Twenty Years of Gut Transplantation for Chronic Intestinal Pseudo-obstruction

Technical Innovation, Long-term Outcome, Quality of Life, and Disease Recurrence

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Objective: To define long-term outcome, predictors of survival, and risk of disease recurrence after gut transplantation (GT) in patients with chronic intestinal pseudo-obstruction (CIPO).

Background: GT has been increasingly used to rescue patients with CIPO with end-stage disease and home parenteral nutrition (HPN)–associated complications. However, long-term outcome including quality of life and risk of disease recurrence has yet to be fully defined.

Methods: Fifty-five patients with CIPO, 23 (42%) children and 32 (58%) adults, underwent GT and were prospectively studied. All patients suffered gut failure, received HPN, and experienced life-threatening complications. The 55 patients received 62 allografts; 43 (67%) liver-free and 19 (33%) liver-contained with 7 (13%) retransplants. Hindgut reconstruction was adopted in 1993 and preservation of native spleen was introduced in 1999. Immunosuppression was tacrolimus-based with antilymphocyte recipient pretreatment in 41 (75%).

Results: Patient survival was 89% at 1 year and 69% at 5 years with respective graft survival of 87% and 56%. Retransplantation was successful in 86%. Adults experienced better patient ($P = 0.23$) and graft ($P = 0.08$) survival with lower incidence of post-transplant lymphoproliferative disorder ($P = 0.09$) and graft versus host disease ($P = 0.002$). Antilymphocyte pretreatment improved overall patient ($P = 0.005$) and graft ($P = 0.069$) survival. The initially restored nutritional autonomy was sustainable in 23 (70%) of 33 long-term survivors with improved quality of life. The remaining 10 recipients required reinstitution of HPN due to allograft enterectomy (n = 3) or gut dysfunction (n = 7). Disease recurrence was highly suspected in 4 (7%) recipients.

Conclusions: GT is life-saving for patients with end-stage CIPO and HPN-associated complications. Long-term survival is achievable with better quality of life and low risk of disease recurrence.

Keywords: graft versus host disease, immunosuppressive regimens—induction, intestinal (allograft function)/dysfunction, intestinal failure/injury, patient survival, quality of life

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Chronic intestinal pseudo-obstruction (CIPO) is a severely disabling and life-threatening disorder with unknown prevalence that precipitates gut failure (GF).[1–8] The syndrome is characterized by gut dysmotility that mimics mechanical obstruction and diagnosis is established by exclusion of anatomic lesions. The syndrome is primary or secondary to systemic disorders with variable involvement of the gut neuromuscular network including the interstitial cell of Cajal. Despite advances in human genetics and gut biology, the pathobiology has yet to be fully defined.[9]

With disease progression, patients develop severe malnutrition and home parenteral nutrition (HPN) is ultimately required in up to 80% of the pediatric and 60% of the adult patients.[1–8] Despite comprehensive management, patients develop GF with impaired quality of life due to incapacitating digestive symptoms and chronic visceral pain.[10–12] With development of CIPO and HPN-associated complications, gut transplantation (GT) is the only available life-saving therapy.[13–22]

Since its 1990 clinical inception, CIPO-GF patients were part of the early GT population.[23,24] With improved result, the procedure has been increasingly used.[25] According to the recently published Intestinal Transplant Registry data, motility disorders are one of the leading indications for transplantation.[26] Despite better outcome, transplantation is still limited to patients who no longer can be maintained on HPN.[25,26]

The outcome of GT among patients with CIPO has been scarcely reported in the literature.[14–22] This study is the world largest single-center experience that address the long-term outcome among both children and adults and the first to define disease recurrence. The results are discussed in the milieu of technical modifications, disease gravity, and need for a multidisciplinary management approach.

MATERIALS AND METHODS

Patient Population

Over 20 years, 536 patients (223 children, 313 adults) underwent 593 GT at the University of Pittsburgh Medical Center. Of these, 55 (10%) had CIPO and were retrospectively studied. At time of transplant, 23 (42%) were children (≥18 year) and 32 (58%) were adults. Inclusion criteria were the diagnosis of CIPO, chronic need for HPN, and development of HPN-associated complications. CIPO was defined by the development of chronic intestinal obstruction symptoms without clinical, radiologic, and endoscopic evidences of mechanical obstructing lesions.[1–4] All patients suffered irreversible GF requiring HPN despite comprehensive medical and surgical management. All patients received pharmacologic therapy including prokinetic and antiemetic agents. Gastric pacing, reductive gut surgery, and external venting were also used for most patients to improve oral tolerance and alleviate visceral pain. The development of HPN-associated life-threatening complications was an essential prerequisite for transplantation.[23]

The diagnosis of CIPO was established before referral by different tertiary centers across the United States with expertise in

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TABLE 1. Clinical Features of Patients With Chronic Intestinal Pseudo-obstruction Who Underwent Intestinal and Multivisceral Transplantation

	Total	Children	Adult	*P*
Total number:				
Patients	55	23 (42%)	32 (58%)	NA
Grafts	62	26 (42%)	36 (58%)	NA
Age, yr*	21.9 ± 14.0	8.8 ± 4.6	30.6 ± 11.1	NA
Sex (female/male)	33/22	11/12	22/10	0.335
Prior abdominal operations*	6 ± 6	4 ± 2	7 ± 7	0.016
Duration of home parenteral nutrition, mo*	61 ± 64	58 ± 47	62 ± 75	0.78
Total serum bilirubin, mg/dL*	3.2 ± 6.6	5.3 ± 8.9	1.7 ± 3.8	0.034
Primary allograft (N = 55)				
Intestine	15 (27%)	11 (48%)	4 (12%)	0.004
Modified multivisceral†	26 (47%)	5 (22%)	21 (66%)	0.001
Full multivisceral‡	14 (26%)	7 (30%)	7 (22%)	0.472
Retransplantation	7 (13%)	3 (13%)	4 (13%)	0.952
Liver-free allograft	2 (29%)	1 (33%)	1 (25%)	
Liver-contained allograft	5 (71%)	2 (67%)	3 (75%)	
Positive T/B cell lymphocytotoxic crossmatch	7 (13%)	1 (4%)	6 (19%)	0.114
Cold ischemia time, h*	7.6 ± 1.4	7.8 ± 1.7	7.5 ± 1.2	0.487
Operation time, h*	12.4 ± 2.8	11.3 ± 3.2	13.1 ± 2.2	0.014
Bone marrow augmentation	8 (15%)	4 (17%)	4 (13%)	0.612
Splenectomy	23 (42%)	13 (57%)	10 (31%)	0.061
Immunosuppression				
Tacrolimus/steroids	7 (13%)	5 (22%)	2 (6%)	0.089
Induction (cytoxan/daclizumab)	7 (13%)	3 (13%)	4 (13%)	0.952
Recipient pretreatment	41 (75%)	15 (65.2%)	26 (81.3%)	0.178
Thymoglobulin	18 (44%)	13 (87%)	5 (19%)	
Campath-1H	23 (56%)	2 (13%)	21 (81%)	
Follow-up, mo*	61 ± 41	70 ± 47	56 ± 37	0.218

NA indicates not applicable.
*Mean ± standard deviation.
†Modified multivisceral graft: stomach, duodenum, pancreas, and intestine.
‡Full multivisceral graft: stomach, duodenum, pancreas, intestine, and liver.

the CIPO syndrome. The initial evaluation process at our center including review of the pertinent medical records confirmed the diagnosis according to the well-established standard criteria.[1–4] With the exception of 5 pediatric cases with Hirschsprung disease, all children had primary or congenital CIPO with 22 adults being diagnosed during their early childhood. The remaining 10 adult patients were diagnosed with secondary CIPO with history of viral illness (n = 3), trauma (n = 3), cerebral palsy (n = 1), catastrophic bariatric surgery (n = 1), diabetes (n = 1), and lymphocytic myenteric ganglionitis (n = 1). The prereferral manometric studies were suggestive of neuropathic pattern in 20, myopathy pattern in 15, mixed in 7, and nondiagnostic in the remaining 13 patients. Gastric involvement was severe in two third of the patients.

The pretransplant work-up also aimed at assessment of transplant candidacy, type of required allograft, and health-related quality of life (HRQOL). Exclusion criteria were the well-established contraindications for transplantation including persistent active infection, failure of drug rehabilitative efforts, hereditary and acquired immune deficiencies, and severely compromised cardiopulmonary functions.[23] The type of allograft was dictated by the extent of abdominal visceral involvement and status of the solid organs particularly the liver and pancreas.

HRQOL was measured in adults with the Quality of Life Inventory (QOLI) survey and socioeconomic status. The QOLI instrument was originally designed and validated for the liver transplant candidates and subsequently applied to HPN and GT patients a few years after initiation of the program.[27,28] The survey is a voluntarily self-assessment questionnaire containing 125 assorted questions addressing 25 domains. Each domain contains 5 questions, to which the patients rate their responses on a 9-point Likert scale, with higher values indicating greater levels of disturbance. The quality of life measures for children were limited to a global health assessment with special focus on education, level of independence, and functional performance utilizing Lansky scale. Clinical features are shown in Table 1.

Transplantation

The type of GT was dictated by extent of foregut involvement and severity of liver damage. With adequate gastric emptying and preserved hepatic functions, 15 (27%) patients received intestine-only allograft (Fig. 1A). Severe impairment of gastric motility was documented in the remaining 40 (73%) patients dictating the need for en-bloc inclusion of the stomach with the intestine and pancreas as a modified multivisceral graft (Fig. 1B). Of these, 14 (35%) suffered liver failure requiring full multivisceral transplantation with inclusion of the liver (Fig. 1C). Inclusion of the pancreas was to maintain the axial blood supply and continuity of the transplanted organs.[23] The colon was transplanted en-bloc with 3 allografts and the right kidney in 1. None of the allografts included donor spleen. The yearly number and type of transplant are shown in Supplementary Figure 1, http://links.lww.com/SLA/B619.

All donors were deceased with a mean age of 17 ± 11 years (range: 1.2–40). All grafts were ABO identical and human leukocyte antigen match was random with 11 (18%) positive T/B cell lymphocytotoxic crossmatch. Pertinent data including donor bone marrow augmentation, splenectomy, cold ischemia, and operative time are shown in Table 1.

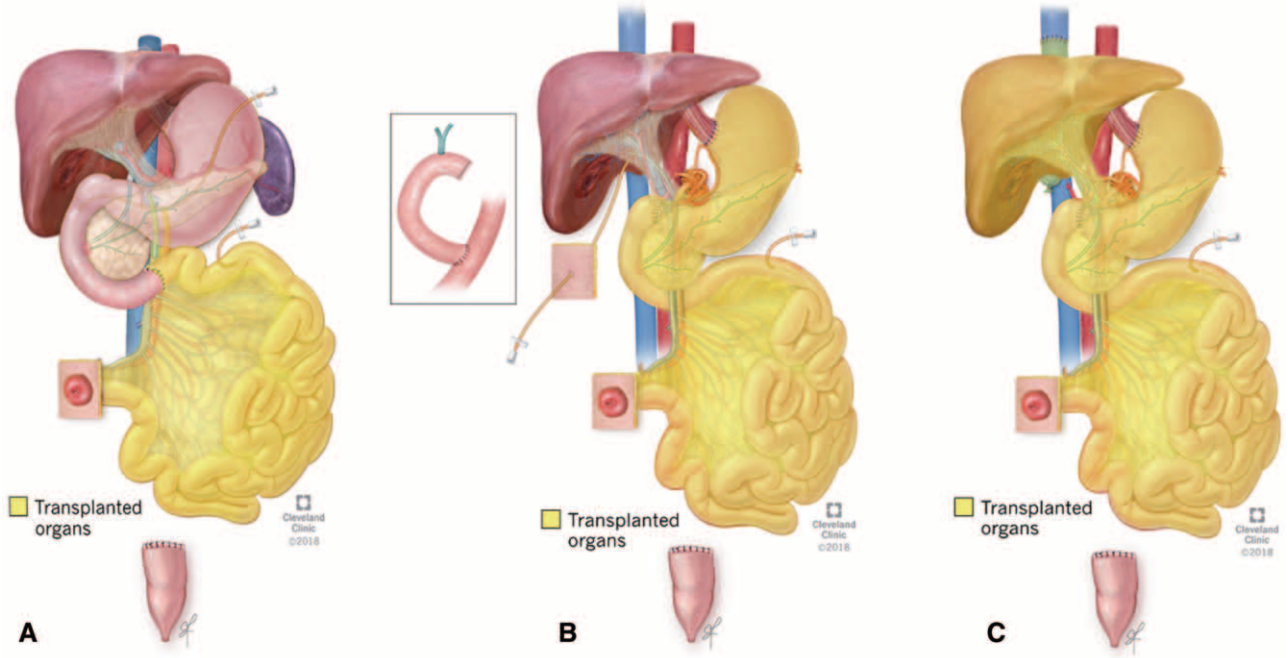

FIGURE 1. The 3 different types of gut transplantation that were given to the patients with CIPO: (A) isolated intestine, (B) modified multivisceral that includes stomach, duodenum, pancreas, and intestine, (C) Full multivisceral that includes stomach, duodenum, pancreas, intestine, and liver. Notice the absence of a distal ileosigmoid/ileorectal anastomosis before adopting the hindgut reconstruction in 1993 and the need for a duct to duct or Roux-en Y (insert) biliary reconstruction with the modified multivisceral procedure before introducing preservation of native spleen and pancreas in 1999.

Surgical Techniques

Two modifications were introduced to the recipient operation: hindgut reconstruction and preservation of native spleen en bloc with the pancreaticoduodenal complex. Hindgut reconstruction was first applied to the CIPO recipients in May of 1993 because of the initial concern of concurrent severe dysmotility of rectosigmoid. With large intestine still in place, subtotal colectomy was performed. After anastomosing the allograft terminal ileum to the rectosigmoid, a simple loop or chimney ileostomy was created to monitor rejection (Fig. 2A). With prior proctocolectomy, an end ileostomy is established.

Preservation of native spleen and pancreas was introduced in December of 1999 after the documented increased risk of post-transplant lymphoproliferative disorder (PTLD) after splenectomy.[29] The technique was applied first to the CIPO modified multivisceral recipients because of the spared function of both organs.[30,31] Retention of native pancreas enhances the islet-cell-mass and exocrine digestive functions. The shortened duodenum was piggy-backed to the allograft duodenum (Fig. 2B) eliminating the need for biliary reconstruction (Fig. 1B).

Immunosuppression

The tacrolimus-based immunosuppressive regimen was determined by era of transplant. With full details described elsewhere, 41 (75%) patients were transplanted in Era-III (7/2001–5/2011) and pretreated with a lymphocyte-depleting agent.[32] Thymoglobulin was used mostly for children and Campath-1H for adults (Table 1). The remaining 14 (25%) patients were transplanted in Era-I (5/90–5/94) and II (6/94–6/01) receiving tacrolimus-steroid-based immunosuppression with cyclophosphamide or daclizumab induction in 7 (Era-II). Severe and steroid resistant rejection was treated with antilymphoid preparations.

Management

The postoperative care included immunologic monitoring, nutritional care, and infectious prophylaxis.[13] Endoscopically guided mucosal and surgically obtained full thickness biopsies were used to diagnose acute and chronic intestinal rejection, respectively.[33] Graft versus host disease was diagnosed by polymerase chain reaction techniques, in-situ hybridization, immunohistochemical staining, and short tandem repeats technique.

Nutritional management included a stepwise enteral/oral feeding with gradual withdrawal of HPN. Intravenous nutrition was reinstituted after allograft enterectomy and in patients with allograft dysfunction. Similar to the non-CIPO population, most recipients received a prokinetic agent during the early postoperative period to enhance oral tolerance and antidiarrheal agents to reduce stoma output. Gut decontamination and prophylactic intravenous antimicrobial therapy were used for all donors and recipients.[23] The development of polymerase chain reaction technology allowed serial monitoring and prompt treatment of Epstein-Bar virus and cytomegalovirus infection infections.[13]

Recipients with progressive oral intolerance were subjected to a thorough evaluation of the visceral allograft. Patients with imaging studies suggestive of progressive bowel obstruction were subjected to abdominal exploration to exclude correctable mechanical causes and perform full thickness allograft biopsies. Persistence of gut dysmotility in the absence of chronic allograft rejection fostered the suspicion of recurrent CIPO.

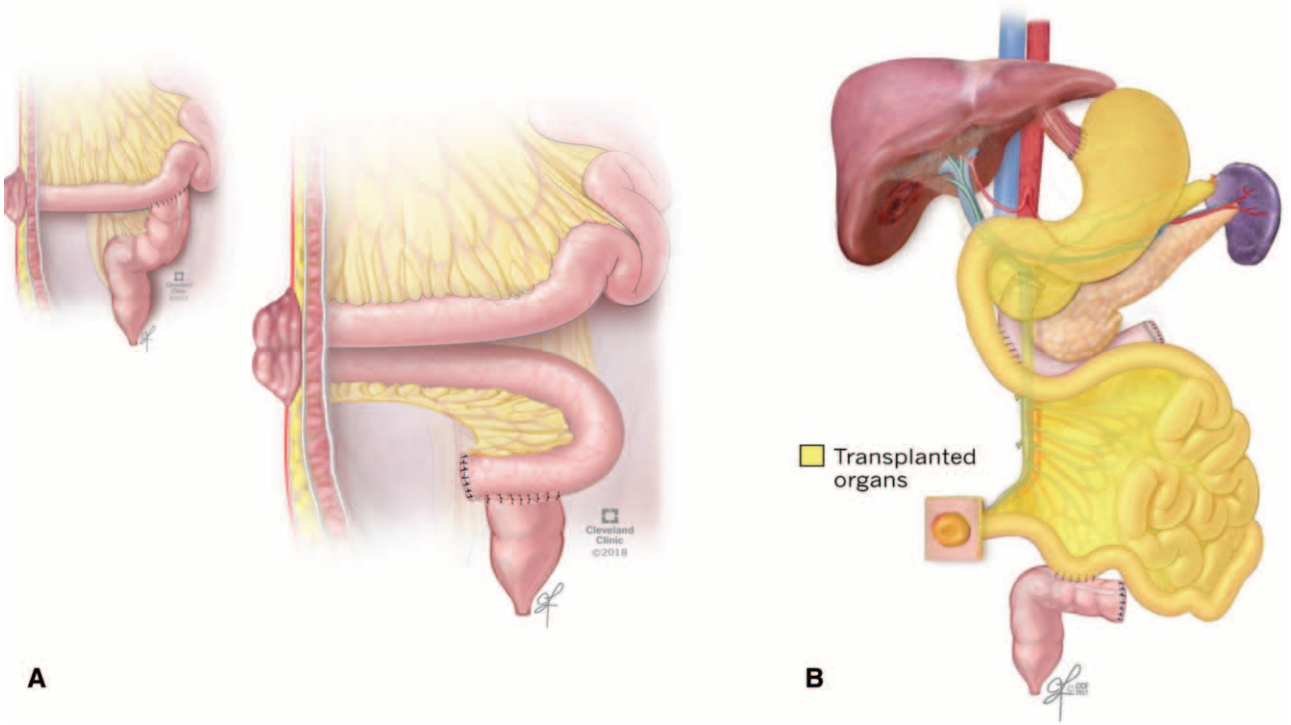

FIGURE 2. The 2 technical modifications that were introduced to the CIPO recipient operation. A, Reconstruction of the hindgut with creation of a simple loop or chimney ileostomy (insert) in patients with preserved native rectosigmoid. Note the low level of the anastomosis with the retained distal sigmoid or upper rectum. B, Preservation of native spleen and pancreas with a short duodenal segment in the modified multivisceral recipients. Note the side to side piggy-back anastomosis between the donor and recipient duodenum to drain the retained native pancreatic and biliary secretions into the visceral allograft.

Statistical Analysis

Data were pooled from a dedicated electronic database after approval of the University of Pittsburgh Institutional Review Board. Data were substratified according to recipient age with adults being older than 18 years of age. The QOLI data were pooled and grouped for the CIPO and non-CIPO contemporaneous patients with complete survey. The post-transplant QOLI data were limited to the CIPO HPN-free transplant survivors with complete survey before and after transplant. Continuous variables were presented as mean ± standard deviation and categorical data as proportions. Differences in group means were tested using standard 2-sample *t* test, and differences in proportion were tested by Pearson Chi-Square exact test. Survival was calculated utilizing Kaplan-Meier method and group comparisons were done using log-rank test. Multivariate risk analysis was performed using Cox Proportional Hazard model. All analyses were performed using SPSS (SPSS, Inc, Chicago, IL).

RESULTS

Clinical Features

Children were presented with a higher serum bilirubin ($P = 0.034$) and adults had a higher number of abdominal surgeries ($P = 0.016$). The number of isolated intestine allografts was higher ($P = 0.004$) among children and the number of modified multivisceral transplantation was higher ($P = 0.001$) among adults with a lengthier operative time ($P = 0.014$). Splenectomy was documented in 23 recipients: 13 (57%) children and 10 (31%) adults. The procedure was done before transplantation in 4 and as part of the standard modified and full multivisceral procedure in 19 recipients. Full data are summarized in Table 1.

Technical Modifications

Hindgut reconstruction was performed in 36 (72%) of 50 patients with retained rectosigmoid. Stoma closure was performed in 31 (86%) at 3 to 6 months after transplant. However, re-creation of a chimney or an end-ileostomy was required in 5 (14%) recipients because of dilated distal ileum and native sigmoid. The remaining 5 recipients died or lost the allograft before stoma closure.

Preservation of native spleen and pancreas was accomplished in 21 (49%) out of 43 patients who were transplanted after 1999 and underwent modified (n = 19) or full (n = 2) multivisceral transplantation. Of these, 20 were adults and one was a child. The rare utilization of the technique among children resulted in the observed higher ($P = 0.06$) incidence of splenectomy (Table 1). There were no related technical or functional complications.

Graft Loss and Retransplantation

Thirty-two (52%) allografts were lost. Death was the primary cause in 22 (69%) with equal distribution among the liver-free and liver-contained allografts. Thirteen (59%) mortalities were children and 9 (41%) were adults. Infection was the cause of 7 (54%) fatalities in children and 6 (67%) deaths in adults. The remaining 6 children succumbed to PTLD (n = 2), chronic rejection (n = 2), mitochondrial disease (n = 1), and HPN-associated native liver failure. Chronic rejection was the cause of the remaining 3 adult mortalities.

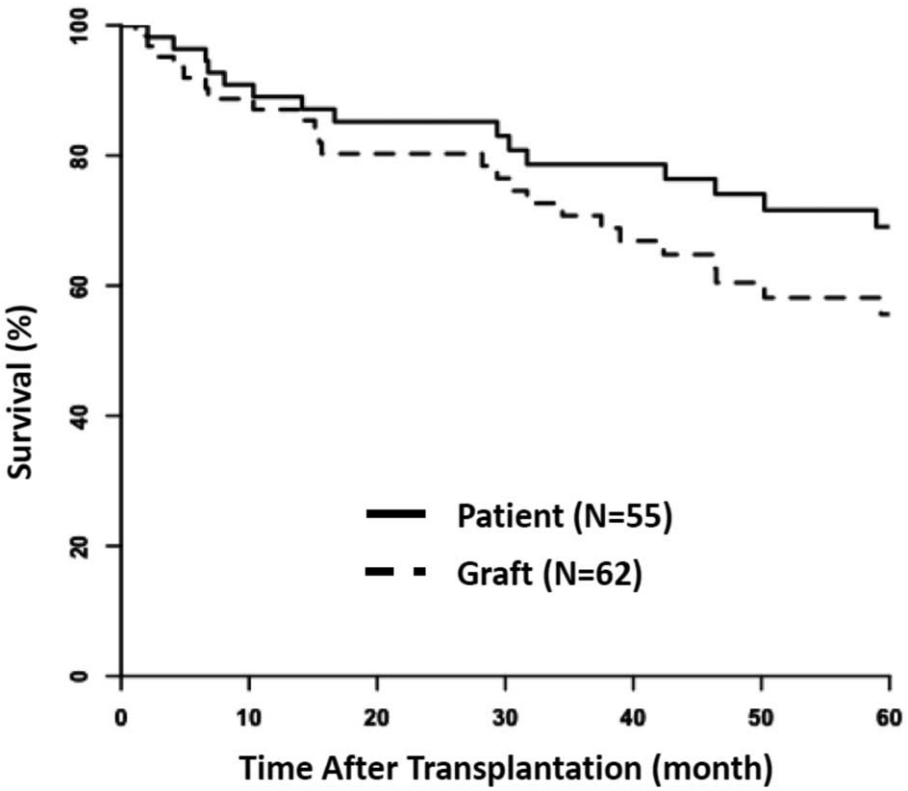

FIGURE 3. The Kaplan-Meier cumulative survival of the patients with chronic intestinal pseudo-obstruction (CIPO) after gut transplantation and the overall graft survival.

The remaining 10 (31%) allografts were lost due to rejection; 4 children and 6 adults. Of these, 7 underwent retransplantation with isolated intestinal (n = 2) and full multivisceral (n = 5) grafts with an overall retransplantation rate of 13%. One of the isolated intestinal allografts was given to a modified multivisceral recipient due to irreversible acute intestinal rejection preserving fully recovered stomach, duodenum, and pancreas. The last 3 recipients had isolated intestine, underwent allograft enterectomy without simultaneous retransplantation, and were relisted with reinstitution of HPN. Retransplantation restored full nutritional autonomy in all but 1 recipient who died of fungal infection (Supplementary Table 1, http://links.lww.com/SLA/B619).

Survival

With a mean follow-up of 61 ± 41 months (range: 2–194), 33 (60%) recipients were alive; 10 children and 23 adults. Of these, 16 survived beyond 5 years and 2 reached the 15-year milestone. Cumulative patient survival was 89% at 1 year and 69% at 5 years with respective graft survival of 87% and 56% (Fig. 3). Compared to the non-CIPO patients, the CIPO recipients experienced unadjusted better ($P > 0.5$) patient (Fig. 4A) and graft (Fig. 4B) survival.

Survival was better among adults (Supplementary Fig. 2, http://links.lww.com/SLA/B619) and during Era-III (Fig. 5). The survival increment was greater with graft ($P = 0.08$) comparing adults to children and with patient ($P = 0.005$) comparing Era of transplant. Inclusion of the liver did not influence survival (Supplementary Fig. 3A, http://links.lww.com/SLA/B619). The leading causes of graft loss were, however, rejection of the liver-free and infection of the liver-contained allografts. Interestingly, the modified multivisceral allograft achieved better ($P > 0.5$) survival compared to the intestine-only allografts (Supplementary Fig. 3B, http://links.lww.com/SLA/B619).

With univariate analysis, recipient pretreatment was the only predictor of survival outcome. The multivariate analysis failed to identify any survival predictors including immunosuppressive regimen, recipient age, allograft type, cross-match, and splenectomy.

Morbidity

Acute intestinal rejection was diagnosed within the first 90 postoperative days in 37 (67%) recipients and chronic rejection was diagnosed throughout the study period in 10 (18%) allografts (Table 2). With the year-2000 clinical availability of the solid phase assay, the presence of circulating donor-specific antibodies (DSAs) were tested in 28 of the acute rejection and 9 of the chronic rejection morbid cases. Preformed DSAs were detectable 10 (36%) of the acute rejection and persistent or de-novo DSAs were measurable in 4 (44%) of the chronic rejection patients. Acute rejection was moderate to severe in 24 (65%) requiring OKT3 and thymoglobulin treatment. Unfortunately, 4 recipients developed irreversible allograft damage requiring full (n = 3) or partial (n = 1) retransplantation. With chronic rejection, 3 underwent retransplantation, 5 died, and remaining 2 were relisted.

PTLD was diagnosed in 7 (13%) and cytomegalovirus infection in 9 (16%) patients (Table 2). PTLD was associated with splenectomy in 4 (57%). Of the 21 patients with preserved native spleen, only 1 (4%) developed self-limited PTLD. Reduced immunosuppression and antiviral therapy were successful in most cases.

Graft versus host disease was histologically diagnosed with detected peripheral blood macrochimerism in 6 (26%) of the pediatric recipients with no single example among adults (Table 2). None of these cases received donor bone marrow and 50% had splenectomy. All patients were successfully treated with steroids.

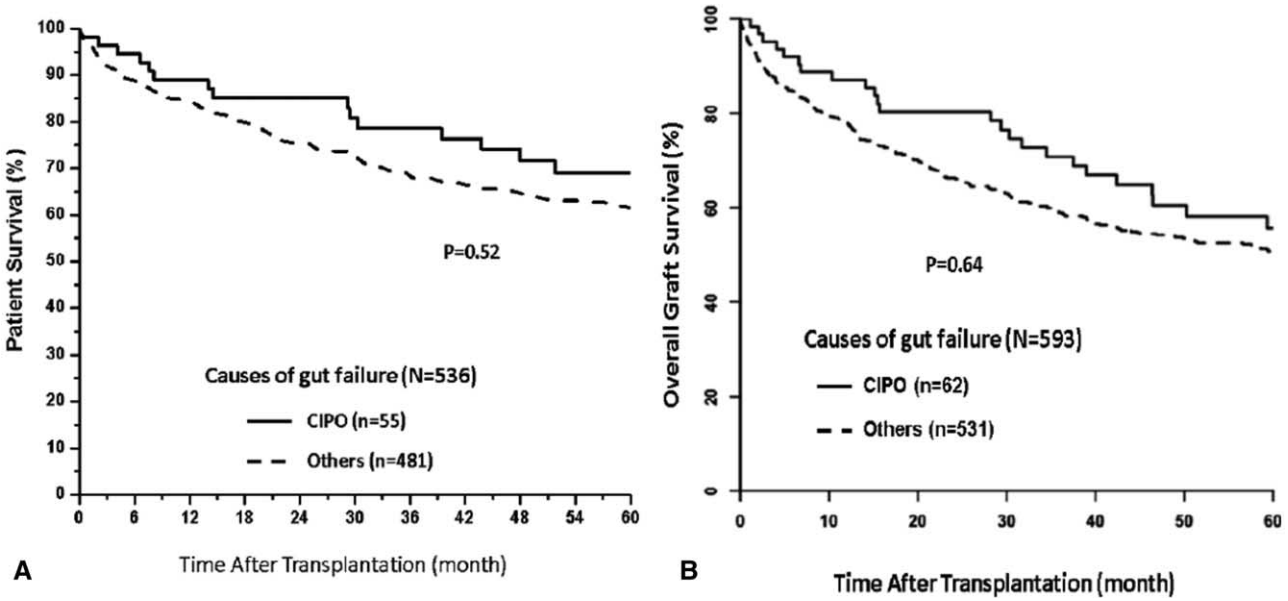

FIGURE 4. Cumulative patient (A) and graft (B) survival of the patients with chronic intestinal pseudo-obstruction (CIPO) and the non-CIPO population.

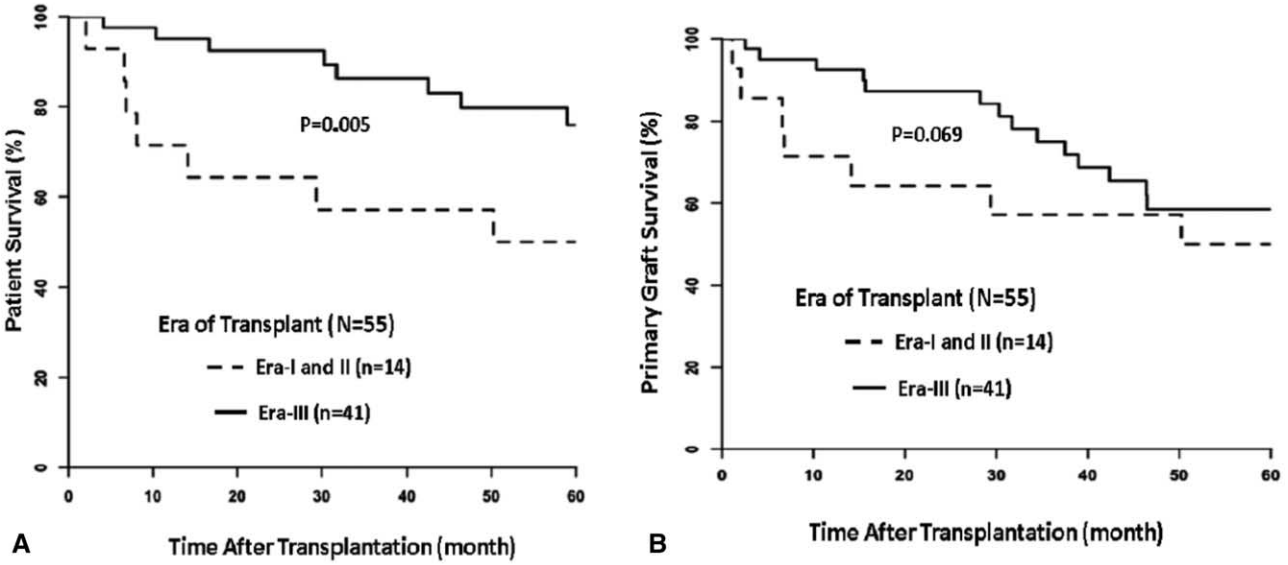

FIGURE 5. Patient with cumulative chronic intestinal pseudo-obstruction (CIPO) and primary graft survival according to era of transplantation: Era-I/II (1990–2000) and Era-III (2001–2011). Patients in Era-III received pretreatment with antilymphoid preparations.

TABLE 2. Morbidity After Intestinal and Multivisceral Transplantation in Patients With Chronic Intestinal Pseudo-obstruction

	Total (N = 55)	Pediatric (n = 23)	Adult (n = 32)	*P*
Acute rejection*	37 (67%) 10 (18%)	15 (65%)	22 (69%)	0.791
Chronic rejection	7 (13%)	6 (26%)	4 (13%)	0.198
PTLD	9 (16%)	5 (22%)	2 (6%)	0.089
CMV	6 (11%)	4 (17%)	5 (16%)	0.861
GVHD		6 (26%)	0 (0%)	0.002

*First 90 postoperative days.
CMV indicates cytomegalovirus infection; GVHD, graft versus host disease; PTLD, post-transplant lymphoproliferative disorder.

Nutritional Autonomy

Discontinuation of HPN was achievable in most recipients early after transplantation. With longitudinal follow-up, 23 (70%) of the 33 survivors maintained full enteral tolerance with normal or higher body mass index in adults and positive growth in children with limited catch-up. The remaining 10 (30%) underwent allograft enterectomy (n = 3) or developed allograft dysfunction (n = 7) requiring reinstitution of HPN.

The 7 survivors with chronic allograft dysfunction were adult female with modified (n = 5) and full (n = 2) multivisceral allografts. All experienced oral intolerance with scintigraphic evidence of delayed gastric emptying and abnormal intestinal transit time. Early chronic rejection was diagnosed in 3. Nutritional autonomy was eroded 2 to 5 years after transplantation with the need to reinstitute HPN therapy. Unfortunately, 5 of the 7 recipients continued to require HPN despite prokinetic therapy and re-creation of ileostomy with gastrojejunostomy in 4. The remaining 2 improved but required intermittent intravenous hydration. In contrast to patients with intact graft function, all of these morbid cases required medical treatment with prokinetic and antiemetic drugs and control of the visceral pain, when present, with mild narcotic agents.

Disease Recurrence

CIPO recurrence was suspected in 4 patients with an over incidence of 7%. The putative diagnosis with established in the 4 recipients with chronic allograft dysfunction after excluding opiate dependency, mechanical bowel obstruction, and histopathologic evidence of structural allograft damage including full thickness biopsy-proven chronic rejection. The 4 patients were multivisceral (2 modified, 2 full) recipients and were considered for retransplantation.

Quality of Life

Most of the pretransplant QOLI domains including digestive symptoms, visceral pain, drug use, physical mobility, anxiety, cognitive/emotional ability, and depression were depressed and at lower levels compared to the non-CIPO patients (Table 3). Interestingly, 25 (45%) patients were receiving high daily doses of opiate and antihistaminic derivatives that required pretransplant comprehensive medical and surgical management. In selected cases, inpatient healthcare facility treatment was required.

With a 4-year median follow-up, 9 adult survivors with complete QOLI survey before and after transplantation showed significant improvement in 15 (60%) of the 25 domains including different digestive, psychosocial and emotional variables. The questions constituting each domain, however, showed negative impact of transplantation on need for sleep medication, forgetfulness, some physical activities, involuntary body movements, and joint pain (Supplementary Table 2, http://links.lww.com/SLA/B619).

Education, marital status, occupation, and functional performance were the milestones of the post-transplant socioeconomic status. Of the 23 survivors with intact graft, 17 were adults at last follow-up and completed high school education or graduated from college. The remaining 6 were children and completed various levels of education with 3 requiring home schooling. Post-transplant marriage was witnessed in 7 (25%) survivors with 1 female giving birth to a healthy child. Of the 17 adult survivors, 12 (71%) achieved total independence; 6 (50%) resumed full/part time employment, 5 (41%) were homemakers, and 1 (9%) did not seek job opportunities because of the fear of losing social security benefits. Utilizing Lansky and Karnofsky scale, the overall functional performance scores were 80% to 100% in 18 (78%) with the remaining 5 (22%) achieving lower scores.

TABLE 3. Pretransplant Quality of Life Domains in 15 of the Chronic Intestinal Pseudo-obstruction and 54 of the Non-CIPO Adult Study Patients

Domain	CIPO (n = 15)	Non-CIPO (n = 54)	*P*
Depression	1.9 ± 1.1	1.1 ± 0.9	0.001
Anxiety	4.5 ± 1.8	3.8 ± 1.6	0.02
Stress experience	4.3 ± 1.8	4.6 ± 1.7	0.52
Coping	2.9 ± 1.3	3.5 ± 1.6	0.048
Drug use	4.3 ± 1.6	1.2 ± 0.9	<0.0001
Pain and discomfort	6.1 ± 2.0	3.6 ± 1.6	<0.0001
Physical mobility	3.8 ± 1.8	3.1 ± 1.7	0.045
Appearance	3.4 ± 1.3	3.5 ± 1.5	0.56
Alcohol use	1.3 ± 0.9	1.2 ± 0.3	0.57
Cognitive/emotional	3.1 ± 1.7	2.9 ± 1.4	0.01
Mental status	3.0 ± 1.5	2.9 ± 1.6	0.34
Impulsiveness/control	4.7 ± 1.5	5.1 ± 1.4	0.12
Finance	3.8 ± 1.8	3.9 ± 2.1	0.67
Parenting	2.2 ± 1.1	2.2 ± 1.3	0.79
Marital relationship	2.3 ± 1.8	2.4 ± 1.9	0.88
Sexuality	4.7 ± 2.2	4.4 ± 2.4	0.65
Digestive symptoms	6.8 ± 1.3	3.2 ± 2.1	<0.0001
Sleep	5.0 ± 2.0	5.0 ± 1.9	0.98
Energy	4.9 ± 1.7	4.7 ± 1.8	0.42
Optimism	3.5 ± 1.7	3.4 ± 1.7	0.66
Leisure/recreation	3.8 ± 1.7	3.9 ± 1.6	0.68
Quality of social support	3.4 ± 1.3	3.5 ± 1.4	0.73
Quality of relationship	3.2 ± 1.3	3.4 ± 1.4	0.79
Medical compliance	2.0 ± 0.9	2.0 ± 1.0	0.85
Medical satisfaction	2.0 ± 1.3	1.7 ± 0.9	0.27

DISCUSSION

Recent years witnessed better understanding of CIPO natural history and evolution of GT.[1,25] CIPO represents 15% to 20% of nonmalignant GF with a low probability of HPN-weaning with a 5-year cumulative dependency of 62% to 74%.[1–8,34–41] Such unfavorable outcome is due to development of disuse villous atrophy and bacterial overgrowth.[7] With disease progression, patients are at risk of life-threatening complications.[1–8] The 1990s clinical introduction of GT added a new dimension to the management of these complex patients.[23]

Since its inception, GT has been utilized to rescue CIPO patients with HPN failure. According to recently published Intestinal Transplant Registry and single-center data, CIPO accounted for 10% to 18% of the indications for transplantation.[13–22,26] Such a wide range reflects differences in clinical practice among North American and European centers with disparities in referral pattern and sample size.[42]

The described herein modifications of hind-gut reconstruction and splenic-preservation along with the pancreaticoduodenal complex were introduced to improve overall outcome. Hindgut reconstruction enhances absorptive functions and improves quality of life. Splenic preservation reduces risk of PTLD.[29–31] In addition, the retained pancreaticoduodenal sweep augments the islet-cell-mass and eliminates need for biliary reconstruction. These advantages explain the reported herein better outcome among the adult population with superior utilization of these surgical modifications.

Extent of foregut involvement and status of native liver largely determine type of required allograft. Patients with residual gastric motor activity and preserved hepatic functions undergo intestine-only transplant. En bloc inclusion of the stomach is preferred in patients with severe global dysmotility and prior gastric resection. The liver is simultaneously replaced to rescue patients with hepatic

failure. In these recipients, en-bloc inclusion of donor duodenum and pancreas is required to maintain integrity of the axial blood supply and gut continuity. The observed herein difference in the type of allograft given to children and adults may signal over-time disease progression in adults with severe gastric involvement and late referral of the pediatric patients with higher susceptibility to HPN-associated hepatic injury.[14]

Regardless of disease gravity, some centers on both sides of the Atlantic do not advocate gastric replacement.[16,18,22] Alternatively, gastrojejunostomy with and without partial gastrectomy is commonly performed. Failure to restore full nutritional autonomy was, however, reported in 20% to 40% of these patients with the development of HPN-associated complications including liver failure.[16,22] Such a policy of gastric-free GT for patients with CIPO can be further disputed by the proven herein survival advantages of modified multivisceral transplantation. Unfortunately, the availability of these gastric contained donor allografts has become increasingly difficult because of the current Organ Procurement Organization policy that prioritizes allocation of pancreas with the kidney and the unwillingness of the liver surgeons to allow retrieval of the celiac trunk with the en-bloc visceral organs. Nonetheless, such a legitimate dispute may continue to be fueled by the current ambiguity of the pathogenesis of CIPO and the lack of evidence-based criteria that guide replacement of the stomach.

Despite being used as a rescue therapy, GT achieved a cumulative CIPO patient survival of 89% at 1 year and 69% at 5 years with better results compared to the non-CIPO population. Similar or inferior results were reported by other few previously published small series (Supplementary Table 3, http://links.lww.com/SLA/B619).[14–22,43] The documented herein disease-specific and previously reported overall survival advantages of the antilymphocyte recipient pretreatment could be partially attributed to simultaneous advances in surgical techniques and postoperative care.[13,32] The observed variation in outcome among the different published series is most probably due to disparity in center experience, sample size, allograft type, immunosuppression, follow-up, and disease gravity associated with diverse hereditary and neuromuscular disorders.

A few collective review articles compared the survival benefits of GT to the survival of patients who continued to tolerate HPN using compiled Medicare and European survey data.[5,6,8] It is sensible to believe that such a comparison is invalid since GT is mostly used to rescue the patients who already failed HPN therapy. In contrast to the low transplant survival rates quoted in these articles, the reported herein 5-year survival is similar or even higher than that reported with HPN in some of the previously published series.[1–8,38] With restored enteral tolerance, GT has the additional potential advantages of being cost effective with improved quality of life.[44,45]

Nutritional autonomy was re-established in most of our study patients a few weeks after transplantation. Similar to other GT recipients, patients with CIPO commonly required intermittent therapy for diarrhea and bacterial overgrowth as a result of abnormal interdigestive and postprandial motor activities.[45,46] With longitudinal follow-up, at least 70% of the recipients maintained their freedom from HPN enjoying unrestricted oral diet. Loss of the restored long-term nutritional autonomy was observed in recipients with intractable rejection and progressive dysmotility of remaining native and transplanted visceral organs.[13–22]

The detrimental effect of CIPO on the HRQOL issues has been widely documented in the literature.[10–12,34,41] Compared to healthy controls, CIPO significantly impairs the HRQOL of both patients and their primary care givers with depressed scores worse than those observed with other chronic gut disorders.[10] There is also a strong correlation between CIPO disease gravity and the impairment of HRQOL measures.

With successful GT, many of the HRQOL issues including psychosocial and emotional status improve as reported herein but in a small cohort of the study population. Interestingly, the improvement in physical activity and socioeconomic milestones were observed at a lower rate compared to our overall transplant population.[45] The Bologna group also reported limited benefits of transplantation on the physical wellness of the patients with CIPO.[47] These results could be due to the chronicity and incapacitating nature of CIPO, cumulative toxicity of maintenance immunosuppression, and progression of the underlying autonomic, connective tissue, and muscular disorders. Recent studies has also suggested the potential harmful effect of altered gut microbiota and circulating neuropeptides on the gut-brain axis.[48,49]

This study is the first to address risk of CIPO disease recurrence. The loss of enteral tolerance was gradual with the ultimate development of negative energy balance requiring reinstitution of HPN. In the light of recent scientific discoveries, disease recurrence can be partially explained by persistence of altered circulating neuropeptides and gut microbiota with disarray of the gut-brain-neuronal-circuit.[48,49] The allograft dysmotility could also be a de-novo phenomenon because of cumulative ischemic and immunologic damage to the allograft myogenic and intrinsic neurogenic circuits including the interstitial cell of Cajal.[46]

In conclusion, GT is an effective therapy to rescue patients with CIPO with end-stage GF. Meanwhile, a multidisciplinary approach is currently needed to optimize patient care with the aim to restore the inborn enteral tolerance, enhance HPN therapy, and promptly identify transplant candidacy.[1,25,35,37,47,50] With the current lack of effective pharmacotherapy and pacing technology, it is our practice to use a wide repertory of surgical options including reductive, reconstructive, and decompressive gut surgery with the intent to treat or as a bridge to transplantation. Further advances in the algorithmic management of these complex patients is foreseen with new discoveries in molecular genetics, gut biology, and transplant tolerance.

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