



REVIEW ARTICLE

Who Needs a Gut Anyway?

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Abstract

This is an up-to-date review on Chronic Intestinal Failure (CIF) and Parenteral Nutrition (PN) as a management strategy for CIF.

CIF and long-term PN are important subjects, but are superficially covered in undergraduate curricula due to the perception that they are relatively specialist areas. PN, as well as being a form of acute nutritional support, is used as a life-sustaining measure for patients with CIF due to conditions such as bowel ischaemia and Crohn's disease. Currently, around 500 patients receive long-term PN in the UK and the numbers are expected to rise with the aging population¹. It is a costly service, requiring a multidisciplinary team effort, along with high frequency patient-healthcare interaction.

This article aims to discuss the current evidence on the causes, management and prognosis of CIF, with a particular focus on PN as a form of nutritional management. While PN seems to improve the prognosis of patients with CIF from a medical point of view, we will also explore how it affects other aspects of a patient's life, such as their social life and mental health.

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Who Needs a Gut Anyway?

Introduction

This is an up-to-date review on chronic intestinal failure (CIF) and parenteral nutrition (PN) as a management strategy for CIF.

CIF and long-term PN are important subjects but not covered in detail at the undergraduate level due to the perception that it is a relatively specialist area within gastroenterology. However, it is an essential aspect of gastroenterology, which must be appreciated and understood by the medical student, particularly because of its associated mortality and morbidity. As well as being a form of acute nutritional support, PN is used as a life-sustaining measure for patients with CIF due to conditions such as bowel ischaemia and Crohn's disease (CD). In the UK, there are currently around 500 patients receiving long-term home parenteral nutrition (HPN) in addition to oral nutrition and artificial enteral nutrition (EN), and the numbers are expected to rise with the ageing population.¹ It is a costly service requiring a multidisciplinary team effort along with high frequency patient-healthcare interaction. We will discuss the current evidence on the causes, management, and prognosis of CIF, with a particular focus on PN as a form of nutritional management. While PN seems to improve the prognosis of patients with CIF

from a medical point of view, we will also explore how it affects other aspects of a patient's life, such as their social life and mental health.

Methods

Articles on CIF were found through PubMed, MEDLINE, and Google Scholar, their abstracts reviewed and then selected on the basis of their relevance. The following is an example of a search strategy using MeSH headings on Ovid:

1. exp "Parenteral Nutrition, Total"/ or exp "Parenteral Nutrition"/ (21019)
2. exp "Quality of Life"/ (113933)
3. 1 and 2 (333)
4. exp "Parenteral Nutrition, Home"/ (940)
5. 2 and 4 (161)

Limited knowledge of total parenteral nutrition (TPN) meant that background reading and meetings with experts in the field had to be undertaken. A meeting was organized with a specialist nurse who provided background information on the use of TPN in NHS Lothian.

Review articles were useful in providing links to relevant primary literature. References for both primary and secondary literature were shared and organized on an online group which was set up on Zotero.

Chronic intestinal failure

Chronic intestinal failure (CIF) is defined as the long-term inability to sustain development and growth through oral nutrition,² or the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balance.³ The jejunum and ileum are the main absorptive surfaces of the gastrointestinal tract, although iron and calcium are preferentially absorbed in the duodenum. Jejunum and ileum absorb and process most of the ingested nutrients including amino acids, glucose, fat, electrolytes, vitamins, and bile salts. Approximately 1 m of functioning small intestine must remain to allow adequate absorption of nutrients. Surgery or disease that leaves less than this causes short bowel syndrome (SBS) and intestinal failure.⁴ Chronic intestinal failure was considered a fatal state or one with poor prognosis, before life-saving techniques such as artificial enteral nutrition (EN), parenteral nutritional (PN) support, and bowel transplant surgery were developed.² Such treatments have given CIF patients a better prognosis, although complications and side effects, such as diarrhoea, infections, and sepsis, may occur.⁵

Causes of CIF

Causes of CIF include congenital defects, dysmotility, obstruction, surgical resection, or disease-associated loss of absorption^{3,5}

The most common causes are SBS and motility disorders.

SBS, which may result from congenital abnormalities or bowel resection, is the most common cause of CIF.^{6,7} In 1993, a multicentre survey in Europe showed that SBS represents the largest subset of patients (35%) that require HPN.⁸ The length of the small intestine in healthy state ranges from 275 to 400 cm.⁶ SBS occurs when less than 200 cm of small bowel remains.⁸ A study conducted by Nightingale *et al.*⁹ showed that the most common underlying diagnosis of SBS is CD; a relapsing inflammatory disease in which 50% of patients experience intestinal complications within 20 years.¹⁰ Patients with a jejunostomy and a jejunal length of less than 100 cm are more likely to need long-term parenteral support due to excessive secretory loss.¹¹ However, oral nutrition is usually sufficient for patients with 50 cm or more of small intestine if the colon is intact and remains in continuity.⁶

Chronic intestinal failure can also arise from motility disorders such as extended Hirschsprung's disease and chronic intestinal pseudo-obstruction (CIPO). CIPO is a rare, disabling disorder in which total bowel length remains normal, but its function is compromised by an impairment of gastrointestinal peristalsis that mimics mechanical obstruction.¹²

Predominant causes of CIF in children are

congenital disorders such as intestinal atresia, gastroschisis, and microvillus atrophy.^{5,7} Other causes of CIF include small-bowel tumour and irradiation.⁷

Artificial enteral nutrition

Artificial EN involves the provision of nutrients through the gastrointestinal tract and is given when a patient cannot ingest, chew, or swallow food, but can still digest and absorb nutrients.¹³ EN is a common method of nutritional supplementation for patients with intestinal failure, both in hospitals and the community.¹⁴

Indications

EN is used in patients with a partially functioning gastrointestinal tract due to both chronic and acute conditions, and ensures that they receive sufficient nutrition while simultaneously stimulating the bowel during recovery.¹⁴ Artificial EN is the first-line nutritional support for critically ill patients in general as well as for those who have undergone surgery.¹⁵ It is recommended that these patients should receive EN as tolerated, and PN only when EN does not meet the requirements for longer than several days to a week, depending on the previous nutritional state¹⁶; this also applies to paediatric patients.¹⁷

Benefits

Several reviews suggest that EN, rather than PN or surgery, is the preferred method of countering malnutrition in acute and chronic intestinal failure.^{16,18} Parenteral nutrition is costly, invasive, and associated with physical, social, and mental complications.¹⁹ For example, the lack of exposure to nutrients and the resulting diminished release of bile and enzymes causes atrophy and inflammation of the intestine, which in turn leads to fatty liver and elevation of liver enzymes.^{4,18} This is more significant when part of the bowel is bypassed. There is also increased infection risk when nutrient-rich solutions are directly infused into the bloodstream.⁴ There is open access from the skin into the bloodstream, which increases the risk of developing bloodstream infections, especially with skin flora. Compared with EN, intestinal transplantation is costly and associated with high morbidity and mortality.¹⁹

Although septic complications due to the translocation of bacteria or bacterial products across a starving atrophied intestinal mucosa have been frequently reported, these are less likely to occur with EN.²⁰ Furthermore, probiotics in feeding solutions have been claimed to support the growth of beneficial intestinal microflora but this is still an area of investigation.¹⁸

Kompan *et al.*²¹ conducted a prospective,

randomized controlled trial involving 28 patients who were treated in intensive care for multiple injuries. They found that patients who started EN immediately after admission were less likely to develop multiple organ failure and intestinal permeability than patients starting EN after 24 hours. This study was limited due to a small sample size and the absence of blinding. The cause of illness and extent of damage to patients before treatment may also have varied greatly. Many studies have provided data suggesting that early EN may have beneficial effects on successful coverage of nutritional requirements, infectious complications, and length of stay in the ICU or hospital.

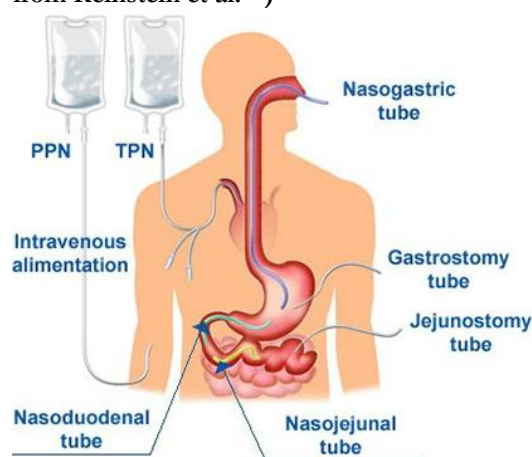
Where possible, and clinically indicated, EN should be employed. Even in intestinal failure, it is advantageous to give continuous EN at slow speed. Sometimes, patients eat small meals 5 or 6 times a day and, if insufficient, they may receive supplementary nocturnal tube feeding. Complementary PN is indicated in cases where the above measures fail.

Administration

There are several ways to access the stomach and intestines in EN. The less invasive methods involve nasogastric, nasoduodenal, and nasojejunal tubes (Figure 1). These methods are used for short-term EN or when the physical condition of the

patient makes it unsafe to perform more invasive procedures. Nasal tubes can be inserted and advanced down into the stomach, the duodenum, or the jejunum. The feed is administered continuously (small amount of feed given without break throughout the day) or cyclically (for instance, every 12 or 24 hours).

Figure 1: Routes of Administration (Adapted from Reinstein et al. 47)



The decision of whether to use continuous or cyclical feeding depends on the patient's physical condition, nutritional requirements, and degree of rehabilitation.²² Patients with CIF who are still able to absorb part of their nutritional requirements can cover their needs with additional nocturnal tube feeding. Some patients insert a thin nasogastric tube themselves and remove the tube during the day successfully with training. A more invasive method of EN involves enterostomy feeding tubes. Gastrostomy or jejunostomy feeding involves accessing the stomach or the jejunum endoscopically and inserting a tube

directly through the gastric or jejunal and abdominal wall. Enterostomy feeding tubes are mostly used when EN is required for at least 8 weeks and when the patient is in a suitable condition for a more invasive procedure.²² Cachectic patients should not receive enterostomy tubes because of a strongly elevated risk of leakage of nutrients into the abdominal cavity. This is due to the lack of adhesion of the stomach or jejunum to the inner side of the abdominal wall in truly cachectic states.

Invasive and less invasive methods of EN exist to provide nutritional support for patients with relatively intact gastrointestinal organs in a more physiological way. Guidelines on different EN regimens are constantly being updated.²²

Complications

There is a risk of feeding tube displacement in EN. Therefore, a small aspirate sample of gastric or intestinal fluid is taken to check the position of the tube end before administering any fluid. Nasogastric feeding can be associated with “dumping syndrome”, which occurs when the patient is suddenly overloaded with feeding formula. This happens when the tube bypasses the stomach, which normally acts as a reservoir for large volumes of food entering the gastrointestinal system.^{22,23}

Parenteral nutrition

Parenteral nutrition is a form of nutritional support for severely malnourished patients who cannot be fed adequately by oral or enteral feeding. In contrast to enteral feeding, the nutrients are administered intravenously. Parenteral nutrition that provides total nutrition including protein, vitamins, energy, electrolytes, and trace elements is referred to as total parenteral nutrition (TPN) (Figure 2).^{5,24}

Figure 2. Total Parenteral Nutrition⁴⁸



Patients requiring long-term parenteral nutrition may be treated at home. Patients must receive training and they or a family member should be competent in managing home parenteral nutrition (HPN) feeding procedures.²⁵ They are supported by specialist nutrition nurses and dietitians and are informed of potential complications.²⁶ Medical problems should be managed by a dedicated physician, closely working together with other members of a nutritional support team consisting of physicians, surgeons, dietitians, nurses, and pharmacists. Physiotherapists and

psychologists also contribute to the care of patients requiring nutritional support. The nutritional support team plays a crucial role throughout the duration of patients' treatment with PN. The team follows the patients closely from the beginning of their training for PN administration to the rest of their treatment to ensure that PN is being administered safely and providing sufficient amount of nutrients. They play a significant role in providing patients and families with necessary mental and emotional support as well as supporting their physical health needs.

Indication

Parenteral nutrition is indicated for patients with either acute or chronic intestinal failure, in cases where they cannot receive or tolerate enteral feeding. Acute conditions include functional obstruction of the gastrointestinal tract (e.g. paralytic ileus), abdominal sepsis, and acid–base, electrolyte, or mineral imbalance. Parenteral nutrition is sometimes only required until intestinal function has recovered sufficiently for patients to meet their full nutritional requirements by oral or enteral route.^{5,24}

Composition of PN solutions

Solutions for PN may be adjusted to each patient's requirement, but most patients use standardized PN solutions.^{5,24} Each standardized PN solution usually comes in a

2–3 L bag containing a balanced mixture of essential and non-essential amino acids, glucose, fat, electrolytes, trace elements, and vitamins. It typically provides 1800–2500 kcal of energy and 10–14 g of nitrogen.^{5,24,27} Standardized PN solutions are supplied by the industry. However, customized PN solutions may differ in composition, depending on the patient's nutritional requirements.²⁷ When not supplied by the industry, PN solutions are usually and preferably made under sterile conditions in the pharmacy.

Administration

Parenteral nutrition solutions are administered intravenously into a large central vein with a high blood flow, normally into the superior vena cava (SVC). This is to minimize damage to the vessel wall resulting from the solution's high osmolarity. In smaller veins, the endothelium will rapidly become irritated by the hyperosmolar PN-mixture, leading to inflammation (phlebitis), which often results in secondary thrombosis and infection, unless the catheter is inserted in a peripheral vein but threading the tip of the catheter into the superior caval vein.²⁷ Catheter-related blood stream infections need to be prevented by employing strict aseptic techniques during insertion and care of the catheter. Access to the SVC is generally obtained through the subclavian vein or

indirectly via a peripherally inserted central line. The position of the catheter is checked by radiography or ultrasound, and a (computerized) pump is connected to the catheter and the PN solution bag. In long-term HPN, the pump controls the volume of nutrients administered over 12–15 hours, and it is claimed that this prevents metabolic disturbances while allowing mobility of the individual during the remainder of the day.^{5,24}

Complications

1. Infection

A clinical trial of 395 patients undergoing surgery showed that infection is one of the most frequent complications of PN, occurring in 14.1% of patients, with *Staphylococcus aureus* and coliforms being the most common infectious organisms.²⁸ Infection specifically occurred in mildly malnourished patients. Benefits of PN were only observed in severely malnourished patients, who exhibited fewer infectious complications than the control group. Infection rates increase when care of the feeding line and the insertion site is poor.

2. Catheter-related problems

Insertion of the venous catheter may damage structures adjacent to the veins, such as the pleural membrane and other smaller veins, causing pneumothorax and haematoma.²⁷ However, in contrast to

infection, a prospective single-centre study by Cotogni *et al.*²⁹ showed that catheter dislocation is uncommon and occurred in only 5% of patients.

3. Thrombophlebitis

Thrombophlebitis refers to the inflammation of the vein leading to thrombus formation. It is common in PN patients, especially if the catheter is inserted into a vein with low blood flow. Signs of thrombophlebitis are erythema and tenderness over the area of the cannulated vein. If major thrombophlebitis is suspected, an ultrasound is performed to confirm the diagnosis, and anticoagulants such as heparin, urokinase, or plasminogen activator can be administered to dissolve the clot.⁵ If unresolved, a new catheter is inserted into a healthy vein.

4. Metabolic complications

The most common metabolic complication in PN is hyperglycaemia. This is treated either by replacing 30% of glucose calories with fat or preferably with insulin treatment.³⁰ Other metabolic complications include hypokalaemia and hypophosphataemia, which are common in severely malnourished patients who are refeed after a long period of starvation.^{5,24}

5. Reduced quality of life

Studies on the quality of life (QoL) of PN

patients provide conflicting evidence. Patients' accounts vary greatly, depending on the severity of their complications and family environment.²⁷ In a study conducted in 48 HPN patients by Persoon *et al.*³¹ involving surveys and structured open-ended interviews, 92% reported at least one psychosocial problem while 50% reported at least one physical problem. A review of 38 articles by Baxter *et al.*³² investigated the QoL of patients receiving HPN due to underlying diseases such as cancer or intestinal failure. Collectively, this showed a mixture of positive and negative impacts of HPN on aspects such as emotional function, social function, nutritional status, and employment status. The different impact of HPN on QoL depends on the severity of the underlying indication for their HPN.³²

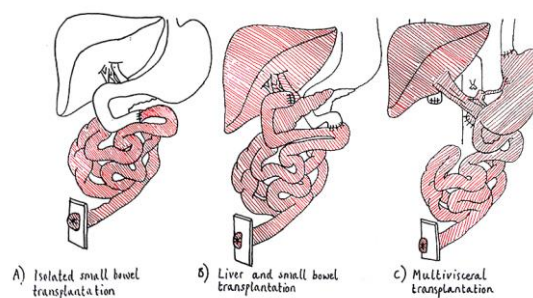
6. Negative emotions

A non-structured interview study showed that a third of HPN patients experience anxiety with regard to treatment complications.³³ They may also feel anger and grief when others are unable to understand their condition.²⁸ Another study demonstrated that 80% of HPN patients experience depression as a consequence of losing their social life, independence, and physical mobility. Additionally, they experience problems with care providers and other complications of HPN.²⁶

Intestinal transplantation

Intestinal transplantation consists of the implantation of an intestinal allograft in patients with CIF, with the intention of restoring intestinal function.³⁴

Figure 3. Intestinal Transplantation (Adapted from Nickkholgh *et al.*⁴⁹)



Indications

Intestinal transplantation is considered to be the most appropriate alternative to PN once PN-associated complications arise. On the basis of a prospective 5-year study in which the survival rates and causes of death of HPN patients were investigated, it was concluded that desmoids (fibrous neoplasms) and complications of HPN are the key indicators for life-saving intestinal transplantation.³⁵ However, absolute criteria for intestinal transplantation are still under debate and not defined.

Operative techniques

Various operative techniques are used for intestinal transplantation, each selected according to the specific needs of the individual patient.

The most common procedure, usually used for adults, consists of transplantation of an isolated segment of small bowel. It is used for patients with CIF and preserved liver function, whereby the entire small bowel and the colon (if unhealthy) is resected down to the pelvic brim. Intestinal and vascular anastomoses are then made and an ileostomy is performed to allow post-operative follow-up.³⁶

Children often require a combined liver and small-bowel transplant as a result of the presence of severe or even end-stage liver disease,³⁷ which usually occurred in children with SBS due to necrotizing enterocolitis, especially in premature babies. In a study that analysed a registry data of 923 intestinal transplantation patients, it was found that 55% of adults received intestinal transplants alone compared with 37% of children under 18 years old. While a spread of ages is not provided in this study, data were acquired from 61 programmes, suggesting that the study included a representative sample of patients.³⁸ Besides children, combined liver and small-bowel transplantation is also given to adults with intestinal failure or end-stage liver failure due to long-term PN. Those with concomitant liver failure and portomesenteric thrombosis may also be candidates for such treatment. Combined liver and small-bowel transplantation can either be performed with organs from the same donor or from 2 separate donors for

each organ. In smaller patients, a combined reduced-size liver and small-bowel graft including the left, right, or extended right lobes of the liver may be of benefit.³⁷

Multivisceral transplantation (the transplantation of 3 or more abdominal organs en bloc)³⁹ is indicated for patients with complex abdominal pathology, such as massive gastrointestinal polyposis, traumatic loss of the abdominal viscera, and extensive abdominal desmoid tumours.³⁷

Perioperative treatment

Perioperative treatment is vital to improve the chances of success for surgery. Intestinal transplantation only came into frequent use in the early 1990s with the introduction of tacrolimus, an immunosuppressive agent that minimizes the risk of organ rejection.³⁷ Tacrolimus is used by itself or in conjunction with other immunosuppressors or corticosteroids.³⁶

Enteral nutrition is started as soon as possible after transplantation and an intestinal biopsy is performed every 48 hours to detect signs of organ rejection. Finally, about 3 months after surgery and complete recovery, ileostomy closure is carried out and the central venous catheter is removed when the patient no longer relies on PN.³⁶

Prognosis

The prognosis for CIF patients receiving HPN is dependent on a number of factors, the most significant being the nature of the underlying disease.⁴⁰

In general, patients taking PN have a 1-year survival rate of 86%, which decreases to 77% and 73% at 3 and 5 years, respectively.⁴¹ A study was conducted to assess the clinical outcome in HPN patients with different underlying disorders. More than 80% of patients with CD, a non-malignant disease, survived for 5 years or more, whilst only 20% of patients with cancer survived for 1 year or longer.⁴² In another study, it was found that PN patients with CD had a mean 10-year survival rate of 88%, and those with intra-abdominal desmoids in familial polyposis had a variable outcome depending on the stage of the tumour.⁴³ 95%, 85%, and 65% of patients survived up to 10 years, for mild, moderate, and severe stage of disease respectively. Of all the underlying conditions, systemic sclerosis led to the poorest prognosis, with only 57% of patients surviving beyond 3 years.

Children commonly have a better outcome with PN than adults. In one study, it was shown that the probability of survival in children on PN, with various underlying conditions, amounted to 97%, 89%, and 81% at 2, 5, and 10 years, respectively.⁴⁰

However, the majority of subjects in this study had primary digestive disorders (76%), which generally have a lower mortality rate than non-primary digestive disorders. Wales *et al.*⁴⁴ investigated mortality among young children with SBS and in other surgical neonates. SBS patients had a fatality rate of 37.5%, over 2 years, compared with 13.3% in patients undergoing surgery without SBS.

In 2005, an observational study was published addressing the results of intestinal transplantation in patients with CIF. In a cohort of 923 patients with intestinal grafts, Grant *et al.*³⁸ found a 1-year survival rate of 81%. This is particularly encouraging because of the potential complications of intestinal transplantation, including significant expression of histocompatibility antigens and colonization with microorganisms.^{45,46}

Currently, there is an ongoing debate as to whether intestinal transplantation is as effective as HPN. The debate revolves around which category of patients may benefit from transplantation. In addition, the question remains as to how to select these patients and which facilities and experience should be present in the centres where they are treated. There may be a category of patients in which transplantation is superior to HPN. Examples are children with CIF combined with end-stage liver failure and in situations where chronic

access to the blood stream for PN has become impossible.

Conclusion

CIF, the long-term inability of the body to maintain a healthy internal environment through nutrition, can be caused by a variety of underlying malignant and non-malignant diseases. PN is a lifesaving therapy in the management of CIF and has significant beneficial effects on longevity and overall quality of life, despite being lower than in a healthy control group. We have explored the most recent literature on the physical, psychological, and social side effects of PN

as a treatment for CIF, and compared it with other management strategies such as EN and bowel transplantation. Although PN is associated with a number of significant side effects such as infection, thrombophlebitis, and metabolic complications, it is currently the preferred method of nutritional support in patients whose bowel fails to absorb sufficient nutrients to maintain normal body composition and function. Combined enteral and parenteral nutrition does appear to have a similar or better prognosis than bowel transplantation.^{38,41-43}

Learning points

What is already known

- Chronic intestinal failure (CIF) is the long-term inability of the body to maintain a healthy internal environment through nutrition.
- The nutritional need in CIF can be managed by enteral tube feeding, parenteral nutrition, or bowel transplant.
- Each method of management is associated with several side effects and complications, some more serious than others.

What this study adds

- Where possible, enteral nutrition should be encouraged at all times as it can speed up the recovery process by physiologically stimulating the bowel and successfully covering the nutritional requirements with least side effects.
- Parenteral nutrition, while associated with a number of significant physical, social, and psychological side effects, is the preferred method of nutritional support in patients whose bowel is not viable for enteral nutrition.
- Bowel transplantation, although potentially curative, is associated with significant mortality and must be applied only in carefully selected cases.
- Patients on long-term HPN are supported by a dedicated nutritional support team, who play a crucial role in supporting patients not only medically but also emotionally and mentally.

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