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Intestinal transplantation: An overview

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Abstract

Intestinal transplantation may become necessary in patients with short bowel syndrome (SBS) who fail intestinal rehabilitation. Most children requiring intestinal transplantation (68%) have SBS due to anatomic loss. Intestinal transplantation can occur in isolation or in combination with other organs. Many children will have advanced liver disease at the time of referral and will undergo combined liver-small bowel transplantation. Considerable progress in immunosuppression has led to decreased rates of acute rejection after transplantation and to improved early allograft survival while minimizing toxicity.Survival with small bowel transplantations has greatly improved over the last 20 years with chronic rejection being the major contributing cause to late graft loss.

Keywords: Intestinal transplantation; Short bowel syndrome; Liver-small bowel transplant; Allograft rejection

1. Indications and evaluation

Intestinal transplantation, either alone or combined with the liver or other organs, may become necessary in patients with short bowel syndrome (SBS) who fail intestinal rehabilitation. The first successful isolated and combined small bowel transplantations occurred almost 25 years ago [1]. Over the last two decades, significant advances have led to markedly improved patient and graft survival. The Centers for Medicare and Medicaid Services (CMMS) has approved intestinal, combined liver-intestinal and multi-visceral transplantation at CMMS approved transplant centers as standard of care for patients with irreversible intestinal failure who cannot be maintained on parenteral nutrition [2,3]. Approved indications for transplantation in intestinal failure patients include: (1) impending liver failure based on the presence of jaundice, elevated liver injury tests (alanine transaminase and aspartate transaminase), splenomegaly, varices, coagulopathy, or cirrhosis on liver biopsy; (2) loss of major venous access defined as thrombosis of two or more central veins including subclavian, jugular and femoral veins; (3) frequent central line associated sepsis consisting of two or more episodes of systemic sepsis per year that require hospitalization; (4) one episode of line related fungemia, septic shock or acute respiratory distress syndrome, or (5) recurrent episodes of severe dehydration despite intravenous fluid supplementation in addition to parenteral nutrition [2,3].

Between 1990 and 2008, 1041 pediatric small bowel transplantations were performed in the United States [1]. Annually, 100–120 pediatric intestinal-containing transplants are performed worldwide [3]. Indications for pediatric intestinal transplantation include failure to achieve more than half of calorie requirements enterally with either growth failure, worsening liver function, loss of central venous access, or recurrent sepsis. Most children requiring intestinal transplantation (68%) have SBS due to anatomic loss with the most common etiologies being gastroschisis (24%), NEC (16%), volvulus (15%), and small bowel atresia (9%) [4].

There are several important issues that must be addressed prior to pursing pediatric intestinal transplantation [1,4]. First, a complete evaluation to determine the necessity for intestinal or combined organ transplantation should be performed at a CMMS approved transplant center. This workup typically includes contrast studies of the upper and lower gastrointestinal tracts and liver biopsy. Next, it must be determined if the recipient can safely undergo a transplant with

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the potential for good functional outcomes. Severe comorbid conditions, such as neurologic injury or bronchopulmonary dysplasia, may limit the chance for functional outcomes and should be considered when deciding appropriateness of transplantation. Finally, it must be determined if the child's caregivers have the capabilities to adequately care for an intestinal transplant recipient including being compliant with the complex medication regimen and observant of signs of infection or rejection.

2. Types of intestinal transplants

Intestinal transplantation can occur in isolation or in combination with other organs. Many children will have advanced liver disease at the time of referral and will undergo combined liver-small bowel transplantation [2,3]. In addition, younger children with preserved liver function may have rapid deterioration after isolated small bowel transplantation; therefore a large proportion of younger children will receive combined liver small bowel transplants [5,6]. The composite liver-small bowel transplant usually will include the duodenum and the head of pancreas; this allows for a technically simpler procedure by not requiring a biliary anastomosis which can be challenging in smaller patients. Multi-visceral transplants will also include the stomach and are performed in children with non-functioning stomachs (e.g. patients with pseudo-obstruction). Recently, several centers have started to transplant the colon along with the small bowel and other organs to improve absorptive capacity; early reports have not demonstrated any additional morbidity and mortality [3,7]. In patients undergoing intestinal transplantation, an ileostomy is performed to allow for easier allograft monitoring with endoscopic biopsies. Routine endoscopic surveillance of the transplanted intestine is performed to assess graft integrity and diagnose rejection.

3. Immunosuppression

Intestinal transplantation poses a significant immunologic challenge because 80% of immune cell normally reside in gut and they are re-populated with recipient cells after transplantation [2]. Acute rejection (ACR) can limit long term survival; it occurs in 60% of pediatric intestinal recipients with a third of cases being severe [8]. Considerable progress in immunosuppression has decreased rates of ACR and led to improved early allograft survival while minimizing toxicity.

Current immunosuppression protocols rely on early lymphocyte depletion to achieve early elimination of graft-specific inflammatory T-cells. Primary induction with either rabbit anti-human thymocyte globulin (rATG) or alemtuzumab is becoming increasingly common [9–12]. These induction therapies deplete recipient lymphocytes in an attempt to promote partial tolerance to the graft and allow for minimization of immunosuppression long term. They may potentially accelerate the elimination of donor specific T-cells by apoptosis and reduce dependence on high dose immunosuppression [9]. Tacrolimus is the most common agent used for maintenance immunosuppression in intestinal transplant recipients. Tacrolimus is a calcineurin inhibitor whose major limiting toxicity is renal damage. The most effective and reliable long term immunosuppression regimens consist of tacrolimus with low dose steroids with or without sirolimus. Some centers have been able to use tacrolimus as a sole agent reserving steroids for episodes of rejection. Although potentially beneficial in terms of limiting side effects, patient and graft survival data on steroid free immunosuppression regimens is still limited.

4. Rejection

Acute cellular rejection (ACR) may be asymptomatic or present with diarrhea, abdominal pain, distention, nausea, vomiting, or a sudden increase or decrease in stomal output [3]. During ACR, there is disruption of the gut mucosal barrier which can lead to fevers and sepsis, therefore fevers and bacteremia must be considered as signs of ACR and should prompt graft biopsies [1].

ACR is most common during the first 90 days post-transplantation. With the use of induction therapy with rATG, ACR occurs in 60% of patients [1]. Early diagnosis and treatment of ACR is critical for successful reversal, therefore scheduled surveillance biopsies of the graft are performed through the ileostomy created at the time of transplantation. A typical early surveillance biopsy schedule includes twice per week in the first month, weekly during the second month, then twice per month for the third month and then monthly [1]. Improved detection and treatment of ACR has led to improved early graft survival [2].

Most episodes of ACR in the early post-transplant period are detected by surveillance biopsies. Histologically, ACR is graded from mild to severe based on the degree of epithelial damage [3]. On biopsy, the mucosa may be friable or ulcerated and the pathology will show a lymphocyte rich infiltrate and crypt apoptosis [1]. Infections with viruses, including adenovirus, calicivirus, and cytomegalovirus, or *Clostridium difficile* can masquerade as rejection; therefore biopsy with interpretation by an experienced pathologist is necessary.

ACR is treated with optimization of tacrolimus and corticosteroids. In cases of steroid resistant ACR, treatment with anti-lymphocyte antibodies may be necessary. During ACR treatment, antiviral prophylaxis should be administered to prevent opportunistic infections. Post-ACR graft biopsies are routinely performed to document resolution.

Chronic rejection is the major cause of late graft loss. Patients can present with abdominal pain with chronic diarrhea, bowel obstruction or gastrointestinal bleeding, weight loss or failure to thrive. Histologically, there is arteriopathy in the graft with blunting of the villi and increased of stromal tissue. In recent series, chronic rejection rates are 10–15% with