Seminars in Pediatric Surgery 26 (2017) 241–249

Contents lists available at ScienceDirect

Seminars in Pediatric Surgery

journal homepage: www.elsevier.com/locate/sempedsurg

Pediatric intestinal transplantation

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ARTICLE INFO

Keywords:
Intestinal failure
Intestinal transplant
Immunosuppression
Infection
Post-transplant lymphoproliferative disease
Quality of life

ABSTRACT

The field of intestinal transplantation has experienced dramatic growth since the first reported cases 3 decades ago. Improvements in operative technique, donor assessment and immunosuppressive protocols have afforded children who suffer from life-threatening complications of intestinal failure a chance at long-term survival. As experience has grown, newer diseases, with more systemic manifestations have arisen as potential indications for transplant. After discussing the historical developments of intestinal transplant as a backdrop, this review focuses on the specific pre-operative indications for transplant as well as the great success that intestinal rehabilitation has witnessed over the past decade. A detailed discussion of evolution of immunosuppressive strategies is followed a general review of the common infectious complications experienced by children after intestinal transplant as well as the current long- and short-term results, including a section on new research on the quality of life in this challenging population of patients.

Introduction and history

The evolution of intestinal transplantation as a life-saving procure for children with complications of intestinal failure has occurred over nearly a half-century. Early attempts were fraught with graft loss from uncontrollable rejection, reperfusion injury, and technical complications; patient mortality was primarily due to opportunistic infections and graft versus host disease. Although multifactorial, the early failure of intestinal transplantation was primarily from failure of proper immunosuppression strategies. Indeed, only two patients have survived long term from this era—one of whom was the recipient of a living related donor intestinal transplant, reported in 1989.[1] Intestinal transplantation became the mainstay of treatment for patients with intestinal failure in the 1990s, with a dramatic increase in the numbers of children receiving intestinal allografts from decreased donors. The introduction of recipient pre-conditioning with anti-thymocyte antibody and the development of tacrolimus, as well as a heightened understanding of the technical aspects of isolated intestinal, as well as more complex composite visceral allografts, were the primary drivers of this progress. Significant advances in pre- and post-transplant management afforded a greater application of the procedure, with more than 1400 pediatric intestinal transplants being performed in the United States since 1990, and a growing global experience with intestinal transplantation being performed on all continents across the globe. As the experience with intestinal transplant has grown, a great deal of work has been done to better define transplant's place in the treatment algorithm for children suffering from intestinal failure. The focus of this review will be the changing practices that have occurred in the field of pediatric intestinal transplant over the past decade with a review of indications, pre-transplant management of specific causes of intestinal failure, and outcomes of transplant.

Etiology of intestinal failure

Intestinal transplantation is a life-saving technique when performed in well selected children at the appropriate time in their disease course. The relative success of intestinal transplant should be tempered against the risks associated with the procedure and immunosuppression, and proper timing of transplant evaluation and transplantation is important at mitigating the risk associated with continued need for parenteral nutrition. Transplant of the intestine is performed, barring a few rare indications, for children with complications of intestinal failure. Intestinal failure is broadly defined as the lack of sufficient intestinal function to provide absorption of nutrients, water and electrolytes for maintenance of

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http://dx.doi.org/10.1053/j.sempedsurg.2017.07.007
1055-8586/

nutritional homeostasis and water balance. In children, adequate intestinal function is also required for growth and maturation, an important component to both physiologic and neurologic development. Pediatric intestinal failure is most commonly caused by short-gut syndrome, often the result of surgical resection of non-viable intestine due to volvulus, gastroschisis, and necrotizing enterocolitis or from long-segment intestinal atresias. These etiologies result in the pure lack of intestinal surface area and enterocyte volume for proper absorption of nutrients. In addition, intestinal failure in children can be due to functional disorders of the intestine and intestinal motility. Enterocyte dysfunction due to microvillus inclusion disease and tufting enteropathy cause a characteristic secretory diarrhea and are inherited forms of intestinal failure that present early in childhood with failure to thrive and dehydration. Motility disorders are also represented as a cause of pediatric intestinal failure, representing a broad group of ill-defined diseases. Long-segment aganglionosis is the most well described as a pathologic entity, with clear absence of ganglion cells in the bowel. Intestinal pseudoobstruction and hollow-visceral myopathies are also included in this subset of patients with functional intestinal disorders and can affect varying lengths of the digestive tract from the esophagus to the rectum and can also cause bladder dysmotility requiring attention to urinary retention and incontinence. In the next section, we will discuss not only the pathophysiology associated with the varied etiologies of intestinal failure, but will also highlight the unique characteristics that may play important roles when considering intestinal transplantation.

Short-gut syndrome (SGS)

Several disease processes can lead to the development of short-gut syndrome. Necrotizing enterocolitis (NEC) is the prototypical disease that leads to subtotal intestinal resection in the neonatal period. The exact etiology of NEC is not understood; however, pathology generally reveals necrosis of large areas of contiguous intestine and the current management of this focuses on preservation of intestinal length and avoidance of immediate operative intervention. NEC is not seemingly associated with other congenital processes and in general, once resection has been accomplished, residual bowel is functionally normal with motility issues occurring in only 10% of patients.[2] Remnant intestinal length after intestinal volvulus should also be functionally normal, however, when associated with gastroschisis, most children will suffer from post-operative dysmotility. Abnormal motility is especially problematic in cases of gastroschisis and concomitant intestinal atresia.[3,4] Several variables have been described, which may be associated with long-term enteral autonomy. The preservation of an ileocecal valve, an intestinal length of more than 15 cm and the ability to establish enteral continuity have been associated with a better chance at enteral autonomy and avoidance of intestinal transplant.[5] Further prognostic studies have confirmed that the residual length of intestine ($>$ 10% expected length), SGS due to NEC or atresia, and presence of an ileocecal valve are predictive of enteral autonomy.[6,7] A remarkable finding in one large study was that children were less likely to achieve enteral autonomy at intestinal rehabilitation centers that were associated with a transplant center. Although this finding is disturbing at first, it can hopefully be explained by selection bias.[6]

Management of short-gut syndrome is complex and recent advances have been made in the avoidance of complications in this group of patients, as well as the proper usage of intestinal rehabilitative and lengthening procedures to augment the absorptive surface in these patients. It is important to recognize that despite the ability of lengthening procedures to increase absorptive surface functional motility is required and that tolerance of enteral nutrition is the only true test of intestinal function. Intestinal rehabilitation should be performed at a center experienced in the workup and coordinated follow-up of these complex children. Despite close multidisciplinary follow-up, one multicenter study published a 27% mortality and 26% intestinal transplant rate in these patients.[8] Frequent, detailed review of these patients is obligatory with assessment of intestinal function as well as potential benefits of lengthening procedures. Frequent enteric bacterial line sepsis, the development of clinically significant bacterial overgrowth and D-lactic acidosis are additional symptoms of dilated and poorly motile intestine that would benefit from exploration and possible lengthening. Ideally, patients undergo carefully staged intestinal rehabilitative surgery and avoid transplant altogether or delay transplant until the development of complications mandate its utility.

Children with intestinal atresia represent a unique segment of patients with short gut associated intestinal failure. Intestinal atresia can be associated with two other interesting conditions that factor into the need for, and safety of intestinal transplantation. Cases of synchronous intestinal and biliary atresia have been described.[9] This association, when characterized by neonatal intestinal failure, can alter disease course with rapid development of cholestasis and liver failure. The diagnosis of biliary atresia is often delayed, having been ascribed to PN-associated cholestasis. Once biliary atresia is diagnosed, every effort should be made to establish the likelihood of achieving enteral autonomy. In patients with limited intestinal loss, isolated liver transplantation is life-saving. However, in patients who are unable to attain $>$ 50% enteral nutritional autonomy, combined liver and intestinal transplant should be entertained.[10]

Although intestinal failure can be associated with decreased lymphocyte counts, careful differentiation between the relative immunodeficiency of short-gut syndrome and a true phenotypic immunodeficiency can be life-saving. Intestinal atresia has been known to be associated with a severe immunodeficiency since the 1990s, having been first described in single case studies of individual patients and a family of affected children.[11,12] Over the ensuing decade, investigators discovered mutations in the TT7A gene, which lead to multiple atresias and a severe combined immunodeficiency.[13] Intestinal transplant has been performed in patients with this combined immunodeficiency with only one of five patients surviving. One patient had undergone pre-transplant stem cell transplantation, but succumbed to influenza less than a year after intestinal transplant. All patients experienced graft versus host disease (GVHD), with three of these patients dying from GVHD in the first 6 months after transplant. The surviving patient has mild chronic GVHD with stable engraftment of intestinal donor derived T-cells.[14] Patients with intestinal failure due to multiple intestinal atresias should have careful assessment of their immune system, especially when intestinal transplant is being considered. Pre-emptive stem cell transplant may be indicated in patients with proven immunodeficiency and mutations in the TTC7A gene.

Motility disorders

Motility disorders represent up to a quarter of patients on the intestinal waiting list,[15] with a large group of children being diagnosed with chronic intestinal pseudoobstruction (CIPSO). There are several causes of intestinal dysmotility, which can be further classified based on pathological findings into myopathic and neuropathic CIPSO. This group is characterized by signs and symptoms of intestinal obstruction without a mechanical basis.[16] These disorders are characterized by diffuse intestine motility dysfunction with hypoperistalsis and varied involvement of other hollow viscera without radiologic evidence of mechanical