Small Bowel/Liver and Multivisceral Transplant

Effective: May 1, 2017

Next Review: March 2018
Last Review: March 2017

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/liver transplantation is performed in patients that have both intestinal and liver failure, and may be combined with the transplantation of other portions of the digestive tract and accessory organs.

MEDICAL POLICY CRITERIA

I  Candidates for all types of small bowel/liver or multivisceral transplant must meet all of the following criteria:
   A  Adequate cardiopulmonary status
   B  Documentation of patient compliance with medical management

II A small bowel/liver transplant or multivisceral transplant may be considered medically necessary for pediatric and adult patients with intestinal failure (characterized by loss of absorption and the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balance), who have been managed with long-term TPN and who have developed evidence of impending end-stage liver failure.

III A small bowel/liver transplant or multivisceral transplant may be considered not medically necessary when criterion I. or criterion II. is not met.
IV A small bowel/liver retransplant or multivisceral retransplant may be considered **medically necessary** after a failed primary small bowel/liver transplant or multivisceral transplant.

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

### CROSS REFERENCES
1. Plasma Exchange (Plasmapheresis), Medicine, Policy No. 05
2. Liver Transplant, Transplant, Policy No. 5
3. Isolated Small Bowel Transplant, Transplant, Policy No. 9

### BACKGROUND
Small bowel/liver transplantation is transplantation of an intestinal allograft in combination with a liver allograft, either alone or in combination with one or more of the following organs: stomach, duodenum, jejunum, ileum, pancreas, or colon. Small bowel transplants are typically performed in patients with intestinal failure due to functional disorders (e.g., impaired motility) or short bowel syndrome, defined as an inadequate absorbing surface of the small intestine 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 the long-term complications of total parenteral nutrition (TPN). These patients may be candidates for a small bowel/liver transplant or a multivisceral transplant, which includes the small bowel and liver with one or more of the following organs: stomach, duodenum, jejunum, ileum, pancreas, and/or colon. A multivisceral transplant is indicated when anatomic or other medical problems preclude a small bowel/liver transplant, and the patient requires removal of all of the native gastrointestinal tract and replacement with a multivisceral graft.

**Note:** Isolated small bowel transplants and isolated liver transplants are considered in separate medical policies (see Cross References section above).

### EVIDENCE SUMMARY
Much of the published literature consists of case series reported by single centers. Authors of these reports as well as narrative reviews observed that while outcomes continue to improve, recurrent and chronic rejection and complications of immunosuppression continue to be obstacles to long term survival.

### REGISTRY DATA
The most recent published report from the international Intestinal Transplant Registry (ITR) reported on 2887 transplants in 2699 patients from 82 transplant programs worldwide. Participation in this registry was considered to be nearly 100% of all intestinal transplants performed in the world since April 1985. The following results were reported:

- Regional practices and outcomes are now similar worldwide.
- Current actuarial patient survival rates at 1, 5, and 10 years post-transplant are 76%, 56%, and 43%, respectively.
- Outcomes of intestinal transplantation improved modestly over the past decade, but rates of graft loss beyond 1 year have not improved.
• The reasons for late graft loss have been difficult to identify due to the low case volumes at most centers.
• Better function was found in intestinal grafts that included a colon segment and/or a liver component.

Better graft survival was also seen in patients who waited at home for intestinal transplant, used induction immune-suppression therapy, and had rapamycin maintenance therapy.

NON-RANDOMIZED TRIALS

Survival Outcomes

The following studies are representative of the current published literature:

Rutter et al. (2016) published the results of intestinal and multivisceral transplants from a single center in the United Kingdom.[2] Between January 1, 2007 and June 30, 2015, 60 transplant procedures were performed in 54 patients. Of these, 35 were multivisceral transplants, nine were modified multivisceral transplants and 16 were small bowel transplants. The median age of recipients was 47 years (range: 18 to 61 years). The median length of follow-up was 21.3 months (range: 0 to 95 months). The 1-year and 5-year patient survival rates were 77% and 62%, respectively. One-year survival by type of procedure was 71% for multivisceral transplant, 85% for modified multivisceral transplant and 92% for small bowel transplant. Five-year survival in these groups was 33%, 65% and 83%, respectively. Most of the deaths occurred in the first year after transplant.

A 2014 single-center Italian case series reported on transplants in 45 patients who received either intestinal transplants alone or a combined transplant procedure.[3] Twelve of the patients had small bowel/multivisceral transplants. Five of these had the procedure due to short-bowel syndrome, two had chronic intestinal pseudo-obstruction (CIPO) and five had Gardner syndrome. Survival rates for the entire patient population were 77% at one year, 58% at three years, 53% at five years and 37% at ten years.

In 2013, Mangus et al. reported on 95 patients who underwent multivisceral transplantation with or without liver transplantation at one site.[4] One-year patient survival was 72% and 3-year survival was 57%. The authors noted a learning curve, with a 48% survival rate for transplants performed between 2004 and 2007 and a 70% survival rate for operations between 2008 and 2010.

A 2013 single-center study included 30 patients accepted for intestinal and multivisceral transplantation.[5] One- and 3-year survival rates were 68% and 61%, respectively. Among patients awaiting transplantation after being accepted as candidates, there was a 34% survival rate.

Long-term survival data were reported on 227 visceral allograft recipients who survived beyond the 5-year milestone. At a mean follow-up of 10 ± 4 years, 92 adults and 85 children were alive, with 118 (67%) of recipients 18 years or older. The most significant risk factors were nonfunctional social support and non-inclusion of the liver in the visceral allograft. Nutritional autonomy was achieved in 160 (90%) survivors. Most achieved self-sustained socioeconomic status with reintegration into society despite coexistence or development of neuropsychiatric disorders. Morbidities with potential impact on global health included dysmotility (59%), hypertension (37%), osteoporosis (22%), and diabetes (11%).
Abu-Elmagd et al., reporting on experience with 500 intestinal and multivisceral transplantsations, also found that the best outcomes in their series were in the intestine-liver allografts reporting 1-and 5-year patient survival of 92% and 70%, respectively.[7]

Lacaille et al. (2016) reported on the outcomes of intestinal transplantation in pediatric patients at a center in Paris, France.[8] Between 1994 and 2014, intestinal transplants were performed in 101 children, including 45 liver/small bowel, four multivisceral, and one modified multivisceral transplant. Patient and graft survival at 18 years for transplants that included a liver were 60% and 46%, respectively.

Nayyar et al. reported improvements in 5-year actuarial patient and graft survival after liver/small bowel transplant since the use of rATG induction began to be used in their pediatric center in 2002 (81% vs. 58% and 76% vs. 52%, respectively).[9] In addition to innovations in immunosuppressive therapy, the authors cited new approaches to management of short gut syndrome including hypoallergenic formulas and modification of enteral nutrition to prevent total parenteral nutrition-induced cholestasis. The authors noted that better understanding of the protective role of the liver in preventing chronic rejection of the small bowel allograft could improve long-term survival after isolated small bowel transplantation.

**Adverse Effects**

Nagai et al. (2016) reported on cytomegalovirus (CMV) infection after intestinal or multivisceral transplantation at a single center in the US.[10] A total of 210 patients had intestinal transplant, multivisceral transplant or modified multivisceral transplant between January 2003 and June 2014. The median length of follow-up was 2.1 years. A total of 34 patients (16%) developed CMV infection a median of 347 days after transplantation. Nineteen patients had tissue invasive CMV disease. A report from another center in the US, 16 of 85 (19%) patients undergoing intestinal or multivisceral transplantation developed CMV infection a mean of 139 days (range: 14 to 243 days) postoperatively.[11]

A 2015 retrospective review reported a number of parameters for intestinal and multivisceral transplants performed on Nordic patients between 1998 and 2013.[12] Twenty out of the 29 patients (69%) received liver-containing allografts. Nineteen of them were multivisceral grafts, including the stomach, the pancreaticoduodenal complex, the liver and the small intestine. The remaining liver-containing allograft was a combined liver and intestinal graft with a segmental pancreas. Three patients (3/8) with a spleen included in their multivisceral graft developed graft-versus-host disease (GVHD). One patient with GVHD and manifestations with skin rash later developed post-transplant lymphoproliferative disorder (PTLD).

A 2012 retrospective review focused on the rate of kidney dysfunction, a recognized complication after non-renal solid organ transplantation, in 33 multivisceral and 15 isolated small bowel transplant patients.[13] A significant decline in kidney function was reported in 46% of patients at one year following transplantation. A significant correlation was found for patient age, pretransplant sCr, estimated GFR (eGFR) at post-transplant day 30, 90, 180, and 270, and tacrolimus live at post-transplant day seven. Lesser decline was found in pediatric patients and patients with multivisceral transplantation compared with adults or isolated small bowel transplantation.

A 2012 retrospective review reported on bloodstream infections among 98 children younger than age 18 years with small bowel/combined organ transplants.[14] Seventy-seven (79%)
patients underwent small bowel transplant in combination with a liver, kidney, or kidney-pancreas, and 21 had an isolated small bowel transplant. After a median follow-up of 52 months, 58 (59%) patients remained alive. 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 patients (69.4%) experienced at least one episode of bloodstream infection. The 1-year survival rate for patients with bloodstream infections was 72% compared to 87% in patients without bloodstream infections (p-value= 0.056 for difference in survival in patients with and without bloodstream infections).

A 2011 article focused on complications after small bowel and multivisceral transplantation. Wu et al. reported on 241 patients who underwent intestinal transplantation.[15] Of these, 147 (61%) had multivisceral transplants, 65 (27%) had small bowel transplants and 12% had small bowel/liver transplants. There were 151 children (63%) and 90 adults. A total of 22 patients (9%) developed graft-versus-host disease (GVHD). Children younger than five years old were more likely to develop GVHD; the incidence in this age group was 16 of 121 (13.2%) compared to 2 of 30 (6.7%) in children between 5 and 18 years and 9 of 90 (4.4%) in adults over 18 years. Among diseases, patients with intestinal atresia were more likely to develop GVHD than those with other conditions (22.2% vs. 2.6%, respectively; p=0.03).

In a 2016 series by Cromvik et al., five of 26 patients (19%) were diagnosed with GVHD after intestinal or multivisceral transplantation at a center in Sweden.[16] Risk factors for GVHD were malignancy as a cause of transplantation and neoadjuvant chemotherapy or brachytherapy before transplantation.

Transplant Recipients with Malignancies

Cruz and colleagues published results from a small case series (n=10) of patients with intra-abdominal desmoid tumors secondary to familial adenomatous polyposis who underwent multivisceral transplant.[17] All patients were able to discontinue home parenteral nutrition by an average 30 days after transplant. Estimated survival was 80% at five years and desmoid tumors reoccurred in one patient 15 months after transplantation. However, conclusions from this study are limited by the small sample size and the lack of a comparison group, factors which do not allow for the isolation of transplant as a causative factor in patient health outcomes.

HIV Positive Transplant Recipients

The subgroup of HIV positive transplant recipients has been controversial due to the long term prognosis for HIV positivity, the impact of immunosuppression on HIV disease, and the interactions of immunosuppressive therapy 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 OPTN permits HIV test positive individuals as organ candidates if permitted by the transplant hospital. Care of HIV test positive organ candidate and recipients should not deviate from general medical practice.”[18]

Retransplantation
Desai et al. reported intestinal retransplantation data from the Organ Procurement and Transplant Network (OPTN) database.[19] Between October 1987 and August 2009, there were 31 cases of small bowel/liver retransplants in adults and 49 in children. Among adults, 1-, 3- and 5-year survival rates after retransplantation were 63.1%, 56.1% and 46.8%, respectively. This compared to survival rates after primary small bowel/liver transplants of 67%, 53.3% and 46% at 1-, 3- and 5-years. Among children, there was a 42.1% survival rate at 1-, 3- and 5 years after retransplantation. Survival rates after primary small bowel/liver transplantation was 67.6%, 56.1% and 51.4%, respectively.

In 2012, Trevizol et al. published a review of literature from the previous five years on intestinal and multivisceral retransplantation.[20] The authors found articles from two centers. Mazariegos and colleagues reported on 15 retransplantations in 14 pediatric patients.[21] By the end of follow-up, four patients had died and ten patients had a normal graft function. TPN was weaned at a mean of 32 days after retransplantation. The 2009 study by Abu-Elmagd and colleagues[7] discussed earlier also reported 47 retransplants after 500 intestinal and multivisceral transplantations in adults and children. This included 31 intestinal retransplants, nine multivisceral retransplants and seven intestinal/liver retransplants. For all types of retransplants combined, there is a 5-year survival rate of 47%.

PRACTICE GUIDELINE SUMMARY

AMERICAN GASTROENTEROLOGICAL ASSOCIATION

In 2003, the American Gastroenterological Association published a position statement on short bowel syndrome and intestinal transplantation.[22] The statement noted that only patients with life-threatening complications due to intestinal failure or long-term total parenteral nutrition have undergone intestinal transplantation. The statement recommended the following Medicare-approved indications, pending availability of additional data:

- Impending liver failure
- Thrombosis of major central venous channels
- Frequent central line associated sepsis
- Frequent severe dehydration.

SUMMARY

There is enough research to show that small bowel/liver and multivisceral transplant and retransplant can improve survival in certain patients. Therefore, these procedures may be considered medically necessary for patients with intestinal failure who have been managed with long-term total parenteral nutrition (TPN) and who have developed evidence of impending end-stage liver failure. Transplants or retransplants are considered not medically necessary when the policy criteria are not met.

REFERENCES


23. BlueCross BlueShield Association Medical Policy Reference Manual "Small Bowel/Liver and Multivisceral Transplant." Policy No. 7.03.05

CODES

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<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
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*Date of Origin: January 1996*