New Liver Transplant Director To Expand Program

James B. Piper, MD
Surgical Director
Liver Transplant Program

Transplant surgeon James B. Piper, MD, is the new surgical director of the liver transplantation program at Inova Fairfax Hospital. In this role, Dr. Piper will grow and expand the hospital's liver transplant program and use new technology and novel approaches for treating children and adults.

Dr. Piper will oversee the implementation of a split-liver transplant program and living-donor liver transplantation for children and adults. He also will focus on new approaches for treating previously inoperable cancers and tumors of the liver.

Dr. Piper is a widely published expert in liver transplantation and a frequent speaker at conferences. Prior to coming to Inova, Dr. Piper oversaw the largest worldwide pediatric liver program at the University of Chicago. In addition, he served in directing roles of the liver transplant programs at New York Medical College in Valhalla, NY, and Louisiana State University Medical Center-Shreveport.

His educational background includes a bachelor's degree from Creighton University in Omaha, NE, and a doctor of medicine degree from the University of Iowa College of Medicine.

Dr. Piper can be reached at **703-970-3229**.

RESEARCH PROTOCOLS

The following protocols are open for enrollment at the Center for Liver Diseases at Inova Fairfax Hospital:

- 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.
- Pegylated Interferon Alfa 2a (PEGASYS) alone or in combination with Ribavirin for chronic hepatitis C.
- Procrit and Growth Factors for treatment of anemia in patients with hepatitis C on Ribavirin/PEG-IFN.
- Adefovir Dipivoxil for the treatment of hepatitis B.
- Emtricitabine for chronic hepatitis B.
- Epidemiology of hepatitis B in the United States.
- Non-Alcoholic Steatohepatitis: Epidemiologic and treatment protocol.
- The use of Interferon Gamma-1B as an anti-fibrotic agent in Hepatitis C.
- Pegylated interferon with or without Thymosin Alpha 1 for chronic hepatitis C.
- Lamivudine with or without monoclond HBV antibody for chronic hepatitis B.

For patient screening or additional information, please call the Center for Liver Diseases at **703-698-3182**, or fax **703-698-3481**.

Publications and Presentations

- J Ong, Z Younossi, V Reddy, LL Price, T Gramlich, J Mayes, N Boparai. Cryptogenic Cirrhosis and Posttransplantation Nonalcoholic Fatty Liver Disease. *Liver Transplantation*, 2001 7(9): 797-801.
- J Ong, Z Younossi, C Speer, A Olano, T Gramlich, N Boparai. Chronic Hepatitis C and Superimprosed Nonalcoholic Fatty Liver Disease. *Liver 2001* 21: 266-271.
- Z Younossi, N Boparai, L Price, M Kiwi, M McCormick, G Guyatt. Health-Related Quality of Life in Chronic Liver Disease: The Impact of Type and Severity of Disease. *The American Journal of Gastroenterology* 2001 96(7): 2199-2205.
- P Mendez, K Saeian, R Reddy, Z Younossi, F Kerdel, S Badalamenti, L Jeffers, E Schiff. Hepatitis C, Cryoglobulinemia, and Cutaneous Vasculitis Associated with Unusual and Serious Manifestations. *The American Journal of Gastroenterology* 2001 96(8): 2489-2493.

Hepatitis C Support Group

Oct 15-21 is National Hepatitis Awareness Week. The Center for Liver Diseases at Inova Fairfax Hospital and The Greater Washington, DC, Chapter of the American Liver Foundation announce a Hepatitis C Support Group. The first meeting will be held Tuesday, Oct. 23, at 7:30 p.m. at Inova Fairfax Hospital, in conference rooms D, E and F.

Attendees will hear presentations from top local physicians, hepatologists, and other health care workers experienced with the care of patients with HCV. Patients are encouraged to discuss issues that are important and enjoy refreshments. All are welcome. For more information, please call **202-872-6600**, or e-mail **alfdc@starpower.net**.

The American Liver Foundation is the only national, voluntary non-profit health agency dedicated to preventing, treating and curing hepatitis and all liver diseases through research, education and support groups.

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

Liver Update is published by the Center for Liver Diseases and 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

INOVA FAIRFAX HOSPITAL

Liver Update

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

Recent Advances in Liver Transplantation

James B. Piper, MD
Surgical Director, Liver Transplant Program

Since 1988, there has been a rapid increase in both the number of centers performing liver transplantation and the number of patients being transplanted, with more than 3000 recipients receiving livers in 131 centers last year in the United States. This dramatic increase is in large part due to the improving results seen following liver transplantation, and has resulted in a tripling of the number of patients on the waiting list.

Despite this increase in demand, the number of cadaveric donors has remained stagnant over a similar time period. Consequently, there has been an increasing organ donor shortage with an alarming increase in the number of patients dying while awaiting transplantation. Unfortunately, no adequate solutions have been identified which could potentially eliminate this severe shortage.

Due to the disparity between the epidemiology of liver disease and the conditions causing brain death in children, the pediatric population has historically been the most disadvantaged in competing for the limited number of organs available. According to national health statistics data, 55 percent of the children born with liver disease will die before their second birthday, if not transplanted. Full-size liver transplants can only be used in recipients who are within 20-30 percent of the donor's weight, and unfortunately, the pediatric population produces very few organ donors. These factors historically have resulted in higher pre-transplant mortality rates in children than were seen in adult patients. This shortage prompted many surgeons to develop mechanisms by which small children could be transplanted using organs from larger livers.

The surgical reduction of cadaveric grafts for use in children was first reported in 1984 by Bismuth and Broelsch. This technique rapidly proliferated throughout the world and resulted in a dramatic decrease in the pre-transplant mortality rate for children, compared with centers not using this technique. Critics of this procedure argued that graft reduction simply redistributed organs that would otherwise be utilized in larger individuals, suggesting that this would lead to a further increase in the organ donor shortage for adults.

Reduced size liver transplants were also considered to be "experimental" and less effective than full size grafts. This assumption was later proven inaccurate, as children less than one year of age have been shown to have improved survivals using reduced

see ADVANCES, page 2

INOVA® FAIRFAX HOSPITAL

FALL 2001

ADVANCES, from page 1

size techniques compared to children receiving full sized organs, and older children's survivals appear to be similar whether a reduced size or full size graft is used. With increased experience in this technique, reduced size liver transplantation has now become the standard of care at most major pediatric liver transplant centers worldwide.

The first large series of split liver transplants was reported by Broelsch at the University of Chicago in 1989 and then again by Emond in 1990. Split liver transplantation was exciting, as this was the first operation ever performed that created new organs that otherwise would not have been available for transplantation. If successful, split liver transplantation could help alleviate the increasing organ donor shortage.

Unfortunately, our experience at the University of Chicago, encompassing 42 cases, concluded that graft and patient survivals were lower than similar control groups receiving full and reduced size grafts. Of great concern was that these decreased survivals appeared to be persistent throughout the entire series and did not improve with early technical advances. Split liver transplantation did serve a crucial role, however, in proving that two livers could be obtained from a single organ, thus paving the way for living donor liver transplantation.

Improvements in the technique of split liver transplantation, which were learned from the living donor experience, coupled with the worsening organs are shortage for adults, has revitalized interest in this technique. It has become clear that the morbidity associated with split liver transplant is higher than that seen from whole organ transplantation, but in the appropriate population this has yielded 90 percent patient survivals for both the right and left lobe transplants.

The technical feasibility of living donor liver transplantation was first described by Smith in 1969, but it was not for almost another 20 years until the first attempt at human transplantation was reported by Raia in Brazil. Although both of the recipients died from apparent medical complications, further supporting the technical feasibility of this exciting new procedure. Strong in Australia was the first to report a successful transplant using the left lobe of the child's mother. Broelsch, at the University of Chicago, was the first to report a full series of living donor liver transplants, where 22 grafts were transplanted into 20 recipients. The overall patient and graft survivals of this first series, 80 percent and 70 percent, were similar to that of other pediatric cadaveric series.

In a follow-up study from The University of Chicago, the techniques of living donor liver transplantation had been refined and a 94 percent one-year patient survival was reported. In Japan, cadaveric transplantation is nonexistent because of Japan's lack of brain death laws. Due to Japan's unique needs, Tanaka established a program at Kyoto University which has now become the largest living donor transplant experience in the world, with survival statistics similar to that seen in the recent University of Chicago series.

The organ donor shortage has continue to increase to a point where the adult population is now experiencing the same unacceptably high mortality rates that children were exposed to back in the 1980's. With the success seen in pediatric living donor liver transplantation, transplant surgeons began to question whether adults recipients could be successfully transplanted utilizing these same technique.

The initial experience at the University of Chicago showed that transplantation of patients who weighed more than 60 pounds, using the traditional left lobe grafts, produced survival rates below expectation. Recently, several papers have been published which describes the reasons for the lower survival rates. The left lobe of the liver represents only 40 percent, or less, of the hepatic parenchymal mass. We now know the survival of transplantation with less than 40 percent of the recipients ideal hepatic parenchymal mass results in poor outcomes. For this reason, adult transplantation utilizing the left lobe of the liver was not considered to be a good option for large children and adults awaiting liver transplantation.

The right lobe of the liver contains approximately 60 percent of the hepatic parenchymal mass. This represents sufficient parenchymal mass for the transplantation of adults, however there was a theoretic concern about the donor's risks from a 60 percent hepatectomy. For this reason, there were only a few scattered reports in the world's literature about right lobe living donor adult transplantation until recently.

As the donor shortage continued to worsen in United States, a renewed interest in the right lobe adult living donor liver transplantation began to surface. Over the past three years, approximately 200 of these procedures have been performed in the United States at an increasing number of transplant centers. The survival rates have been consistent with those seen in pediatric populations, however it does appear that the risks to the donor are greater. In United States, there has been at least two documented donor deaths, resulting in the American Society of Transplant Surgeons to issue a paper urging caution about the use of this revolutionary new procedure.

Despite the urge for caution, adult living donor liver transplantation seems to be one of the only ways available to the overcome this dramatic increase in pretransplant mortality, and therefore appears to be modality that will flourish in the foreseeable future.

Update on Chronic Hepatitis B

Janus P. Ong, MD
Advanced Hepatology Fellow

Chronic hepatitis B virus (HBV) infection is the most common cause of end-stage liver disease and hepatocellular carcinoma (HCC) in the world. Areas of the world with high endemicity include Africa and Asia, with prevalence rates of five to 20 percent. In the U.S., the prevalence of chronic hepatitis B is relatively low, estimated at 0.2 percent of the general population.

Routes of transmission vary between areas of low prevalence and those with high prevalence of chronic hepatitis B. In Africa and Asia, chronic hepatitis B is acquired in the perinatal period through vertical transmission or during childhood through close contact within families; while most of the cases in the U.S. are acquired in adulthood, generally through sexual contact and injection drug use.

FORMS OF CHRONIC HEPATITIS B

Chronic hepatitis B can be divided into two major forms: HBeAg positive and HBeAg negative. Chronic hepatitis B has been traditionally defined as the persistence of HBsAg, HBeAg, and HBV-DNA in serum. The spectrum of liver diseases in patients with HBeAg positive chronic hepatitis B range from those with mild liver disease to patients with end stage liver disease and HCC.

The natural history of this form of chronic hepatitis B is variable. Some patients seroconvert from HBeAg positive to antibody to HBeAg (anti-HBe). This event is often accompanied by normalization in serum aminotransferases and significant decreases in HBV-DNA often to levels not detectable by commercially available techniques. HBeAg seroconversion often marks the evolution from chronic hepatitis B to the so-called inactive carrier state. This transition is significant because the inactive carrier state is associated with normal serum aminotransferases and on liver biopsy, mild or no abnormalities. These patients are believed to have non-progressive liver disease and a decreased, albeit finite risk, for HCC.

There are however, some patients who after HBeAg seroconversion redevelop increased serum aminotransferases accompanied by increased HBV-DNA levels. These patients constitute the second form of chronic hepatitis B – HBeAg negative chronic hepatitis B – and are likely to have a variant of hepatitis B that has a mutation in the precore or core promoter region of the virus. This form of chronic hepatitis B is commonly seen in the southern part of Europe and Asia and less commonly in the U.S., although this is likely to change as demographics change with the influx of immigrants particularly from Asia. Both forms of chronic hepatitis B are alike in that both may progress to cirrhosis; however, they appear to be different with respect to rates of progression and response to treatment.

TESTING FOR HBV-DNA

As with other chronic viral infections, viral nucleic acid testing in blood is increasingly becoming an important part of the management of these patients. There are several commercially available assays for HBV-DNA that have varying limits of sensitivity, ranging from 102 for the polymerase chain reaction (PCR) based assays to 105 copies/ml and different ranges of linearity. This lack of standardization can lead to confusion, as ultrasensitive assays are now detecting the presence of HBV-DNA in patients who have traditionally been referred to as "inactive carriers" without apparent liver disease.

Most experts still believe that an HBV-DNA level of > 105 to 106 is considered significant and more likely to be associated with active viral replication and active liver disease. This would be within the limits of detection of most of the non-PCR assays. Efforts are now being undertaken to develop a standard for nucleic acid testing in chronic hepatitis B that will take into consideration the various HBV genotypes that have been recently described.

TREATMENT OF HEPATITIS B

Who to treat?

The treatment of chronic hepatitis B has for its goal the prevention of progression of liver disease by suppression of viral replication. Evidence from many studies have shown that patients who have active viral replication (HBV-DNA positive and/or HBeAg positive) and who have evidence of liver disease on biopsy are more likely to develop progressive liver disease. Therefore, treatment is generally recommended for the patient with (1) persistently abnormal serum aminotranferases who has (2) active viral replication and (3) evidence of chronic hepatitis on liver biopsy. At the present time, treatment of inactive carriers or of patients with normal serum aminotransferases is not recommended.

What treatment to use?

Currently, there are two approved medications for the treatment of chronic hepatitis B – interferon (IFN) and lamivudine. IFN was approved in 1992 and was the only approved option until 1998. The usual regimen consists of five million units every day or 10 million units three times a week given subcutaneously for 16 weeks. In a meta-analysis of 15 randomized, controlled trials, HBeAg seroconversion was documented in about one- third of patients.

Long-term follow-up of patients who achieved HBeAg seroconversion showed improvement in survival

see UPDATE, page 4

UPDATE, from page 3

compared to patients who did not achieve seroconversion. HBeAg seroconversion may be accompanied by a transient rise in serum aminotransferases. Factors that have been shown to predict a favorable response include low HBV-DNA levels, high serum aminotransferases, and evidence of active liver disease on liver biopsy.

In patients with HBeAg negative chronic hepatitis B, the efficacy of IFN has been more difficult to assess primarily because of the heterogeneity of the patient populations and differences in the regimens used. Response in these studies has been defined as a sustained loss of detectable HBV-DNA accompanied by a persistently normal ALT. Response rates of up to 40 to 60 percent have been shown, but relapses are high, resulting in a sustained response rate of only about 15 to 25 percent.

The main drawbacks of IFN therapy are the adverse side effects, which may become intolerable to some patients. Because IFN can cause immunologic clearance of HBV infected hepatocytes, patients with advanced liver disease and cirrhosis can decompensate further with this form of treatment. Therefore, patients with advanced liver disease or at risk for decompensation should not be treated with IFN.

Lamivudine is a nucleoside analogue that inhibits HBV replication. Several large randomized clinical trials have shown it to be as effective in inducing HBeAg seroconversion as IFN in HBeAg positive patients. Discontinuation of lamivudine treatment in patients who do not achieve HBeAg seroconversion generally results in relapse with reappearance of HBV-DNA in serum. In patients with HBeAg negative chronic hepatitis B, lamivudine has also been shown to be highly effective in suppressing viral replication which is accompanied by improvements in liver histology. However, relapse is likewise very high after discontinuation of treatment.

Extended use of lamivudine was employed to address the issue of relapse after discontinuation of therapy. This strategy has been associated with the emergence of resistant strains of HBV and recurrence of liver disease at rates of 25 percent at one year, 50 percent at two years, and 75 percent at three years. The natural history of lamivudine resistant chronic hepatitis B and its management is currently not defined.

Other nucleoside/nucleotide analogues for HBV are currently in various phases of development. Adefovir dipivoxil is a promising agent that has completed phase III clinical trials. Aside from having potent antiviral activity, viral resistance has not been described and lamivudine-resistant strains of HBV have been shown to remain susceptible. Combination therapy with two or three nucleoside/nucleotide analogues is currently being evaluated.

SURVEILLANCE FOR HEPATOCELLULAR CARCINOMA IN CHRONIC HEPATITIS B

Among the complications of chronic hepatitis B, hepatocellular carcinoma (HCC) is one of the most feared. HCC often develops in patients with cirrhosis but has also been shown to appear in HBV patients who do not have cirrhosis, although at a lower rate than cirrhotics. Aside from cirrhosis, other risk factors for HCC include age, male sex, and a family history of HCC.

Among the therapies available for HCC, resection and liver transplantation are the only options that offer a chance for a cure. These therapeutic modalities are however only curative in the early stages when the lesions are small and extrahepatic spread is absent. Surveillance for HCC is therefore important in patients at risk. The optimal approach to HCC surveillance is not established. There are several lines of evidence that point to periodic alpha-fetoprotein testing with semi-annual or annual ultrasound examinations being sensitive in detecting early HCC.

LIVER TRANSPLANTATION IN HEPATITIS B

Liver transplantation is the only option for patients with end-stage liver disease related to chronic hepatitis B infection. Early results for transplantation for HBV were poor generally due to large numbers of delayed graft failures from recurrent HBV infection. With the advent of prophylactic regimens effective in preventing recurrence of HBV after transplantation, results are much more encouraging.

At the present time, standard practice in the U.S. includes the use of HBIg immunoprohylaxis given at the time of transplantation and then on a periodic basis. Recurrence of HBV varies with the regimen used and on the hepatitis B replicative status at the time of the transplant.

Drawbacks of this approach include the high cost and the potential side effects associated with the HBIg infusions. The availability of lamivudine has expanded the options for prophylaxis against HBV recurrence after transplantation. However the use of lamivudine alone, or in conjunction with other agents, is not yet established.

The management of patients who have recurrence of HBV in the allograft is more challenging. Lamivudine may be effective but viral resistance remains a major issue. The introduction of newer nucleoside analogues offers alternatives for therapy either as monotherapy or combination therapy in the future.