Combined Liver/Small Intestinal Transplantation in Children

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A small group of patients with intestinal failure will develop total parenteral nutrition (TPN) induced liver failure. The only therapeutic option that offers the potential for long-term survival is combined liver/small intestinal transplantation (LITX). Over the past 4 years, we have performed 5 LITX in 5 children. During this same time period, 6 other patients with TPN induced liver failure died awaiting transplantation (average 106 days; range 20-261). Donors were pretreated with antilymphocyte therapy & bowel prep (mechanical and antibiotics). The average cold ischemic time was 8 hours. All recipients received a composite graft of liver and small intestine only; arterialization of the graft was provided through an aortic conduit. The recipient portal vein was anastomosed end-to-side to the donor portal vein. Donor and recipient intestine were anastomosed proximally with the distal end of the donor bowel brought out as a terminal ileostomy. Immunosuppression consisted of induction therapy with OKT3 combined with cyclosporine and prednisone (n = 3) and FK506 (n = 1). One patient was converted to FK506. Infection prophylaxis consisted of acyclovir, immunoglobulin, and intravenous Amphotericin B. Three patients were able to discontinue TPN, 4, 5, and 15 weeks postoperatively. Histologic evidence of rejection was present in 3 patients precipitating the removal of the intestinal allograft in 1 patient and conversion to FK506 in another. In another patient necrotizing arteritis precipitated the removal of the small bowel allograft. There was no clinical evidence of graft vs. host disease in any of the patients nor has any patient developed a post transplant lymphoproliferative disorder. Motility studies were performed in 1 patient demonstrating normal migrating motor complexes. Survival of the 5 patients was 811, 390, 368, 80 and 7 days; 2 of the patients have died. Conclusion: Our experience with LITX demonstrates the relative safety and effectiveness of this procedure. The major obstacle to its application is a lack of suitable donors.

Intraoperative Peroral and Transapical Cholangioscopy

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1090 Intraoperative cholangioscopies and 14 transapical cholangioscopies were performed between 1975-1993. Most frequently (820 patients) cholangioscopy was performed for choledocholithiasis and for (708 patients) cholangitis. In the remaining patients we diagnosed: duct neoplasms, non-neoplastic obstructions, iatrogenic damages or bile duct cysts. The results of intraoperative cholangioscopy were compared to those of intraoperative cholangiography and ERCP. We observed that the effectiveness and sensitivity of cholangioscopy was higher as compared to radiological findings. Youngen index for the bile duct diseases in case of cholangioscopy ranged from 0.96 to 1.0, while in case of cholangiography or ERCP from 0.01 to 0.69. Peroral transapical cholangioscopy was performed after endoscopic papillotomy. The indication for the examination was suspected bile duct neoplasms and extrahepatic ducts obstruction. Obtained results recommend cholangioscopy as the most effective method in diagnosing bile duct diseases.

Clinical Results of the Rectosigmoid Surgery

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Surgical intervention in the middle or upper region of the rectum is technically difficult because of the anatomical inaccessibility of the site. We have developed a practical rectoscopic technique using a Bues’s transanal endoscopic microsurgery system, and applied this for 30 patients with 15 creeping adenomas, 14 rectal carcinomas and a rectal carcinoid. Performing such rectoscopic surgery is less aggressive than other procedures. In all cases, the postoperative course was unventful, with no complication and the patient was discharged at the latest on the eighth day after the operation.

This technique for rectoscopic surgery involves minimal intervention and short hospitalization.

Biliary Stones Lithotripsy, Comparison of Different Methods

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“Difficult” bile duct stones are defined those whose conventional endoscopic treatment is unable to clear them from the common bile duct. We have compared our experience on Electrohydraulic lithotripsy (EHL), External shock wave lithotripsy (ESWL), Alexandrite laser lithotripsy (ALL), Mechanical lithotripsy (ML) and solvent dissolution with MTBE.

42 patients with “difficult” bile stones were treated with these methods singularly or in combination, eventually with a percutaneous endoscopic approach and according to the availability of the methods. When all the methods failed to clear the stones from the bile ducts, a biliary endoprosthesis was inserted.

Results The first treatment for all the patients was as follows, after diagnostic ERC, EUS and nasobiliary drainage:

- MTLB 5 failure 3
- ML 16 failure 8
- EHL 9 (5 PTC) failure 2
- ALL 5 failure 4
- ESWL failure 2

Stones’ clearance was achieved in 38 pts. 4 pts had biliary endoprosthesis. No deaths were seen. Related complications were 1 after MTBE and 1 after ML. The patients with endoprosthesis are well after 2 years of follow-up.

Conclusions The results of the different methods depend on stones’ composition. EHL is the method with the significantly better results while ML results depend on technical problems.

Submucosal Fibrin Adhesion – Early Elective Endoscopic Therapy for Treatment of Ulcer Bleeding

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Submucosal Fibrin Adhesion (SFA) has proved an effective therapy for ulcer hemorrhage. Together with the concept of early elective endoscopy (that means close endoscopic follow-up and postadhesions until the stigmata have disappeared and the ulcerground is clean) it is more effective than thermal and sclerosing techniques. The aim at the initial bleeding is (1) the hemostasis, (2) additionally, a clear endoscopic improvement must be seen that means: the visible vessel thin, submucous clots around, ulcerground swollen. SFA does not induce tissue destruction, as histological examination shows. That’s why the new concept of early elective endoscopic therapy by postadhesions could be developed. Early elective endoscopy means: (1) close endoscopic follow-up and (2) postadhesions until the ulcer ground is clean. Our results in more than one thousand bleeding patients from 1987 to 1993 show low rates of relapse bleedings (<1%), of urgent surgery (<1%), or mortality related to the bleeding (1%). About 40% of the patients treated so far needed repeated application of fibrin glue, because of persisting stigmata, thus clearly indicating the high risk that a rebleeding occurs during the period of three days that follow a bleed. The frequency of postadhesions cannot be predicted. This way, a new concept of early elective endoscopy with prophylactic treatment of bleeding stigmata (esp. the visible vessel) has been established and has to be compared with the concept of early elective surgery.

Conclusion: SFA offers an effective, nonoperative treatment for ulcer hemorrhage, even for patients at high risk (high age, severe underlying diseases). Special care should be given to the purely technical details of handling the Duo-probe and the adhesive. Precondition, furthermore, is the strict maintenance of close endoscopic follow-up (daily) and postadhesions.

The VIDEO shows the technique, handling of probe and material, special examples of treatments, difficulties and pitfalls of the method, our results as a summary.
11 Use of PCR to Individually Tailor Interferon Dosage in Chronic Hepatitis C


Although interferon-α (IFN) is widely used in the treatment of chronic hepatitis, the optimal dosage remains to be defined. Given the high cost of IFN, it is desirable to use the lowest effective dose. This dose is probably variable from one patient to another. We therefore decided to study the feasibility of detecting HCV-RNA by PCR to individually tailor doses and to compare the response rate obtained with that of a standard dose schedule.

Patients with chronic hepatitis C were divided into two groups. All patients received 18 µIU/m 2 week in three doses for 6 weeks following by reduction to 9 µIU/week. For patients in group 1, the dose was maintained for the following 18 weeks. However, those patients who normalised transaminases with the higher dose but who relapsed later had their dose increased to 18 µIU/week again. For patients in group 2, PCR was performed monthly and the dose reduced every 2 months provided that serum HCV-RNA was negative. Dose reductions were to 4.5 µIU/week, then 3 µIU/week and finally 1.5 µIU/week. The study is ongoing and we report here the results after 6 months treatment.

Results: There were 22 patients in gp 1 and 28 patients in gp 2. Four patients were withdrawn before the end of 6 months period in gp 1 because of non-response and in gp 2, three patients were withdrawn for non-response and 1 for another cause of side-effects. At the start of therapy, ALT were similar in both groups (115 ± 25 vs 116 ± 15.54). At 6 months ALT levels were significantly reduced but with no difference between the 2 groups (45.5 ± 15.54 vs 27.5 ± 13.38). On an intention to treat basis ALT was normalised in 11/22 (50%) in gp 1 and 15/28 (53.6%) in gp 2. HCV-RNA was negative in 12/28 (43%) patients in gp 2. In group 1, at month 6, 15 patients (83%) were receiving 9 µIU/week and 3 patients (17%) 18 µIU/week. In gp 2, 5 patients (21%) were receiving 3 µIU/week. Of these, 4 (80%) were HCV-RNA negative 8 patients (33%) received 4.5 µIU/week (6 (75%) HCV-RNA negative), 7 patients (29%) received 9 µIU/week (2 (22%) HCV-RNA negative) and 4 patients (17%) received 18 µIU/week, none of whom were HCV-RNA negative.

Conclusions: This study shows that after an induction dose, it is possible to use PCR to individually tailor interferon dosage allowing the use of lower doses than currently recommended, without compromising response rates, thus allowing substantial economies. This study also shows that in responding patients the dose can usually be lowered, whilst in non-responders, increasing the dose above 9 µIU/week is not beneficial. There is significant variation between patients in the dose of IFN required.

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12 Human Lymphocyte Proliferative Response to the Hepatitis B Virus Pre-S1 Synthetic Antigen

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The course of hepatitis B virus (HBV) infection depends on the host's immune responses to the hepatitis B virus antigens. This is a very important component of mature virion and plays an essential role in virion attachment and assembly.

Pre-S1(20-49) antigen was analysed for its ability to stimulate peripheral blood mononuclear cells (PBMCs) from patients with chronic hepatitis B (HBV) infection. Patients were classified into high responders (HRS) and low responders (LRS). The HRS group had a significantly higher proliferative response to the Pre-S1 antigen than the LRS group. In addition, the HRS group had a significantly higher proliferative response to the Pre-S1 antigen than the LRS group.

PBMCs of the majority of patients after recovery from hepatitis B infection respond with significant proliferation to stimulation with Pre-S1.

Pre-S1-induced T-cell specific proliferation was not detectable in healthy individuals. Compared to the vigorous T-cell response to Pre-S1 antigen in convalescents, the T-cell responses of chronically infected and HBsAg-positive patients were significantly depressed. The proliferative responses to PHA and anti-CD3 MoAbs of PBMCs of CHB patients were significantly lower in comparison to the responses of PBMCs of convalescents and healthy individuals.

Proliferative responses of T-cells from CHB and HBsAg-positive patients to alloantigens in MLR were significantly diminished as compared to the response of cells from convalescents and from healthy control individuals.

Our data confirm the suggestion that unresponsiveness to the Pre-S1 antigen facilitates chronic hepatitis B infection and/or viral persistence.

13 Low Substitution Rate in Precore/Core Gene of Hepatitis B Virus in Asymptomatic Carriers

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Hepadna viruses are DNA viruses, but they replicate via a RNA intermediate. High substitution rate in nucleotide sequences of the hepatitis B virus precore/core gene has been found in patients with chronic hepatitis B virus infection, but a relatively lower evolution rate has also been reported. To investigate the accurate substitution rate of the hepatitis B virus precore/core gene, sera of 12 asymptomatic carriers from 4 families with clustered hepatitis B virus infection were analyzed by polymerase chain reaction and direct sequencing.

The diversities of precore/core nucleotide sequences in these asymptomatic carriers were 0.16% to 1.3% as compared with a prototype adr sequence. The diversities of nucleotide sequences of the precore/core gene among members from different families were from 0.1% to 0.4%. The diversities between mothers and children of the same family were only 0 to 0.16%. The substitution rate in nucleotide sequence of hepatitis B virus precore/core gene was estimated to be between 0 and 9.8 x 10^-5 per site per year with a median of 0.

We conclude that the evolution rate of hepatitis B virus precore/core gene in asymptomatic carriers could be as stable as those of DNA genomes.

14 Detection, Incidence and Prognostic Significance of Allograft CMV Infection Following Orthotopic Liver Transplantation

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CMV infection remains a serious complication after liver transplantation and its trigger function on acute and chronic rejection is discussed. The aim of the present study was to find the best method to detect CMV infection of the transplant, to determine its incidence and to examine its clinical relevance and prognostic significance.

A total of 294 specimen (biopsies and explants) from 60 orthotopic liver transplantation (OLTX) patients were examined by routine light microscopy, in situ hybridization (ISH), immunohistology (IH) and CMV-DNA PCR. 27 of the 294 specimen were examined by PCR following DNA extraction from snap-frozen material. The probability for a transplant to acquire CMV infection and its prognostic significance on patient survival was determined (Kaplan and Meier). In addition, the correlation between CMV infection and acute as well as chronic rejection was examined. The combination of ISH and IH revealed the highest number of CMV-positive biopsies (15%), with IH alone detecting 80% of them. In the subgroup examined by CMV-DNA PCR the detection of positivities was not increased. The probability for the transplant to acquire CMV-infection within the first year after transplantation is 40% with a peak of infections within the first 6 weeks after OLTX and a probability of 35%. From 27 rejection episodes in transplants with an early CMV-infection, 20 occurred before and 7 after CMV-infection indicating a trigger function of acute rejection on CMV-infection but not vice versa. Out of 25 transplants with an observation period greater than 60 days, 31% of grafts with CMV infection developed chronic rejection; whereas, none of 9 grafts without CMV infection did. Finally, patients with a CMV infection of the graft had a significantly reduced one-year survival rate (58%) compared to patients without graft CMV-infection (87%; p = 0.03), with cause of mortality mainly due to infectious complications. These data demonstrate the clinical importance and prognostic significance of the early detection of CMV infection.