Small Bowel Transplantation

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58.1 History

The introduction of parenteral nutrition (PN) in 1969 transformed survival for children with intestinal failure. However, long-term PN has parenteral nutrition is accompanied by significant morbidity such as sepsis, cholestasis, and loss of venous access as well as poor quality of life for the child and their families. Intestinal transplantation (IT) has therefore been pursued as an attractive and potentially curative option.

The development of intestinal transplantation draws parallels from the development of other solid organ transplants. The first attempts at intestinal transplantation in the 1960s were unsuccessful and it was not until the evolution of effective immunosuppressive regimens that intestinal transplant entered clinical practice. In 1988, Deltz and colleagues from Kiel in Germany performed the first successful human IT using cyclosporin albeit with limited patient survival. Later development of tacrolimus-based regimens improved outcome and ensured the worldwide acceptance of its viability as a treatment option. Grant and colleagues from the University of Western Ontario published a case report of a combined intestinal and liver transplant with greater than 1 year survival. A combination of improvement in immunosuppressive drugs, recipient assessment, and surgical technique have led to much-improved graft and patient survival in recent years.

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58.2 Indications

Candidates for intestinal transplantation have *irreversible intestinal failure* accompanied by *either failure of parenteral nutrition* (loss of venous access, recurrent life-threatening sepsis, intestinal failure associated with liver disease) or *poor quality of life that could be improved by transplantation*. Common causes of intestinal failure in children include:

- Extensive bowel resection, e.g., following midgut volvulus, necrotizing enterocolitis
- Intestinal atresia
  - For example, Multiple Intestinal Atresia caused by mutations in TTC7A gene on Ch 2p21
- Gastroschisis
  - For example, closed gastroschisis
- Megacystis Microcolon Hypoperistalsis syndrome
  - Mutations in the MYLK gene on Ch 3q21
- Degenerative intestinal leiomyopathy
- Hirschsprung disease—involving small and large bowel
- Chronic Idiopathic Intestinal Pseudo-obstruction (CIIP)
- Microvillus inclusion disease (MVID) (rare)—autosomal recessive
  - Mutations of MYO5B gene on Ch18q21
  - Diagnosed by EM features on mucosal biopsy
- Tufting enteropathy (rare)
  - Mutations in the EPCAM gene on Ch2p21

58.3 Assessment

Candidates for IT should still have at least two central veins accessible and be referred before liver dysfunction deteriorates.

– ↑ risk of waiting list mortality is for children with advanced liver disease.

Although the inclusion of the liver in the graft may confer an immune-protective effect on the intestinal graft in the longer term, there is increased mortality in the first year following combined liver and intestinal transplantation.

Multidisciplinary assessment must be made to ensure the patient:

- Fulfils the indications for transplantation.
- There are no contraindications to transplantation.

The team includes a hepatologist, gastroenterologist, surgeon, anesthetist, transplant coordinator, specialist nurses, dietician, social worker, psychologist,

physiotherapist, and pharmacist. Renal review is also important as up to 40% of patients suffer from renal impairment following transplantation.

58.3.1 Abdominal Domain Expansion

Many children are small and may have a reduced abdominal domain due to short bowel syndrome or gastroschisis. Such patients may undergo surgery as an attempt to increase this intra-abdominal domain. Typically, this involves abdominal spacers or subcutaneous tissue expanders inserted to allow at least skin closure over the graft. It may be difficult to tolerate such procedures and the implants can erode through the skin or become infected.

58.3.2 Nutritional Preassessment

- Detailed evaluation of nutritional status and potential for further gut rehabilitation.

Contrast studies may be needed to evaluate the length of residual bowel, and anatomy. Poor gastric emptying is an indication for inclusion of the stomach in the graft. This might also highlight possible non-transplant surgical options such as relief of intestinal obstructions, restoration of bowel continuity, slowing bowel motility, or bowel lengthening procedures.

58.3.3 Evaluation of Central Veins

Usually with Doppler Ultrasound or CT/MR angiogram to define venous anatomy and accessibility. This evaluation may be coupled with recommendations to try to preserve venous access and to decrease risk of sepsis such as line access technique, use of biopatches around the line exit site and antibiotic or anticoagulation line locks.

58.3.4 Viral Screening

Past and present infections and immunity to viral hepatitis, HIV, herpes simplex, varicella zoster, rubella, measles, mumps, EBV, and CMV are established.

The family is seen by a clinical psychologist to assess their ability to understand the process and to identify particular areas for additional psychological support. Practical support may also be needed around the time of transplant and in the longer term and therefore input from a family support worker is essential. It is useful for the family to spend some time on the hospital ward and intensive care unit to familiarize themselves with the environment, staff, and working timetable prior to the transplant admission.

The multidisciplinary team will determine if the patient should be a candidate for transplantation, what intestinal components will be included and whether a liver should be included or not. If the patient is not a candidate, they may be kept under review for reassessment at a future date or rejected if there are clear contraindications to transplant that cannot be improved. It should be noted that due to the discrepancy between the size of pediatric recipients and the availability of size-matched donors, the family needs to be aware of a potentially long wait for transplantation.

58.4 Surgery

58.4.1 Donor Selection

This includes matching of blood group and donor-to-recipient size.

- Approximately half of all pediatric recipients are <10 kg but the majority of potential organ donors are older children and therefore grafts may require reduction in size.
- Screening for risk of infection, malignancy, or potential bowel injury and ideally should have been under intensive care for less than 3 days with minimal inotropic support. HLA matching may be considered particularly if there is a history of previous transplantation or presence of donor-specific antibodies.

The intestine is highly sensitive to ischemic injury and therefore rapid donor surgery and implant are the objective. The ideal cold ischemia time is <8 h and only donations after brain death are currently considered. In order to minimize the cold ischemia time of the graft, recipient surgery may commence as soon as the donor organs are assessed, particularly if there is a prior history of surgery in the recipient which may complicate the explant.

The following intestinal containing grafts may be used (Fig. 58.1):

- *Isolated bowel*—small intestine ± large intestine.
- *Combined liver and bowel*—usually en bloc and including pancreas to preserve vascular supply.
- *Multivisceral*—3 or more organs en bloc, e.g., liver, intestine, and pancreas, ± stomach ± kidney ± spleen.
- *Modified multivisceral*—as in multivisceral, but without liver

58.4.2 Donor Surgery

Donor protocols vary between institutions but are essentially divided into three phases:

- 1st phase—dissection of the donor graft while the donor circulation is intact.
- 2nd phase—cold perfusion of the organs with the University of Wisconsin preservation and exsanguination.
- 3rd phase—ex situ preparation of the graft on the back table. The donor bowel may be first decontaminated using an intraluminal antibiotic lavage.

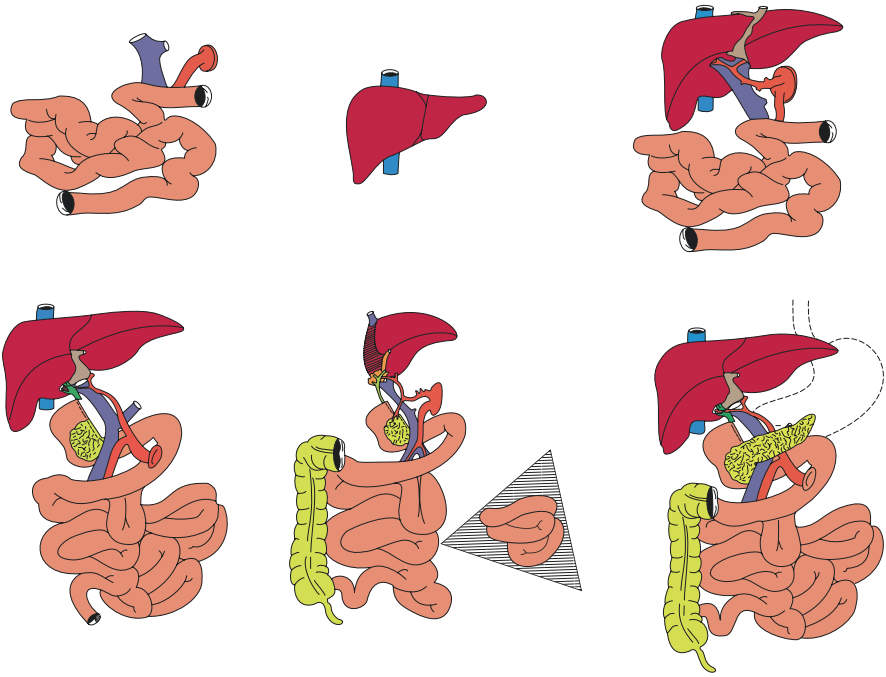

Fig. 58.1 Types of grafts: isolated intestine, isolated liver for short bowel syndrome, multivisceral grafts including pancreas and stomach with reduced size composite grafts

Cecum, ascending colon, and duodenum are mobilized to expose the aorta and inferior vena cava (IVC). The aorta is isolated and a wide bore infusion catheter is inserted. In all cases, it is important to retrieve good quality lengths of iliac vessels to use for vascular reconstructions in the recipient surgery.

58.4.2.1 Isolated Intestine Retrieval

The colon is further mobilized from the left of the field to expose the root of the mesentery and allowing division of the ligament of Treitz. The spleen is mobilized and with it the tail of the pancreas toward the aorta and the root of the mesenteric vessels. The pylorus is exposed and can be divided with a linear stapler. The right, middle, and left colic vessels are divided and the colon is divided at the pelvic brim. Warm dissection is now complete and cold perfusion is commenced, venting the blood from the supradiaphragmatic vena cava. The intestine is removed en bloc with the pancreas by dividing the portal vein at the confluence with the splenic vein stump kept with the vein to use as a patch and the superior mesenteric artery and coeliac axis are taken with a section of the aorta (Carrel patch). The pancreas can then be removed from the bowel on the back table.

58.4.2.2 Combined Liver and Intestine Retrieval

Donors of combined grafts are usually neonates or infants and the small caliber of the vessels must be considered; procuring the descending aorta provides a good caliber inflow. The procedure commences in the same way as for isolated intestinal retrieval. The gallbladder is dissected and the biliary system is flushed through the cystic duct before being ligated. Dissection proceeds as above to mobilize the spleen, pancreas, and intestine, followed by cold perfusion. The aorta is divided above the renal arteries and the descending aorta may be taken as well by splitting the diaphragm. The descending aorta can then be used as a conduit. The IVC is divided and the liver, intestine, pancreas, and spleen are removed en bloc for further dissection on the back table. The spleen is removed and the splenic artery ligated, preserving the gastroduodenal and inferior pancreaticoduodenal artery supply to the pancreas and duodenum.

58.4.2.3 Multivisceral Graft Retrieval

The procedure is similar to that for combined liver and intestine retrieval, but dissection is extended to include the stomach and/or the kidneys as required. Key to this is the preservation of the gastric arterial supply from the left gastric artery and care to avoid damage during mobilization of the colon. The graft is removed en bloc, transecting at the level of the proximal stomach/distal esophagus.

58.4.3 Recipient Surgery

Commenced in coordination with the donor team to achieve the shortest possible ischemic time. Access is achieved through a midline incision and the abdominal cavity examined. We use basiliximab (IL2 receptor antibodies) as our immunosuppression induction agent but other regimens have employed Campath (Alemtuzumab) or ATG as induction agents.

58.4.3.1 Isolated Intestinal Graft

Recipient bowel is resected and removed. Using donors' vessels, conduits are constructed on the aorta and IVC. Donor intestine is anastomosed to the conduits to provide systemic blood supply and drainage to the graft. The proximal bowel is attached to the recipient jejunum with a wide side to side anastomosis and similarly the distal ileum is anastomosed to the colon in a side-to-side fashion. A distal loop ileostomy is formed. This remains in situ to provide access for serial graft biopsy surveillance and will be reversed once the graft is established.

58.4.3.2 Combined Liver and Intestinal Graft

The implant is largely performed en bloc. The recipient pathological bowel is dissected as above, leaving the bowel attached only by the superior mesenteric vascular pedicle. The recipients' liver is mobilized as in an isolated liver transplant, ligating the hepatic artery and the bile duct. The liver is dissected from the IVC and the portal vein is anastomosed to the IVC to create a portocaval shunt to drain the foregut remaining in situ. The intestinal graft arterial inflow is prepared as an aortic conduit as in an isolated graft but the portal outflow is via the intact portal vein.

Prepared liver/intestinal graft is brought to the table and the liver hepatic venous anastomosis is performed in the usual piggy-back fashion. The SMA is then anastomosed to the aortic conduit to restore perfusion to the graft. Any perfusion fluid may be vented through the splenic vein stump before ligation. Intestinal continuity is restored as described for isolated intestinal transplantation. Note the pancreas is included in the graft to maintain perfusion to the foregut.

58.4.3.3 Multivisceral Transplantation

The implantation varies depending on the organs implanted but an en bloc graft maintains the vena cava continuity of the graft. Portocaval shunting is not required as venous drainage is maintained within the graft. The arterial inflow is formed again using an aortic conduit. The proximal intestinal anastomosis is made to a gastric "patch" of fundus. Removal of the SMA may lead to compromise of perfusion of the right and middle colon, requiring removal. The left colonic perfusion is maintained through the preserved inferior mesenteric artery and vein. The distal ileal anastomosis and stoma are formed as above.

Both nasogastric and nasojejunal tubes are left in situ at the end of the procedure for drainage and nutrition respectively. Care must be taken to close the abdomen without increased abdominal pressure; a staged closure may be necessary using a temporary silastic patch for the first few days while edema resolves with planned secondary closure a few days later with or without a biological patch.

58.4.4 Postoperative Care

- Aim for neutral fluid balance.
- Abdominal compartment pressure may inhibit formal abdominal wall closure. Abdominal pressure measurements may be performed using a transduced urinary catheter.
- Serial US in the first-week help detect any vascular issues, abdominal collections, and can monitor for peristalsis in the graft.
- Nutrition can be commenced enterally via the jejunal tube as early as the 1st day and PN can be weaned as tolerated.
- Broad spectrum antibiotics, antivirals, and antifungal agents are employed and sepsis is treated aggressively.
- Anticoagulation is initiated to reduce the risk of vessel thrombosis as a heparin infusion and continued longer term with antiplatelet therapy.
- Immunosuppression is a combination of steroid and calcineurin inhibitor.
  - Weekly graft surveillance biopsies are commenced to detect early evidence of rejection but symptoms may include temperature, malaise, increased stoma effluent, or blood in the stoma effluent.
  - Biopsy is required to make the diagnosis but stoma effluent should also be tested for viral infections.
  - Mild rejection can be managed with pulsed high-dose steroids but treatment may be escalated to basiliximab or ATG in moderate to severe rejection.
  - Differentials for acute intestinal bleeds also include CMV enteritis and portal hypertension variceal bleeding and later graft versus host disease.

- Patients should be monitored for hypertension which may be exacerbated by steroids and should be treated along with monitoring of renal function, particularly if a renal graft has been included.
- Preservation of native pancreas and addition of graft pancreas may lead to a period of hypoglycemia in the postoperative period and blood sugar should be monitored regularly.

58.4.5 Complications

58.4.5.1 Rejection (Common)

Presence of gut lymphocytes may contribute to rejection with the development of antibodies. The inclusion of the liver in the graft may offer an immune-protective effect to the graft as rejection rates are lower than in isolated grafts. However, the role of development of donor-specific antibodies (DSA) is still not completely clear as their presence is not necessarily coincident with rejection. DSA, however, are associated with increased risk of chronic rejection and graft loss.

There are no reliable serum markers for rejection and therefore we are reliant on biopsies and monitoring of intestinal effluent volume and nature to detect rejection. Oral gentamicin administration with serum levels may help give an indication of increased bowel permeability in advance of symptoms. Rejection does not necessarily occur in continuity and therefore a negative biopsy but with persistent symptoms necessitates an endoscopy and biopsy of any suspicious mucosal appearances. The presence of a stoma allows biopsies to be performed on the ward without anesthesia. Biopsy changes seen in early acute rejection include lymphocytic infiltration of the mucosa and increased crypt apoptosis but further advancing rejection may result in villous blunting, confluent crypt apoptosis, and eventually loss of the mucosa. Serial biopsies may be required to monitor progression of disease and response to treatment.

Chronic rejection is histologically distinct with features of vasculitis, focal loss of crypts, and patchy fibrosis of the lamina propria. Clinical features can be subtle with failure to tolerate feeds and chronic pain. The vascular changes cannot be seen on mucosal biopsy samples and therefore a full-thickness biopsy is indicated to confirm the diagnosis.

58.4.5.2 Sepsis

EBV and CMV infection as well as rotavirus, norovirus, respiratory syncytial virus, herpes virus, and adenovirus are significant causes of infection and early detection is important.

- CMV—enteritis with inflammation of the crypts leading to decreased enteral absorption.
- EBV may be a prelude to Post-Transplant Lymphoproliferative Disease (PTLD) (see below).

58.4.5.3 Post-transplant Lymphoproliferative Disease

Occurs in up to 20% of IT.

- Often associated with (but not exclusively due to) de novo EBV. Surveillance for EBV infection and early treatment with modification of immunosuppression is essential as presentation can be subtle with lymphadenopathy, malaise, and hypoalbuminemia.
- Diagnosis is made by endoscopy and biopsy of any lymphadenopathy. EBER staining will highlight EBV-infected lymphocytes. The majority of cases are of polymorphic PTLD but monomorphic PTLD can occur and has a very malignant course.

As well as reduction of immunosuppression, rituximab can be used to target lymphocytes. Directed cytotoxic T-lymphocytes are a novel approach to eliminating the malignant cell population.

58.4.5.4 Graft Versus Host Disease (GVHD)

Occurs in <7% of recipients and usually within the first 2 years with mortality rates of up to 70%.

Onset can be rapid and aggressive compared with other transplant patients. Clinical features include low-grade pyrexia, a flitting skin rash that progresses rapidly, corneal lesions, lung disease, and native bowel. Early skin biopsy of any rash is important to allow rapid initiation of treatment before the disease escalates; and is associated with sepsis following initiation of escalated immunosuppression. Treatment usually involves steroids, thymoglobulins, and Campath (alemtuzumab). Recently, our unit has used extracorporeal photophoresis with some success.

58.5 Outcomes

- Currently, about six children undergo intestinal transplantation a year in the United Kingdom with a median waiting time of 188 days.
- One year patient survival rates ~85% at 1 year and ~60% at 5 years.
- Patient survival at 5 years is 30% for liver containing grafts versus 72% for intestinal only grafts.
- Between 75 and 90% of patients achieve nutritional autonomy.

It should not be forgotten that due to the need for size-matched grafts, up to 85% of prospective donors are rejected and there is a waiting list mortality. Also, with the improving patient survival rates, we are increasingly addressing longer-term complications such as GVHD, PTLD, and chronic rejection. However, the prospect of improved quality of life for these patients is a strong driver to find solutions to these challenges.

Further Reading

Chiou FK, Beath SV, Wilkie GM, et al. Cytotoxic T-lymphocyte therapy for post-transplant lymphoproliferative disorder after solid organ transplantation in children. Pediatr Transplant. 2018; 22(2) doi: 10.1111/petr.13133.

Mazariegos GV, Abu-Elmagd K, Jaffe R, et al. Graft Versus Host Disease in intestinal transplantation. Am J Transplant. 2004;4:1459–65.

Norsa L, Gupte G, Ramos Boluda E, et al. Life of patients 10 years after a successful pediatric intestinal transplantation in Europe. Am J Transplant. 2018;18:1489–93.

Soltys KA, Bond G, Sindhi R, et al. Pediatric intestinal transplantation. Semin Pediatr Surg. 2017;26:241–9.