Advances in Small Bowel Transplantation

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ABSTRACT

Small bowel transplantation (SBT) is a life saver procedure in patients with intestinal failure. The biggest obstacle to intestinal transplantation is graft rejection. It is the main factor in morbidity and mortality. Rejection has a negative impact on survival of the graft. The acute rejection occurs in 50-75%, and the chronic rejection occurs in 15% of the patients.

Immune monitoring is crucial after SBT. Unlike other types of transplantation, the intestine lacks a reliable and minimally invasive marker to predict rejection. The diagnosis of acute rejection is performed by clinical, endoscopic and pathologic anatomy. Protocol biopsies and histological analysis remain the gold standard for allograft monitoring, but neither is free of complications, especially in smaller grafts. Up to 30% of biopsies are nondiagnostic and multiple biopsies may be required to exclude rejection. So, ancillary assays are increasingly used in SBT such as measurements of citrulline and calprotectine in the blood, cytofluorographic analysis of peripheral immune cell population, cytokine profiling and the quantitation of distinct gene set changes. Developments in the understanding of genes provide promise that limited gene sets, taken from blood or from intestinal biopsies, will enhance pathological diagnosis. Bone marrow mesenchymal stem cell transplantation with SBT and tissue engineering are promising procedures.

Keywords: ŧSmall bowel transplantation; intestinal transplantation; stem cell transplantation; intestine

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INTRODUCTION

The small bowel transplantation (SBT) has developed less, when compared to other solid organ transplantations. Currently, it is the only chance of cure for patients with intestinal failure who develop complications related to the use of parenteral nutrition. The number of SBT is relatively small compared to all other types of solid organ transplantations. Although declining in volume in the United States since 2007, probably due to bowel rehabilitation programs and recent developments in surgical techniques such as tapering enteroplasties, the number of small bowel transplantation increased substantially in the last 5 years in Europe, China and Japan.[1] It is estimated that 2-3 people per million inhabitants per year had intestinal failure of whom 15% are candidates for SBT for irreversible intestinal failure and complications of parenteral nutrition.[2] The mortality in this group is high, reaching 40% at five years in patients having less than 50 cm of healthy small bowel left due to infections and/or thrombosis of vessels and having liver disease.

SBTs are complex procedures in patients with compromised clinical conditions. It comprises of a number of surgical procedures of which the principal is the transplantation of the small intestine. Although there are variations of terminology, the current classification includes four groups according to the inclusion of the liver and/or the stomach in the graft: isolated, liver-intestinal, multivisceral and modified multivisceral transplantation.[3] Although combined liver and intestine was the most common type of small bowel graft in the past, the frequency has declined from 68% in 2007 to 39% in 2011. Isolated small bowel transplantation (including stomach, pancreas or colon) has been increasing in frequency.[4] There is a need for intense immune suppression because of the large immune response to the graft. Thus, opportunistic infections and neoplastic diseases are more prevalent compared to other solid organ transplants. Due to the large amount of tissue transplanted, graft versus host disease (GVHD) is also more prevalent in comparison to other solid organ transplantations. Finally, it is the most expensive transplant procedure.

Currently, the failures of parenteral nutritional therapy are candidates for SBT. Complications of parenteral nutrition usually accepted as indications are: thrombosis of two of the six major venous accesses; liver disease; episodes of catheter-related infections (two or more per year, fungemia, shock or respiratory failure); alterations of growth and

development in children and refractory electrolyte changes. Patients dependent on parenteral nutrition without complications are not candidates for intestinal transplantation, nowadays.

Surgical techniques

The SBT can involve some others abdominal organs to be transplanted with the small intestine. The severity of the liver disease determines the organs to be transplanted, so that patients with mild liver disease (no evidence of portal hypertension, mild hepatic fibrosis on liver biopsy) can be offered an isolated intestinal, or a modified multi-visceral graft, including stomach if dysmotility of the foregut is a prominent clinical problem. The preferred technique is the composite graft where the liver and intestine with bile ducts, duodenum, and head of a pancreas can be implanted en bloc with minimal disruption to the vascular and other structures connecting the organs; or the organs can be retrieved from the donor, separated, and implanted individually, which is known as non-composite combined liver and small bowel transplantation. The selection of organs to be included will depend on the underlying disease, quality of other abdominal organs, presence and severity of liver disease and the number of previous abdominal surgeries. The isolated small bowel graft (Figure 1) is indicated in the presence of irreversible intestinal failure in the absence of severe hepatic dysfunction. The determination of liver disease severity and reversibility is held more securely by liver biopsy. The presence of bridging fibrosis or cirrhosis indicates the necessity of replacement of the liver. A recent study showed an association between the levels of bilirubin, platelet count and albumin level in the presence of liver failure in children in parenteral nutrition.[5]

The arterial anastomosis is established through the superior mesenteric artery graft to the aorta. The venous drainage is made through the superior mesenteric vein to the inferior vena cava (Figure 2) or the mesenteric portal system. The venous drainage into the portal system should always be preferred due to its physiologic and possible immunologic advantages but depends on the technical feasibility of accessing the recipient portomesenteric axis. In patients with modest portal hypertension presented with mild splenic enlargement, for whom the decision has been made to perform isolated small bowel transplantation in the absence of low platelet counts, gastroesophageal varices, and intrahepatic cholestasis, the venous outflow should be drained into the recipient IVC. Other studies showed no difference in survival, however, the

cumulative episodes of infection rate by bacteria of the gastrointestinal tract was higher in patients with systemic drainage, suggesting a protective role of the liver.[6] Anastomosing to portal vein is more technically demanding but does offer restoration of physiological drainage of the gut via the portal system. In practice, anastomosing to mesenteric superior vein is technically easier and is seldom associated with major problems in terms of outcome.

In all types of SBT an ileostomy is performed for endoscopic surveillance, facilitating the diagnosis of rejection and perfusion disorders.

Combined liver and small bowel transplantation offers a treatment option in cases where there is irreversible liver damage and has been more commonly applied in pediatric cases, where PN related liver disease has been more of a problem than in the adult population. This group of patients competes for scarce liver grafts. U.S. data show that 74% of the patient candidates for intestinal transplantation require an associated liver.[7] Enhancement of allocation models and early referral to SBT can be a solution to this problem. The grafts can be deployed separately, or in a more convenient way, en bloc. To maintain the liver and intestine en bloc, it is necessary to include the pancreatoduodenal arc graft. This avoids the dissection of hilar structures, which can be difficult in small children. Alternatively, liver and intestine can be transplanted separately which has the advantage that if the intestinal graft should develop severe rejection, it could potentially be removed without requiring retransplantation of the liver. But, the disadvantage of this technique is that it requires multiple vascular anastomosis and biliary reconstruction with the attended risk for complications.

Controversies exist regarding the inclusion of the colon and spleen grafts. Patients who received an intestinal graft without ileocecal valve usually do not have well-formed stools and are more likely to become dehydrated. It was thought that inclusion of the colon in small intestine grafts increases the risk of graft failure or death rate, so it has previously been avoided. But, recent studies showed that inclusion of the colon did not increase morbidity or mortality and bloodstream infections, but only brought benefits especially in pediatric patients.[8]

Preservation of the native liver, spleen and pancreaticoduodenal complex when possible has had a great influence. These different modifications are applied for patients who are in need of multivisceral transplant with preserved liver functions,

particularly those with Gardner and pseudo-obstruction syndromes. Sparing the native spleen also has potential advantage of reduced risk of post-transplant lymphoproliferative disorder.

After showing the beneficial effect of spleen transplantation in promoting tolerance in animal experiments,[9] a recent research demonstrated that adding the spleen to the multivisceral transplantation graft yielded better outcomes in terms of low acute rejection without altering the incidence of GVHD.[10] Inclusion of the donor spleen with the multivisceral graft was also introduced with the notion of reducing infection and enhancing mixed chimerism.

Other notable contributions include *en bloc* retrieval of the distal esophagus with the multivisceral graft which facilitates to harvest foregut organs.

Although it is not used widely, microendoscopy helps to visualize the transplant mucosa and to monitor the blood flow during the surgery. Upile et al.[11] argue that the method is of value intraoperatively as well as in the postoperative period, and that monitoring can be performed from the serosal or the mucosal surface of the transplant. Thus, this method helps to assess the viability of the graft. But, as with endoscopy, the procedure is very demanding and not suited to be performed with 1 or 2-hour intervals.

Loss of the abdominal domain in small bowel transplant recipients due to extensive adhesions, secondary to multiple prior surgeries, shortage of appropriate recipient size matched donors, abdominal wall scarring due to fistulas, ostomies repeated laparotomies and post perfusion graft edema make the primary abdominal wall closure difficult. A primary tension free closure of the abdominal wall is achievable in 50-85% of recipients. Aside from reduced-size grafts to facilitate the primary closure, various strategies have been introduced to reconstruct and enlarge the abdominal wall. Some of the strategies that have been employed are usage of tissue expanders, staged abdominal closure with mesh, bioengineered skin equivalents, acellular dermal matrix, vascularized or nonvascularized rectus muscle fascia grafts, skin grafts and finally vascularized abdominal wall transplantation from same donor.[12,13] Abdominal wall transplantation allows primary skin and abdominal wall closure without causing abdominal compartment syndrome. But, it has some disadvantages like the need for complex vascular anastomosis, longer operative time and higher morbidity rate. The use of avascular rectus allofascia is also reported with good results.[14]

Donor preparation

Ideal donors are preferably younger and with little or no vasoactive drugs. Patients with short bowel syndrome have the abdominal cavity retracted, and need the usage of smaller donors (30 to 40%). With the development of effective drugs for prophylaxis and treatment of cytomegalovirus seropositive donors are accepted, avoiding only for receivers with negative serology. Decontamination of the gastrointestinal tract and use of antibodies in donor lymphocytes showed no benefits related to infection, rejection episodes or incidences of GVHD. These donors are also suitable for harvesting liver and pancreas grafts. The grafts sharing the same bloodstream bring challenges to the simultaneous harvesting of these grafts, but is possible to perform the procedure without compromising the graft.

Intestinal mucosa is sensitive to ischemic injury. When the intestinal graft is harvested from non-heart beating donors (NHBDs), the infectious-related mortality was higher and the absorptive function lower. Histological examination confirmed a higher grade of ischemic injury in the NHBD grafts that correlated with the clinical data. An experimental study suggested that non-heart-beating donation may not be suitable for small bowel transplantation.[15]

Living donor small bowel transplantation is a relatively new type of transplantation which is suitable especially for children with intestinal failure who develop acutely decompensated liver failure. It can be performed successfully simultaneously or sequentially to reduce the morbidity and mortality while waiting on the list. Small bowel grafts consisted of 150 cm of an ileum segment with or without left lateral liver graft depending on the liver function of the patients. A largest case series article reports that none of the donors changed their life style, work habits, or psychologic condition after donation.[16]

Organ preservation

The University of Wisconsin (UW) solution has been considered the gold standard for the preservation of all organs of the digestive system. However, there are reports about the usage of other solutions, like Celsior, and HTK which gives similar results as the UW solution in ischemic periods up to 8 h in SBT. Although there is no significant difference in terms of graft survival, initial function, endoscopic appearance or transplant pancreatitis between HTK and UW as preservation solutions in small bowel grafts, HTK has the advantage of better flushing the microvasculature due to its low viscosity.[17]

Postoperative management and complications

Surgical complications (bleeding, fistula, dehiscence and wound infection) may cause episodes of rejection and opportunistic infections, postoperatively. The biggest obstacle to intestinal transplantation is graft rejection. It is the main factor in morbidity and mortality. Rejection has a negative impact on survival of the graft. The acute cellular rejection occurs in 50-75% of patients, most commonly in the first 90 days. Chronic rejection occurs in 15% of patients.[18] The consequences of severe rejection are considerably higher than other solid organs with 50% mortality rate.

Immunological complications

SBT represents a major immunological challenge compared with other solid organs as more than 80% of the immune cells inhabit the small intestine. Previous reports have suggested that the small intestinal allograft (particularly the ileum) is the most susceptible organ to acute rejection (AR) in frequency and severity when compared with other allografts and it has been recognized as the "Achilles heel" and critical organ of multivisceral transplantation. Besides, after the transplantation, the small intestine is repopulated with recipients' enterocytes within 10 weeks, which makes the graft highly chimeric.[17] Thus, the presence of recipient lymphocytes within intestinal submucosa may not necessarily indicate a process of rejection. This bidirectional exchange of immune cells is responsible for GVHD with 7-13% incidence rate.[18,19] The incidence, risk factors and impact on survival of GVHD were analyzed in a retrospective study.[18] Risk factors for GVHD were young age, multi-organ graft recipients and splenectomized cases. The potential role of donor T cells in the pathophysiology of GVHD has been analyzed.[18] The study showed that levels of donor derived T cells chimerism correlates with clinical course of GVHD.

Out of 11 patients, 64% showed clinical features of GVHD with all of them having detectible donor T cell chimerism. The study reported that all the patients responded to increase in immune suppressive therapy, and three of them died due to sepsis and multiorgan failure.

Another immunological complication is inflammatory bowel disease-like disease (IBD) after transplantation. The incidence of IBD in the patients with solid organ transplantation is 10 times more than the expected incidence of IBD in the general population.[20] Posttransplant IBD is correlated with cytomegalovirus infection, Epstein-Barr virus, posttransplant lympho-proliferative disorder and use of

tacrolimus.[21] Another possible mechanism can be the donor lymphocytes having the genetic information for an abnormal inflammatory response. The intestinal inflammation coming from failure of physiological control by regulatory donor-derived T cells may manifest as an Arthus-like reaction in the colonic mucosa.[22] In a study, the usage of anti-TNFα showed dramatic clinical and histological improvement in two children.[23] Anti-TNFα therapy also has some benefits in treating steroid and thymoglobulin resistant AR episodes.

In the process of AR, gene expression of TNFα is upregulated early after transplantation with a further increase as previously described,[25] which is known to be associated with immune regulatory processes, activation and induction of apoptosis and T cell proliferation.[25] In several case reports, infliximab has been shown to be a therapeutic option for AR, especially in patients with refractory rejection.[26]

TNFα mRNA-expression is slightly elevated after isogenic and allogenic transplantations after 24 h reperfusion as expression of ischemia reperfusion injury, but it reaches excessively increased expression levels after allogenic transplantation in the intestinal muscular layer after 168 h reperfusion during the manifestation of AR.[24]

Rejection

The diagnosis of AR is performed by clinical, endoscopic and pathologic anatomy. The gold standard for the diagnosis of acute cellular rejection is histology. The routine ileostomy facilitates endoscopic assessment and biopsies. The endoscopic surveillance is held two to three times per week in the first three months, being held once a month from then and according to the situation.[27] A number of endoscopic findings may be associated with AR: mucosal erythema, congestion, shortening and flattening of the villi, friability and ulcerations. Endoscopy alone has a sensitivity of only 52% but a specificity of 93%.[27] On suspicion of rejection several biopsies should be performed because the lesion can spare a few segments.

One important consequence of local innate immune activation is increased activity of antigen presenting cells, which, in turn, can increase sensitization to donor antigens. Use of the lymphocyte-depleting agents for induction, and long-term tacrolimus, with steroids for episodes of AR, has been quite successful in protecting grafts against T cell mediated rejection. In contrast, antibody mediated rejection (AMR) continues to be a major problem,

particularly since it is relatively insensitive to corticosteroids.[28]

Successful intestine and multivisceral transplantation across a positive cross match have been described.[29] Donor specific antibody (DSA) formation in the serum of the recipient associated with AMR is similar to other solid organ transplants. In contrast with preformed DSA, de novo DSAs have been shown to be associated with adverse clinical outcomes, mainly acute and chronic rejection.[29] De novo DSAs seem to appear in approximately one fourth of the patients after transplantation as a result of alloreactive humoral responses and are associated with increased incidence of chronic rejection and graft loss. But histologic findings of AMR in SBT are not yet well-defined due to nonspecific C4d staining in mucosal biopsies and absence of mesenteric arterial structures in the biopsies.[30] AMR is not only an obstacle to transplantation in presensitized recipients, but DSAs are increasingly recognized as causes of long-term chronic rejection and late allograft failure.[31] This recognition has followed the development of new technologies, particularly single antigen fluorescent (Luminex) bead assays, to detect DSAs. There is increasing recognition that DSA causes of late graft loss due to dysfunction and rejection. Mesenteric arteriopathy, an important mechanism which underlies the pathophysiology, is highly dependent on DSA. Complement seems to play a particularly important role in late dysfunction and chronic rejection of other organs, as well.

Immune Monitoring

Immune monitoring is crucial after small bowel transplantation. Recipients experience around 50 - 75% of the AR, more than 10% lymphoproliferative diseases due to over immune suppression and more than 10% chronic rejection which was ended up with graft loss within 5 years after transplantation especially in children.[31]

Unlike other types of transplantation, the intestine lacks a reliable and minimally invasive marker to predict rejection. Protocol biopsies and histological analysis remain the gold standard for allograft monitoring, but neither is free of complications, especially in smaller grafts. Up to 30% of biopsies are nondiagnostic and multiple biopsies may be required to exclude rejection.[32] Best if performed in the context of auxiliary testing of tissue and concomitant systemic biomarker evaluation. Among auxiliary assays increasing in use are measurements of citrulline level in the blood,[33]

cytofluorographic analysis of peripheral immune cell population,[34] cytokine profiling, and the quantitation of distinct gene set changes.[35] Developments in understanding of genes provide promise that limited gene sets, taken from blood or from intestinal biopsies, will enhance pathological diagnosis and endorse the morphological impression seen in the intestinal grafts.

a. *Biomarkers*

Dentritic cells (MDC) are potent antigen presenting cells and serve as markers for the recipients who are prone to AR. Plasmacytoid CD123 (PCD) dendritic cells which may have tolerogenic potential are known to increase during the rejection-free posttransplant period. A single center study done with 23 children declares that the children experienced AR have significantly higher MDCs/PDCs ratio compared to nonrejectors.[36] The carboxyfluorescein succinimidyl ester (CFSE) mixed leucocyte response (MLR) identifies T cytotoxic cell proliferation as a marker of AR in solid organ transplantation. The ratio of donor and third-party-induced proliferative CFSE T cells, which is measured by flow cytometry, was assessed as the immune reactivity index for each subset. Immune reactivity index of more than 1 shows increased risk of rejection and index less than 1 signifies decreased risk. The sensitivity and specificity of the test for detection of AR in intestine transplantation is 87.5 and 83.3%, respectively.[37]

It has been reported that miRNAs (micro RNA) have a critical role in immune regulation. The expression of 384 miRNAs and 280 mRNAs associated with immune, inflammatory and apoptotic pathways were comprehensively examined and the study revealed a miRNA signature occurring during intestinal AR.[36] These results seem to reflect an association not only with T cells but also with B-cell-mediated immune responses during AR. The over expression of miR-142 and miR-223 might promote T-cell predominant differentiation and mediate graft injury during intestinal AR. Furthermore, the results established a positive association between miRNA/mRNA pairs during intestinal AR. The data suggested that miRNAs have a critical role in the activation of infiltrating cells during intestinal AR.

These differences in miRNA expression patterns can be used to identify novel biomarkers and therapeutic targets for immunosuppressive agents. Wide interpatient variability reduces the ability to set cutoff points for rejection across the normal population. Nonetheless, these predictive and discriminative biological

markers require further large-scale in-depth studies.

Nucleotide Oligomerization Domain (NOD)-2, plays an important role in limiting innate immune activation. NOD2 is a pattern recognition receptor found on macrophages, dendritic cells and paneth cells that sense bacterial products. Defects in this sensor are thought to result in impaired expression of intestinal antibacterial peptides and other defects in innate immune responses, which could trigger an activation of immune cells through microorganism that might contribute to the rejection process. It is therefore possible that the structural shifts observed during rejection are a result rather than a cause of an exacerbated immune response. Strategies that suppress the levels of enterobacteria might therefore constitute a viable therapeutic alternative to improve small intestinal allograft survival. In healthy individuals, continuous secretion of antimicrobial peptides by paneth cells is controlled by the intracellular bacterial recognition protein. Patients with NOD2 polymorphisms who undergo SBT are at significantly greater risk for early rejection, decreased survival and death due to sepsis.[39]

Besides biomarkers which identify ARs, some markers have been investigated to find out the recipients who are prone to AR attacks. Although these markers have more than 90% sensitivity and specificity for predicting AR and appear as promising results, routine monitoring in the clinical setting has not been established.

b. *Imaging tests*

Imaging modalities like positron-emission tomography, other radioactive tracers such as ^{111}In-labeled platelets, radiolabelled white cell scintigraphy, and MRI have been investigated in terms of predicting AR. But none of these techniques were found to be useful due to low volume of SBT did not make possible to the interpretation of the any possible changes.

In an animal experiment, measuring luminal fluid changes with using new modified perfusion system along with FITC-inulin allowed real-time determinations of fluid and/or electrolyte movement along the small intestine.[40] By this way, it will be possible to follow-up any intestinal dysfunction reliably.

Laser doppler monitoring is another noninvasive monitoring method, and the method allows continuous monitoring. Monitoring by laser doppler is easy to perform and noninvasive, but the monitoring device has to be attached to the intestine. The implantable doppler seems at a glance the most ideal solution for

monitoring the grafts, as it is extremely fast and allows continuous monitoring. Yet even if the implantable doppler might be low in specificity, it still represents a fast and sensitive screening. Placement of the implantable doppler at the vascular pedicle in an intestine can be a challenge. To obtain an early warning regarding venous congestion, the monitoring device has to be placed around the vein of the transplant, and with the thin wall of the visceral veins the placement itself might induce venous congestion.

c. ***Stool tests***

Stool examinations were thought to be one of the predictors of AR. Recent discoveries around intestinal flora in the settings of various diseases may provide a viable model for studying intestine allograft injury with reference to alterations in the gut microflora after transplantation. Alterations in intestinal microflora have already been shown in intestine transplant recipients. During episodes of rejection, the proportions of phylum Firmicutes and the order Lactobacillales were signify-cantly decreased, while those of the phylum Proteobacteria, especially the family Enterobacteriaceae, were signify-cantly increased. So, especially Firmicutes, could be used to discriminate between nonrejection and active rejection.[41] The analysis showed an improvement in detecting differences between healthy transplants and rejection when compared to absolute cell numbers by determining the enterobacteria/total bacteria ratio. A cut-off point of <49.7% of Firmicutes would hereby discern active rejection with 90.0% sensitivity and 90.9% specificity.

Early results of stool testing for calprotectin, an S-100 protein released from infiltrating lymphocytes, has shown promise for surveillance of the intestine graft with elevations noted in some prior to the onset of histologic changes of AR and normal levels consistently associated with normal histology. The fecal content of calprotectin depends on migration of neutrophils into the intestinal lumen and has proven to be a sensitive marker of disease activity for inflammatory intestinal diseases.[42] It is recommended that the recipients with high levels of calprotectin should undergo intestinal biopsy. Another study showed that stool calprotectin levels of the recipients with rejection were significantly higher than the patients with viral enteritis or normal biopsies. The analysis suggested that the optimal cutoff level to distinguish rejection from other diagnosis is 92mg/kg with sensitivity of 83% and specificity of 77%.[43] Another suggested predictor is IGF-1. During episodes of intestinal dysfunction calprotectin levels significantly increase

and IGF-1 levels decrease.[53] In the patients with low IGF-1 levels and high calprotectin should have enteral feeding interrupted and put back on TPN till cause of high calprotectin is determined.

Citrulline is a protein released from enterocytes which the levels show negative correlation with the function of the small bowel graft.[33] From its enterocyte specific origin it first gained interest in intestinal failure as a marker. Although diminishing in plasma levels of citrulline appear to be associated with mucosal damage, it does not reliably predict rejection. In a recent study, citrulline was assessed as marker of the patient with wide variety of intestinal pathology and lack of predictor of rejection.[44]

The fecal content of alpha-1 antitrypsin can be used as a marker for loss of plasma proteins to the gastrointestinal lumen. Increased losses into feces can be caused by inflammatory diseases leading to enhanced vascular wall permeability, gut erosions causing loss of interstitial fluid, increased venous pressure, and lymphatic obstruction.[44]

d. ***Other predictors***

Motility of the transplanted intestine is crucial for transplant outcome. The interstitial cells of Cajal, with their pacemaker function, play an important role by regulating propulsive intestinal motility in the initial absence of extrinsic signaling. Local inflammatory and immunological changes in the tunica muscularis of transplanted intestines also result in dysmotility, both after ischemia/ reperfusion injury and during rejection. So, dysmotility can be one of the predictors of acute rejection.[45]

Bile acid analysis, serum gentamicin levels, Granzyme B and perforin analysis, proinflammatory mediator leukotriene E4, vitamins B2, B5 and B6 were tested as markers of rejection after small bowel transplantation, but none of these were found to be sufficiently reliable.[46]

Immune suppressive therapy

Several strategies and immunosuppressive regimens were utilized in SBT.[27] Best results were obtained with induction therapy with anti-lymphocyte antibodies, monoclonal or polyclonal, being used in most centers.[7,27] The most commonly used drugs for induction are thymoglobulin, alemtuzumab, basiliximab and daclizumab.

The maintenance immune suppression with tacrolimus is carried out; keeping the first month levels 12 to 15 ng/ml and reduced to 12 to 8 ng/mL after this initial period.[10] As in the other abdominal organ transplants, cortico-steroids are also used,

and removed in accordance with the type of grafts and preference of each center.

Although improvements in immune suppressants have resulted in better control of rejection after SBT, the incidence of rejection remains high, with rates of acute and chronic rejection after SBT. So, some novel attempts are examined in SBT, like bone marrow mesenchymal stem cell (BMMSC) transplantation in addition to SBT.[47,48] Bone marrow mesenchymal stem cells (BMMSCs) have shown immune-suppressive activity in transplantation. BMMSCs are able to inhibit immunologic refractory cells attacking transplanted organs and have the ability to enhance or maintain the re-epithelization process of small intestinal epithelium. In an animal study, infusion of BMMSCs suppressed AR in SBT, and that the immune regulatory effect of these cells were found to be due to the balance of Th1/Th2, Th17/Treg, and their related cytokines and NK cell activity, as well as Treg expansion.[48] Chimerism and tolerogenic regiments that induce Tregs and prevent the development of DSA are important treatment goals for the future. Recent studies have documented BMMSC synthesis and the release of several cytokines and growth factors such as, interleukin-11, hepatocyte growth factor, fibroblast growth factor-2 and insulin-like growth factor-I. Each of these factors has previously been described as facilitating intestinal mucosa repair, either through enhancement of cell proliferation or inhibition of epithelial cell apoptosis, or by a combination of both. Some beneficial effects of BMMSC transplantation with SBT were shown in the clinical settings.[47]

Tissue engineering

Although still in experimental phases, recent developments in identification and propagation of small bowel stem cells and advances in tissue engineering promise that realistic alternatives to the deceased donors can be seen in the future. In the animal model, short segments of small bowel which were manufactured by seeding intestine stem cell organoids onto collagen scaffolds demonstrated improved growth after placing in continuity with remnant bowel surgically compared to control animals without tissue engineered bowel.[49] These kinds of developments suggest that the future efforts may be targeted more toward repair of injured bowel or growth of new intestine tissues from autologous stem cells.

CONCLUSION

As a conclusion of these developments, morbidity and mortality rates of small bowel transplantation have decreased, lately. As the experience of the centers increase and the mechanism of immune

alloreactivity are elucidated, authors' belief is that the success in this field will be enhanced**.** Stem cell transplantation and tissue engineering are seen as promising procedures for the future.

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Figure 1. Isolated intestinal graft

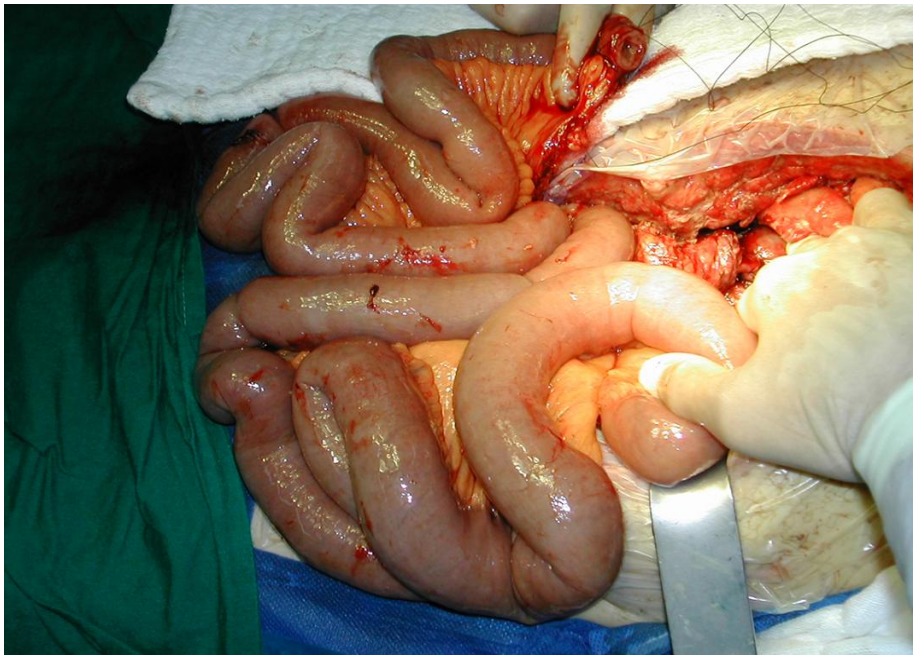

Figure 2. Mesenteric venous and arterial anastomosis of the small intestinal graft