Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

***Current Policy Effective Date: 9/1/24**
(See policy history boxes for previous effective dates)

Title: Transplant-Small Bowel (Isolated)

Description/Background

Solid organ transplantation offers a treatment option for patients with different types of end stage organ failure that can be lifesaving or provide significant improvements to a patient's quality of life.[1] Many advances have been made in the last several decades to reduce perioperative complications. Available data supports improvement in long-term survival as well as improved quality of life particularly for liver, kidney, pancreas, heart, and lung transplants. Allograft rejection remains a key early and late complication risk for any organ transplantation. Transplant recipients require life-long immunosuppression to prevent rejection. Patients are prioritized for transplant by mortality risk and severity of illness criteria developed by the Organ Procurement and Transplantation Network (OPTN) and United Network of Organ Sharing (UNOS).

SHORT BOWEL SYNDROME

Short bowel syndrome 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 the small intestine. The spectrum of clinical disease is widely variable from only single micronutrient malabsorption to complete intestinal failure, defined as the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes.[2] In adults, etiologies of short bowel syndrome include ischemia, trauma, volvulus, and tumors. In children, gastroschisis, volvulus, necrotizing enterocolitis, and congenital atresia are predominant causes. Although the actual prevalence of short bowel syndrome is not clear primarily due to under-reporting and a lack of reliable patient databases, its prevalence is estimated to be 30 cases per million in the U.S.[2]

Treatment

The small intestine, particularly the ileum, does have the capacity to adapt to some functions of the diseased or removed portion over a period of 1 to 2 years. Prognosis for recovery depends on the degree and location of small intestine damage. Therapy is focused on achieving

adequate macro- and micro-nutrient uptake in the remaining small bowel. Pharmacologic agents have been studied to increase villous proliferation and slow transit times, and surgical techniques have been advocated to optimize remaining small bowel.

However, some patients with short bowel syndrome are unable to obtain adequate nutrition from enteral feeding and become chronically dependent on total parenteral nutrition (TPN). For patients with short bowel syndrome, the rate of parenteral nutrition dependency at 1, 2, and 5 years has been reported to be 74%, 64%, and 48%, respectively.[2] Patients with complications from TPN may be considered candidates for small bowel transplant. Complications include catheter-related mechanical problems, infections, hepatobiliary disease and metabolic bone disease. While cadaveric intestinal transplant is the most commonly performed transplant, there has been recent interest in using living donors.

Intestinal transplants (including multi-visceral and bowel/liver) represent a small minority (0.6%) of all solid organ transplants. In 2021, 96 intestinal transplants were performed in the U.S. [3] Overall, both the number of new patients added to the intestinal transplant waiting list (n=142) and the number of intestinal transplants performed increased slightly from their lowest levels in 2019.

Regulatory Status

Solid organ transplants are a surgical procedure and, as such, are not subject to regulation by the U.S. Food and Drug Administration.

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation Title 21, parts 1270 and 1271. Solid organs used for transplantation are subject to these regulations.

Medical Policy Statement

The safety and effectiveness of an isolated small bowel transplant have been established. It may be considered a useful therapeutic option for carefully selected individuals who meet the selection criteria.

Inclusionary and Exclusionary Guidelines

Inclusions:

Appropriate patients for isolated small bowel transplant include:

- Cadaveric transplants for adult and pediatric patients (using a cadaveric transplant) 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 severe complications due to TPN.

- A small bowel transplant using a living donor for adult and pediatric patients (when a cadaveric transplant is not available) for patients who meet the criteria noted above for a cadaveric intestinal transplant.
- A small bowel retransplant after a failed primary small bowel transplant.

Small Bowel Specific Guidelines
Individuals who are developing or have developed severe complications due to total parenteral nutrition (TPN) include, but are not limited to, the following: multiple and prolonged hospitalizations to treat TPN-related complications (especially repeated episodes of catheter-related sepsis) or the development of progressive liver failure. In the setting of progressive liver failure, small bowel transplant may be considered a technique to avoid end-stage liver failure related to chronic TPN, thus avoiding the necessity of a multi-visceral transplant. In those receiving TPN, liver disease with jaundice (total bilirubin above 3 mg/dL) is often associated with development of irreversible progressive liver disease. The inability to maintain venous access is another reason to consider small bowel transplant in those who are dependent on TPN.

Exclusions (organ-specific):

- A small bowel transplant for adult and pediatric patients with intestinal failure who are *able* to tolerate TPN.
- A small bowel transplantation for adult and pediatric patients is considered investigational in all other situations.

Potential contraindications):
Note: Potential contraindications are subject to the judgment of the transplant center:

1. Known current malignancy, including metastatic cancer;
2. Recent malignancy with high risk recurrence;
3. History of cancer with a moderate risk of recurrence;
4. Untreated systemic infection making immunosuppression unsafe, including chronic infection;
5. Other irreversible end-stage disease not attributed to small bowel disease;
6. Stable systemic disease that could be exacerbated by immunosuppression;
7. Psychosocial conditions or chemical dependency affecting ability to adhere to therapy.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

44132 44133 44135 44136 44715 44720
44721

Other codes (investigational, not medically necessary, etc.):

N/A

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function¾including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

SMALL BOWEL TRANSPLANTATION

Clinical Context and Therapy Purpose

The purpose of a small bowel transplant in individuals who have an intestinal failure is to provide a treatment option that is an alternative to or an improvement on existing therapies. Parenteral nutrition has been a mainstay of therapy for patients with intestinal failure for decades.[4] Medical advances have resulted in improved survival in parenteral nutrition-dependent patients, primarily through an increased likelihood of weaning (i.e., achieving enteral autonomy) and reduced rates and progression of intestinal failure-associated liver disease and other life-threatening complications of prolonged parenteral nutrition administration.

The following **PICOs** were used to select literature to inform this review.

Populations

The relevant population of interest is individuals with intestinal failure.

Interventions

The therapy being considered is small bowel transplant. Small bowel transplantation is provided in a hospital setting by specialized staff who are equipped to perform the surgical procedure and manage postsurgical intensive care.

Comparators

The following practices are currently being used to make decisions about intestinal failure: medical management and parenteral nutrition.

Outcomes
The general outcomes of interest are overall survival and treatment-related adverse events (e.g., immunosuppression, graft failure, surgical complications, infections). See the Adverse Events section for a detailed discussion. Short-term follow-up ranges from immediately post-surgery to 30 days post transplantation; lifelong follow-up (out to at 10 years or more given current survival data) is necessary due to ongoing immunosuppressive drugs and risk of graft failure.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Case Series
The majority of the published literature consists of relatively small case series, mainly reported by single centers in the United States, Japan, and Europe. Tables 1 and 2 summarize the characteristics and results of the case series, respectively. Many case series have included small bowel/liver transplantations and multi-visceral transplantations which are addressed in other medical policies.

The main reason for transplantation across case series was short bowel syndrome. Other reasons included congenital enteropathies and motility disorders. Most common outcomes reported were survival rates and weaning off total parenteral nutrition (TPN). Several studies have presented survival rates by type of transplantation, while others have combined all types of transplants when reporting survival rates. When rates were reported by type of transplant, isolated transplantations had higher survival rates than multi-visceral transplants (see Table 2).

Several investigators have reported higher survival rates in transplantations conducted more recently than those conducted earlier.[5,6] Reasons for improved survival rates in more recent years have been attributed to the development of more effective immunosuppressive drugs and the learning curve for the complex procedure.

In 2010, Sudan published a review of current literature on long-term outcomes after intestinal transplantation.[7] Sudan noted that intestinal transplantation had become standard therapy for patients with life-threatening complications from parenteral nutrition therapy. Data from current single-center series has indicated 1-year patient survival rates between 78% and 85% and 5-year or more survival rates between 56% and 61%. Concerning pediatric intestinal transplant patients, most achieve normal growth velocity at 2 years post-transplant. However, oral aversion is common; tube feedings are necessary in 45% of children. Sudan also reported on

parental surveys of quality of life for pediatric transplant patients in which intestinal transplant patients appear to have modestly improved quality of life compared with patients remaining on TPN and slightly worse than matched school-age controls without intestinal disease.

Authors of these series, as well as related reviews, have observed that while outcomes have improved over time, recurrent and chronic rejection and complications of immunosuppression continue to be obstacles to long-term survival. A separate discussion of complications follows the evidence tables.

Table 1. Summary of Key Case Series Characteristics for Transplantations

Study	Location	N	Median Age (Range), y	Interventions		Follow-Up (Range), mo
				Treatment	n	
Lacaille et al (2017)[8]	France	110	5.3 (0.4 to 19)	• Isolated IT • Combined liver IT • Multivisceral graft	60 45 5	Of 55 alive: • 17 at <5 y • 17 at 5 to 10 y • 21 at ≥10 y
Garcia Aroz et al (2017) [9]	U.S.	10	1.5 (0.7 to 13)	• Isolated IT • Combined liver IT	7 3	6/7 alive at follow-up ≥10 y
Dore et al (2016)[10]	U.S.	30	0.2 (0.1 to 18)	• Isolated IT • Combined liver IT • Multivisceral graft	6 6 18	28 (4 to 175)
Rutter et al (2016)[11]	U.K.	60	1.8 (0 to 8)	• Isolated IT • Multivisceral graft • Modified multivisceral	16 35 9	21.3 (0 to 95)
Lauro et al (2014)[12]	Italy	46	34 (NR)	• Isolated IT • Combined liver IT • Multivisceral graft	34 6 6	51.3
Ueno et al (2014) [5]	Japan	24	0 to 2 y: 6[c] • 3 to 6 y: 6 • 7 to 18 y: 8 • ≥19 y: 4	• Isolated IT • Combined liver IT	23 1	NR
Benedetti et al (2006)[6],[a]	U.S.	11	27 (1.5 to 50)	• Isolated IT	11	NR

IT: intestinal transplantation; NR: not reported
[a] All living donors
[b] Twelve living donors and 12 cadaveric donors
[c] Reported as age range and n

Table 2. Summary of Key Case Series Results for Transplantations

Study	Interventions		Survival		Off TPN	
	Treatment	n	Years	%	Measure	%
Lacaille et al (2017)[8]	• Isolated IT • Combined liver • Multivisceral graft	60 45 5	OS at 10 Patient survival for liver-containing grafts at 10 and 18 Patient survival for isolated IT at 10 and 18	52; 48; 45 59; 56	All combined at last FU	73

Garcia Aroz et al (2017)[9,a]	• Isolated IT • Combined liver IT	7 3	All combined:	70	All combined at last FU	100
Dore et al (2016)[10]	• Isolated IT • Combined liver IT • Multivisceral graft	6 6 18	9 10 2.5	83 33 67	All combined: • in 31 days • at last FU	 71 62
Rutter et al (2016)[11]	• Isolated IT • Multivisceral graft • Modified multivisceral	16 35 9	1 5	92; 71; 85 83; 33; 65		NR
Lauro et al (2014)[12]	• Isolated IT • Combined liver IT • Multivisceral graft	34 6 6	All combined: 1 3 5 10	 77 58 53 37		NR
Ueno et al (2014) [5]	• Isolated IT • Combined liver IT	23 1	All combined: 1 5	 86 68		80
Benedetti et al (2006)[6,a]	• Isolated IT	11	1 3	82 82		100

IT: intestinal transplantation; NR: not reported
[a] All living donors
[b] Twelve living donors and 12 cadaveric donors

Adverse Events

Systematic Reviews

One issue discussed in intestinal transplantation literature is earlier referral to avoid combined liver and intestine transplantation.[13] It has been suggested that removing the restriction on intestinal transplantation to patients who have severe complications from TPN and recommending earlier transplantation may improve survival. However, in a review of the status of intestinal transplantation, Vianna et al (2008) identified no randomized trials that compared intestinal transplantation with long-term TPN; therefore, optimal timing for earlier transplantation has not been established.[14]

Case Series

In 2016, Wu et al investigated the incidence and risk factors of acute antibody-mediated rejection (ABMR) among patients undergoing intestinal transplantation (N=175).[15] Patients were 25 years of age. Acute ABMR was diagnosed by clinical evidence; histologic evidence of tissue damage; focal or diffuse linear C4d deposition; and circulating anti-human leukocyte antigen antibodies. Of the 175 intestinal transplants, 58% were liver-free small intestine grafts, 36% included a liver graft, and 6.3% were retransplantations. Eighteen cases of acute ABMR were identified, 14 (14%) among the patients undergoing first liver-free transplantation, 2 (3%) among patients undergoing liver/small bowel transplantations, and 2 (18%) among the patients undergoing retransplantation. Graft failure occurred in 67% of patients with acute ABMR. The presence of a donor-specific antibody and a liver-free graft were associated with the development of acute ABMR.

Florescu et al (2012) have published several retrospective reviews of complications in a cohort of 98 pediatric patients. Twenty-one (21.4%) of these children had an isolated small bowel transplant; the remainder had combined transplants. Their 2012 study reported that 68 (69%)

of the 98 patients developed at least 1 episode of bloodstream infection.[16] Among patients with an isolated small bowel transplant, the median time to infection for those who developed one was 4.5 months (95% CI, 2.4 to 6.7 months). Also in 2012, these researchers reported that 7 (7%) of 98 patients developed cytomegalovirus disease; only 1 had an isolated small bowel transplant.[17] In 2010, Florescu et al reported that, in 25 (25.5%) of 98 cases reviewed who developed at least 1 episode of fungal infection, Candida infection was most common.[18] Mortality rates did not differ significantly between patients who did (32.3%) and did not develop a fungal infection (29.8%; p=0.46).

Other series have reported on renal failure after intestinal transplantation. For example, in 2014, Calvo Pulido et al in Spain reported on 21 adults who underwent intestinal transplantation; 17 were isolated small bowel transplants.[19] Thirteen (62%) patients experienced renal failure; the etiology included high ileostomy output, immunosuppression, and medical treatment. Boyer et al (2013) reported that 7 of 12 children who had an isolated small bowel transplant developed renal function complications at some point after surgery.[20] Before treatment, all patients had normal renal functioning.

Living Donor Transplants

Cadaveric intestines have been most commonly used, but recently there has been interest in using a portion of intestine harvested from a living, related donor. Potential advantages of a living donor include the ability to plan the transplantation electively and better antigen matching leading to improved management of rejection. Small case reports have been published of 1 or 2 patients with different lengths of the ileum or jejunum.[21-24] While there appear to be minimal complications to the donors, of the 6 cases reported, 5 recipients remain on TPN for at least part of their nutrition. One patient remains healthy and is off TPN.

Tables 1 and 2 provide details on additional case series that used living donors (Garcia Aroz et al [2017],[9] Ueno et al [2014],[5] Benedetti et al [2006][6]). In general, survival rates of recipients with living donors are comparable to rates for recipients of cadaveric donations. Living related donors were reported to have an uneventful recovery. Weight loss and diarrhea were reported among donors, but recovery was without complications.

HIV Positive Transplant Recipients

The 2013 HIV Organ Policy Equity Act in the United States permitted scientists to research organ donations from a person with HIV to another HIV-infected person.[25] In 2015, the Organ Procurement and Transplant Network updated its policies to be consistent with the HIV Organ Policy Equity Act.[26] The Organ Procurement and Transplant Network and United Network for Organ Sharing (UNOS) policies specify that organs from HIV-positive patients be used only for HIV-positive transplant recipients.

Current OPTN policy permits HIV-positive transplant candidates.[27]

The British HIV Association and the British Transplantation Society (2017) updated their guidelines on kidney and pancreas transplantation in patients with HIV disease.[28] These criteria may be extrapolated to other organs:

- Adherent with treatment, particularly antiretroviral therapy
- Cluster of differentiation 4 count greater than 100 cells/mL (ideally >200 cells/mL) for at least 3 months
- Undetectable HIV viremia (<50 HIV-1 RNA copies/mL) for at least 6 months

- No opportunistic infections for at least 6 months
- No history of progressive multifocal leukoencephalopathy, chronic intestinal cryptosporidiosis, or lymphoma.

Section Summary: Small Bowel Transplantation
Small bowel transplant is an infrequently performed, and only relatively small case series, generally single-center, are available. Risks after small bowel transplant are high, particularly related to infection, but may be balanced against the need to avoid the long-term complications of TPN dependence. In addition, early small bowel transplant may obviate the need for a later combined liver/small bowel transplant. Guidelines and U.S. federal policy no longer view HIV infection as an absolute contraindication for solid organ transplantation.

SMALL BOWEL RETRANSPLANTATION

Clinical Context and Therapy Purpose
The purpose of small bowel retransplant in individuals who have failed small bowel transplant and do not have contraindication(s) for retransplant is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following **PICOs** were used to select literature to inform this review.

Populations
The relevant population of interest is individuals who have failed small bowel transplant and do not have contraindication(s) for retransplant.

Interventions
The therapy being considered is a small bowel retransplant. Small bowel transplantation is provided in a hospital setting by specialized staff who are equipped to perform the surgical procedure and manage postsurgical intensive care.

Comparators
The following practices are currently being used to make decisions about the intestinal failure of an initial small bowel transplant: medical management and parenteral nutrition.

Outcomes
The general outcomes of interest are overall survival and treatment-related adverse events (e.g., immunosuppression, graft failure, surgical complications, infections). See the Adverse Events section for initial transplants for detailed discussion.
Short-term follow-up ranges from immediately post-surgery to 30 days post-transplantation; lifelong follow-up (out to at 10 years or more given current survival data) is necessary due to ongoing immunosuppression drugs and risk of graft failure.

Case Series
A few case series from single institutions and one analysis using data from the UNOS database have provided evidence on the use of retransplantation in patients who failed primary small bowel transplant. Case series characteristics and results are detailed in Tables 3 and 4, respectively.

Desai et al (2012) has published the most comprehensive reporting of outcomes after repeat small bowel transplant in the United States.[29] They evaluated data in the UNOS database on patients who underwent small bowel transplants in the United States between 1987 and 2009.

Table 3. Summary of Key Case Series Characteristics for Retransplantations

Study	Location	N	Median Age (Range), y	Interventions		Follow-Up (Range), mo
				Treatment	n	
Lacaille et al (2017)[8]	France	10	13 (5 to 16)	• Isolated IT • Combined liver IT	3 7	4
Desai et al(2012)[29]	U.S.	72 adults; 77 children	NR	Adults: • Isolated IT • Combined liver IT Children: • Isolated IT • Combined liver IT	 41 31 28 49	NR
Abu-Elmagd et al(2009)[30]	U.S.	47	NR	• Isolated IT • Combined liver IT • Multivisceral graft	31 7 9	NR

IT: intestinal transplantation; NR: not reported

Table 4. Summary of Key Case Series Results for Retransplantations

Study	Interventions		Survival		Off TPN
	Treatment	n	Years	%	
Lacaille et al (2017)[8]	• Isolated IT • Combined liver IT	3 7	All combined at last follow-up:	30	NR
Desai et al (2012)[29]	Adults: • Isolated IT • Combined liver IT Children: • Isolated IT • Combined liver IT	 41 31 28 49	Adults: 1/3/5 (isolated IT); 1/3/5 (Combined liver IT) Children: 1/3/5 (isolated IT); 1/3/5 (Combined liver IT)	 80/47/29; 63/56/47 81/74/57; 42/42/42	NR
Abu-Elmagd et al (2009)[30]	• Isolated IT • Combined liver IT • Multivisceral graft	31 7 9	All combined: 1 5	 69 47	NR

IT: intestinal transplantation; NR: not reported; TPN: total parenteral nutrition.

Section Summary: Small Bowel Retransplantation

Data from only a small number of patients undergoing retransplantation are available. Although limited in quantity, the available data after retransplantation have suggested reasonably high survival rates after small bowel in patients who continue to meet criteria for transplantation.

SUMMARY OF EVIDENCE

For individuals who have intestinal failure who receive a small bowel transplant, the evidence includes case series. Relevant outcomes are overall survival, morbid events, and treatment-related mortality and morbidity. Small bowel transplant is infrequently performed, and only relatively small case series, generally single-center, are available. Risks after small bowel transplant are high, particularly related to infection, but may be balanced against the need to avoid the long-term complications of total parenteral nutrition dependence. In addition, early small bowel transplant may obviate the need for a later combined liver/small bowel transplant. Transplantation is contraindicated in patients in whom the procedure is expected to be futile due to comorbid disease or in whom post-transplantation care is expected to significantly worsen comorbid conditions. Guidelines and U.S. federal policy no longer view HIV infection as an absolute contraindication for solid organ transplantation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have failed small bowel transplant without contraindication(s) for retransplant who receive a small bowel retransplant, the evidence includes case series. Relevant outcomes are overall survival, morbid events, and treatment-related mortality and morbidity. Data from only a small number of patients undergoing retransplantation are available. Although limited in quantity, the available data after retransplantation have suggested a reasonably high survival rate after small bowel in patients who continue to meet criteria for transplantation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

In response to requests, BCBSA received input from 2 physician specialty societies and 2 academic medical centers while this policy was under review for July 2009. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. The consensus of those providing input was that small bowel transplant should be performed in patients who are developing severe TPN-related complications and that small bowel transplant from living donors may be considered when cadaveric intestinal transplants are not available.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Gastroenterological Association (AGA)

In 2003, the American Gastroenterological Association produced a medical position statement on short bowel syndrome and intestinal transplantation.[31] It recommends dietary, medical and surgical solutions. Indications for intestinal transplantation mirror those of CMS. The guidelines acknowledge the limitations of transplant for these patients. The statement recommended the following Medicare-approved indications, pending availability of additional data:

1. “Impending or overt liver failure.…
2. Thrombosis of major central venous channels….
3. Frequent central line-related sepsis….

4. Frequent severe dehydration."

The AGA published an expert review on management of short bowel syndrome in 2022.[32,] Their best practice statements mirror the CMS recommendations, stating that individuals with short bowel syndrome and intestinal failure experiencing TPN complications should be referred early for intestinal transplantation consideration. They state that individuals with short bowel syndrome and intestinal failure with high morbidity or low acceptance of TPN should also be considered for early listing for intestinal transplantation on a case-by-case basis.

American Society of Transplantation
In 2001, the American Society of Transplantation issued a position paper on indications for pediatric intestinal transplantation.[33] The Society listed the following disorders in children as potentially treatable by intestinal transplantation: short bowel syndrome, defective intestinal motility, and impaired enterocyte absorptive capacity. Contraindications for intestinal transplant to treat pediatric patients with intestinal failure are similar to those of other solid organ transplants: profound neurologic disabilities, life-threatening comorbidities, severe immunologic deficiencies, nonresectable malignancies, autoimmune diseases, and insufficient vascular patency.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov did not identify any ongoing or unpublished trials that would likely influence this review.

Government Regulations

National:
Effective for services performed on or after April 1, 2001, this procedure is covered only when performed for patients who have failed total parenteral nutrition (TPN) and only when performed in centers that meet approval criteria.[34]
1. Failed TPN
The TPN delivers nutrients intravenously, avoiding the need for absorption through the small bowel. TPN failure includes the following:

- Impending or overt liver failure due to TPN induced liver injury. The clinical manifestations include elevated serum bilirubin and/or liver enzymes, splenomegaly, thrombocytopenia, gastroesophageal varices, coagulopathy, stomal bleeding or hepatic fibrosis/cirrhosis.
- Thrombosis of the major central venous channels; jugular, subclavian, and femoral veins. Thrombosis of two or more of these vessels is considered a life-threatening complication and failure of TPN therapy. The sequelae of central venous thrombosis are lack of access for TPN infusion, fatal sepsis due to infected thrombi, pulmonary embolism, Superior Vena Cava syndrome or chronic venous insufficiency.
- Frequent line infection and sepsis. The development of two or more episodes of systemic sepsis secondary to line infection per year that requires hospitalization indicates failure of TPN therapy. A single episode of line related fungemia, septic shock and/or Acute Respiratory Distress Syndrome are considered indicators of TPN failure.
- Frequent episodes of severe dehydration despite intravenous fluid supplement in addition to TPN. Under certain medical conditions such as secretory diarrhea and non-constructible gastrointestinal tract, the loss of the gastrointestinal and pancreatobiliary secretions

exceeds the maximum intravenous infusion rates that can be tolerated by the cardiopulmonary system. Frequent episodes of dehydration are deleterious to all body organs particularly kidneys and the central nervous system with the development of multiple kidney stones, renal failure and permanent brain damage.

2. Approved Transplant Facilities

Intestinal transplantation is covered by Medicare if performed in an approved facility. The criteria for approval of centers will be based on a volume of 10 intestinal transplants per year with a 1-year actuarial survival of 65 percent using the Kaplan-Meier technique.

Local:

There is no local coverage determination on this topic.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Transplant-Heart
- Transplant-Heart-Lung (Combined)
- Transplant-Liver
- Transplant-Lung-Lobar Lung
- Transplant-Pancreas
- Transplant-Small Bowel- Liver-Multi-visceral

References

1. Black CK, Termanini KM, Aguirre O, et al. Solid organ transplantation in the 21 st century. Ann Transl Med. Oct 2018; 6(20): 409. PMID 30498736
2. Massironi S, Cavalcoli F, Rausa E, et al. Understanding short bowel syndrome: Current status and future perspectives. Dig Liver Dis. Mar 2020; 52(3): 253-261. PMID 31892505
3. U. S. Department of Health and Human Services (DHHS). Organ Procurement and Transplantation Network National Data. 2020;https://optn.transplant.hrsa.gov/data/. Accessed June 22, 2020
4. Sudan D. The current state of intestine transplantation: indications, techniques, outcomes and challenges. Am J Transplant. Sep 2014; 14(9): 1976-84. PMID 25307033
5. Ueno T, Wada M, Hoshino K, et al. Impact of intestinal transplantation for intestinal failure in Japan. Transplant Proc. Jul-Aug 2014; 46(6): 2122-4. PMID 25131121
6. Benedetti E, Holterman M, Asolati M, et al. Living related segmental bowel transplantation: from experimental to standardized procedure. Ann Surg. Nov 2006; 244(5): 694-9. PMID 17060761
7. Sudan D. Long-term outcomes and quality of life after intestine transplantation. Curr Opin Organ Transplant. Jun 2010; 15(3): 357-60. PMID 20445450
8. Lacaille F, Irtan S, Dupic L, et al. Twenty-eight years of intestinal transplantation in Paris: experience of the oldest European center. Transpl Int. Feb 2017; 30(2): 178-186. PMID 27889929

9. Garcia Aroz S, Tzvetanov I, Hetterman EA, et al. Long-term outcomes of living-related small intestinal transplantation in children: A single-center experience. Pediatr Transplant. Jun 2017; 21(4). PMID 28295952
10. Dore M, Junco PT, Andres AM, et al. Surgical Rehabilitation Techniques in Children with Poor Prognosis Short Bowel Syndrome. Eur J Pediatr Surg. Feb 2016; 26(1): 112-6. PMID 26535775
11. Rutter CS, Amin I, Russell NK, et al. Adult Intestinal and Multivisceral Transplantation: Experience From a Single Center in the United Kingdom. Transplant Proc. Mar 2016; 48(2): 468-72. PMID 27109980
12. Lauro A, Zanfi C, Dazzi A, et al. Disease-related intestinal transplant in adults: results from a single center. Transplant Proc. Jan-Feb 2014; 46(1): 245-8. PMID 24507060
13. Matarese LE, Costa G, Bond G, et al. Therapeutic efficacy of intestinal and multivisceral transplantation: survival and nutrition outcome. Nutr Clin Pract. Oct 2007; 22(5): 474-81. PMID 17906271
14. Vianna RM, Mangus RS, Tector AJ. Current status of small bowel and multivisceral transplantation. Adv Surg. 2008; 42: 129-50. PMID 18953814
15. Wu GS, Cruz RJ, Cai JC. Acute antibody-mediated rejection after intestinal transplantation. World J Transplant. Dec 24 2016; 6(4):719-728. PMID 28058223
16. Florescu DF, Qiu F, Langnas AN, et al. Bloodstream infections during the first year after pediatric small bowel transplantation. Pediatr Infect Dis J. Jul 2012; 31(7): 700-4. PMID 22466325
17. Florescu DF, Langnas AN, Grant W, et al. Incidence, risk factors, and outcomes associated with cytomegalovirus disease in small bowel transplant recipients. Pediatr Transplant. May 2012; 16(3): 294-301. PMID 22212495
18. Florescu DF, Islam KM, Grant W, et al. Incidence and outcome of fungal infections in pediatric small bowel transplant recipients. Transpl Infect Dis. Dec 2010; 12(6): 497-504. PMID 20626710
19. Calvo Pulido J, Jimenez Romero C, Morales Ruiz E, et al. Renal failure associated with intestinal transplantation: our experience in Spain. Transplant Proc. Jul-Aug 2014; 46(6): 2140-2. PMID 25131125
20. Boyer O, Noto C, De Serre NP, et al. Renal function and histology in children after small bowel transplantation. Pediatr Transplant. Feb 2013; 17(1): 65-72. PMID 22882667
21. Fujimoto Y, Uemoto S, Inomata Y, et al. Living-related small bowel transplant: management of rejection and infection. Transplant Proc. Feb 1998; 30(1): 149. PMID 9474986
22. Gruessner RW, Sharp HL. Living-related intestinal transplantation: first report of a standardized surgical technique. Transplantation. Dec 15 1997; 64(11): 1605-7. PMID 9415566
23. Jaffe BM, Beck R, Flint L, et al. Living-related small bowel transplantation in adults: a report of two patients. Transplant Proc. May 1997; 29(3): 1851-2. PMID 9142299
24. Tesi R, Beck R, Lambiase L, et al. Living-related small-bowel transplantation: donor evaluation and outcome. Transplant Proc. Feb-Mar 1997; 29(1-2): 686-7. PMID 9123480
25. Colfax G. HIV Organ Policy Equity (HOPE) Act Is Now Law. 2013; https://obamawhitehouse.archives.gov/blog/2013/11/21/hivorgan-policy-equity-hope-act-now-law. Accessed May 2024.
26. United Network for Organ Sharing (UNOS). OPTN policies, procedures implemented to support HOPE Act. 2015; http://www.unos.org/optn-policies-procedures-implemented-to-support-hope-act/. Accessed May 2024.

27. Organ Procurement and Transplantation Network (OPTN). Organ Procurement and Transplantation Network Policies. 2020; https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf. Accessed May 2024.
28. Working Party of the British Transplantation Society. Kidney and Pancreas Transplantation in Patients with HIV. Second Edition (Revised). British Transplantation Society Guidelines Macclesfield, UK: British Transplantation Society; 2017.
29. Desai CS, Khan KM, Gruessner AC, et al. Intestinal retransplantation: analysis of Organ Procurement and Transplantation Network database. Transplantation. Jan 15 2012; 93(1): 120-5. PMID 22113492
30. Abu-Elmagd KM, Costa G, Bond GJ, et al. Five hundred intestinal and multivisceral transplantations at a single center: major advances with new challenges. Ann Surg. Oct 2009; 250(4): 567-81. PMID 19730240
31. American Gastroenterological Association. American Gastroenterological Association medical position statement: short bowel syndrome and intestinal transplantation. Gastroenterology. Apr 2003; 124(4): 1105-10. PMID 12671903
32. Iyer K, DiBaise JK, Rubio-Tapia A. AGA Clinical Practice Update on Management of Short Bowel Syndrome: Expert Review. Clin Gastroenterol Hepatol. Oct 2022; 20(10): 2185-2194.e2. PMID 35700884
33. Kaufman SS, Atkinson JB, Bianchi A, et al. Indications for pediatric intestinal transplantation: a position paper of the American Society of Transplantation. Pediatr Transplant. Apr 2001; 5(2): 80-7. PMID 1132854433.
34. Centers for Medicare and Medicaid Services. National Coverage Determination for Intestinal and Multi-visceral Transplantation (260.5). 2006; https://www.cms.gov/medicare-coveragedatabase/details/ncddetails.aspx?NCDId=280&ncdver=2&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=intestinal+transplantation&KeyWordLookUp=Title&KeyWordSearchType=And&bc=gAAAACAAAAAAAA%3d%3d&. Accessed May 2024.
35. Blue Cross Blue Shield Association. Isolated Small Bowel Transplant. Medical Policy Reference Manual. Policy #7.03.04, Issue 5:2014, original policy date 12/1/95, last review date September 2024.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through May 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
9/1/12	6/12/12	6/19/12	Joint medical policy established. The combined policy "Small Bowel or Small Bowel/Liver-Multivisceral Transplants" has been split into 2 separate policies: Isolated Small Bowel Transplant and Small Bowel/Liver-Multivisceral Transplant. Updated description, rationale and references
7/1/14	4/8/14	4/15/14	Routine maintenance. Statement added that small bowel retransplant may be considered established after a failed primary small bowel transplant. References updated and renumbered.
9/1/15	6/19/15	7/16/15	Routine maintenance Pediatric patients added to the exclusion regarding patients with intestinal failure who are able to tolerate TPN. References updated and renumbered.
9/1/16	6/21/16	6/21/16	Routine policy maintenance. No changes to policy status.
9/1/17	6/20/17	6/20/17	Routine policy maintenance. No change to policy status.
9/1/18	6/19/18	6/19/18	Routine policy maintenance, updated rationale section, added references 7-11 and 14. No change in policy status.
9/1/19	6/18/19		Routine policy maintenance, added references 26 and 27. No change in policy status.
9/1/20	6/16/20		Routine policy maintenance. No change in policy status.
9/1/21	6/15/21		Routine policy maintenance. No change in policy status.
9/1/22	6/21/22		Routine policy maintenance, no change in policy status.
9/1/23	6/13/23		Routine policy maintenance. No change in policy status. Vendor managed: N/A (ds)
9/1/24	6/11/24		Rationale updated, reference #32 added. Changes made to

			inclusion/exclusion section. Title changed to: Transplant-Small Bowel (Isolated). Vendor managed: N/A (ds)

Next Review Date: 2nd Qtr. 2025

Previous consolidated medical policy history for Small Bowel or Small Bowel/Multi-Visceral Transplantation

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
6/13/02	6/13/02	6/13/02	Joint medical policy established
11/8/04	11/8/04	12/6/04	Routine maintenance
11/15/05	11/15/05	9/26/05	Routine maintenance
9/1/06	7/10/06	7/6/06	Routine maintenance
9/1/07	7/1/07	8/26/06	Routine maintenance
11/1/08	8/19/08	10/30/08	Routine maintenance

No further review will be done on the <u>consolidated</u> policy; refer to separate policies on

- Small Bowel Transplant-Isolated and
- Small Bowel/Liver and Multivisceral Transplant

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: TRANSPLANT-SMALL BOWEL (ISOLATED)

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply. Transportation, meals and lodging expenses related to the transplant are not covered unless specifically noted in the member's certificate/rider.
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.