RESULTS OF LIVER TRANSPLANTATION

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Orthotopic liver transplantation has become a standard mode of therapy for terminal liver disease *(Nakhleh et al., 1990)*. Liver transplantation services have expanded dramatically in recent years as indications for liver replacement have broadened, contraindications have diminished, and referrals to transplant centers have increased *(Gordon et al., 1990)*. Due to variety of factors, such as better initial selection of candidates for the procedure, refinements in the techniques of organ procurement and surgical grafting, the introduction of cyclosporine A, and improvements in the pre-and postoperative management of such patients, the life expectancy of patients undergoing OLT has increased considerably over the last several years *(Alder et al., 1988)*. Recent data regarding surviral show a 69.7% and 62.8% 1 and 5 year actuarial survival *[Gordon et al., 1986 (b)]*. The vast majority of the postoperative deaths have occurred within the first 2 postoperative months and are related primarily to sepsis *(Starzl et al., 1982)*. Rejection is also frequent albeit controllable problem after OLT *(Alder et al., 1988)*.

Liver transplantation for most forms of chronic liver disease is associated with a 15 to 30 per cent mortality in the first year, but longer term survival is excellent, and disease recurrence is rare. Important exceptions include transplantation for primary liver cancer, in which disease recurrence within 18 to 36 months is common, and for chronic active hepatitis B, in which reinfection is common but the outcome quite variable. Patient survival after liver transplantation [illegible] failure is excellent if patients are referred early enough and

are able to receive the transplant before systemic complications such as stage IV coma, renal failure, or metabolic acidosis occur *(Gordon et al., 1990)*. The incidence of malignant disease arising de novo after transplantation appears to be increased. The increased risk is especially true for lymphomas which appear to relate to Epstein-Barr virus infection *(O'Grady and Portmann, 1991)*.

*** Stratifying The Causes of Death**

Shaw et al., (1989) examined the causes of death of patients who underwent liver transplantation and stratified those causes into 4 categories:

1) Category 1 adult deaths, those directly related to the morbidity of patients prior to transplantation, occur more commonly in the patients with high risk scores. Category 1 deaths in both adults and children occur most commonly after 1 month but before 3 months following transplantation.

2) Category 2 deaths, those directly related to surgical or technical complications, are relatively rare (6 of 44 patients) and occur most commonly within one month of transplantation.

3) Category 3 deaths, those directly related to failures of immunosuppression to control allograft rejection, occur most commonly between 3 and 6 months after transplantation.

4) Category 4 deaths, those with unusual and often unpredicted causes, can occur at any interval after transplantation, and have been the only cause of death in children and adults 9 months or more after transplantation; they are the most frequent cause of death in adults with low risk scores.

In their study *Shaw et al., (1989)* estimated the risk score equation as follow:

- Encephalpathy score equals 0 for no history of encephalopathy, + 1 for

transplantation.

- Ascites score equals 0 for no ascites, + 1 for mild to moderate ascites, regardless of diuretic use, and + 2 for massive ascites not controlled with diuretics.

- Malnutrition score equals 0 for normal nutritional status, +1 for mild to moderate malnutrition, and +2 for severe malnutrition.

- Serum bilirubin score equals -1 for a serum bilirubin level less than 171 m mol/L.

- Age score equals +1 for patients greater than 40 years.

- Transfusion score equals +1 if operative blood loss is greater than 35 U of packed red blood cells.

- Coagulopathy score equals -1 for prothrombin time less than 15 seconds.

If the resultant score is greater than 5, substract 2 points if patients less than 25 years old and substract 1 point if the operative blood loss was less than 10 U of packed red blood cells.

The actuarial 1 year survival rates for patients who were prospectively scored as having high risk, medium risk and low risk of mortality following transplantation were 44.5%, 85% and 90.4% respectively ***(Shaw et al., 1989)***.

From their study ***Shaw et al., (1989)*** discovered the following: 1) The inexorable role of pretransplantation morbidity in influencing outcome in some patients, 2) The relatively minor role that surgical errors played in causing death, 3) The recognition that rejection and the morbidity associated with attempts to control recurrent episodes can have devastating results, and 4) The sheer variety of events that can cause the death of patients who otherwise appeared to have done well.

Shaw et al., (1989) were tempted to argue that timely intervention or compulsive evaluation of patient's history, signs, and symptoms may have

prevented death in category 4 deaths. Reduction in the number of deaths with category 3 causes is pimarily dependent on the development of new immunosuppressive agents. Sepsis, rather than allograft failure, was the primary cause of death in all of these patients, primarily because of an aggressive policy of retransplantation. Reduction in the number of deaths with category 2 has attended the development of a number of technical advances and in fact, to routinization of the procedure in a number of centers. Reducing mortality in the high-risk patients may be facilitated by better care and preparation of terminally ill patients prior to transplantation, and providing patients for liver transplantation at an earlier stage in their disease before they develop the variety of complications that make them unlikely to survive any surgical procedure.

The results of the study of ***Alder et al., (1988)*** suggested that patients with parenchymal liver diseases are at increased risk of early postoperative death after OLT because of bacterial and/or fungal infection, as compared with patients operated upon for cholestatic liver diseases.

From the study of ***Busuttil et al., (1987)*** at UCLA school of medicine, los Angeles, California; sixty-three of the 83 patients (76%) are alive (adults 72%, children 80%). The 1 and 2 year actuarial survival rate is 73% (adults 68%, children 78%). Thirty-eight of 43 patients (88%) who had transplantation in the past year are alive. Of 14 perioperative variables assessed as predictors of early mortality, only postoperative dialysis and presence of severe rejection had statistical signifcance. 70% of adults returned to work and 84% of children had normal or accelerated growth.

The actuarial survival at 1 year in the entire Birmingham series is more than 70% in primary biliary cirrhosis more than 5% in other chronic liver disease and acute liver failure, but less than 40% for malignancies. The results from Pittsburgh,

USA, reported actuarial survival of 74% at 1 year and 64% at 5 years after transplantation ***(Burra and Elias 1990)***.

Lastly, the impact of liver transplantation on hepatology is moving beyond the management of end-stage disease and the five year survival rates of 65% are beginning to influence views as to what is the best longterm treatment for patients with chronic liver disease at different stages of the disease process. Indeed, most patients with liver disease should be considered potential candidates for transplantation, and should not be subjected to procedures that might prejudice its outcome without consideration of the broader implications. Previous complex biliary tract surgery, or construction of vascular shunt greatly increases the difficulty of liver transplantation and, while in some patients these operations are lifesaving, in many instances it may be more prudent to proceed to early transplantation ***(O'Grady and Williams 1988)***.

Disease Recurrence

Many of the indications for transplantation have the potential to recur, albeit with substantial modification of the disease process ***(O'Grady and Portmann 1991)***.

The most obvious example is maligant disease and, apart from small hepatocellular carcinomas arising in cirrhotic livers, the risk is "substantial". Although the morphology of the tumour remains unchanged, the growth rate appears to be increased by a factor of up to five fold by immunosuppressive therapy but this effect is least marked in patients maintained on cyclosporine ***(O'Grady and Portmann 1991)***.

Reinfection with the hepatitis Bvirus is a major problem effecting morbidity and mortality after liver transplantation. Recurrence of viral infection is also potential risk after liver transplantation for hepatitis A acute liver failure and both

Acute and chronic liver disease after NANB hepatitis *(O'Grady and Portmann 1991)*.

The results of the study of *[Wright et al., 1992 (b)]* indicate an increased susceptibility to "recurrent autoimmune chronic hepatitis "characterized by piecemeal necrosis and a dense portal inflammatory infitrate. Moreover, the presense of any biliary tract lesion responsible for the histologic findings was excluded by cholangiography in each case at the time of the disease recurrence defined histologically. Moreover, these histological findings suggestive of recurrent autoimmune chronic active liver disease occurred in the absence of any evidence for viral hepatitis either before or after OLT.

About the recurrence of primary biliary cirrhosis, there is now general agreement that the immunological stigmata persist, especailly antimitochondrial antibodies and raised IgM in serum. Furthermore,it is clear that in some patients associated autoimmune conditions progress or develop de novo after transplantation. Evidence of primary biliary cirrhosis recurrenc was found in nine of 10 liver biopsies taken more than one year after transplantation *(Polson et al., 1989)*.

The precoagulant state which is a feature of the Budd-Chiari syndrome can lead to rethrombosis of the hepatic veins, although involvement of the hepatic artery or portal vein is more likely after transplantation *(O'Grady and Portmann 1991)*.

Quality of Life After OLT

In the past 20 years, liver transplantation has emerged as the treatment of choice for many symptomatic patients with acute and chronic liver disease. Now that an 80% 1-year survival rate is commonplace, and long-term surviaval beyond this is expected in many liver transplant recipients, patients and physicians have

begun to look beyond quantity of life to quality of life after transplantation *(Brown and Lucey, 1991)*.

In terms of psychiatric status, social and behavioral functioning and intelligence, patients surviving liver transplantaiton do not differ from levels defining the normal population. Most of these patients have returned to work full-fime and children have attended school. Thus, compared to their pretransplant state, they are remarkably improved and effectively have been transfered from a population of chronologically ill hospital-bound patients to that of normal working individual who are capable of enjoying and contributing to their own life and to the society at large *(Van Thiel et al., 1984)*.

From the study of *Busuttil et al., (1987)* seventy per cent of the discharged adults have returned to gain full employment and virtually complete rehabilitation to their premorbid condition. The remainder have shown significant improvement, without a single patient demonstrating regression. When growth and development were monitored in pediatric patients, 59-86% of the children demonstrated acceleration of weight, height, or weight-for height ratio.

Moreover, ***Brown and Lucey (1991)*** stated that :

a) menstruation returns in concert with restored hepatic function, and b) Pregnancy is possible and relatively safe after liver transplantation. Indeed, liver transplantation can sustain the life of mother and fetus even in the extreme circumstances of decompensated liver failure during pregnancy.

Retransplantation

There are many causes of posttransplantation liver dysfunction of which primary non function, immunologic rejection, and technical difficulties relating to the surgery can result in need for retransplantation ***(Pimstone et al., 1990)***.

In Pittsburgh experience, the need for retransplantation is about 20 to 25% of liver recipients ***(Shaw et al., 1985)***. The incidence of retransplantation at UCLA is 20% ***(Busuttil et al., 1987)***.

The overall patient survival rates of 55% at 2 months and 46% at 6 months after a second OLT and the actuarial survival of 43% at 1 year and 35% at 4 years clearly document that the initial 6 months postoperative period and specifically the first 2 months after retransplantation constitute the period of highest risk for mortality for patients undergoing a second OLT. With regard to the cause of first graft failure, the greatest second-graft survival rate was achieved by patients in the chronic rejection group (65%). The group with the poorest second graft survival rate consisted of those patients with ischemic injury (23%) as the cause of the failure of their first gaft. No significant difference for second-graft 6 months survival was evident for patients in the different disease groups used to classify the original liver disease cholestatic liver diseases (CHLD) 44%, parenchymatous liver diseases (PLD) 48%, fulminant hepatic failure (FHF) 50%, neoplastic liver diseses (NLD) 50%, and miscelaneous liver diseases (MIS) 37%). Among patients with PLD, those with HBV=induced cirrhosis showed a signinficontly poorer 6 mo survival (16.6%) than did all remaining groups (57.8%) ***(Quiroga et al., 1991)***.

Advanced age and an excessive requirement for blood and blood products at the time of the first OLT appears to represent a risk factor for early death after a second OLT ***(Quiroga et al., 1991)***.