## *Editorial*

# Liver Transplantation in Children

Pediatric liver transplantation (LT) is now routine treatment for children dying of end stage liver failure in developed countries(1). The indications for transplantation include acute and chronic liver failure, inherited metabolic liver disease and unresectable hepatic tumors. The major indication worldwide is children with biliary atresia who have had an unsuccessful Kasai porto-enterostomy, accounting for 76% of children transplanted under the age of 2 years in Europe and America(2). Fulminant hepatic failure secondary to viral hepatitis or poisoning is the main indication for acute liver failure(3).

The dramatic increase in the survival rate throughout the 1990's in most International Centers has been sustained with most reporting one year actuarial survival rates of >90% in elective patients and >70% in acute liver failure. Long term survival figures for 10-15 years are >80%(1-3). Many elements have contributed to the improved survival following liver transplantation. These include improved pre-operative management such as the treatment of hepatic complications and the importance of intensive nutritional support(4). Development of better preservative solutions and surgical techniques, such as reduction hepatectomy, split liver transplantation and the introduction of living related liver transplantation, has extended liver transplantation to infants under the age of one year and weighing less than 10 kg, effectively reducing the waiting list mortality from 25% to 5%(5-7). Surgical complications have reduced, but sepsis and rejection remain significant issues.

The development of effective methods of diagnosis, prophylaxis and treatment of Cytomegalovirus (CMV) with ganciclovir or valganciclvir means that this is no longer a significant cause of mortality but morbidity remains high. In contrast, the absence of specific therapy for Ebstein Barr virus (EBV), means that infection rates are high in those children who are EBV negative pre transplant, but pre-emptive reduction of immunosuppression in response to rising EBV titres is usually effective as is treatment with rituximab or adoptive T cell therapy(9,10).

Furthermore, the incidence of acute and chronic rejection has fallen following advances in immunosuppression with drugs, which are more easily absorbed such as cyclosporin microemulsion (Neoral) or more potent such as Tacrolimus(11,12). The use of induction immunosuppression with monoclonal antibodies (IL-2 inhibitors) such as daclizumab, a humanised antibody and basiliximab, a chimeric antibody(13) and maintenance immunosuppression with renal sparing drugs such as mycophenolate mofetil or Sirolimus (Rapamycin) may reduce long-term renal dysfunction(14,15).

A more recent approach is the development of steroid free immunosuppressive regimes(16), which reduce hypertension, stunting and the cosmetic side effects of steroid therapy and appear effective in the short term but may be associated with an increase in the development of de-novo autoimmune hepatitis in 2-3% of children(17). This unusual disorder is associated with an increasing incidence of non-specific autoantibodies (ANA, SMA and rarely LKM), graft hepatitis and elevated immunoglobulins and may be related to the progressive development of graft hepatitis with

fibrosis, recently reported from Birmingham which might limit graft function in time(18).

As long term survival increases, attention has now focused on the quality of life achieved by children undergoing transplantation. Long term studies in children and adolescents have demonstrated the nutritional and endocrine rehabilitation achieved following successful liver transplantation(19). Although there is clear maintenance of psychosocial development both physically and intellectually (19,20), recent studies suggest that there may be deficits in cognitive functioning which may be related to long-term immunosuppression (22).

The success of pediatric liver transplantation in developed countries has increased the awareness and highlighted the need for such procedures in the developing world(23). Given that liver transplantation is performed in two to three children per million in the West, between two to three thousand children would require liver transplantation in India every year, as the indications are similar. It as been seven years since the first successful pediatric liver transplant was performed in India in 1998(24). Thirteen transplants have been performed at the Apollo center, New Delhi of which 8 have been successful. Another 16 transplants have been performed at 6 other centers. The longest follow up is 7 years and the first successful recipient is leading a normal life and attending regular school. Continuous advancement has been witnessed in the past few years, with improved training of medical staff and development of specialized multidisciplinary teams following strict protocols.

As there is a tremendous need in India, efforts need to be made to increase the availability of liver transplantation. There still is a lack of awareness on existing liver transplant facilities in India even within the medical fraternity. Late referrals further diminish the chance of survival. Although the cost of liver transplantation in India is less than one fourth to one third of that in the US, cost definitely is an issue for most families. Furthermore, cultural barriers with a bias towards the girl child and clear male predominance in patients undergoing the procedure are problems that still exist. A big challenge is the scarcity of cadaveric donors in India. Therefore, living related liver transplantation is currently the only realistic option. Awareness of this modality, development of a cadaver program, indigenous production of consumables and immunosuppressive agents will hopefully, help in firmly establishing liver transplantation in India.

**D.A. Kelly,**
*Professor of Pediatric Hepatology,*
*Birmingham Children's Hospital,*
*Birmingham B4 6NH, and*
*University of Birmingham,*
*Edgbaston, Birmingham, England*
*and*
**Anupam Sibal,**
*Consultant Pediatric Gastroenterologist*
*and Hepatologist,*
*Apollo Center for Advanced Pediatrics,*
*Indraprastha Apollo Hospitals,*
*New Delhi 110 076, India.*
*E-mail: anupamsibal@apollohospitals.com*

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