Small bowel transplantation in children

Small bowel transplantation is no longer experimental, but is now a well established option for children with complications related to intestinal failure. Advances in surgical techniques along with the availability and a better understanding of immunosuppressive drugs have, in the last decade, resulted in a greatly improved outcome.

Intestinal transplantation (ITx) as a treatment for infants and children with intestinal failure (IF) has come of age. Replacement therapy for organ failure of other organs such as kidney, liver and heart were successfully developed during the 1960s but did not reach widespread clinical application until the cyclosporin era of immune suppression in the early 1980s (Reyes et al, 2002).

ITx lagged behind as the intestine was found to be an organ with special problems of its own immunogenicity, which was marked and persistent; its interface with the enteric lumen was colonized with bacteria and there was transfer of a heavy load of the donor's immune cells at the time of engraftment (Reyes et al, 2002). In addition, organ preservation was more fragile than in other transplantations, and consequences of ischaemic reperfusion injury more severe. At the same time, treatment of IF with parenteral nutrition (PN) had developed to give many patients with IF a reasonable quality of life, although central venous line complications of sepsis, venous thrombosis and PN-associated liver disease emphasized that a lifetime on PN was not a cure (Gupte et al, 2006).

Sporadic cases of ITx were reported in the 1970s but all recipients died of technical complications, sepsis or rejection. Optimism of success in the cyclosporin era was short-lived as most grafts were lost to rejection. A total of 15 cases were reported between 1985 and 1990 using cyclosporin immune suppression, but graft survival in these cases ranged from 10 days to 49 months. The 'liver effect' of immune protection was highlighted by Grant et al's report in 1990 of an adult transplant patient receiving a combined liver and intestinal graft surviving long term on full enteral nutrition (Grant et al, 2005). One child from the cyclosporin era, who received a neonatal donor intestine, is still alive 19 years post transplant. However, the introduction of more effective tacrolimus immune suppression by Starzl in 1990 allowed for reports of 60% 1-year graft survival by 1993. Current 1-year survival of 90% is being reported from some centres as a result of modifications in immune suppression, better surgical techniques, and improved post-transplant management and monitoring of the infectious consequences of immune suppression (Grant et al, 2005).

PN remains the current standard of care for infants and children with IF with a 1-year survival of 90% and 5-year survival of 75% (Gupte et al, 2006). The main causes of IF in the paediatric age group are short bowel, dysmotility syndromes and congenital diarrhoeal disease (*Table 1*).

Indications, contraindications and types of transplant

Indications for consideration for transplant assessment are IF and the potentially lethal complications of PN, namely loss of central venous access from thrombosis of central veins and PN-induced cholestasis, which can rapidly progress to established irreversible liver disease, otherwise termed IF-associated liver disease (IFALD) (Kaufman et al, 2001). In the case of the latter a combined intestinal and liver transplant would be indicated.

There are few contraindications but complete loss of venous access and untreated immune deficiency syndromes because of the risk of unrestrained graft *vs* host disease are considered absolute. Relative contraindications would be the degree of other systemic co-morbidities (Kaufman et al, 2001). There is no lower age or size limit and a history of multiple previous laparotomies is not a contraindication, although both may carry a waiting list mortality risk of nearly 50% in the <10 kg size recipients because of the national shortage of size-matched donors. According to UK Transplant figures, the numbers of paediatric donors in the UK has decreased over the last 5 years from over 75 per year to the current figure of 25 in 2005/06.

Patients with short bowel syndrome who are thought to have the potential to achieve independent enteral tolerance through intestinal adaptation and/or concom-

Table 1. Causes of intestinal failure

Short bowel syndrome	Gastroschisis (atresia and dysmotility)
	Necrotizing enterocolitis
	Intestinal atresia
	Mid-gut volvulus
Dysmotility	Intestinal aganglionosis
	Intestinal pseudo-obstruction
	Degenerative intestinal leiomyopathy
	Megacystis microcolon hypoperistalsis syndrome
Congenital diarrhoeal disease	Microvillous inclusion disease
	Tufting enteropathy

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mitant non-transplant surgery (closure of stomas, intestinal plication and lengthening procedures, with motility having priority over length) and who develop irreversible IFALD, would be considered for isolated liver transplant in the expectation that the adaptation process would be facilitated by replacement of a severely diseased liver with a healthy organ, which at the same time relieves consequences of portal hypertension (Botha et al, 2006).

Figure 1. Isolated bowel transplantation in children with mild or no liver disease.

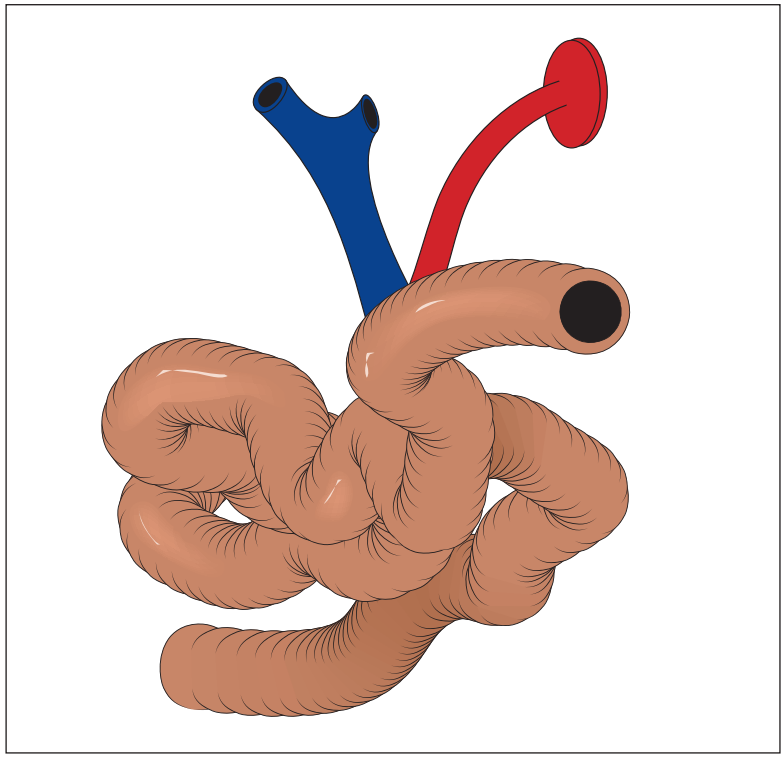
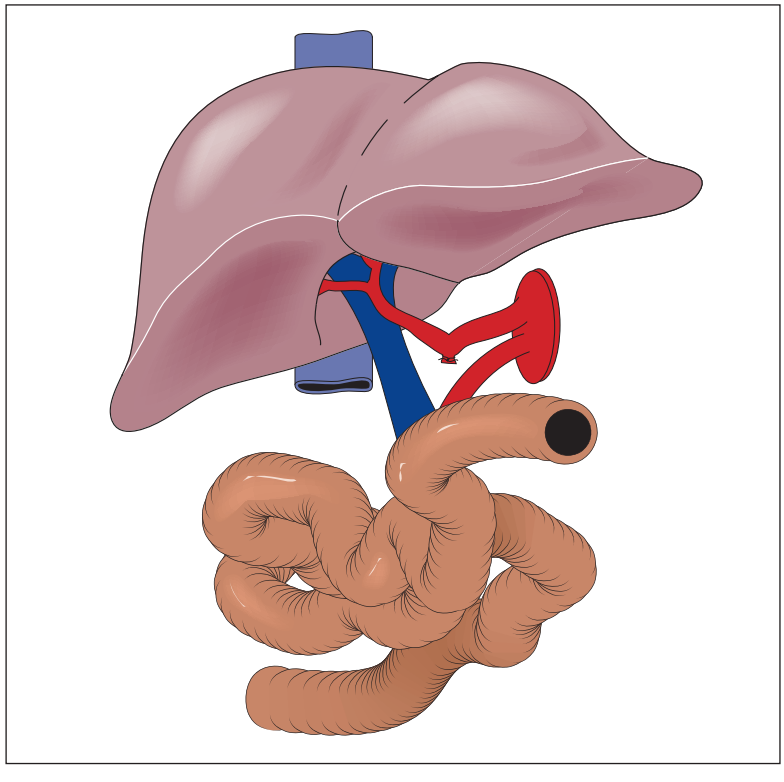


Figure 2. Combined liver and bowel transplantation in children with moderate or severe liver disease.



The pre-transplant workup for ITx is the same as other solid organ transplants with focus on the preservation of central venous access patency and adequacy of function of residual foregut and documentation of urinary tract anatomy in dysmotility syndromes.

The ideal donor would be that of a stable cadaveric heart-beating donor (preferably cytomegalovirus (CMV) and Epstein–Barr virus (EBV) negative) 20% smaller than the recipient. However, because of the shortage of donors of suitable size novel techniques have been developed to either increase the size of the recipient abdomen and/or reduce the size of the graft by back-table excision of donor intestine and liver in the case of combined transplants.

Types of transplant procedures

Isolated intestine for minimal or mild liver disease and impaired venous access (Sudan et al, 2000) (*Figure 1*):

- Segmental or full-length small intestine
- Living related segmental small intestine
- Small bowel and colon.

Liver and intestine for moderate to severe liver disease with evidence of significant portal hypertension (Sudan et al, 2001) (*Figure 2*):

- 'Classical' separate liver and intestine
- 'En bloc' liver, bile ducts, duodenum, head of pancreas and intestine in continuity as a composite graft whole or reduced.

Multivisceral transplantation, which includes liver and intestine with an additional organ, i.e. whole pancreas, stomach and/or kidney (Kato et al, 2002) (*Figures 3* and *4*). There is a considerable debate about the exact definition of multivisceral transplant within the small bowel transplant community, but the above definition seems to be acceptable.

Techniques of transplantation

The procurement operation is a complex procedure requiring a separate team of experienced transplant surgeons. The donor is given antibiotic and antifungal agents enterally by nasogastric tube as selective gut decontamination along with standard intravenous antibiotic prophylaxis. The graft must be handled with great care with in-situ cold flush and storage using the University of Wisconsin preservation solution. The donor organs, usually having been procured en bloc with the arteries of supply intact up to the thoracic aorta, are further prepared on the back table. The hepatoduodenal-pancreas organ cluster is kept intact although the liver may be appropriately reduced in size as required. It is advisable to keep the cold ischaemic time to less than 8 hours. Both stomach and colon may be included in the graft.

The recipient operation may be challenging as there is frequently a history of multiple previous surgeries leading to dense vascularized adhesions from por-

tal hypertension. Details of the procedures are well described but in principle the foregut portal circulation is decompressed with a porto-caval shunt (Sudan et al, 2001). The diseased viscera are removed and the appropriate graft is then sutured in situ. It is acceptable for the venous drainage to be to the inferior vena cava in isolated intestinal transplants. In multivisceral transplants the 'clean sweep' operation may be performed whereby all the abdominal contents anterior to the main vessels are removed from the gastric body to the distal colon, including the duodenum, pancreas, spleen and rest of intestine (Kato et al, 2002).

The proximal anastomosis may be a gastro-jejunostomy or jejuno-jejunostomy in continuity. The distal bowel continuity is restored by end-to-end anastomosis with a proximal venting stoma, which is used for biopsy access in the post-transplant period or the distal end may be brought out as an end stoma.

Stomas may be closed some time after the original engraftment when the graft has 'settled in' immunologically speaking. This is usually not considered until after the first year post-transplant with a stable graft in the absence of rejection.

Medical and surgical complications

Graft rejection

The patient is treated with immunosuppressive medication to prevent rejection of the graft. Most regimens currently include induction with an antilymphocyte immunoglobulin along with steroids and tacrolimus. The health of the graft must be maintained for mucosal integrity as a defence against bacterial invasion and translocation into the circulation. Rejection usually occurs within the first few weeks after transplantation. Clinical features of rejection can be variable and cannot be easily distinguished from that of viral enteritis.

Figure 4. Multivisceral transplant including stomach.

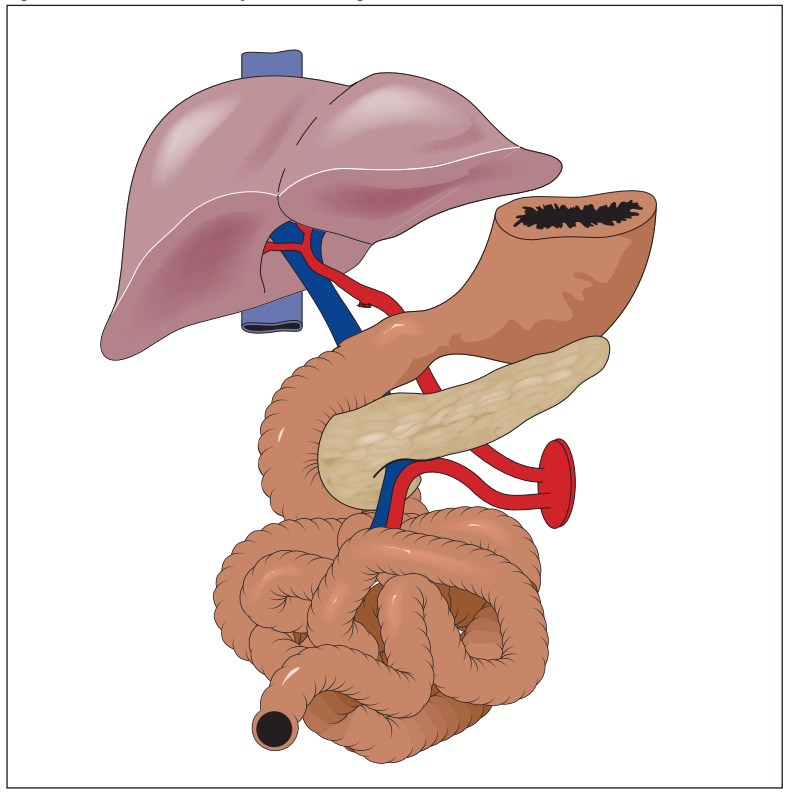


Figure 3. Multivisceral transplant.

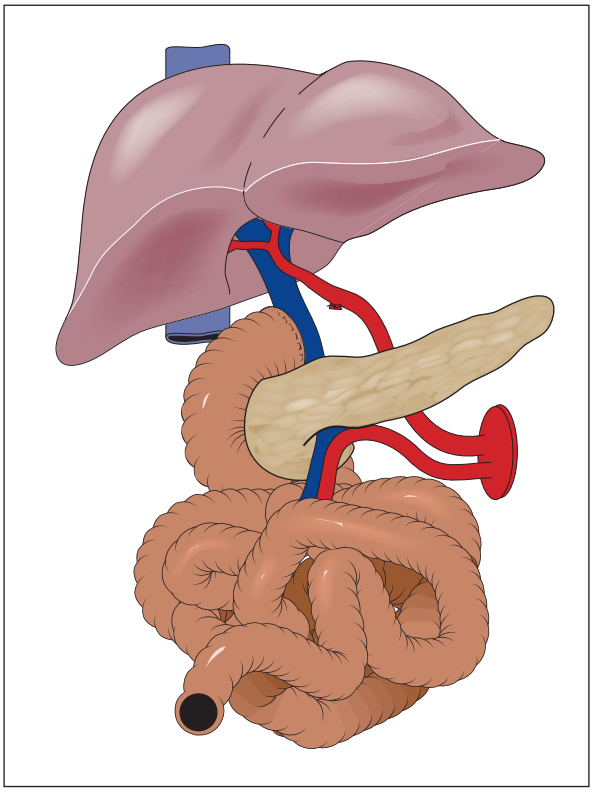
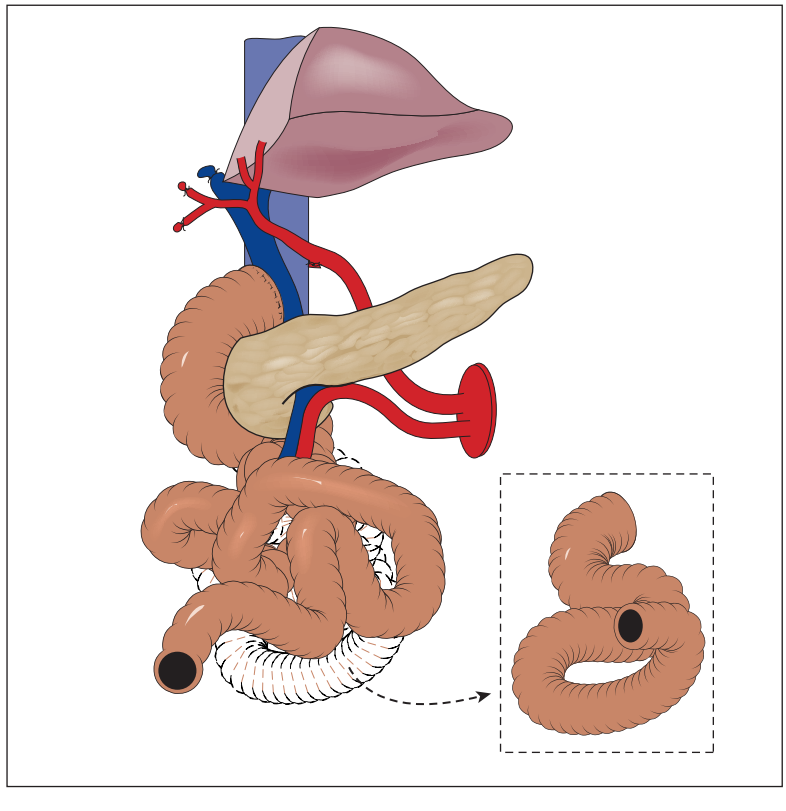


Figure 5. Reduced liver and bowel transplant.



There are currently no reliable non-invasive markers of rejection. Serum citrulline, a marker of mucosal mass, has shown some promise; however, the differentiation between rejection and infection can make the levels difficult to interpret (Pappas et al, 2002). The diagnosis of rejection is made on histopathological examination of graft tissue from endoscopic biopsies. It is usually graded as mild, moderate or severe (Lee et al, 1996). Mild or moderate rejection is treated by optimizing the immunosuppression and with pulse doses of intravenous methylprednisolone (10–20 mg/kg to a maximum of 400 mg). Severe rejection, characterized by diffuse ulcerations and denuded mucosa throughout the graft, is notoriously difficult to treat and is associated with a poor prognosis. Treatment strategies with OKT3, thymoglobulin and recently infliximab (anti-tumour necrosis factor (TNF) alpha monoclonal antibody) have been tried with variable success (Fishbein, 2004).

In the last decade, the introduction of induction agents like interleukin-2 (IL-2) blockers, campath (anti CD52) and thymoglobulin has decreased the incidence of acute rejection within the first few weeks following ITx. This is reflected in reported improved survival from major intestinal transplant centres in the USA.

Infection

The intestinal transplant registry records infection as a significant factor accounting for 60–70% of deaths (Grant et al, 2005). The high incidence of bacterial infections is likely to be the result of bacterial translocation occurring across a compromised intestinal mucosal barrier because of reperfusion injury, disruption of the lymphocytes, rejection and potent immunosuppressive agents (Reyes et al, 2002). Broad spectrum antibiotics are routinely administered during the postoperative period along with selective decontamination of the gut with oral antibiotics and antifungal agents.

Post-transplant infectious enteritis, CMV and EBV related post-transplant lymphoproliferative disease (PTLD) can lead to significant morbidity in the context of heavy immunosuppression. Infectious enteritis is noted in 39% of the population following intestinal transplantation with viruses (adenovirus, rotavirus and calcivirus) and protozoa (*Giardia lamblia*, cryptosporidium) (Ziring et al, 2005). The prompt recognition of infectious enteritis can be difficult as the clinicopathological picture can mimic acute rejection and hence it is important to make the distinction. The treatments are diametrically opposite – one requiring increased immune suppression (rejection) and the other reduced immune suppression (infection). Rotavirus and adenovirus enteritis can trigger episodes of acute rejection and can result in graft loss (Ziring et al, 2005).

CMV infection and EBV-related PTLD are seen more commonly in the paediatric intestinal transplant population in the setting of seropositive donor to seronegative recipient and owing to the high intensity of immunosuppression used. Different tests (antigenaemia, viral load) are used to make the diagnosis of CMV infection and can be effectively treated with intravenous gancyclovir. The incidence of PTLD following intestinal transplantation was historically reported to be as high as 30–40%. A confirmed diagnosis of EBV-related PTLD needs histopathological examination of affected tissue. EBV viral load measured by polymerase chain reaction (PCR) is helpful to indicate ongoing EBV viraemia, but does not confirm the diagnosis of PTLD (Green et al, 2000).

In children, presentation with recurrent infections, hypoalbuminaemia, anaemia, thrombocytopenia and neutropenia should alert the physician to perform investigations to exclude PTLD. Imaging of the abdomen and the chest for lymphadenopathy may be necessary to arrive at the diagnosis. Endoscopic procedures, along with EBV in situ hybridization staining of gut biopsies, may be necessary to confirm the diagnosis in children without lymphadenopathy. Pre-emptive reduction of immunosuppression in the context of EBV viraemia has been demonstrated to prevent the progression to PTLD (Reyes et al, 2002). With the advent of EBV PCR monitoring and pre-emptive reduction of immunosuppression, there has been a considerable improvement in the outcome of PTLD (Grant et al, 2005).

Graft *vs* host disease

Despite the high lymphocyte load within the intestine, the incidence of graft *vs* host disease has been reported from the largest single centre experience to be 8.5%. This is less of a problem than expected (Mazariegos et al, 2004). Optimization of tacrolimus immunosuppression and steroid administration is the treatment of choice and usually leads to a favourable outcome.

Surgical complications

Intestinal perforation, seen in up to 40% of cases, usually occurs within the first 2 postoperative weeks following ITx and is notoriously difficult to manage (Reyes et al, 2002). The symptoms and signs of acute peritonitis can be masked as the children are on high dose steroids thus requiring a high index of suspicion. Abdominal imaging and contrast studies may be needed to confirm the diagnosis. Surgical control of the perforation either by primary closure or by insertion of a T tube into the perforation to create a controlled fistula is mandatory.

Other complications such as adhesive obstruction, pancreatitis, development of biliary sludge with partial obstruction and wound and stomal issues are frequent but can be successfully managed (Abu-Elmagd et al, 2001). Abdominal compartment syndrome can be avoided by recognition that the graft is likely to swell over the first 24–48 hours post-transplant and the abdomen cannot be closed with any degree of tension. In most cases the abdominal contents are initially contained in a silastic pouch which is sequentially reduced in size

over the following days to weeks. Once the skin can be closed without tension the abdominal wall, which may be deficient can be replaced using a bio-absorbable material such as Surgisis (Cook Biotech, Limerick, Ireland) or Permacol (Tissue Science Laboratories, Basingstoke). This is termed staged abdominal closure. Early skin closure is facilitated by the placement of tissue expanders during the pre-transplant waiting period.

Nutritional outcome and quality of life

More than 90% of the survivors are established on enteral nutrition following ITx (Grant et al, 2005). The median time to establish children on an oral diet varies as it is dependent on the pre-transplant oral intake. Children with a diagnosis of pseudo-obstruction, who have not eaten normally before ITx find it extremely difficult to establish oral intake and may need psychological and speech therapy input. Few studies exist in the literature addressing the issue of long-term growth in ITx.

With the recent rapid advances and improved survival following ITx, issues regarding the quality of life in long-term survivors have come to the forefront. Sudan et al (2004) have reported similar scores in all domains measured in intestinal transplant recipients as compared with normal children.

Living related ITx

Living related ITx is an option to address the deaths on the waiting list and expand the pool of donors (Testa et al, 2004). The proponents of the procedure claim the advantages of reduced cold ischaemia time, the ability to select recipients in an optimal condition and the opportunity to plan a tolerance inducing immunosuppression protocol (Starzl et al, 2003). However, the graft per se does not offer any immunological advantage and most individuals would still need to be maintained on lifelong immunosuppression. Thus, living related ITx has not been widely adapted in major ITx centres and is restricted to select centres.

Outcome

Data from the intestinal transplant registry presented at the IXth Small Bowel Transplant Symposium in Brussels in 2005, reported a 1-year survival of 90% and 3-year survival of around 70–80%. In a univariate and multivariate analysis conducted within the registry the poor prognostic variables were: hospitalization at the time of transplant; age under 2 years; and centres performing less than 10 transplants in total (Grant et al, 2005).

Conclusions

The advances in the surgical techniques and immunosuppressive strategies made in the last decade are reflected in the current era of improved outcomes following ITx. ITx in the next 20 years will continue to evolve and has the potential to be considered as an alternative strategy to home PN in selected patients. BJHM

Conflict of interest: none.

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KEY POINTS

- Early referral to a transplant centre is encouraged so that children can be considered for isolated bowel transplantation, which may result in better utilization of donor organs, which are a scarce resource.
- Children under 2 years of age needing a liver and small bowel transplant have a worse outcome because of the scarcity of size-matched donor organs and high waiting list mortality.
- Innovative surgical techniques like graft size reduction, use of abdominal tissue expanders and staged abdominal closure have improved the chances of small children being considered for transplantation.
- Induction agents like interleukin-2 blockers and anti-lymphocyte preparations have reduced the incidence of acute rejection.
- Advances in the surgical strategies and medical management has resulted in a current 80% 3-year survival following intestinal transplantation.