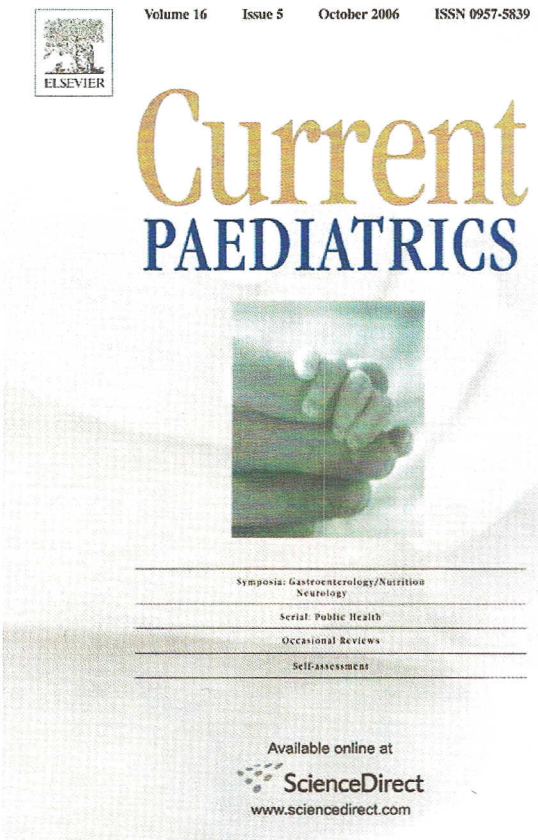

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Chronic complications of short bowel syndrome

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Intestinal failure;
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Summary
Short bowel syndrome (SBS) is a clinical condition characterized by a loss of intestinal length or competence resulting in a malabsorption of nutrients, fluids, and/or electrolytes. The likelihood that enteral autonomy can be restored in a patient with SBS is influenced by the length, location and function of the remaining bowel. SBS is a complex disease and encounters multiple acute and chronic complications. The real challenge in SBS comes from managing the many chronic complications that arise. The most common problems that can be found in the acute or chronic stages are diarrhoea, fluid and electrolytes abnormalities, and nutrient loss. Many of the chronic complications come from the use of total parenteral nutrition (TPN), including catheter-associated infection, venous thrombosis, metabolic complications, anaemia, hepatic dysfunction, demineralization of bone and rickets. Complications not related to TPN include bacterial overgrowth, nutritional deficiencies and renal stones. It is our aim to review the evidence found in the literature regarding the risk factors, diagnosis and management of chronic complications of SBS.

Definition

Short bowel syndrome (SBS) intestinal failure results from surgical resection, congenital defect or disease-associated loss of absorption, and is characterized by the inability to maintain protein-energy, fluid, electrolyte or micronutrient balances when on a conventionally accepted normal diet.[1] Regardless of multiple attempts to describe this syndrome on the basis of the intestinal length, there appears to be no minimum small bowel length to define SBS. The essential defect is the lack of adequate mucosal surface to achieve enteral nutrition autonomy. The degree of malnutrition depends not solely on the length of the intestinal resection but also on the location of resection, the presence or absence of a competent ileocecal valve, the presence or absence of a colon and the functioning capacity of the remaining intestine.[2]

The intrinsic characteristics of the remaining intestine after small bowel resection are crucial in determining the functional ability of the bowel. There are three major types of bowel anatomy in SBS: (1) jejunocolic anastomosis, (2) end-jejunostomy, and (3) jejunoileal anastomosis. The third group is the least common, but is associated with the best overall prognosis.[3] Patients at the greatest nutritional risk generally have a duodenostomy or a jejunoileal anastomosis with <35 cm of residual small bowel, jejunocolic or ileocolic anastomosis with <60 cm of residual small intestine, or an end jejunostomy with 115 cm of residual small bowel.[4,5]

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Complications

Watery diarrhoea fluid losses and electrolyte imbalance

The management of SBS is a multistage process. It begins with a process of total parenteral nutrition (TPN) followed by a combination of enteral feedings with intravenous (IV) nutrition, continuous enteral feeding only, weaning to bolus feeding and solid foods, and finally dietary modification alone.[6]

As enteral feedings are tolerated, TPN should be weaned proportionally; fluid and electrolyte imbalance is frequent in the process of weaning TPN. Careful monitoring of the hydration status, serum electrolytes, throughout this time is important to provide adequate replacement fluid. Excessive osmotic fluid load is the most common cause of diarrhoea. The use of continuous enteral feedings, altering enteral type formula to a low carbohydrate, high fat formula, or diluting enteral formulas may be beneficial in diminishing the output. While solid food feedings are traditionally initiated with high carbohydrate foods, children with SBS do better with high-fat, high-protein foods. Meats are probably the best food group to start, as they provide a less osmotic load to the small bowel and the fat provides an additional stimulant for the intestinal adaptation.[2,6–8] Frequent small meals are recommended to avoid diarrhoea.

A small number of patients tolerate the necessary enteral feedings to maintain nutritional balance, but still need extra fluids for the maintenance of a good hydration and electrolyte balance. In these patients, normal or half-normal saline, as well as different IV electrolytes (potassium, sodium and bicarbonate) can be added to the patient's formula to meet their fluid and electrolytes requirement.[2] Continued sips of oral rehydration solution (ORS) through the day is also useful to maintain a positive fluid balance. If the enteral route cannot meet the patients' fluid needs, extra IV fluids may be used at night.

Small bowel bacterial overgrowth (SBBO)

The human gastrointestinal tract typically contains 300–500 bacterial species. Most bacterial species are acquired during the birth process when microbes from the mother and surrounding environment colonise the gastrointestinal tract of the infant.[9] Although some changes to the flora may occur during later stages of life, the composition of the intestinal microflora remains relatively constant. In the normal gastrointestinal tract, bacterial counts increase and a gradual transition from aerobic to anaerobic organisms occur in more distal segments of the intestine. Because of peristalsis and the anti-microbial effects of the gastric acid, the stomach and the proximal intestine contain relatively low numbers of microbes, 10^3–0^5 CFU/ml. They usually are lactobacilli, enterococci, oral streptococci and other Gram-positive aerobic or facultative anaerobes reflecting the bacterial flora of the oropharynx. The ileum has higher bacterial numbers (10^8 CFU/ml) than the upper bowel and is considered a transition zone preceding the associated lymphoid tissue.[10,11] The colon is the primary site of microbial colonization because of slow turnover and is characterized by large numbers of bacteria (10^{10}–10^{12} CFU/ml) containing anaerobes such as *Bacteroides*, *Porphyromonas*, *Bifidobacterium*, *Lactobacillus* and *Clostridium*. Most of the bacteria in the intestine are facultative organisms and provide multiple beneficial functions related to intestinal epithelial turnover, motility, blood flow and mucosa-associated lymphoid tissue. Enteric bacteria have the role of deconjugating bile salts as well as producing micronutrients, such as vitamin B12, folate and vitamin K. Anaerobic bacteria of the colon metabolize unabsorbed dietary sugars, which are converted into short-chain fatty acids and used as energy source by the colonic mucosa. They are also important in the metabolism and activation of some medications such as sulfasalazine.[9,12,13]

SBBO is a fairly common and treatable complication of paediatric SBS. SBBO is defined as an excessive increase in the number of bacteria ($>10^5$ CFU/ml) in the upper gastrointestinal tract, leading to the development of symptoms.[2] Aetiologic factors in the development of SBBO can regroup in three different categories: (1) anatomic abnormalities: prior abdominal surgical procedures, loss of the ileocecal valve, fistulas, strictures, and blind loops. (2) Functional abnormalities: intestinal dysmotility, reduction of gut-associated lymphoid tissue after resection, inflammatory conditions. (3) Multifactorial: malnutrition of the host abnormalities of the immune system, cirrhosis.[6,11] With the preservation of the ileocecal valve, it would be reasonable to expect that the absorption of fluid or nutrients would improve by delaying the transit time of the intestinal contents. This concept has not been supported by experimental evidence.[14] Although the ileocecal valve forms a physical barrier to reflux colonic material into the small bowel, results from both experimental animal models and human studies have failed to identify a major effect on either bacterial translocation or SBBO after resection of the valve.[15]

Symptoms of SBBO result mainly from nutrient malabsorption due to inflammation of the intestinal epithelium, a varying degree of villous atrophy and increase bile salt deconjugation, resulting in steatorrhea and malabsorption of fat-soluble vitamins. Abdominal cramping, bloating, diarrhoea, dyspepsia, and/or weight loss are the most common symptoms. A gradual development of abdominal distention with a succussion splash may be seen on physical examination. Carbohydrate malabsorption caused by SBBO can contribute to diarrhoea as a result of increased formation of short-chain organic acids that in turn increase the osmolarity of the intestinal fluid. anaemia may also result from malabsorption, occult blood loss (bleeding from anastomotic ulcerations), and/or vitamin B12 deficiency. In addition, patients who were previously stable on their enteral nutrition regimen may fail to advance enteral feedings for a period of time.[2,12,16,17] D-lactic acidosis is a neurological complication of SBBO with symptoms of ataxia, delirium, seizures and eventually coma. D-lactic acidosis is a result of bacterial activity and carbohydrate overload to the colon resulting in accumulation of D-lactate in the blood. D-lactic acidosis should be considered in patients who have metabolic acidosis with high serum anion gap and normal lactate level. Development of the syndrome requires the following conditions: (1) carbohydrate malabsorption with increased delivery of nutrients to the colon, (2) colonic bacterial flora of a type that produces D-lactic acid,

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(3) ingestion of large amounts of carbohydrate, (4) diminished colonic motility, allowing time for nutrients in the colon to undergo bacterial fermentation, and (5) impaired D-lactate metabolism.[18] Systemic distribution of bacterial antigen–antibody complexes may cause rashes, arthritis, and nephritis. Colitis or ileitis may also occur due to SBBO. This may resemble Crohn's disease, although a diffuse inflammatory picture is more common.[2,17]

Although diagnosis of bacterial overgrowth is classically based upon demonstration of an increase of bacterial content by aspiration and direct culture of jejunal contents, these methods have several limitations that include the potential contamination of the specimen by oropharyngeal bacteria during intubation, and the fact that the bacterial overgrowth may be patchy and therefore missing by a single aspiration.[19] For this reason, a variety of non-invasive diagnostic tests have been devised for the diagnosis of SBBO; these are based largely on the excretion of hydrogen in exhaled breath generated by the metabolism of carbohydrate by the luminal bacteria.[20] The hydrogen breath test is the most common alternative method to diagnoses SBBO. It uses carbohydrate (glucose, lactulose and xylose) as a substrate. Markedly elevated fasting breath hydrogen levels (>20 ppm) or a rapid rise in breath hydrogen (increase of exhaled H_2 >10 ppm greater than baseline on two consecutive samplings), is suggestive of bacterial overgrowth.[6] False-positives can occur with rapid intestinal transit with subsequent metabolism of the glucose within the colon by normal colonic bacteria.[21] To overcome this limitation, lactulose, a non-absorbable disaccharide, has been advocated because it will detect the presence of SBBO anywhere in the small bowel. In general, both the glucose and lactulose hydrogen breath tests have shown unsatisfactory abilities to predict SBBO.[22] The hydrogen breath test is also limited in 15–27% of the population who produce methane instead of hydrogen after ingestion of lactulose, a limitation that may be overcome by simultaneous measurement of expiratory methane.[19] Other alternative tests have been used: ^{14}C, ^{13}C, D-xylose breath test, measurement of products of luminal bacteria metabolism in urine (increase indicans) or blood (increase D-lactate levels), the ^{14}C-glicocholate breath test and the string test all have disappointing results.[13] Small bowel biopsies demonstrating inflammatory changes, villous blunting and the presence of adherent or intracellular bacteria support the diagnosis of pathologic SBBO, especially when the small bowel is dilated, motility is poor or there is a partial obstruction.

Treatment of SBBO commonly involves rotating broad-spectrum oral antibiotics, which are often effective in reducing the number of bacteria. Ideally, the choice of the anti-microbial agent should reflect in vitro susceptibility testing but is sometimes impractical because many different bacterial species with different antibiotic sensitivities coexist.[23] A trial of empiric antibiotics can be used with success, evaluating the improvement of symptoms associated with SBBO (lessening of diarrhoea, weight gain, reduction of gas-related symptoms). Antibiotic treatment must cover both aerobic and anaerobic bacteria. Because the underlying mechanism(s) responsible for causing SBBO are unlikely to change in SBS patients, a periodic treatment of 7–14 days/Q month or more continuous use of alternate antibiotics may be necessary. The most frequently used are metronidazole (10 mg/kg/q8 h), trimethoprim–sulfamethoxazole (5 mg/kg/q12 h), oral gentamicin (5–10 mg/kg/q8 h), extended-spectrum penicillins, and cephalosporins. When significant intestinal inflammation is present, anti-inflammatory therapy with sulfasalazine or corticosteroids may be used. In older children, who often withhold large volumes of stool, regular toileting and weekly flushing with polyethylene glycol solution via the enteral feeding tube may help.[24] Normal gastric acid secretion decreases pathogenic bacterial proliferation, and if suppressed, may predispose to SBBO. The use of anti-motility agents such as loperamide may exacerbate bacterial overgrowth and may be contraindicated in patients whose gastrointestinal motility is already delayed. Surgical corrections of anatomic abnormalities, such as stricture, fistula, diverticula, are often helpful. Segments of dilated, poorly peristaltic bowel may be corrected with lengthening operations such as Bianchi—Step enteroplasty.[25]

Probiotics are one of the newest therapies for SBBO. Probiotics (*Lactobacillus* and *Bifidobacterium*) are live microorganisms, that when ingested, colonize the intestine, establish themselves as part of its flora, and are beneficial to human health by preventing or treating certain pathologies.[26] Several mechanisms of actions have been identified with the use of probiotics: production of substances that prevent bacterial proliferation, competitive inhibition of bacterial adhesion, competitive consumption of nutrients, modification of toxin receptors through enzymatic mechanisms, and stimulation of the immune system. Lactobacillus species produce nutrients, mainly short-chain fatty acids, and anti-microbial products such as pyroglutamate. They also remove potentially toxic substances from the intestine.[2,27,28] All of these factors lead to the observation that probiotic therapy in SBBO may be effective in reducing the use of antibiotic therapy and in controlling symptoms related to bacterial overgrowth. The term of prebiotic (fructooligosaccharides, galactooligosaccharides and inulin) refers to a non-digestible food ingredient that selectively targets the growth and/or activity of one or a limited number of bacteria in the colon, and has the potential to improve the host's health. The combination of probiotics and prebiotics is called symbiotic therapy, and has been used to improve intestinal function and decrease bacterial overgrowth in SBS.[29]

Nutritional support is an essential part of the management of SBBO because it can produce malnutrition and could be the cause of failure to wean off TPN in children with SBS.[16] Carbohydrate restriction with an increase in fat and protein intake is useful to decrease the development of gas-related symptoms and osmotic diarrhoea in children because most bacteria ferment only carbohydrate and fat is an excellent caloric source.[2,13] In patients with significant bile acid losses, a high fat diet may increase stool output and increase the risk of oxalate nephropathy.[30]

Complications of parenteral nutrition

The main complications commonly associated with long-term use of parenteral nutrition are:

1. Central venous catheter (CVC)-related infections.
2. Venous thrombosis.
3. Intestinal failure associated-liver disease (IFALD).

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CVC-related infections

CVC-related infections are a major cause of morbidity and mortality in the United States. Coagulase-negative staphylococci, *Staphylococcus aureus*, aerobic Gram-negative bacilli and *Candida albicans* are the most common causes.[31] In neonates episodes of sepsis were associated with a 30% increase in the bilirubin levels.[32] With the first-line infection, 90% of infants may develop cholestasis.[33] CVC infections may be suspected if the child develops clinical signs such as fever, metabolic acidosis, thrombocytopenia, glucose instability or a new onset of reoccurring vomit. After appropriate cultures of blood and catheter samples are performed, empirical IV anti-microbial therapy should be started and changed to a narrower-spectrum therapy once the infecting microorganism(s) has(have) been identified. The duration of therapy should be guided by the organism identified. Fungal CVC infection or persistent pyrexia with positive blood cultures after 48 h of appropriated antibiotics are indications to remove the CVC.[34] CVC infections may result from either poor catheter care technique or bacterial overgrowth. The former appears more common even in patients in whom enteric organisms are found to cause CVC infection. A careful analysis of catheter care technique should always be the first step to reduce or prevent CVC infections.

Central venous thrombosis (CVT) and pulmonary embolism (PE)

CVT and PE are potentially fatal conditions in patients dependant on parenteral nutrition occurring in 39% of children.[35] Although venous thrombosis is a common sequela of central venous catheterization, the vast majority of patients remain asymptomatic. Clinical symptoms of CVT are swelling in the neck, face or limbs, prominent superficial veins or pain on starting TPN. CVT is confirmed using echocardiography Doppler ultrasound, computed tomography or venography. Symptoms of PE vary from none to severe, such as tiredness, chest pains, dyspnoea, hemoptysis, and syncope. Spiral computed tomography is a safe stand-alone test for diagnosis of PE. Recurrent episodes of line infections with repeated CVC changes frequent blood sampling and concentrated glucose solutions predispose to CVT. Acute symptomatic thrombosis may be treated with thrombolytic agents, but anti-coagulation remains the most common therapeutic approach.[34,36] Some children (regardless of rigorous care and aggressive strategies to prevent CVC infection) may develop impaired venous access and need referral for intestinal transplantation.[37]

IFALD

IFALD is a major cause of death in children with SBS. The incidence increases in inverse proportion to age.[38] IFALD develops in 40–60% of infants who required long-term TPN for intestinal failure and 15–40% of adults on home parenteral nutrition.[39] Approximately, 15% of patients who receive prolonged TPN for > 1 year will developed end-stage liver disease (ESLD), which is associated with 100% mortality within 2 years of onset. The combination of chronic inflammation and intestinal failure appears to be necessary for the development of ESLD with prolonged TPN.[40]

The hepatic dysfunction can present a broad spectrum of pathologic entities, including cholestasis (more common in infants 40–60%), steatosis (more common in adults 40–55%), biliary sludge, cholelithiasis, fibrosis and cirrhosis.[39]

Many reports have found that prematurity and/or small for gestational age infants with SBS are the main causes in the development of liver disease, supporting the hypothesis that IFALD is largely attributable to physiological immaturity of the hepatobiliary system.[41,42] Total bile salt pool, hepatic uptake, synthesis of bile salts and enterohepatic circulation are reduced in prematures.[43]

SBBO and CVC infections, especially with Gram-negative organisms, release endotoxins activating multiple pro-inflammatory mediators (including tumour necrosis factor) that interfere with the function of hepatocyte membrane transporters, can result in increases in levels of liver test and jaundice.[44,45] Intestinal stasis with subsequent SBBO has been associated with IFALD and is probably related to the reduction of bile flow, production of secondary bile salts and sepsis from bacterial translocation.[39]

Lack of enteral feedings with subsequent reduction of gastrointestinal hormones such as cholecystokinin (CCK), motilin, glucose-dependant insulinotropic polypeptide, secretin, pancreatic polypeptide, glucagons and vasoactive intestinal peptide may reduced gallbladder contractibility and the development of intestinal stasis.[39,46]

Disrupted enterohepatic circulation caused by ileal disease, resection and lack of enteral nutrition with a subsequent reduction of hepatocellular bile acid, bile secretion, and gallbladder contraction increases the likelihood of progressive liver injury.[42,47]

Components of TPN with a deficit of amino acids (taurine or cysteine) or excessive lipids have been related with IFALD. Taurine is one of the main bile acid conjugates in neonates. Taurine increases bile flow and protects against toxic bile salts, such as lithocholic acid, which has shown to produce bile duct hyperplasia, gallstone formation and intrahepatic cholestasis.[48] Controversial reports exist about the benefits of taurine supplementation.[49] The use of > 1 g/kg/day of lipid infusions have been associated with chronic cholestasis.[47] Excessive intake of long-chain polyunsaturated fatty acids with subsequent lipoperoxidation,[50] accumulation of phospholipids[46] or phytosterols[51] has been suggested as possible mechanisms of IFALD.

Biliary disease (sludge, gallstone, acalculous cholecystitis) may also occur in patients who are dependant on parenteral nutrition. As many as 20% of infants receiving PN developed cholelithiasis. A combination of malabsorption of bile acids, altered bilirubin metabolism and gallbladder stasis secondary to reduction in CCK and other gut hormone production are important factors in the aetiology of cholelithiasis.[52]

Parenteral nutrition with excessive glucose intake may induce insulin resistance and subsequent steatosis[53]

Prevention of IFALD can be achieved with: (1) aggressive enteral feedings ensuring at least 20–30% of total daily caloric intake through the enteral route (promotes enterohepatic circulation, decrease biliary disease and stimulate the release of gut hormones). (2) Prevention of

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sepsis (the most important strategy) with a rapid response to the treatment of CVC infection and bacterial overgrowth. (3) The new pediatric parenteral solutions that provide appropriate amino acids as well as taurine. (4) Limiting total energy overload, avoiding obesity. (5) Intermittent infusion of PN. (6) Restriction of IV lipid emulsions, although this remains controversial. [32,52,54–57]

Nutritional deficiency states

Once the patient with intestinal failure has been weaned off parenteral nutrition, the patient should be monitored more frequently for micronutrient deficiencies. Macronutrients such as fat, proteins and carbohydrates are usually absorbed in adequate amounts, but micronutrients such as minerals, trace elements and vitamins are frequently deficient. At least 100 cm (in adults) of ileum is necessary to absorb the circulating bile salts; however, with major ileal resections, faecal bile salt loss exceeds the rate of hepatic synthesis of bile acids. Lack of bile salt absorption inhibits fat absorption, and consequently causes fat-soluble vitamins (A, D, E) and divalent cation (calcium, magnesium, and zinc) deficiencies. Therefore, these patients require large doses of vitamins A, D and E to avoid deficits. Liquid preparations may be necessary, because tablets or capsules are usually excreted intact. Except for vitamin B12, which requires an intact stomach (for intrinsic factor) and ileum (to absorb the intrinsic factor—B12 complex), patients with SBS can absorb water-soluble vitamins. Vitamin B12 absorption should be measured and if subnormal, injection of 200 μm/month should be started. Enteral feeding can also be supplemented with the specific deficient micronutrient, zinc, potassium, bicarbonate, magnesium, although magnesium supplements often result in osmotic diarrhoea. In this case, frequent small doses added in the ORS solution and sipped over the course of the day or some special magnesium preparations may be required.[2,6,58] The serum zinc concentration is not sensitive and is not a specific indicator of zinc deficiency, although a reduced concentration of zinc in association with low serum alkaline phosphatase levels and/or normal serum albumin suggests deficiency. The losses of zinc are about 12 mg/l of stool and because the absorption of zinc is about 30% of intake, patients should receive 36–40 mg of zinc gluconate by mouth per liter of output, or 50–100 mg/day in adult patients.[58]

Renal stones

Oxalate in the diet normally binds to dietary calcium and is excreted in the stool. In patients with distal small bowel resection and fat malabsorption, dietary calcium binds to free fatty acids and the free oxalate pass to the colon in which is readily absorbed. Bile salts and fatty acids increase colonic absorption of oxalate.[59] Hyperoxaluria is associated with renal stone formation and calcium oxalate nephrocalcinosis. Treatment involves having a low oxalate diet and taking cholestyramine to bind bile salts and citrate to prevent stone formation. Low oxalate diet usually excludes cocoa, peanuts products, tea, coffee, wheat germ, rhubarb, beets, collards, spinach, tofu and soybeans and restrict citrus drinks, tomatoes and fruit.[58]

Prolonged PN is associated with an ongoing bone osteopenia, affecting mainly the cancellous bone.[60] However. Dellert et al. found that the bone mineral content in SBS children was not different from the control subjects after adjustment for weight and height. It was different when adjusted for age.[61] The metabolic bone disease observed in patients dependant on home PN today is for the most part asymptomatic, which is remarkably different from what was seen in the past when PN solutions has high content of aluminum[62] The long-term consequences of the continuing osteopenia remain unanswered.

In conclusion, the chronic management of SBS is complex and encounters multiple complications. The goals are to decrease diarrhoea, to maintain normal hydration and nutritional status thus preventing severe chronic complications related with the use of parenteral nutrition such as IFALD and CVC infections. With the appropriate medical and dietary therapy many patients with intestinal failure can be weaned from parenteral nutrition resolving the major risk factors of morbidity and mortality in these patients.

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