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Intestinal failure in adults and children

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ABSTRACT

Intestinal failure (IF) is rare, but it represents one of the most complex medical-surgical management pathologies, both in adults and children. The first-line treatment is parenteral nutrition (PN). However, new alternatives in the field of intestinal rehabilitation have opened up in recent decades, with the rise of multidisciplinary teams and the development of new hormone therapies as the first non-symptomatic approach to IF.

Keywords: Intestinal failure. Short bowel syndrome. Intestinal Rehabilitation Unit. Teduglutide. Parenteral nutrition. Intestinal transplant.

DEFINITION, CLASSIFICATION AND ETIOLOGY

In 2015, the European Society for Clinical Nutrition and Metabolism (ESPEN) established the current definition of intestinal failure (IF) as "the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth" (1). In addition, the functional and pathophysiological classification of IF was formalized (Table 1). In Europe, the prevalence of chronic parenteral nutrition (PN) dependent IF is estimated to

be 5-20 cases per million inhabitants (2).

Short bowel syndrome (SBS) is the most common cause of chronic IF (excluding tumor related causes) in both adults and children (75 % and 50 % of cases respectively), followed by alterations in intestinal motility and diseases of the intestinal mucosa. Intestinal fistulas are a rare cause in adults and children (2).

ADAPTATION AND INTESTINAL REHABILITATION

Intestinal adaptation is the compensatory phenomenon that occurs in the years following an intestinal resection and is characterized by structural and functional changes in the remaining intestine, which result in an increase in its absorptive capacity (3).

The most relevant clinical factors to achieve digestive autonomy are the length of the residual intestine, the preservation of the ileocecal valve, having a normal gastrointestinal motility and the absence of severe liver disease. In addition, a younger age at the time of intestinal resection and the diagnosis of necrotizing enterocolitis in pediatric patients are associated with a better prognosis (4). With regard to biomarkers related to increased intestinal adaptability, plasma citrulline may be useful. A concentration below 20 μmol/l predicted the presence of permanent IF in a study of 57 adult patients (sensitivity: 92 % and specificity: 90 %) (5).

The goal of intestinal rehabilitation is the restoration of the loss of intestinal function and weaning of PN. This includes different approaches such as nutritional (optimization of oral diet, enteral or parenteral nutrition), pharmacological (antisecretory, antidiarrheal, prokinetic, and oral or intravenous supplements of liquids, vitamins and minerals) and surgical approaches (autologous intestinal reconstruction techniques and intestinal transplantation). Currently, studies show that the multidisciplinary management of IF by a specialized medical-surgical team is associated with an increase in survival and a lower risk of complications related to PN, such as venous thrombosis, infections related to central venous catheter and hepatopathy associated with IF (6). The criteria for the referral of patients with IF to an Intestinal Rehabilitation Unit for evaluation of intestinal transplantation are currently established in both adults and children and are summarized in table 2 (7,8).

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NUTRITIONAL TREATMENT

Enteral nutrition

The main stimulus for intestinal adaptation after a surgical resection is the introduction of enteral feeding as soon as possible. The choice of substrate type, quantity and route of enteral nutrition administration should be individualized in each patient.

With regard to the type of substrate, oligomeric and lactose-free formulas are not indicated in adults. Except for intestinal resections that affect the duodenum or proximal jejunum, as macronutrients are absorbed mainly in the first 100-150 cm of the jejunum. With regard to lipids, it is not clear whether a high-fat diet has more advantages than a diet with a lower lipid intake. Fat is the most high-calorie macronutrient, but it delays gastric emptying and produces early satiety. On the other hand, medium-chain triglycerides do not supply essential fatty acids. However, they can be absorbed directly into the portal circulation, unlike long-chain fats, and their administration is beneficial to patients with a continuous colon (9). In infants, breast milk contains components that facilitate intestinal adaptation mechanisms (growth factors, amino acids, immunoglobulins, etc.) and breastfeeding may decrease the risk of liver disease associated with IF (10). When breastfeeding is not possible, there is no consensus on whether to use whole protein formulas with a greater trophic potential on the intestine, protein hydrolysate or amino acid formulas. Elementary formulas, such as breastfeeding, are associated with a shorter duration of parenteral support and a lower risk of allergies (11).

Regarding the mode of administration, continuous flow enteral feeding improves the absorption of macronutrients compared to fractional oral administration. However, the latter entails more physiological cyclic changes in the levels of the various gastrointestinal hormones needed for adaptation. An optimal strategy could be the combined administration of continuous enteral nutrition at night and fractional oral nutrition during the day (10). Moreover, the location and length of the intestinal resection will determine the type and severity of micronutrient deficiency (vitamins and minerals). Monitoring of micronutrient levels in the blood on a regular basis is indicated and supplementation, when necessary. Patients with ileal resections may often need vitamin B12 supplements. Sublingual and intranasal administration of this vitamin has recently become available, although there are insufficient data on its effectiveness.

Parenteral nutrition

The individualized intravenous administration of water, electrolytes and macro and micronutrients is fundamental for the treatment of IF, pending intestinal adaptation. However, a 95 % probability of permanent bowel failure has been reported after two years of PN dependence in adults (12). Patients receiving parenteral support require special monitoring, including follow-up measures regarding hydration status, body weight, intestinal losses and blood and urinary profiles. It is desirable to reduce, as far as possible, the number of daily hours of infusion of PN to ensure hepatoprotection and a better quality of life of the patient. Water and electrolyte requirements vary depending on the age, weight and clinical status of each patient and are modified when there are increased losses. Energy needs should be estimated, taking into account the basal metabolism, the needs of the disease and the physical activity of the patient.

Dextrose is the main source of carbohydrates. Glucose intakes range from 3-6 g/kg/day in an adult to a maximum of 15 g/kg/day in the nursing infant. The protein intake must constitute between 12 and 16 % of the total caloric intake and protein nitrogen must be optimized to ensure sufficient energy intake. A recent study showed that parenteral-infused amino acids can provide up to 17 % less protein substrate compared to dietary proteins (13). The recommended maximum daily intake of lipids is 2-3 g/kg/day for children. In adults, less than 1 g/kg/day is recommended if lipid emulsions rich in linoleic acid (omega-6) are used to prevent liver toxicity (14). There is a correlation between a high intake of polyunsaturated fatty acids and liver involvement, mainly cholestasis. The presence of phytosterols in lipid emulsions of plant origin is also related to an impaired liver function. In contrast, the possible protective role of including lipid solutions is being investigated, such as α-tocopherol as an antioxidant. For this reason, the most recent interest is directed to new lipid emulsions, including olive oil, fish, soy and/or medium chain triglycerides. All current lipid emulsions are safe and there is still no conclusive data on the clinical advantages of some compared to others (15). However, the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) recommends the use of lipid emulsions with fish oil, especially if a prolonged use of PN (16) is expected. The use of fat-soluble and water-soluble vitamins and trace elements in parenteral solutions remains

controversial. Supplementation is recommended if there is no or very limited oral intake.

It should be borne in mind that the long-term use of PN may be associated with catheter-related complications (infections, thrombosis and occlusion), metabolic complications (hepatopathy, bone disease and renal failure) and a deterioration in the quality of life. Thus, the dependence on parenteral support should be reduced as much as possible and suppressed when possible.

Non-hormonal drug treatments

Table 3 shows the main non-hormonal drug treatments used in IF (2,9,10,11).

Hormonal drug treatments

The most promising results are those related to teduglutide, which is a subcutaneous glucagon-like peptide 2 (GLP-2) analogue approved for the treatment of patients with CIS over one year of age and dependent on PN. Repeated and continuous administration of exogenous GLP-2 promotes the growth of the mucosa of the small intestine. However, all changes in intestinal morphology reverse rapidly after cessation of treatment. Its clinical effectiveness was analyzed in a phase III placebo-controlled study (STEP), in which a response of at least a 20 % reduction in PN volume was achieved (17). The STEPS-2 and STEPS-3 open-label extension studies with two and three year olds, respectively, were designed to evaluate long-term effectiveness (18,19). The rate of responders was 63 % at week 24 and 93 % at two years. Preclinical pediatric outcomes have also been promising (20).

Other modified GLP-2 analogues, such as glepaglutide, are currently being investigated with the aim to increase the half-life and therefore gain the advantage of weekly or monthly administration. Other growth factors and trophic hormones that have been studied with controversial results include growth hormone, epidermal growth factor, insulin-like growth factors and glutamine.

Surgical treatment

The surgical objective in IF is to preserve as much functionality of the intestine as possible. Many patients with intestinal resections suffer from complications arising from the disease

itself or from previous surgeries, such as anastomosis dehiscence, intestinal obstruction, abscesses or intestinal fistulas. An early surgical approach using routine techniques can significantly improve bowel function (15). In addition, it is important to remember that patients with IF require the placement of central catheters and sometimes, the technique may be more complicated if there are associated thrombotic complications. The introduction of interventional radiology techniques has greatly favored this point.

In later phases, the restoration of intestinal transit is particularly beneficial, especially if the distal segment corresponds to the small intestine and/or ileocecal valve. In addition, the inclusion of the colon improves absorption and regulates motility. The technique of *refeeding* allows the physiological pathway to be imitated, collecting the losses of the proximal stoma and infusing them by the distal lumen, until it is possible to finally reestablish the transit (21).

There are different techniques to promote the intestinal adaptation process (22,23):

1. Techniques to improve intestinal peristalsis
    - Simple enteroplasties.
    - Longitudinal intestinal elongation/LILT/Bianchi's technique: consisting in the unfolding of the leaf of the mesentery of the dilated loop through the creation of an avascular plane. Two isopropulsive, vascularized and complete hemiases are obtained, together with the longitudinal division of the dilated intestinal loop, which are subsequently placed in continuity (Fig. 1).
    - Transverse serial enteroplasty/STEP: multiple non-complete cross-sections are performed in alternate directions by means of an automatic stapler, preserving a minimum luminal diameter of 2 cm and generating a zigzag pattern (Fig. 2).
2. Techniques to prolong intestinal transit

There are several techniques for this purpose, including the interposition of antiperistaltic segments of the small intestine, interposition of colon segments, the creation of recirculating handles and the creation of valves that mimic the effects of the ileocecal valve. Pacemakers have also been placed in the distal intestine that counteract the generation of electrical impulses from the proximal duodenum to slow the transit.

3. Techniques to increase the absorptive surface. Neomucosa

It has been experimentally proven that the intestinal mucosa grows on intestinal defects covered with patches of serosa or the abdominal muscle wall. This has also been investigated with non-biological materials, such as Dacron® and Goretex®.

4. Intestinal transplant

This represents the last therapeutic alternative in patients with severe complications due to PN, such as irreversible liver damage related to parenteral nutrition or loss of central venous accesses (24). According to recent data from the World Registry of pediatric intestinal transplantation, the overall survival of the patient per year and at five years is 72.7 % and 66.1 %, respectively, and 57.2 % per year and 48.8 % at five years for the graft. The highest survival per year was associated with previously untransplanted patients and grafts that included the liver (25).

There are different modalities:

- Isolated intestinal: the graft includes the entire small intestine, with or without the colon, which is controversial. This is indicated in patients with intestinal failure that is not associated with liver damage or gastric motility disorder.
- Hepatointestinal: indicated in IF associated with irreversible liver damage. Currently the graft includes the pancreatic duodenal block complex, which avoids biliary complications.
- Standard multivisceral: the graft includes three or more abdominal viscera and is currently applied when the graft contains the stomach or part of it. This is indicated in cases of intestinal failure in which the stomach and/or pancreas have to be removed at the receptor.
- Modified multivisceral: consists of the transplantation of the stomach, duodenopancreatic complex and intestine without the liver. Unlike the standard multivisceral, portal venous return occurs through an anastomosis to the native portal vein of the receptor. Intestinal continuity is achieved with a proximal gastrogastric anastomosis and an ileocolic anastomosis distal to the ileostomy.

CONCLUSIONS

The management of IF has made great strides in recent years and PN remains the first-line treatment. However, digestive autonomy is more feasible thanks to advances in intestinal

rehabilitation, especially in the last two decades with the emergence of hormonal treatments. At this point, studies of the cost-effectiveness of new therapies are a priority. Intestinal transplantation is reserved as an extreme therapeutic alternative for patients with severe complications associated with PN.

Gene therapy aimed at intestinal stem cells, the application of devices capable of inducing autologous bowel growth and the creation of intestinal tissue-by-tissue engineering are therapeutic options that could improve the prognosis of patients with IF in the future.

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Table 1. Functional and pathophysiological classification of intestinal failure

Functional classification of intestinal failure
Type I: relatively common and self-limiting, which can occur after a wide range of abdominal surgeries or other pathologies that affect proper gastrointestinal function. Only parenteral nutrition (NPT) is required for short periods of time Type I: less common but more serious. It includes infectious, metabolic and nutritional complications that follow extensive surgical resections. NPT is required for weeks or months Type III or chronic bowel failure. It requires prolonged or permanent NPT due to its severity
Pathophysiological classification of intestinal failure
Intestinal failure can be classified into five major pathophysiological conditions, which may originate from various gastrointestinal or systemic diseases: 1. Intestinal dysmotility 2. Extensive small bowel mucosal disease 3. Intestinal fistula 4. Short bowel 5. Mechanical obstruction

Table 2. Criteria for referral to Intestinal Rehabilitation Units

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1. Irreversible IF
2. Complications related to NPT
   - Irreversible liver damage
   - Loss of deep venous accesses by thrombosis (two or more of the four upper deep venous accesses)
   - Severe sepsis related to deep venous accesses
   - IF leading to early death: ultra-short intestinal bowel, congenital intestinal mucosa disorders and poor quality of life as in some cases of chronic intestinal pseudo-obstruction
3. Request by the patient or family

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Table 3. Medical therapies for intestinal failure

Class and examples	*Comments*
Anti-secretory agents	
Histamine H2 receptors (e.g., ranitidine) Proton-pump inhibitors	It reduces hyperacidity after intestinal resection Recommended for use at least six months after surgery The optimal duration of treatment is unknown Related to increased respiratory and gastrointestinal infections
Loperamide	It slows down intestinal transit and reduces fecal excretion of sodium and water in adults with a short bowel and ostomy No evidence of benefits in children
Bile acid sequestrates (e.g., cholestyramine)	Used for bile salts malabsorption after ileal resection It can reduce fat absorption No evidence of benefits in children
Octreotide	Used in adults with high losses due to ostomy and for short periods of time Risk of cholelithiasis No evidence of benefits in children
Racecadotril	It inhibits gastrointestinal hypersecretion It has not been evaluated for intestinal failure
Pancreatic enzymes (substitute treatment)	For cases associated with pancreatic insufficiency
Prokinetic agents	Little evidence of effectiveness Trial treatment with prokinetics is recommended in patients with intestinal

	motility dysfunction No evidence of benefits in children
Cisapride	Useful in delaying gastric emptying in patients with foregut anomalies
Erythromycin, clarithromycin	Demonstrated effectiveness
Cyproheptadine	It improves gastric accommodation and stimulates appetite
Prucalopride	Serotonin receptor agonist with demonstrated effectiveness
Antiemetic agents	Little evidence of its effectiveness Neurological and cardiac effects No evidence of benefits in children
Antibiotic agents	Useful in bacterial overgrowth Not routinely recommended in cases of short bowel with preserved colon Recommended periodic antibiotic cycles in cases of chronic intestinal motility dysfunction Indiscriminate use increases the risk of fungal infection, antimicrobial resistance, and *Clostridioides difficile* infection
Probiotic agents	No evidence of benefits Risk of sepsis

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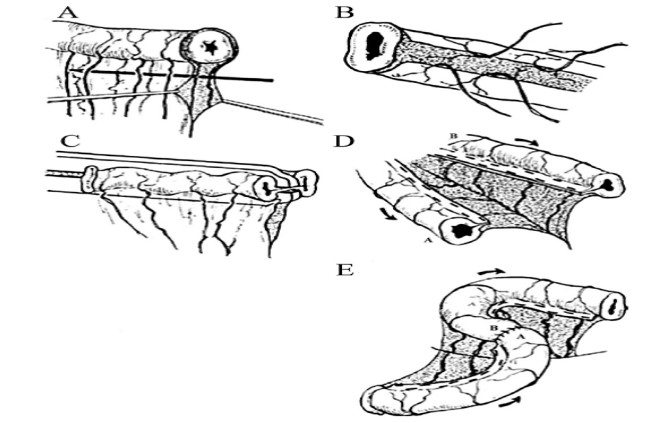

Fig. 3. Bianchi procedure or LILT. (A) separating the two leaves of the mesentery of the isolated small bowel segment. (B) Creating a funnel on the mesenteric site for dividing the small bowel. (C), (D) Separating the small bowel by introducing a surgical stapler. This can also be done by cutting the bowel half. (E) The two bowel loops are then anastomosed together in a isoperistaltic manner (Obtained from Bianchi A, [35]).

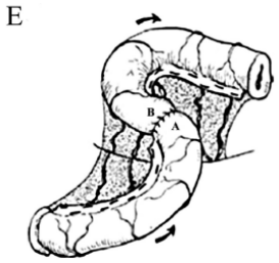

Fig. 1. Longitudinal intestinal elongation or Bianchi procedure. Based on the mesentery splitting principle to achieve two isopropulsive hemiases, vascularized and complete.

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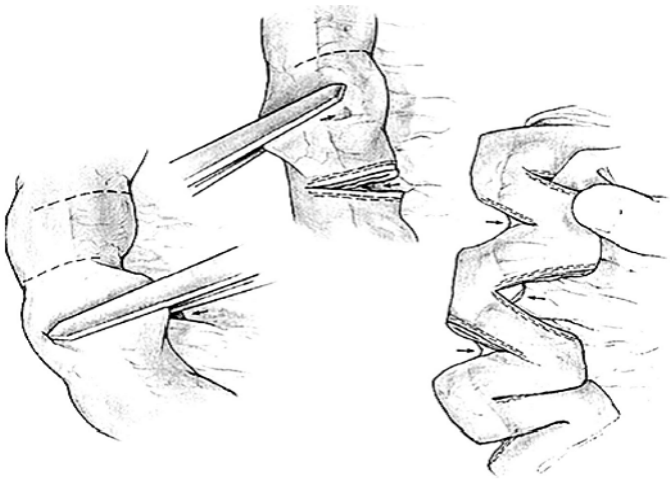

Fig. 4. Schematic view of STEP. Perpendicular to the longitudinal axis, a stapler line is made preserving a 2 cm luminal diameter. After multiple staples, the bowel is lengthened (Adapted to Kim et al. [53]).

Fig. 2. Serial transverse enteroplasty (STEP). Intestinal lengthening is achieved from multiple incomplete cross sections, without manipulating the mesentery or exposing the intestinal lumen.