Nutrition Interventions Before and After Adult Intestinal Transplantation: The Pittsburgh Experience

The care of patients with intestinal failure is complex and requires a multifaceted approach delivered by a multidisciplinary team. Success is rarely achieved in isolation. The advent of intestinal and multivisceral transplantation has added a new dimension to the care of these patients and is now considered a valid therapeutic option for patients with irreversible intestinal and parenteral nutrition failure. The objective is to restore nutritional autonomy to patients with a complex past surgical history and equally complex post-transplant immunosuppressive regimen in the context of a newly created surgical anatomy. The recent evolution in nutrition management which allows for early and progressive enteral feeding using a complex polymeric formula is safe and effective. Full clinical nutritional autonomy is achievable among most intestinal and multivisceral recipients allowing the consumption of an unrestricted oral diet with the added benefit of improved quality of life. Special consideration is given to the nutritional care both before and after surgery in order to maximize outcomes.

INTRODUCTION

The care of patients with intestinal failure is complex and requires a number of therapies delivered by a multidisciplinary team. Many of these patients are managed long-term on parenteral nutrition (PN) and remain free of complications, with a reasonable quality of life. Others are candidates for intestinal rehabilitation procedures designed to restore nutritional autonomy through the use of surgical reconstruction, modified diet, specialized nutrients such as standard medications, glutamine and growth factors. However, for those patients with irreversible intestinal and PN failure, intestinal and multivisceral transplantation is the only lifesaving therapeutic option. Over the last two decades, survival has improved as the management strategies and care of these patients has evolved (1).
However, along with these advances a range of nutrition issues that require specific management strategies both before and following transplantation have occurred. The University of Pittsburgh has the largest single center experience in the world having performed over 500 intestinal transplants. This review will cover the University of Pittsburgh Medical Center’s experience related to nutritional aspects of intestinal transplantation during the entire perioperative period.

INDICATIONS AND CONTRAINDICATIONS

Irreversible intestinal failure, with failure of the currently available conventional therapeutic modalities including PN, is required for intestinal and multivisceral transplantation (2–4). PN failure has been defined as significant biochemical or histological evidence of liver injury, loss of central venous access, frequent line sepsis, and recurrent episodes of severe dehydration (see Table 1) (5).

According to the Intestinal Transplant Registry, most of these transplants are performed for short bowel syndrome, neoplastic disorders, splanchic thrombosis, and motility disorders (Table 2) (6). In each case, the decision to proceed with transplantation should be made only after exhausting other medical and surgical interventions designed to enhance intestinal absorption (see “Lessons” below). The evaluation for transplantation is extremely comprehensive and includes assessment of nutritional status, residual gut functional capacity, and assessment of PN and primary disease complications. It is important to refer patients early for transplant evaluation in order to optimize surgical outcomes and potentially utilize non-transplant rehabilitation techniques (Table 3). The contraindications for intestinal transplantation were primarily established based upon historical experience with other abdominal organ transplantation procedures and include significant cardiopulmonary insufficiency, advanced malignancy, severe immune deficiency syndromes, and life threatening intraabdominal or systemic infections (3).

TYPE OF TRANSPLANTATION

Intestinal transplantation includes three different types of surgical procedures. Isolated intestinal transplant is performed when the intestine fails to adapt following medical and surgical rehabilitation attempts, thus requiring continuation of PN. The combined liver-intestinal transplant is indicated for patients with combined intestinal and PN-associated liver failure and patients with liver failure associated with portal and mesenteric venous thrombosis. Multivisceral transplantation, whether full or modified (i.e., without the liver), is indicated for diffuse gastrointestinal disorders (continued on page 15)
such as dysmotility syndromes, hereditary neoplasms, and extensive vascular thrombosis (7).

**PREOPERATIVE CARE**

Once the decision is made to proceed with transplantation, the goal during the preoperative stage is to optimize nutritional status, preserve hepatic and renal function, and to keep the patient free from infection until organs become available. Almost all of these patients are PN-dependent prior to transplant and optimizing nutritional status in the face of deteriorating hepatic function can be challenging. It is important to prevent overfeeding of all macronutrients and, in particular, intravenous lipid emulsions (8–9). Although most of these patients are underweight, occasionally there are patients who are overweight and must be placed on a PN prescription that induces weight loss without negatively impacting nutritional status. In these situations, permissive underfeeding is utilized. Serum vitamin and trace element levels are measured at the time of evaluation and all deficiencies are cor-
rected (Table 4). Patients undergo dual-energy absorptiometry (DXA) to determine the baseline status of bone mineral density and to guide further therapy. In patients with osteopenia and osteoporosis, treatment is initiated in the pretransplant phase to prevent disease progression. The treatment is individualized for each patient and may include the use of calcium and vitamin D supplementation, biphosphonates, recombinant human parathyroid hormone (PTH) 1–34, estrogen, or testosterone.

Prior to transplantation, many of these patients will have extraordinary fluid losses. Once the patient is transplanted, they will receive a number of potentially nephrotoxic drugs (Table 5). Thus, it is important to preserve renal function during the preoperative phase by preventing dehydration. Patients will sometimes present dehydrated with both clinical and biochemicals signs of dehydration, and often complain of thirst. This causes them to drink more by mouth which generally results in increased gastrointestinal output thus exacerbating the dehydration. The problem is worsened when they consume excess amounts of hyper- and hypoosmolar solutions. It is not unusual for these patients to require as much as four liters of volume in the PN solution. Many will also require supplemental intravenous fluids in addition to the PN. Although all attempts are made to cycle the PN infusion over a 12 hour period, it is not unusual to provide the PN over longer periods or even continuously in order to prevent periods of dehydration and damage to the kidneys. This approach often allows for better fluid utilization without fluid overload. If fluid status cannot be maintained with this approach, standard intravenous fluids such as normal saline can be infused when the patient is not on PN. Antidiarrheal and antisecretory medications are also used to slow output (see Table 3). Although the patients are PN dependent prior to transplant, most eat for pleasure. In some instances, oral intake may be restricted in order to prevent large losses via the gastrointestinal tract.

### POSTOPERATIVE MANAGEMENT AND TRANSITION TO CLINICAL NUTRITIONAL AUTONOMY

Intestinal transplantation is relatively new. The first multiseceral graft consisting of a stomach, duodenum, pancreas, small bowel, colon and liver was performed in a 3-year-old girl in Pittsburgh in 1987 (10). Aptly, due to the relatively short period of time the procedure has been available and the complexity of management, most of the trials have been observational with historical controls. The protocols of nutrition management used during the recovery phase and transition to clinical nutritional autonomy vary among each transplant center (11). Most of the published reports provide information on what is commonly done in the individual transplant centers, particularly the nutritional aspects. However, the nutritional management has evolved over the years.

Ultimately, the goal of intestinal transplantation is to allow the patient to eat an unrestricted diet which maintains nutrient, fluid and electrolyte balance. During

(continued on page 19)
the transition phase, dynamic and complex management strategies are often required (12). Nutrient, fluid, and electrolyte requirements are met through a stepwise progression of transitions from PN to oral diet. This transition occurs fairly rapidly after the surgery.

Immediately postoperatively, PN is started to support the patient in the early postoperative phase. At this point, the PN prescription changes dramatically from the prescription used during the preoperative phase. The patient no longer requires the large volumes of PN that were necessary to maintain hydration before transplantation. Generally, the volume of PN is reduced to one or two liters. Depending on the center, enteral nutrition is initiated by nasogastric tube, nasoduodenal tube, gastrostomy tube, or jejunostomy tube. Delayed gastric emptying often mandates the use of transpyloric feeding, even in those centers that typically feed into the stomach. The Pittsburgh experience with initiation of enteral feedings has evolved so that at the time of transplantation, a feeding jejunostomy is placed directly into the new allograft and a nasogastric tube is placed for decompression of the stomach. This approach is used to minimize the risk of aspiration from delayed gastric emptying, enhance patient comfort and acceptance, and allow for oral intake (12–13).

The intestinal allograft should be utilized as soon as possible following surgery. Feedings can be given by mouth or via a feeding tube. Oftentimes, this is done simultaneously. Enteral feedings are initiated when allograft motility is established by the appearance of gas and effluent from the stoma. This often coincides with decreased abdominal distention as the ileal inflammatory response to ischemia-reperfusion injury diminishes around postoperative days 3–7 (14). Enteral feedings are started at full strength, generally 5–10 mL hour. As the rate is advanced, the PN is gradually tapered. Opiates, loperamide, soluble fiber supplements are used for high stomal output or diarrhea. If delayed gastric emptying occurs after transplantation, prokinetic agents (e.g. Metoclopramide and Erythromycin) are used to treat the dysmotility and fiber is avoided (15–17).

The choice of enteral feeding formula remains somewhat controversial. Since the lymphatics are disrupted at the time of procurement of the organs, it was assumed that these patients required a low fat, predigested or elemental formula to prevent chylos accumulation. With regard to the concern over malabsorption, early in the Pittsburgh experience, an isotonic elemental diet that contained peptide-based protein, medium-chain triglycerides, and glutamine was used (18). However, there have been no data to suggest significant malabsorption of the intestinal allograft early after transplantation (19–20). Though some centers continue to use elemental formulas (low-fat or fat-free formulas in the first month or so after transplant), our center has taken a more progressive approach and the methodology of enteral feeding has evolved to include the use of a polymeric formula containing whole, complex components instead of a predigested product. Replete™ (Nestlé Nutrition, Glendale, CA) has been successfully used in our center due to its relatively high protein content and low potassium concentration. The lower potassium content in these formulas is helpful because tacrolimus can cause hyperkalemia (Table 6). Although no controlled trials in this patient population exist, in our institution, the patient is empirically switched to a fiber-containing formula if diarrhea develops.

Oral diet is usually started within the first two weeks after transplantation. After demonstration of tolerance to clear liquids, a regular diet is prescribed. Gastric emptying and subsequent potential risk of aspiration is carefully monitored by abdominal exam, nausea or vomiting. The major limiting factor for rapid, early establishment of full oral feeding is the development of transient postoperative gastric atony in some recipients (15). Patients are advised to eat small, frequent meals and avoid eating prior to bedtime in order to reduce the risk of reflux and aspiration. As oral intake increases, the enteral feeding rate is reduced. Eventually, the tube feeding is transitioned to supple-

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<tr>
<td>Replete with Fiber</td>
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mental nocturnal feedings in order to maximize the patient’s oral intake and freedom during the day. Enteral tube feedings are discontinued when the patient has achieved full oral nutrition autonomy.

The transition from PN to oral nutrition occurs fairly rapidly. The data on the time required to transition these patients is extremely limited. In one study from our institution, the mean time that enteral feeding was started was 10.3 ± 6.9 days (range: 3–35). PN was discontinued in all patients, mean = 30.8 ± 25 d (range: 9–132) of transplantation. And, achievement of full clinical nutritional autonomy, whereby the patients were off all enteral and parenteral feedings and consuming an oral diet occurred at a mean of 57 ± 36 days (21).

ORAL DIET

Can a patient who receives an intestinal transplant eat normally? One of the most heated debates has been whether or not to use a low fat diet after transplantation in order to reduce the risk of malabsorption and chyloous ascites. The theoretical basis for this recommendation is that the lymphatics are severed at the time of organ procurement. However, the data used to support this practice was based solely on practice surveys during the early development of intestinal transplantation (22–24). Yet in each of these surveys, the reported risk of chyloous ascites was low (<7%) and this early practice of limiting fat was based on minimizing the potential risk for this complication. There has never been a controlled trial to evaluate this theory. Spontaneous reconstitution of the lymphatic channels between the donor and recipient generally occurs within one month and indicates the self-limiting nature of fat malabsorption in the absence of chronic graft damage (18). In the early Pittsburgh experience, low-fat, predigested enteral formulas were used, along with a low-fat diet (18). This was based on clinical observation of formula tolerance and the results of the fecal fat excretion and D-xylene absorption tests (18). However, it is our current clinical practice to use a complex polymeric enteral formula and an unrestricted diet for most patients except in those who develop a chyloous leak. If a leak develops, they are placed on a low-fat diet (12). Clinical experience, patient tolerance, and quality of the allograft guide the selection of an enteral product.

Contrary to common food aversions observed in the pediatric population, most adult intestinal recipients are eager to begin an oral diet. It is interesting to note that many will have a “favorite” food that they have long anticipated consuming as soon as possible after transplant. However, it has also been our experience that in some instances there are barriers to oral intake. These are often learned. There may be fear of eating due to previous discomfort associated with consumption of food. Cognitive restructuring to change beliefs and perceptions of food is generally required. It is important to provide support and guidance during this period. For those adults who never learned to eat due to lifelong intestinal failure, the introduction of new foods is attempted slowly. The use of small frequent meals, prokinetic agents (i.e. Reglan) and appetite stimulants (i.e. Marinol) will aid in the transition for those patients with anorexia and early satiety (18).

It has also been our anecdotal experience that patients will often express a desire for foods that previously were not enjoyed or consumed. They will often ask if their donor liked the particular food. This observation lends credence to the theory that there is a very close relationship between the mind and the gut.

In considering that many of these patients have been unable to eat by mouth for years or even most of their lives, a fairly liberal approach is taken with regard to the type of food that we allow them to eat. Although they can consume an unrestricted diet, the nutrition management of intestinal and multivisceral recipients would be incomplete without a comprehensive educational program that includes: healthy food choices, weight management, food safety, food and drug interactions and even contemporary nutrition issues such as vitamin and mineral supplementation and trans fats. Although, topics such as trans fats do not relate specially to small bowel transplantation, our goal is to educate the patients on healthy eating habits. Most of these patients had chronic gastrointestinal disorders before transplantation that resulted in inability to eat or enjoy food, with the subsequent development of poor eating habits. Our goal is to have the patient enjoy an unrestricted oral diet that is healthful, flavorful, and rich in nutrients. Food is more than nutrition and encompasses not only pleasure and achievement of satiety, but also fulfillment of emotional, social, cultural, and religious needs.
MONITORING NUTRITIONAL STATUS AND LONG-TERM FOLLOW-UP

Clearly, these patients are able to eat normally, but does the transplanted bowel function to the same degree as a native bowel and can these patients maintain nutritional and fluid status? The nutritional status of the recipients is evaluated by the recipient’s ability to maintain or gain weight and to achieve adequate serum albumin concentrations in the absence of inflammation. Micronutrient status, including vitamin and trace elements, are measured before transplantation and every 6 months after transplantation (Table 4). All deficiencies are corrected before transplantation while the patient is still PN dependent; if an abnormal serum value is identified after transplantation, it can be corrected with oral supplementation. Deficiencies are captured at the biochemical level before clinical symptoms develop. The only significant serum vitamin deficiency noted after transplantation in our patient population has been serum pyridoxal 5-phosphate (vitamin B6) (21).

Although most patients do well after transplant and are able to enjoy an unrestricted oral diet, there are some potential long-term complications with nutritional implications. Overweight and occasionally morbid obesity have been observed following intestinal transplantation (25). Overweight and obesity are complex multifactorial chronic diseases that develop from an interaction of genotype, lifestyle and environment. In the setting of intestinal transplant other factors such as the allograft and immunosuppression must be considered in this equation. As a result, a comprehensive educational program including diet, exercise and psychological and social interventions is part of our multidisciplinary team approach for the postoperative care of this unique population.

In the Pittsburgh experience, chronic rejection was documented in 15% of visceral allografts (1). When this occurs, the patient may be placed on full or partial PN. This may be intermittent or permanent until a decision is made to proceed with retransplantation.

QUALITY OF LIFE

Nutrition deals with the very crux of our existence. And the desire to eat by mouth is one of the most powerful motivating factors in life. For many patients, transplantation is a rescue therapy for a serious life-threatening disease; for others it represents freedom from the routine of PN, infections and other related complications. But the desire to eat is universal and primal. Most intestinal and multivisceral transplant recipients describe an enhanced and much-improved quality of life. They experience improved nutritional status and are able to eat normally. These are objective, quantifiable outcomes which can be easily measured. This overall improvement in quality of life after intestinal transplantation has been documented using various validated self-administered questionnaires (26–30). The improvements in other aspects of life such as cognitive, emotional, and psychosocial states are more abstract and difficult to define.

In addition to eating, the absence of a stoma has a tremendous impact on the quality of life. For those patients with native colon or rectum, the stoma created at the time of transplant, can be reversed in 3–6 months. This allows the patient to have normal bowel movements.

LESSONS FOR THE CLINICIAN

Is the Patient a Candidate for Intestinal Rehabilitation?

Intestinal rehabilitation refers to a collection of techniques designed to enhance absorptive capacity, improve nutritional status, reduce the need for PN and/or optimize the use of PN through the use of modified diet, fiber supplementation, oral rehydration solutions, specialized nutrients (e.g. glutamine), medications, enteral nutrition, tropic factors (e.g. growth hormone, GLP-2) and reconstructive surgery (Table 3). Any patient who is a potential candidate for intestinal transplantation should be considered for non-transplant rehabilitation.

Early Referral

With the largest single center experience in the world, much has been ascertained over the last two decades (1). One of the most important considerations is early referral to an intestinal failure center for evaluation. In many cases, it may be possible to rehabilitate the remnant bowel and avoid transplantation. If the patient...
does require transplantation, early referral may result in the patient receiving an isolated small bowel transplant instead of a combined liver/intestine, particularly in those with only a small amount of fibrosis associated with cholestasis. Isolated intestinal transplantation in jaundiced patients has been shown to reverse liver disease even in a patient with a total bilirubin of 20 mg/dL at transplantation (31). However, if the hepatic dysfunction has progressed to the point of dense bridging fibrosis, a combined liver/small bowel transplant would be considered.

Vascular Access

Another major concern with late referrals is lack of vascular access (see Table 1). Unfortunately, many of the long-term PN patients have thrombosed their major vessels making it difficult to achieve and maintain access sufficient to allow transplantation.

Minimize PNALD

An important consideration is minimization of the risk of PNALD (also referred to as Intestinal Failure Associated Liver Disease—IFALD). PNALD is not a benign condition and should be treated aggressively to avoid permanent liver damage. The prevalence has been reported to range between 15 and 85% (32–34) and is much greater in infants than in older children or adults. Associated abnormalities include steatosis and steatohepatitis, fibrosis, cholestasis, and cirrhosis. Although, hepatic aminotransferase abnormalities are both insensitive and nonspecific indicators of liver pathology (35) these values are typically followed as markers of PNALD. Total serum bilirubin concentration may begin to increase in some adults after 10 weeks or more of PN (36). Increases in the serum alkaline phosphatase concentration may be observed as well (37), although this abnormality may in part be related to the metabolic bone disease that occurs in patients who receive long-term PN (38). The etiology of PNALD is multifactorial making it difficult to isolate hepatic complications that result solely from PN. Malnutrition, nutrient deficiencies in PN, potential toxic PN components, and a lack of protective elements such as choline are likely to contribute (39–42). For those patients with short bowel syndrome, a shortened length of the remnant bowel has been implicated as a risk factor for liver dysfunction (43–44). Altered bile absorption (due to loss of enterohepatic circulation in some), altered release of gut hormones, bacterial translocation, tumor necrosis factor associated with sepsis, and bacterial overgrowth are other potential factors (45). The risk of PNALD can be minimized if corrective action is taken (see Table 7).

Ongoing Monitoring of Vitamin and Mineral Status

It is not uncommon to see long-term PN patients referred to our program who have never been monitored for micronutrient deficiencies. Customization of the vitamins and trace element portion of the PN prescription is important. Although there are standard intravenous multivitamin and multi-trace element preparations, it has been our observation, as well as others that these do not always meet the needs of patients with intestinal failure (46). This is particularly important for those patients with excessive gastrointestinal losses or for patients with hepatobiliary insufficiency (see Table 8).

The ability to customize the vitamin portion of the PN solutions is more difficult due to the lack of some individual intravenous vitamin preparations. There are no individual intravenous forms of vitamins A, D, E, or B2.
Table 8.
Dosing of Individual Vitamin and Minerals for Long-term PN Patients

- Intravenous zinc—2 mg/kg of enteral loss for a total of 6–12 mg/d
- Selenium—60–100 µg per day
- Copper—0.3 to 0.5 mg per day
- Manganese—30–60 µg per day
- Both copper and manganese should be discontinued when serum aminotransferase and alkaline phosphatase levels are >2 times normal, and serum levels should be rechecked every 6–12 months thereafter
- Both serum and tissue levels of chromium have been shown to be high
  - Most patients will require between 5–10 micrograms per day
- Individual ascorbic acid, folate and thiamine preparations are commercially available and can be added in addition to the multivitamin preparation if serum values are low
- Carnitine is required for the transport of fatty acids from the cytosol into the mitochondria during the breakdown of lipids for energy metabolism
  - Intravenous carnitine can be added to the PN solution if the patient’s serum values are low
  - Usual dose is 250–500 mg per day

CONCLUSION

Intestinal and multivisceral transplantation is a viable therapeutic option for patients with gastrointestinal failure. With successful engraftment, most recipients achieve full clinical nutritional autonomy within a short period of time, enjoy an unrestricted diet, and experience a positive impact on quality of life. The nutritional management of this patient population has witnessed a continuous improvement over the years and will continue to evolve. Early referral for SB transplant evaluation is important to optimize outcome and provide the patient with the best therapeutic option.

References


(continued from page 22)


