Small Bowel/Liver and Multivisceral Transplant*

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DESCRIPTION

This policy addresses transplantation of the intestinal allograft in combination with liver allograft, and multivisceral transplant which typically includes the small bowel/liver in combination with one or more other abdominal visceral organs such as the stomach and pancreas.

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. 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 Organ Procurement and Transplantation Network and United Network of Organ Sharing.

Small Bowel/Liver and Multivisceral Transplant
In 2021, 41,355 transplants were performed in the United States procured from 34,813 deceased donors and 6,542 living donors. Intestinal transplants occur less frequently than other organ transplants, with 10 or fewer patients receiving liver-intestine transplant each year from 2008 to 2019. Small bowel and liver or multivisceral transplant is usually considered in adults and children who develop serious complications related to parenteral nutrition, including inaccessibility (e.g., due to thrombosis) of access sites, catheter-related sepsis, and cholestatic liver disease.

Short Bowel Syndrome and Other Conditions Causing Intestinal Failure
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 small intestine. In some instances, short bowel syndrome is associated with liver failure, often due to long term complications of total parenteral nutrition (TPN).

Some conditions are more closely associated with pediatric intestinal failure while others are more common with intestinal failure in adults.

The following are pediatric conditions causing intestinal failure:

- Short bowel syndrome following extensive bowel surgeries (midgut volvulus)
- Congenital malformations (e.g., intestinal atresia, gastroschisis, aganglionosis)
- Absorptive impairment (e.g., microvillus involution disease, chronic intestinal pseudo-obstruction)
- Infections of gastrointestinal tract (e.g., necrotizing enterocolitis)

The following are adult conditions causing intestinal failure:

- Crohn's disease
- Tumors of the mesenteric root and retroperitoneum (e.g., desmoid tumor)
- Short bowl syndrome following extensive surgeries secondary to mesenteric ischemia (following thrombosis, embolism, volvulus or trauma)
- Chronic intestinal pseudo-obstruction
- Small bowel tumors such as Gardner's Syndrome (familial colorectal polyposis)

The chronic use of TPN is often associated with life-threatening complication including:

- Catheter related sepsis
- Catheter related thrombosis
- Severe dehydration
- Parenteral nutrition associated liver disease (PNALD)

Treatment
A small bowel/liver transplant or a multivisceral transplant includes the small bowel and liver and one or more of the following organs: stomach and pancreas. The type of

transplantation depends on the underlying etiology of intestinal failure, quality of native organs, presence or severity of liver disease, and history of prior abdominal surgeries. A multivisceral transplant is indicated when anatomic or other medical problems preclude a small bowel/liver transplant. Complications following small bowel/liver and multivisceral transplants include acute or chronic rejection, donor-specific antibodies, infection, lymphoproliferative disorder, graft versus host disease, and renal dysfunction.

Transplantation of Small Bowel/Liver Transplant or Multivisceral Transplant

Clinical Context and Purpose

The purpose of small bowel and liver transplant alone or multivisceral transplant in patients who have intestinal failure and evidence of impending end-stage liver failure is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does small bowel and liver transplant alone or multivisceral transplant improve the net health outcome in individuals with intestinal failure and evidence of impending end-stage liver failure?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with intestinal failure and evidence of impending end-stage liver failure.

Interventions

The therapy being considered is small bowel and liver transplant alone or multivisceral transplant.

Comparators

The following practices are currently being used to make decisions about intestinal failure and evidence of impending end-stage liver failure: medical management and parenteral nutrition.

Outcomes

The general outcomes of interest are overall survival (OS), morbid events, and treatment-related mortality and morbidity, including short and long-term graft survival and one- and five-year OS.

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
- Within each category of study design, studies with larger sample sizes and longer duration were preferred

Review of Evidence
A TEC Assessment (1999) focused on multivisceral transplantation and offered the following conclusions:

- "Multivisceral transplantation in patients with small bowel syndrome, liver failure, and/or other gastrointestinal problems such as pancreatic failure, thromboses of the celiac axis and the superior mesenteric artery, or pseudo-obstruction affecting the entire gastrointestinal tract is associated with poor patient and graft survival. Pediatric and adult patients have a similar 2- and 5-year survival of 33% to 50%. However, without this procedure, it is expected that these patients would face 100% mortality.

Regulatory Studies and Case Series
The published literature consists of a registry study and case series, mainly reported by single centers in the U. S. and Europe. Many case series have included isolated small bowel transplantations.

Reasons for transplantations were mainly short bowel syndrome. Other reasons included congenital enteropathies and motility disorders. Most common outcomes reported were survival rates and weaning off total parenteral nutrition. 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 multivisceral transplants.

Several investigators have reported higher survival rates in transplants conducted more recently than those conducted earlier. 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.

Authors of these publications, 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 of long-term survival.

Summary of Key Registry Studies and Case Series Characteristics for Transplantation

Study	Country	N	Interventions/Treatment	Follow-up Range
Raghu et al. 2019	International	2080	• Isolated intestinal transplant (IT) • Combined liver IT • Multivisceral graft (including modified [intestine and stomach without liver] and full [intestine, stomach and liver])	5 years
Lacaille et al. 2017	France	110	• Isolated intestinal transplant (IT) • Combined liver IT • Multivisceral graft	55 patients alive • 17 at <5 years • 17 at 5-10 years • 21 at ≥ 10 years
Garcia Aroz et al. 2017	U.S.	10	• Isolated intestinal transplant (IT) • Combined liver IT	6 out of 7 alive at ≥ 10 years
Dore et al. 2016	U.S.	30	• Isolated intestinal transplant (IT) • Combined liver IT • Multivisceral graft	28 (4-175 months)
Rutter et al. 2016	U.K.	60	• Isolated intestinal transplant (IT) • Combined liver IT • Modified multivisceral graft	21 (0-95 months)

Summary of Key Registry Studies and Case Series Results for Transplantations

Study	Interventions/Treatment, n	Survival	Off Total Parenteral Nutrition (TPN)
Raghu et al. 2019	• Isolated intestinal transplant (IT) (n 725) • Combined liver IT (n 966) • Multivisceral graft (including modified [intestine and stomach without liver] and full [intestine, stomach and liver]) (n389)	All transplantations combined: • Patient survival: 72.7% at 1 year; 57.2% at 5 years • Graft survival: 66.1% at 1 year; 47.8% at 5 years	Not reported (NR)
Lacaille et al. 2017	• Isolated intestinal transplant (IT) (n 60) • Combined liver IT (n 45) • Multivisceral graft (n 5)	• 59% at 10 years; 54% at 18 years • 48% at 10 years • Not reported (NR)	All transplantations combined: • 73% at last follow-up
Garcia Aroz et al. 2017	• Isolated intestinal transplant (IT) (n 7) • Combined liver IT (n 3)	All transplantations combined: • 70%	All transplantations combined: • 100% at last follow-up
Dore et al. 2016	• Isolated intestinal transplant (IT) (n 66) • Combined liver IT (n 18) • Multivisceral graft	• 83% at 9 years • 33% at 10 years • 67% at 2.5 years	All transplantations combined: • 71% in 31 days • 62% at last follow-up
Rutter et al. 2016	• Isolated intestinal transplant (IT) (n 16) • Combined liver IT (n 35) • Modified multivisceral graft (n 9)	• 92% at 1 year; 37% at 5 years • 71% at 1 year; 33% at 5 years • 85% at 1 year; 65% at 5 years	Not reported (NR)

Complications
Several case series have focused on complications after small bowel and multivisceral transplantation. For example, (2020) Spence et al. performed a retrospective chart review of intra-abdominal and bloodstream infection in adults undergoing intestinal or multivisceral transplant at a single center in the U.S. A total of 103 adult patients (median age, 44 years) were included who received 106 intestinal or multivisceral transplants between 2003 and 2015. Intra-abdominal infection occurred in 46 (43%) patients, and concurrent bloodstream infection occurred in 6 (13%) patients. The median time to first intra-abdominal infection was 23 days (interquartile range, 10-48). All-cause mortality was not significantly different between patients with versus without intra-abdominal infections (p=0.654). The authors concluded intra-abdominal infections are common in intestinal or multivisceral transplant recipients, but despite this complication found no increased risk of mortality.

(2016) Nagai et al. reported on cytomegalovirus infection after intestinal or multivisceral transplant at a single center in the United States. Cytomegalovirus (CMV) infection is the most prevalent infectious complication after solid organ transplantation, and recipients of isolated intestinal transplantation (IIT)/multivisceral transplantation (MVT) are among those at the highest risk. Limited clinical data exist regarding CMV infection after IIT/MVT. The aim of this study was to analyze risk factors for post-transplant CMV infection and to assess the efficacy and validity of their prophylaxis and treatment regimens in intestinal transplantation. Medical records of 210 IIT/MVT patients were retrospectively reviewed. Post-transplant CMV prophylaxis regimen consisted of ganciclovir followed by 1 year of valganciclovir. The addition of CMV immunoglobulin (CMVIG) was decided according to donor/recipient CMV serostatus (D/R). All results of CMV PCR and/or pp65 antigenemia, and pathological reports were reviewed. Time to the incidence of CMV infection (viremia and/or tissue invasive disease) and risk factors for CMV infection were investigated. CMV infection was observed in 34 of 210 (16%) with a median onset of 347 days. Rejection was significantly associated with CMV infection (P = 0.01, odds ratio = 2.61). In the high-risk serostatus group (D+/R-), prophylactic CMVIG and induction with high-dose rabbit antithymocyte globulin (>10 mg/kg) were associated with a lower CMV infection rate on univariate analysis. The CMVIG remained to be an independent factor on multivariate analysis (P = 0.04, hazard ratio = 0.93/dose). Mortality associated with CMV infection occurred in 4, and CMV infection adversely affected patient survival (P = 0.001, hazard ratio = 2.71).

(2016) Timpone et al. performed retrospective review on all patients who underwent small intestine or multivisceral transplantation from November 8, 2003 through November 30, 2008. Those with Cytomegalovirus (CMV) viremia and invasive disease were identified. Intravenous ganciclovir (GCV) resistance was suspected in patients who continued to have viremic episodes or invasive disease despite appropriate GCV treatment. Genotypic analyses were performed to detect the presence of GCV resistance genes UL97 and UL54. During the study period, 88 small intestine or multivisceral transplants were performed on 85 patients. Of the 88 transplantations, 16 patients developed CMV viremia with or without end-organ disease (18.2%) and 5.7% developed

GCV-R CMV infection. In patients diagnosed with CMV infection, 31.3% (5/16) had GCV-R CMV infection. Of patients with GCV-R CMV infection, 80% (4/5) developed CMV allograft enteritis, resulting in allograft explantation in 3 patients. All patients with GCV-R CMV infection were CMV donor positive/recipient negative. Patients with tissue-invasive CMV disease were 18 times more likely to be infected with GCV-R CMV (95% confidence interval 1.24-260.93; P-value 0.0341). The authors concluded, small intestinal and multivisceral transplant recipients have a higher rate of GCV-R CMV infection compared with other solid organ transplant recipients, which is often associated with tissue-invasive disease and allograft loss.

(2016) Wu et al. investigated the incidence and risk factors of acute antibody-mediated rejection (ABMR) among patients undergoing intestinal transplantation (N=175). All 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 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 and 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.

(2016) Cromvik et al. investigated the incidence, clinical picture, risk factors and outcome of graft-versus-host disease (GVHD) in a cohort of patients who underwent intestinal or multivisceral transplant. All transplanted patients (n = 26) were retrospectively analyzed with respect to donor- and recipient-derived risk factors. The diagnosis of GVHD was based on clinical signs, chimerism analyses of leukocytes, and histopathologic findings in biopsy specimens. Five of 26 patients (19%) were diagnosed with GVHD, of which three had skin GVHD, one had skin and bone marrow GVHD, and one had passenger leukocyte syndrome. Only multivisceral-transplanted patients developed GVHD. Risk factors for development of GVHD were an underlying tumor diagnosis and neoadjuvant chemo- or brachytherapy administered before intestinal transplantation. All patients were given high-dose corticosteroids as first line treatment for their GVHD, and all survived their episodes of GVHD. The authors concluded, the risk of GVHD appears to be increased in recipients of multivisceral transplantations who received chemotherapy due to an underlying malignancy. The reasons may be the large amount of lymphoid tissue in these types of grafts, and the cytotoxic effects of the malignancy and chemotherapy on healthy recipient tissues. These patients should be monitored closely for the development of GVHD.

In a retrospective study, Florescu et al. (2012) reported on bloodstream infections among 98 children (>18 years) with small bowel and combined organ transplants. Seventy-seven (79%) underwent small bowel transplant in combination with a liver, kidney, or kidney and pancreas, and 21 had an isolated small bowel transplant. After a median follow-up of 52 months, 58 (59%) patients had survived. The 1-year survival rate was similar in

patients with combined small bowel transplant (75%) and those with isolated small bowel transplant (81%). In the first year after transplantation, 68 (69.4%) patients experienced at least 1 episode of bloodstream infection. The 1-year survival rate for patients with bloodstream infections was 72% compared with 87% in patients without bloodstream infections (p=.056 for the difference in survival in patients with and without bloodstream infections).

Wu et al. (2011) reported on 241 patients who underwent intestinal transplantation. Of these, 147 (61%) had multivisceral transplants, 65 (27%) had small bowel transplants, and 29 (12%) had small bowel/liver transplants. Recipients included 151 (63%) children and 90 (37%) adults. Twenty-two (9%) patients developed graft-versus-host disease. Children younger than 5 years old were more likely to develop this condition (13.2% [16/121]) than children between 5 and 18 years (6.7% [2/30]) and adults older than 18 years (4.4% [9/90]).

Section Summary
Intestinal transplantation procedures are infrequently performed and only one registry study and relatively small case series, generally, single center, are available. For patients experiencing significant complications from total parenteral nutrition (TPN), which can lead to liver failure and repeated infections, the literature has shown reasonably high post-transplant survival rates in patients who have a high probability of death without treatment.

Human Immunodeficiency Virus-Positive Transplant Recipients
Solid-organ transplant for patients who are HIV-positive was historically controversial, due to the long-term prognosis for HIV positivity and the impact of immunosuppression on HIV disease. No studies reporting on outcomes in HIV-positive patients who received small bowel and liver or multivisceral transplants were identified in literature reviews.

Current Organ Procurement Transplantation Network policy permits HIV-positive transplant candidates.

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

- Adherent with treatment, particularly antiretroviral therapy
- CD4 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
Transplantation of Small Bowel/Liver or Multivisceral Organs

Intestinal transplantation procedures are infrequently performed and only 1 registry study and relatively small case series, generally single-center, are available. For patients experiencing significant complications from TPN, which can lead to liver failure and repeated infections, this literature has shown reasonably high posttransplant survival rates in patients who have a high probability of death without treatment. Guidelines and U.S. federal policy no longer view HIV infection as an absolute contraindication for solid organ transplantation.

Retransplantation of Small Bowel and Liver or Multivisceral Organs

Clinical Context and Purpose
The purpose of small bowel and liver transplant alone or multivisceral retransplant in patients who have failed small bowel and liver or multivisceral transplant without contraindications for retransplant is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does small bowel and liver retransplant alone or multivisceral retransplant improve the net health outcome in individuals with a failed small bowel and liver or multivisceral transplant and no contraindications to retransplant?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest are individuals with a failed small bowel and liver or multivisceral transplant without contraindications for retransplant.

Interventions
The therapy being considered is small bowel and liver retransplant alone or multivisceral retransplant.

Comparators
The following practices are currently being used to make decisions about failed small bowel and liver or multivisceral transplant when there are no contraindications to retransplant: medical management and parenteral nutrition.

Outcomes
The general outcomes of interest are overall survival (OS), morbid events, treatment related mortality, and treatment related morbidity, including short and long-term graft survival and one-and five-year OS.

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
- Within each category of study design, studies with larger sample sizes and longer duration were preferred

Case Series

Evidence for the use of retransplantation to treat individuals who have failed intestinal transplantations includes several case series, mostly from single institutions. Among the case series reasons for retransplantations included: acute and chronic rejection, Cytomegalovirus (CMV), liver failure, lymphoproliferative disorder and graft

(2018) Ekser et al. reviewed and compared outcomes of intestinal retransplantation with primary intestinal transplant (Itx), which included isolated ITx, modified multivisceral transplantation (mMVTx), and full MVTx, between 2003 and 2014 at Indiana University. Graft loss in intestinal transplantation (ITx) is close to 25% in the first year and 50% at 5-year post-transplantation. Although technically and immunologically challenging, intestinal retransplantation is now the 4th most common indication for ITx. Of 218 ITx, 18 (8.3%) were retransplantation. Causes of graft loss were rejection (78%), pancreatitis (11%), and severe intestine dismotility (11%). MVTx (16/18, 89%) was the preferred retransplantation option. In 7 (39%) patients, graftectomy was performed between primary and intestinal retransplantation. Median interval between primary ITx and retransplantation was 421 days. Although patient and graft survival rates at 1 year, 3 years, and 5 years were comparable between primary and retransplants, the number of retransplants was limited in the follow-up after post-transplant year 3.

(2017) Lacaille et al. reported on the achievements in pediatric intestinal transplantation (ITx) and define areas for improvement. After a period (1987-1990) of nine isolated small bowel transplants (SBTx) where only one patient survived with her graft, 110 ITx were performed on 101 children from 1994 to 2014: 60 SBTx, 45 liver-small bowel, four multivisceral (three with kidneys), and one modified multivisceral. Indications were short bowel syndrome (36), motility disorders (30), congenital enteropathies (34), and others (1). Induction treatment was introduced in 2000. Patient/graft survival with a liver-containing graft or SBTx was, respectively, 60/41% and 46/11% at 18 years. Recently, graft survival at 5/10 years was 44% and 31% for liver-containing graft and 57% and 44% for SBTx. Late graft loss occurred in 13 patients, and 7 of 10 retransplanted patients died. The main causes of death and graft loss were sepsis and rejection. Among the 55 currently living patients, 21 had a liver-containing graft, 19 a SBTx (17 after induction), and 15 were on parenteral nutrition. ITx remains a difficult procedure, and retransplantation even more so. Over the long term, graft loss was due to rejection, over-immunosuppression was not a significant problem. Multicenter studies on immunosuppression and microbiota are urgently needed.

Summary of Key Case Series Characteristics for Retransplantations

Study	Country	N	Median Age (Range), y	Interventions		Follow-Up , mo
				Treatment	n	
Ekser et al. (2018)	U.S.	18[b]	27.0 (17.4)[a] (0.9 to 57)	• Isolated ITx • Modified multivisceral transplant • Multivisceral graft	1 1 16	NR
Lacaille et al. (2017)	France	10	13 (5 to 16)	• Isolated ITx • Combined liver ITx	3 7	4
Desai et al. (2012)	U.S.	72 (adults) 77 (children)	NR	Adults: • Isolated ITx • Combined liver ITx Children: • Isolated ITx • Combined liver ITx	 41 31 28 49	NR
Abu-Elmagd et al. (2009)	U.S.	47	NR	• Isolated ITx • Combined liver ITx • Multivisceral graft	31 7 9	NR
Mazariegos et al. (2008)	U.S.	14	9.4 (3.2 to 22.7)	• Isolated ITx • Combined liver Itx • Multivisceral graft	1 3 10	55.9

Itx: intestinal transplantation; NR: not reported.
[a] Mean (standard deviation).
[b] Of a cohort of 218 transplants or retransplant procedures.

Summary of Key Case Series Results for Retransplantations

Study	Interventions		Survival	Off TPN
	Treatment	n		
Ekser et al. (2018)	• Isolated ITx • Modified multivisceral transplant • Multivisceral graft	1 1 16	Graft survival: • 71% at 1 y; 56% at 3 y; 44% at 5 y Patient survival: • 71% at 1 y; 47% at 3 y; 37% at 5 y	NR
Lacaille et al. (2017)	• Isolated ITx • Combined liver Itx	3 7	All transplantations combined: • 30% at last follow-up	NR
Desai et al. (2012)	Adults: • Isolated ITx • Combined liver ITx Children: • Isolated ITx • Combined liver ITx	Adults: 41 31 Children: 28 49	Adults: • 80% at 1 y; 47% at 3 y; 29% at 5 y • 63% at 1 y; 56% at 3 y; 47% at 5 y Children: • 81% at 1 y; 74% at 3 y; 57% at 5 y • 42% at 1 y; 42% at 3 y; 42% at 5 y	NR
Abu-Elmagd et al. (2009)	• Isolated ITx • Combined liver ITx • Multivisceral graft	31 7 9	All transplantations combined: • 69% at 1 y • 47% at 5 y	NR
Mazariegos et al. (2008)	• Isolated ITx • Combined liver ITx • Multivisceral graft	1 3 10	All transplantations combined: • 71% at last follow-up	100%

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

Section Summary: Retransplantation of Small Bowel and Liver or Multivisceral Organs

Evidence for retransplantation derives mostly from single center case series, though 1 series used records from the UNOS database. Although limited in quantity, the available follow-up data after retransplantation have suggested reasonably high survival rates after

small bowel and liver transplants and multivisceral retransplantation in patients who continue to meet criteria for transplantation.

Summary of Evidence
For individuals who have intestinal failure and evidence of impending end-stage liver failure who receive a small bowel and liver transplant alone or multivisceral transplant, the evidence includes a registry study and a limited number of case series. These transplant procedures are infrequently performed, and few reported case series exist. However, results from the available case series have revealed fairly- high post procedural survival rates. Given these results and the exceedingly poor survival rates of patients who exhaust all other treatments, transplantation may prove not only to be the last option but also a beneficial one. Transplantation is contraindicated for patients in whom the procedure is expected to be unsuccessful due to comorbid disease, or in who post-transplantation care is expected to significantly worsen comorbid conditions. The evidence is sufficient to determine that the technology results in a meaningful improvement in net health outcomes.

For individuals who have failed small bowel and liver or multivisceral transplant, the evidence for retransplant includes case series. Although limited in quantity, the available post- retransplantation data have suggested reasonably high survival rates. Given exceedingly poor survival rates without retransplantation of patients who have exhausted their treatments, evidence of postoperative survival from uncontrollable studies is sufficient to demonstrate that retransplantation provides a survival benefit in appropriately selected patients. Retransplantation is contraindicated for patients in whom the procedure is expected to be unsuccessful due to comorbid disease or in whom post transplantation care is expected to significantly worsen comorbid conditions. The evidence is sufficient to determine that the technology results in a meaningful improvement in net health outcomes.

Practice Guideline and Position Statement

American Gastroenterological Association (AGA)
(2003) The AGA produced a medical position statement on short bowel syndrome and intestinal transplantation. It recommends dietary, medical, and surgical solutions. Indications for intestinal transplant mirror those of Medicare in patients who fail TPN therapy for one of the following reasons:

- Impending or overt liver failure as evidence by elevated serum bilirubin and/or liver enzymes, splenomegaly, thrombocytopenia, gastroesophageal varices, coagulopathy, stomal bleeding or hepatic fibrosis/cirrhosis
- Thrombosis of major central venous channels (2 thromboses in subclavian, jugular or femoral veins)
- Frequent central line related sepsis (2 episodes of systemic sepsis secondary to line infection per year, 1 episode of line related fungemia, septic shock or acute respiratory distress syndrome (ARDS))
- Frequent severe dehydration

Until better data become available, these parameters are likely to be widely recognized as the indications for intestinal transplantation. (*Accessed October 2022*)

American Society of Transplantation (AST)
(2001) The AST issued a position paper on indications for pediatric intestinal transplantation. The position paper included the following:

"Parenteral nutrition represents standard therapy for children with short bowel syndrome and other causes of intestinal failure. Most infants with short bowel syndrome eventually wean from parenteral nutrition, and most of those who do not wean tolerate parenteral nutrition for protracted periods. However, a subset of children with intestinal failure remaining dependent on parenteral nutrition will develop life-threatening complications arising from therapy. Intestinal transplantation can now be recommended for this select group. Life-threatening complications warranting consideration of intestinal transplantation include parenteral nutrition-associated liver disease, recurrent sepsis, and threatened loss of central venous access. Children with liver dysfunction should be considered for isolated intestinal transplantation before irreversible, advanced bridging fibrosis or cirrhosis supervenes, for which a combined liver and intestinal transplant is necessary. Irreversible liver disease is suggested by hyperbilirubinemia persisting beyond 3-4 months of age combined with features of portal hypertension such as splenomegaly, thrombocytopenia, or prominent superficial abdominal veins; esophageal varices, ascites, and impaired synthetic function are not always present." (*Accessed October 2022*)

Regulatory Status

Small bowel/liver and multivisceral transplantation are surgical procedures and, as such, are not subject to regulation by the U.S. Food and Drug Administration (FDA).

The FDA 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.

PRIOR APPROVAL

Prior approval is required.

POLICY

See the Related Medical Policy

- 07.03.04 Small Bowel Transplant*

Initial Combined Cadaveric Small Bowel and Liver or Multivisceral Transplant

A combined small bowel and liver or multivisceral transplant may be considered **medically necessary** for pediatric and adult individuals when:

- Intestinal failure characterized by loss of absorption and the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balance; **and**
- Who have been managed with long-term total parenteral nutrition (TPN) **and**

The individual is developing or has developed severe complications due to total parenteral nutrition (TPN) to include **one or more of the following**:

  - Thrombosis of two or more major central venous channels (subclavian, jugular, or femoral veins); **or**
  - Frequent central line related sepsis as evidenced by **one of the following**:
    - Two or more episodes of line-induced systemic sepsis per year; **or**
    - One episode of line-related fungemia, septic shock or acute respiratory distress syndrome; **or**
  - Frequent episodes of dehydration despite total parenteral nutrition (TPN) and intravenous fluid supplement; **and**

One of the following:

- Biopsy proven fibrotic changes within the liver indicating that the total parenteral nutrition (TPN) associated liver dysfunction is irreversible; **or**
- Clinical assessment of significant portal hypertension where biopsy may not be available, warranted, or considered safe to perform.

Not Medically Necessary

A combined small bowel and liver transplant *or* multivisceral transplant for pediatric and adult individuals performed for any other conditions not listed above will be considered **not medically necessary**.

Initial Living Donor Combined Small Bowel and Liver Transplant

Small bowel transplantation using a *living donor* intestine and/or liver may be considered **medically necessary** when a cadaveric intestine is *not* available for transplantation in an individual who meets the above criteria for a cadaveric small bowel transplant.

Retransplant

Retransplantation in pediatric and adult individual of a *combined small bowel and liver transplant* or *multivisceral transplant* to is considered **medically necessary** if the individual meets the criteria above in the following:

- Acute rejection
- Chronic rejection
- Non-function of the grafted organ(s)
- Return of disease

Policy Guidelines

Potential Contraindications

The following are potential contraindications to a solid organ transplant and are *subject to judgement of the transplant center*:

- Known current malignancy, including metastatic cancer
- Recent malignancy with high risk of recurrence
- History of cancer with moderate risk of recurrence
- Untreated systemic infection making immunosuppression unsafe, including chronic infection
- Other irreversible end stage disease not attributed to intestinal failure
- Systemic disease that could be exacerbated by immunosuppression
- Psychosocial conditions or chemical dependency affecting ability to adhere to therapy

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 44135 Intestinal allotransplantation; from cadaver donor
- 44136 Intestinal allotransplantation; from living donor
- 47135 Liver allotransplantation; orthotopic, partial or whole, from cadaver or living donor, any age
- 47399 Unlisted procedure liver (the following code may be used to represent liver allotransplantation, heterotopic, partial or whole, from cadaver or living donor, any age when performed in conjunction with small intestinal transplant or multivisceral transplant)
- S2053 Transplantation of small intestine and liver allografts
- S2054 Multivisceral transplant

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POLICY HISTORY

Date	Reason	Action
November 2022	Annual Review	Policy Revised
November 2021	Annual Review	Policy Revised
November 2020	Annual Review	Policy Renewed
November 2019	Annual Review	Policy Renewed
November 2018	Annual Review	Policy Revised
November 2017	Annual Review	Policy Renewed
November 2016	Annual Review	Policy Revised
November 2015	Annual Review	Policy Revised
December 2014	Annual Review	Policy Revised
February 2014	Annual Review	Policy Revised
March 2013	Annual Review	Policy Revised
March 2012	Annual Review	Policy Renewed
March 2011	Annual Review	Policy Revised

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

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