

Isolated Small Bowel Transplant

Effective: March 1, 2019

Next Review: January 2020

Last Review: January 2019

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Small bowel transplants are performed to treat intestinal failure in patients that require total parenteral nutrition (TPN) and are having serious TPN complications.

Note: A small bowel transplant may be performed in conjunction with other visceral organs, including the liver, duodenum, jejunum, ileum, pancreas, or colon. When the small bowel and liver are transplanted in conjunction with other gastrointestinal organs, the procedure is referred to as a multivisceral transplant. Small bowel/liver transplants and multivisceral transplants are considered separately (see cross-reference list below).

MEDICAL POLICY CRITERIA

- I. Candidates for all types of small bowel transplant must meet all of the following criteria:
 - A. Adequate cardiopulmonary status; and
 - B. Documentation of patient compliance with medical management
- II. Cadaveric Donor

A small bowel transplant using a cadaveric intestine may be considered **medically necessary** in adult and pediatric patients with intestinal failure (characterized by loss of absorption and the inability to maintain protein-energy, fluid, electrolyte, or

micronutrient balance), who have established long-term dependency on total parenteral nutrition (TPN) and are developing or have developed one or more of the following severe complications due to TPN:

- A. TPN intolerance to the point that multiple and prolonged hospitalizations are required to treat TPN-related complications
- B. The development of progressive but reversible liver failure
- C. Inability to maintain venous access

III. Living Donor

- A. A small bowel transplant using a living donor may be considered **medically necessary** only when a cadaveric intestine is not available for transplantation in a patient who meets the criteria noted above for a cadaveric transplant (I-II).
- B. A small bowel transplant using living donors is considered **not medically necessary** in all other situations.

IV. A small bowel retransplant is considered **medically necessary** after a failed small bowel transplant.

V. A small bowel transplant is considered **not medically necessary** for patients with intestinal failure who are able to tolerate TPN.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- Diagnosis and Indication for transplant

CROSS REFERENCES

1. [Small Bowel/Liver and Multivisceral Transplant](#), Transplant, Policy No. 18

BACKGROUND

Intestinal failure is a serious medical condition which results from surgical resection, congenital defect, or disease-associated loss of absorption and is characterized by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balance.^[1] Short bowel syndrome, one type of intestinal failure, is a condition in which the absorbing surface of the small intestine is inadequate due to extensive disease or surgical removal of a large portion of small intestine. Etiologies of short bowel syndrome include: volvulus, atresias, necrotizing enterocolitis, gastroschisis, desmoid tumors, and trauma. Patients with short bowel syndrome are unable to obtain adequate nutrition from enteral feeding and become dependent upon total parenteral nutrition (TPN). Patients with complications from TPN, such as catheter-related mechanical problems, infections, hepatobiliary disease, and metabolic bone disease, may be considered candidates for small bowel transplant.

Intestinal transplants, including multivisceral and bowel/liver, represent a small minority of all solid organ transplants. In 2015 and 2016, 141 and 147 intestinal transplants, respectively, were performed in the United States, of which all but two were from deceased donors.^[2] While cadaveric intestinal transplant is the most commonly performed transplant, there has been more recent interest in using living related donors. Potential advantages of a living donor include the ability to plan the transplant electively and better antigen matching, leading to improved management of rejection.

EVIDENCE SUMMARY

Ideally, for intestinal transplant to be considered as a replacement for total parenteral nutrition (TPN), head-to-head comparisons of transplantation versus TPN are needed, preferably in well-designed randomized controlled trials (RCTs). Further, for chronic conditions such as intestinal failure, comparative trials with long-term follow-up are necessary in order to determine the durability of any beneficial treatment effects, and to establish guidelines regarding the timing of intestinal transplant. In order to establish the net benefit of using living donors versus cadaveric intestinal transplant for treatment of intestinal failure, clinical trials that compare these therapies are needed, and the impacts on health outcomes for both the donors and recipients must be considered.

The current literature on small bowel transplantation included the following general observations:

- The importance of timely referral for intestinal transplantation was emphasized to avoid the necessity of combined liver and intestine transplantation.
- While outcomes continue to improve, obstacles to long-term survival remain. Recurrent and chronic rejections and complications of immunosuppression are significant issues in bowel transplantation.
- It has been suggested that improvements in survival over the last 10–15 years may justify removing the restriction of intestinal transplantation to patients who have severe complications of TPN.^[3] However, as noted by Vianna in their report on the status of intestinal transplantation, no randomized trials compare intestinal transplantation to long-term parenteral nutrition, and optimal timing for earlier transplantation has not been established.^[4]

SYSTEMATIC REVIEWS

This policy was initially based on 1995 and 1999 BlueCross BlueShield Association Technology Evaluation Center (TEC) assessments.^[5,6] The 1995 assessment concluded that in children, small bowel transplant was associated with improved survival compared to TPN. This assessment also concluded that in adults, the outcomes for small bowel transplant were worse than those associated with TPN.

The 1999 TEC assessment reevaluated the data on adults, specifically focusing on the probability of adult patient and graft survival with small bowel transplant compared to TPN, and whether successful outcome of small bowel transplant improves health outcomes or reduces adverse outcomes.^[6] The assessment reported that bowel transplants in adults produce patient survival rates from 27%-58% at 4 or 5 years. Graft survival rates (and presumably independence from TPN) range from 13%-30%. It is unknown whether this represents a net benefit to these patients, since some patients may survive for long periods of time on TPN. The TEC assessment also indicated that some patients with increasingly severe TPN-

associated complications may face a high probability of impending mortality such that the risk of continued medical management is higher than the risk of transplantation. However, at this point in time, it is not possible to predict which patients will survive longer on TPN versus small bowel transplant.

In 2010, Sudan published a systematic review of current literature on long-term outcomes after intestinal transplantation.^[7] The author noted that intestinal transplantation has become standard therapy for patients with life-threatening complications from parenteral nutrition therapy. Data from current single-center series indicate a 1-year patient survival rate of 78-85% and a 5+ year survival rate of 56-61%. With respect to pediatric intestinal transplant patients, the majority achieve normal growth velocity at two years post-transplant. However, oral aversion is a common problem; tube feedings are necessary in 45% of children. Sudan also noted that parental surveys of quality of life in pediatric transplant patients have shown that intestinal transplant patients appear to have modestly improved quality of life compared to patients remaining on TPN and slightly worse than matched school-age controls without intestinal disease.

RANDOMIZED CONTROLLED TRIALS

No RCTs were identified that compared intestinal transplantation with ongoing parenteral nutrition with or without subsequent small bowel/liver or multivisceral transplantation.

NONRANDOMIZED STUDIES

Despite the lack of RCTs, isolated small bowel transplantation has become an accepted alternative to continued total parenteral nutrition (TPN) to avoid the need for multivisceral transplantation in carefully selected patients with intestinal failure who are developing severe complications related to total parenteral nutrition (TPN).

The following is a summary of non-randomized trials that are representative of the available data on small bowel transplantation from living donors and post-transplantation complications.

Living Donor

The literature related to living-related intestinal transplant consists of small case reports of 1 to 11 patients in which different lengths of the ileum or jejunum were used.^[8-15] While there appeared to be minimal complications to the donors, of the cases reported a significant number of recipients remained on TPN for at least part of their nutrition while others remain healthy and off TPN.

Ueno reported on 21 intestinal transplant patients that underwent transplantation between 1996 and 2012 at one of five institutions.^[16] Twelve transplants came from living donors. All but one patient received an isolated small bowel transplant for intestinal failure. The overall 1- and 5- year survival rates were 86% and 68%, respectively. In the 15 patients who underwent transplantation after 2006, 1-year survival was 92% and 5-year survival was 83%.

Gangemi and Benedetti published a literature review of living donor small bowel transplantation reports from 2003 to 2006; all of the reports listed Benedetti as author.^[17] The authors commented that, "Due to the excellent result in modern series of deceased donor bowel transplantation, widespread use of the procedure [living donor] should not be recommended, in consideration of the potential risks to donor. Furthermore, few centers have acquired the necessary experience with the procedure." Benedetti also reported outcomes

from 4 children and 7 adults who underwent 12 living-related small bowel transplantations between 1998 and 2004.^[18] All donors were reported to have had uneventful recovery following removal of up to 40% of the small intestine. The 3-year patient survival was 82%, with graft survival of 75%. Longer follow-up from the earlier cases was not reported.

Complications

In 2016, Limketkai published a retrospective study on mortality and graft rejection rates in 1115 cases of intestinal transplants performed from May 1990 through June 2014.^[19] Of these, 142 transplants were done for Crohn's disease (CD). Transplants were rejected in 33.3% of patients without CD and 36.9% of patients with CD. The actuarial risk of death for patients with CD at one, five, and ten years post-transplant 22.5%, 50.3%, and 59.7%, respectively. Patients without CD had similar mortality risks.

In 2014, Calvo Pulido reported on 21 adults who underwent intestinal transplantation; 17 were isolated small bowel transplants.^[20] Thirteen patients (62%) experienced renal failure; the etiology included high ileostomy output, immunosuppression and medical treatment.

In 2013, Boyer reported that 7 of 12 children who had an isolated small bowel transplant had renal function complications at some point after surgery.^[21] Prior to treatment, all of the patients had normal renal functioning.

Florescu have published several articles retrospectively reviewing complications in a cohort of 98 pediatric patients. Twenty-one of these children (21.4%) had an isolated small bowel transplant; the remainder had combined transplants. These articles include a 2012 study that reported that 68 of the 98 patients (69%) developed at least one episode of bloodstream infection.^[22] Among the patients with an isolated small bowel transplant, the median time to infection for those who became infected was 4.5 months (95% confidence interval [CI]: 2.4 to 6.7 months). Also in 2012, the researchers reported that 7 of 98 patients (7%) developed cytomegalovirus (CMV) disease; only one of these had an isolated small bowel transplant.^[23] A 2010 study by this group retrospectively reported on the incidence of fungal infection after pediatric small bowel transplantation among patients treated between 2003 and 2007 at a single center.^[24] The average length of follow-up was not reported. A total of 25 of 98 cases reviewed (26%) developed at least one episode of fungal infection; *Candida* infection was most common. During the study period, the mortality rate did not differ significantly between patients who did and did not develop a fungal infection (32.3% vs. 29.8%, respectively), but the authors stressed the importance of better screening tools to identify and prevent fungal infections.

As noted previously, Sudan reported oral aversion to be a common problem in pediatric patients with tube feedings necessary in 45% of children following small bowel transplantation.^[7]

Retransplantation

Desai have published the most comprehensive reporting of outcomes after repeat small bowel transplant in the United States. A 2012 publication evaluated data in the UNOS database on patients who underwent small bowel transplants in the U.S between October 1987 and August 2009.^[25] The investigators identified 41 repeat isolated small bowel transplants in adults and 28 in children. Thirty-nine of the adults (95%) and 27 (96%) of the children had a previous isolated small bowel transplant; the remaining patients had an initial combined small bowel and liver transplant.

Among adults, survival rates after retransplant were 80% after 1 year, 47% after 3 years and 29% after 5 years. Comparable survival rates for primary isolated small bowel transplant were 84% after 1 year, 67% after 3 years and 54% after 5 years. Survival was significantly lower after repeat isolated small bowel transplant compared to primary isolated small bowel transplant, $p=0.005$.

Among children, patient survival was 81% after 1 year, 74% after 3 years and 58% after 5 years. These rates did not differ significantly from rates after primary isolated small bowel transplant (85% after 1 year, 71% after 3 years and 64% after 5 years, respectively).

HIV POSITIVE TRANSPLANT RECIPIENTS

This subgroup of recipients has long been controversial due to the long term prognosis for HIV positivity and the impact of immunosuppression on HIV disease. Although HIV positive transplant recipients may be a research interest of some transplant centers, the minimal data regarding long term outcomes in these patients consist primarily of case reports and abstract presentations of liver and kidney recipients. Nevertheless, some transplant surgeons would argue that HIV positivity is no longer an absolute contraindication to transplant due to the advent of highly active antiretroviral therapy (HAART), which has markedly changed the natural history of the disease.

The Organ Procurement and Transplantation Network (OPTN) considers HIV+ organ candidates to be acceptable recipients “if permitted by the transplant hospital. Care of HIV test positive organ candidate and recipients should not deviate from general medical practice.”^[26]

PRACTICE GUIDELINE SUMMARY

AMERICAN GASTROENTEROLOGICAL ASSOCIATION (AGA)

The AGA issued a medical position statement on short bowel syndrome and intestinal transplantation citing that intestinal transplants have only been performed in patients with life-threatening complications attributable to their intestinal failure and long-term TPN therapy and that standards of care for this type of transplantation are still evolving.^[27]

SUMMARY

There is enough research to show that small bowel transplants can improve health outcomes in certain patients with intestinal failure with serious complications from total parenteral nutrition (TPN). Therefore, isolated small bowel transplant may be considered medically necessary in patients that meet the policy criteria.

There is enough research to show that small bowel transplant does not improve health outcomes in patients with intestinal failure who are able to tolerate TPN. Therefore, small bowel transplant may be considered not medically necessary for these patients.

There is enough research to show that small bowel retransplant improves health outcomes in patients that have had a failed small bowel transplant. Therefore, for patients with failed small bowel transplant, retransplant may be considered medically necessary.

REFERENCES

1. O'Keefe, SJ, Buchman, AL, Fishbein, TM, Jeejeebhoy, KN, Jeppesen, PB, Shaffer, J. Short bowel syndrome and intestinal failure: consensus definitions and overview. *Clin Gastroenterol Hepatol*. 2006 Jan;4(1):6-10. PMID: 16431298
2. Organ Procurement and Transplantation Network (OPTN). National Data. [cited 01/17/2019]; Available from: <https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/>
3. Matarese, LE, Costa, G, Bond, G, et al. Therapeutic efficacy of intestinal and multivisceral transplantation: survival and nutrition outcome. *Nutr Clin Pract*. 2007 Oct;22(5):474-81. PMID: 17906271
4. Vianna, RM, Mangus, RS, Tector, AJ. Current status of small bowel and multivisceral transplantation. *Adv Surg*. 2008;42:129-50. PMID: 18953814
5. TEC Assessment 1995. "Transplants Involving the Small Bowel." BlueCross BlueShield Association Technology Evaluation Center, Vol. 10, Tab 27.
6. TEC Assessment 1999. "Small Bowel Transplants in Adults and Multivisceral Transplants in Adults and Children." BlueCross BlueShield Association Technology Evaluation Center, Vol. 14, Tab 9.
7. Sudan, D. Long-term outcomes and quality of life after intestine transplantation. *Curr Opin Organ Transplant*. 2010 Jun;15(3):357-60. PMID: 20445450
8. Gruessner, RW, Sharp, HL. Living-related intestinal transplantation: first report of a standardized surgical technique. *Transplantation*. 1997 Dec 15;64(11):1605-7. PMID: 9415566
9. Jaffe, BM, Beck, R, Flint, L, et al. Living-related small bowel transplantation in adults: a report of two patients. *Transplant Proc*. 1997 May;29(3):1851-2. PMID: 9142299
10. Fujimoto, Y, Uemoto, S, Inomata, Y, et al. Living-related small bowel transplant: management of rejection and infection. *Transplant Proc*. 1998 Feb;30(1):149. PMID: 9474986
11. Tesi, R, Beck, R, Lambiase, L, Haque, S, Flint, L, Jaffe, B. Living-related small-bowel transplantation: donor evaluation and outcome. *Transplant Proc*. 1997 Feb-Mar;29(1-2):686-7. PMID: 9123480
12. Cicalese, L, Baum, C, Brown, M, et al. Segmental small bowel transplant from adult living-related donors. *Transplant Proc*. 2001 Feb-Mar;33(1-2):1553. PMID: 11267417
13. Wu, GS, Wang, WZ, Song, WL, Lin, R, Duraj, FF. The living-related small bowel transplant: the first case in China. *Transplant Proc*. 2000 Sep;32(6):1218. PMID: 10995917
14. Cicalese, L, Sileri, P, Coady, N, et al. Proposed protocol to reduce bacterial infectious complications in living related small bowel transplant recipients. *Transplant Proc*. 2002 May;34(3):950. PMID: 12034255
15. Wada, M, Ishii, T, Kato, T, et al. Living-related small bowel transplantation: two cases experiences. *Transplant Proc*. 2005 Mar;37(2):1381-2. PMID: 15848727
16. Ueno, T, Wada, M, Hoshino, K, et al. Impact of intestinal transplantation for intestinal failure in Japan. *Transplant Proc*. 2014 Jul-Aug;46(6):2122-4. PMID: 25131121
17. Gangemi, A, Benedetti, E. Living donor small bowel transplantation: literature review 2003-2006. *Pediatr Transplant*. 2006;10(8):875-8. PMID:
18. Benedetti, E, Holterman, M, Asolati, M, et al. Living related segmental bowel transplantation: from experimental to standardized procedure. *Ann Surg*. 2006 Nov;244(5):694-9. PMID: 17060761

19. Limketkai, BN, Orandi, BJ, Luo, X, Segev, DL, Colombel, JF. Mortality and Rates of Graft Rejection or Failure Following Intestinal Transplantation in Patients With vs Without Crohn's Disease. *Clin Gastroenterol Hepatol*. 2016 Nov;14(11):1574-81. PMID: 27374004
20. Calvo Pulido, J, Jimenez Romero, C, Morales Ruiz, E, et al. Renal failure associated with intestinal transplantation: our experience in Spain. *Transplant Proc*. 2014 Jul-Aug;46(6):2140-2. PMID: 25131125
21. Boyer, O, Noto, C, De Serre, NP, et al. Renal function and histology in children after small bowel transplantation. *Pediatr Transplant*. 2013 Feb;17(1):65-72. PMID: 22882667
22. Florescu, DF, Qiu, F, Langnas, AN, et al. Bloodstream infections during the first year after pediatric small bowel transplantation. *The Pediatric infectious disease journal*. 2012 Jul;31(7):700-4. PMID: 22466325
23. Florescu, DF, Langnas, AN, Grant, W, et al. Incidence, risk factors, and outcomes associated with cytomegalovirus disease in small bowel transplant recipients. *Pediatr Transplant*. 2012 May;16(3):294-301. PMID: 22212495
24. Florescu, DF, Islam, KM, Grant, W, et al. Incidence and outcome of fungal infections in pediatric small bowel transplant recipients. *Transpl Infect Dis*. 2010 Dec;12(6):497-504. PMID: 20626710
25. Desai, CS, Khan, KM, Gruessner, AC, Fishbein, TM, Gruessner, RW. Intestinal retransplantation: analysis of Organ Procurement and Transplantation Network database. *Transplantation*. 2012 Jan 15;93(1):120-5. PMID: 22113492
26. Organ Procurement and Transplantation Network (OPTN) Policies. 2017. [cited 01/17/2019]; Available from: <https://optn.transplant.hrsa.gov/governance/policies/>
27. American Gastroenterological Association medical position statement: Short bowel syndrome and intestinal transplantation. *Gastroenterology*. 2003;124(4):1105-10. PMID: 12671903
28. BlueCross BlueShield Association Medical Policy Reference Manual "Isolated Small Bowel Transplant." Policy No. 7.03.04

CODES

Codes	Number	Description
CPT	44132	Donor enterectomy (including cold preservation), open; from cadaver donor
	44133	Donor enterectomy (including cold preservation), open partial, from living donor
	44135	Intestinal allotransplantation; from cadaver donor
	44136	Intestinal allotransplantation; from living donor
	44715	Backbench standard preparation of cadaver or living donor intestine allograft prior to transplantation, including mobilization and fashioning of the superior mesenteric artery and vein
	44720	Backbench reconstruction of cadaver or living donor intestine allograft prior to transplantation; venous anastomosis, each
	44721	Backbench reconstruction of cadaver or living donor intestine allograft prior to transplantation; arterial anastomosis, each
HCPCS	None	

Date of Origin: January 1996