

Intestinal Transplantation for Short Gut Syndrome Attributable to Necrotizing Enterocolitis

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ABSTRACT. *Background.* Necrotizing enterocolitis (NEC) is a life-threatening condition of the neonatal age, which frequently requires surgical intervention. After extensive bowel resection, a small proportion of these patients may develop chronic short gut syndrome (SGS) and require chronic total parenteral nutrition (TPN) use. Intestinal transplantation has been performed in these patients as a life-saving option.

This study reviews our experience with intestinal transplantation for SGS attributable to NEC emphasizing the mode of presentation, natural history, timing, and outcome.

Methods. A retrospective chart review was performed for all pediatric patients who underwent small bowel transplantation for NEC at the University of Miami between August 1994 and March 1999.

Results. Eleven transplants were performed for 10 patients with NEC (8 male and 2 female; median age: 1.75 years [range: 10 months to 10.1 years]). Procedures performed were isolated intestinal transplants ($n = 2$), combined liver-intestinal transplants ($n = 6$), and multivisceral transplants ($n = 3$). All patients were born prematurely with median birth weight of 1.640 kg (range: 810 g to 2.730 kg). They developed NEC in the first few days of life and subsequently underwent an average of 5 surgeries per patient before transplant. Transplant was indicated for liver failure in 8 patients and recurrent central line sepsis in 2 others.

At present, 6 patients are alive with an overall 1-year and 3-year actuarial survival of 60% and a median follow-up of 29 months (range: 9–46 months). Six children have been weaned off TPN after a median time of 71 days (range: 19–131) from transplantation. All survivors are at home with functional grafts.

Conclusion. Intestinal transplantation provided a reasonable outcome in patients with NEC-associated SGS who had already developed life-threatening complications related to TPN. Intestinal transplantation replaced the diseased intestine and liver, enfranchised patients from TPN, and conferred improved quality of life. These patients should be actively considered for intestinal transplantation and referred to a transplant center as soon as possible. *Pediatrics* 2000;105(2). URL: <http://www.pediatrics.org/cgi/content/full/105/2/e25>; *necrotiz-*

ing enterocolitis, short gut syndrome, intestinal transplantation, liver/intestinal transplantation, multivisceral transplantation.

ABBREVIATIONS. NEC, necrotizing enterocolitis; SGS, short gut syndrome; TPN, total parenteral nutrition; CMV, cytomegalovirus; GVHD, graft versus host disease.

Necrotizing enterocolitis (NEC) is a relatively common life-threatening condition of the neonatal period, which frequently requires emergency surgical intervention.^{1–3} It often affects a large segment of the small and large bowel, and it often requires extensive bowel resections, leading to the development of short gut syndrome (SGS) attributable to extensive surgical resection.⁴ After a variable period of adaptation, the gastrointestinal function recovers in the majority cases; therefore, most patients undergoing surgery have a good quality of life in the long-term without significant morbidity.^{5,6} However, a small proportion of patients develops chronic dependence on total parenteral nutrition (TPN) and associated life-threatening complications, such as liver failure, recurrent catheter sepsis, and loss of intravenous access, and they require intestinal transplantation as an extreme life-saving option.^{7–11} This article reviews our experience with intestinal transplantation for SGS attributable to NEC focusing on the mode of presentation, natural history, timing, and outcome.

METHODS

A retrospective chart review was performed for all children who underwent small bowel transplantation for NEC at the University of Miami between August 1994 and March 1999. Medical records for all patients were reviewed for data regarding past medical and surgical history, pretransplant assessment, transplant procedures, and posttransplant complications. Current status of survivors was evaluated for overall development status (weight and height percentile), motor and neurological function, and late morbidity.

Survival after transplantation was calculated by the Kaplan-Meier method.

RESULTS

Between August 1994 and March 1999, 10 children were transplanted at the University of Miami for NEC. There were 8 male and 2 female with a median age of 1.75 years (range: 10 months to 10.1 years) at transplantation. All patients were referred for assessment for transplantation with the diagnosis of intes-

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tinal failure secondary to NEC. During the same period, 35 children underwent intestinal transplantation in our center. NEC was the most common indication in children with 11 transplants performed in 10 patients (28.6%). The indications in children for transplantation other than NEC were gastroschisis (6), megacystis microcoln (3), intestinal atresia (3), Hirschsprung's disease (3), volvulus (5), microvillus inclusion (2), pseudoobstruction (2), and absence of muscularis propria (1).

Past Medical–Surgical History

All patients were born prematurely and the mean gestational age was 33 weeks (range: 25–35). Birth weight was documented in all cases but 1 and had a median value of 1.640 kg (range: 810 g to 2.730 kg). In 3 cases, the infant had a twin sibling, but none of the sibling pairs developed NEC.

Median age at onset of symptoms was 5 days (range: 3 days to 5 weeks). The majority of infants presented with bloody stool, abdominal tenderness, distention, and associated respiratory problems (Table 1). Three infants presented with intestinal perforation and peritonitis, and another infant presented with pneumatosis intestinalis and free air in the portal vein.

Because of clinical deterioration, all children underwent emergency surgery. In 4 patients, disease involved only the small bowel, in 3 it involved the small bowel and the right colon, in 2 the small bowel and right and transverse colon, and in the remaining 1 the small bowel and the entire colon (Table 1). There was an average of 5 surgeries (range: 3–8) per patient consisting primarily of small and large bowel resections, gastrostomy/jejunostomy and ileostomy. After the serial surgeries, the patients had an average of 15 cm (range: 0–35 cm) of remaining small bowel. Two patients had recurrent NEC after the initial surgical treatment and underwent additional resections.

All patients developed intestinal failure and were dependent on TPN thereafter. The course of the disease was often complicated at some stage during follow-up by intestinal and/or colonic strictures ($n = 5$), dislodgment of central line catheters ($n = 7$) and/or feeding tubes ($n = 7$), wound infections/dehiscence ($n = 5$), abdominal abscess ($n = 3$), enterocutaneous fistulas ($n = 2$), and feeding related problems ($n = 9$). Nine patients had at least 1 episode of central venous catheter-related infections. Four patients underwent a small bowel lengthening procedure (Bianchi procedure) and 2 underwent valve placement to slow down intestinal transit.^{12,13}

Pretransplant Assessment

At the time of pretransplant assessment, all patients had SGS and were dependent on TPN. Median length of TPN was 21 months (range: 10 months to 10.1 years). Eight patients had developed chronic cholestatic liver disease and signs of portal hypertension (esophageal varices [$n = 5$], ascites [$n = 5$], gastrointestinal bleeding [$n = 3$], and various degrees of muscle wasting, weight loss, weakness, renal failure, anemia, and thrombocytopenia).

TABLE 1. Clinical Features of Patients With NEC

Patient	Sex	Birth Weight (Grams)	Gestation (Weeks)	Disease Onset (Days)	Symptoms at Presentation	Organs Involved	Age at Tx (Years)	Bowel Involved	Bowel Remaining	Ileo-cecal Valve	Tx	Outcome
1	M	1600	31	6	RB, AT, air in PV, and pneumoperitoneum	SB + colon	1.9	SB + R and T colon	23-cm jejunum	No	I-P (I° tx)	Retx for severe acute rejection at 11 d
2	F	2730	35	35	AD and BS	SB + colon	2.1	SB + colon	—	No	MV (III° tx)	Died at 3 mo of MOF
3	M	1560	31	3	AD and AT	SB	5.1	SB	25-cm ileum	Yes	MV	Alive at 32 mo
4	M	—	33	3	BS, AD, AT, and RD	SB	10.1	SB	—	Yes	I	Died at 56 d of cardiac arrest
5	M	1640	32	5	AD and F	SB	1.6	SB	35-cm jejunum	No	L-I-K (2)-P	Died at 3 d of MOF
6	M	2150	35	3	AD and L	SB	1.6	SB	—	Yes	L-I	Alive at 26 mo
7	M	810	25	3	IP, AD, AT, and RD	SB + colon	9.9	SB + R and T colon	30-cm jejunum	No	MV	Alive at 21 mo
8	M	1520	33	6	BS, IP, AD, and AT	SB + colon	10	SB + colon	7-cm jejunum	No	L-I-P	Alive at 9 mo
9	M	2510	35	21	AD	SB	1.4	SB + R and T colon	15-cm jejunum	No	L-I	Alive at 45 mo
10	F	2290	34	5	IP, AT, and RD	SB + colon	1.4	SB	6-cm jejunum and 8-cm ileum	Yes	L-I	Alive at 46 mo
						SB + colon	2.4	SB + R colon	0-cm SB	No	L-I	Died at 38 d of aortic anastomosis disruption

PV indicates portal vein; SB, small bowel; I, intestine; L, liver; P, pancreas; MV, multivisceral (transplant); K, kidney; AD, abdominal distention; AT, abdominal tenderness; IP, intestinal perforation; RB, rectal bleeding; BS, bloody stools; RD, respiratory distress; F, fever; L, lethargy; Tx, transplantation; M, male; F, female.

Their median serum aspartate aminotransferase was 269 U/L (range: 40–695) and alanine aminotransferase was 173 U/L (range: 35–289), median serum total bilirubin was 12.6 mg/dL (range: 2–30), median serum albumin was 3.2 g/dL (range: 2.2–3.4), and median serum prothrombin time was 15 seconds (range: 11–17). In 2 other patients, intestinal transplantation was indicated for recurrent central line sepsis. Four had recurrent episodes of sepsis attributable to central line infection and loss of venous access.

Because of the severity of their disease, all but 1 child were in the 5th percentile for weight and height at pretransplant assessment. Most children had at least minimal delay in motor, speech, and neurological development. In particular, 1 child had a permanent acoustic impairment attributable to drug ototoxicity, 1 had a motor impairment, and another child, who had suffered from intraventricular hemorrhage, had a global delay of his oro-motor skills and receptive and expressive language.

One patient developed multisystem organ dysfunction along with the progression of liver failure. At the time of transplant, this patient was in mechanical ventilation, in inotropic drugs, and in renal failure.

Transplant Surgery

Eleven transplants were performed in 10 patients. One patient was retransplanted because of severe acute rejection that did not respond to the treatment. They included 2 isolated intestinal transplants, 6 combined liver-intestinal transplants, and 3 multivisceral transplants. Diagnosis of associated liver disease in 8 patients who had hepatic replacement was based on pretransplant needle biopsies when available or otherwise on clinical observation and confirmed by histologic examination at the time of transplant.

A multivisceral graft including the stomach and the pancreas was used in 2 cases because of severe adhesions in upper abdomen in 1 case and hemorrhagic pancreatitis in the other. Another multivisceral transplant was performed for the patient who received liver and intestinal transplant and lost the graft because of severe acute rejection of the intestine. The donor pancreas was implanted in 3 cases of liver-intestinal or isolated intestinal transplants for technical reasons.^{9,10,14} One patient received 2 kidneys with the multivisceral graft because of concomitant end-stage renal disease attributable to chronic glomerulonephritis (Table 1). Grafts were obtained from ABO-compatible donors; lymphocytotoxic cross-match was negative in all cases except the patient who had retransplantation. The median donor age was 2 years (range: 13 days to 8 years). Cytomegalovirus (CMV)-negative donors are preferred but CMV-positive donors were used in 6 cases and they were stratified as follows: D+/R- ($n = 5$), D+/R+ ($n = 1$), D-/R+ ($n = 4$), and D-/R- ($n = 1$).

The donor and recipient surgeries were performed by the standard technique previously described.^{8–11,15,16} In 3 cases, the graft had to be

reduced because of donor/recipient size mismatch. In 1 case, the right lobe of the liver and a portion of the jejunum were resected; in 2 other cases, the left lobe of the liver was removed; and in 1 case, a small portion of the distal ileum was resected together.

Eight explant liver biopsies of the patients who received a liver/intestinal or a multivisceral graft showed liver cirrhosis, intracellular cholestasis, and bile duct proliferation. Histologic changes in the native liver were limited to nonspecific chronic inflammation in 2 cases of isolated intestinal transplantation.

Immediate Postoperative Period

In 9 cases, postoperative immunosuppression consisted of a triple therapy with tacrolimus (Prograf, Fujisawa Inc, Deerfield, IL), steroids, and mycophenolate mophetil (Cellcept, Roche Laboratories Inc, Nutley, NJ) as described elsewhere.¹⁷ Muromonab-CD3, in association with tacrolimus and steroids, was used in 1 patient as induction therapy for 21 days, and in 4 cases, it was used for severe acute rejection. One patient received triple therapy of tacrolimus, steroids, and daclizumab (Zenapax, Roche Laboratories Inc).¹⁰

The patients received Gancyclovir and CMV-specific immune globulin (Cytogam, MedImmune Inc, Gaithersburg, MD) to prevent CMV infection. Standard antifungal (amphotericin) and antiprotozoal (trimethoprim-sulfamethoxazole) and antibacterial (ampicillin/sulbactam) agents also were administered. The monitoring, histologic diagnosis, and treatment of rejection has been described elsewhere.^{11,18,19}

Bone marrow cells obtained from the vertebrae of the same donor were infused intravenously in 7 patients to increase leukocyte chimerism.²⁰ Infusions of 10×10^8 cells/kg were given in 2 divided doses (days 0 and 5) in 4 cases and in 5 divided doses (days 5, 14, 21, 28, and 90) in 3 cases.

The median hospital stay for survivors was 64 days (range: 31–120). The major medical postoperative complications were: severe acute rejection ($n = 4$), mild-moderate acute rejection ($n = 7$), liver preservation injury ($n = 2$), seizures ($n = 3$), pneumonia ($n = 4$), bacteremia ($n = 5$), acute respiratory distress syndrome ($n = 1$), atypical mycobacteria-associated enterocolitis ($n = 2$), mild skin changes consistent with graft versus host disease (GVHD; $n = 2$), and hypertrophic cardiomyopathy ($n = 1$).

The major surgical complications were peritonitis ($n = 1$), lower gastrointestinal bleeding ($n = 4$), duodenal stump fistula ($n = 1$), biliary leak ($n = 1$), disruption of ileorectal anastomosis ($n = 1$), abdominal hematoma ($n = 3$), enteric fistula ($n = 1$), reflux esophagitis ($n = 1$), abdominal abscess ($n = 2$), and disruption of aortic anastomosis ($n = 1$).

Two patients underwent graft enterectomy because of severe acute rejection resistant to treatment. In 1 case, retransplantation was attempted but the patient succumbed after 38 days of severe acute rejection and multiorgan failure. The other patient died of cardiac arrest attributable to hyperkalemia while

waiting for a suitable donor. One patient died from disruption of aortic anastomosis. The patient who was in multiorgan dysfunction before transplantation died 3 days after transplant from progressive cardiopulmonary failure.

Long-Term Follow-up

At present, 6 patients are alive with an overall 1-year and 3-year patient survival of 60%, 54% with a median follow-up of 29 months (range: 9–46 months; Fig 1).

Two NEC patients are alive nearly 4 years after transplant and another patient is approaching 3 years. All survivors have been weaned off TPN after a median time of 71 days (range: 19–131 days) from transplantation. One of these children thrives on an oral diet alone and 5 receive supplemental overnight enteral feeding to support their nutritional needs. All survivors are at home with functional grafts. Three of them have a normal developmental and social status. Two other infants with significant preexisting neurological problems gradually gain weight and height. One baby transplanted 9 months ago has a mild speech and motor impairment but is improving.

DISCUSSION

NEC is an acute devastating disease of the neonatal period characterized by inflammation and hemorrhage of the bowel mucosa, often necessitating extensive resection of the small and large bowels. Children who survive the primary surgical intervention usually require additional operations because of recurrent episodes of NEC or NEC-related complications, such as intestinal stricture or obstruction, anastomotic leak, enterocutaneous fistulas, abdominal hematoma, or abscess.^{4,21} De-

spite the complicated clinical course, 60% of long-term survivors who underwent surgery usually have good quality of life and only few may have neurologic and growth development delays primarily related to the length and severity of their illness, which lasts since birth.^{4,22–24} Approximately 27% of patients develop SGS secondary to extensive intestinal resection.⁴ This is usually a temporary phenomenon, and after a variable period of adaptation varying between 3 months and 2 or 3 years usually resolves spontaneously.^{5,25} Only a small proportion of patients develop chronic SGS requiring dependence on TPN. Patel et al⁴ identified, among 42 long-term survivors with NEC who underwent surgical resection, 4 (10%) patients with SGS and chronic dependence on TPN. After a variable time (months to years) these patients may develop liver cirrhosis, ascites, and signs of portal hypertension.²⁶ This subgroup of patients have poor quality of life, their clinical course often being complicated by numerous readmissions for NEC-related abdominal surgeries, central venous catheter-related infections, dislodgment of central line catheters and/or feeding tubes, wound infections and dehiscence, developmental delay, and TPN-associated liver failure.^{4,27} It has been demonstrated that these patients have a worse prognosis than patients with SGS attributable to other primary diseases.²⁸ The introduction of intestinal transplantation offers them the only chance for survival.

Intestinal transplantation replaces the diseased intestine and liver, enfranchises patients from TPN, and is associated with improved quality of life in patients who would otherwise have an extremely poor prognosis.^{10,29} Also, it relieves these patients

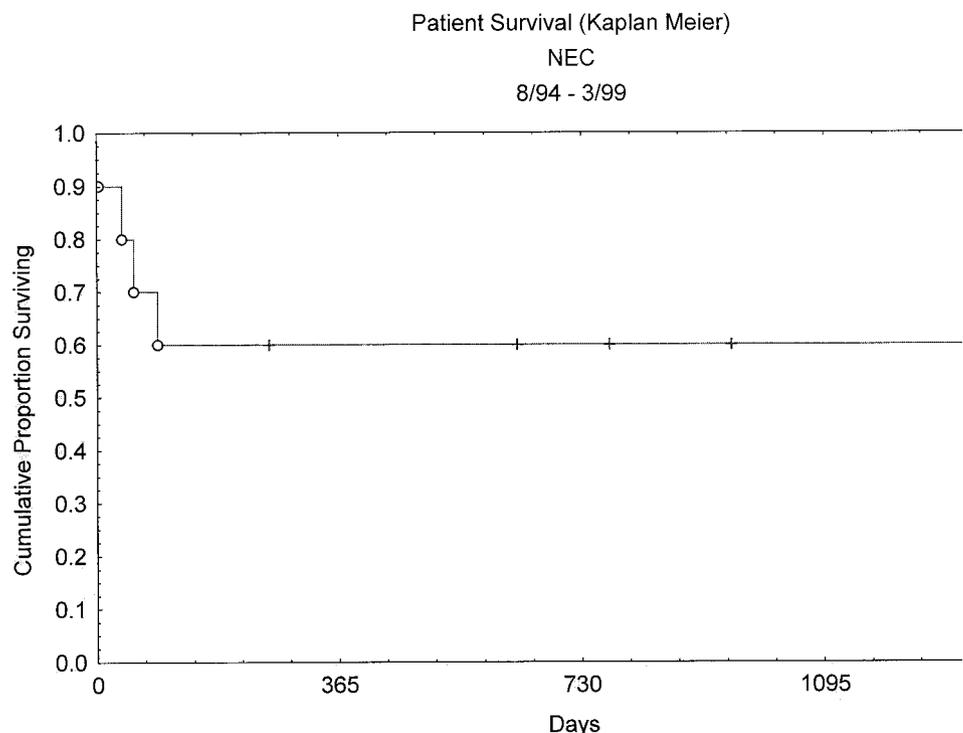


Fig 1. Long-term survival of NEC patients (Kaplan-Meier method).

from the expenses of chronic home intravenous hyperalimentation, which may reach \$150 000 to \$200 000 per patient per year.⁹ However, these patients must be carefully assessed before transplantation to exclude conditions that preclude transplantation.

Results of intestinal transplantation continue to improve and 1-year patient/graft survival of 72%/55% have been reported.¹¹ Experience in intestinal transplantation with NEC patients is still limited; to the best of our knowledge, this is the first report in the literature. In this series, intestinal transplantation for SGS attributable to NEC yielded 1- and 3-year patient survival rates of 60% and 54%, respectively. All living patients who survived the first year after transplantation remained alive thereafter; in addition, they are off TPN, have functional grafts, and have an acceptable developmental status. This experience shows that intestinal transplantation may represent a life-saving option in children with SGS attributable to NEC, at least for an intermediate-term follow-up.

Higher survival rates may be achieved with better selection and timing. Survival in children also depends on appropriate organ availability, because size-matched organs are not easily found. In 4 cases, the grafts were too big and had to be reduced to accommodate them in the recipient. Technical variations in case of donor/recipient size mismatch may allow a larger number of recipients to receive a graft and decrease waiting list periods.³⁰

Intestinal rejection is still a major cause of early mortality and graft loss.^{10,18} Two of 4 deaths and 3 graft losses were attributable to severe acute graft rejection resistant to treatment.

GVHD is also of major concern after intestinal transplantation. It may present with a broad spectrum of severity varying from mild skin changes to life-threatening clinical condition.³¹ In this series, we observed only 2 cases with GVHD manifested by minor skin changes and both clinically unremarkable.

The aforementioned improvements in management of premature infants has recently determined an increase in the number of NEC cases recorded every year in the United States and of those who survive to initial aggressive treatment. Consequently, we may expect a concomitant increase of patients suffering from long-term morbidity attributable to NEC and referred for intestinal transplantation. Because no effective medical treatment and prevention is yet available for children with SGS attributable to NEC, these patients should be identified early and considered for intestinal transplantation. Patients should be referred to a transplant center as soon as chronic dependence of TPN has developed and before they reach to a terminal condition.

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Pediatrics 2000;105;e25

DOI: 10.1542/peds.105.2.e25

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