Isolated Small Bowel Transplant

Description

A small bowel transplant may be performed in conjunction with other visceral organs, including the liver, duodenum, jejunum, ileum, pancreas, or colon. Isolated small bowel transplant is commonly performed in patients with short bowel syndrome. Small bowel/liver transplants and multivisceral transplants are considered in a separate policy (see related policy).

Background

A small bowel transplant is typically performed in patients with short bowel syndrome. This 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 adults, etiologies of short bowel syndrome include ischemia, trauma, volvulus, and tumors. In children, gastroschisis, volvulus, necrotizing enterocolitis, and congenital atresias are predominant causes.

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). 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 multivisceral and bowel/liver) represent a small minority (0.6%) of all solid organ transplants. In 2011, 129 intestinal transplants were performed in the United States, of which all but 1 was from deceased donors. In 2012, 106 intestinal transplants were performed in the U.S.; all were from deceased donors.
Regulatory Status

Small bowel transplantation is a surgical procedure and, as such is not subject to regulation by the U.S. Food and Drug Administration.

Related Policies

7.03.05 Small Bowel/Liver and Multivisceral Transplant

Policy

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

A small bowel transplant using cadaveric intestine may be considered medically necessary in adult and pediatric patients with intestinal failure (characterized by loss of absorption and the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balance), who have established long-term dependency on total parenteral nutrition (TPN) and are developing or have developed progressive complications due to TPN.

A small bowel transplant using a living donor may be considered medically necessary only when a cadaveric intestine is not available for transplantation in a patient who meets the criteria noted above for a cadaveric intestinal transplant.

A small bowel transplant using living donors is considered not medically necessary in all other situations.

A small bowel transplant is considered investigational for adults with intestinal failure who are able to tolerate TPN.

A small bowel transplant may be considered medically necessary after a failed primary small bowel transplant.

Policy Guidelines

Potential contraindications subject to the judgment of the transplant center:

1. Known current malignancy, including metastatic cancer
2. Recent malignancy with high risk of recurrence
3. History of cancer with a moderate risk of recurrence
4. Systemic disease that could be exacerbated by immunosuppression
5. Untreated systemic infection making immunosuppression unsafe, including chronic infection
6. Other irreversible end-stage disease not attributed to intestinal failure
7. Psychosocial conditions or chemical dependency affecting ability to adhere to therapy
Candidates should meet the following criteria:

- Adequate cardiopulmonary status
- Documentation of patient compliance with medical management.

HIV [human immunodeficiency virus]-positive patients, who meet 2001 guidelines of the American Society of Transplantation, could be considered candidates for small bowel transplantation.

**Small Bowel Specific**

Intestinal failure results from surgical resection, congenital defect, or disease-associated loss of absorption and is characterized by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balance. (2) Short-bowel syndrome is one case of intestinal failure.

Patients who are developing or have developed progressive 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 multivisceral 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.

**Rationale**

This policy is based on 2 Technology Evaluation Committee (TEC) Assessments conducted in the 1990s. A 1995 TEC Assessment concluded that in children, small bowel transplant was associated with improved survival compared to total parenteral nutrition (TPN) as the associated adverse outcomes for small bowel transplant were offset by severe TPN-related complications. (3) This Assessment also concluded that, in adults, the outcomes for small bowel transplant were worse than that associated with TPN. A 1999 TEC Assessment reevaluated the data on adults and concluded that, since it is not possible to predict which patients would survive longer on TPN versus small bowel transplant, transplantation may be considered a reasonable option in selected adults. (4)

Much of the published literature consists of relatively small case series. For example, in 2014, Ueno et al in Japan reported on 21 intestinal transplant patients; all but one received an isolated small bowel transplant for intestinal failure. (5) The overall 1- and 5- year survival rates were 86% and 68%, respectively. In the 15 patients who underwent transplantation after 2006, 1-year survival was 92% and 5-year survival was 83%.

These reports, as well as reviews of observational data, observe that while outcomes continue to improve, obstacles to long-term survival remain. Recurrent and chronic rejections and complications of immunosuppression are significant issues in bowel transplantation.
One issue in the literature is the importance of timely referral for intestinal transplantation to avoid the necessity of combined liver and intestine transplantation. (6) It has been suggested that recent improvements in survival may justify removing the restriction of intestinal transplantation to patients who have severe complications of TPN. However, as noted by Vianna et al in their 2008 report on the status of intestinal transplantation, no randomized trials compare intestinal transplantation with long-term TPN, and optimal timing for earlier transplantation has not been established. (7)

Another issue in the literature is the rate of various complications after small bowel transplant. Florescu et al have published several articles retrospectively reviewing complications in a cohort of 98 pediatric patients. Twenty-one of these children (21.4%) had an isolated small bowel transplant; the remainder had combined transplants. A 2012 study reported that 68 of the 98 patients (69%) developed at least one episode of bloodstream infection. (8) Among the patients with an isolated small bowel transplant, the median time to infection for those who became infected was 4.5 months (95% confidence interval [CI], 2.4 to 6.7 months). Also in 2012, the researchers reported that 7 of 98 patients (7%) developed cytomegalovirus (CMV) disease; only 1 of these had an isolated small bowel transplant. (9) In 2010, Florescu et al reported that 25 of 98 cases reviewed (25.5%) developed at least one episode of fungal infection; Candida infection was most common. (10) The mortality rate did not differ significantly between patients who did and did not develop a fungal infection (32.3% vs. 29.8%, respectively; p=0.46).

Several other series have reported on renal failure after intestinal transplantation. In 2013, a research group in France reported that 7 of 12 children who had an isolated small bowel transplant had renal function complications at some point after surgery. (11) Before treatment, all of the patients had normal renal functioning. In 2014, Calvo Pulido in Spain reported on 21 adults who underwent intestinal transplantation; 17 were isolated small bowel transplants. Thirteen patients (62%) experienced renal failure; the etiology included high ileostomy output, immunosuppression, and medical treatment.

**Living donors**

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. (13-16) 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.

Benedetti et al reported outcomes from 4 children and 7 adults who underwent 12 living-related small bowel transplantations between 1998 and 2004. (17) All donors were reported to have had uneventful recovery following removal of up to 40% of the small intestine. The 3-year patient survival was 82%, with graft survival of 75%. Longer follow-up from the earlier cases was not reported. Gangemi and Benedetti published a literature review of living donor small bowel transplantation reports from 2003 to 2006; all of the reports listed Benedetti (et al.) as author. (18) The authors comment that, “Due to the excellent result in modern series of deceased donor bowel transplantation, widespread use of the
procedure [living donor] should not be recommended, in consideration of the potential risks to donor. Furthermore, few centers have acquired the necessary experience with the procedure.

In June 2010, Sudan published a review of current literature on long-term outcomes after intestinal transplantation. (19) In this paper, the author notes that intestinal transplantation has become standard therapy for patients with life-threatening complications from parenteral nutrition therapy. Data from current single-center series indicates a 1-year patient survival rate of 78% to 85% and a 5+ year survival rate of 56% to 61%. With respect to pediatric intestinal transplant patients, the majority achieve normal growth velocity at 2 years post-transplant. However, oral aversion is a common problem; tube feedings are necessary in 45% of children. Sudan also reports on parental surveys of quality of life in pediatric transplant patients in which intestinal transplant patients appear to have modestly improved quality of life compared to patients remaining on TPN and slightly worse than matched school-age controls without intestinal disease.

Retransplantation

Desai et al have published the most comprehensive reporting of outcomes after repeat small bowel transplant in the United States. A 2012 publication evaluated data in the UNOS database on patients who underwent small bowel transplants in the United States between October 1987 and August 2009. (20) The investigators identified 41 repeat isolated small bowel transplants in adults and 28 in children. Thirty-nine of the adults (95%) and 27 (96%) of the children had a previous isolated small bowel transplant; the remaining patients had an initial combined small bowel and liver transplant.

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

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

Practice Guidelines and Position Statements

The United Network for Organ Sharing (UNOS) policy on identification of transmissible diseases in organ recipients states, “A potential candidate for organ transplantation whose test for HIV is positive should not be excluded from candidacy for organ transplantation unless there is a documented contraindication to transplantation based on local policy.” (21)

In 2001, the Clinical Practice Committee of the American Society of Transplantation (AST) proposed that the presence of AIDS could be considered a contraindication to kidney transplant unless the following criteria were present. (22) These criteria may be extrapolated to other organs:

- CD4 count >200 cells/mm-3 for more than 6 months
- HIV-1 RNA undetectable
• On stable antiretroviral therapy for more than 3 months
• No other complications from AIDS (e.g., opportunistic infection, including aspergillus, tuberculosis, coccidioses mycosis, resistant fungal infections, Kaposi’s sarcoma, or other neoplasm).

In 2006, the British HIV Association and the British Transplantation Society Standards Committee published guidelines for kidney transplantation in patients with HIV disease. (23) As described above, these criteria may be extrapolated to other organs. The guidelines, which are similar to those cited here, recommend that any patient with end-stage organ disease with a life expectancy of at least 5 years is considered appropriate for transplantation under the following conditions:

• CD4 greater than 200 cells/mL for at least 6 months
• Undetectable HIV viremia (<50 HIV-1 RNA copies/mL) for at least 6 months
• Demonstrable adherence and a stable HAART regimen for at least 6 months
• Absence of AIDS-defining illness following successful immune reconstitution after HAART.

U.S. Preventive Services Task Force Recommendations

Not applicable

Summary

A small bowel transplant using cadaveric intestine may be considered medically necessary in patients with intestinal failure (characterized by loss of absorption and the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balance), who are developing severe complications total parenteral nutrition related complications, to obviate the subsequent need for a multivisceral transplant.

Small bowel transplantation using a living donor may be considered medically necessary only when a cadaveric intestinal transplant is not available due to the risk to the living donor. Routine use of living-donor intestinal transplants is considered not medically necessary because the net health outcome associated with this procedure is reduced (compared to cadaveric transplant) because of donor-related morbidity.

A small bowel transplant is considered investigational for adults with intestinal failure who are able to tolerate TPN as no randomized trials which compare intestinal transplantation to long-term parenteral nutrition, and optimal timing for earlier transplantation have been performed.

A small bowel transplant may be considered medically necessary after a failed primary small bowel transplant.
Medicare National Coverage

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. (24)

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-constructable 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.

References

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This policy was approved by the FEP® Pharmacy and Medical Policy Committee on September 18, 2015 and is effective October 15, 2015.

**Signature on file**

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