a surrounding margin of normal liver are thermally destroyed. A small probe is centered within the tumor mass under imaging guidance and an electrode array is deployed. RF energy is applied for 15-30 minutes until a target temperature or a characteristic level of tissue impedance is reached, which indicates thermal necrosis. Currently available probes allow treatment of lesions of up to five centimeters in diameter, and up to five lesions can be treated.

Early results are encouraging, with major complication rates of two to three percent and local recurrence rates of about 10-15 percent at one year for lesions less than four centimeters in diameter. RFA is truly a minimally invasive therapy: it can in fact frequently be safely performed on an outpatient basis. To date, the Division of Vascular and Interventional Radiology has performed over 33 RFA procedures at Inova Fairfax Hospital, with a cumulative experience of more than 60 procedures. RFA is generally performed percutaneously, but several cases have been done in the operating suite cooperatively with transplant surgeons.

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Publications and Presentations

Publications

- Younossi ZM, Mullen KD, Zakko W, Hodnick S, Brand E, Barnes DS, Carey WD, McCullough AC, Easley K, Boparai N, Gramlich T. A randomized, double-blind controlled trial of interferon alpha-2b and ribavirin vs. interferon alpha-2b and amantadine for treatment of chronic hepatitis C non-responder to interferon monotherapy. *J Hepatol.* 2001 Jan;34(1):128:33.
- Younossi ZM. Chronic liver disease and health-related quality of life. *Gastroenterology.* 2001 Jan;120(1):305-7.
- Falck-Ytter Y, Younossi ZM, Marchesini G, McCullough A. Clinical Features and Natural History of Nonalcoholic Steatosis Syndromes. *Seminars in Liver Disease* 2001. Vol. 21, No.1: 17-26.
- Shermock KM, Temple ME, Younossi ZM. A pharmacoeconomic appraisal of therapies for hepatitis B and C. *Expert Opinion on Pharmacotherapy.* 2001 February Vol. 2, No. 2:205-211.

Presentations

- American Association for the Study of Liver Diseases, Clinical Update in Hepatology, Marina del Rey, CA: Non-Alcoholic Steatohepatitis.

Chemoembolization (CE), an interventional radiology technique that was refined in the early 1980's, has proven beneficial in selected patients with hepatic malignancy. CE can produce significant increases in survival in patients with HCC who have adequate hepatic reserve. Chemoembolization combines the cytotoxic effects of high dose regional chemotherapy with devascularization of the tumor bed to provoke tissue ischemia and prolong the dwell time of the chemotherapy. To date, CE has not been proven effective for CRC, although early studies have suggested some benefit. Chemoembolization carries a 30-day morbidity and mortality of approximately five and one percent, respectively.

The future of liver cancer therapy appears to lie with combination therapies. Radiofrequency ablation can help convert patients to surgical

candidates, or it can offer an effective palliative effect with minimal patient risk or discomfort.

Chemoembolization has proven useful as a bridge to transplantation in patients with HCC, and CE has been combined with RFA to create larger zones of thermal necrosis. Other methods of depositing energy into the tumor bed are being tested, including high intensity focused ultrasound (HIFU), microwave, laser and radioactive microspheres.

At Inova Fairfax Hospital, we have developed a multidisciplinary model for patient assessment and therapy. Patients can be scheduled by calling interventional radiology at 703-698-3241 or Inova Transplant Center at 703-698-2986.

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, 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

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