Endoscopy Following Pediatric Intestinal Transplant

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ABSTRACT

Objectives: Biopsies remain the criterion standard in the diagnosis of intestinal transplant (ITx) rejection, and gastrointestinal endoscopy plays a pivotal role in patient management. Herein, we describe a single-center 23-year endoscopic experience in pediatric ITx recipients.

Methods: A retrospective review of endoscopy and pathology reports of all ITx recipients < 18 years old transplanted between 1991 and 2013 was performed with the aim of describing the procedural indications, findings, and complications.

Results: A total of 1770 endoscopic procedures within 1014 sessions were performed. A combination of esophagogastroduodenoscopy and ileoscopy was the most common procedure (36%). Increased stool output (35%) and surveillance endoscopy (32%) were the most common indications. A total of 162 episodes of biopsy-proven rejection were diagnosed. The first episode of rejection occurred at a median of 1 month after ITx. Of histology-proven rejections, 45% had normal-appearing endoscopies. The rate of procedural complications, including but not limited to bleeding and perforation, was 1.8%.

Conclusions: Endoscopy with biopsy plays a significant role in the care of ITx recipients. Multiple procedures are required for graft surveillance, diagnosis of rejection, subsequent treatment, and follow-up of therapy. The gross endoscopic appearance, particularly in mild to moderate acute cellular rejection, does not correlate well with histology. Complex anatomy, complication rates that are higher than patients with non-ITx pediatric endoscopy, and timely histologic interpretation by experienced pathologists are reasons that these procedures should be performed at centers accustomed to caring for ITx recipients. The field would benefit from the development of a noninvasive biomarker to reliably and efficiently detect rejection.

What Is Known

- Endoscopy with biopsies remains the criterion standard for diagnosis of intestinal transplant rejection.
- The rate of serious or life-threatening complications in children undergoing endoscopy is estimated < 1%; the rate of serious endoscopic complications for pediatric intestinal transplant recipients is not well described.

What Is New

- An endoscopic complication rate of 1.8% was observed over a 2-decade experience at a large pediatric intestinal transplant center.
- Increased awareness of the higher risks and specific nuances in the care of these patients is essential as is the need to develop a noninvasive biomarker to reliably detect rejection.

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Intestinal transplantation (ITx) is a lifesaving operation for children with intestinal failure who develop advanced intestinal failure–associated liver disease, loss of central venous access needed for parenteral nutrition, or life-threatening fluid and electrolyte problems (1). Advancements in organ allocation, surgical techniques, immunosuppression, and posttransplant monitoring have translated into significant improvements in patient and graft survival (2).

Timely diagnosis and treatment of graft dysfunction has been an instrumental part of improved outcomes. After ITx, a noninvasive test to determine the etiology of allograft dysfunction and to differentiate infectious enteritis from acute cellular rejection (ACR) has yet to be developed. Therefore, serial endoscopies with mucosal biopsies have been the standard invasive tests for allograft surveillance and rejection diagnosis since the inception of ITx. Histologic criteria have been agreed upon to grade ACR, thus solidifying the role of post-ITx endoscopy (3). Creation of an ileostomy at the time of ITx allows for direct access to facilitate the monitoring of graft function. With early recognition of graft dysfunction, immunosuppression can be tailored accordingly. There are few reports on endoscopy in pediatric ITx patients. The purpose of the present study is to characterize and analyze the endoscopic experience at a large pediatric ITx center.
METHODS

This institutional review board–approved analysis included all endoscopies performed by a single ITx center over a 23-year period from 1991 to 2013. A retrospective review of a prospectively maintained database and medical record review included all ITx recipients <18 years of age at the time of transplant. All of the endoscopy and pathology reports were also reviewed. Surgical techniques, immunosuppression, and outcomes have been previously described (4,5).

Procedure Protocols and Techniques

Endoscopy of ITx recipients was performed for 2 main reasons: surveillance monitoring or allograft dysfunction with suspected rejection. Our post-ITx surveillance protocol was weekly for the first 4 to 6 weeks, every other week in month 2, and monthly in months 3 through 6. Surveillance endoscopy was also performed before ostomy takedown and repeat establishment of gastrointestinal (GI) continuity. During the first month after ITx, typically only ileoscopy was performed to avoid intubation and manipulation of the proximal anastomosis. All of the ITx recipients had end ileostomy (n = 18, 20%), end ileostomy + proximal ileocolostomy (n = 51, 56%), loop ileostomy (n = 13, 14%), or proximal end ileostomy + ileoileostomy and ileocolostomy (n = 9, 10%) created during the transplant procedure to facilitate surveillance and accurate monitoring of stool output and consistency.

Symptomatic reasons for endoscopy included allograft dysfunction with increased stool output (≥30 cm²·kg⁻¹·day⁻¹), GI bleeding, persistent Epstein-Barr virus (EBV) or cytomegalovirus (CMV) viremia, or marginal weight gain. For patients who presented acutely with an increase in stool output, our practice evolved into sending a first line of stool studies (which currently includes stool cells, Clostridium difficile, adenovirus, rotavirus, norovirus, viral culture, and early viral antigen). If these stool studies were negative and stool outputs remained elevated for 72 to 96 hours, then we proceeded with second line of stool studies (bacterial culture, ova and parasite, cryptosporidium, and giardia) and endoscopy.

Preparation for endoscopy varied significantly depending on clinical indication, age, and clinical status (ie, hydration status and renal function) of the patient. Patients who underwent routine surveillance were typically placed on a clear liquid diet the day before their procedure and were made nil per os before the procedure according to their age. Patients undergoing upper endoscopy and/or ileoscopy rarely received additional bowel preparation. In the patients undergoing colonoscopy, additional bowel preparation including GoLytey (Braintree Laboratories, Braintree, MA) or magnesium citrate may have been administered. Given the frequency of renal insufficiency in this population, bowel preparation was typically administered conservatively (6).

Preprocedure laboratory tests were performed to ensure a platelet count of ≥50,000 μL and international normalized ratio of ≤1.5 to decrease the risk of bleeding. Biopsy forceps used were either Boston Scientific 2.8 or 2.0 mm (Boston Scientific, Marlborough, MA) depending on the age and size of the patient. Endoscopes used were Olympus GIF 160, GIF H180, and PCF 160 AL (Olympus America, Center Valley, PA).

Esophagogastroduodenoscopy (EGD) and ileoscopy were performed with appropriately sized endoscopes. In patients in whom the proximal anastomosis between native and transplanted small bowel was difficult to reach with shorter endoscopes (ie, >100 cm from mouth), a colonoscope was used. For colonoscopy, typically a PCF 160 AL was used, but in younger recipients and in patients with a shorter length of colon, a standard upper endoscope could be used.

In the majority of patients undergoing EGD, 2 to 3 sites each consisting of 2 to 3 biopsies were taken every 5 to 10 cm from the proximal graft, ideally ≥10 cm beyond the anastomosis of the native and transplanted small bowels. For ileoscopies, 2 to 3 sites each consisting of 2 to 3 biopsies were also taken every 5 to 10 cm from the distal graft. Depending on the patient’s anatomy and risks, the distal graft was typically surveyed up to 50 to 60 cm from the ostomy or ileocolonic anastomosis. A total of 1 to 2 sites of the native duodenum, jejunum, and/or colon were obtained to help differentiate rejection from infection because rejection should affect only transplanted bowels.

Owing to their complex medical histories and frequent significant sedation requirements, the majority of patients typically required the care of the pediatric anesthesia team. Patients with delayed gastric emptying and a history of aspiration or respiratory issues with procedures often underwent general anesthesia with endotracheal intubation. Nearly all of the ileoscopies alone were performed with deep sedation without intubation.

The visual appearance of the bowel was assessed by the endoscopists (a combination of gastroenterology fellow in training and attending physicians experienced in the care of ITx recipients). Standard descriptors of mucosal appearance included erythematous, friable, ulcerated, denuded, or grossly unremarkable. Assessments for the villous appearance (normal or blunted) and the vascular pattern were also made.

All of the biopsy samples were processed within 24 hours. Immunohistochemical tissue staining for adenovirus and CMV became our standard practice with the selective use of EBV-encoded small RNA and other hemopathology staining on a case-by-case basis if there were concerns for posttransplant lymphoproliferative disease (PTLD). Biopsies were reported to have absence of indefinite, mild, moderate, or severe ACR per criteria established in 2004 (3). Enteritis was also reported.

Biopsy-proven mild to moderate ACR episodes were treated with high-dose intravenous methylprednisolone bolused over 7 days. Anti-thymocyte globulin was generally reserved for episodes of severe rejection. Infectious enteritis was treated with supportive care and in some instances with antibiotics when appropriate. Following the diagnosis of either acute rejection or infection, treatment was initiated, and patients were observed closely for clinical response. Subsequent follow-up endoscopies were performed as frequently as biweekly to monthly to track histologic changes closely (Fig. 1).

RESULTS

During this time period 74 children received 91 ITx. A total of 1770 endoscopies were performed during 1014 endoscopy sessions in 71 children (Tables 1 and 2). Their ages ranged from 9 months to 18 years at the time of transplant. The mean age at the time of transplant was 4.7 ± 4.3 years and median age was 2.8 years (1.3, 7.7 years). After ITx, 76% of children underwent ostomy takedown at 16 months (11,24). Overall, 1- and 5-year survivals among pediatric ITx recipients was 80% and 68% of patients, and 68% and 59% of graft survival.

The procedures included 708 ileoscopies, 725 EGDs (upper enteroscopies), and 337 colonoscopies. The most common type of endoscopy session was EGD + ileoscopy (36% of the endoscopy sessions).

The most common indications for endoscopy were increased stool output, accounting for 35% of the endoscopy sessions, and surveillance (32%). The remaining indications included follow-up of allograft from recent rejection episodes, GI bleeding, obstructive symptoms, and other indications, which can be found in Table 2.
General endotracheal anesthesia was the most commonly used method for sedation, accounting for approximately two thirds of patients compared with conscious or deep sedation.

Among 1770 endoscopies (9%), 162 episodes of biopsy-proven rejection were detected. Of these, 45% had a normal gross appearance to the endoscopists. A total of 7 patients with PTLD involving the GI tract were diagnosed via endoscopy.

Thirty-two serious complications were documented (Table 2). The most frequent complications included GI bleeding (13 patients) and perforation (11 patients). The serious complication rate overall was 1.8% (32/1770). No deaths and 1 graft loss resulted from these complications.

Among patients who sustained perforations, the age at the time of complication ranged from 1 to 12 years. Overall, most perforations occurred within the first 6 months after ITx; however, there were 3 perforations that occurred 2 to 4 years out from ITx. The majority of perforations occurred during ileoscopies (9/11), whereas 2 were during colonoscopies. Of the 11 perforations, 8 underwent exploratory laparotomy, and 3 were medically managed with bowel rest and broad-spectrum antibiotics. Among the 8 surgically managed perforations, 6 required resection of small bowel (range 1–12 cm) and ultimately underwent primary repeat anastomosis or placement of a diverting ostomy. The remaining 2 exploratory laparotomies underwent peritoneal washout with the inability to identify the perforation site, presumably because the site had already sealed off. One patient did lose the entire graft because of delayed recognition of perforation. This child developed peritonitis and subsequent sepsis with hypotension, contributing to the ischemic necrosis of the transplanted bowel.

**DISCUSSION**

The majority of early post-ITx care is performed at specialized centers. The community gastroenterologist should be aware of the unique needs of ITx patients, however, when they return home to their local community. Potential complications from endoscopy, comorbid medical conditions, and complex anatomy are factors that differentiate post-ITx patients from the general pediatric GI patient.

**Indications for Endoscopy**

A significant number of post-ITx endoscopies are performed as surveillance. In an asymptomatic patient, particularly in the early
Posttransplant time period, surveillance endoscopy is routinely used as the criterion standard at ITx centers to allow for early detection and effective treatment of rejection. Frequent and early endoscopies are performed given the high prevalence of ACR in the early posttransplant period (2). Indeed, this has been the case at our institution where the median time to the first episode of ACR is 35 days.

Although stool output is closely measured and recorded daily in the early post-ITx period, waiting for stool outputs to rise before performing endoscopy early on after ITx would be synonymous with waiting for a liver transplant recipient to become jaundiced before performing a liver biopsy to delineate their cause of graft dysfunction. Such an approach delays early diagnosis and treatment and may significantly reduce the chances for successful treatment.

The field of ITx lacks a consistent biomarker to screen for and diagnose ACR. Unlike liver or kidney transplantation, which rely on changes in transaminases or serum creatinine, such a marker is lacking in ITx. An acute increase in ostomy outputs often raises concern in ITx patients, but this is a nonspecific finding, which can be secondary to variation in enteral intake, infectious enteritis, or rejection. Stool calprotectin has been heralded as a potential biomarker, but it has significant interpatient variability and is unable to differentiate between infection and rejection (7). Serum citrulline has also been considered; however, it has not been shown to predict asymptomatic rejection and also has significant variability between patients (8). Immune cell function assay (Cylex ImmuKnow; Viracor-IBT Laboratories, Lee’s Summit, MO) has been investigated, and although it may be used as an adjunctive diagnostic tool, it cannot replace endoscopy with biopsy (9).

Finally, the newly Food and Drug Administration–approved Pleximmune test (Plexision, Pittsburgh, PA) is designed to predict the risk of ACR after pediatric liver or intestine transplantation but is yet to be used in a large multicenter study.

Beyond surveillance, other indications for endoscopy include symptoms such as diarrhea, fever, vomiting, abdominal pain, GI bleeding, and abdominal distension. In such patients, endoscopy with biopsies can help in evaluating for PTLD, tissue invasive CMV infection, and rejection. Endoscopy may also be indicated for gastrostomy-jejunostomy tube replacement, the evaluation of the health of the graft before ostomy takedown, or surveillance following the treatment of rejection or PTLD.

Infectious enteritis is a common complication in immunosuppressed ITx patients (10), and endoscopy can help to differentiate rejection and infection, especially when initial stool studies are negative yet patients continue to have elevated stool outputs. Infectious enteritis, in particular adenovirus, can also present concomitantly with a rejection episode.

Finally, graft-vs-host disease (GVHD) of the GI tract is an extremely rare but serious complication that can occur when donor immune cells in the transplanted bowel attack the native remnant bowel. Histologic evaluation is essential in diagnosing GVHD (11).

Type of Endoscopy

Based on clinical experience and previously published work (12), it is known that the pattern of ITx rejection may be patchy. Therefore, sampling of both suspicious and normal-appearing bowel in multiple graft locations is necessary to identify histologic evidence of rejection. Studies have shown that the ileum is most reliable in the detection of rejection, whereas jejunal sampling alone may miss rejection episodes. Our ability to broadly survey the transplanted allograft is limited to the more proximal and distal portions of the graft with the majority of the middle portion of the graft unreachable. This represents a major limitation of endoscopy.

In our experience, the most common type of procedure performed was EGD + ileoscopy, thereby allowing for surveillance of both proximal (jejunal) and distal (ileal) grafts. Diagnostic yield from endoscopy can be increased by performing ≥2 to 3 biopsies at multiple locations typically separated by 5 to 10 cm. It is also important to evaluate the native bowel and to perform biopsy on it to allow for adequate evaluation of an infectious process, PTLD, or medication’s adverse effects (ie, mycophenolate-associated enteritis). This is an extremely important point because the differential diagnosis of pathology affecting the transplanted allograft alone as compared with both the native bowel and transplanted allograft are unique. Capsule endoscopy to visualize all of the allograft is a consideration, but given the relatively young age of this cohort of patients, their propensity to dysmotility, and their high number of prior abdominal surgeries, this must be approached with caution.

Rejection

Histology is critical in the diagnosis of ACR because gross endoscopic findings can be misleading. Advancements including zoom magnification endoscopy have not replaced histologic examination for the diagnosis of rejection (13). Gross findings, including erythema, nodularity, pallor, and edema, are nonspecific. Even frank ulcerations, although suspicious for rejection, may be consistent with other diagnoses including infection. Sigurdsson et al (14) reported that 37% of patients with ACR would have been missed without biopsies. This was consistent with previous findings that mucosal visualization alone was not sensitive enough to establish a diagnosis and would miss patients with mild ACR (15–17). Our experience is congruent with these previous findings in that nearly half of biopsy-proven rejection episodes had grossly normal-appearing endoscopies.

Although gross findings may be unreliable in patients with mild or moderate ACR, in patients with severe exfoliative ACR, endoscopists will often have a strong sense of the clinical problem and may even elect to initiate treatment before the biopsy results being reported. Despite being the criterion standard for rejection, there are limitations to endoscopy with biopsy. Rejection of the graft can be patchy in nature, and endoscopy is unable to survey the entire transplanted bowel. As reported by Pasternak et al (18), in patients with mild and moderate rejection, histologic findings are absent in ~20% of tissue samples. Furthermore, although useful for diagnosing ACR, endoscopic biopsies do not yield the full thickness biopsies needed to diagnose chronic rejection. Finally, although the field of knowledge of antibody-mediated rejection including C4d staining has grown, this diagnostic tool has not been validated in recipients of ITx.

Posttransplant Lymphoproliferative Disease

PTLD is an uncommon but fatal complication of ITx. The prevalence of PTLD in our pediatric ITx population is 16%. The median time to diagnosis of PTLD following ITx is 20 months with 31% diagnosed in the first year. Presentation and clinical symptoms associated with PTLD vary greatly but can include fever, weight loss, hema-/thrombocytopenia, abdominal distension, obstruction, and diarrhea. In our experience, 7 patients ≥23 years developed PTLD involving the GI tract that was diagnosed histologically via endoscopic biopsies. These GI presentations account for 58% of the PTLD, which we have observed. Grossly, most PTLD lesions were found incidentally on biopsy in that they did not stand out dramatically to the endoscopists. Five of these 7 patients had PTLD involving the transplanted ileum, whereas 2 had PTLD in their native colon. Time to diagnosis ranged from 1.7 to 107 months after ITx.
Complications

There is a paucity of integrated, consistent data on the incidence of complications in non-ITx pediatric endoscopy. In non-ITx patients, the EGD complication rate is reported as 2.3%, most of which were hypoxia related (66%) and reversible (19). In this same study of EGDs, the bleeding rate was 0.3% (28 episodes of 10,236 procedures), and there were no perforations (19). The overall rate of serious or life-threatening complications in children undergoing upper or lower endoscopy is estimated to be <1% (20).

In adults without ITx, the overall endoscopic complication rate has been estimated at 1.9% including serious and nonserious complications, with a perforation rate of 0.09% (21). Serious upper endoscopy complication rate is estimated at 0.15% (22), whereas serious colonscopy complication rate is 0.2% (23). The rate of perforation in screening colonoscopies for adults ranged from 0.01% to 0.1% (24). A large single-center pediatric study of roughly 30,000 procedures revealed a perforation rate of 0.014% for EGD and 0.028% for colonoscopy (25).

Our overall complication rate was 1.8%, with a rate of 0.6% for perforation and 0.7% for bleeding. The remaining complications (0.5%) included hematoma (n = 6), gastric mucosa avulsion (n = 1), and distention from retained air causing respiratory issues and early termination of the endoscopy (n = 1). A limitation of the present study is that our database was not designed to include cardiopulmonary complications including hypoxia, wheezing, bradycardia, or arrhythmias because our focus has been on GI-related complications. One life-threatening complication of endoscopy is perforation. In our experience, there is a higher risk of perforation in patients with ITx compared with other populations. This is likely multifactorial given the multiple surgical anastomoses, atypical anatomy, and immunosuppressed state of these patients. Although the majority of the perforations necessitated surgical exploration, overall patient recovery was good with prompt medical and surgical care. Given the higher rate of complications, atypical anatomy, and need for timely histologic diagnosis, we recommend that endoscopy of patients with ITx be performed by teams at ITx centers in an attempt to minimize the risk of complications. The endoscopists need to be familiar with the patients’ anatomy, and there must be surgical expertise present to take these children promptly to the operating room in the event of perforation. Continuity of care is also important, and a limited number of designated endoscopists are best able to follow endoscopic changes over time. Patients should be monitored, especially closely after endoscopy. Abdominal pain, distension, or abnormal vitals ought to prompt evaluation with abdominal radiographs (cross table lateral and plain abdominal film), blood tests, and early notification to the surgical transplant team. Although hemostasis is observed directly after each biopsy, bleeding following endoscopy may still occur, may not present immediately, and requires timely recognition by caregivers and the transplant team. Finally, biopsies should be read by pathologists with ITx expertise and experience to allow for prompt and accurate diagnosis and treatment.

CONCLUSIONS

Endoscopy with biopsy remains the criterion standard for surveillance of the graft and detection of rejection in ITx patients. Although the complication rate is higher in this specialized population compared with the general population, rates remain acceptable given the benefit and knowledge afforded from the diagnostic procedure. Regardless, ongoing research is necessary to develop reliable, noninvasive biomarkers, which can successfully differentiate infectious enteritis and rejection. Given the higher complication rate, endoscopy with biopsy in patients with ITx should be performed at a specialized center with multidisciplinary teams who are intimately familiar with these children.

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