91 Intestinal and multivisceral transplantation

ABDOMINAL CLOSURE

ABDOMINAL CLOSURE

One of the most challenging parts of a multivisceral/intes tinal transplant is achieving abdominal closure. Multiple previous laparotomies and enterocutaneous fistulae can result in a rigid abdominal wall and loss of the abdominal domain esections. Many techniques to owing to extensive bowel r achieve primary closure under these circumstances have been Alexis Carrel , 1873–1944, French surgeon, received the Nobel Prize in Physiology or Medicine in 1912 for developing a method of suturing blood vessels. developed. These include preoperative tissue expansion, the use of biological meshes and plastic surgery techniques (e.g. vascularised pedicle flaps). Transplantation allows novel techniques to be used, includ - ing transplantation of part or all of the abdominal wall from a donor. The rectus sheath from the donor can be used as a non-vascularised sheet of fascia. Prior to implantation the muscle and fat are removed from the rectus abdominis graft, ving the fascial and peritoneal components. This can then lea be used as a biological ‘mesh’. Unlike other biological mesh it vascularises rapidly . Skin coverage is achieved by mobilisa - tion of the recipient’s skin and subcutaneous tissues, although rarely a skin graft is needed. Vascularised abdominal wall grafts can also be used where the anterior abdominal wall with its over lying subcutaneous - fat and skin is transplanted using the inferior epigastric arteries - and veins as the vascular inflow and outflow . - -

Figure 91.5 Intraoperative picture following exenteration. Intraopera

tive photograph of a multivisceral block (stomach, liver, small bowel, pancreas and colon) following reperfusion.

ASSESSMENT FOR TRANSPLANTATION

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Assessment for a multivisceral/intestinal transplant requires a multidisciplinary approach, including: /uni25CF transplant surgeons; /uni25CF intestinal failure physicians; /uni25CF transplant anaesthetists; /uni25CF hepatologists; /uni25CF psychiatrists and/or psychologists; /uni25CF radiologists; /uni25CF infectious disease physicians; /uni25CF transplant specialist nurses; /uni25CF dieticians. Assessment of venous access and the degree of liver fibrosis is critical. Patients on PN for a substantial time or who have - ultra-short gut are at high risk of developing IFALD. They will need a liver biopsy as part of the assessment process. Detailed venous mapping is essential in all candidates. Appropriate assessment of the cardiovascular and respi - ratory systems is necessary . Upper and lower gastrointestinal endoscopies may be necessary . Cross-sectional imaging of the abdomen to assess the - abdominal anatomy is central to operative planning. Significant renal impairment may result in the need to con - sider inclusion of a kidney a t the time of transplant. Patients should ha ve anaesthetic and psychiatric assessment and dietetic review .

2 are evaluated for the possibility of simultaneous renal transplantation

BACKGROUND

BACKGROUND

Intestinal and multivisceral transplantation can be a life-saving therapy for patients with complications from the treatment of intestinal failure. Indications for this highly specialised type of transplant are broadening to include acute vascular catastrophes and some otherwise irresectable intra-abdominal tumours (e.g. desmoids and pseudomyxoma peritonei). Since the first successful multivisceral transplant in the late 1980s, more than 4000 transplants have taken place worldwide and outcomes continue to improve. Intestinal transplantation is the most challenging area of abdominal transplantation, with higher rates of complications than other transplant groups. These complications include rejection, sepsis, post-transplant lymphoproliferative disease (PTLD) and graft-versus-host disease (GVHD). Graft and patient outcomes for isolated intestinal trans plants are close to those for long-term parenteral nutrition (PN). The role of intestinal transplantation may be changing with earlier referral to try to avoid the complications of long term PN , including intestinal failure-associated liver disease (IFALD).

Early postoperative

Early postoperative

Many patients considered for multivisceral/intestinal trans - plantation have underlying prothrombotic tendencies. A defined prothrombotic disease may be characterised but a ombotic episodes without a history of multiple previous thr - specific diagnosis necessitates a need for anticoagulation after transplantation. Balancing the risks of bleeding and thrombo - sis after transplant is challenging. Enteric anastomotic leaks can occur after transplanta - tion, most commonly if an oesophagogastric anastomosis is /uni25CF undertaken. Given that the enteric anastomoses are performed on previously ischaemic bowel, often under circumstances where inotrope requirements are substantial, the rate of anas tomotic leaks is surprisingly low . When an enteric leak does occur, the immunosuppressed state of the patient can result in an atypical presentation. Therefore, a high index of suspicion is needed should a patient fail to progr ess as expected postoperatively . Proximal enteric anastomotic leaks, especially involving the oesophagus, are the most challenging to deal with. Oesoph agogastric anastomotic leaks have a significant morbidity and mortality in the general population and are even more chal lenging to manage in an immunosuppr essed patient. The use ® of an EndoVac has improved management of these patients. A vacuum (vac) sponge fixed to a nasogastric tube is placed endoscopically in the cavity at the site of the leak. This controls the leak and facilitates healing without operative intervention. Intra-abdominal collections are common and should be treated by aggressive radiological drainage where possible. T hese collections may be chylous and may require nutritional modifications, either PN or (if the patient is enterally fed) a medium-chain triglyceride diet should be adopted.

intestinal transplantation. Surgical Medical Early Vascular (thrombosis, Renal impairment bleeding, secondary Drug related (PRES, haemorrhage, mycotic TMA, pancreatitis) aneurysm) Infections (viral, bacterial, fungal) Enteric leak (anastomotic or non- GVHD anastomotic) PTLD Abdominal collections Acute cellular rejection (chylous, pancreatic, infected) Pancreatitis (graft or native) Stomal complications Late Thrombosis Renal impairment Mycotic aneurysm Acute cellular rejection Hernias Chronic rejection Stomal complications PTLD Immunosuppression- related malignancy GVHD, graft-versus-host disease; PRES, posterior reversible en cephalopathy syndrome; PTLD, post-transplant lymphoproliferative disease; TMA, thrombotic microangiopathy.

FURTHER READING

FURTHER READING

Abu-Elmagd K, Mazariegos G, Armanyous S et al . Five hundred - patients with gut malrotation: thirty years of experience with the introduction of a new surgical procedure. Ann Surg 2021; 274 (4): 581–96. Matsumoto CS, Subramanian S, Fishbein TM. Adult intestinal transplantation. Gastroenterol Clin North Am 2018; 47 (2): 341–54. Tzakis AG, Kato T , Levi DM et al . 100 multivisceral transplants at a single center. Ann Surg 2005; 242 (4): 480–90; discussion 491–3.

INDICATIONS FOR

INDICATIONS FOR

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Immunosuppression and rejection

Immunosuppression and rejection

The rate of acute cellular rejection for intestinal grafts is higher than for any other abdominal organ. This is reflected in the magnitude of immunosuppression required. As with other solid organ transplants acute cellular rejection is most common in the first few months after transplantation, although it can occur at any time. Michael Anthony Epstein , b. 1921, Professor of Pathology , University of Bristol, Bristol, UK. Yvonne Barr , 1931–2016, virologist who emigrated to Australia. Epstein and Barr discovered this virus in 1964. regimens commonly utilise an induction agent, usually a lymphocyte-depleting antibody such as antithymocyte glob - ulin (ATG) or alemtuzumab. Paediatric regimens commonly use non-depleting antibody induction. Maintenance imm uno - suppression comprises a calcineurin inhibitor (most commonly tacrolimus), an antimetabolite (mycophenolate or azathioprine) and prednisolone. In addition, some programmes supplement this with early addition of an mTOR (mammalian target of rapamycin) inhibitor (sirolim us or everolimus). Acute cellular rejection is usually initially manifested in the terminal ileum. Rarely other organs (liver/pancreas) may be a ff ected without intestinal rejection. Rejection most commonly presents with increased stoma output or diarrhoea, sometimes with an associated fever. Sev ere (exfoliative) acute cellular rejection with loss of intestinal mucosa results in rapid bacterial translocation and sepsis . In any intestinal transplant recipient presenting with sepsis or septic shock, a diagnosis of rejection needs to be considered. Endoscopic assessment and biopsy of the graft are required for the diagnosis and assessment of the severity of acute cel - lular rejection. Graft surveillance in a protocolised manner is performed in some programmes; others respond to symptoms suggestive of rejection (i.e. an incr ease in stoma output). At endoscopy , rejection can range from mild, with some erythema of the mucosa, to moderate, with some ulceration, to severe, with confluent loss of mucosa. At biopsy , salient fea - - tures of rejection are an inflammatory infiltrate in the lamina propria, crypt loss and ulceration and an increase in apoptotic bodies in the base of the crypts. Rejection is treated primarily with high-dose intravenous pulsed steroids. If the rejection is steroid resistant then fur - ther lymphocyte depletion may be needed with either ATG or alemtuzumab. - -

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Infectious complications

Infectious complications

Infection is the leading cause of death in multivisceral/ intestinal transplant recipients. This is as a consequence of the degree of immunosuppression and also the potential for bacterial translocation across the graft mucosa. Opportunistic infections, common to all solid organ transplant recipients, such as cytomegalovirus (CMV), Pneumocystis jirovecii (PJP), adenovirus, Epstein–Barr virus (EBV) and fungal infections, are all more common following intestinal transplantation. Appro - priate prophylaxis with antiviral (valganciclovir or aciclovir), antifungal (fluconazole) and anti-PJP (co-trimoxazole) agents is critical. Infective enteritis is common among transplant recipients and can mimic rejection, thus it is important to send stool for culture and viral polymerase chain reaction when a patient presents with a high-output stoma or diar rhoea. Rejection trig - gered by infection is possible and a high index of suspicion and early r epeat endoscopy are important if clinical improvement does not occur. PTLD is a potential complication of immunosuppression for any patient after transplant. The incidence in intestinal trans plant recipients is higher than for other solid organ transplant recipients – up to 17% in some series. This is likely to be due to both the level of immunosuppression and the amount of lymphoid tissue associated with an intestinal-containing graft. PTLD should be considered if there is a persistent positive EBV viraemia or B symptoms such as night sw eats, unexplained fevers and weight loss. If diagnosed with PTLD the first-line treatment is usually with rituximab and immunosuppression reduction. This has to be done with great caution in multi visceral/intestinal transplant recipients because of the risk of rejection and the consequences thereof. The extent of lymphoid tissue associated with the multi visceral/intestinal graft increases the risk of GVHD. Outcomes from GVHD in this patient group can be very poor. The most common pr esenting symptoms of GVHD are a rash, fever and bone marrow suppression. Optimal management of GVHD is unclear and proposed strategies include both enhancement and also reduction of immunosuppression. Management is guided by the level of peripheral T-cell chimerism. There is an increasing trend towards withdrawing immunosuppression ini tially to rebalance the equilibrium between the host and donor immune systems. Bone marrow involvement and ultimately failure is almost universally fatal. Deterioration in renal function is common to all solid org transplant groups but is most marked following multivisceral/ intestinal transplantation. The cause of this is multifactorial b ut is likely to include contributions from the physiological insult of surgery , the use of nephrotoxic medication (e.g. tac rolimus) and fluid losses associated with the stoma. It is imper ative to maintain good hydration postoperatively and home intravenous fluids may be needed initially post discharge. Immunosuppression modifications including con version from calcineurin inhibitor-based protocols to mTOR inhibitors may prevent further deterioration of renal function. These inter ventions need to be undertaken with caution as they may pre cipitate an episode of acute cellular rejection.

Introduction

INTRODUCTION

The first reported intestine-containing transplant in humans was performed in 1966, when a short segment of duodenum was included in a pancreas transplant. This was followed by attempts to transplant more substantial amounts of intestine, but these did not result in long-term survival. It was not until 1988 that the first ‘successful’ intestine-containing transplant was reported. At this time intestinal transplants were a rarity but with increasing experience (both surgical and immunological) out comes have improved, making intestinal transplantation a rel atively routine procedur e. Changes in immunosuppression regimes (depleting Burrill Bernard Crohn , 1884–1983, gastroenterologist, Mount Sinai Hospital, New Y ork, NY , USA, described regional ileitis in 1932. antibodies and tacrolimus) have improved rates of rejection, a complication that is di ffi cult to control and can be life- threatening. In 1996 the International Intestinal Transplant Registry was established and reported a total of 180 transplants per - formed in 25 centres worldwide. By 2019 this number was over 4100, with almost doub le the number of active centres. The majority of transplants have been performed in the USA and Europe, with the most prolific units performing o ver 10 adult transplants per year. With improvements in the management of paediatric intes - tinal failure the number of multivisceral and intestinal trans - plants in this group has fallen.

Both the medical and surgical complications associated • with intestinal transplantation The outcomes associated with intestinal transplantation •

Learning objectives

Learning objectives

To understand: The indications for intestinal transplantation â€¢ The assessment process for intestinal transplantation â€¢ The different transplant types â€¢

OUTCOMES

OUTCOMES

Graft and patient outcomes vary depending on the type of transplant undertaken with survival post-multivisceral trans plant being markedly poorer than isolated small intestinal transplant. As with many transplant groups, outcomes are improving over time and the outcomes in the last published Intestinal Transplant Registry report in 2015 show ed continued improvement in both 1- and 5-year patient survival. In 2019 the overall 1-year patient survival for intestinal-only grafts was all intestinal transplant ago the 1-year patient survival for recipients (intestine only and multivisceral grafts) was 70%. - Five-year survival rates have also improved and the long-term results of intestinal-only transplants are now comparable to those of long-term PN. Intestinal transplantation may have progressed to the stage at which it may be o ff ered to patients on PN to improve their quality of life rather than just for those with life-threatening complications of PN.

POST-TRANSPLANT COMPLICATIONS

POST-TRANSPLANT COMPLICATIONS

With the complexity of multivisceral/intestinal transplantation complications are common (Table 91.3).

PREOPERATIVE PLANNING

PREOPERATIVE PLANNING

The decision regarding the type of transplant to be performed is dependent on a variety of patient factors. Intraoperative flexibility is necessary and may change the type of transplant undertaken. A robust plan for adequate venous access is necessary and may require pretransplant venous reconstruction by the inter ventional radiology team or surgical reconstruction. If substantial intraoperative blood loss is predicted, selec tive arterial embolisation may be considered. Commonly this will involve the superior mesenteric artery and coeliac axis, but more selective embolisation can be undertaken if preser vation of the stomach or the pancreaticoduodenal comple planned.

SUMMARY

SUMMARY

- Multivisceral and intestinal transplantation remains a complex and uncommon treatment, however it can be life-saving. The risks are high but with improvements in surgical techniques, - especially the introduction of preoperative embolisation, the intraoperative risks have improved. With this and a better understanding of how to manage the varied and complex postoperative complications, outcomes continue to improve. Intestinal transplantation for patients on PN was previously reserved for those with life-threatening complications of this treatment. Outcomes have improved such that, in certain cir - cumstances , it can now be o ff ered to improve quality of life. - With time, improvement in patient management may allow intestinal transplantation to fulfil the same role for patients on PN as kidney transplantation currently o ff ers those on dialysis: to improve both quality and length of life. an T he need for liver-containing grafts will always remain for those who require a liver transplant but are unable to have a single-organ transplant for anatomical reasons. W ith improve - ments in liver functional assessment and increasing awareness - of the possibility of earlier intestinal transplantation, it may be - possible to reduce and hopefully eliminate the need f or liver transplantation for IFALD. The benefits for the individual in terms of improved survival and also the population with better organ utilisation are substantial. The main cause of death in multivisceral and intestinal - transplant recipients remains sepsis. This is frequently associ - - ated with a preceding episode of severe acute cellular rejection and so further dev elopments in immunosuppression regimens will be necessary to continue to improve patient outcomes.

THE TRANSPLANT

THE TRANSPLANT

Multivisceral/intestinal transplants are almost invariably performed with organs donated from deceased brain dead donors. A small number of living donor intestinal transplants have been performed. In intestinal and multivisceral transplant procedures the donor and recipient operations occur simultaneously; this is not the case for liver and kidney transplantation. This is to minimise cold ischaemia time (the intestine is intolerant of isc haemia and ideally cold ischaemia times of less than 6 hours are required). The recipient operation is often complex and technically challenging. Portal hypertension, extensive adhesions and dis torted anatomy all result in these patients having surgically hostile abdomens, making the explant challenging. Substantial b lood loss and transfusion may result in severe coagulopathy . Preoperativ e embolisation can reduce blood loss significantly . The extent of the explant is dependent on what transplant is required, a full multivisceral being the most extreme (Figure 91.2). At retrieval the organs are retrieved en bloc (Figure 91.3 with the vascular inflow coming from the coeliac axis and superior mesenteric artery (SMA) and the venous outflow from either the portal vein (in a non-liver-containing graft) or the vena cava when a liver is implanted. This tec hnique was first described by Starzl in the 1990s. Thomas Earl Starzl , 1926–2017, Distinguished Professor of Surgery , University of Pittsburgh School of Medicine, Pittsburgh, PA, USA. Referred to as ‘the father of modern transplantation’. He was awarded the USA ’s highest honour for scientific achievement, the Medal of Science, in 2005. - - - x is -),

Extent of resection Proximal enteric anastomosis Duodenum or proximal jejunum Small intestine and part of colon Proximal stomach or Stomach, pancreas, spleen, oesophagus small intestine and part of colon Duodenum or proximal jejunum Liver, small intestine and part of colon Proximal stomach or Liver, stomach, pancreas, oesophagus spleen, small intestine and part of colon (a) (b) Figure 91.2 Intraoperative picture following exenteration. (a) Clamp on the retrohepatic cava in preparation for caval anastomosis (venous out /f_l ow for the multivisceral graft). (b) Clamp on the donor thoracic aorta anastomosed to the infrarenal aorta of the recipient (arterial in /f_l ow to the multivisceral graft). Figure 91.3 Intraoperative picture following exenteration. Multivisceral graft (stomach, small bowel, pancreas and liver) immediately prior to implantation. The graft is preserved using University of Wisconsin solution.

Arterial inflow to the graft is usually achieved from the infrarenal aorta. Commonly a section of donor thoracic aorta is used as an arterial conduit, onto which the donor aortic patch containing SMA and coeliac artery is anastomosed (Figure 91.4). In intestine-only grafts (not including the pancreas) the inflow is the SMA, which is either anastomosed directly to the aorta (as a Carrel patch) or the recipient SMA or a conduit can be fashioned from donor iliac vessels. When undertaking a liver-containing graft, venous outflow from the whole graft is via the hepatic veins and inferior vena cava (IVC). For non-liver-containing grafts the venous outflow his can be drained either systematically is via the portal vein. T via the IVC or into the portal circulation. Following

reperfusion of the graft (Figure 91.5) the enteric anastomoses are performed. This requires a proximal enteric anastomosis and a distal stoma or anastomosis. In some cir cumstances (modified multivisceral transplant) a biliary anas tomosis may be required. ximal bowel anastomosis may be either oesophago The pro gastric, oesophagojejunal, gastrogastric, gastrojejunal or jeju nojejunal. If an oesophagogastric or gastrogastric anastomosis is performed, then a pyloroplasty is necessary (the block lacking vagal innervation). , but, where An end stoma is the simplest option distally safe, a primary distal anastomosis can be considered. In most circumstances a covering ileostomy is performed. This allows ready access to the graft for endoscopic surveillance.

Figure 91.4 Intraoperative picture following exenteration. A Carrel patch (donor superior mesenteric artery and coeliac artery) onto an aortic conduit constituting the arterial in /f_l ow to the multivisceral block.

TRANSPLANTATION

Complications from PN for irreversible intestinal failure are the most well-established indications for intestinal transplantation - (Table 91.1). Short bowel syndrome (SBS) is the most frequent cause for the need for PN. The aetiologies of SBS vary between the adult and paediatric population. The most common causes for SBS in the paediatric pop - ulation are volvulus, gastroschisis, necrotising enterocolitis and intestinal dysmotility or pseudo-obstruction. The last two result in functional SBS. The most common causes for SBS in adults result from bowel resections owing to mesenteric ischaemia, inflamma - tory bow el disease (most commonly Crohn’s disease), benign tumour resection and dysmotility or pseudo-obstruction. Until recently , intestinal transplantation was only consid - ered for patients with complications of PN, including loss of - vascular access, recurrent life-thr eatening line infections (espe - - cially fungal infections) and IFALD. Increasingly patients are being transplanted for quality-of-life indica tions, although this remains controversial. /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF If the indication for transplant is IFALD, the degree of liver impairment influences the organs required at transplant. Mild to moderate liver fibrosis may allow an isolated intestinal transplant to be undertaken. This results in improved patient outcomes, better organ utilisation and reversal of liver fibrosis with discontinuation of PN. Severe liver fibrosis or cirrhosis will necessitate a liver-containing graft. Indications for intestinal transplantation continue to change and now include to facilitate the resection of some tumours (desmoids and pseudomyxoma peritonei). In this situ a tion, without intestinal transplantation, extensive evisceration would render the patient dependent on PN. Hepatic cirrhosis with extensive portomesenteric thrombosis may make isolated liver transplantation technically impossible , so multivisceral transplantation may be considered for some individuals. Acute widespread splanchnic ischaemia (arterial and venous) is a rare but growing indication for super-urgent intes tinal and multivisceral transplantation as well as other acute abdominal catastrophes.

1.

Life-threatening complications of parenteral nutrition a. Progressive IFALD or non-IFALD Assessed by biochemistry and biopsy Combined intestinal and liver transplant is best considered in the presence of advanced liver disease (portal hypertension or advanced /f_i brosis) b. Severe sepsis More than one life-threatening episode of catheter-related sepsis for which no remediable cause can be identi /f_i ed Endocarditis or other metastatic infection c. Limited central venous access Venous access limited to three major conventional sites in adults (above and below the diaphragm) and two major conventional sites above the diaphragm in children Conventional central venous sites are de /f_i ned as internal jugular, subclavian and femoral veins 2. Very poor quality of life thought likely to be correctable by transplantation 3. Surgery to remove a large proportion of the abdominal viscera considered untenable without associated multivisceral transplantation (e.g. extensive desmoid disease, extensive critical mesenteric arterial disease) 4. Localised malignancy considered amenable to curative resection requiring extensive evisceration (e.g. localised neuroendocrine tumours). Particular caution should be exercised in this group and patients should

be discussed in a multidisciplinary multicentre forum (e.g. National Adult Small Intestinal Transplant [NASIT] forum) 5. Where the transplantation procedure is expected to preclude the possibility of future intestinal transplantation (e.g. loss of venous access or further human leukocyte antigen sensitisation) 6. Where the need for subsequent intestinal transplantation is considered likely and the risk of death is increased by excluding the intestine from the graft Examples include predictable problems related to administering immunosuppression (e.g. line sepsis), or continuing severe intestinal disease such as diabetic visceral neuropathy , or ultra-short bowel syndrome, which may cause /f_l uid, electrolyte and acid–base balance problems that would damage an existing or planned renal graft 7. Transplantation of additional organs for feasibility reasons a. Renal transplantation b. Adults and children with corrected GFR of <45 /uni00A0 mL/min/m GFR, glomerular /f_i ltration rate; IFALD, intestinal failure-associated liver disease. Adapted from NHS Blood and Transplant (https://www.odt.nhs.uk/transplantation/small-bowel/).

TYPES OF TRANSPLANT

TYPES OF TRANSPLANT

Multivisceral or intestinal transplant covers a number of di ff erent ‘cluster’ transplants, as shown in Table 91.2 and Figure 91.1 .

Full multivisceral transplant Liver and small bowel transplant Figure 91.1 Types of intestinal transplant. SMA, superior mesenteric artery. Modi /f_i ed multivisceral transplant Left gastric artery Hepatic artery SMA Splenic artery Portal vein Middle colic artery Ileocolic artery Small bowel, pancreas and colon transplant

Transplant Organs included Small intestinal and colon Small intestine and colon (with/ transplant without pancreas) Modi /f_i ed multivisceral transplant Stomach, pancreas, small intestine and colon Liver and small bowel transplant Liver, pancreas, small intestine and colon Multivisceral transplant Liver, stomach, pancreas, small intestine and colon