Gestione multidisciplinare nel paziente con sindrome dell'intestino corto

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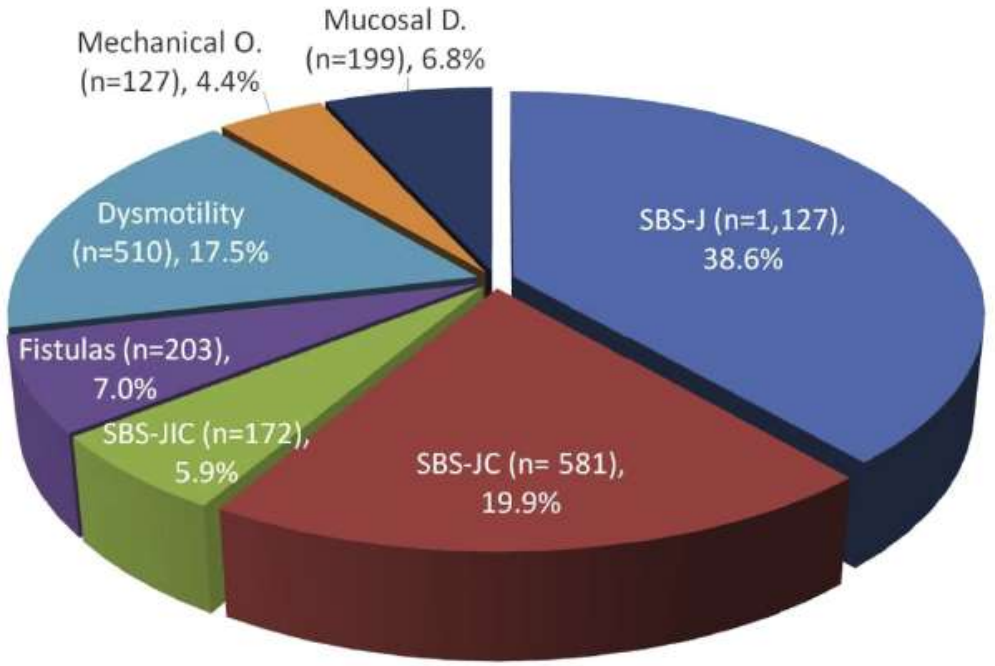
e-SPEN guideline

ESPEN guidelines on chronic intestinal failure in adults

Loris Pironi [a, *], Jann Arends [b], Federico Bozzetti [c], Cristina Cuerda [d], Lyn Gillanders [e], Palle Bekker Jeppesen [f], Francisca Joly [g], Darlene Kelly [h, i], Simon Lal [j], Michael Staun [f], Kinga Szczepanek [k], André Van Gossum [l], Geert Wanten [m], Stéphane Michel Schneider [n], the Home Artificial Nutrition & Chronic Intestinal Failure Special Interest Group of ESPEN

La sindrome dell'intestino corto (SBS) è la causa più frequente di Insufficienza Intestinale Cronica



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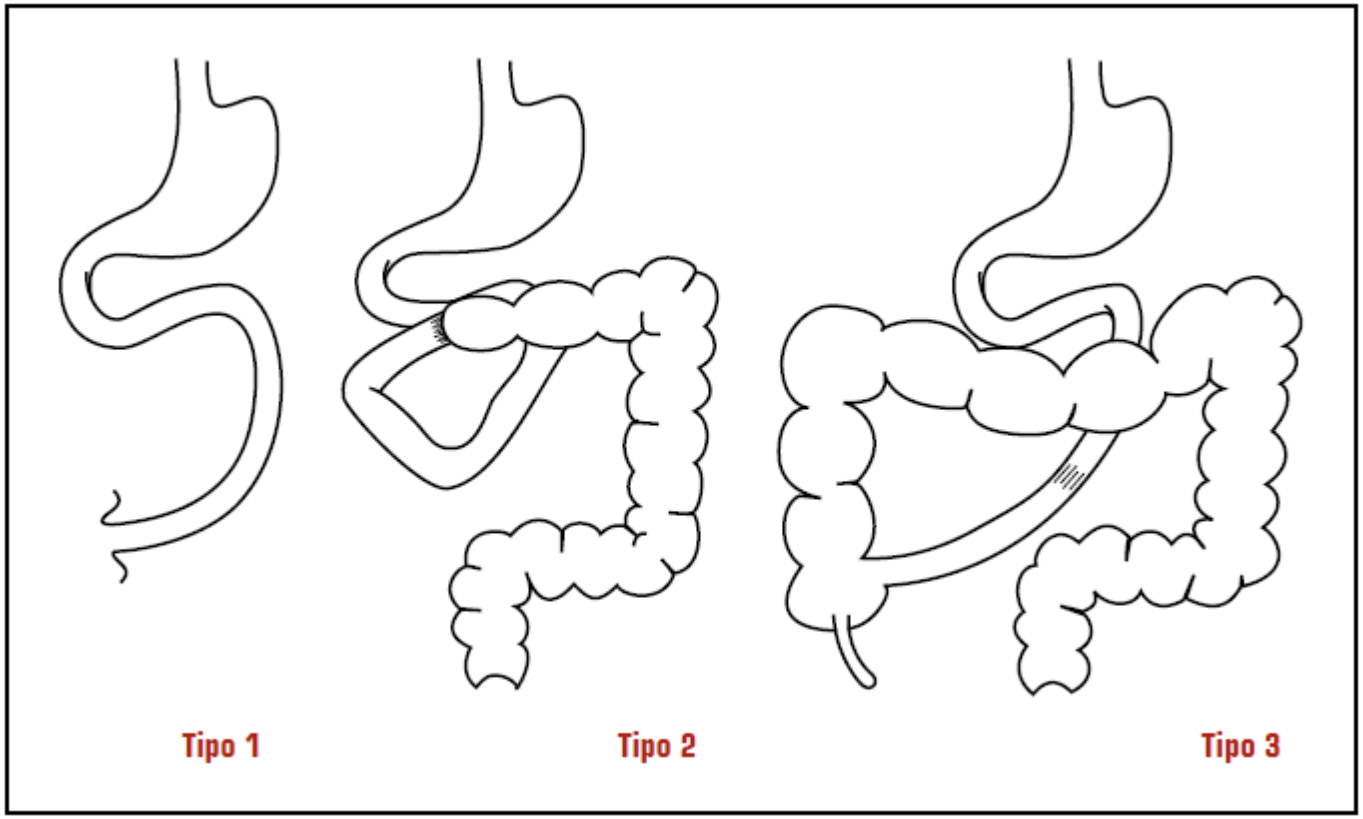
Definition

Intestinal failure is defined 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.

The reduction of gut absorptive function that doesn't require any intravenous supplementation to maintain health and/or growth, can be considered as "intestinal insufficiency" (or deficiency).

Short bowel syndrome : classification

«A small bowel lenght less than 200 cm»



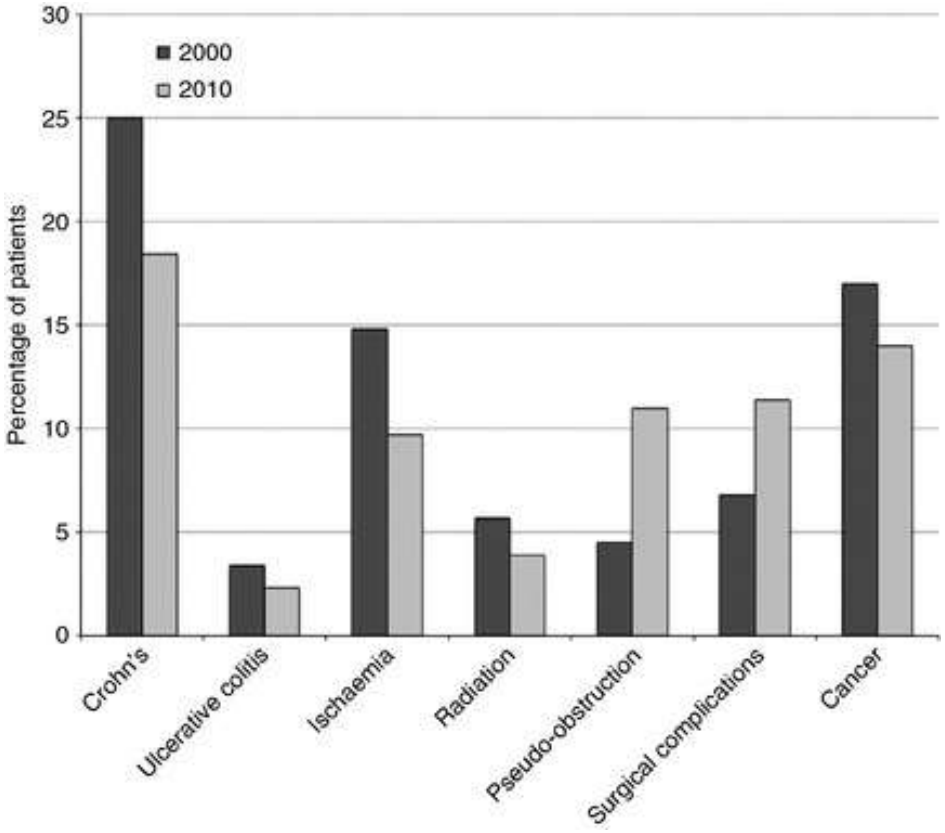
End-jejunostomy

Jejuno-colic anastomosis

Jejuno-ileal anastomosis
Ileo-caecal valve and colon in continuity

Short bowel syndrome: etiology

- Mesenteric ischemia
- ✓ Arterial thrombosis or embolism
- ✓ Drug abuse
- ✓ Coagulation disorders
- Crohn's disease
- Radiation enteritis
- Post-surgical intraabdominal adhesions
- Post-operative complications



Both massive resections (75%)and repeat resections (25%) can lead to SBS

Short bowel syndrome : sources of prevalence data

- Indirect estimates on home parenteral nutrition utilization (administrative data)
- Web-based registry (Sweden)
- Data from patients'associations (HANA, *Un filo per la Vita, PINNT*)
- Data from scientifical societies (SINPE, ESPEN)

Chronic IF requiring HPN

Incidence

- 2–3 cases/million (Europe)[1,3]
- 2.3 cases/million (UK, 2007)[3]
- 3.7 cases/million (UK, 2010)[3]
- 6.5 cases/million (UK, 2015)[4]

Prevalence

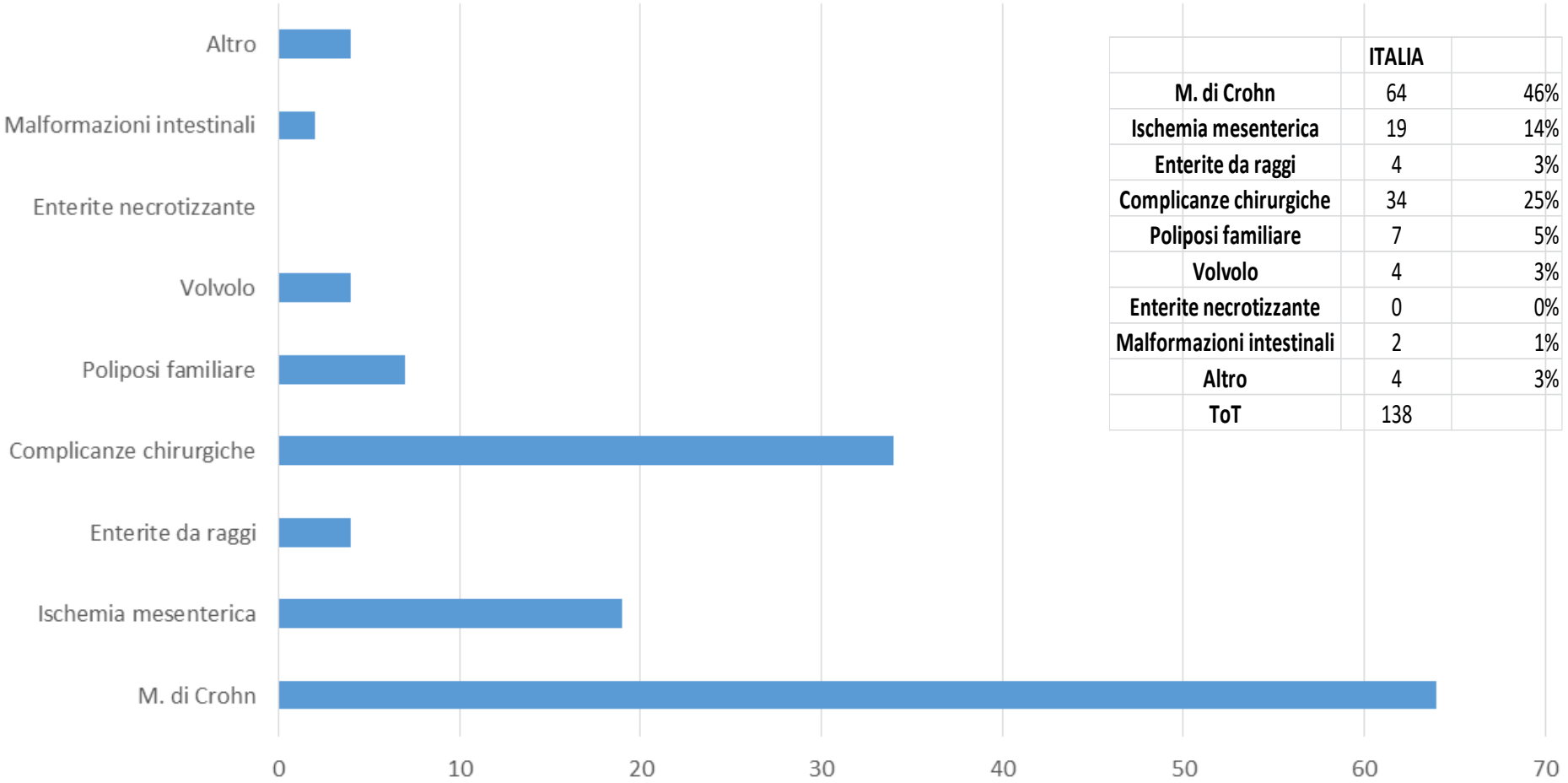
- 0.4/million (Poland)[1]
- 5/million (Spain)[1]
- 10–18/million (UK)[3,4]
- 30/million (Denmark)[1]
- 5-20/million (Europe)[5]

Chronic IF due to benign disease has been included in the 2013 Orphanet list of rare diseases[2]

1. Jeppesen. JPEN J Parenter Enteral Nutr 2014;38(1Suppl):8S–13S
2. Orphanet Report Series. Prevalence of rare diseases: Bibliographic data. October 2013
3. BANS Report 2011, BAPEN. www.bapen.org.uk
4. BANS Report 2016, BAPEN. www.bapen.org.uk
5. Pironi L, et al. Clin Nutr 2016;35(2):247–307

HPN, home parenteral nutrition
IF, intestinal failure

Prevalenza della sindrome dell'intestino corto in Italia



	ITALIA	
M. di Crohn	64	46%
Ischemia mesenterica	19	14%
Enterite da raggi	4	3%
Complicanze chirurgiche	34	25%
Poliposi familiare	7	5%
Volvolo	4	3%
Enterite necrotizzante	0	0%
Malformazioni intestinali	2	1%
Altro	4	3%
ToT	138	

From October 2018 to October 2019 106 AIGO members filled the survey form, 36 reported to have patients with short bowel syndrome in follow-up

Short bowel: need of increased awareness

- 5-year outcomes are improving:
- 36% are weaned from TPN
- 39% still on TPN

Overall survival 65%

Crohn's disease patients have better prognosis

- Cost of illness high
- High rate of hospitalizations (40% for underlying disease, 30% for HPN complications)
- Strict monitoring
- Hematochemistry every 1-3 months
- Vitamin and trace elements every 6 months
- US every year
- DEXA every year
- Liver biopsy

Multidisciplinary Expert Team

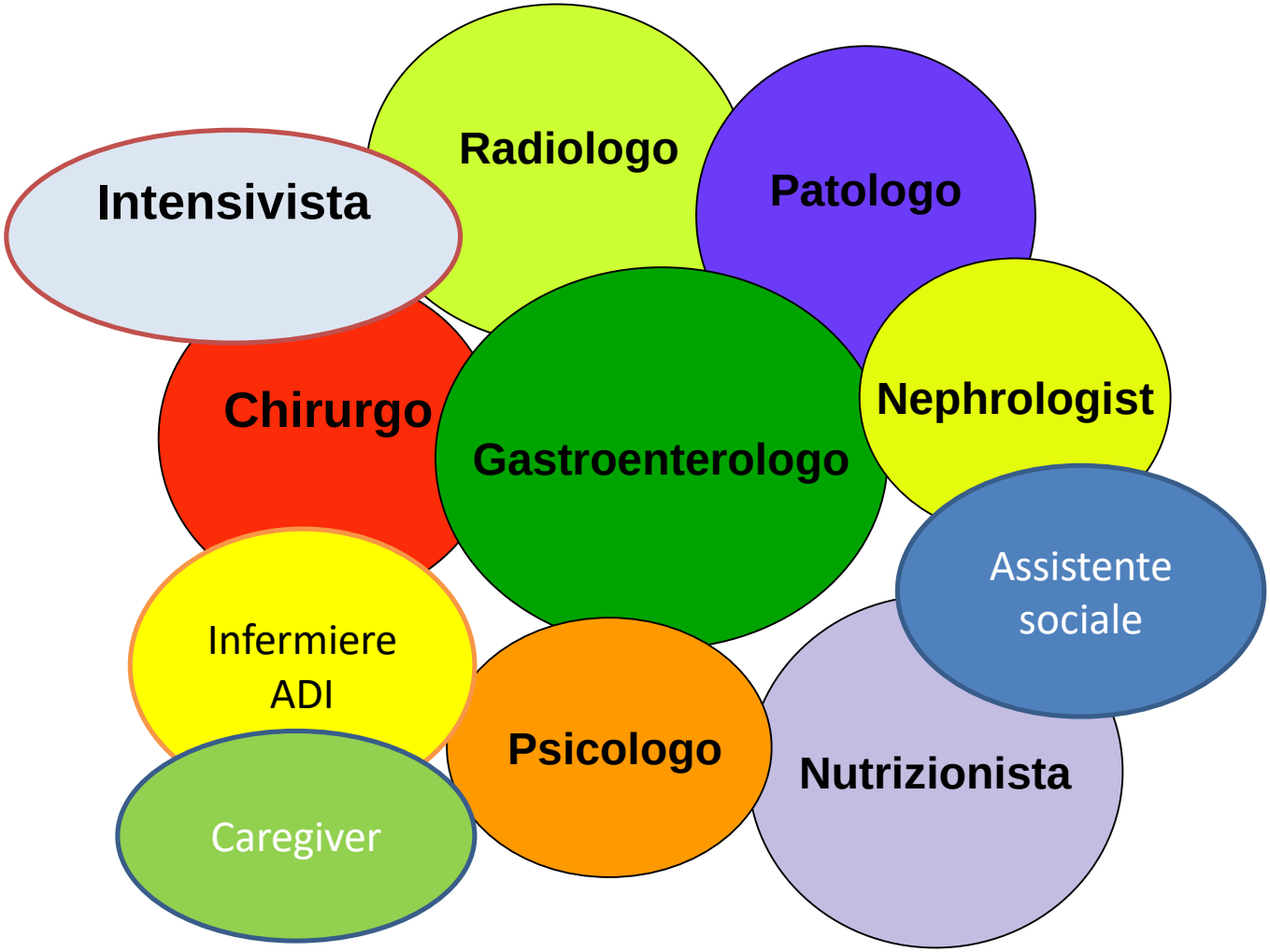


Table 3
Major complications of short bowel syndrome: risk factors, prevention and treatment.

	Main risk factors	Measures for prevention and treatment
Dehydration and sodium depletion	• Gastric hypersecretion (early 6 post-operative months) • Jejunostomy with <100 cm of residual small bowel ("secretors") • SBS without a colon in continuity	Optimize fluid and sodium balance to have: • urine volume >800 ml/day • urinary sodium >20 mmol/L PPI and/or ranitidine Avoid hypotonic or hypertonic beverages Oral rehydration solution
Magnesium deficiency	• Jejunostomy • Ileum and right colon resection • Fat malabsorption • Hyperaldosteronism secondary to dehydration • Impaired PTH activation and 1,25 hydroxy-vitamin D formation	Optimize fluid and sodium balance and hydration status Oral organic salt of magnesium Reduce or avoid excess lipid in the diet Oral 1-α hydroxy-cholecalciferol IV magnesium
Potassium deficiency	Jejunostomy with <50 cm of residual small bowel Hyperaldosteronism secondary to dehydration Magnesium deficiency	Optimize fluid and sodium balance and hydration status Correct magnesium deficiency Potassium supplementation (oral, IV)
Renal failure	• Dehydration • CRBSI • Nephrocalcinosis • Kidney stones	Optimize fluid and sodium balance Optimize CVC care Prevent urinary calcium oxalate formation
Calcium oxalate kidney stones	• SBS with a colon in continuity and fat malabsorption (enteric hyperoxaluria) • Pyridoxine or thiamine deficiency • Excess of ascorbic acid • Dehydration • Low urinary citrate • Low urinary magnesium	Reduce or avoid excess lipid in the diet Reduce food with high oxalate content Oral calcium at mealtime (1 gr) Oral cholestyramine Optimize fluid balance Optimize acid-base balance Optimize magnesium status Limit ascorbic acid supplementation
IFALD-cholestasis	• SBS with <50 cm of residual small bowel • SBS without colon • CRBSI episodes • Chronic intra-abdominal inflammation and/or small bowel bacterial overgrowth • Interrupted bile acid enterohepatic circulation • Oral fasting • PN-Overfeeding • IV soybean lipid emulsion >1 g/Kg/day	Avoid oral fasting Optimize CVC care Treat intra-abdominal inflammation foci Rehabilitative surgical procedures Optimize IV feeding IV soybean lipid emulsion <1 g/Kg/day and/or IV fish oil lipid emulsion
Gallstones	Prolonged oral fasting Interrupted bile acid entero-hepatic circulation Prolonged treatment with anticholinergic and narcotic drugs	Limit periods of oral fasting Limit narcotic or anticholinergic treatment Oral and/or enteral feeding as much as possible
D-lactic acid acidosis	• SBS with a colon in continuity • Carbohydrate and soluble fiber based diet • Ingestion of rapidly fermentable simple sugars • Feeding D-lactate containing food • High blood and urinary oxalate • Thiamine deficiency • Antibiotic and/or probiotic courses • Dehydration • Decreased renal function • Decreased liver function	Low carbohydrate and simple sugar diet Antibiotics active against D-lactate producing bacteria Thiamine supplementation Reduction of oxalate absorption Optimize fluid balance

Diarrhoea the most prevalent symptom (increased motility, malabsorption, secretory, bacterial overgrowth, pancreatic dysfunction)

Short bowel Syndrome:
Not only the gut!

Therapy of short bowel syndrome

- **Home parenteral nutrition (HPN)**
- **Supportive measures**
  - Antidiarrhoics: loperamide, PPI, octreotide, cholestyramine
  - Diet poor in lipids and oxalates
  - ONS and/or enteral tube feeding
- **Growth Factors**
  - Growth hormone
  - Teduglutide
- **Surgery**
  - Rehabilitative surgery
  - Intestinal transplantation

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ESPEN Guideline

ESPEN guideline on home parenteral nutrition

Loris Pironi [a, *], Kurt Boeykens [b], Federico Bozzetti [c], Francisca Joly [d], Stanislaw Klek [e], Simon Lal [f], Marek Lichota [g], Stefan Mühlebach [h], Andre Van Gossum [i], Geert Wanten [j], Carolyn Wheatley [k], Stephan C. Bischoff [l]

Statement 1

For a safe HPN program, the patient and/or the patient's legal representative have to give fully informed consent to the treatment proposed.

Strong consensus (95.7% agreement)

Statement 2

For a safe HPN program, the patient has to be sufficiently metabolically stable outside the acute hospital setting.

Strong consensus (91.3% agreement)

Statement 3

For a safe HPN program, the patients home environment has to be adequate to safely deliver the therapy proposed.

Strong consensus (95.7% agreement)

Statement 4

For a safe HPN program, the patient and/or the caregiver has to be able to understand and perform the required procedures for the safe administration of therapy.

Strong consensus (95.7% agreement)

Recommendation 6

The patient and/or the caregiver should be trained by a NST to safely infuse the PN with appropriate monitoring and prompt recognition of any complications.

Grade of Recommendation GPP – Strong consensus (100% agreement)

Recommendation 7

The prescribed nutritional admixture and ancillaries required for safe and effective therapy should be delivered by an experienced/certified health care provider.

Grade of Recommendation GPP – Strong consensus (95.7% agreement)

Recommendation 8

The NST should provide appropriate monitoring and treatment for routine and/or emergency care, with appropriate contact details provided to the patient 24 h per day, seven days per week.

Grade of Recommendation GPP – Strong consensus (100% agreement)

The expertise of the NST is crucial: better outcomes and lower costs of care

Clinical Nutrition 39 (2020) 1645–1666

ESPEN Guidelines on Parenteral Nutrition: Home Parenteral Nutrition (HPN) in adult patients

Michael Staun[a], Loris Pironi[b], Federico Bozzetti[c], Janet Baxter[d], Alastair Forbes[e], Francesca Joly[f], Palle Jeppesen[a], Jose Moreno[g], Xavier Hébuterne[h], Marek Pertkiewicz[i], Stefan Mühlebach[j], Alan Shenkin[k], André Van Gossum[l]

2. Nutritional support team for HPN

The expertise of a nutrition support team (NST) is recommended for HPN.

The core NST consists of a physician, nutrition nurse specialist, senior dietician and senior clinical pharmacist. The NST will prepare management protocols to facilitate patient education, help to minimize complications, assist cost-containment, and audit the practice.

For long-term treatment, patients and/or carers are trained to manage parenteral nutrition at home. All patients requiring this complex treatment should have coordinated care from an expert nutrition support team (NST). The NST should provide both physical and psychological or emotional support for all patients who are discharged from hospital with home parenteral nutrition (HPN).

NSTs are usually affiliated to a particular discipline – most commonly gastroenterology or surgery or both. The minimum core composition of the team should include a physician (e.g. gastroenterologist, gastrointestinal surgeon, clinical biochemist), a nutrition nurse specialist, a senior dietician and a senior clinical pharmacist.

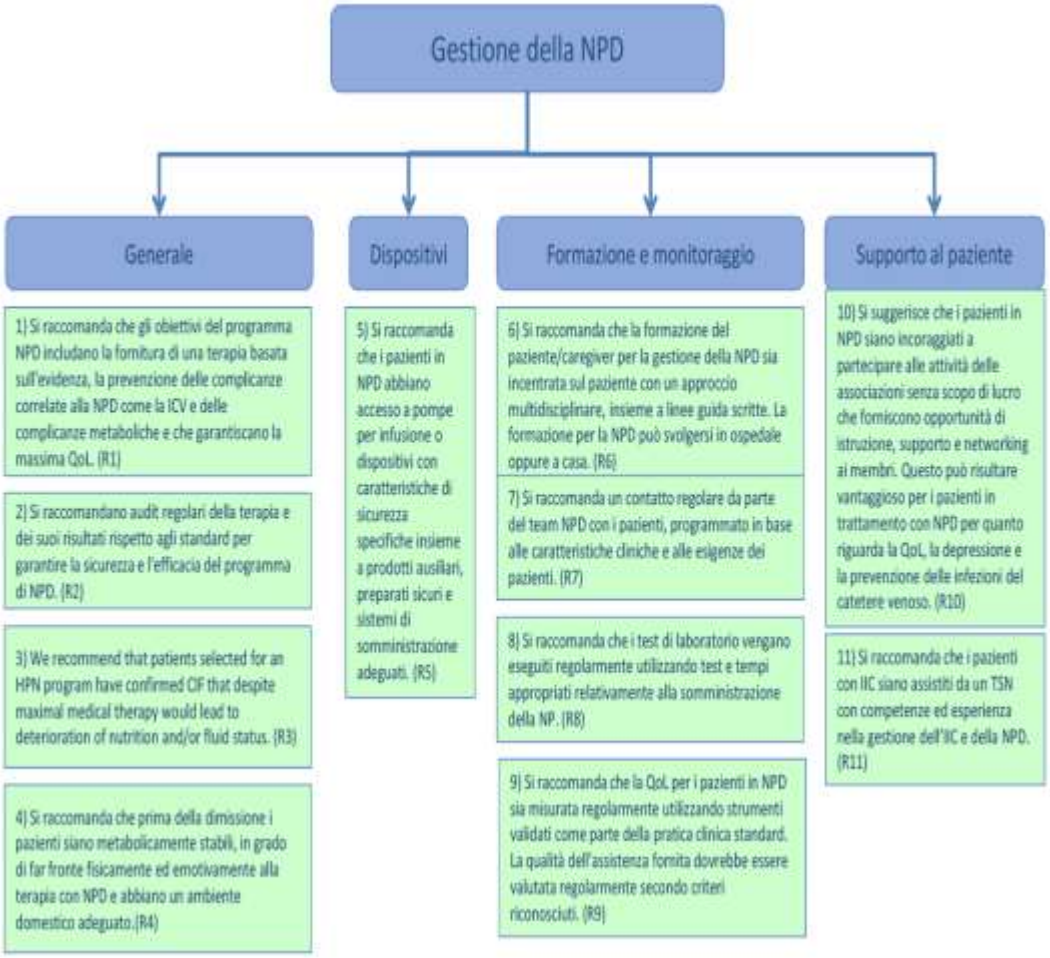
The tasks of the team should include minimizing the complications of parenteral nutrition by ensuring adherence to management protocols (particularly catheter care) and the management and auditing of complications, including catheter complications (e.g. sepsis and central vein thrombosis) and metabolic complications (such as liver and bone disease and micronutrient imbalance). Where a national registry of HPN patients exists, the team should report to this.

Clinical Nutrition 28 (2009) 467–479

2021

Linea guida pratica ESPEN: nutrizione clinica nell'insufficienza intestinale cronica

Cristina Cuerda[a], Loris Pironi[b,c], Jann Arends[d], Federico Bozzetti[e], Lyn Gillanders[f], Palle Bekker Jeppesen[g], Francisca Joly[h], Darlene Kelly[i], Simon Lal[j], Michael Staun[g], Kinga Szczepanek[k], André Van Gossum[l], Geert Wanten[m], Stéphane Michel Schneider[n]; Stephan C. Bischoff[o]; Annarita Eramo[p]; Gian Marco Giorgetti*[p]; and the Home Artificial Nutrition & Chronic Intestinal Failure Special Interest Group of ESPEN.

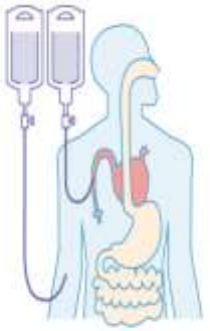


To provide safely HPN:
Use of infusion pumps and adequate Catheters
Training of the caregivers
Appropriate monitoring
An expert nutrition team

ESPEN Guideline

ESPEN guideline on home parenteral nutrition

Loris Pironi [a,*], Kurt Boeykens [b], Federico Bozzetti [c], Francisca Joly [d], Stanislaw Klek [e], Simon Lal [f], Marek Lichota [g], Stefan Mühlebach [h], Andre Van Gossum [i], Geert Wanten [j], Carolyn Wheatley [k], Stephan C. Bischoff [l]



7. Which nutritional PN admixture bag should be chosen?

Statement 5

The HPN-admixture shall meet the patient's requirement.

Strong consensus (95.7% agreement)

Recommendation 39

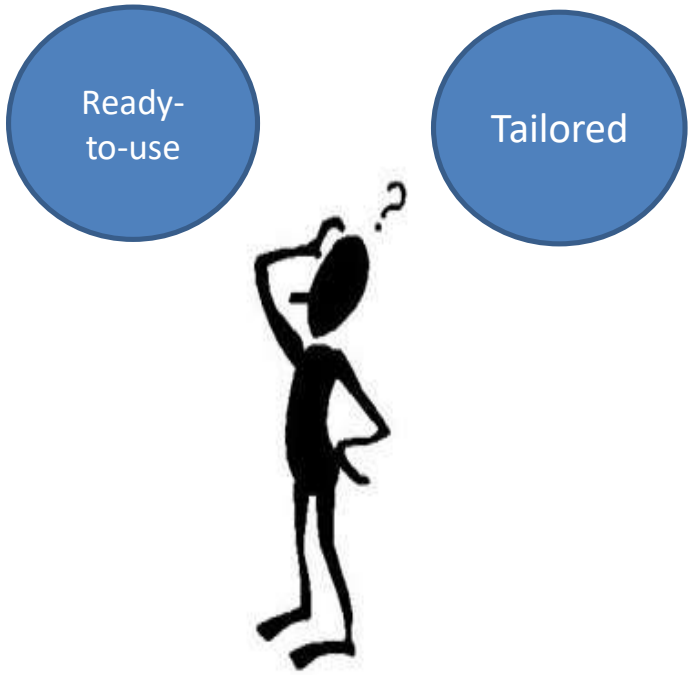
Either commercially available ready-to-use admixtures or customized and tailored to the individual patient's requirements admixtures can be used for HPN.

Grade of Recommendation GPP – Strong consensus (95.7% agreement)

Recommendation 40

Customized and tailored HPN admixtures can be prepared either by individual compounding or by ready-to-use prepared and adapted commercial multi-chamber bags, according to the manufacturer instructions and using aseptic admixture technique preferably in a laminar flow cabinet.

Grade of Recommendation GPP – Strong consensus (100% agreement)



Clinical Nutrition 39 (2020) 1645–1666

HPN monitoring

Parameters, frequency (after baseline assessment) and setting of monitoring on patients on HPN.

Parameter	Frequency	Setting
General condition	Daily if unstable, twice weekly to once a week if stable	Nurse at home
Body temperature		Patient and/or caregivers
Body weight	Daily if unstable, twice weekly to once a week if stable	In the hospital (outpatient visit)
		Nurse at home
		Patient and/or caregivers
Body mass index	Monthly	In the hospital (outpatient visit)
		Nurse at home
Fluid balance	The frequency and type of parameters will depend on	Nurse at home
- Urine output	etiology of CIF, and stability of patients	Patient and/or caregivers only in case of training program
- Stoma output	In case of high stool output (end jejunostomy), the	
- Number or consistency of stools	monitoring after the first discharge should be daily, then	
- Presence of edema	twice weekly to once a week when stable	
Catheter cutaneous exit site	Daily	Nurse at home
		Patient and/or caregivers only in case of training program
Full count blood	The frequency and type of parameters will depend on	At home
C-reactive protein	etiology of the underlying condition requiring HPN and the	Verify at each visit
Serum glucose	stability of patients	
Serum and urine electrolytes and minerals	Weekly or monthly, then every three to four months when	
(Na, Cl, K, Mg, Ca and P)	stable	
Serum Urea and Creatinine		
Serum bicarbonates		
Urine analysis		
Serum albumin and prealbumin	Monthly, then every three to four months when stable	At home
		Verify at each visit
Serum liver function tests including INR	Monthly, then every three to four months when stable	At home
		Verify at each visit
Liver ultrasound	Yearly	In hospital
Serum Folate, vitamins B12, A and E	Every six to twelve months	Dosage at home or in the hospital
Serum ferritin iron,	Every three to six months	Dosage at home or in the hospital
Serum 25-OH Vitamin D	Every six to twelve months	Dosage at home or in the hospital
Serum zinc, copper, selenium	Every six to twelve months	Dosage in the hospital
Serum Manganese	Yearly	Dosage in the hospital
Bone densitometry (DEXA)	Every twelve to eighteen months	In the hospital

Review article: the management of long-term parenteral nutrition

M. Dibb, A. Teubner, V. Theis, J. Shaffer & S. Lal

Catheter related complications

- Catheter-related infections (0,14 – 0,83 episodes/patient –year)
- Catheter occlusion (0,07 episodes/year)
- Central vein thrombosis (0,01-0,03 episodes/year)
- Catheter malfunction

Metabolic complications

- Nephrolitiasis
- Liver disease (IFALD) 19 – 75%
- Osteopathy

Low quality of life

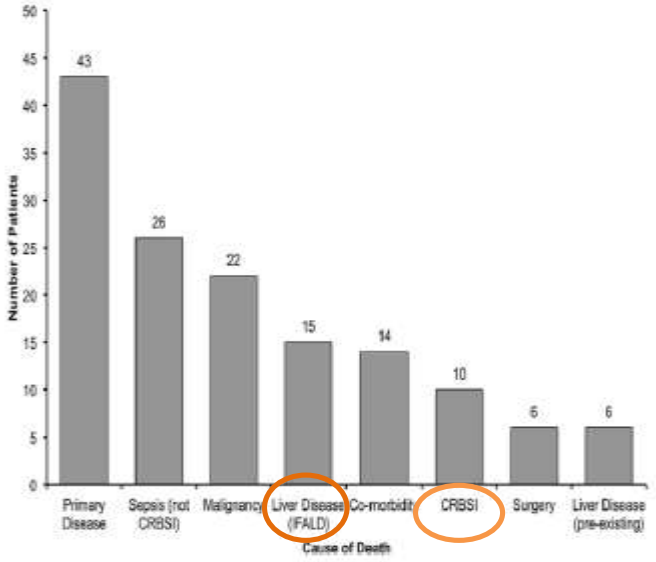
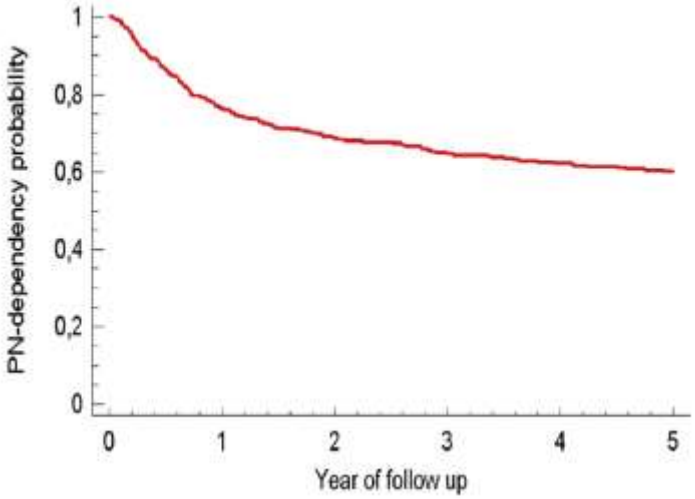


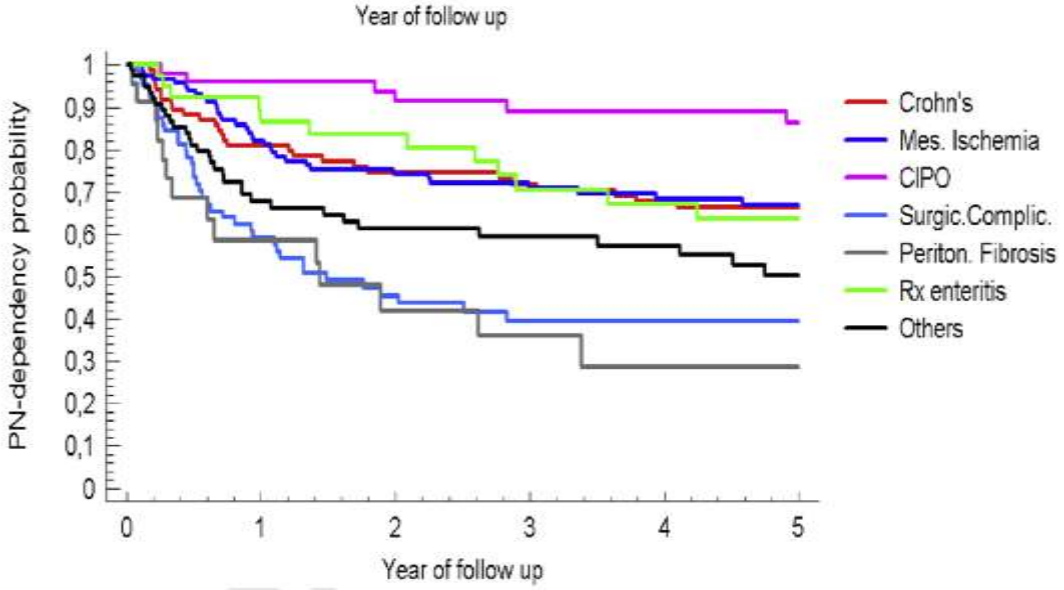
Fig. 1. Causes of death in patients receiving home parenteral nutrition. CRBSI; Catheter related blood stream infection. IFALD; Intestinal failure associated liver disease.

Aliment Pharmacol Ther 2013; **37**: 587–603

Five-year survival and causes of death in patients on home parenteral nutrition for severe chronic and benign intestinal failure

Francisca Joly [a, *], Janet Baxter [b], Michael Staun [c], Darlene G. Kelly [d], Yi Lisa Hwa [d], Olivier Corcos [a], Antonella De Francesco [e], Federica Agostini [f], Stanislaw Klek [g], Lidia Santarpia [h], Franco Contaldo [h], Cora Jonker [i], Geert Wanten [j], Luisa Chicharro [k], Rosa Burgos [k], Andre Van Gossum [l], Cristina Cuerda [m], Nuria Virgili [n], Loris Pironi [f], on behalf of the ESPEN HAN CIF group





SBS: alimentazione orale consentita?

Nutrienti	SBS con colon	SBS senza colon
Carboidrati	• 50-60% delle calorie totali • Preferire quelli complessi • Limitarne gli zuccheri semplici	• 40-50% delle calorie totali • Preferire quelli complessi • Ridurre al massimo gli zuccheri semplici
Grassi	• 20-30% delle calorie totali • È indicato l'uso di olio MCT • Assicurare un adeguato intake di acidi grassi essenziali	• 30-40% delle calorie totali • Assicurare un adeguato intake di acidi grassi essenziali
Proteine	• 20% delle calorie totali	• 20% delle calorie totali
Fibre	• Fibre solubili	• Non essenziali
Fluidi	• ORS (o bevande ipotoniche se presente tutto il colon)	• ORS di solito necessarie
Ossalati	• Ridurne l'apporto	• Non necessaria alcuna restrizione

Clinical Management Issues 2008; 2(4)

ESPEN guidelines on chronic intestinal failure in adults

37. **We suggest the use of enteral tube feeding in combination with oral feeding in patients with CIF with a low-level of HPN dependence (i.e. B1 category of clinical classification) and in whom the expected gain with tube feeding could allow them to wean off HPN.**(Grade of evidence: **low**)

For patients with SBS, who are believed to benefit from enteral feeding, studies suggest that elemental and polymeric diets are similar in terms of nutrient absorption and fluid and electrolyte loss

Clinical Nutrition 35 (2016) 247–307

Therapy of short bowel syndrome

- **Home parenteral nutrition (HPN)**
- **Supportive measures**
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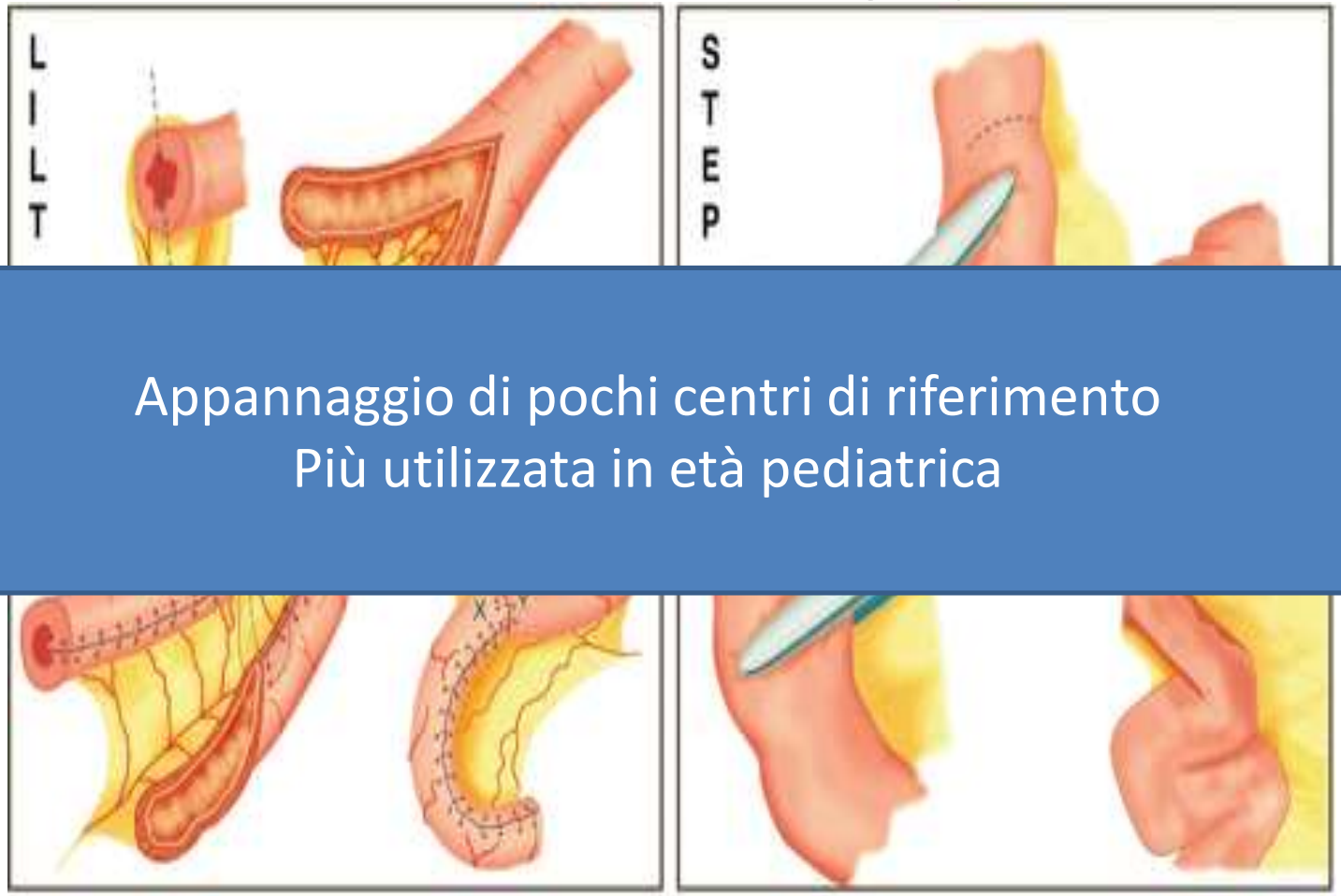
Rehabilitative surgery



Appannaggio di pochi centri di riferimento
Più utilizzata in età pediatrica

Surgical procedure for bowel lengthening:

- LILT : Longitudinal intestinal lengthening and tapering
- STEP: serial transverse enteroplasty

Intestinal transplantation

Centers for Medicare and Medicaid–approved indications for intestinal transplantation

Failure of parenteral nutrition

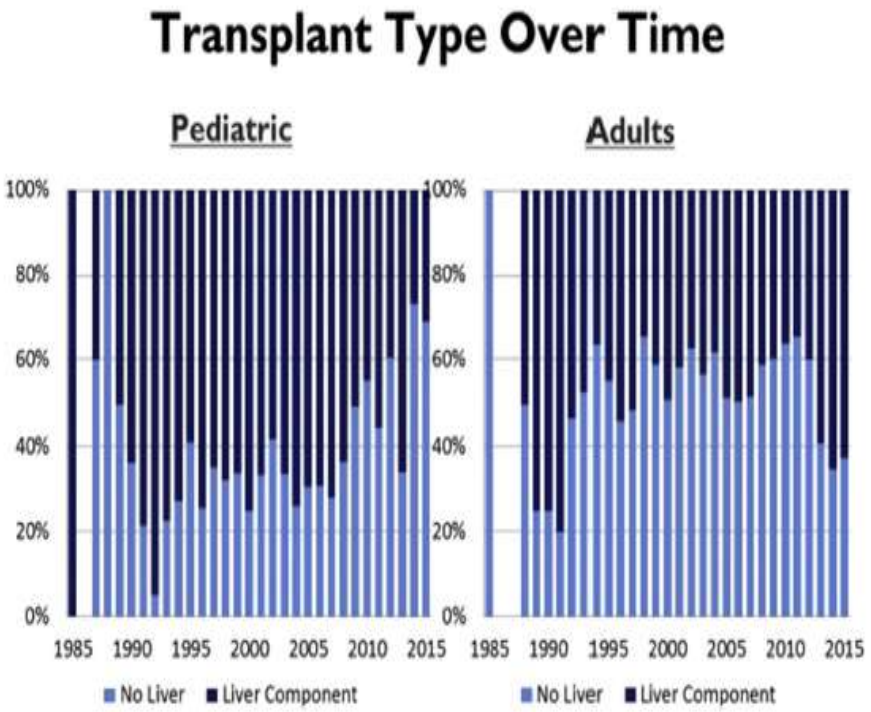
- Impending (total bilirubin 3–6 mg/dL, progressive thrombocytopenia, and progressive splenomegaly) or overt liver failure (portal hypertension, hepatosplenomegaly, hepatic fibrosis, or cirrhosis) because of parenteral nutrition liver injury
- Central venous catheter-related thrombosis of 2 central veins
- Frequent central line sepsis
  - Two episodes per year of systemic sepsis secondary to line infections requiring
  - hospitalization
  - A single episode of line-related fungemia
  - Septic shock or acute respiratory distress syndrome
- Frequent episodes of severe dehydration despite intravenous fluid in addition to parenteral nutrition

High risk of death attributable to the underlying disease

- Desmoid tumors associated with familial adenomatous polyposis
- Congenital mucosal disorders
- Ultrashort bowel syndrome (residual bowel 20 cm in adults)

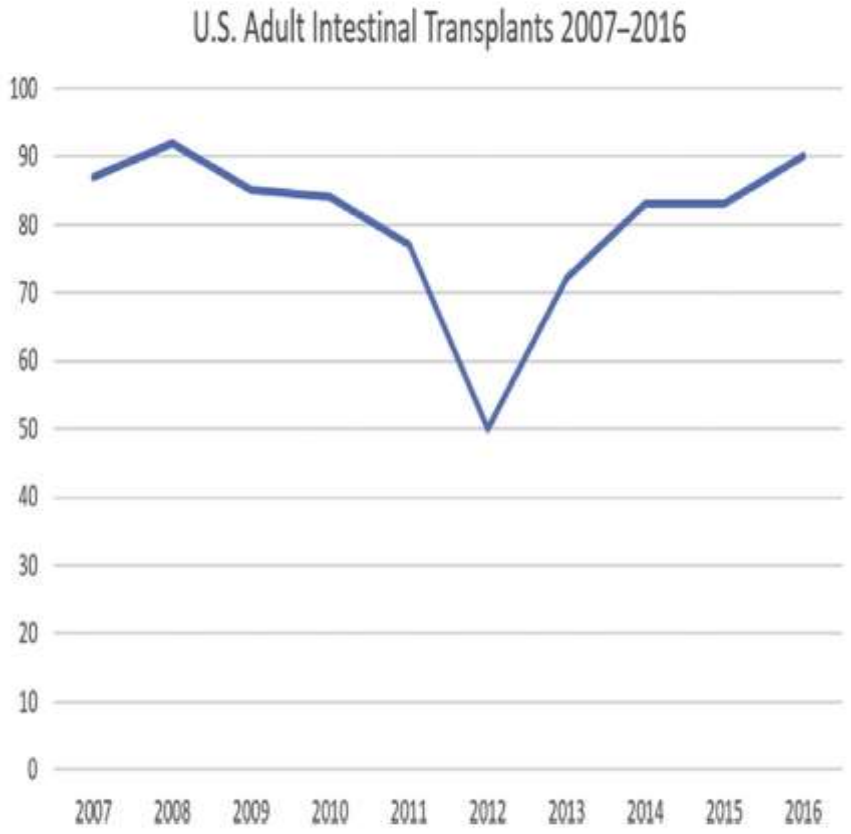
Intestinal failure with high morbidity or low acceptance of parenteral nutrition

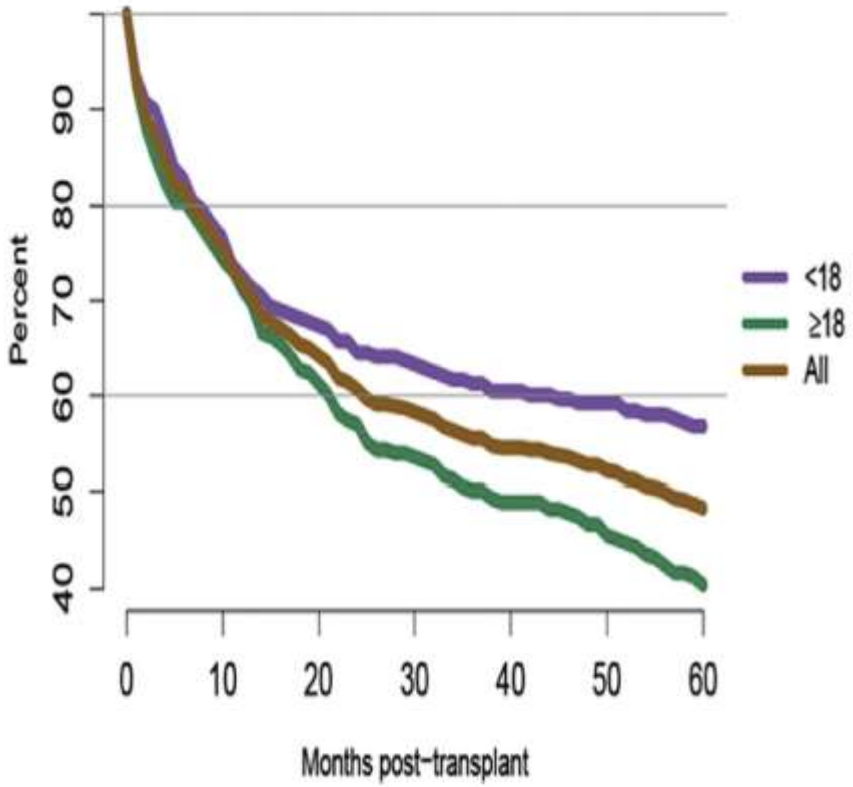
- Frequent hospitalization
- Inability to function
- Patient unwillingness to accept long-term parenteral nutrition



Gastroenterol Clin North Am. 2018 June ; 47(2): 341–354.

Intestinal transplantation





One year graft survival 70%
Three year graft survival 56%

Gastroenterol Clin North Am. 2018 June ; 47(2): 341–354.

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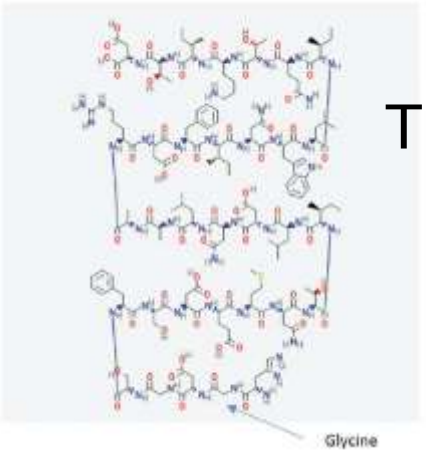
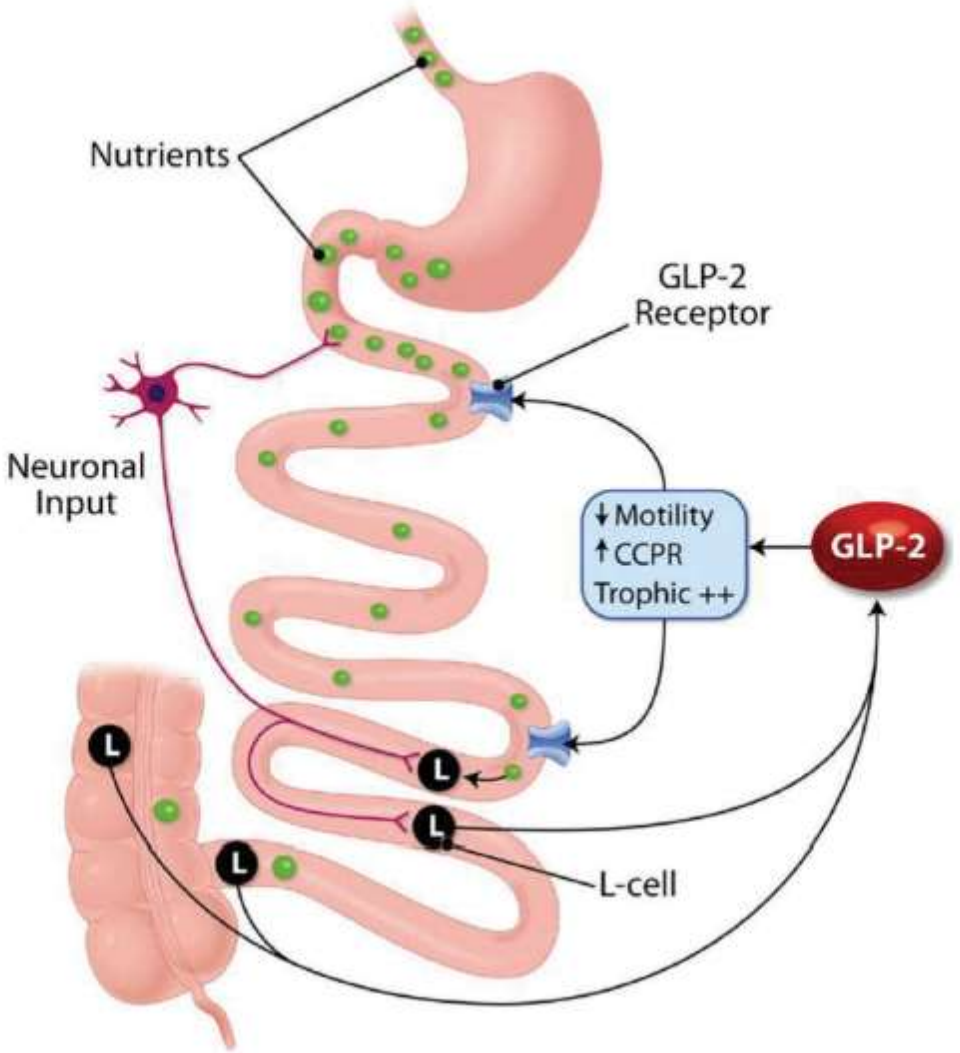
  - Rehabilitative surgery
  - Intestinal transplantation



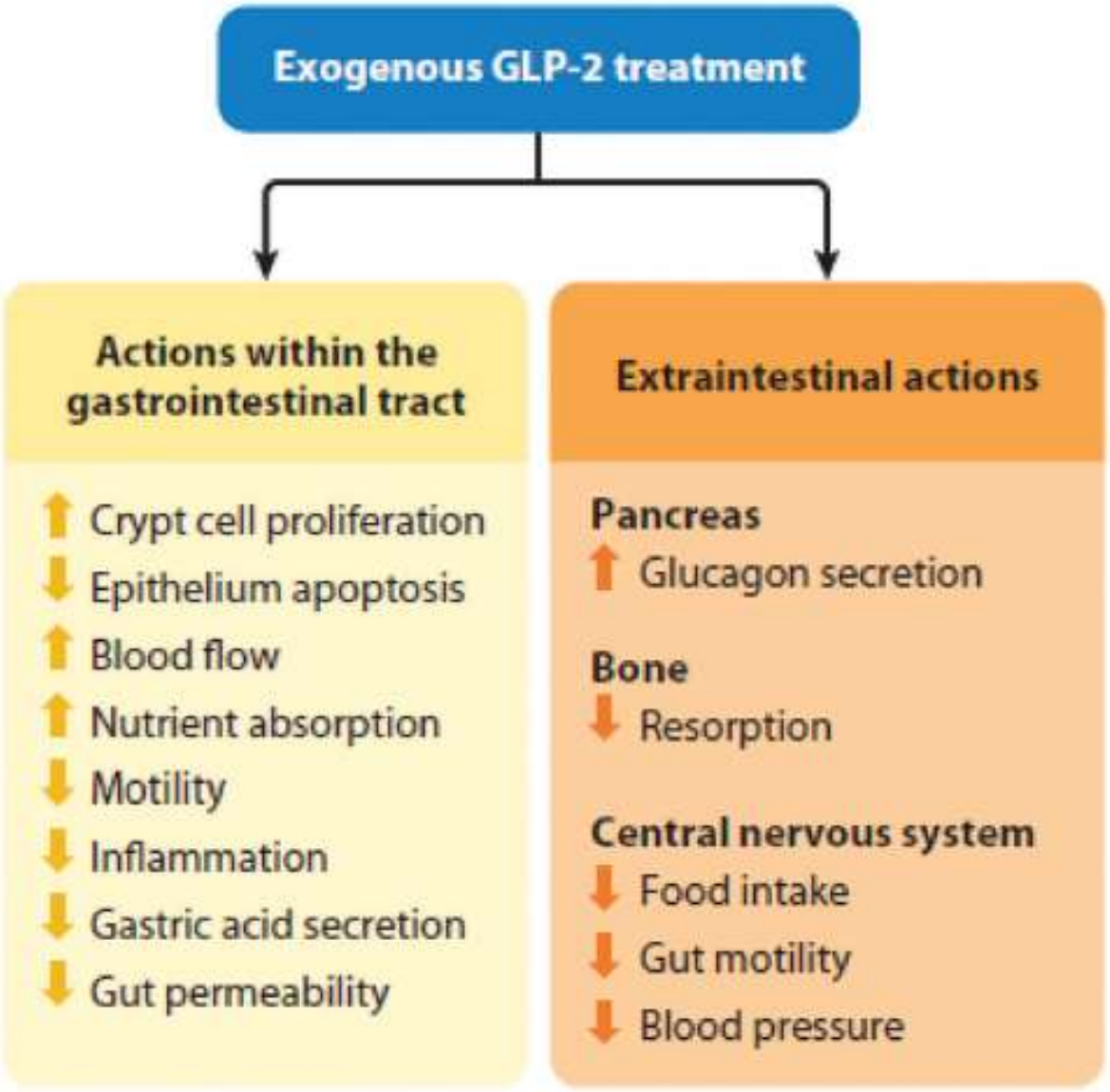
TEDUGLUTIDE as a novel therapeutic agent for SBS

GLP-2 is a peptide produced by enterocytes after food ingestion.

Teduglutide is a dipeptidyil-peptidase degradation resistant GLP-2 analogue

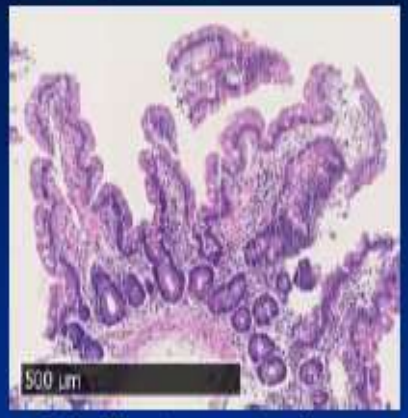


TEDUGLUTIDE : mechanism of action



Response to Teduglutide Histologic

Pre-teduglutide



- 3:1 villus to crypt ratio
- Longest villi measure 1.6 mm in length

1.5 years on teduglutide

- Duodenal mucosa with dilated lymphatics
- 6:1 villus to crypt ratio
- Longest villi measure 3mm in length

Images courtesy of Dr. Mohammad Shokouh-Amiri, UIC Department of Pathology

STEPS PROGRAMME: CLINICAL TRIALS TEDUGLUTIDE

Study[a]	Description	Outcomes
Jeppesen et al[48]	Phase III clinical trial. SBS males and females ≥18 y receiving PN ≥3 d/wk for ≥12 mo. Randomized to teduglutide 0.05 mg/kg/d (n = 35), teduglutide 0.10 mg/kg/d (n = 32), or placebo (n = 16) for 6 mo.	1. PN volume 2. Responder rate[b] 3. Complete PN weaning 4. Intestinal adaptation 5. Safety
Jeppesen et al[50] (STEPS)	Phase III clinical trial. SBS males and females ≥18 y on PN ≥3 d/wk for ≥12 mo. Previously teduglutide-treated subjects not eligible. Subjects randomized to receive teduglutide 0.05 mg/kg/d (n = 43) or placebo (n = 43) for 6 mo.	1. PN volume 2. PN infusion frequency 3. Responder rate 4. Safety
Jeppesen et al,[42,c] Jeppesen et al,[43,c] Fujioka et al[45,c] (STEPS-2)	*Open-label extension of STEPS.* Treatment in STEPS/STEPS-2: teduglutide/teduglutide 0.05 mg/kg/d (n = 30), placebo/teduglutide 0.05 mg/kg/d (n = 29), or not randomized/teduglutide 0.05 mg/kg/d (n = 6) for 18–24 mo.	1. PN volume 2. PN infusion frequency 3. Responder rate 4. Complete PN weaning 5. Safety
Iyer et al[44,c] (STEPS-3)	*Open-label extension of STEPS/STEPS-2.* Teduglutide 0.05 mg/kg/d (n = 14), with STEPS/STEPS-3 treatment of teduglutide/teduglutide (n = 5; treatment duration ≤42 mo), placebo/teduglutide (n = 6; treatment duration ≤36 mo), or not treated/teduglutide (n = 3; treatment duration ≤36 mo).	1. PN volume 2. PN infusion frequency 3. Complete PN weaning 4. Safety

Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome

P B Jeppesen,[1] R Gilroy,[2] M Pertkiewicz,[3] J P Allard,[4] B Messing,[5] S J O'Keefe[6]

Table 1 Criterion values for the graded response score

		Week 20 maintained at week 24			
		<20% reduction in PV	20–39% reduction in PV	40–99% reduction in PV	100% reduction in PV
Week 16 maintained to week 20	<20% reduction in PV	0	1	2	3
	20–39% reduction in PV	0	2	3	4
	>40% reduction in PV	0	3	4	5

The criterion values relied on the timing and reduction from baseline in weekly parenteral volumes (PV). The protocol-defined reduction was set at a minimum of 20% and a maximum of 100%. The timing of onset and the duration of response incorporated the responses at week 16 maintained to week 20 and week 20 maintained at week 24.

Table 3 Summary of results for the graded response score (GRS)

	Criterion value					
	0 <20% reduction in parenteral support	1	2	3	4	5 Off parenteral support
Placebo	15 (94%)	0 (0%)	1 (6%)	0 (0%)	0 (0%)	0 (0%)
Teduglutide 0.10 mg/kg/day	24 (75%)	2 (6%)	4 (13%)	0 (0%)	2 (6%)	0 (0%)*
Teduglutide 0.05 mg/kg/day	19 (54%)	6 (17%)	6 (17%)	0 (0%)	2 (6%)	2 (6%)

Number (%) of patients within the criterion value groups.
Comparison of 0.10 mg/kg/day of teduglutide vs placebo, p=0.16. Comparison of 0.05 mg/kg/day teduglutide vs placebo, p=0.007. p Value based on a rank ANCOVA adjusting for multiple comparisons in the primary efficacy analysis.
*One patient was weaned off parenteral support at week 24 with a score of 4.
For GRS score, refer to table 1.

Gut 2011;**60**:902–914. doi:10.1136/gut.2010.218271

Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome

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Table 7 Treatment-emerging adverse events (AEs) and serious adverse events (SAEs)

	Placebo (n=16)	Teduglutide 0.10 mg/kg/day (n=32)	Teduglutide 0.05 mg/kg/day (n=35)
Subjects with AE, n (%)	15 (94%)	31 (97%)	33 (94%)
Subjects with SAE, n(%)	5 (31%)	11 (34%)	13 (37%)
Subjects with any AE or SAE leading to study discontinuation, n (%)	1* (6%)	2* (6%)	6 (17%)
Event description by system organ class			
Cardiac disorders	0	0	1
Cardiac failure congestive	0	0	1
Gastrointestinal disorders	0	2	6
Abdominal distension	0	0	1
Constipation	0	0	2
Haemorrhoidal haemorrhage	0	0	1*
Nausea	0	0	1
Pancreatitis	0	1	0
Small intestinal obstruction	0	1*	0
Vomiting	0	0	1
General disorders and administration site conditions	0	0	1
Asthenia	0	0	1
Infections and infestations	1*	1*	0
Catheter sepsis	1*	1*	0
Investigations	0	0	1
Drug level increased	0	0	1
Nervous system disorders	0	0	3*
Coma	0	0	1*
Dysgeusia	0	0	1*
Hypersomnia	0	0	1*

What are the new findings?

- This is the first long-term (24 weeks) randomised placebo-controlled study of teduglutide in patients with short bowel syndrome dependent on parenteral support.
- Teduglutide was safe, well tolerated and led to restoration of intestinal functional and structural integrity through significant intestinotrophic and pro-absorptive effects.

How might it impact on clinical practice in the foreseeable future?

- Teduglutide has the potential to reduce the burden often seen with parenteral support in patients with short bowel syndrome with intestinal failure, and could add to the limited clinical treatment armamentarium in treating patients with short bowel syndrome.

Gut 2011;**60**:902–914. doi:10.1136/gut.2010.218271

Teduglutide Reduces Need for Parenteral Support Among Patients With Short Bowel Syndrome With Intestinal Failure

PALLE B. JEPPESEN,* MAREK PERTKIEWICZ,‡ BERNARD MESSING,§ KISHORE IYER,‖ DOUGLAS L. SEIDNER,¶ STEPHEN J. D. O'KEEFE,# ALASTAIR FORBES,** HARTMUT HEINZE,‡‡ and BO JOELSSON§§

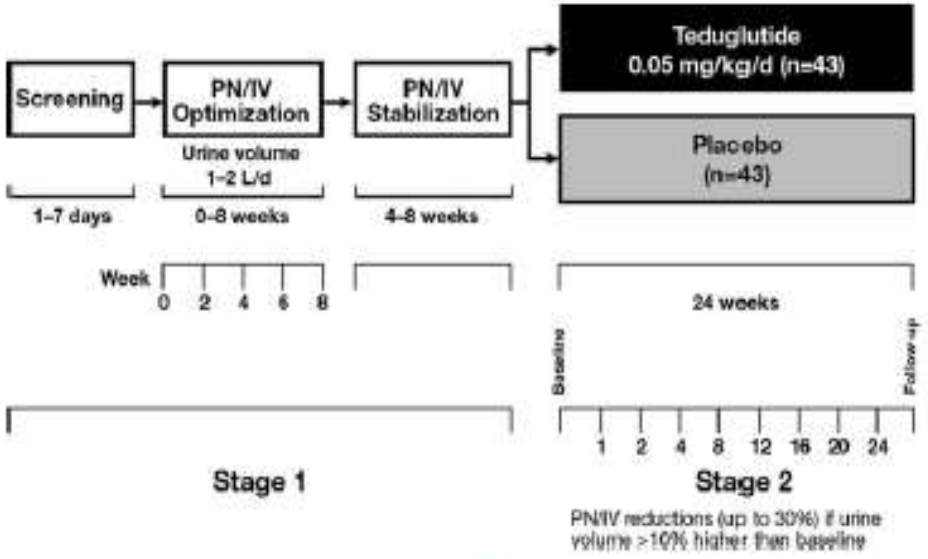

Figure 1. Study design.

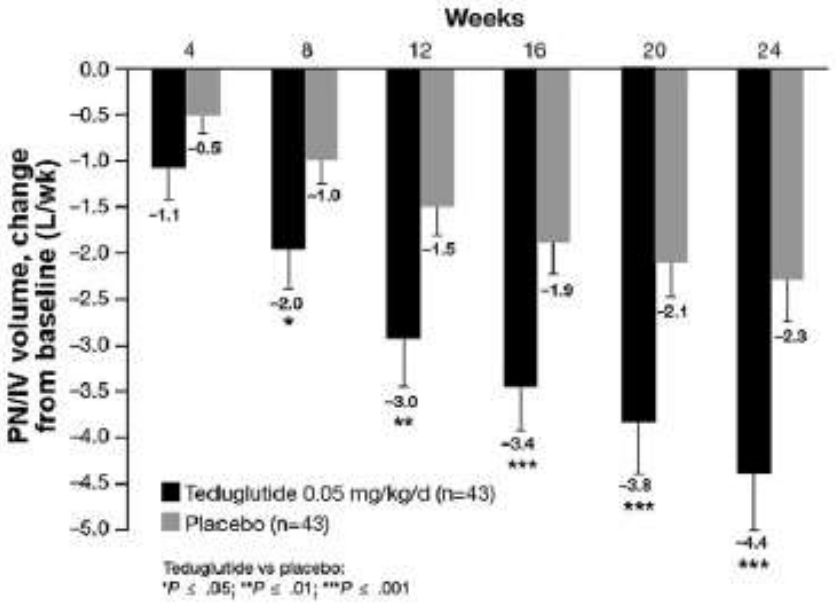

Figure 2. Mean (SE) absolute reduction in parenteral support.

Responders were 63% in the teduglutide group and 30% in the placebo group, p=0.002

GASTROENTEROLOGY 2012;143:1473–1481

Single-Center Experience with the Use of Teduglutide in Adult Patients with Short Bowel Syndrome

Journal of Parenteral and Enteral Nutrition
Volume 42 Number 1
January 2018 225–230

DOI: 10.1002/jpen.1011
wileyonlinelibrary.com
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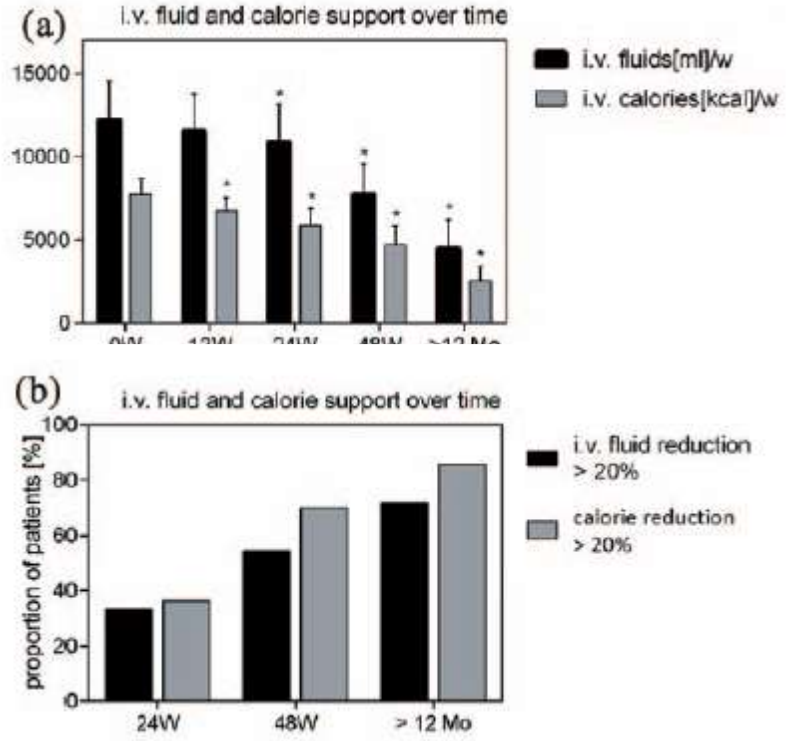
Table 1. Baseline Characteristics of 18 Patients.

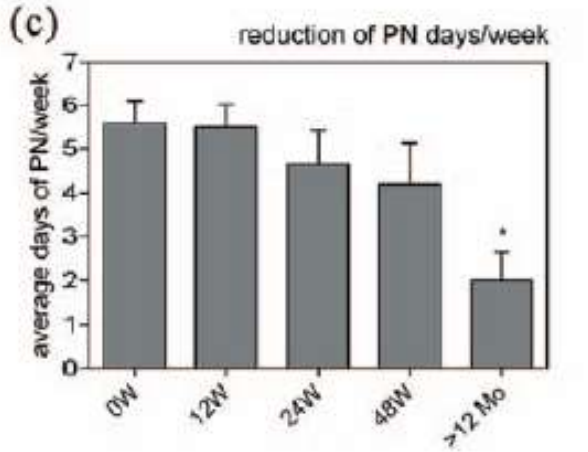
	N	Median (Range)
Gender	M = 7, F = 11	
Colon in continuity	15	
End stoma	3	
Age		47 (20–81)
Time between last bowel resection and initiation of teduglutide		4 yrs (1–13 yrs)
Time on PN/IV prior to teduglutide		36 months (4–96 months)
Weekly PN/IV volume prior to teduglutide		9.9 L (2.7–30 L)
PN/IV calories prior to teduglutide		682 kcal/d (0–1823 kcal/d)
Small bowel length		55 cm (6–180 cm)

A retrospective real life analysis from a tertiary referral center
All patients exposed to teduglutide
From 2009 to 2015
11 patients were totally weaned
From parenteral nutrition at a
Median times of 10 months
(range 3 – 36 months)
>50% achieved enteral autonomy after months.
10/11 who achieved enteral
Independence had the colon

GLP-2 analog teduglutide significantly reduces need for parenteral nutrition and stool frequency in a real-life setting

Ther Adv Gastroenterol
2018, Vol. 11: 1–11





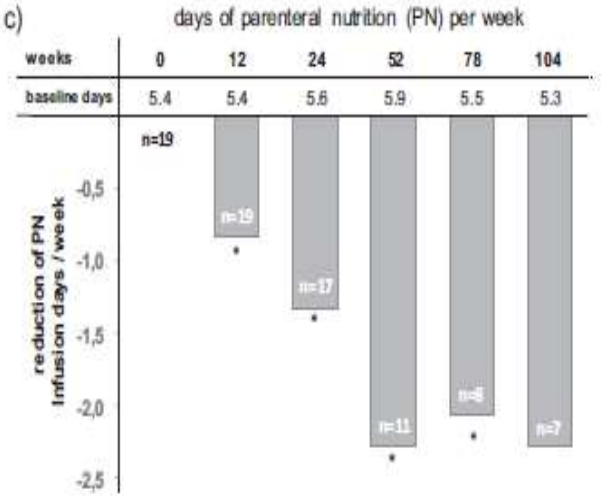
……in contrast to randomized, controlled studies reduction of parenteral support took longer

early clinical markers of response: increase in stool consistency and reduction of stool frequency as well as sensation of thirst. Top responders patients with colon in continuity

Experience with teduglutide treatment for short bowel syndrome in clinical practice

Table 1
Demographic and clinical patient characteristics prior to teduglutide treatment.

Patient characteristics before teduglutide treatment	
Patients exposed to teduglutide (since October 2014), n	27
Female sex, n (%)	14 (52%)
Age, [years]	
Mean ± SD	51 ± 17
Median (range)	53 (21–82)
BMI, [kg/m^2]	
Mean ± SD	21.3 ± 2.6
Median (range)	21.4 (15.3–27.2)
Cause of major intestinal resection, n (%)	
Vascular disease	12 (44%)
Inflammatory bowel disease	4 (15%)
Traumatic injury	3 (11%)
Postsurgical obstructive intestinal adhesions	4 (15%)
Other (volvulus, aganglionosis, perforated sigmoid diverticulitis)	4 (15%)
Duration of chronic IF, [years]	
Mean ± SD	4.3 ± 5.8
Median (range)	2.9 (0.6–23.3)
Patients with colon in continuity, n (%)	21 (78%)
No colon resection, n (%)	5 (24%)
Partial colon resection, n (%)	16 (76%)
Remnant small bowel length in patients with colon in continuity, [cm]	
Mean ± SD	45 ± 34
Median (range)	46 (0–140)
Unknown, n (%)	3 (14%)
Patients with stoma, n (%)	6 (22%)
Duodenostomy, n (%)	1 (17%)
Jejunostomy, n (%)	1 (17%)
Ileostomy, n (%)	3 (50%)
Descendostomy, n (%)	1 (17%)
Remnant small bowel length in patients with stoma, [cm]	
Mean ± SD	205 ± 173
Median (range)	150 (70–450)
Unknown, n (%)	2 (33%)



21% weaned from HPN
79% reduction parenteral volume

Clinical Nutrition xxx (2018) 1–11

Six-month outcomes of teduglutide treatment in adult patients with short bowel syndrome with chronic intestinal failure: A real-world French observational cohort study

F. Joly [a, b, *], D. Seguy [c], A. Nuzzo [a], C. Chambrier [d], P. Beau [e], F. Poullenot [f], R. Thibault [g], L. Armengol Debeir [h], S. Layec [i], V. Boehm [a], J. Lallemand [j], D. Quilliot [k], S.M. Schneider [l]

Results: At week 24, 85% of patients were responders and 24% had been weaned off PS, with a 51% reduction of PS needs and 1.5 ± 0.2 days off PS per week. Response to teduglutide was influenced by a higher baseline oral intake ($p = 0.02$). Weaning off PS was influenced by the presence of colon ($p = 0.04$), a lower PS volume ($p = 0.03$) and a higher oral intake ($p = 0.01$). There were no differences based on age, bowel length or SBS-IF causes.

IV energy supplementation	Volume of the IV supplementation (mL)			
	≤1,000 (1)	1,001 – 2,000 (2)	2,001 – 3,000 (3)	>3,000 (4)
Distribution of patients at baseline				
No parenteral support	0	-	-	-
Fluids and electrolytes	6	1	0	0
Parenteral nutrition	18	14	8	7
Distribution of patients at Week 24				
No parenteral support	13	-	-	-
Fluids and electrolytes	6	0	0	0
Parenteral nutrition	20	7	6	2

Fig. 2. Distribution of the 54 patients at baseline and 24 weeks after teduglutide treatment according to ESPEN clinical classification of intestinal failure.

Univariate and multivariate analysis of risk factors associated with weaning off PS 24 weeks after teduglutide treatment.

	Weaned n = 13	Non-weaned n = 41	Unadjusted *p value*	Multivariate *p value*
Age, years, mean (SD)	55 (13)	51 (16)	0.41	0.06
BMI, kg/m^2, mean (SD)	20 (3)	22 (5)	0.11	
Short bowel syndrome causes, n (%)				
Crohn's disease (vs. others)	4 (31)	12 (29)	0.91	0.06
Bowel anatomy				
Group 1 (vs. others), n (%)	**2 (15)**	**17 (42)**	**0.11**	**0.04**
Group 2 (vs. others), n (%)	10 (77)	23 (56)	0.18	
Remnant bowel length, cm, mean (SD)	66 (32)	60 (46)	0.70	0.51
Remnant colon length, %, mean (SD)	59 (34)	46 (42)	0.25	
Reverse bowel loop, n (%)	1 (8)	2 (5)	0.70	
Intestinal failure features, mean (SD)				
Basal PS volume, mL/day	**738 (272)**	**1867 (1253)**	**<0.001**	**0.03**
Basal oral intake, kcal/day	**2845 (787)**	**2294 (657)**	**0.02**	**0.01**
Feces volume, g/day	1207 (920)	1822 (1233)	0.11	
Steatorrhea, g/day	38 (32)	35 (21)	0.73	

Clin Nutrition 2020

Safety and Efficacy of Teduglutide (Gattex) in patients with Crohn's disease and need for parenteral support due to short bowel syndrome associated intestinal failure

Crohn's Disease patients on teduglutide

Gender	Age	Disease Duration (years)	Disease Location	Disease Phenotype	# of bowel resections	Ostomy	Medications
Female	46	25	Ileo-colonic	Penetrating	3	Ileostomy	Certolizumab, budesonide, prednisone
Female	37	14	Ileo-colonic	Penetrating	2	Ileostomy	Methotrexate, budesonide, Ustekinumab
Male	56	38	Ileo-colonic	Penetrating	3	None	None
Female	38	17	Ileo-colonic	Penetrating	6	Ileostomy	Adalimumab
Female	41	23	Ileo-colonic	Penetrating	3	Ileostomy	None
Male	45	26	Ileo-colonic	Penetrating	4	Colostomy	Infliximab, thiopurine
Female	60	19	Ileal	Stricturing	3	None	Narcotics
Female	68	46	Ileo-colonic	Stricturing	8	Ileostomy	Mesalamine, narcotics
Male	59	45	Ileo-colonic	Stricturing	6	Ileostomy	None
Female	59	35	Ileal	Stricturing	5	None	Thiopurine, prednisone
Female	49	19	Ileo-colonic	Stricturing	1	None	Ustekinumab, narcotics
Female	72	48	Ileo-colonic	Stricturing	4	Ileostomy	Thiopurine
Male	51	31	Ileo-colonic	Stricturing	5	None	Vedolizumab, thiopurine

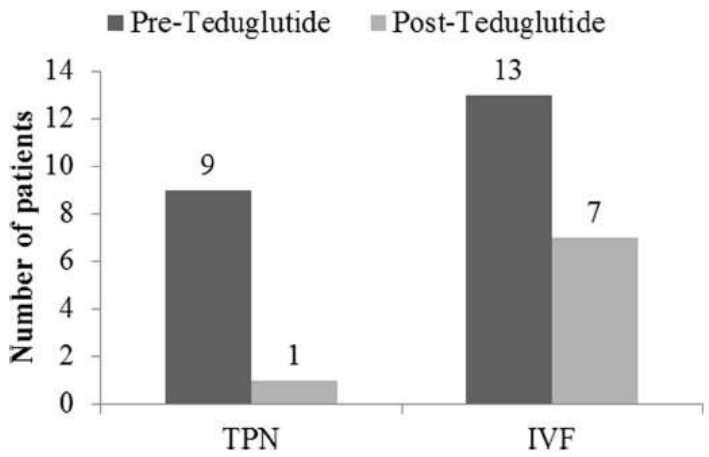
Kochar et al. Page 8

More than 50% on immunosuppressants

Adverse event profile of Crohn's disease patients on teduglutide

Adverse Event	On Immunosuppression (n=8)	Not on Immunosuppression (n=5)
Pancreatitis	1	0
Asymptomatic elevation of lipase and amylase	1	0
Abdominal Pain	2	0
Nausea	0	1
Intermittent obstructive symptoms	0	1
Catheter related sepsis	3	1

J Clin Gastroenterol. 2017 July ; 51(6): 508–511.



Endoscopic surveillance

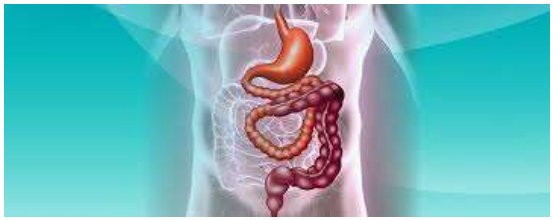
- The development of GI polyps is a safety concern
- Colonoscopy screening is mandatory at the beginning of therapy
- and on follow-up
- In the STEPS 3 study 3 patients developed polyps, in 2 adenomas were diagnosed; in STEPS 2 9 reported polyps, 5 were confirmed for adenoma
- Timing of follow-up colonoscopy not established, the ongoing Clinical Registry will provide indications, one-year colonoscopy is presently recommended

Esperienza Teduglutide in SBS adulto Regione Sicilia

Caso	Età	Sesso	Etiologia	Stomia	Data inizio NPD	N giorni NPD (esordio)	Data inizio teduglutide	Peso corporeo (inizio terapia)	N giorni NPD (ultima visita)	Peso corporeo (ultima visita)
AG	54	F	Complicanze chirurgia	Colostomia	07/2016	7/7	12/07/2018	36,7	0/7	43
PA	36	M	Ischemia mesenterica	Digiunostomia	04/2020	7/7	26/11/2020	45	7/7	62,5
PF	81	M	Ischemia mesenterica	Ileostomia	01/2021	7/7	20/07/2021	51	3/7	65

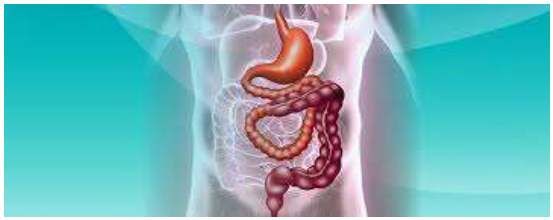
Tutti seguiti dal nostro PICC team per manutenzione accessi venosi
Tutti hanno ottenuto una riduzione del numero di evacuazioni/ sacchetti stomia

Conclusions (1)



- SBS is a rare but disabling condition with high direct and indirect costs both for patients and caregivers and the health system
- HPN is the mainstay of treatment but achieving parenteral nutrition independency is the ultimate goal of managemen
- The increasing diffusion of home-care facilities for parenteral nutrition and novel technical devices have reduced complications and increased life expectancy
- Surgery has a limited role
- An evidence-based used of supportive measures (PPI, loperamide, diet, ONS) is the basis of standard management.

Conclusions (2)



- Teduglutide represents a novel opportunity to a further reduction of morbidity and possible weaning from HPN
- The STEPS programme has demonstrated efficacy of teduglutide in reducing the volume of parenteral nutrition and in obtaining parenteral independence
- Real life studies have confirmed RCTs results
- Safety seems excellent but further observational registries could offer a better insight especially as far as concerns the occurrence of polyps and the need of endoscopic surveillance
- A better definition of predictors of response is warranted to select patients given the costs of therapy; duration of therapy should also be defined
- Teduglutide has been recently proven effective and safe also in children → reimbursed also in pediatric population
- Future fields of research will be the use of teduglutide in patients with active Crohn's disease
- Research ongoing on novel long-acting GLP2 analogues.
- Future perspectives : tissue bioengineering and stem cell therapies.

Thanks for your attention