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REVIEW

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# Pediatric intestinal and multivisceral transplantation: a new challenge for the pediatric intensivist

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**Abstract** *Introduction:* With increasing survival rates, intestinal transplantation (ITx) and multivisceral transplantation have reached the mainstream of medical care. Pediatric candidates for ITx often suffer from severe multisystem impairments that pose challenges to the medical team. These patients frequently require intensive care preoperatively and have unique intensive care needs postoperatively. *Methods:* We reviewed the literature on intensive care of pediatric intestinal transplantation as well as our own experience. This review is not aimed only at pediatric intensivists from ITx centers; these patients frequently require ICU care at other institutions. *Results:* Preoperative management focuses on optimization of organ function, minimizing ventilator-induced lung injury, preventing excessive edema yet maintaining adequate organ perfusion, preventing and controlling sepsis and bleeding from varices at enterocutaneous interfaces, and optimizing nutritional support. The goal is to extend life in stable condition to the point of transplantation. Postoperative care focuses on optimizing perfusion of the mesenteric circulation by maintaining intravascular volume, minimizing hypercoagulability, and providing adequate oxygen delivery. Careful monitoring of the stoma and its output and correction of electrolyte imbalances that may require renal replacement therapy is critical, as are monitoring for and aggressively treating infections, which often present with only subtle clinical clues. Signs of intestinal rejection may be non-specific, and early differentiation from other causes of intestinal dysfunction is important. Understanding of the expanding armamentarium of immunosuppressive agents and their side-effects is required. *Conclusions:* As outcomes of ITx improve, transplant teams accept patients with higher preoperative morbidity and at higher risk for complications. Many ITx patients would benefit from earlier referral for transplant evaluation before severe liver disease, recurrent central venous catheter-related sepsis and venous thromboses develop.

**Keywords** Intestinal failure · Multivisceral transplantation · Bowel transplantation · Intensive care · Rejection · Tacrolimus

## Introduction

Intestinal transplantation (ITx) was considered an "experimental" procedure until it attained certification in 2001 from the US Centers for Medicare & Medicaid Services (CMS). As with the evolution of liver transplantation, increased experience, improved surgical techniques, and advances in postoperative care and immunosuppressive therapy have moved ITx into the medical mainstream. In selected experienced centers, ITx is now remarkably successful with up to 90% 3-year patient survival and 95% freedom from parenteral nutrition after isolated ITx [1, 2]. These results have led to increasing application of ITx as the treatment for intestinal failure (IF) when parenteral nutrition fails. Currently, approximately 175 ITx's are performed annually in the United States, with annual increases in volume [3]. The Pediatric Intensivist is a primary member of the transplant team and is involved in the evaluation and management of these patients from the time of referral for ITx [4].

We reviewed current intensive care experience with this unique patient population, and highlight successful management strategies based on a literature search in MEDLINE using the search terms Intestinal, Transplantation, Pediatric and Children, as well as extensive review of the "year in review in intensive care medicine" series from the last 2 years [5–10]. This review is not aimed only at pediatric intensivists from ITx centers. Some of the greatest challenges with these patients present at the referring institutions where they are frequent consumers of PICU resources.

## Indications for intestinal transplantation (Table 1)

A recent multicenter European survey [11] has shown that ITx candidacy varies greatly among different centers. The basic indication for ITx is irreversible IF. Threatened progression of early and/or mild parenteral nutrition-associated liver disease in patients with IF usually indicates transplantation of the intestine alone. The expectation is that postoperative withdrawal of parenteral feeding will arrest the progression of liver disease [12]. When severe fibrosis or cirrhosis accompanies IF, particularly with signs of portal hypertension, transplantation of both intestine and liver are required. Motility disorders may involve severe impairment of gastric emptying and may mandate multivisceral transplantation (to include the stomach). The consensus of the transplant community is that loss of half of the usual access sites, the internal jugular and subclavian veins, is sufficient to warrant referral [13]. These patients may require several months of TPN after surgery, and the complexity of post transplant care demands adequate central venous access. Late referrals with poor i.v. access may render the patients ineligible for transplantation. Contraindications to surgery are listed in Table 1.

## Management of critically ill children awaiting intestinal transplantation

The most common indications for transfer of ITx candidates into the PICU are sepsis and active gastrointestinal tract bleeding, either of which may precipitate multiorgan failure. Many candidates are less than 1 year old, and even when not in frank respiratory failure, many have a history of prematurity, chronic lung disease and ventilator-dependence due to bronchopulmonary dysplasia. Recurrent, frequent and severe infections by antibiotic-resistant nosocomial bacteria and fungi are likely due to compromised reticuloendothelial function and indwelling central venous catheters, and secondary venous thrombosis is common. In contrast with patients with chronic liver disease alone, hypoxemia due to hepatopulmonary syndrome is uncommon in patients with both chronic liver disease and IF.

Many infants also have parenteral nutrition-associated liver disease [18] and present with portal hypertension and thrombocytopenia, resulting in bleeding from the mucocutaneous junction of gastrostomy, ileostomy, or entero-cutaneous fistulae. Unlike patients with advanced liver disease and an intact gastrointestinal tract, bleeding from large esophagogastric varices is unusual. Blood loss from stomas may be massive, producing hypovolemic shock, and requires frequent transfusions of blood products with all their associated complications, including sodium and volume overload; pulmonary hypertension may develop.

The challenge of the intensive care team is to improve marginal organ function and manage complications during the often prolonged wait for a suitable graft. Principles of management include optimization of respiratory status, minimization of ventilator-induced lung injury, maintenance of adequate perfusion to preserve residual liver function, and maintenance of hemostasis while avoiding edema due to fluid overload, hypoalbuminemia, and capillary leak from chronic cytokine release. Regular diuretics and supplemental electrolytes are frequently required. Recurrent low-grade stomal bleeding can be controlled with local pressure, application of silver nitrate or thrombin, and—if bleeding vessels are visible—cauterization or suture control. At Georgetown, pediatric house staff are trained to perform these tasks.

As with liver failure from other etiologies, prolonged QT interval is a frequent finding, and may be exacerbated by medications known to prolong QT such as octreotide. The QTc interval should be routinely monitored because of the risk of torsade de pointes in such patients [19, 20].

**Table 1** Indications and contraindications for pediatric intestinal transplantation

| Indications for intestinal transplantation |
|---|
| End-stage intestinal failure (permanent requirement for partial or complete intravenous alimentation that is no longer tolerated [14]) as manifested by:<br>a. Progressive liver disease with/without portal hypertension<br>b. Impending loss of adequate central venous access to deliver nutrition<br>c. Recurrent catheter-related sepsis |
| *Etiology for end-stage intestinal failure* |
| 1. Anatomic short bowel syndrome with loss of more than 75% of the small bowel [15], due to:<br>a. In neonates, predominantly:<br>i. Midgut volvulus usually secondary to malrotation<br>ii. Necrotizing enterocolitis<br>iii. Jejuno-ileal atresia<br>iv. Gastroschisis<br>b. In older children:<br>i. Late-onset volvulus<br>ii. Massive abdominal trauma<br>iii. Crohn's disease<br>iv. Desmoid tumors involving the root of the mesentery that are associated with familial adenomatous polyposis (16,17) |
| 2. Functional intestinal failure (despite adequate length) due to:<br>a. Long segment Hirschsprung's disease<br>b. Idiopathic pseudo-obstruction<br>c. Congenital seccretory diarrhea syndromes (i.e., microvillus inclusion disease) |
| **Contraindications for intestinal transplantation** |
| 1. Absolute contraindications:<br>a. Profound neurological disability<br>b. Life-threatening irreversible disease (unrelated to the digestive system)<br>c. Human immunodeficiency virus infection<br>d. Unresectable malignancies |
| 2. Relative contraindications:<br>a. Oxygen-dependent respiratory insufficiency<br>b. Inadequate vascular access to allow successful transplantation<br>c. Multi-system autoimmune disease<br>d. Social circumstances that may compromise adequate post-operative care of the transplanted patient. |

Despite the often extraordinary efforts of any critical care team, failure is common simply due to the lack of size-matched organs for small children. A significant proportion of children die on the ITx wait list, the majority of whom are less than 1 year old and weigh less than 10 kg [21].

## Operative procedure

In intestinal transplantation, the operative approach must be individualized. Because of variable indications and recipient anatomy, flexibility in planning the donor and recipient operations is critical [22].

In *isolated intestinal transplantation* the entire jejunoileum is placed into the abdominal cavity with reestablishment of both vascular and enteral continuity. Gastrostomy, jejunostomy or the combined "G-J" tubes are placed to avoid prolonged need for nasogastric suction and facilitate early feeding. In *combined liver/intestine transplantation* the liver and intestine graft with or without a segment of colon, the duodenum and at least a portion of the pancreas and biliary tree is implanted en bloc. The native foregut (stomach, pancreas, duodenum and spleen) is preserved. In *multivisceral transplantation* the new allograft includes the stomach, liver, pancreas and intestine; all corresponding native structures are resected.

## Post-operative management

A multidisciplinary approach to patient management with joint daily bedside rounds of the gastroenterologist, intensivist, surgeon, pharmacist and nutritionist is critical to optimal post-operative outcomes. Critical care immediately after intestinal transplantation (Table 2) is influenced by the overall state of health of the patient at the time of surgery, specific organs included in the composite graft, hemodynamic stability in the operating room, and immediate graft function. Removal of the foregut with the multivisceral transplant requiring an esophagogastric anastomosis complicates the post-operative course of multivisceral recipients. Chylous ascitic leakage is more commonly found after institution of enteral feeding in these patients than after isolated intestinal transplants, mandating the use of parenteral nutrition

**Table 2** Immediate postoperative monitoring of small bowel transplant recipients at Georgetown University Hospital

| | |
|---|---|
| *Cardiovascular* | *Hematologic* |
| Adequate graft perfusion | Monitor prothrombin time, INR and platelet count frequently |
| Bedside Doppler examination of the stoma | allow relative hypocoagulability |
| Adequate oxygen delivery | use fresh frozen plasma and platelet transfusions sparingly |
| Good capillary refill and blood (perfusion) pressure | *Infections* |
| Adequate CVP | Obtain daily surveillance blood cultures, white blood cell counts |
| Hematocrit goal of 27–30% | Monitor for possible catheter-related infections |
| Lower blood viscosity and relative hypocoagulability | When necessary, obtain cultures from abdominal drain fluid |
| Arterial oxygen saturation >95% | Consider bronchoscopy/bronchoalveolar lavage for pneumonia |
| Serum lactate levels | Look for subtle signs of intra-abdominal infection |
| Perfusion pressure (avoidance of vasoconstrictor agents if possible) | Obtain weekly viral studies |
| Control of hypertension | *Gastrointestinal/nutrition* |
| Monitor QT interval | Monitor liver function tests frequently |
| *Respiratory* | In multivisceral transplant recipients, monitor serum amylase and lipase levels |
| Monitor blood gases; maintain normal gas exchange and adequate oxygenation | Look for signs of rejection |
| Protective lung ventilation with low tidal volumes and peak plateau pressures | Abdominal pain, cramping, or signs of obstruction, fever |
| Assess diaphragmatic function if difficulty weaning from the ventilator | Monitor ileostomy output carefully for volume, color and consistency |
| *Renal/electrolytes* | Perform ileoscopies with mucosal biopsies twice a week for 6 weeks post operatively |
| Frequent monitoring of BUN and creatinine | Monitor tacrolimus serum levels daily |
| High tacrolimus levels correlate closely with renal function | Monitor abdominal drain fluid volume and color; when in doubt, obtain bilirubin levels |
| Frequent monitoring and correction of glucose, electrolytes and bicarbonate | Monitor daily nutritional intake (calories, protein, fat, glucose electrolytes and trace elements) carefully |
| Hyperglycemia should be aggressively corrected; insulin infusion may be required | |
| Hypomagnesemia may potentiate tacrolimus neurotoxicity and levels should be closely monitored | |

or medium chain triglyceride diets in these patients until the disrupted lymphatics seal.

In general, patients with liver failure prior to transplant (combined liver/intestine or multivisceral recipients) have a more complex course than those patients receiving an intestinal graft alone, because impaired respiratory, renal, and cardiac function that are present before surgery do not correct immediately after organ replacement. Severe coagulopathy and portal hypertension as well as a more pronounced reperfusion injury make the transplant operation significantly more difficult, transfusion requirements higher, and may result in postoperative fluid overload.

**Table 3** Results of pediatric intestinal transplantations at Georgetown University Hospital 12/2003–12/2007

| | All | Isolated bowel | Liver/bowel | Multivisceral |
|---|---|---|---|---|
| *N* | 38 | 8 | 20 | 10 |
| Survival (%) | 81.6 | 87.5 | 85.0 | 70.0 |
| Survival to postoperative PICU discharge (%) | 97.4 | 100 | 100 | 90.0 |
| Graft survival in survivors (%) | 100 | 100 | 100 | 100 |
| Acute intestinal rejection (%) | 13.2 | 12.5 | 15.0 | 10.0 |
| Acute liver rejection (%) | 0 | 0 | 0 | 0 |
| Median ventilator days | 9.5 | 1.5 | 9 | 22 |
| Median ICU days | 18.5 | 7.5 | 18 | 41 |
| Causes of death | | (1) drug-resistant pneumonia in a patient with cystic fibrosis | (1, 2) septic shock<br>(3) acute rejection/ sepsis | (1) disseminated aspergillosis<br>(2) ARDS, renal failure, sepsis<br>(3) Graft versus host disease |

Severe infections and the need for reoperation for peritonitis in the first week post-transplant are also more common in patients with multivisceral transplants. Vital organ function typically continues to deteriorate in these patients in the early post-operative period as a result of the extreme pathophysiological stresses associated with transplant surgery. As a result, duration of mechanical ventilation and time interval to successful enteral feeding are longer in these patients (Table 3). Poor vital organ function can be surmounted with appropriate critical care support if good graft function is obtained early and maintained thereafter. In contrast, severe preservation injury and associated poor initial graft function amplifies existing multi-system dysfunction that may lead to death of the patient.

## The intestinal graft

A viable intestinal graft is indicated by a healthy-appearing ileal stoma with a strong Doppler signal. Serum lactate levels, which often rise significantly during the first 12–24 post-operative hours, typically fall to normal thereafter, whereas continued elevation suggests occult gut ischemia that may indicate surgical exploration. Post-operative ileus generally persists for several days, during which proximal graft decompression is essential to avoid distention that increases resistance to mural blood flow and the risk of graft ischemia. After this time, detection of bowel sounds, stoma drainage, and tolerance of gastric tube occlusion indicate that enteral feeding can begin. When graft size does not match the size of the abdominal cavity, compartment syndrome may develop, jeopardizing perfusion to the fresh graft and the kidneys as well as restricting diaphragmatic mobility. When suspected, monitoring of intraabdominal pressure [23] may be helpful in assessing the need for surgical intervention. Alternatively, the abdomen may be left open with temporary silastic closure and staged definitive closure.

## The liver graft

Following a combined liver/intestine transplant, absence of donor-to-recipient portal vein and hepatic artery anastomoses inherent to isolated liver transplantation reduce the risk of early thrombosis and resultant hepatic necrosis. Rather, early hepatic function depends on the degree of ischemia-reperfusion injury to the entire graft, adequacy of intestinal graft perfusion that constitutes the primary source of portal vein inflow, and the overall cardio-pulmonary stability of the patient. Within the first 24–48 h, falling serum aminotransferase levels indicate the lack of ongoing hepatic injury. Progressive falls in serum bilirubin concentration, serum lactate level and prothrombin time/INR confirm early onset and maintenance of hepatic metabolic and synthetic function.

## Cardiovascular

The primary challenge of early post-operative management is maintenance of adequate intestinal graft perfusion that, as noted above, can be monitored with Doppler examination of the stoma at the bedside, thereby assisting with hemodynamic and fluid management. Assurance of oxygen delivery to the newly grafted organ is of paramount importance. It is defined by the equation: $DO_2 = [(Hgb \times 1.34 \times SaO_2) + (PaO_2 \times 0.003)] \times$ cardiac output. Hemoglobin oxygen saturation >95% and hematocrit between 27 and 30% provide the optimal balance between oxygen carrying capacity and viscosity that, when high, reduces cardiac output and microcirculation. Tissue perfusion is also preserved by maintenance of a relatively hypocoagulable state. An INR of 2–3 and platelet count as low as $40 \times 10^{-6}$/L are not usually associated with spontaneous bleeding, and plasma and platelet transfusions should generally not be given if post-operative intra-abdominal bleeding is absent.

Hemodynamic stability is critical for graft viability and function. Cardiac output should be normal to high, based primarily on adequate volume status (assessed by central venous pressure in conjunction with clinical examination) rather than inotropic support, as early postoperative hypotension is usually due to hypovolemia secondary to intraoperative sub-optimal fluid administration, shifts of fluid out of the intravascular compartment, and high peritoneal fluid losses. In light of protein loss from peritoneal fluid, albumin is usually given. Ideally, maintaining adequate hematocrit, oxygenation and preload will lead to adequate tissue perfusion. However, if vasopressor and/or inotropic support are necessary, agents with a predominance of alpha receptor activity, i.e., norepinephrine, should be avoided, since these vasoconstricting agents tend to produce acceptable blood pressure at the expense of graft perfusion.

After the acute postoperative phase, either hypotension or hypertension may be encountered. Hypotension may result from dehydration secondary to high stoma output that is, in turn, due to hyperperistalsis of the denervated graft and/or enteropathy usually due to rejection or infection. Periodic hypertension is often due to acute hypervolemia, calcineurin-inhibitor-induced nephrotoxicity, and steroids and is managed by short-acting calcium channel blockers such as nifedipine with a switch to long acting agents, if frequent doses are required. Dose requirements may be altered by absorption and intestinal graft function. Beta-blockers are commonly employed in patients with extended liver failure who have left ventricular hypertrophy. As in the preoperative period, QTc should be closely monitored to avoid torsade de pointes; offending medications commonly given mainly after transplant include tacrolimus, pentamidine, macrolides (azythromycin, erythromycin), methadone and chloral hydrate.

## Respiratory

Many recipients have compromised respiratory function preoperatively. After transplant, generous fluid administration required to maintain graft capillary blood flow risks pulmonary edema, leading to intrapulmonary shunts, especially with pre-existing lung disease. Decreased chest wall and abdominal wall compliance secondary to edema, large graft size, ascites, and pleural effusions may further compromise pulmonary function. High inspired oxygen concentrations and distending airway pressures needed to maintain desired hemoglobin oxygen saturation greater than 95% may lead to further pulmonary injury. In patients with severe lung disease, permissive hypercarbia may minimize such injury, with target tidal volumes of 6–8 cc/kg body weight and plateau pressures <30 cm $H_2O$, as per the ARDSnet protocol [24]. High frequency oscillatory ventilation is sometimes required to achieve adequate oxygenation while maintaining low intra-alveolar pressures. Patients with a multivisceral transplant are at an increased risk for transient diaphragmatic dysfunction that can be assessed with ultrasonography or fluoroscopy. This may prolong the mechanical ventilatory course but is almost always reversible with conservative management. The trachea of most patients with isolated small intestinal transplants can be extubated within the first 24–48 h after surgery. Patients with multivisceral transplants usually remain intubated for several days, particularly when large graft size mandates delayed abdominal closure (Table 3), however, the priority must be early extubation to reduce the risk of ventilator-associated pneumonia. Pre-existing lung disease is a major determinant of duration of postoperative mechanical ventilation.

## Renal

Renal dysfunction occurs in up to 25% of transplant recipients due to the cumulative effects of cirrhosis and delayed liver graft function, episodic hypotension, and exposure to nephrotoxic agents (i.e., aminoglycosides and tacrolimus). Maintenance of adequate cardiac output may help maximize renal perfusion. Some transplant centers use of low-dose dopamine 2.5–5.0 μg/kg/min or fenoldopam 0.03–0.1 μg/kg/min to improve renal blood flow, although proof of efficacy is lacking. When extra-corporeal renal support is needed, we prefer continuous venovenous hemodiafiltration (CVVHD) to avoid rapid volume shifts that may adversely affect organ perfusion. Oliguria and resistance to diuretic therapy may result in excessive fluid retention following initial post-transplant resuscitation, leading to prolonged ventilation and to potential delays in abdominal closure in patients with a prosthetic mesh covering the abdominal wound.

## Electrolytes

Post-operative electrolyte surveillance protocols with close monitoring of electrolytes are essential. Metabolic acidosis, hypokalemia, hypocalcemia, hypophosphatemia, and hypomagnesemia are common post-operatively, and may reappear following initiation of enteral nutrition because of increased fecal losses that require continued intravenous and later enteral replacement. Postoperative hyperglycemia is also common, irrespective of whether all or part of the pancreas is included in the composite graft, and close blood glucose monitoring is required. The value of tight glycemic control with continuous intravenous insulin infusions [25] has been recently challenged [26]. A multicenter pediatric study is underway in North America. Insulin therapy is sometimes required following multivisceral transplantation, as the native pancreas is removed and insulin secretion by the pancreas graft may be delayed.

## Hematologic

Anemia, neutropenia, and thrombocytopenia are common postoperatively, especially in patients with preoperative liver dysfunction and persistent hypersplenism, and may be aggravated by myelosuppressive medications such as ganciclovir, anti-lymphocyte globulin, and some antibiotics. Neutropenia is rarely severe enough to indicate growth factor therapy, e.g., filgrastim.

## Pain control

In patients with liver dysfunction, careful selection of sedatives and analgesics is necessary because of the potential for prolonged and/or excessive effect and benzodiazepines should be avoided whenever possible. Perioperative epidural infusion of analgesics may reduce the need for systemic medications and their untoward cardiorespiratory effects [27].

## Infections

Infection is a major risk in the early post-operative period, reflecting the placement of a non-sterile organ, i.e., the intestinal graft, into a frequently non-sterile abdominal cavity in the setting of profound immunosuppressive therapy. Multi-drug resistant bacteria are common due to prolonged previous hospital stays and repeated antibiotic exposure. Later, invasive fungal infection becomes common, particularly in those with motility disorders and with pre-transplant diabetes mellitus, corticosteroid therapy and renal insufficiency. After transplant, hyperglycemia, poor graft function, and renal failure continue to promote

infection, as does intensification of immunosuppression necessitated by rejection [16, 17]. After the first post-transplant month, the cumulative effect of intense immunosuppressive therapy renders patients susceptible to numerous additional opportunistic viral, and protozoan pathogens, such as cytomegalovirus, Epstein–Barr virus, and rarely Pneumocystis carinii [28, 29]. Strict adherence to aseptic technique during invasive procedures, dressing changes, and hand washing before and after each patient contact are essential, as is adherence to the Guidelines for the Prevention of Intravascular Catheter-Related Infections issued by the Center for Disease Control [30].

The Central Venous Catheter Bundles modeled after the Johns Hopkins Hospital protocol [31, 32] have been particularly successful in reducing line infections at our institution. When positive cultures are obtained through the central venous catheter, especially with negative concomitant peripheral cultures, one must keep in mind that only about 8% of colonized catheters result in true infection [33], and the challenges imposed in finding venous access sites in these patients, who may have had multiple venous thromboses from years of total parenteral nutrition. An attempt to salvage the catheter by treating with antibiotics through the line is reasonable [34]. However, if the patient's condition continues to deteriorate, or if the culture contains fungi, replacement of the catheter is mandated. Routine pre-operative magnetic resonance venography and postoperative Doppler ultrasound evaluation have been very helpful in finding venous access sites.

Prophylactic intravenous broad-spectrum antibiotic and anti-fungal agents are typically given for several days after transplantation or until initial endoscopic biopsy confirms graft mucosal integrity. Initial choice of antibiotics depends on the nature of infections occurring during the late pre-transplant period; thereafter, antibiotic choice is more often guided by culture results. Anti-viral prophylaxis, initially ganciclovir, is administered routinely for several months after transplant. Thereafter, surveillance for CMV and EBV viremia using PCR methodology guides resumption of therapy [29].

Sites of early post-transplant infection include the abdominal cavity, bloodstream, urinary tract, and lungs. Usual symptoms and signs of infection in these and other locations such as fever, tachycardia, abdominal pain, abdominal tenderness, and dysuria along with leukocytosis may be subtle or absent due to intense immunosuppressive therapy, particularly corticosteroids, and appropriate post-operative pain control. Early recognition requires continuous clinical suspicion supplemented by frequent cultures of normally sterile sites, specifically blood and urine, as well as invasive diagnostic procedures. Bronchoscopic lavage should be performed for acute respiratory deterioration or persistent pulmonary infiltration [35]. Similarly, suspicion of peritonitis may require prompt abdominal re-exploration, particularly within the first week following transplant. Presence of bacteria in fluid obtained from peritoneal drains is less meaningful, as colonization develops quickly.

## Rejection and other early alterations in graft function

Recognition of changes in stoma output is essential to assessment of graft health, and ileostomy output should be regularly assessed for volume, color and consistency. Stomal output in the first week after transplantation when little or no feeding is given is usually no more than 20 mL/kg/day, for children and 300 mL/day for adolescents. Blood in the stool should clear within the first few days. Graft rejection, which occurs with a prevalence of about 30% may be first identified 1–2 weeks after transplant, usually within the first 2–3 post-transplant months.

Because there is no reliable circulating biomarker for intestinal rejection, diagnosis is based on the clinical course, endoscopic appearance of the allograft in surveillance endoscopy that is performed weekly to monthly within the first post-transplant year (initially via the ileal stoma), [36, 37], and the histology of biopsy specimens. New feeding intolerance with emesis and increased stomal output suggest early rejection; onset of cramping suggests progressive disease. Blood in stomal effluent or friable or bleeding stoma imply a late diagnosis of advanced rejection. Fluid losses may be high enough to require replacement to avoid severe dehydration. Less commonly, stomal output may be reduced rather than increased with feeding intolerance, indicating radiological evaluation for mechanical obstruction and, potentially, operative intervention. Perforation, either of the graft or remnant small bowel, is unusual but may occur within the setting of early ischemia-reperfusion injury and protracted, severe rejection. Internal herniation of the intestine may result in obstruction and requires surgical intervention. If the graft includes other organs such as the liver or kidney, appropriate serum markers for injury of those organs can be followed, but the majority of rejection episodes involve the intestinal portion of the composite graft alone.

While most episodes of acute rejection do not require ICU care, severe rejection may lead to graft mucosal exfoliation with risk for severe fluid losses, sepsis, and multi-organ failure with "cytokine storm". When septic shock occurs in the absence of graft rejection, a balance must be struck between reducing the level of immunosuppression to allow recovery from infection and maintaining sufficient immunosuppression that minimizes the risk of catastrophic, secondary graft rejection. Implementation of the Surviving Sepsis protocol [38, 39] for these patients may be lifesaving, but the mortality from severe, exfoliative allograft rejection remains high.

## Nutritional management

When the primary indication for transplantation is declining central vein access, patients that are managed by a competent intestinal failure team usually present with appropriate nutritional status. Pre-transplant nutritional management of patients who are in both liver and intestinal failure is more challenging [40]. These patients may present for transplantation either with excessive fat stores because of historical attempts to promote maximal body size for successful organ matching or with some degree of body fat (and skeletal muscle) depletion resulting from caloric restriction intended to slow progression of parenteral nutrition-associated liver failure.

Following transplantation, volume and electrolyte status usually allow resumption of parenteral nutrition on the second to fourth post-operative day. The brief interruption of meaningful caloric intake and careful attention to balance of electrolytes, particularly potassium, calcium, phosphorus, and magnesium, in the PICU will prevent refeeding syndrome (rapid fall in phosphate, magnesium and potassium, along with an increasing extracellular fluid volume that may occur when previously malnourished patients are fed with high carbohydrate loads). Resolution of ileus generally permits initiation of enteral feeding by 5–7 days after transplant starting with an electrolyte solution; the jejunal route is often preferred, as delayed gastric emptying is common. Thereafter, amino acid or short peptide-based isotonic or hypotonic formula is infused in small but increasing volumes while parenteral calories are correspondingly reduced until the intestinal transplant can fully accommodate all nutritional needs of the patient. Excessive or deficient energy and nitrogen intake may be detrimental to recovery, and indirect calorimetry may be useful for determining resting energy expenditure as compared to clinical estimation alone. Formulas containing standard quantities of long-chain triglycerides are started several weeks after transplantation, when retroperitoneal lymphatic drainage has been re-established.

## High stomal output

Stomal output exceeding 40–50 mL/kg/day often results in dehydration. There are numerous causes of high output other than graft rejection. Early increases in response to enteral nutrition have been attributed to rapid intestinal transit associated with disconnection of the graft from the central nervous system. Presumed neurogenic diarrhea may respond to anti-peristaltic agents such as high-dose loperamide (Imodium®) and diphenoxylate (Lomotil®). Increases in stoma output caused by infection with Rotavirus and Norovirus typically occur more suddenly and in higher volumes [over 100 mL/kg/day] than are typical of acute rejection, and may result in acute dehydration and hypovolemic shock; resistance to anti-peristaltic agents is typical [41].

The nephrotoxic effects of tacrolimus and other agents may lead to impaired concentrating ability; polyuria may continue until hypotension supervenes. Because of concurrent medication-induced reductions in baseline GFR, blood urea nitrogen levels may become very high. Absence of anticipated oliguria during periods of high stoma output may delay recognition of dehydration by both family and health care providers. Treatment consists of prompt restoration of intravascular volume, immediate intestinal biopsy to identify the cause of the diarrhea, and adjustments in immunosuppression based on diagnosis; treatment of rejection (increased immunosuppression) may be detrimental if the correct diagnosis is viral enteropathy.

## Immunosuppressive therapy

Numerous regimens have been employed to induce the high degree of immunosuppression required to prevent initial rejection of the allograft [42, 43]. Standard agents include methylprednisolone in combination with tacrolimus (Prograf®). Methylprednisolone is administered in doses as high as 50 mg/kg in total during the first post-operative week, subsequently converted to low-dose [0.1–0.2 mL/kg/day] oral prednisone. Tacrolimus is administered either through the gastrointestinal tract or intravenously to achieve a whole blood trough level as high as 25 ng/mL during the first post-operative month and tapered progressively thereafter. In recent years, this regimen is often supplanted with the interleukin-2 receptor antagonists basiliximab (Simulect®) and daclizumab (Zenapax®) as well as anti-lymphocyte preparations such as Thymoglobulin® and alemtuzumab (Campath®). Maintenance immunosuppressive therapy often employs anti-proliferative agents such as rapamycin (sirolimus, Rapamune®) and mycophenolate mofetil (CellCept®) in combination with low-dose tacrolimus (5–10 ng/mL), with or without prednisone [44, 45].

## Outcomes and upcoming challenges

A recent European report of 10 years of pediatric intestinal transplantation [2] shows a 3-year survival rate of 71.5%. Twenty-nine percent of the patients died within 4 months of grafting, mostly from infectious complications [46]. Table 3 shows recent results for 38 pediatric intestinal transplants from our center from the last 4 years. The International Intestinal Transplant Registry updates survival data every few years, but single center experience often achieve higher survival rates. In our experience, one year survival of 85% has been achieved for all recipients of intestinal transplants. As outcomes of

ITx improve, transplant teams accept patients with higher pre-operative morbidity and organ dysfunction and at higher risk for complications. Early referrals for transplant evaluation before severe liver disease, recurrent central venous catheter-related sepsis and venous thromboses develop will increase the likelihood of survival to transplant and will reduce the risk of post operative morbidity.

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