Chapter 9
Total Parenteral Nutrition and Inflammatory Bowel Disease: Indications, Long term Outcomes, and Complications

Priya Loganathan, Alyce Anderson, William Rivers, Claudia Ramos Rivers, Mahesh Gajendran, and David G. Binion

Introduction

Intestinal failure is associated with the inability to maintain protein, energy, electrolyte, fluid, or micronutrients balance while the individual is receiving a conventional diet. Total parenteral nutrition (TPN) is a life saving modality which can sustain individuals who are unable to eat with specialized, high osmolality intravenous fluids administered into a high velocity flow central vein. TPN has demonstrated an important role in sustaining individuals with life-threatening disease. Given the strong propensity for intestinal damage and dysfunction in patients with inflammatory bowel disease (IBD), a subset of IBD patients require TPN as a result of extensive small bowel injury/stricture formation and associated obstructive symptoms that prevent adequate oral intake. IBD patients also frequently report a history of extensive small bowel surgery with loss of mucosal absorptive surface. Together, obstructive disease and surgical manipulation of the gut represent the two most common IBD related complications that will require parenteral nutrition support. TPN can also be useful in the setting of perioperative nutritional support, and function to restore nutritional status in malnourished individuals who require surgery. Perioperative TPN has been shown to improve operative outcomes and assists the individual in regaining the ability to tolerate foods. Programs for intestinal rehabilitation, TPN, and new medications that function to accelerate intestinal

P. Loganathan, M.B.B.S. • A. Anderson, B.S. • W. Rivers, B.S. • C.R. Rivers, M.D.
D.G. Binion, M.D. (✉)
Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh School of Medicine, UPMC Presbyterian Hospital, 200 Lothrop Street, Pittsburgh, PA 15143, USA
e-mail: binion@pitt.edu

M. Gajendran, M.B.B.S.
Department of Internal Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

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adaptation represent important advances in the care of IBD patients suffering from intestinal failure and short bowel syndrome (SBS). In the following sections we review the history of TPN in IBD management.

Background

The Development of Total Parenteral Nutrition and Home Intravenous Fluid Support

The concept of providing nutrient and fluid support intravenously dates back to the seventeenth century, when Sir Christopher Wren and Robert Boyle experimented with the injection of animals with a variety of substances including oil and wine. Later, Wilkinson described the intravenous infusion of an electrolyte salt solution into a patient dying from cholera in 1963, which was followed by the introduction of TPN by Lawson in 1965. The use of exclusive parenteral intravenous nutrition support was demonstrated by Dudrick, Willmore, and Vars who showed that the administration of continuous hypertonic dextrose and amino acids into a central vein could provide sufficient calories, ensuring adequate nutrition and growth initially in beagle puppies, and subsequently in human infants [1].

Following these early clinical discoveries, TPN has emerged as an established modality to provide intravenous nutrition to patients with a nonfunctioning gastrointestinal (GI) tract and in patients who are unable to obtain sufficient nutrition via enteral routes. The successful implementation of TPN as a treatment modality reflects the increasing number of physicians with expertise in intestinal rehabilitation, the availability of specialty pharmacies to formulate and provide parenteral nutrition to patients for home infusion, the advent of central venous access catheters usable by patients, and finally better access to home nursing care expertise to assist patients with the initiation and routine use of TPN. In the USA between 1989 and 1992, the annual prevalence of home parenteral nutrition (HPN) use was 120 per 100,000 individuals. This number was estimated as 40,000 patients in the USA were on HPN as of 1997 [2].

TPN: Basic Principles of Administration

Routine use of TPN involves important logistic issues. These logistics include central venous access devices, specialty pharmacies capable of formulating the intravenous product, and nursing support.

Delivery of TPN to central veins as opposed to peripheral veins is essential, as the hypertonicity of this fluid would cause injury/sclerosis to low flow peripheral veins. Central veins have estimated flow rates of 1000 cm^3/h, while peripheral veins have flow rates which are typically 10 % of flow that characterizes central veins.

The optimal location for central access is the subclavian vein, as this site carries the lowest risk of infection. At the present time, ultrasound guided placement of the catheter is recommended to avoid potential complications associated with subclavian access. When TPN is anticipated for a prolonged time period, more permanent central lines are preferred. Stable central lines used in TPN administration include percutaneous intravenous central catheters (PICC) placed in the brachial vein, tunneled subclavian central catheters with a cuff serving to anchor the line and prevent infections (i.e., Hickman, Broviac, Hohn, Groshong catheters), and implanted ports (i.e., Infusaport, Mediport). The choice of venous access is dependent on a variety of factors but not limited to, patient preference, IBD complications, and frequency and necessity of access the catheter. For example, daily use of TPN favors a tunneled line or PICC line, while intermittent access may work best for a subcutaneous port. In the setting of IBD, many patients have ostomies, which further complicates TPN administration. An ostomy site increases the potential for bacterial contamination on the abdominal wall, and warrants placement of the venous access device on the contralateral side of the body. When subclavian access is no longer available due to venous damage (i.e., vanishing venous access), alternative central access sites can include tunneled PICC lines into the internal jugular vein, femoral veins, and lumbosacral veins.

TPN solution macronutrients can be formulated in either 3 in 1 or 2 in 1 solutions. The 3 in 1 solution includes a combination of protein, carbohydrate, and lipid components in a single mixture, while the 2 in 1 solution only contains amino acid and carbohydrate components. Administration of intravenous fat emulsion of greater than 3 g/kg per day has been associated with hepatic dysfunction, one of the important reasons for providing a variety of solutions for long term TPN support. Although 2 in 1 solutions may prevent long term lipid injury to the liver, adequate fat absorption from the gut will be required to prevent development of essential fatty acid deficiency over time.

TPN administration requires pharmaceutical expertise to determine optimal pH and macronutrient concentrations. This pharmaceutical expertise is essential to prevent precipitation of ingredients which has the potential to result in iatrogenic pulmonary emboli. Filters of 1.2 μm for 3 in 1 solutions and 0.22 μm for 2 in 1 solutions are mandated by the FDA to prevent accidental infusion of particulates.

Indications for TPN in IBD: Overview

IBD consists of two primary disease classifications, Crohn's disease (CD) and ulcerative colitis (UC). Worsening malnutrition has historically been the major indication for TPN in the treatment of IBD. Malnutrition was most frequently observed in the setting of small bowel inflammation in CD, as compared to UC where inflammation is typically limited to the colon. In past decades, malnutrition was commonly encountered as adult CD patients would present clinically weighing typically 10 % less than ideal body weight. More recent data suggests that CD patients under their ideal body weight are in fact rare, and the majority of CD patients will be

above their ideal body weight [3]. In pediatric IBD, two-thirds of hospitalized CD patients have hypoalbuminemia, anemia, and negative nitrogen balance at presentation prior to the initiation of therapy. In addition to weight loss and protein caloric malnutrition [4] vitamin deficiency and deficiency of trace elements are hallmark features of active IBD.

There are various underlying mechanisms which contribute to nutritional deficiency in IBD, including extensive bowel disease impairing mucosal function and the ability to absorb nutrition, anatomic short bowel due to extensive surgical resection(s) with loss of absorptive surface area, anorexia, postprandial pain and food aversion due to luminal stenosis, and intermittent partial obstruction along with bacterial overgrowth. In patients who are unable to maintain nutritional needs (or regain losses) with an injured gastrointestinal tract, TPN represents an essential modality to both prevent further nutritional deficiency, restore nutritional homeostasis and prevented long term complications of nutritional deficiency.

The potential benefits of initiating TPN must also be counterbalanced by potential negative factors. Specifically, TPN high cost and potential serious complications and adverse reactions, including thrombosis, loss of venous access and infection, most commonly associated with the central venous catheter. The appropriate use of TPN in the management of IBD relies on the selection of appropriate candidates with significant nutritional deficits which cannot be corrected within a short time period using enteral approaches. Guidelines for the optimized use of TPN have been developed by the American Society for Parenteral and Enteral Nutrition (ASPEN) (Table 9.1).

Table 9.1 Guidelines for use of TPN in IBD and quality of evidence

TPN and Crohn's disease
Category A
Parenteral nutrition is not the primary treatment in intraluminal Crohn's disease
Category B
TPN is indicated in Crohn's patients who are:
Malnourished
At risk of becoming malnourished
Have inadequate or unsafe oral intake
Have a non (or poorly) functioning or perforated gut
Or gut is inaccessible (obstructed gut, a short bowel, high intestinal output, enterocutaneous fistula)
Specific deficiency like trace elements, vitamins should be corrected by appropriate supplementation
TPN and Ulcerative colitis (UC)
Category B
TPN is indicated in UC patients only when they are malnourished or at risk of being malnourished before or after surgery if they cannot tolerate food or enteral feed
No role for TPN during acute inflammatory state for enabling bowel rest

Category A suggests good research based evidence to support the recommendation

Category B suggests fair research based evidence to support the recommendation

Thus, TPN is reserved for very specific indications where the success of enteral nutrition is either impossible or poor. The following is a pragmatic list of the most common indications for the use of TPN in the management of IBD:

1. Impossible enteral nutrition.
2. To prepare the nutritionally depleted IBD patient for surgery and support through the postoperative period.
3. Post multiple major bowel resections for Crohn's disease resulting in SBS.
4. For a patient who failed to respond to maximum medical therapy and in whom surgery is to be avoided if possible.
5. In malnourished IBD patients with growth retardation.
6. Presence of intestinal fistula.
7. Avoidance of enteral nutrition.
8. Clinical features suggestive of ileus or subileus concerning the small intestine.

Specific Indications for TPN in IBD

Supportive Therapy for Short Bowel Syndrome and Life Sustaining Therapy

SBS is the term used to describe the clinical condition where the gastrointestinal tract fails to sustain nutritional and absorptive function due to the congenital or acquired loss of intestinal anatomy. SBS most commonly develops in patients who have suffered a loss of two-thirds of the length of their small intestine. However, the relationship between resection length and development of SBS and intestinal failure is highly variable between patients, and often reflects the age and underlying health of the individual, the time over which enterectomy(ies) were performed (i.e., a single massive resection will result in SBS more commonly than multiple smaller resections over multiple years), the remaining anatomic segments of bowel, motility patterns, and the capacity for the individual to undergo intestinal adaptation. In general, older individuals who suffer from oncologic and vascular insults, as well as massive single resections, are at the highest risk for developing SBS and requiring parenteral intravenous support. CD patients who are at risk for SBS are typically younger individuals, more commonly subjected to multiple, smaller resections. Historically, up to 16 % of individuals developing SBS as a complication of intestinal surgery suffered from CD [5].

SBS can lead to

Loss of absorptive surface area
Loss of site-specific transport processes
Loss of site-specific endocrine cells and gastrointestinal (GI) hormones
Loss of ileocecal valve

The major complication of extensive enterectomy is loss of absorptive surface area, but intestinal adaptation and redundancy of function will allow the majority of patients to tolerate this insult. In individuals where the adaptive process is insufficient, chronic high diarrheal output and dehydration will ensue. Evaluation of individuals suffering from this acquired SBS will require detailed dietary histories to determine the effects of specific foods and liquids on fecal output. The major goal of intestinal rehabilitation is to prevent the need for parenteral fluid support by modifying diet to maximize nutrient absorption while minimizing malabsorption, most frequently of simple carbohydrates and water which are often ingested in excess amounts by individuals suffering from SBS and chronic dehydration. Emphasis on monitoring fluid balance is essential in this early SBS physiology, as significant short and long term morbidity and mortality can be associated with volume loss, electrolyte shifts, and acute and chronic dehydration. Diarrhea in SBS originates in the vasculature prior to being pumped into the gastrointestinal lumen where it will fail to be reabsorbed in the second half of the GI tract due to anatomic loss. Diarrhea in SBS results in malabsorption of macro and micronutrients, electrolytes, and water. This malabsorption of water and electrolytes leads to voluminous diarrhea, hyponatremia, and hypokalemia [6]. The careful management and appropriate nutritional support is needed for these patients, especially in the case of parenteral nutrition. Success of interventions to manage SBS will immediately impact the daily input and output tally, and will also provide early guidance on the individual with high losses who will require intravenous support. These individuals who fail to respond adequately to oral rehydration solution and dietary modifications (separating solid foods from liquids at mealtime) will likely require either daily intravenous volume support or TPN. Permanent TPN support is needed in patients with less than 120 cm of intestine without colon in continuity and less than 60 cm with colonic continuity [7]. TPN administered as in home option not only avoids prolonged hospitalization but also delays the need for surgery [8].

Volume and Calorie Replacement

TPN can be administered either through central line or a peripherally inserted central catheter (PICC), but generally central line is preferred. Central TPN provides the patient with the majority of nutrients including carbohydrates, protein, fat, vitamin, salt, and trace elements. The subclavian vein is the usual site for catheterization. During the first few days volume can be adjusted to 30–40 mL/kg body weight/day depending on the patient hydration status [9]. The well-nourished adult patient should receive 25–30 kcal/kg BW/day via central access and for a malnourished patient it can be up titrated accordingly. For postoperative patients, 35–45 kcal/kg BW/day might be necessary. Composition of TPN is given in Table 9.2.

Amino acids in the parenteral nutrition solution are tailored to maintain a stable nitrogen balance. The amount of protein in TPN typically varies from 0.8 to 1.5 g/kg/day according to the need of the patient. In rare situations where IBD has resulted

Table 9.2 Composition of TPN

Nutritional element	Volume	Calories	Amount	Function
Amino acids	1000	340	85 g in well nourished	Stable nitrogen balance
			To 125 g in high catabolism state	
Dextrose	1000	340	100 g and adjusted according to the serum glucose level	Important source of calorie
Fat	500	550	50–70 %—linoleic acid	Source of essential fatty acid
			5–10 %—linolenic acid	
Glutamine supplementation			0.3–0.5 g/kg/day	Intestino-trophic effect, decrease IL6 production
Trace elements and vitamin			5 mL/day	Integral part of human enzymes function and for the synthesis of DNA

in a protein losing enteropathy/colopathy, higher amounts of amino acid support can be considered (i.e., 2.0 g/kg/day). Postoperative patients and individuals with an increased catabolic metabolism (i.e., extensive mucosal ulceration) require more amino acids in their TPN compared to well-nourished patients. Amino acid support in TPN includes glutamine, which is felt to be an essential amino acid for gut health, as it plays a significant role in providing energy to enterocytes [10]. Additional components of TPN support include high concentrations of dextrose, an inexpensive and important source of calories and available in varied concentration.

Use of Teduglutide in Conjunction with TPN

Teduglutide is a glucagon-like peptide 2 analogue, which was developed to promote intestinal adaptation, restoration of intestinal integrity, and ultimately decreasing the need for TPN support in patients suffering from SBS. It is a subcutaneously administered synthetic protein which differs from native GLP2 analogue by the substitution of glycine for alanine at the second position from the N-terminus. This substitution makes it resistant against dipeptidyl peptidase-4 and thereby increasing its half-life from 60–90 min (native GLP-2) to 180–330 min (Teduglutide) [11]. Studies have shown that teduglutide improves intestinal function and structural integrity through significant intestinotrophic and pro absorptive effects [12]. Repeated administration of teduglutide is thought to stimulate intestinal epithelial crypt cell growth and reducing enterocyte apoptosis which results in increased villous height, plasma Citrulline concentration, and lean body mass. Additional

mechanisms attributed to teduglutide which may benefit SBS include decreased gastric acid secretion and gastric emptying and stimulating intestinal blood flow thereby increasing the intestinal barrier function, leading to improved fluid and nutrient and absorption [13]. Teduglutide was shown to be well tolerated and effective in CD patients on TPN in the pivotal trial and improved disease activity scores in 44 % of CD patients in a separate study who were not on TPN [14].

Primary Therapy: Gut Rest in Patients with Severe Illness

Primary medical therapy for CD relies on induction treatment with steroids and/or biologic anti-TNF agents, and maintenance treatment with immunomodulators and biologics (anti-TNF agents and alpha4 integrin inhibitors). Therapy with aminosalicylates and antibiotics have been used in specific subgroups of patients, but failed to show the success of immunomodulators and biologic agents. Despite the increase in available medical options, there are a subset of patients who may fail to respond to medical therapy. Surgical intervention for medically refractory inflammatory disease will often be considered in CD, but is more ominous in patients with both small and large bowel involvement as the colectomy and end ileostomy will not guarantee clinical remission. Relapse of CD will generally be followed by small bowel resection, which raises the potential for SBS in patients who have failed all medical options going on the require additional surgery [15]. In this rare, but very serious cohort of CD patients, bowel rest with TPN to provide exclusive nutritional support can achieve clinical remission in up to 77 % of individuals. The exact mechanism of a TPN/bowel rest treatment approach is not precisely known, and mechanisms have been hypothesized to include reduction in enteric flora dependent on enteral intake as a "prebiotic" substrate, decreased production of gut hormones, decreased autonomic stimulation, and simply halting the digestive process. In the setting of enterocutaneous fistula, the interruption of oral intake and digestion will typically cause a decrease in the secretion of digestive fluids (i.e., pancreatic enzymes and bile) into the lumen which can potentially track into the fistula, effectively "digesting" the wound and preventing it from healing. Maintaining an NPO status will often allow enterocutaneous fistula to demonstrate spontaneous closure. In the setting of partial small bowel obstruction, maintaining an NPO status will decrease abdominal pain. Thus TPN and bowel rest promotes resolution of CD symptoms such as diarrhea, abdominal pain, and abdominal masses; also it improves sense of well-being and improves the body weight [16]. Attempts to demonstrate and confirm the beneficial effect of TPN in the management of CD have been challenged by the heterogeneity of patients. Greenberg and colleagues at the University of Toronto led a multicenter, prospective controlled trial which failed to demonstrate an advantage of bowel rest using TPN as opposed to good enteral nutrition support. Furthermore, many studies consistently showed that TPN and bowel rest had lower remission rates for penetrating disease, colonic

involvement, or ulcerative colitis. The therapeutic concept of bowel rest in the management of CD has been debated since 1980s, but appears to be limited to a small subset of patients and its clinical benefit does not appear to extend to the majority of patients.

Complications of Parenteral Nutrition

Although TPN is efficacious in malnourished patients and individuals who are not able to sustain themselves through enteral intake, this efficacy comes at the cost of potential complications. Complications of TPN are numerous including gastrointestinal, infectious, metabolic, vascular, biliary, and mechanical issues can contribute to the patient's morbidity and potentially mortality (Table 9.3).

Mechanical Complication

Parenteral nutrition requires venous access either peripherally or centrally. Cannulation of the subclavian, internal jugular, or femoral veins with advancement of the catheter to the superior or inferior vena cava achieves central venous accesses. Peripheral or midline catheter placement is considered to be peripheral access, and these access points do not have sufficient flow to allow for the high osmolality of TPN. Cannulation success depends upon the anatomic site and the operator's experience. Mechanical complication is often related to the catheter itself, but this complication can include catheter misplacement upon insertion, thrombotic occlusion, and catheter displacement or migration after it was placed.

Catheter misplacement: Improper placement of the central line may cause serious conditions like pneumothorax, vessel injury leading to hemothorax, brachial plexus injury, and even cardiac arrhythmia [17]. Malposition, arterial puncture, and subcutaneous hematoma are the other potential complications of catheter misplacement [18].

Thrombophlebitis/venous thrombosis: Intravenous catheters can cause endothelial injury and inflammation of the vessel. This can lead to disruption of the intimal layer of the vein, thrombosis, and accumulation of a fibrin sheath along the outer surface of the catheter [19]. Serious consequences can include intracardiac thrombosis and pulmonary embolus. Venous thrombosis may lead to distension of neck veins, swelling of the face and ipsilateral arm and can eventually progress to superior vena cava syndrome [20].

Nonthrombotic occlusion: Due to precipitation of various elements in TPN, nonthrombotic occlusion of the vessel lumen can occur [21]. It is both time consuming and challenging to differentiate between thrombotic and nonthrombotic occlusions.

Table 9.3 Complications of parenteral nutrition

Overview of parenteral nutrition related complication:
I. Mechanical/vascular
Catheter misplacement—organ damage
Embolization
Thrombus formation
Nonthrombotic occlusion
Thrombophlebitis
II. Infectious
Catheter related bloodstream infection (CRBSI)
Septicemia
III. Metabolic
Fluid imbalance
Electrolyte/mineral imbalance
Acid–base disturbance
Glucose intolerance
Metabolic bone disease
Refeeding syndrome
IV. Biliary
Cholestasis
Cholangitis
Cholecystitis
Cholestatic liver dysfunction
Cholelithiasis
V. Nutritional
Trace metal deficiency
Vitamin deficiency
Malnourishment leading to Immunosuppression
Fatty acid deficiency
VI. Gastrointestinal
Villous atrophy—In animal studies

Vanishing venous access: Long term TPN (administered through a central catheter) predisposes the patient to central vein stenosis or thrombosis. Repeated venous access can cause exhaustion of veins [22].

Air embolism: A rare, but serious, complication of air being inserted into the catheter while on TPN must be closely monitored [23].

Infective Complication

This is the second most common complication during parenteral nutrition treatment. Infective complications can arise from many potential sources. Microbes introduced through the catheter pose a significant risk for infection while infection through parenteral nutritional solutions is not as common.

Catheter related bloodstream infection (CRBSI) and catheter related bacteremia are characterized by positive cultures from peripheral blood and the indwelling catheter both producing positive cultures with the same microorganisms, without any other known source of infection [24]. Infection of the catheter insertion site is defined by the presence of inflammation, pus, quantitative culture of the proximal catheter segment and/or tip of the catheter with $>10^3$ colonies or semiquantitative culture of >15 colonies from fluid uptake from the insertion site [25] (Table 9.4).

Attempts to salvage catheters which have become contaminated have been attempted. Instilling catheters with a high concentration antibiotic solution in sufficient amounts to fill the lumen of the catheter (i.e., antibiotic lock) has proven to be successful in infective complications, most commonly with *Staphylococcus epidermidis*. Antibiotic sensitivity data from organisms isolated from blood cultures is the preferred strategy, and this approach has been most successfully used with vancomycin. There are case reports of antibiotic locks successfully rescuing catheters using amikacin, imipenem, aminoglycosides, and amphotericin, although the majority of gram negative and fungal line infections will require catheter removal [26].

Table 9.4 The wide spectrum causative organisms

Gram Positive
Staphylococcus aureus
Enterococcus durans
Streptococcus viridans
Peptostreptococcus
Propionibacterium
Gram Negative
Escherichia coli
Pseudomonas aeruginosa
Klebsiella pneumoniae
Enterobacter cloacae
Fungus
Candida albicans
Candida glabrata
Candida guilliermondii
Mycobacterium
Mycobacterium avium
Mycobacterium chelonae
Mycobacterium fortuitum

Metabolic Complications

Early metabolic complications of the TPN treatment can include fluid volume overload, hyperglycemia, hypokalemia, hypophosphatemia, hypomagnesaemia, refeeding syndrome, hypochloremic acidosis, and other electrolyte abnormalities.

Hyperglycemia/glucose intolerance: Initial hyperglycemic reactions can develop due to the bolus of TPN and potassium infusions. The patient must be closely monitored for hyperglycemia during this process. Chromium is an important micronutrient that becomes deficient in a long term TPN patient. Chromium has been shown to play a role in glucose intolerance, gestational diabetes, and type 2 diabetes mellitus. Studies have shown that 200 mcg/day of supplemental chromium improves the glucose variables, such as HbA1c, in those who are mildly glucose intolerant [27].

Refeeding syndrome: Malnourished patients who receive TPN are at an increased risk of developing refeeding syndrome [28]. Refeeding syndrome can be defined as the fatal shifts in fluids and electrolytes that may occur after receiving artificial feeding after a period of calorie deprivation/starvation (which may be as short as 5 days). This sudden intracellular shift is caused by hormonal and metabolic changes, leading to fluctuations in electrolyte levels and potentially serious clinical consequences including cardiac arrhythmias, mental status changes, coma, seizure, and cardiac failure. The hallmark electrolyte abnormalities associated with refeeding is hypokalemia, which is mechanistically believed to result from glycemia induced insulin secretion that causes potassium to shift into the cells, leading to loss of potassium in the extracellular spaces. Insulin also promotes synthesis of protein, glycogen, and fat, and this acceleration of metabolism can lead to rapid cellular uptake of magnesium, potassium, and thiamine, potentially causing an insufficiency of these nutrients. Thiamine (Vitamin B1) is an important coenzyme in carbohydrate metabolism and its rapid deficiency can result in Wernicke's encephalopathy (ocular abnormalities, ataxia, confusion state, hypothermia, and coma) or Korsakoff's syndrome (retrograde and anterograde amnesia, confabulation) [29]. Therefore customized TPN formulations which include extra thiamine, potassium, magnesium, and phosphorus are required to avoid refeeding complications during the initiation of enteral nutrition. Likewise, careful, close monitoring of these electrolytes is required to ensure no.

Fluid/electrolyte disturbance: Fluid overload is a common side effect of TPN infusion ranging from ankle edema to pulmonary congestion. Closely monitoring the fluid intake and urine output is important during the entire course of TPN treatment. Special attention to fluid and electrolyte balances should be implemented in patients with renal disease and in pregnant women [30] (Table 9.5).

Table 9.5 Electrolyte imbalance during TPN [30–32]

Problem	Symptom	Management
Hyperkalemia	Nausea, slow heart rate, confusion, restlessness, diarrhea, abdominal distention	Potassium should be withheld from TPN solution until underlying problem is resolved. If severe, treat with prescribed IV doses of bicarbonate, glucose, insulin, and calcium for cardioprotective effect
Hypokalemia	Flaccid muscles (atonia), malaise, fish mouth breathing, tachycardia, and arrhythmia	Regular monitoring of serum K+ and adjustments of potassium in TPN
Hyperosmolar, Hyperglycemic, Nonketotic coma (HHNK)	Hyperglycemia, absence of ketone bodies, confusion, eventually coma can rapidly advance to death if untreated	Stop hypertonic infusion and hydrate with large amounts of hypotonic solution, IV insulin with careful monitoring. Electrolyte abnormality has to be corrected
Hypomagnesemia	Hallucinations, vertigo, ileus, and hyperreflexia	Additional amounts of magnesium sulfate can be added to TPN solution
Hypercalcemia	Extreme thirst, increased urination, confusion	Treated on the basis of calcium level
		Mild <12 mg/dL: hydration
		Moderate 12–14 mg/dL: Hydration and Bisphosphonates
		Severe >14 mg/dL: Iv isotonic saline, Calcitonin, and Bisphosphonates
Hypocalcemia	Paresthesias, confusion, positive Chvostek's sign, tetany	Daily calcium supplement in solution
Hypermagnesemia	Headache, Loss of Deep tendon reflex, hypocalcemia	Magnesium replacement
Hyperphosphatemia	Hyperreflexia, carpopedal spasm	Limit phosphate intake, phosphate binders
Hypoglycemia	Diaphoresis, confusion, agitation	Dextrose infusion
Hypermagnesemia	Blocks neuromuscular conduction, depresses the conduction system in heart	Furosemide may increase its excretion
		Calcium gluconate antagonize the neuromuscular blocking effect
Hypophosphatemia	Mental deterioration	Additional amounts of phosphate added to daily TPN regimen based on levels
	Lethargy that may lead to coma. Hemolytic anemia may also occur	

Hepatobiliary Complication

Liver complications are common during TPN treatment (25–75 % of all TPN patients) and can occur within several days after initiating therapy with the majority of these hepatobiliary complications being mild and transient. The most severe hepatobiliary complication is TPN associated cholestasis (TPNAC). This potentially fatal condition can develop rapidly and will progress to fibrosis, cirrhosis, and portal hypertension. TPNAC has been linked to inflammatory activity and there is a case report of a CD patients resolving cholestasis following treatment initiation with the anti-TNF antibody infliximab [33]. Cholestasis and biliary sludge can lead to acalculous cholecystitis, due to a lack of gallbladder stimulation by cholecystokinin. Factors associated with liver dysfunction include deficiency of essential fatty acids, imbalances in the composition of amino acids, fat deposition in the liver, deficiency of choline, and absence of enteral nutrition intake [34].

Micronutrient Malnutrition

Micronutrient malnutrition can occur during long term TPN management. Chronic TPN can lead to deficiency of trace metals, fatty acids, and electrolytes, leading to the respective manifestation of deficiency symptoms. Table 9.6 shows the common micronutrient deficiencies seen in IBD patients and their clinical features.

Table 9.6 Micronutrient deficiencies

Nutrient	Clinical feature of its deficiency
Vitamins	
• A	Night blindness, dry skin and hair
• B1	Beriberi, Wernicke Korsakoff syndrome
• C	Anemia, bleeding gums, dry hair, easy bruising, nosebleed
• D	Muscle weakness, osteomalacia, rickets in children
• E	Defective platelet aggregation, Hemolysis
Chromium	Alopecia, T-cell disturbance, perineal acrodermatitis, Reduced serum alkaline phosphate levels
Selenium	Reduced levels of glutathione peroxidase level, myocarditis, and myalgia
Molybdenum	Color blindness, irritability, and tachycardia
Essential fatty acids	Dermatitis, lackluster skin and increased rate of trienoic: Tetraenoic plasma fatty acids
Zinc	Xerosis, acne, Eczema, alopecia, stomatitis, affects hunger sensation leading to anorexia, diarrhea
Choline	Fatty liver, hemorrhagic kidney necrosis

Gastrointestinal Complication

Long term TPN has been shown to cause intestinal villi hypoplasia in experimental rats. Studies on the human gastrointestinal tract have also shown a significant decrease in jejunal villi with TPN, although not to the same extent as in rodents [35]. Intestinal immunological cells have also been shown to express decreased homeostatic cellular activity and to decrease in number within patients on parenteral nutrition [36].

Costs of TPN and Quality of Life

Patients being treated with parenteral nutrition have been shown to benefit the most from a HPN treatment plan when comparing cost effective interventions due to its success in keeping the patient out of the hospital. Based on national data, HPN is 5 times more expensive than home enteral nutrition [2]. Direct costs for HPN includes the infusion pump, administration kits, catheter dressing kits, and nutrient solution. In 1992, Medicare allowance for HPN was estimated to be between $238 and $390 per day, or $86,000–$140,000 per year. It is important to know that these charges do not include medical visits, laboratory monitoring, home nursing support, or hospitalization for complications during parenteral nutrition. Medicare paid 80 % of these charges and remaining 20 % was provided by a secondary insurance provider or by the patient [37]. In European countries and Canada, the total cost of both home parenteral and enteral nutrition is covered by the National Health Services [2]. In order to be the most cost effective, it has been shown that following periodic reassessment for compliance, determining the appropriateness of parenteral formulation, infusion regimen, status of intestinal adaptation, and oral nutrient intake are important interventions for HPN patients [38].

As per Jeppesen et al., HPN was associated with a lower sickness impact profile overall, and is associated with a lower IBD Questionnaire score when compared with the patients not receiving HPN [39]. There is a significant improvement in quality of life when patients are transferred to HPN from hospitals [40].

Summary

The appropriate use of TPN in the treatment of IBD is limited to a small number of patients who are challenged with life-threatening complications involving malnutrition, SBS, and severe/refractory inflammation. Given the strong potential for complications and cost, TPN is reserved for situations where enteral nutrition has either failed or is contraindicated. The lack of clear data demonstrating the efficacy of parenteral nutrition and bowel rest as primary therapy for the treatment of IBD has positioned its role as adjunctive and supportive therapy. At the present time, more effective medical treatment options for IBD have decreased the need for TPN as a

rescue modality. Future investigation to further develop new agents which promote intestinal adaptation may decrease the need for TPN support in IBD patients with severe and refractory illness. At present, TPN remains a “last ditch” life saving modality for extremely ill IBD patients with limited medical and surgical options, which can include multi-visceral organ transplantation.

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