ORIGINAL ARTICLE

Including colon in intestinal transplantation: a focus on post-transplant renal function – a retrospective study

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SUMMARY

Intestinal transplant recipients experience a high rate of renal complications secondary to dehydration due to increased ostomy output. It is hypothesized that inclusion of donor colon in the intestinal allograft may improve renal function in patients without functional native colon by improving fluid absorption. A single-center retrospective study of intestinal transplant recipients compared outcomes of patients receiving *en bloc* colon as part an intestinal allograft (ICTx), and those not receiving colon (CCNTx), as well as a control group of intestinal transplant recipients with functional native colon (ITx). Forty-seven patients (ICTx $n = 17$, CCNTx $n = 15$, ITx $n = 15$) were studied. One-year post-transplant renal function, as measured by change in glomerular filtration rate (GFR) and blood urea nitrogen (BUN) from baseline, was superior in ICTx (mean delta-GFR of −1.31 and delta-BUN of −1.46) compared to CCNTx (−6.54 and 17.54, $P = 0.05$ and $P = 0.17$, respectively) and similar to the ITx controls (0.55 and 2.09). Recipients of donor colon experienced a higher rate of ileostomy reversal when compared to CCNTx (62.5% vs. 20%, $P = 0.0008$), which was similar to the ITx controls (60%). These findings support the inclusion of *en bloc* donor colon in the intestinal allograft for recipients without functional native colon.

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Introduction

Intestinal transplantation is indicated in patients with irreversible intestinal failure and associated life-threatening complications [1,2]. While the procedure has increased in frequency in recent decades (five performed in the United States in 1990 to 146 in 2016), survival rates for these procedures have not changed for the last decade [1,3]. Complications affecting survival rate include graft rejection, infection, and reduced ability to reabsorb fluids and electrolytes leading to dehydration [4,5].

The inclusion of a colon in intestinal transplants was a commonly accepted practice until the mid-90s, when evidence suggested that including a colon increased graft loss, bacterial translocation, and rejection rates [6–9]. However, more recent evidence from the last decade has identified no increased rates of rejection, graft loss,

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or infection from incorporating a colon into the transplanted graft [10–13]. In fact, rejection of the colon is similar to that of the intestinal graft, and rejection of the colon in isolation of the intestinal graft is exceedingly rare [14,15].

Tacrolimus is the mainstay of maintenance immunosuppression for intestinal transplant recipients. However, this agent has nephrotoxic properties, often leading to a decline in renal function with prolonged use [16]. Intestinal transplant recipients in particular experience the highest rates of post-transplant renal disease of all nonrenal transplants [17]. Given the adverse renal effects of these procedures and immunosuppressive agents, hydration is extremely important to the health of the graft and patient. One proposed method to avoid dehydration in intestinal transplant recipients is the inclusion of a colon allograft within the intestinal transplant in patients with pre-existing colonic dysfunction and/or resections. Since the colon functions to reabsorb water and sodium, the proposed mechanism of this strategy would be to prevent prerenal kidney injury [10,12].

Recipients with colon included in their intestinal allograft have improved formation of stools and reduced rates of dehydration and incontinence [13]. Other expected benefits of transplanting a colon include enhanced fluid reabsorption, reduced need for IV fluid supplementation, and improved kidney function [12]. The aim of this study was to assess the risks and benefits of including a colon in intestinal transplant patients, with specific focus on post-transplant renal function, rates of graft rejection, and survival.

Patients and methods

Study design and patients

A single-center retrospective study of adult and pediatric intestinal transplant patients over a 6-year period (2012–2018) was conducted at the University of Nebraska Medical Center. Prior to 2015, *en bloc* colon was rarely used at this transplant center; however, a programmatic shift in 2015 to include colon in those intestinal recipients without functional native colon was adopted.

In 2015, our institution changed clinical practice to begin including colonic allografts in all intestinal transplant patients that did not have functional native colon remaining at the time of their operation. Patients were categorized into three study groups. Group ICTx (Intestine + Colon Transplant) was defined as patients that had received a colon allograft as part of their intestinal transplant. Group ITx (Intestine Transplant) was defined as patients with nondiseased native colon who consequently were not candidates for a colon graft with their intestinal transplant. Group CCNTx (Colon Candidate, No Colon Transplant) was defined as patients that had a diseased or resected native colon before transplant, and consequently were candidates for a colon allograft, but did not receive one. We define native colon as any length of retained recipient colon, including recto-sigmoid colon. Patients were included in the study starting in reverse chronological order until equal-sized study groups were formed. Pediatric patients were defined as those with an age of 18 or less at the time of transplant.

Isolated intestinal transplant preferentially using portal venous drainage, or *en bloc* multivisceral transplant (liver, small bowel, pancreas with or without colon) was performed using techniques described in detail elsewhere [18]. When colon was included in the intestinal allograft, the right and transverse colon were retained *en bloc* with the intestinal graft. We routinely create either an end ileostomy or loop ileostomy of the allograft, and therefore, there is enteric discontinuity of the downstream native or transplant colon in the immediate post-transplant period. Either basiliximab or thymoglobulin induction immunosuppression, followed by tacrolimus and steroid maintenance immunosuppression, are typically used. Protocol allograft intestinal biopsy is performed weekly for the first month, followed by for cause allograft biopsy.

The Institutional Review Board at the Nebraska Medical Center approved this study (IRB approval number: 755-17-EP).

Variables

Variables were collected for each patient through retrospective chart review of their electronic medical record.

Demographic variables that were collected included gender, age at transplant, organs transplanted, and etiology of intestinal failure. Outcome variables included ileostomy reversal date, length of follow-up, and death. Graft survival was defined as time to patient death or graft explant. Rejection was defined as the earliest pathology report demonstrating either mild, moderate, or severe acute cellular rejection. Patients that experienced mortality before an episode of rejection were censored from these data. Finally, date of enteral autonomy was defined as first date on which enteral nutrition was sustained for a minimum of 2 weeks post-transplant.

Renal function outcomes collected included average volume of total IV fluids per day (sum of TPN and intravenous fluid volume) at time of transplant, average volume of total IV fluids per day one year after ileostomy reversal, number of septic episodes within the first year after transplant, and number of infections of an abdominal or urinary tract origin within the first year after transplant. Glomerular filtration rate (GFR) and blood urea nitrogen (BUN) at time of transplant and one year after transplant were recorded. GFR and BUN at one year post-transplant were recorded from routine outpatient follow-up visits. We excluded any data from inpatient admissions or emergency room visits around the one-year post-transplant time.

GFR for pediatric patients was calculated based on the formula GFR = kL/P_{Cr}, where k is a constant (0.33 for preterm infants, 0.45 for full-term infants, 0.55 for kids and teenage girls, and 0.70 for teenage boys), L is the length/height of the patient in centimeters, and P_{Cr} is the plasma creatine level in mg/dL [19]. GFR for adult patients was calculated by our lab, which uses the Cockcroft-Gault formula.

In all data collections, individuals who died prior to time of analysis were excluded from that particular analysis.

Statistical analysis

Continuous and categorical variables were compared between groups using parametric and nonparametric one-way analysis of variance (ANOVA) analysis. Graft survival, rejection-free survival, time to enteral autonomy, and time to ileostomy reversal were analyzed by means of the Kaplan–Meier method. Septic episodes and infection rates were analyzed with nonparametric one-way ANOVA. Nonparametric one-way ANOVA was used to analyze changes in GFR and BUN at the time of transplant to 1 year after transplant. Statistical analysis was completed using SAS® (SAS Institute Inc., Cary, NC, USA) and PRISM® (GraphPad Software, San Diego, CA, USA).

Immunosuppression

Induction immunosuppression was basiliximab for most patients. Thymoglobulin was selected for individuals deemed to be high risk for rejection (based on sensitization). Prednisone was given daily for 1 year after intestinal transplant, then every other day for the year following. Tacrolimus maintenance immunosuppression was used in all patients immediately post-transplant with target trough levels of 15–20 ng/ml for post-transplant week 0–6, 12–15 ng/ml for post-transplant week 6–3 months, 10–12 ng/ml for post-transplant 3–6 months, 7–10 ng/ml from 6 months to 1 year, and 5–10 ng/ml for patients greater than 1 year from transplant. Clinical judgement on selective titration was utilized in patients with infection or PTLD. Additionally, mycophenolate was used as a strategy to reduce target tacrolimus levels.

Results

Twenty-one adult and 26 pediatric intestinal transplant patients were identified for inclusion in the study. This included 28 males (60%), with an age of 14.5 ± 17.3 years (median ± SD) at the time of transplant (Table 1). The groups were similar in demographics, organs transplanted (other than colon), and etiology of intestinal failure. No patients were excluded from the study population for any reason.

Graft survival and rejection-free survival were statistically no different between study groups (1). 1-year graft survival was 63.5% in ICTx, 73% in ITx, and 93% in CCNTx. Median time to the first rejection episode was 121 days for both the ICTx and ITx groups. 1-year rejection-free survival was 38.5% in ICTx, 31.4% in ITx, and 66% in CCNTx. These results illustrate that inclusion of a colon did not increase the likelihood of rejection, graft explant, or patient death. Similarly, the number of infections or septic episodes within the first year after transplant showed no difference when a colon was included in the graft and when it was not ($P = 0.31$ and $P = 0.48$, respectively, Figure 1).

Patients in the CCNTx group showed significantly longer time to ileostomy reversal than the ICTx or ITx groups ($P = 0.0008$) (Figure 2). Ostomy reversal rates for each group were as follows: 62.5% for ICTx, 60.0% for ITx, and 20.0% for CCNTx. Median time to ostomy reversal was 153 days for ICTx, 181 days for ITx, and 427 days for CCNTx. The patients in the CCNTx group that were able to achieve ileostomy reversal despite no functional native colon remaining received ileo-rectal anastomosis. The ICTx group was the only group with over half of the patients reaching enteral autonomy within 2 months of their procedure (Figure 2). However, median time to reach enteral autonomy showed no significant difference between the groups ($P = 0.70$) (Figure 2).

Patients in the CCNTx group had significantly lower GFR one year post-transplant when compared to the other study groups ($P = 0.05$) (3). While this was not accompanied by a statistically significant increase in BUN level, there is a trend showing

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Table 1. Demographics and underlying case of intestinal failure

Characteristic	ICTx (n = 17)	ITx (n = 15)	CCNTx (n = 15)
Sex (n, %)			
Male	11 (65)	9 (60)	8 (53)
Age at transplant			
Pediatric age (mean ± SD)	10.1 ± 4.1	5.2 ± 3.7	6.2 ± 5.2
Adult age (mean ± SD)	37.0 ± 18.5	32.1 ± 7.9	34.7 ± 16.1
Adults (n, %)	8 (47.1)	6 (40.0)	7 (46.7)
Organs transplanted (n, %)			
LSBP	12 (70.6)	11 (73.3)	11 (73.3)
SB	3 (17.6)	4 (26.7)	4 (26.7)
SBPK	1 (5.9)	0 (0)	0 (0)
SBK	1 (5.9)	0 (0)	0 (0)
Etiology of intestinal failure (n, %)			
Gastroschisis	2 (11.8)	2 (13.3)	2 (13.3)
Necrotizing enterocolitis	3 (17.6)	2 (13.3)	1 (6.7)
Neuropathic pseudo-obstruction	1 (5.9)	1 (6.7)	4 (26.7)
Metastasis/Tumor	4 (23.5)	1 (6.7)	0 (0)
Crohn's	1 (5.9)	0 (0)	2 (13.3)
Intestinal atresia	1 (5.9)	3 (20)	0 (0)
Malrotation/Volvulus	2 (11.8)	1 (6.7)	1 (6.7)
Other*	3 (17.6)	5 (33.3)	5 (33.3)

*Included Hirschsprung's, Ehlers–Danlos, trauma, malabsorption, microcolon, arterial thrombosis, and unknown intestinal failure.
LSBP, liver small bowel pancreas; SB, small bowel; SBK, small bowel kidney; SBPK, small bowel pancreas kidney.

increased BUN levels in the CCNTx group (P = 0.17) (Figure 3).

Intravenous fluid requirements after transplant were analyzed as a proportion of the average fluids required per day at 1-year poststoma reversal compared to pre-transplant requirements (Figure 4). Adult patients in the CCNTx group showed the least improvement in IV fluid requirements (down 49.9% from time of transplant), while the ITx group showed the most improvement (down 81.9% from time of transplant) (Figure 4). All pediatric patients in the ITx group were able to be completely weaned from supplemental IV fluids within 1 year of transplant (Figure 4). The pediatric patients that received a colon (ICTx) had the lowest rate of complete weaning from IV fluids (Figure 4). The pediatric patients in the ITx group had the greatest proportional reduction in IV fluids per day (ml/kg/day) (Figure 4).

Discussion

In this single-center retrospective study, inclusion of donor colon in intestinal allograft was not associated with any significant difference in overall allograft or patient survival. However, intestinal transplant recipients who received colon as part of their graft demonstrated increased time to their first rejection episode. These findings differ from one source that found that colonic inclusion significantly worsened graft survival when compared to patients that did not receive colon [6]. Our findings are consistent with more recent analysis of a larger cohort of patients, which found that patient survival at 3 years was significantly improved when a colon was included in patients for which it was indicated [1]. Finally, time of rejection-free survival was best in the CCNTx group, which differs from the results of one study that showed that rejection was reduced in patients that received colon [13]. Colonic inclusion also showed no increase in the number of infections nor septic episodes requiring hospitalization within the first year of transplant, consistent with prior studies [11].

Patients that received a colon had ileostomy reversal rates similar to those that did not require a colon as they had healthy native colon *in situ*. Conversely, patients without native colon present that did not receive a colon graft showed significantly worse rates of ileostomy reversal. This is likely due to selection bias in the CCNTx group, in which patients likely had dysfunctional or insufficient rectal length to justify stoma reversal. Patients that received allograft colon experienced the best rates of weaning from TPN within 2 months of transplant of any group. However, we cannot attribute

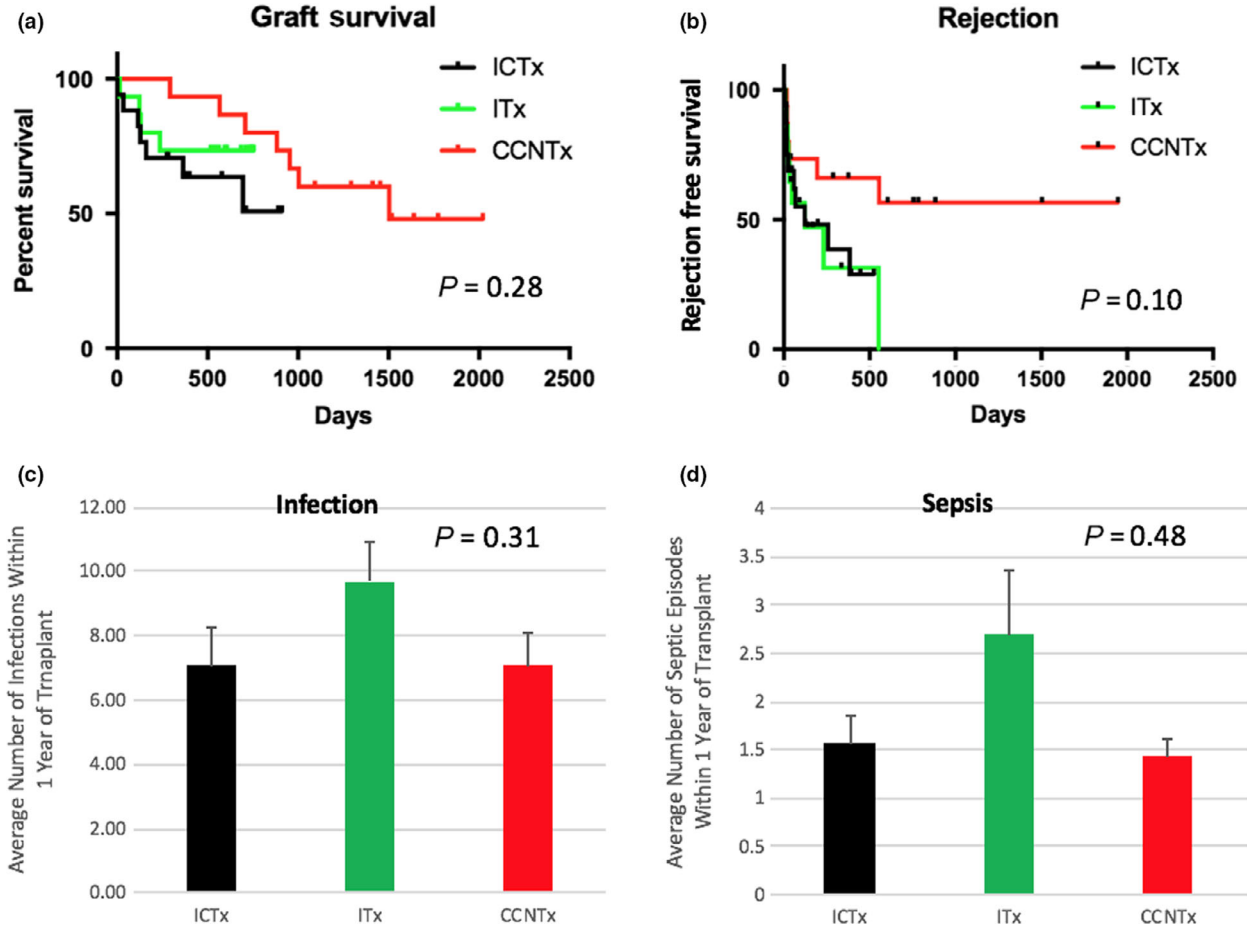
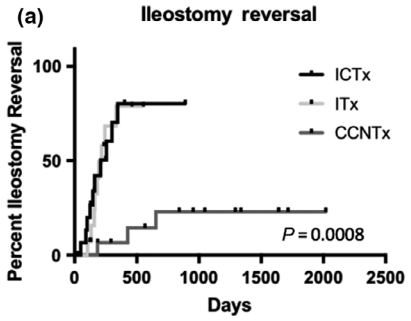


Figure 1 Graft Survival, Rejection, and Infection Rates following intestinal transplant. (a) Analysis of graft survival via Kaplan–Meier analysis. (b) Time to first rejection episode via Kaplan–Meier analysis. (c) Number of infections requiring hospital visits within the first year of transplant (Mean ± SE). (1) Number of septic episodes in each group within first year of transplant (Mean ± SE).



(b)

Group	% on TPN 2 months after transplant
ICTx	47.1%
ITx	60.0%
CCNTx	66.7%

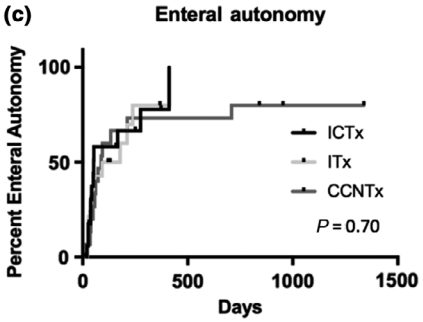


Figure 2 Time to Ileostomy Reversal and Enteral Autonomy. (a) Time from transplant to ileostomy reversal. (b) Proportion of transplant recipients achieving enteral autonomy within 2 months following transplant. (c) Time from transplant to achievement of enteral autonomy.

this finding to inclusion of donor colon in the allograft since stoma reversal was typically not performed until after this time period.

Adult and pediatric patients in the ITx group showed the greatest reduction in daily IV fluid requirements at 1-year postostomy-reversal out of any group. Meanwhile, patients in the ICTx and CCNTx groups showed high levels of variability in their ability to wean from IV fluid supplementation at this timepoint (Figure 4). This is likely due the fact that a smaller proportion of patients in the CCNTx group had their ostomies reversed, creating heterogeneity in this cohort. Notably, patients in the CCNTx group showed more deterioration in renal function than any other group, likely as a

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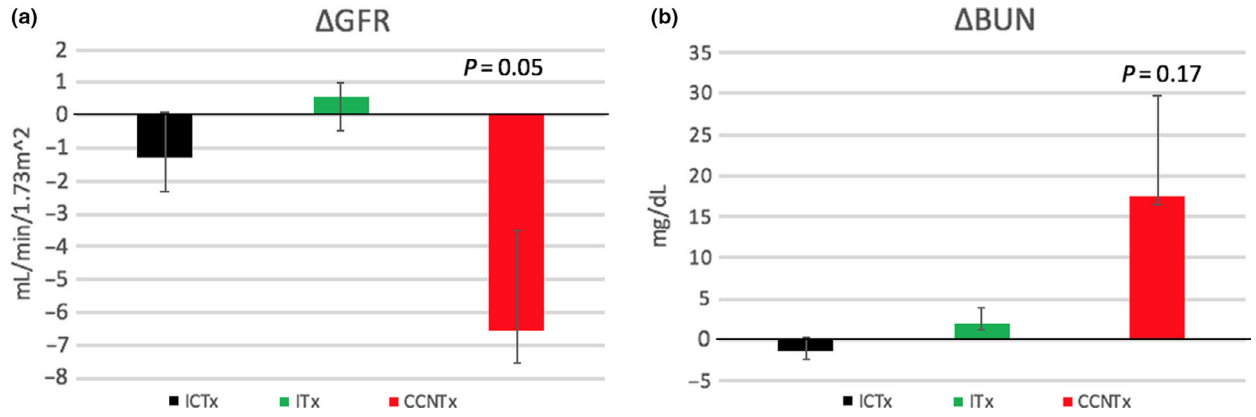

Figure 3 Renal function in intestinal transplant recipients at 1 year post-transplant relative to pretransplant baseline. (a) Change in glomerular filtration rate (GFR) from time of transplant to 1 year after transplant (Mean ± SE). (b) Change in BUN from time of transplant to 1 year after transplant (Mean ± SE).

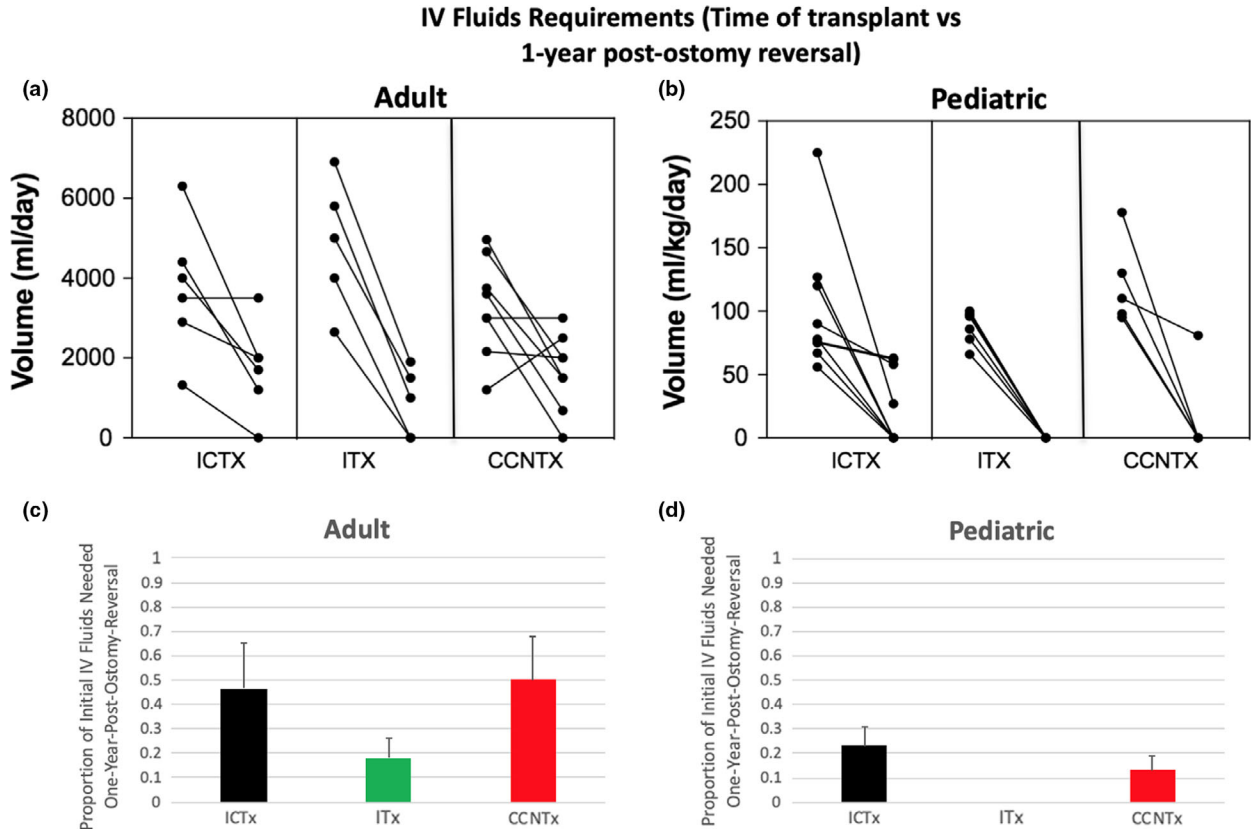

Figure 4 Total intravenous fluid requirements (TPN and IV fluids) in intestinal transplant recipients following ileostomy reversal compared with pretransplant requirements. (a) Daily IV fluid requirements (ml/day) prior to transplant compared to 1 year after ostomy reversal for adult patients. (b) Daily IV fluid requirements (ml/kg/day) prior to transplant compared to 1 year after ostomy reversal for pediatric patients. (c) The proportion of the average daily IV volume required at 1-year postileostomy reversal relative to pretransplant requirements (adult patients) Mean ± SE. (d). The proportion of the average daily IV volume required at 1-year postileostomy reversal relative to pretransplant requirements (pediatric patients) Mean ± SE. Patients that did not achieve ileostomy reversal were not included.

result of reduced rates of water reabsorption due to absence of native or transplant colon.

This study is limited on the basis of being a single-center experience with a limited data set but strengthened by analysis of relatively contemporary cohorts after the implementation of a programmatic transition to include *en bloc* colon with intestinal transplants during a time period in which the medical care of patients underwent

no changes. Notably, the survival analysis (Figure 1A) is limited by a shorter duration of follow-up presently available for the ICTx patients in whom median graft and patient survival has not been reached and therefore limits comparison of median survival time between groups.

Overall, the present study provides novel findings of improved rates of ileostomy reversal and renal protection provided by the inclusion of *en bloc* colon in the intestinal allograft in intestinal transplant recipients who do not have functional native colon. Paired with our confirmation of prior literature demonstrating no appreciable increased risk of rejection nor infection in colon recipients, the present data support the ongoing use of *en bloc* colon in intestinal transplant allografts.

Authorship

CE and SM: designed research study, performed research study, collected data, analyzed data, and wrote the paper. BJS: designed research study and wrote the paper. LV, WJG, DFM, and ANL: designed research study, performed research study, and wrote the paper.

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Conflicts of interest

The authors have declared no conflicts of interest.

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