Intestinal failure

Past, present and future

***Olivier Goulet** MD, PhD*

Pediatric Gastroenterology-Hepatology-Nutrition

National Reference Center for Rare Digestive Diseases
Center for Intestinal Failure Rehabilitation
and Intestinal Transplantation (CIFRIT)

Hôpital Necker-Enfants Malades
University Sorbonne-Paris-Cité
Paris Descartes School of Medicine

olivier.goulet@nck.aphp.fr

Intestinal failure

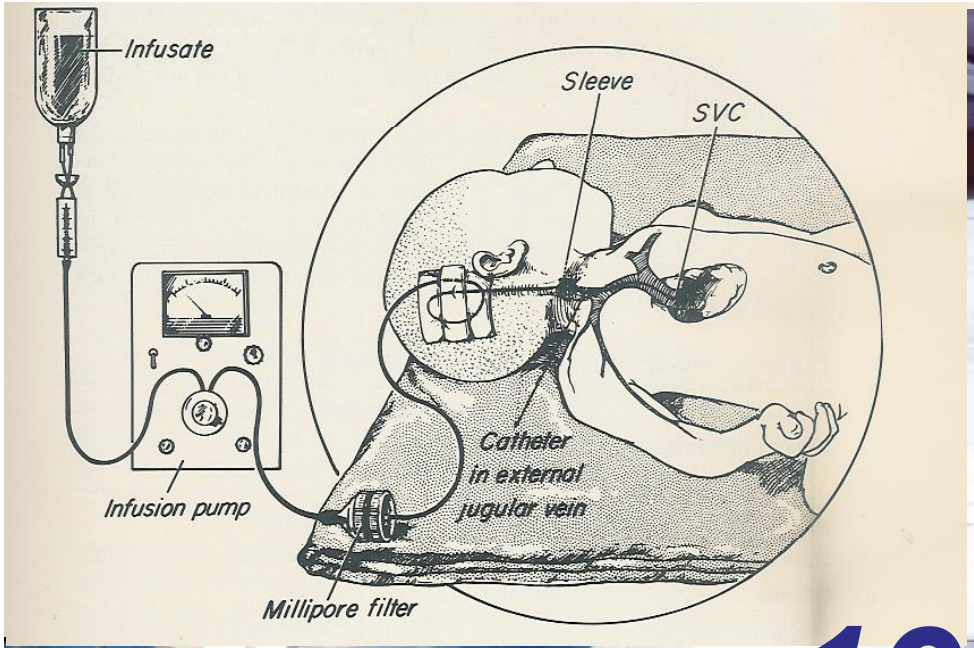
Definition

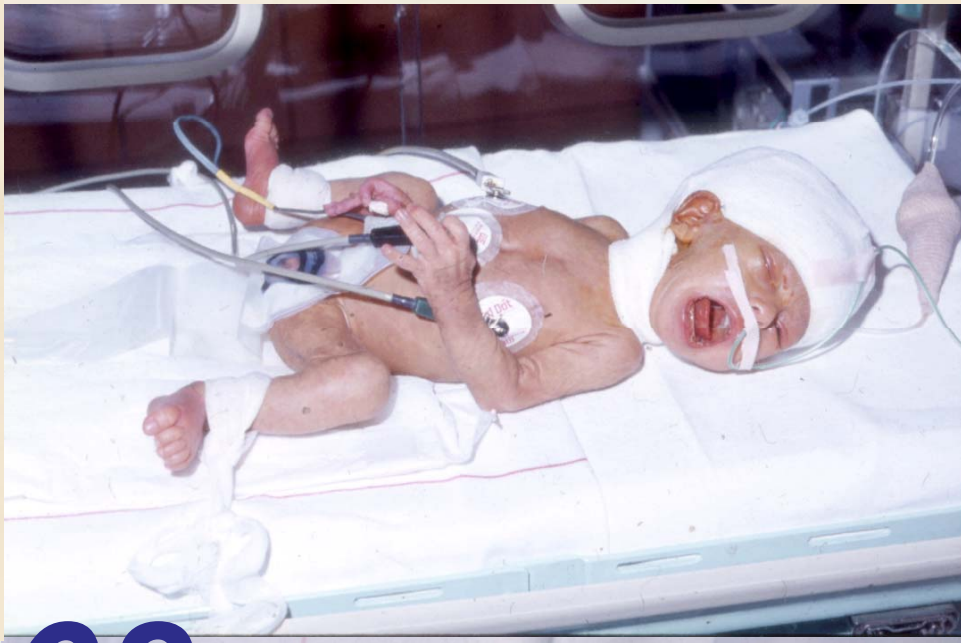
Inability of the GI tract to provide sufficient digestion / absorption capacities to cover nutritional requirements for growth and development of the child that requires parenteral nutrition

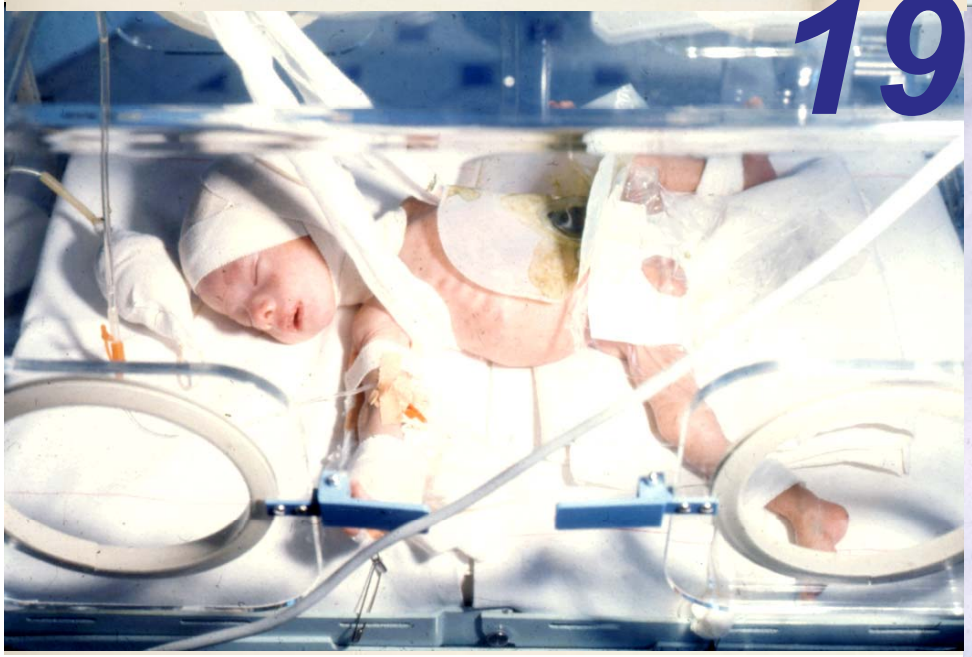
Intestinal failure

In the past

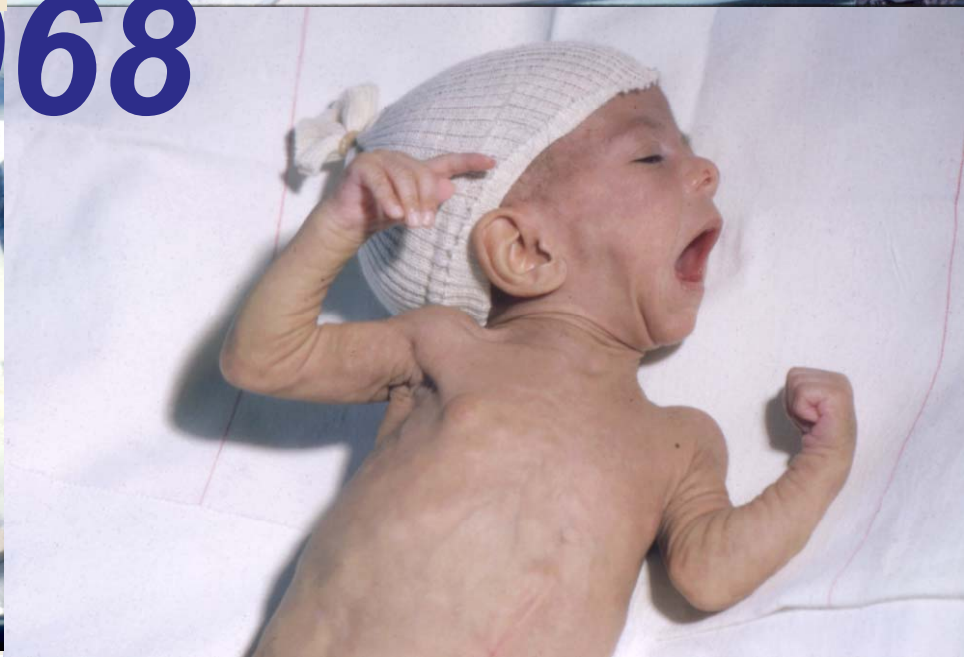
- 60’s implemented pediatric TPN
- 70’s increasing indications for PN

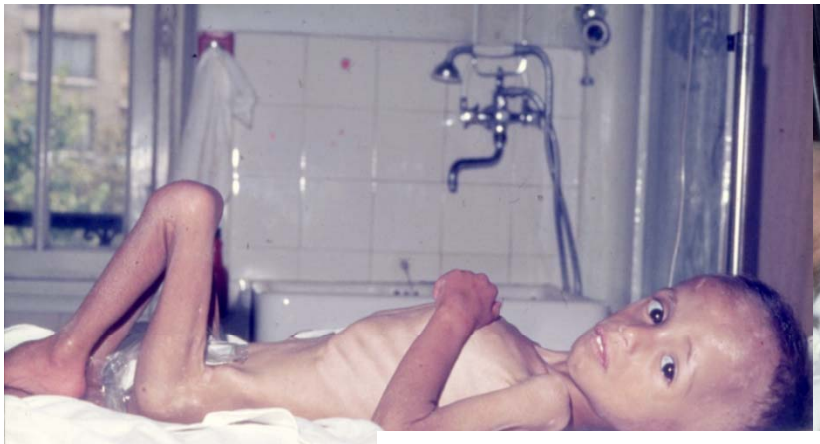

Infusate
Sleeve
SVC
Catheter
in external
jugular vein
Infusion pump
Millipore filter

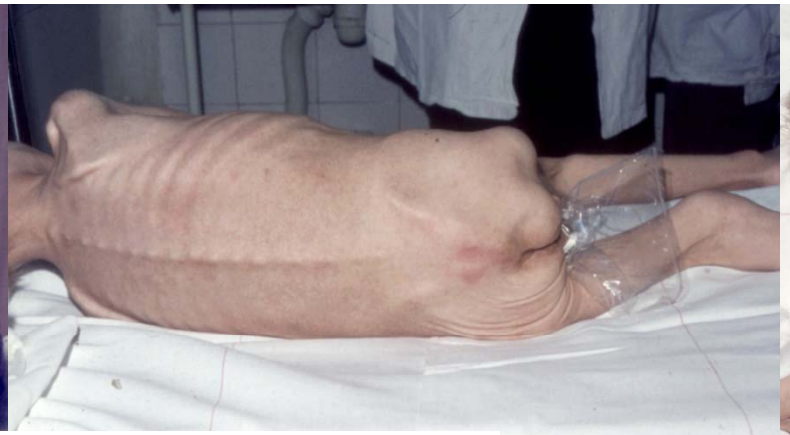


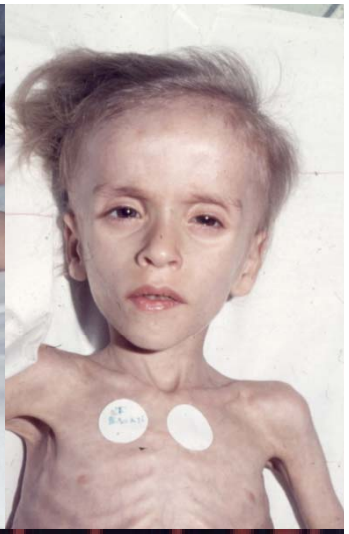


1968

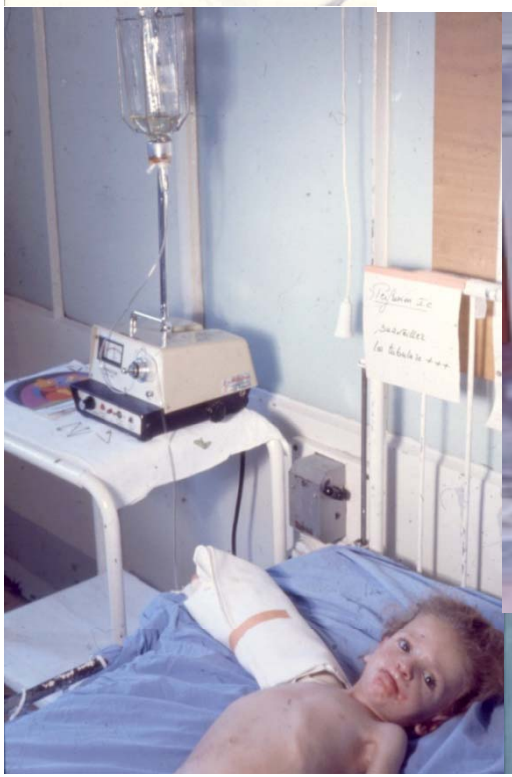


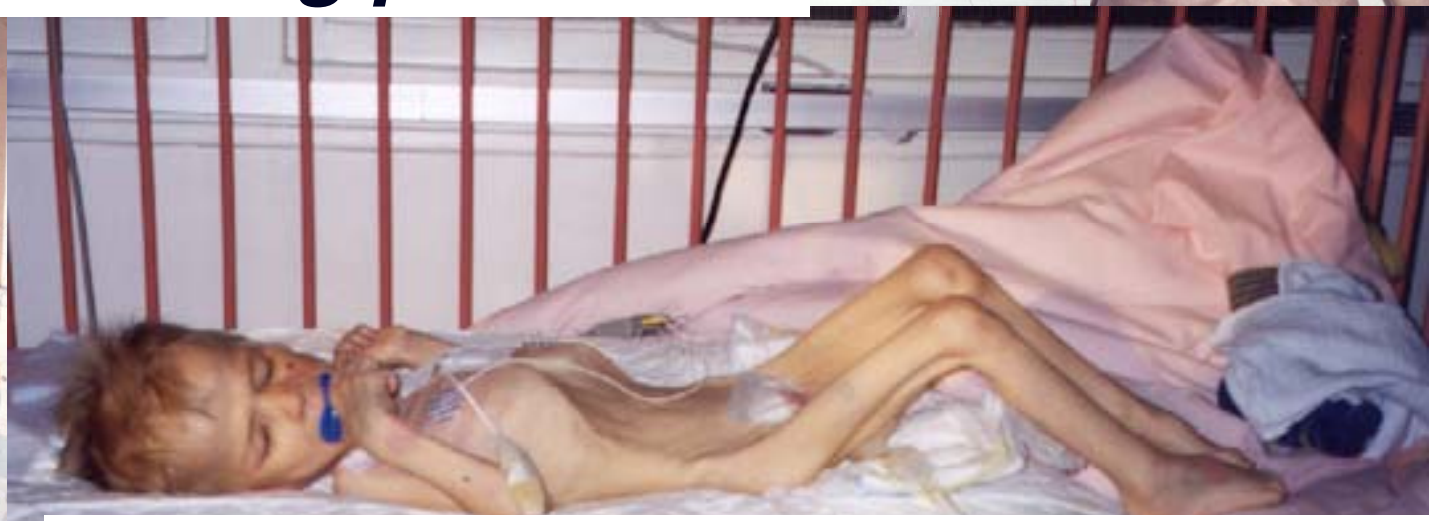






Life saving procedure





Be aware of refeeding syndrome

Protein-energy malnutrition

Intestinal failure

PN related complications

- Technical: catheters, infusion pumps
- Catheter related infections
- Deep venous thrombosis
- End stage liver cirrhosis

Morbidity and mortality induced doubt in the long term safety of PN, justifying alternatives such as intestinal transplantation

Intestinal failure

In the past

- 60’s implemented pediatric TPN
- 70’s increasing indications for PN
- 80’s home parenteral nutrition
- 90’s intestinal transplantation

Intestinal transplantation

Birmingham
Boston(2)
Charleston
Chicago(3)
Dallas
Florida
Iowa City
Kansas City
Los Angeles
Madison
Miami
Minneapolis
New Orleans
New York
Oklahoma City
Omaha
Pittsburgh
Rochester
St. Louis
Stanford

London
Toronto

Torreon
Bologna

Sao Paulo

Buenos Aires

Birmingham
Cambridge
Leeds
London

Brussels
Leuven

Coimbra

Göteborg
Stockholm
Uppsala

Paris
Lyon
Nice

*Madrid**
Barcelona

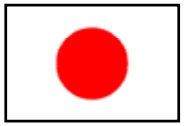
Neumünster
Tübingen
Berlin

Geneva

Bergamo
Milano
Rome
Modena

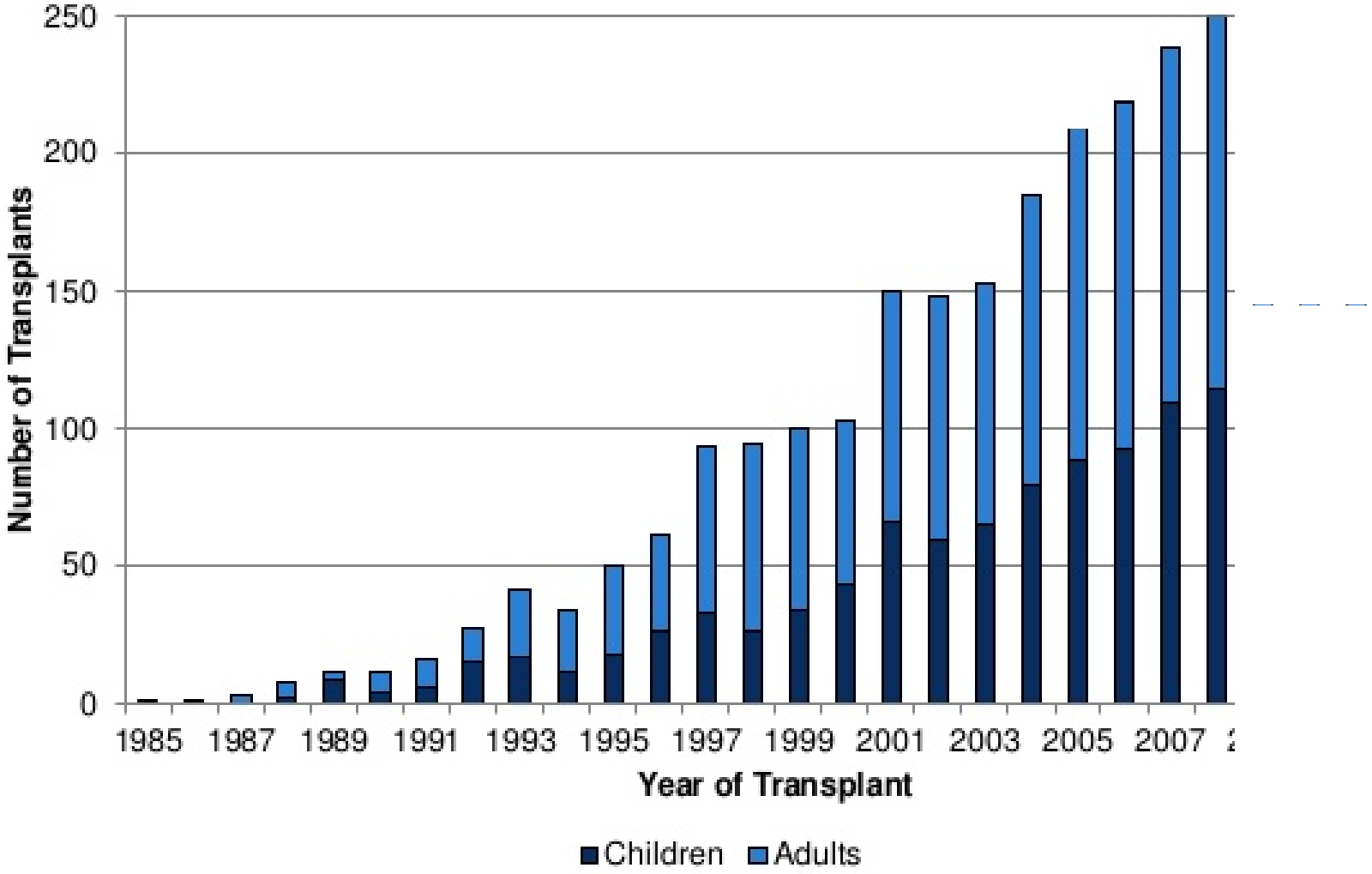
Innsbruck

Nanjing
Tianjin
Wuhan
*Xi'an**

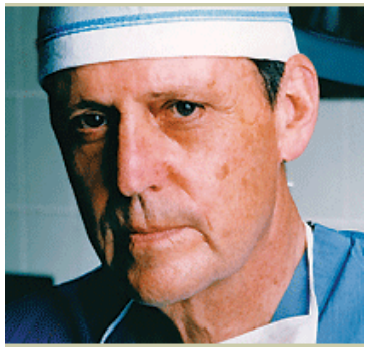


Kyoto
Osaka

Intestinal Transplants Performed

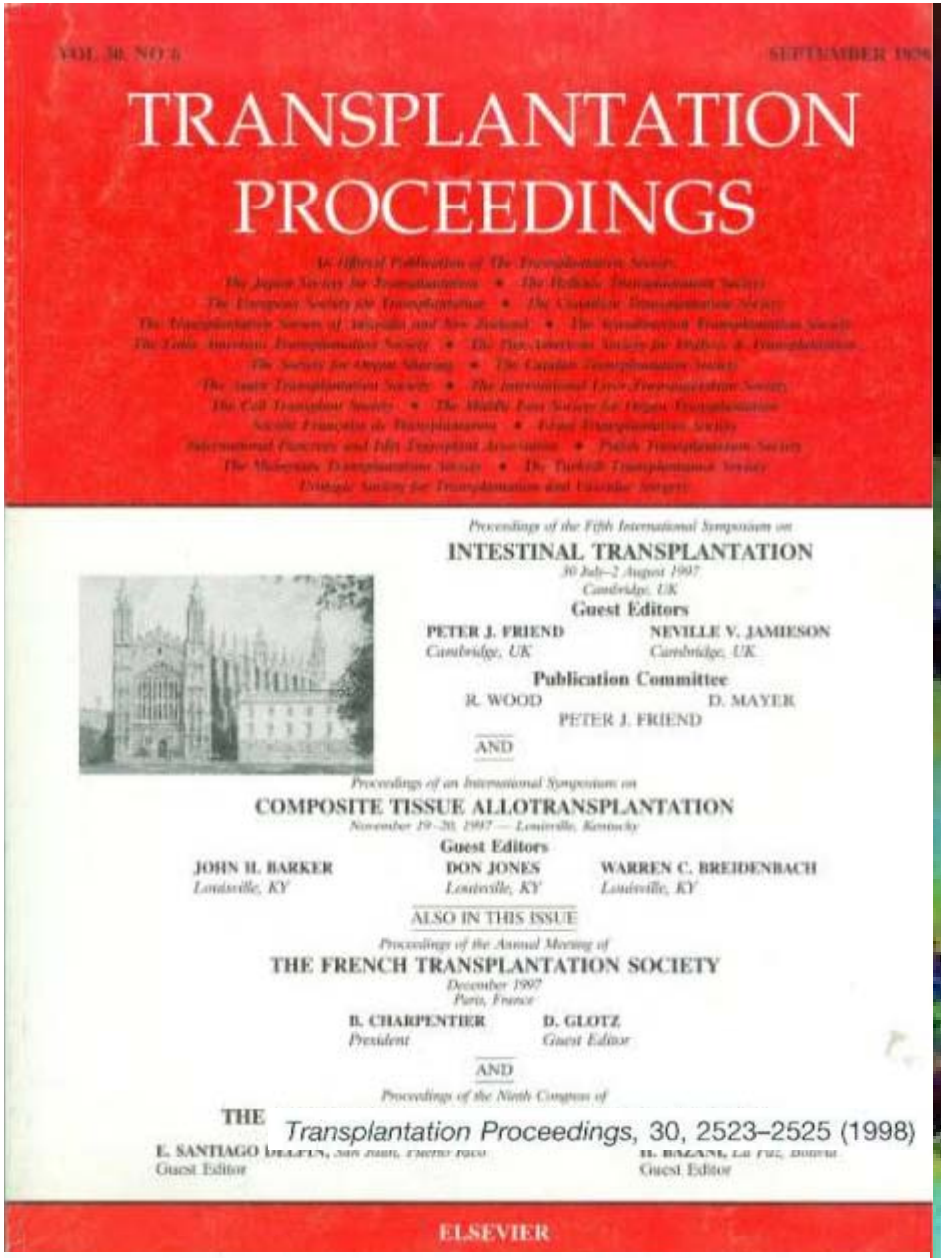


Intestinal failure



In the past

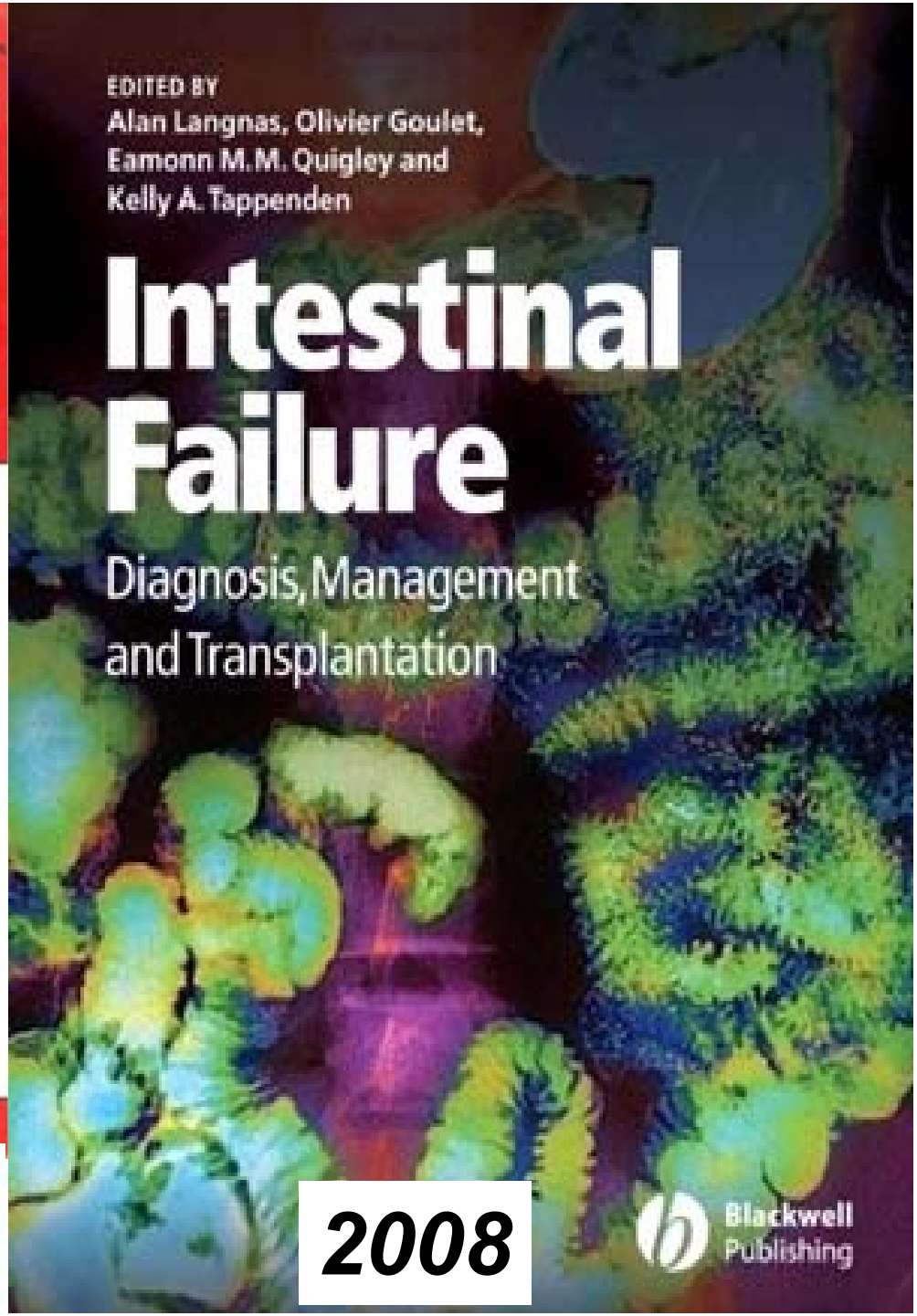
- 1989 London: experimental
- 1991 Ontario: 1° liver-intestine
- 1993 Paris: Failure of cyclosporine
- 1995 Pittsburgh: tacrolimus onset
- 1997 Cambridge : *Intestinal failure*



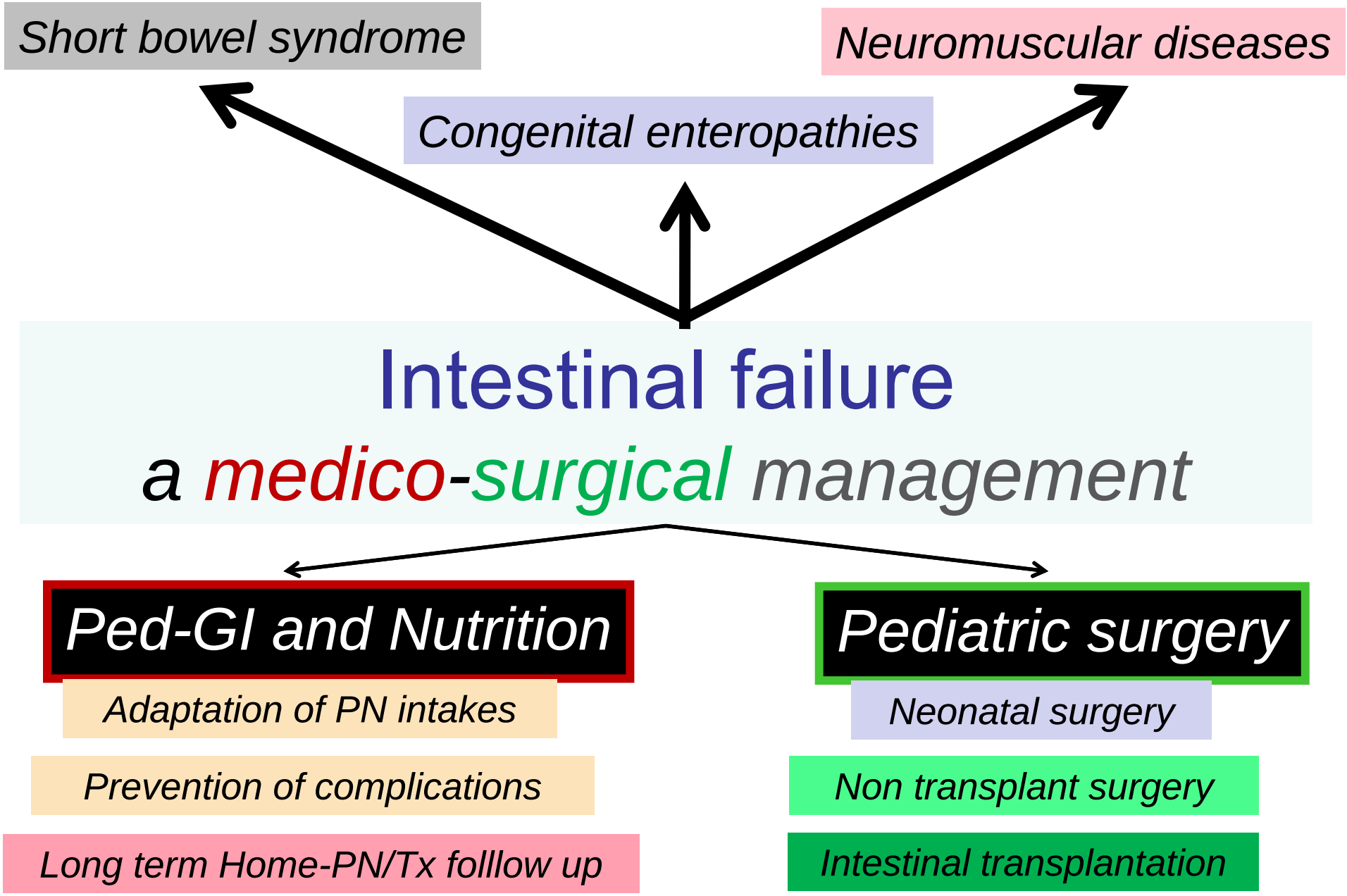
Intestinal Failure in Children

O. Goulet

1998



2008



O.Goulet Intestinal Failure. Transpl Proc 1998

Intestinal failure

In the past

- 60's implemented pediatric TPN
- 70's increasing indications for PN
- 80's home parenteral nutrition
- 90's intestinal transplantation
- **> 2000: «Intestinal rehabilitation»**

NCBI Resources How To

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed | intestinal rehabilitation children | Search

Create RSS Create alert Advanced

Article types
Clinical Trial
Review
Customize ...

Text availability
Abstract
Free full text
Full text

PubMed Commons
Reader comments
Trending articles

Format: Summary **Sort by**: Most Recent **Per page**: 20 **Send to**

Search results

Items: 1 to 20 of 603

<< First < Prev Page 1 of 31 Next > Last >

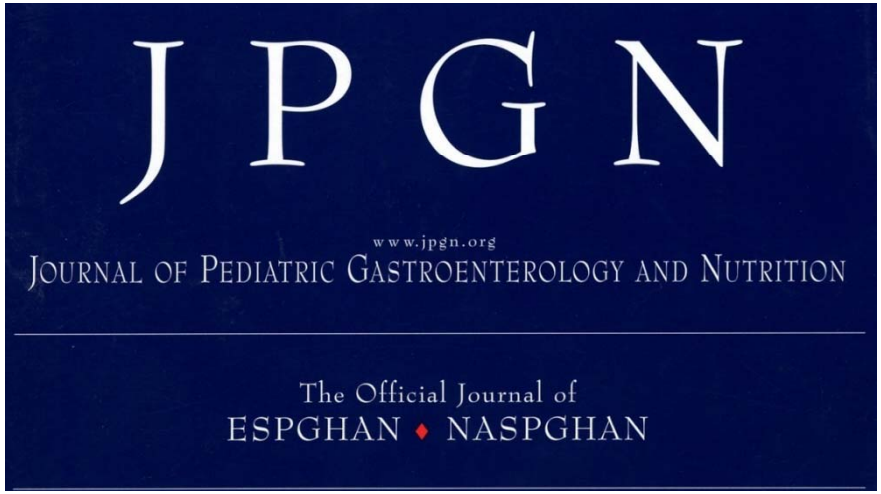
1. Impact of multidisciplinary teams for management of **intestinal** failure in **children**.
Belza C, Wales PW.
Curr Opin Pediatr. 2017 Apr 4. doi: 10.1097/MOP.0000000000000493. [Epub ahead of print]
PMID: 28379928
Similar articles

Results by year

Download CSV

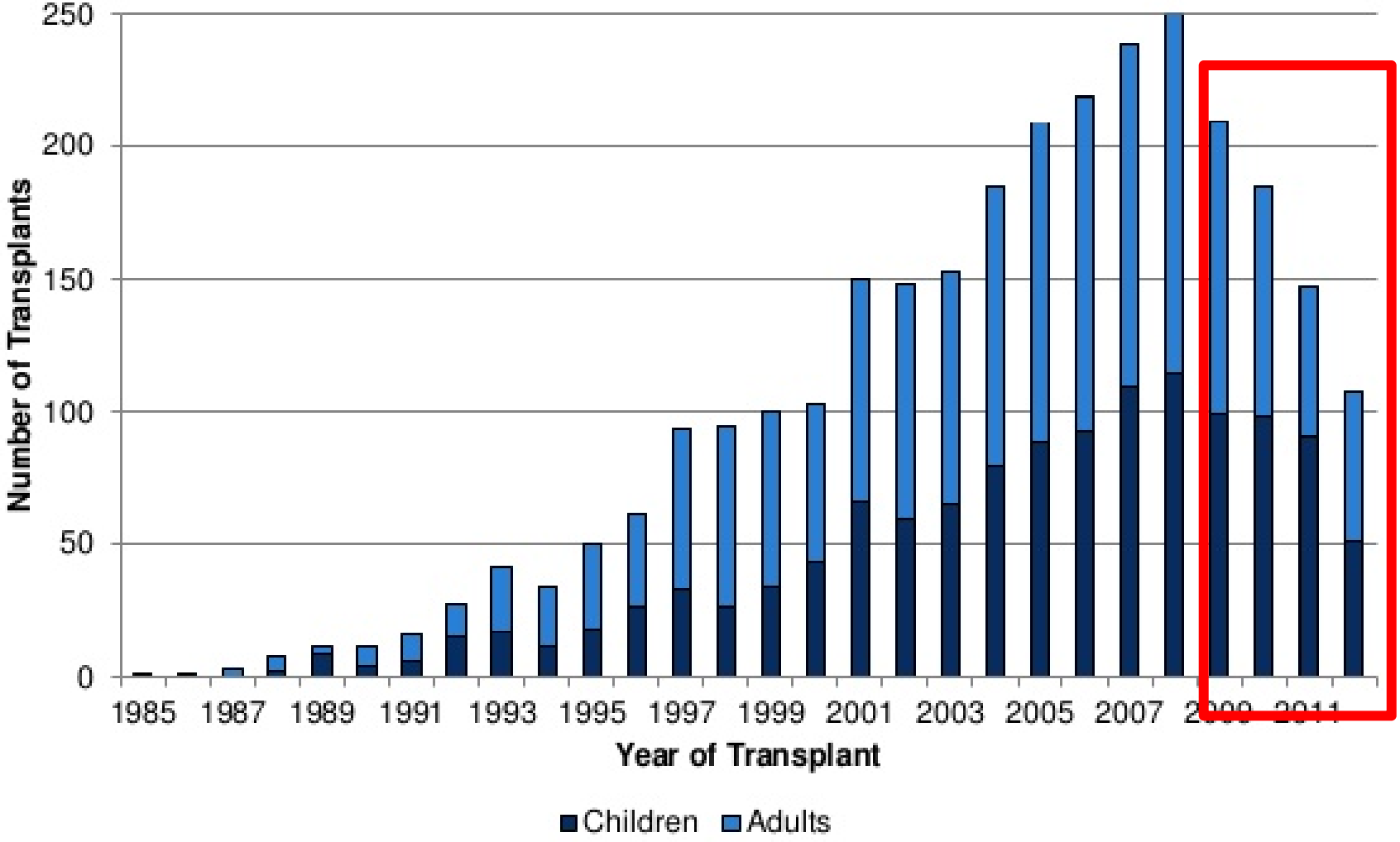
PMC Images search for *intestinal rehabilitation children*

ESPGHAN – ESPEN Guidelines on Paediatric Parenteral Nutrition



2005

Intestinal Transplants Performed



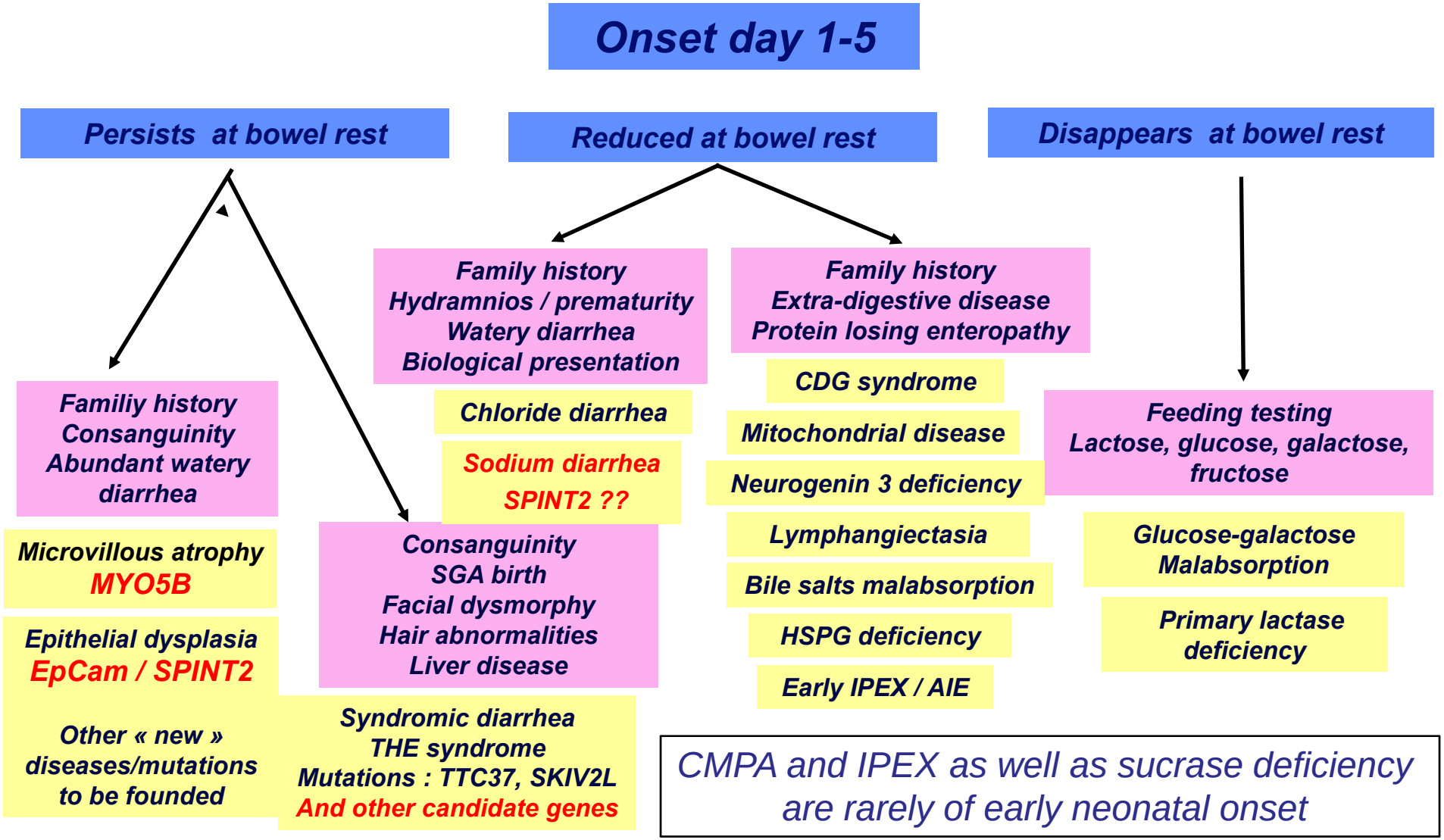
Intestinal failure

Causes in children

- Some congenital enteropathies
- Neuromuscular intestinal diseases
- Short bowel syndrome

Very distinct situations with different degree of « intestinal insufficiency » achieving different courses of IF

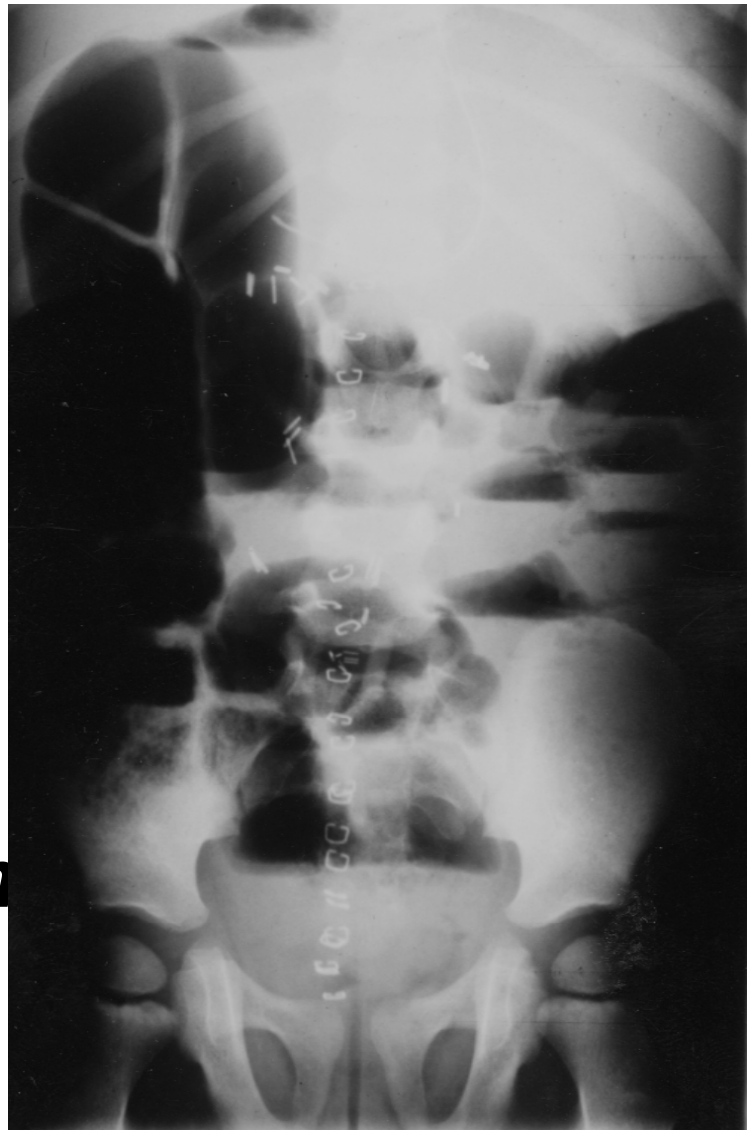
Clinical approach of early onset severe diarrhea



Intestinal pseudoobstruction

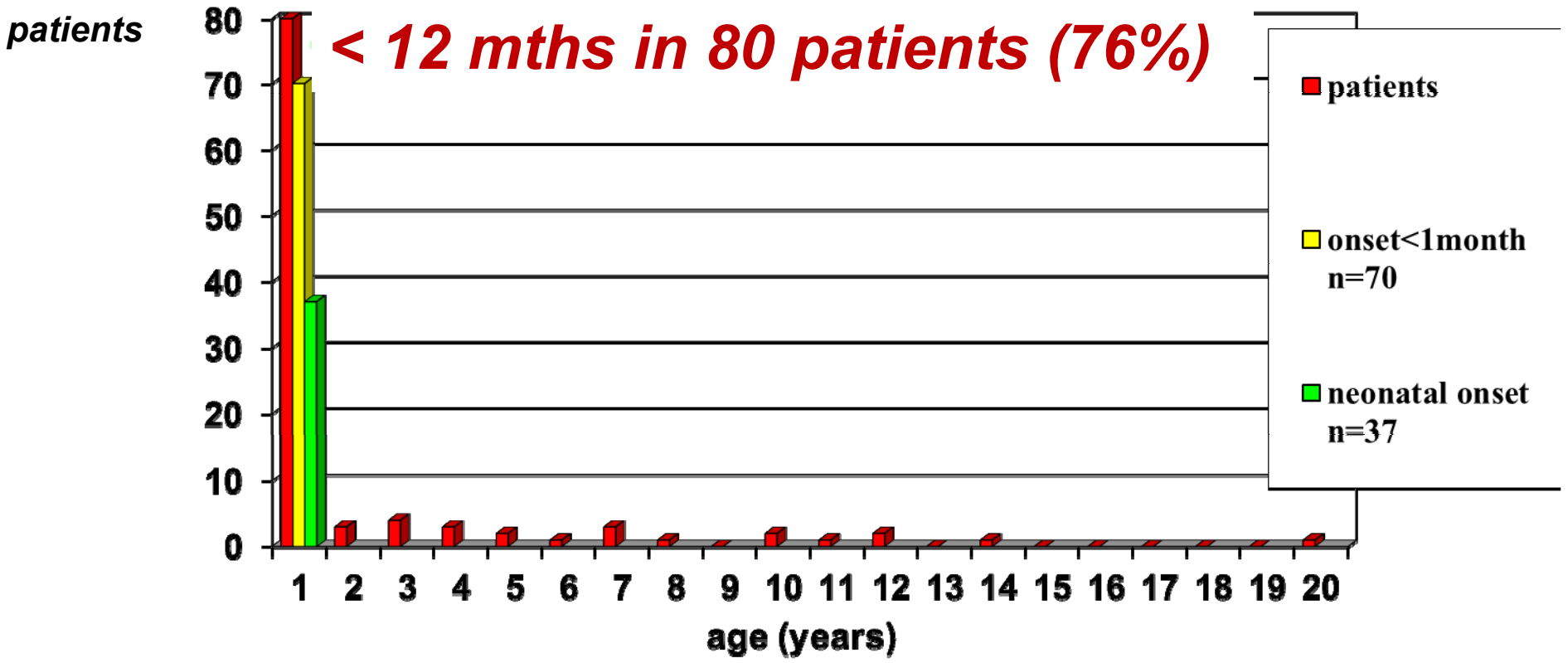
Definition

CIPO is characterized by repetitive episodes or continuous symptoms and signs of bowel obstruction, including radiographic documentation of dilated bowel, in the absence of a fixed lumen occluding lesion



Intestinal pseudoobstruction

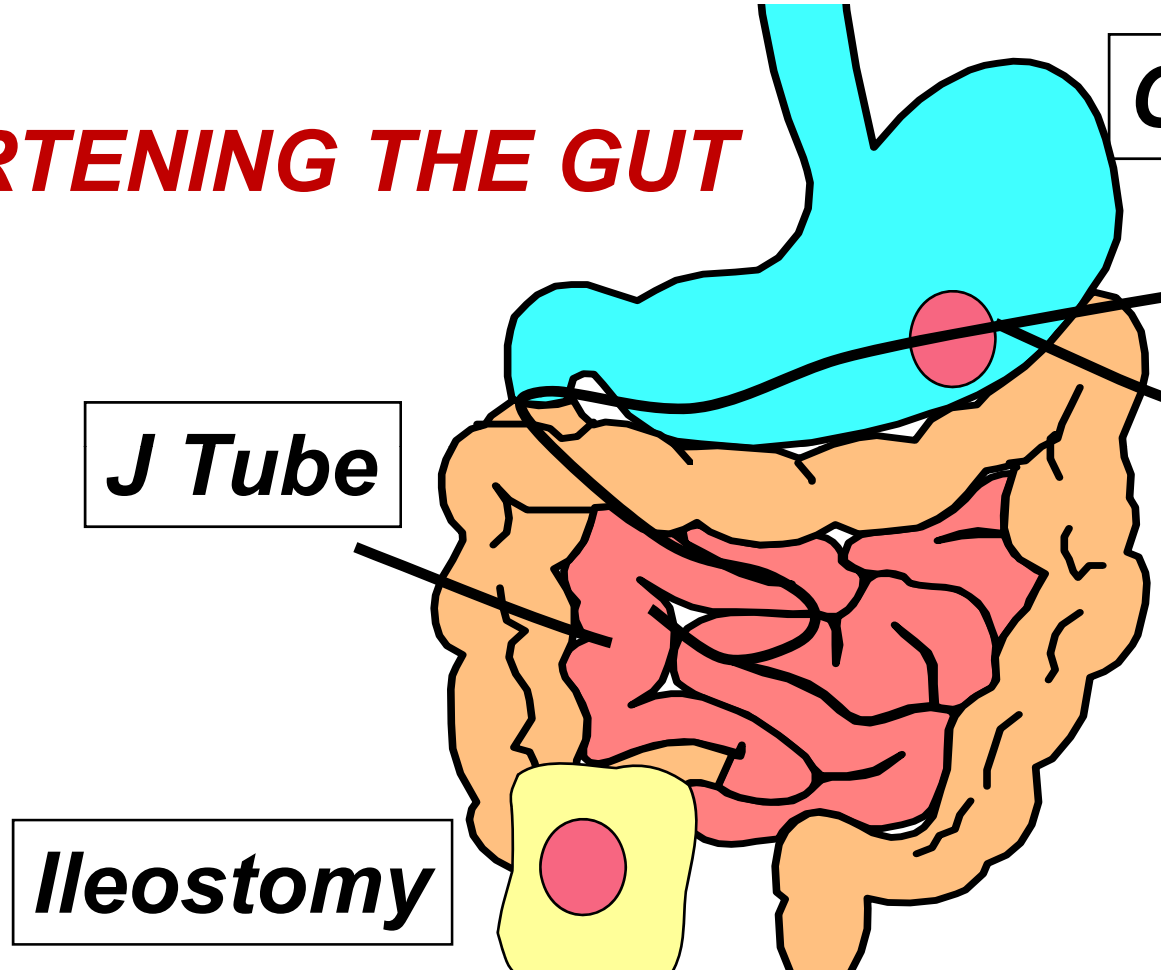
Age at onset

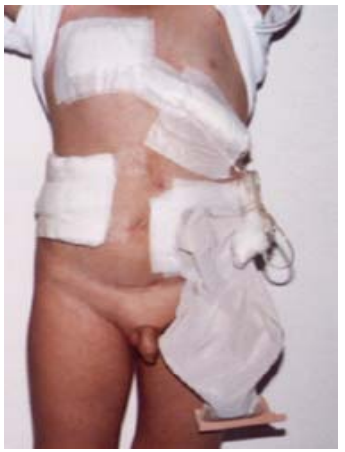


Faure C, Goulet O et al Dig Dis Sci 1999; 44:953-959

Surgery in pseudo-obstruction

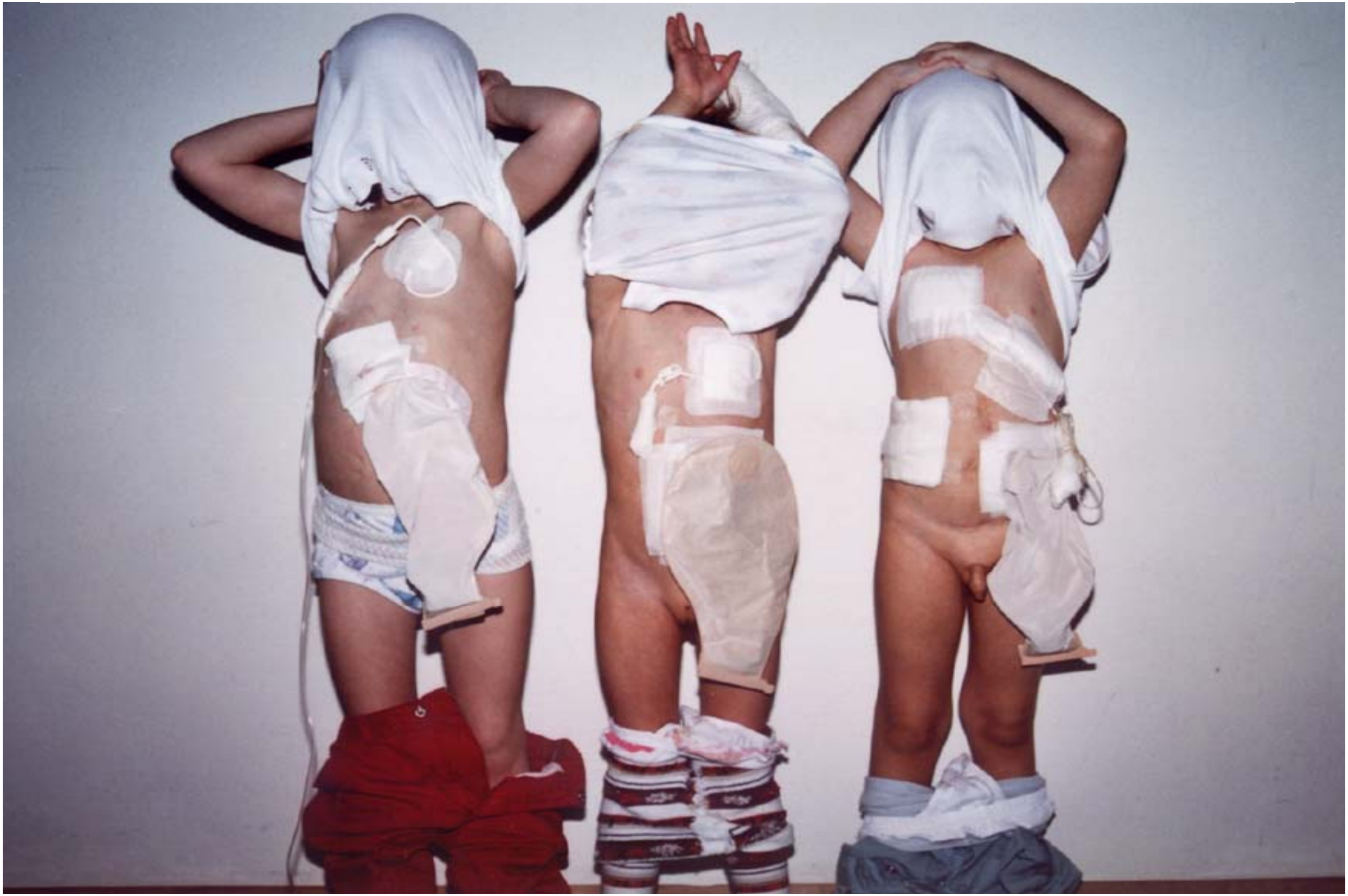
SHORTENING THE GUT





Intestinal transplantation may be indicated in selected cases because of PN limits and/or poor QOL

Chronic intestinal pseudo-obstruction



Quality of Life Outcomes in Congenital Chronic Intestinal Pseudo-Obstruction

	Normal	CIPOS	P
Self care mobility	96	79	< 0.001
School Social activities	94	68	< 0.001
Pain free	82	52	< 0.001

Compared to both normal and JCA, CIPOS have

- ***Decreased self esteem***
- ***Increased anxiety***

Digestive Diseases and Sciences, Vol. 47, No. 9 (September 2002), pp. 1965–1968 (© 2002)

CIPOS : Team effort

- Pediatric GIH
- Dietitian / nutritionist
- Pediatric surgeon
- Anesthesiologist
- Infectious disease
  - *line sepsis, bacterial overgrowth*

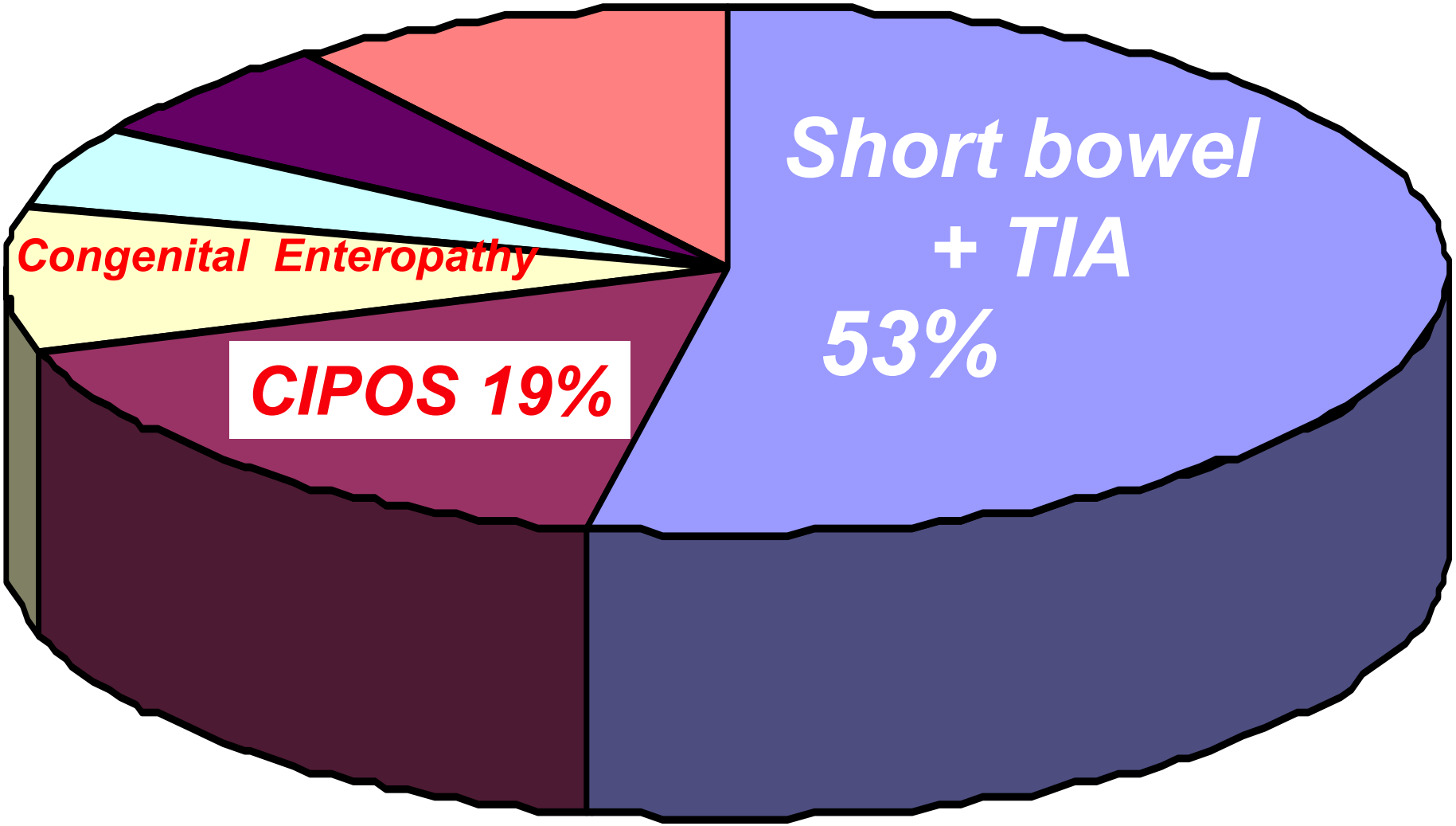
- ***Dietitian/nutritionist***
- ***Psychologist***
- ***Social worker***
- ***Other subspecialists,***
  - ***based on co-morbidities***

Intestinal transplantation

Criteria for performing in CIPOS

- **Permanent intestinal failure**
  - *Daily gastric aspiration*
  - *High level of PN dependency*
  - *Onset of PN and IF related complications*
- **Poor quality of life for child and family**

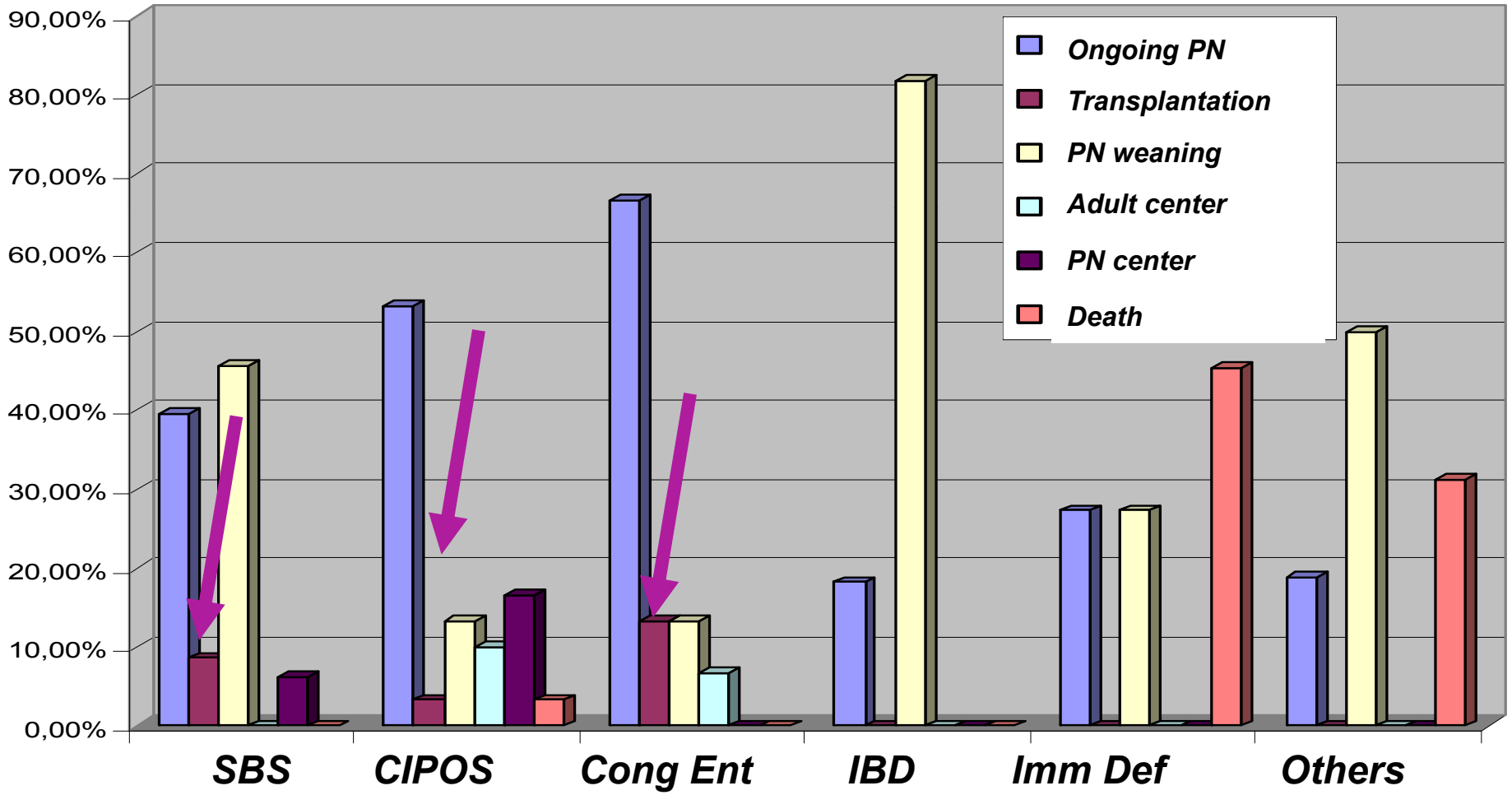
Paris Necker Home PN Programme 2000-2015
253 patients



Abi Nader et al Am J Clin Nutr 2016

Paris Necker Home PN Programme 2000-2015
253 patients

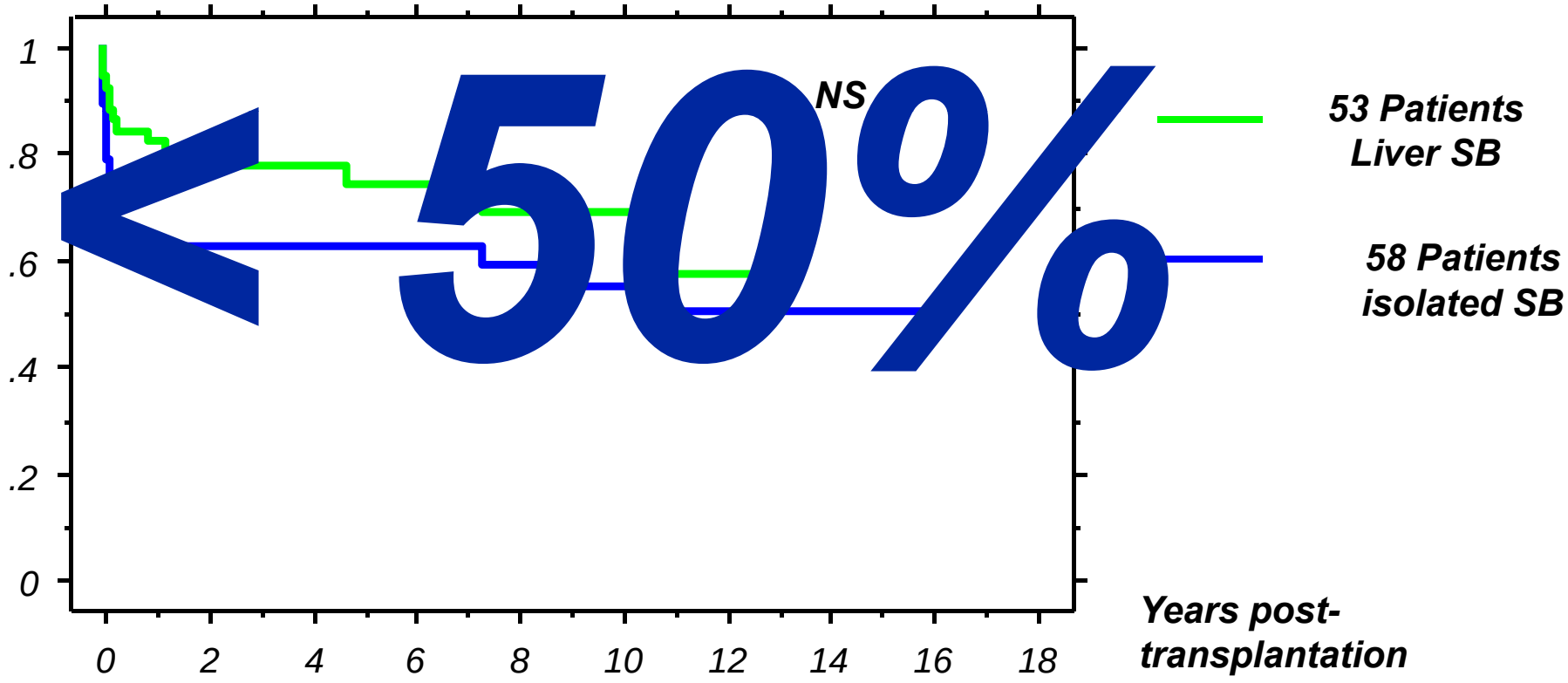
Outcome



Abi Nader et al Am J Clin Nutr 2016

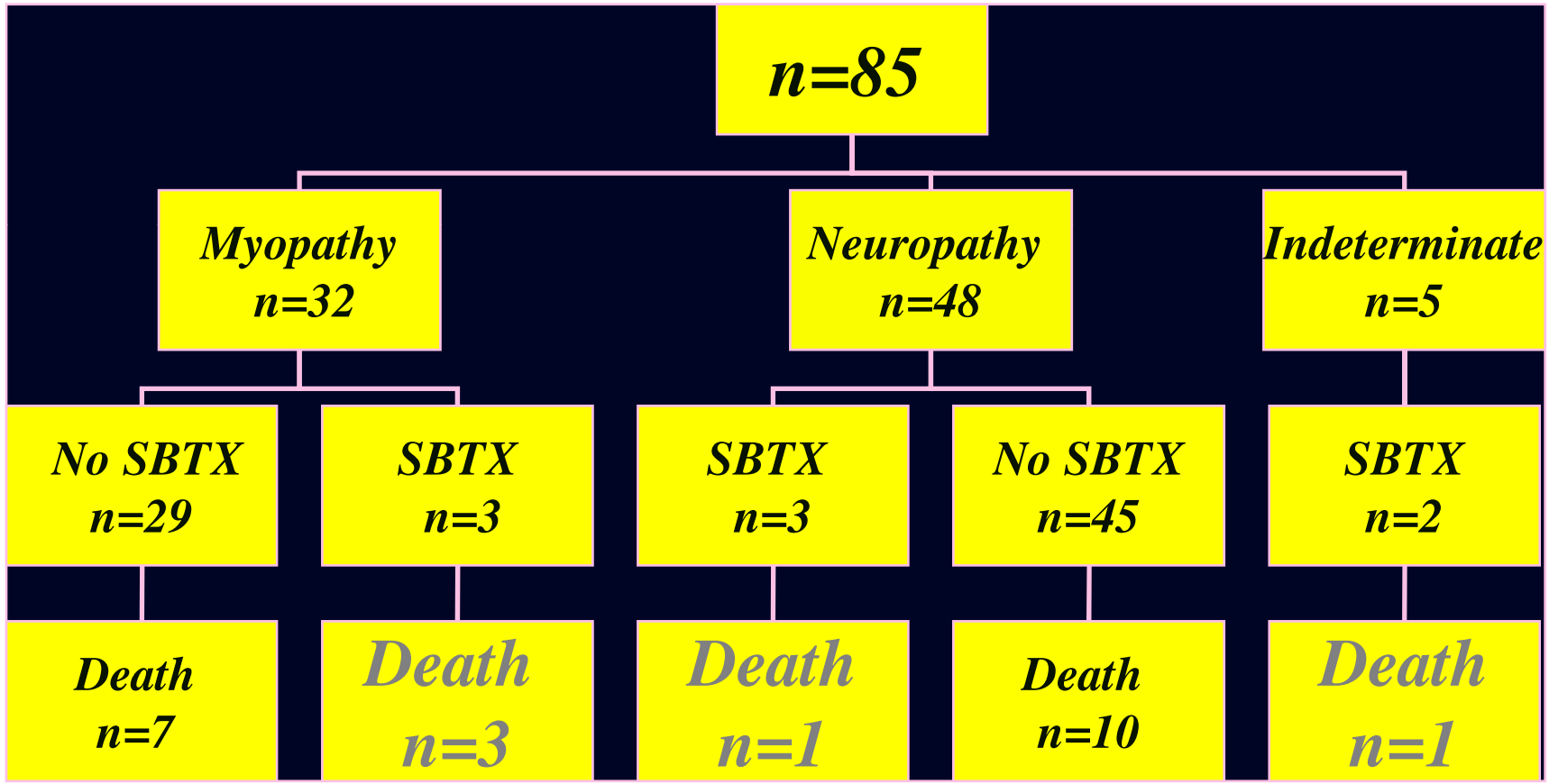
Patient survival and by graft type

Necker 1994-2016



CIPOS and transplantation

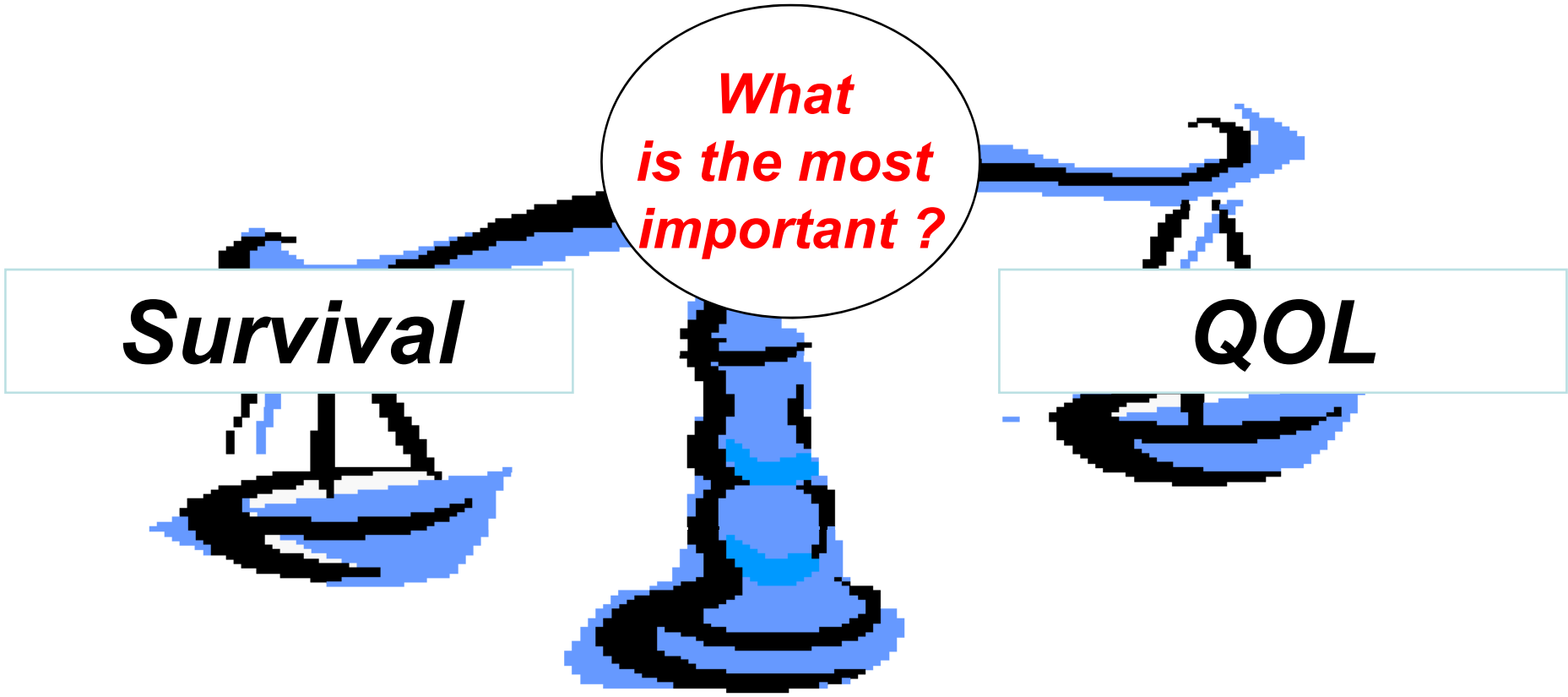
long-term outcome



62.5% post Tx death

Mousa H, et al. Dig Dis Sci. 2002;47:2298-305.

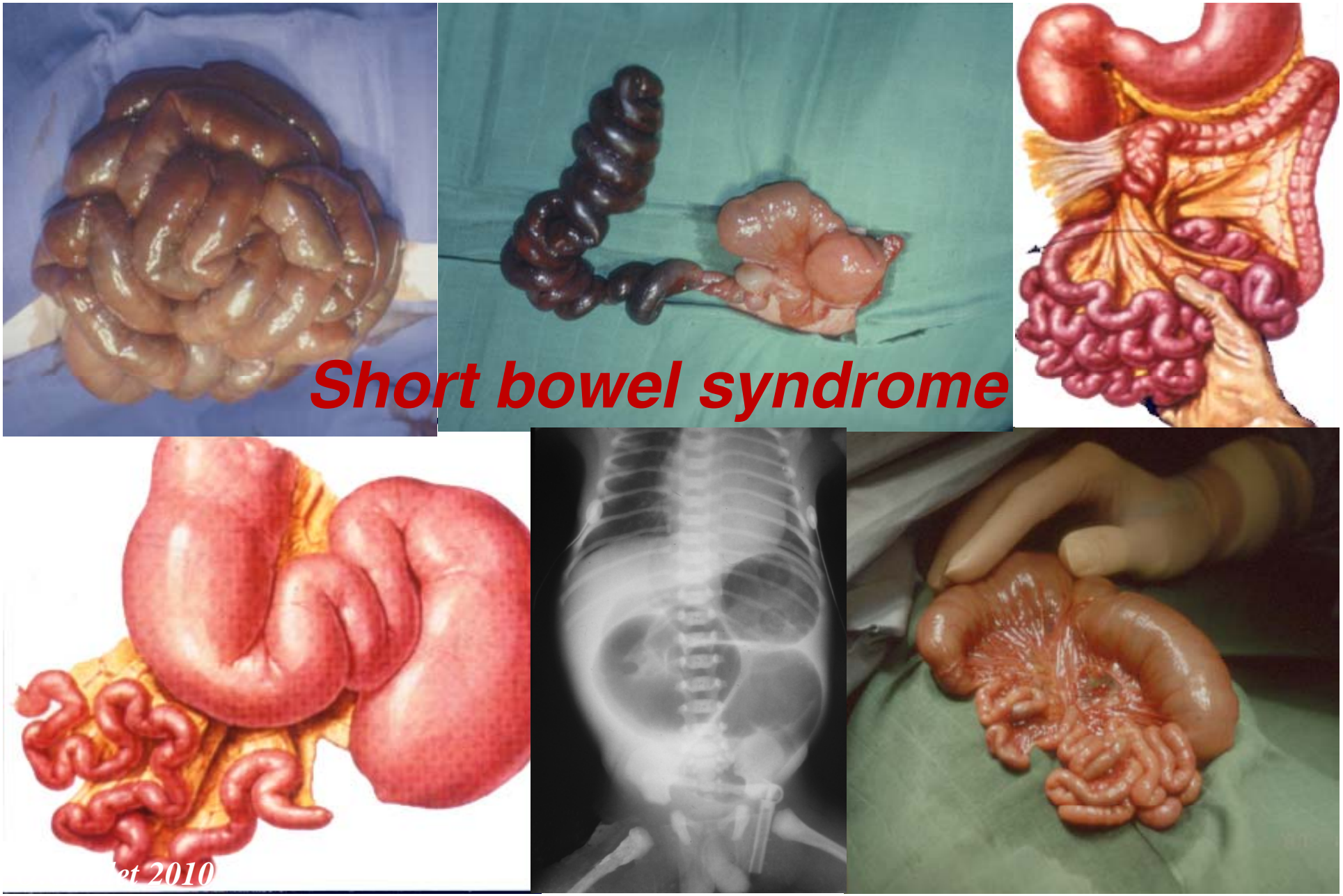
From Home-PN to ITx



Intestinal pseudoobstruction

Main issues

- **The most « desesperating » digestive disease**
- **Who knows the best therapeutic option ??**
- **Failure of most pharmacological approach**
- **The concept of «intestinal reduction» is poor**
- **Multiple surgery worse long term outcome**
- **Place and timing of intestinal transplantation?**


Short bowel syndrome

Short Bowel Syndrome (SBS)

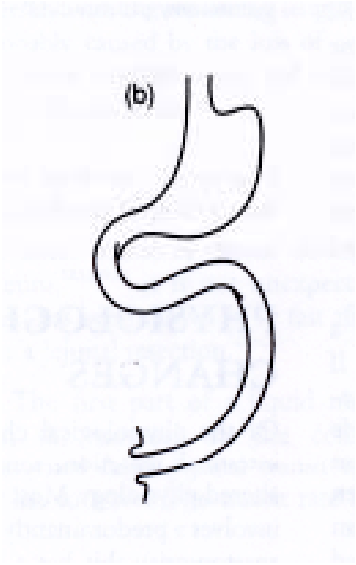
leading cause of severe intestinal failure

Definition

SBS is a clinical condition characterized by **malabsorption and rapid transit** after more or less **extensive resection** of the small intestine and requiring **parenteral nutrition**

Goulet et al Gastroenterology 2006

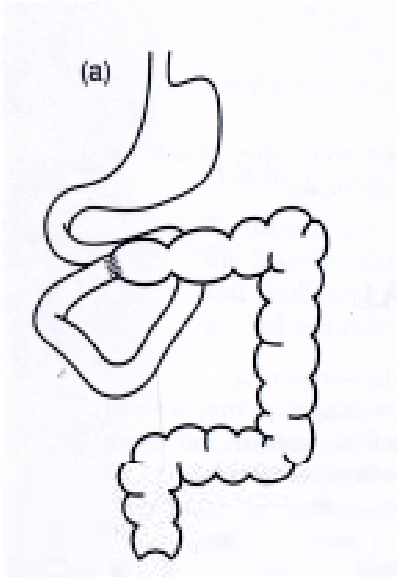
Anatomy of short bowel causing intestinal failure in childhood



Enterostomy : type I

≤ 40 - 80 cm

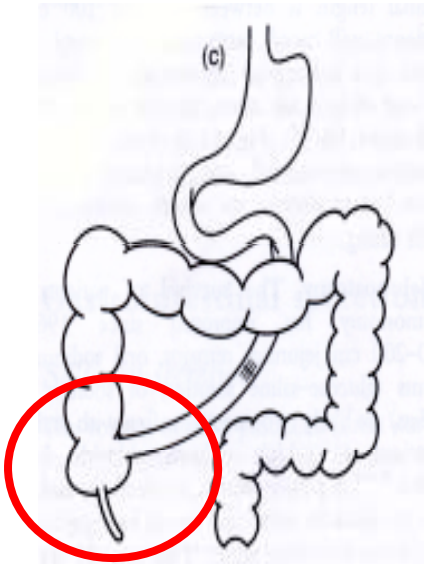
Aganglionosis
Extensive NEC



Jejuno-colic : type II

≤ 40 - 80 cm

Atresia/gastroschisis
Extensive NEC



Jejuno-ileocolic: type III

≤ 20 - 80 cm

Mid gut volvulus
Atresia

Adaptation of Remnant Intestine

Physiological process

Short segment

Nutrients

Diminished Absorptive surfaceSA

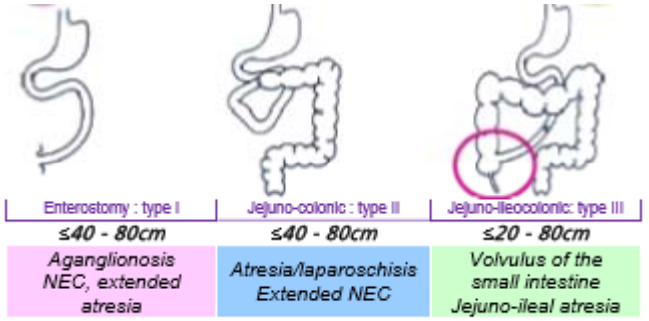
Reduced Nutrient Absorption

Diarrhea
Mucosal Inflammation

- Dehydration
- Electrolyte disturbance
- Perianal excoriation

Adapted Intestine

Increased Nutrient Absorption



Adaptation of Remnant Intestine

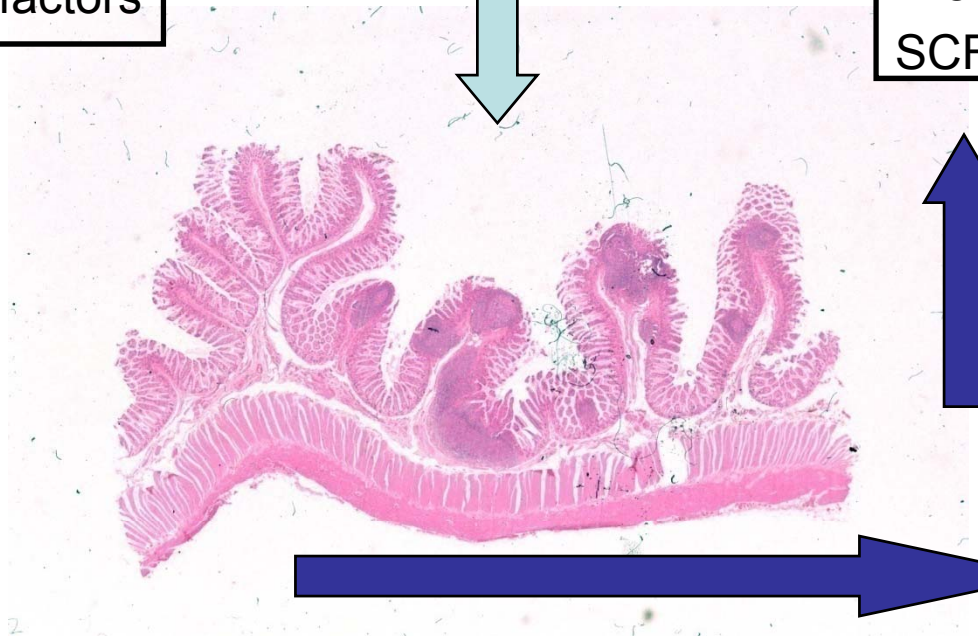
HORMONAL FACTORS

LUMINAL FACTORS

Enteroglucagon
Glucagon-like peptide 2
Peptide YY
Secretin
Growth Hormone
IGF-1
Endogenous growth factors

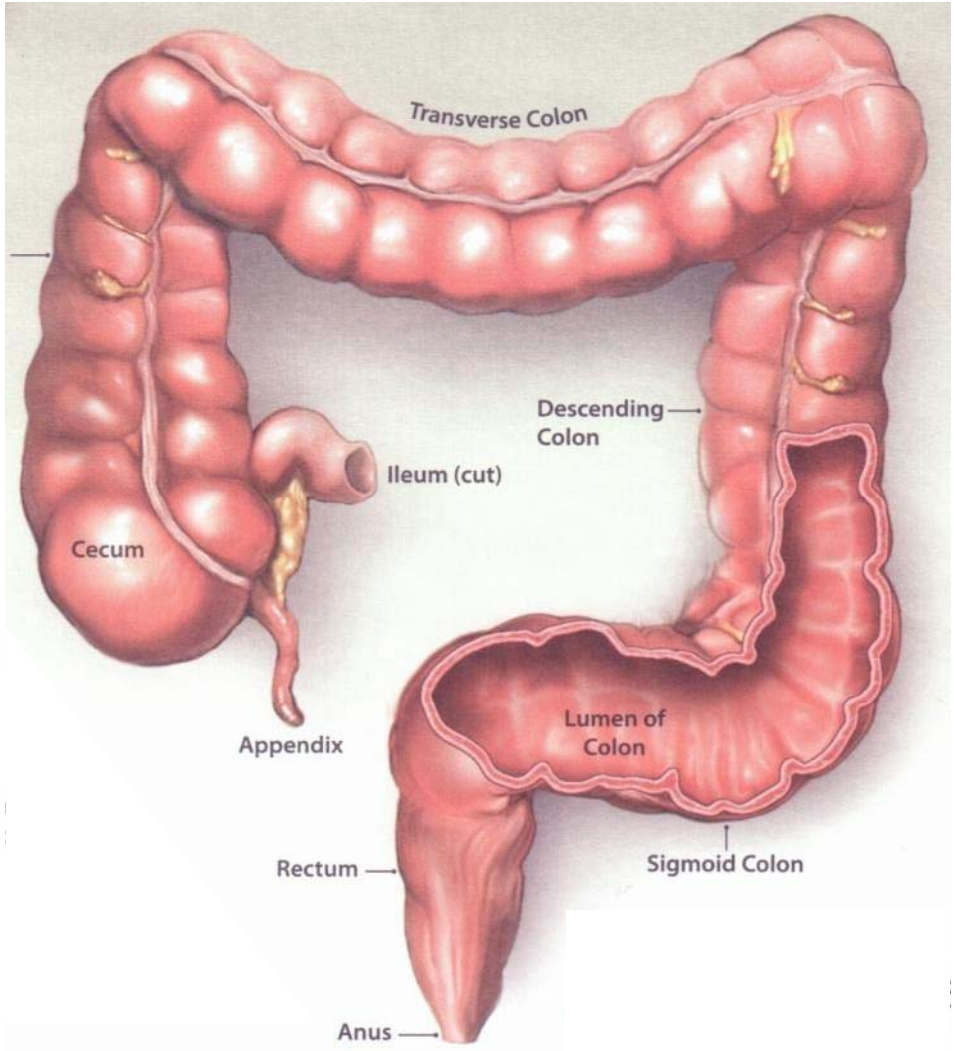
Gastrin
CCK
Neurotensin

IGF-1,
Polyamines
Long chain TG
Protein
Glutamine
Pre-biotics, probiotics
SCFA-butyric acid

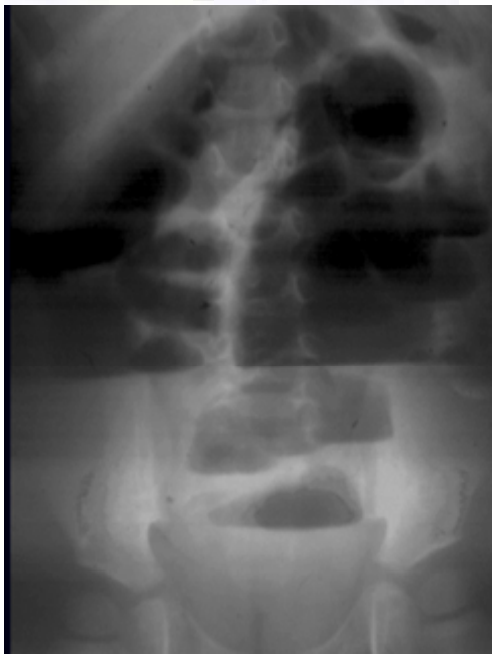


DiBaise et al Am J Gastroenterol 2004;99(7):1386.

Short bowel syndrome

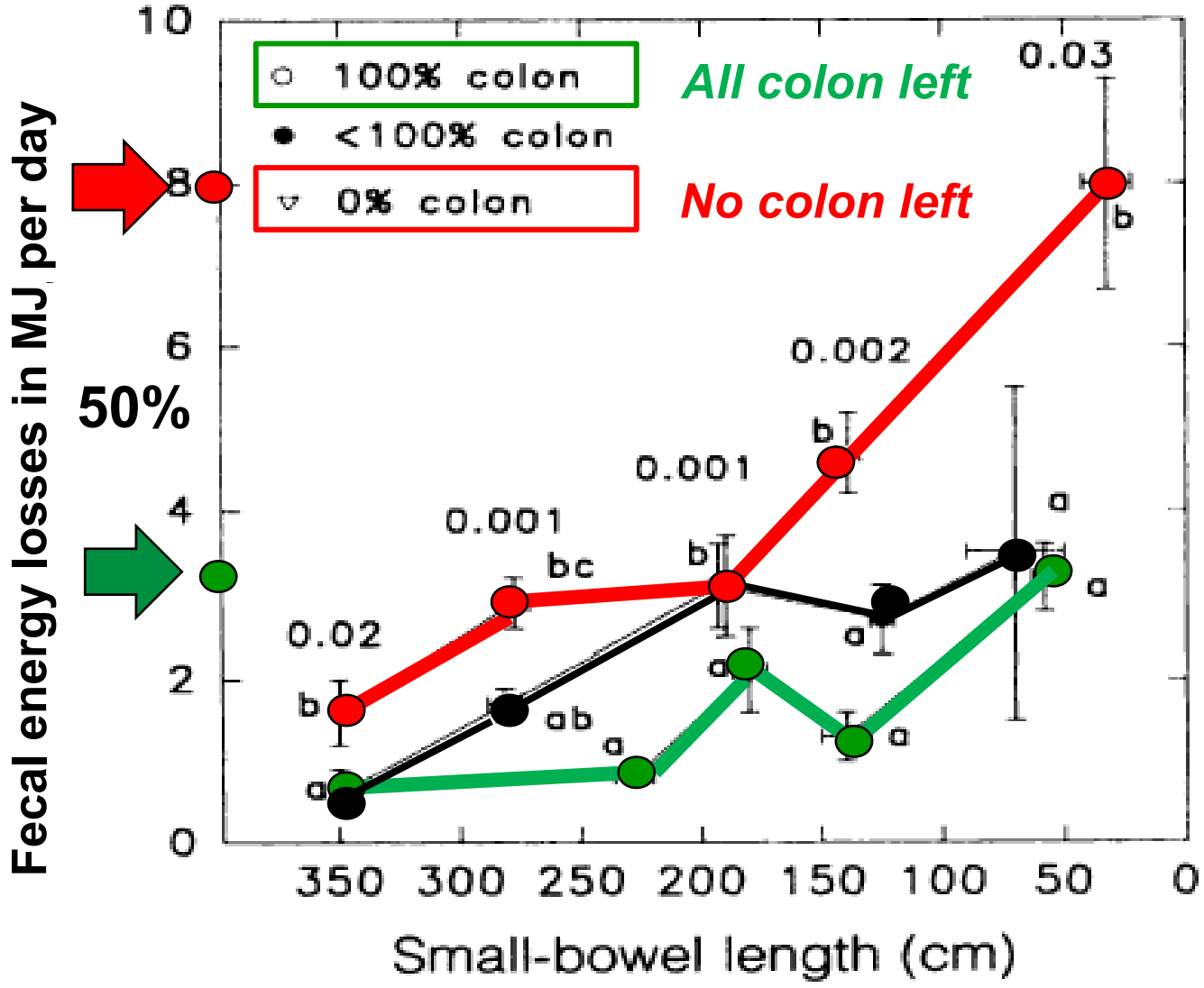


Importance of the colon

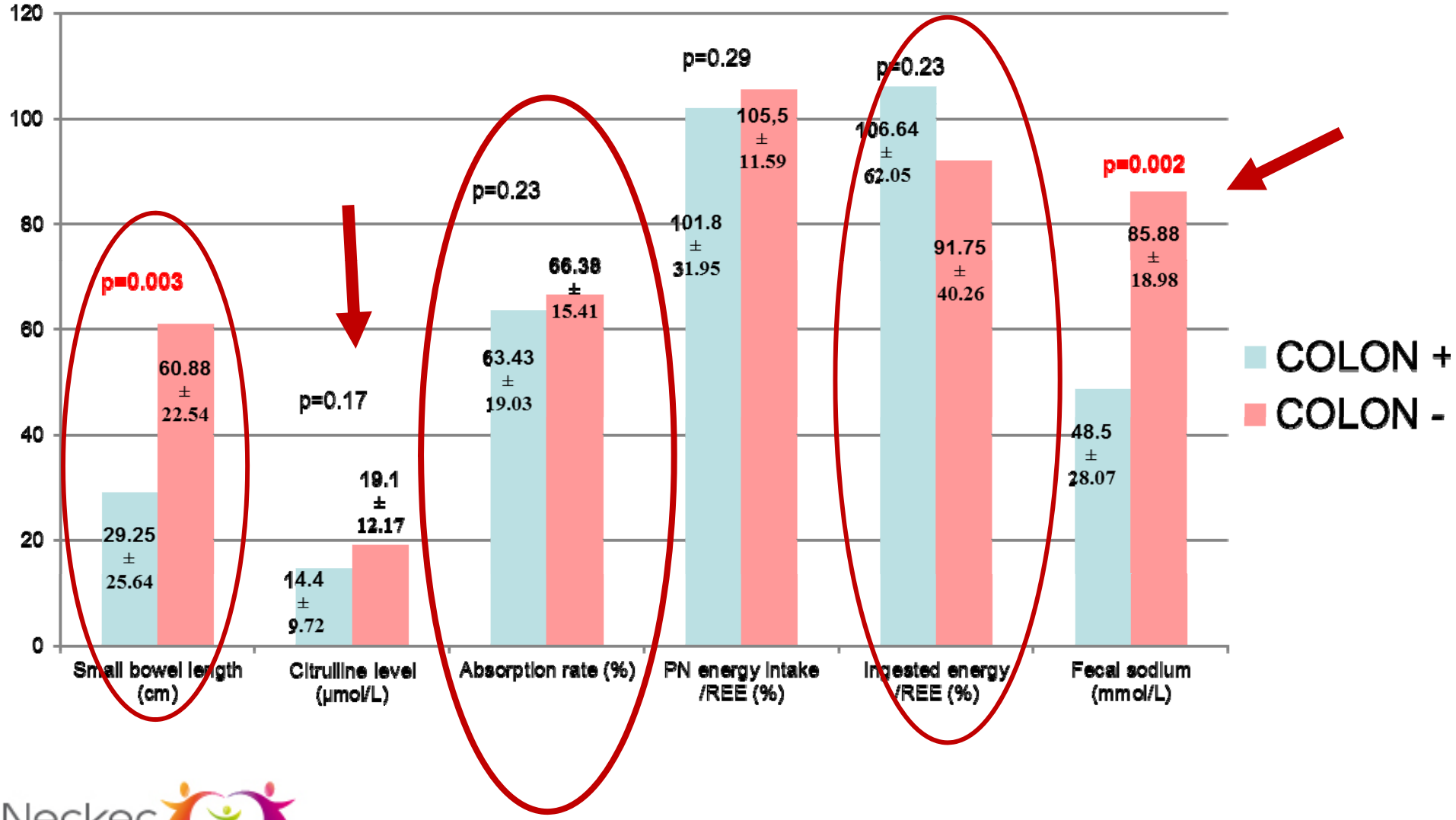


Importance of colonic support for energy absorption as small-bowel failure proceeds[1–3]

Inge Nordgaard, Birthe S Hansen, and Per B Mortensen ***Am J Clin Nutr 1996***



Role of the colon in energy salvage



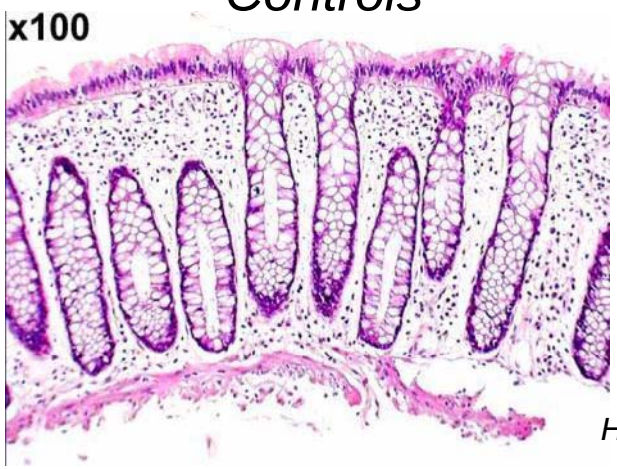
Necker ENFANTS MALADES HÔPITAL UNIVERSITAIRE

Abbi Abou S……Goulet O 2017 JPGN submitted

Morphology of the colonic mucosa

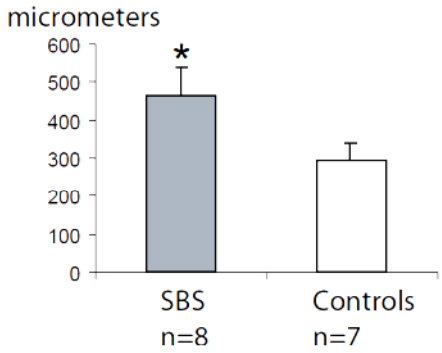
SBS

Controls

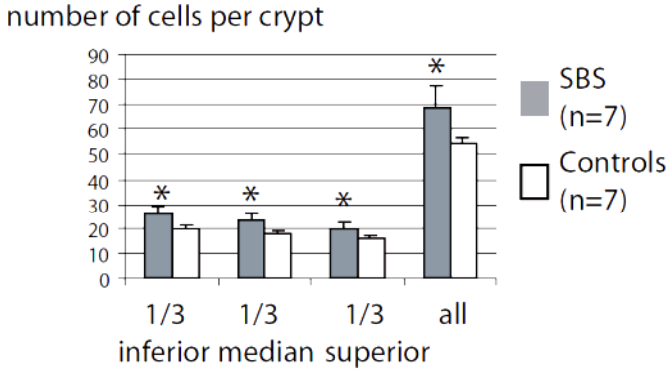


Haematoxylin – Eosin
transverse colon

Crypts size



Epithelial cells



35 % of crypts size

25 % of total number of epithelial cells / crypt

Joly et al 2009

Colon plays a major role

by reducing time for PN weaning

by improving diet energy salvage

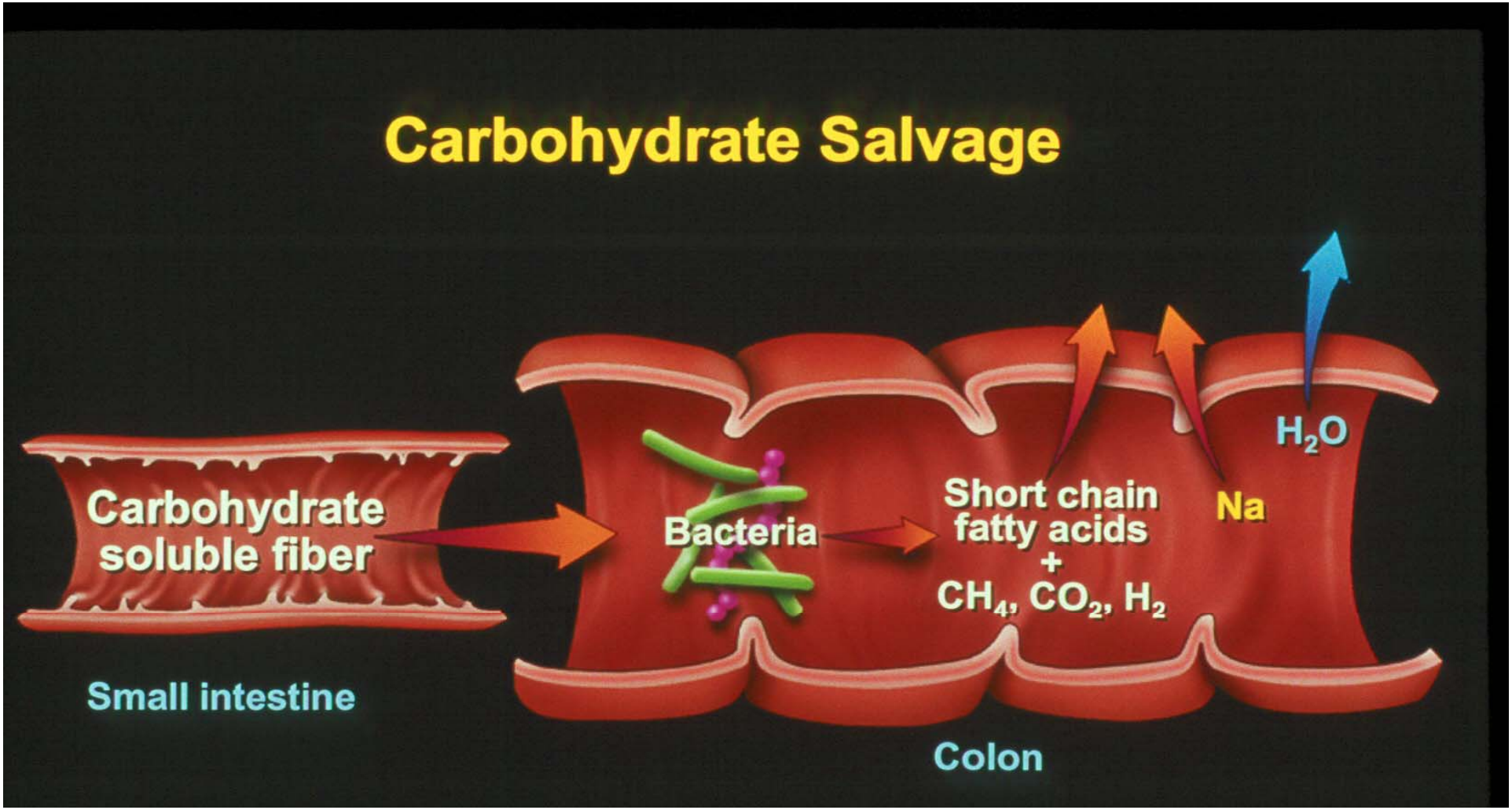
Hyperplasia of colonic mucosa and colonic microbiota

Preserve microbiota

Promote SCFA and growth factors

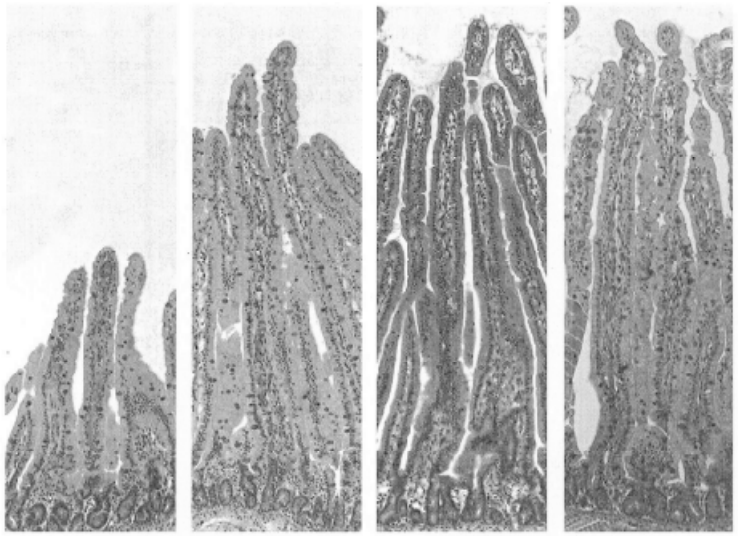
Sachs et col. J Pediatr Gastroenterol Nutr 1995; Musch et col. Am J Physiol 2002
Ziegler et col. Am J Clin Nutr 2002; Lardy et col. Dis Dis Sc 2005; Joly et al 2009
Goulet et al J Pediatr Gastroenterol Nutr 2009, Goulet et al Clin Nutr 2012

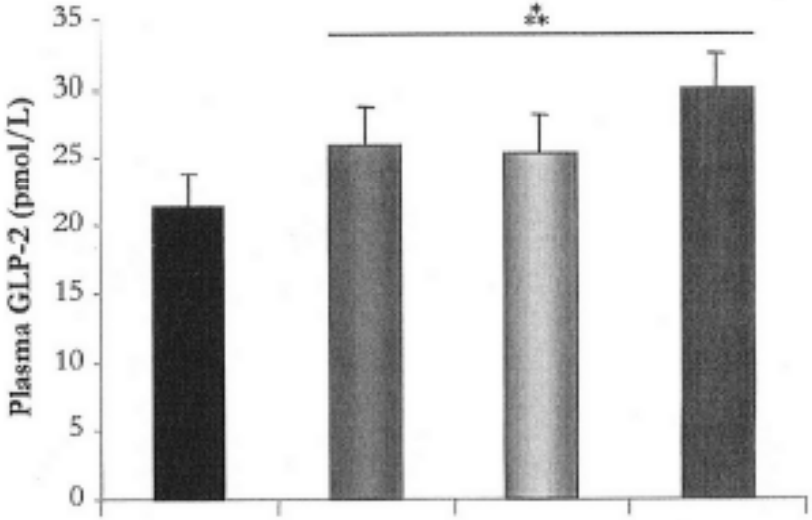
Role of the colon in energy salvage



Jeppesen et al. JPEN 1999;23:S101-S105

Short chain fatty acids and GLP-2





Plasma GLP-2 levels

Parenteral butyrate after 80% resection in the piglet

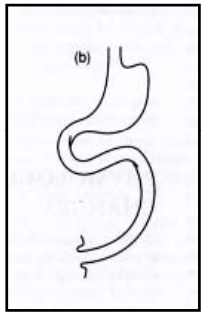
- Butyrate is the SCFA responsible for augmenting intestinal adaptation
- Increases proliferation and decreases apoptosis
- GLP-2 may be the mediator

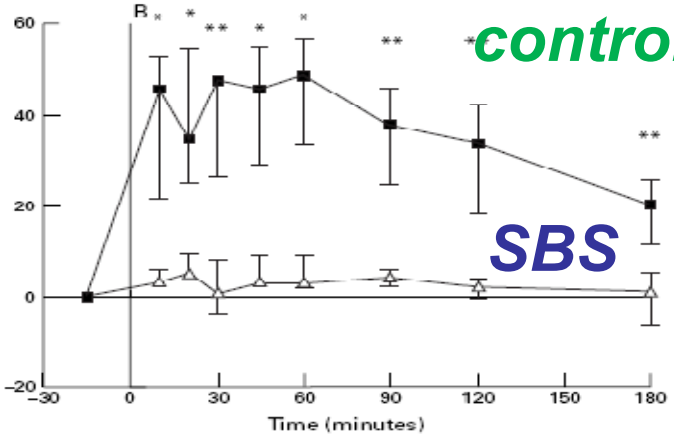
Bartholome et al JPEN 2004;28:210-223

Concentration of GLP 2 in SBS patients

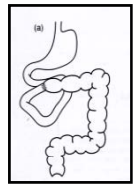
Post prandial production of GLP2 in type 1 and type 2 SBS

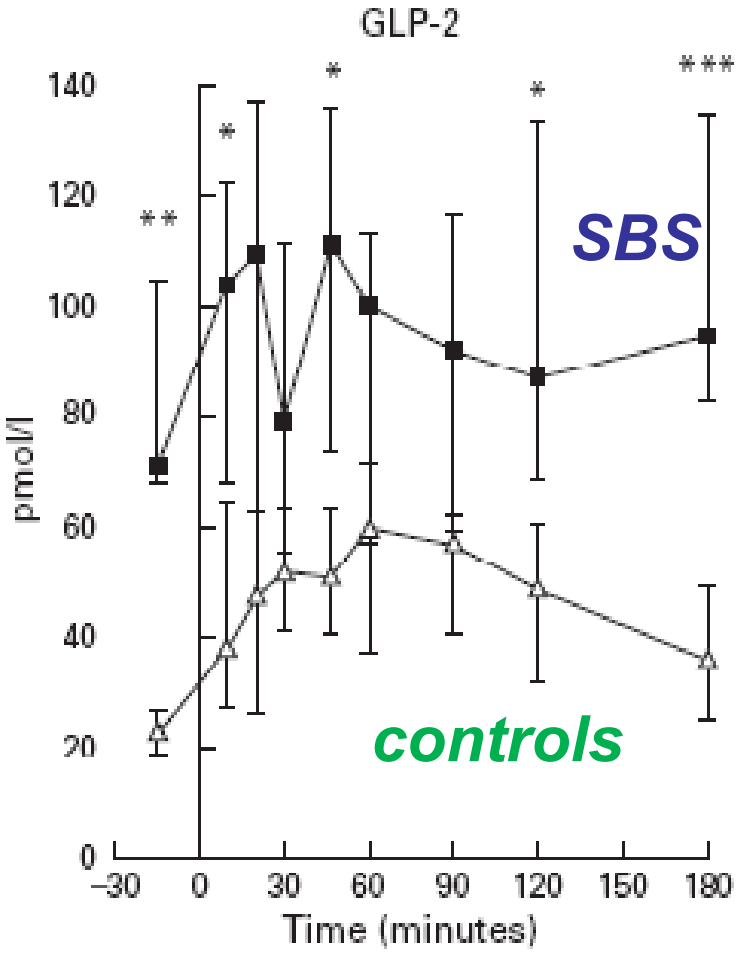
SBS type 1





SBS type 2



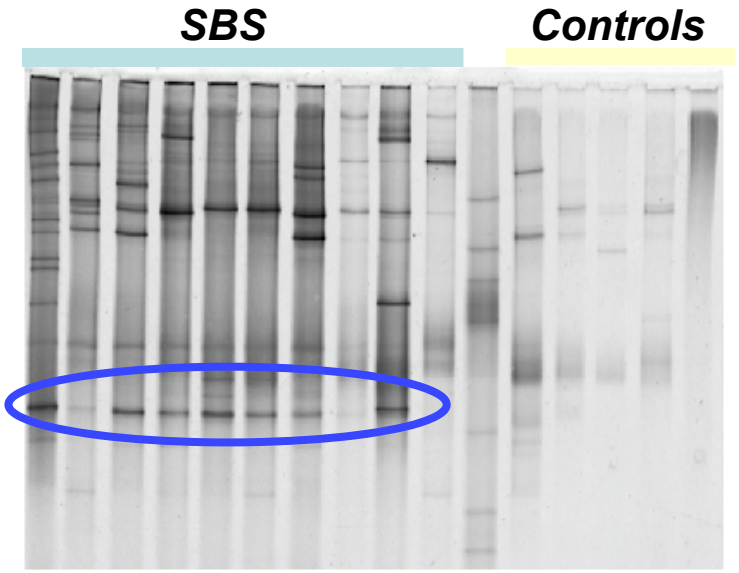


Type L enterochromafin cells : ileum and colon

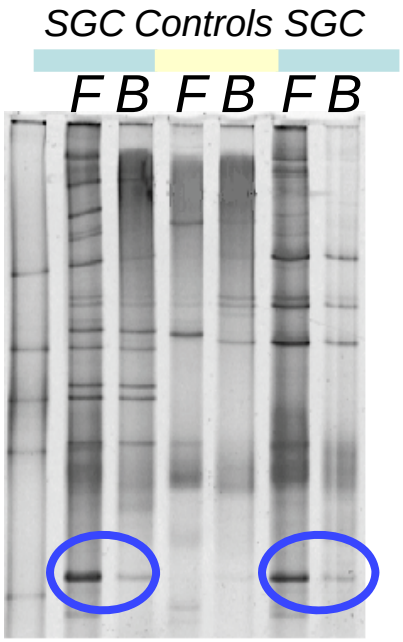
Jeppesen PB et al, Gut 1999; 45:559-563 et Gut 2000; 47:370-76.

Evidence of SBS « specific » bacterial strain

Lactobacillus, TTGE, feces



Lactobacillus, TTGE, feces (F) and biopsies (B)



L. mucosae

- *Detection of L. mucosae only in SBS patients (n=7/8)*
- *Same amounts of L. mucosae in feces and biopsies (PCRq)*

Joly et al 2010

Intestinal microbiota in Short Bowel Syndrome

SBS patients, with colon in continuity, harbor a specific fecal microbiota that we called *"lactobiota"* because it is enriched in the ***Lactobacillus/Leuconostoc*** *group and depleted in anaerobic micro-organisms (especially Clostridium & Bacteroides).*

In some patients, the lactobiota-driven fermentative activities lead to an accumulation of fecal D/L-lactates and an increased risk of D-encephalopathy.

Mayeur C et al Microorganisms 2016

Intestinal microbiota

	Beneficial
Bacterial flora	Microbiota
Intestine	Colon
Intestinal barrier	Improved
Trophic consequences	Hyperplasia Small bowel & colon
Mechanisms	SCFA butyrate induced GLP_2
Outcome	Intestinal autonomy

Negative effects of intestinal microbiota

- **Oxalic lithiasis**
  - Prevalence 15-60% (adult)
  - Oxalate produced from fat malabsorption
- **D-lactic acidosis**
  - Rare but severe encephalopathy
  - Dysbiotic colonic microbiota
  - Role of *Bactobacillus mucosa ?*

D-Lactic acidosis in short bowel syndrome

D-Lactic Acidosis in Short-Bowel Syndrome Managed With Antibiotics and Probiotics

Uchida, Hideki Yamamoto, Yoshiyuki Kisaki, Junko Fujino, Yuki Ishimaru, and Hitoshi Ikeda

Rare but very serious complication

REFERENCES

1. Georgeson KE: Su... Neill JA, Rowe MI, Grosfeld JL (eds): Pediatric Su... ...r-Year Book, 1998, pp 1223-1232
2. Bongaerts G, Bakkeren J, Severijne... ...d acidosis in children with short small bowel. J ... Nutr 30:288-293, 2000
3. Mayr JM, Schober PH, Weissensteiner U, et al: Mor... mortality of the short-bowel syndrome. Eur J Pediatr Surg 9:231-... 1999
4. Godey F, Bouasria A, Ropert M, et al: Don't forget to test for D-lactic acid in short-bowel syndrome. Am J Gastroenterol 95:3675-3677, 2000
5. Oh MS, Phelps KR, Traube M, et al: D-lactic acidosis in a man with the short-bowel syndrome. N Engl J Med 301:249-252, 1979
6. Uribarri J, Oh MS, Carroll HJ: D-lactic acidosis: A review of clinical presentation, biochemical features, and pathophysiologic mechanisms. Medicine (Baltimore) 77:73-82, 1998
7. Scully TB, Kraft SC, Carr WC, et al: D-lactate-associated encephalopathy after massive small-bowel resection. J Clin Gastroenterol 11:448-451, 1989
8. Cross SA, Callaway CW: D-Lactic acidosis and selected cerebellar ataxias. Mayo Clin Proc 59:202-205, 1984
9. Day AS, Abbott GD: D-lactic acidosis in short-bowel syndrome. N Z Med J 112:277-278, 1999
10. Hove H, Mortensen PB: Colonic lactate metabolism and D-... acidosis. Dig Dis Sci 40:320-330, 1995
... Marini MI, Pons S, D'Agostino D, et al: Abnormal fecal flora ... short-bowel syndrome: An in vitro study on effect of ... duction. Dig Dis Sci 41:1649-1652, 1996
... J, Naber T, et al: D-lactic acidemia and aciduria ... ts with short-bowel syndrome. Clin Chem 41:107-...
13. Bongaerts G..., ... al: Role of bacteria in the pathogenesis of sho... ed D-lactic acidemia. Microb Pathog 22:285-2...
14. Kanamori Y, Hashizume K, Su... ...ation therapy with *Bifidobacterium breve, Lactobu...* oligosaccharides dramatically improved the intestin... with short-bowel syndrome: A novel synbiotics therapy ... ...l failure. Dig Dis Sci 46:2010-2016, 2001

J Pediatr Surg 39:634-636.

Negative effects of intestinal microbiota

- **Oxalic lithiasis**
  - Prevalence 15-60% (adult)
  - Oxalate produced from fat malabsorption
- **D-lactic acidosis**
  - Rare but severe encephalopathy
  - Dysbiotic colonic microbiota
  - Role of *Bactobacillus mucosa ?*
- **Anastomotic ulcerations**
  - More frequent in SBS type 2 *(jejuno-colic anastomosis)*
  - Role of NOD2/microbiota ??
- **Small intestinal bacterial overgrowth**
  - More frequent in SBS type 2 *(jejuno-colic anastomosis)*
  - Worsened by unappropriate and agressive ube feeding

Short bowel syndrome

Aims of management

- Maintenance of growth and development with ***parenteral nutrition ("time bridge")***
- Encouraging intestinal adaptation
- Establishing oral > enteral nutrition
- Preventing / treating complications

  catheter related sepsis, venous thrombosis, intestinal-failure associated liver disease, PN related bone disease, impaired quality of life

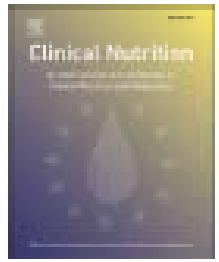
Short bowel syndrome

Individualized strategy

Contents lists available at SciVerse ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu



Review

Neonatal short bowel syndrome as a model of intestinal failure: Physiological background for enteral feeding☆

O. Goulet[a], J. Olieman[b], J. Ksiazyk[c], J. Spolidoro[d], D. Tibboe[e], H. Köhler[f], R. Vural Yagci[g], J. Falconer[h], G. Grimble[i], R.M. Beattie[j,*]

Goulet et al Clin Nutr 2013

Short bowel syndrome

Individualized strategy

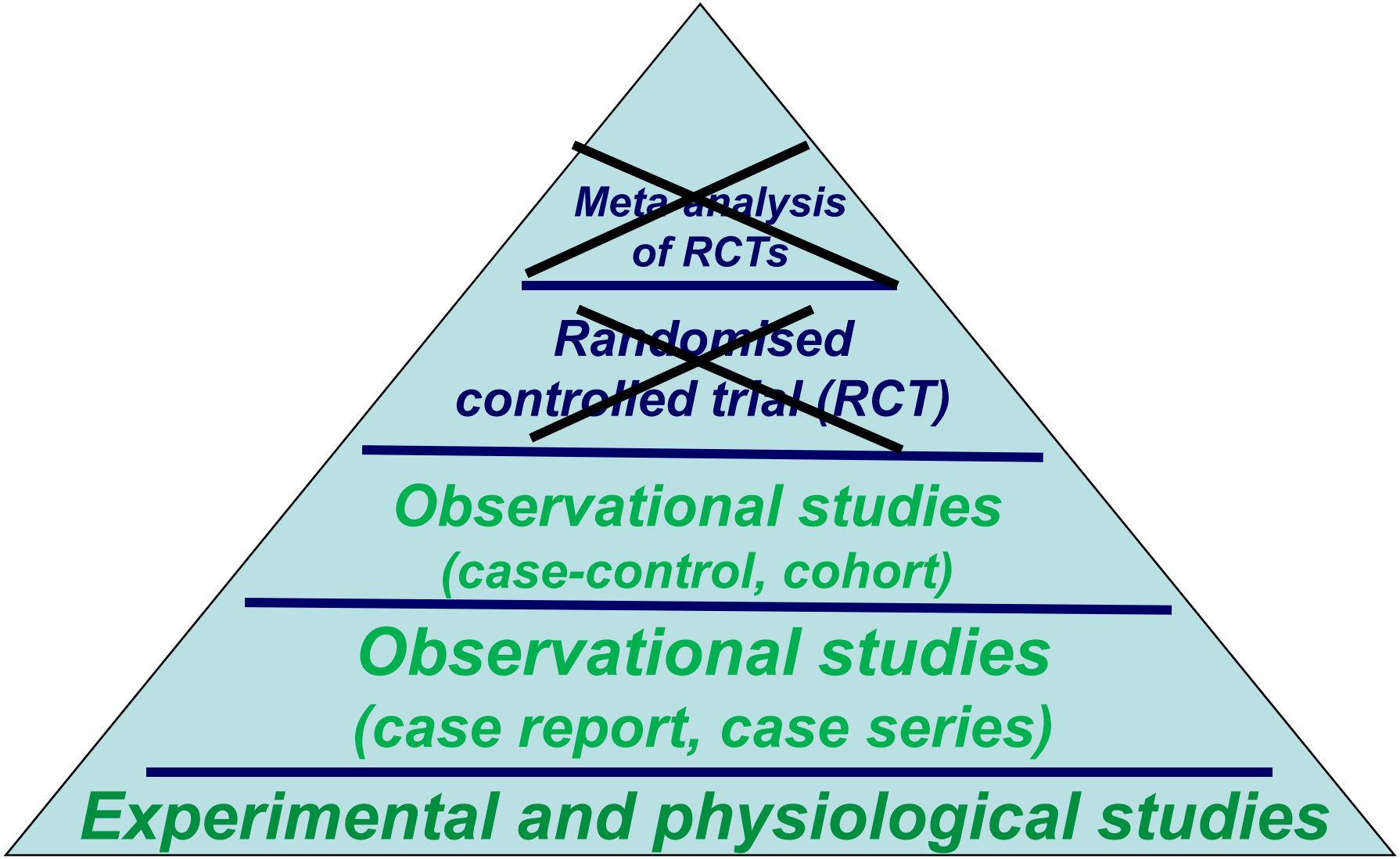
- ***Many differences between patients***
  - ***Underlying cause of the SBS***

    (gastroschisis, NEC, atresia)
  - ***Anatomy and bowel length***
  - ***Number of surgical procedures***
  - ***Motility of the remnant intestine***

Adapt strategy but respect physiology

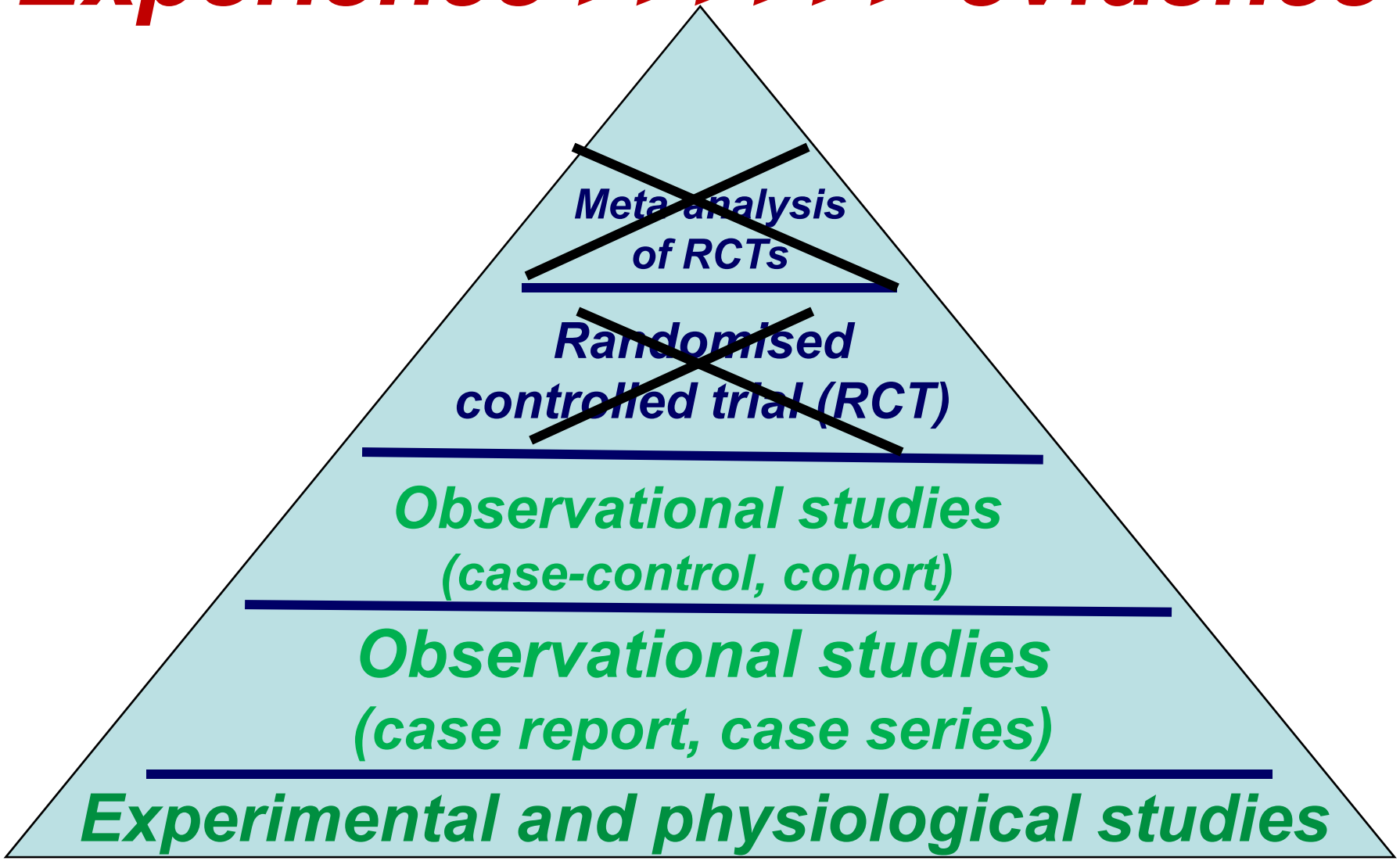
Short bowel syndrome

Type of diet and mode of delivery



Short bowel syndrome

Experience >>>>>> evidence



Short bowel syndrome

Parenteral nutrition

- ***Nutritional status***
- ***Avoid gut overload***
- ***Cyclic PN intake***
- ***Prevent sepsis***
- ***Home management***

Oral feeding

- ***More physiological***
- ***EGF from salivary glands***
- ***Self regulation of intakes***
- ***Digestive secretions***
- ***Fasting / feeding balance***
- ***Gut bacterial clearance***
- ***Prevent eating disorders***

Continuous enteral tube feeding ??

Enteral tube feeding « à la carte »

In « our » pediatric SBS patients

– Poor eater or non prevented eating disorders

– Gastrostomy is better than NGT …? nobody nows

– Consequences of ***« artificial hyperphagia »***

– Nocturnal ETF for replacing 1 PN night

– Avoidance of additional technique and devices

- Child and parents quality of life (QoL)
- Increased stool output when nocturnal PN + ETF
- Daily bolus tube feeding **without missing oral feeding**

Don't be too far from physiology

and promote normal behavior

PARIS DESCARTES

Short bowel syndrome

« Our » management in clinical practice

- The most physiological = oral feeding
- The most logical = hydrolysates (MCT)
- The most experienced = hydrolysates
- The most diversified = role (+) of fibers

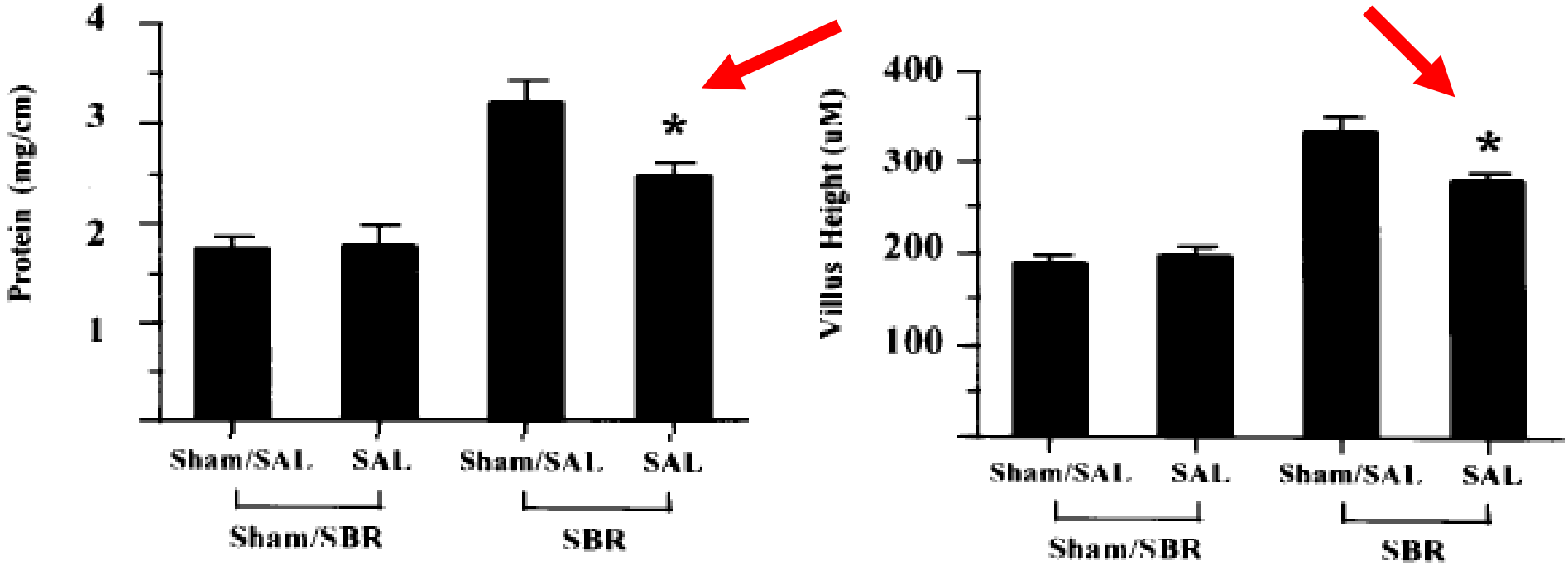
Physiology-tolerance-cost-efficacy

Experienced > evidence based

Goulet et al Clin Nutr 2013

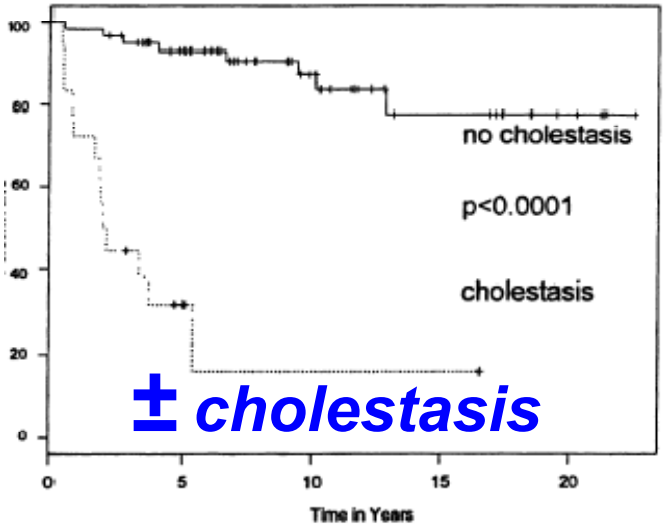
Adaptation after small bowel resection is attenuated by sialoadenectomy The role for endogenous epidermal growth factor

Ileal mucosa after 50% proximal bowel resection (SBR) or bowel transection (Sham)

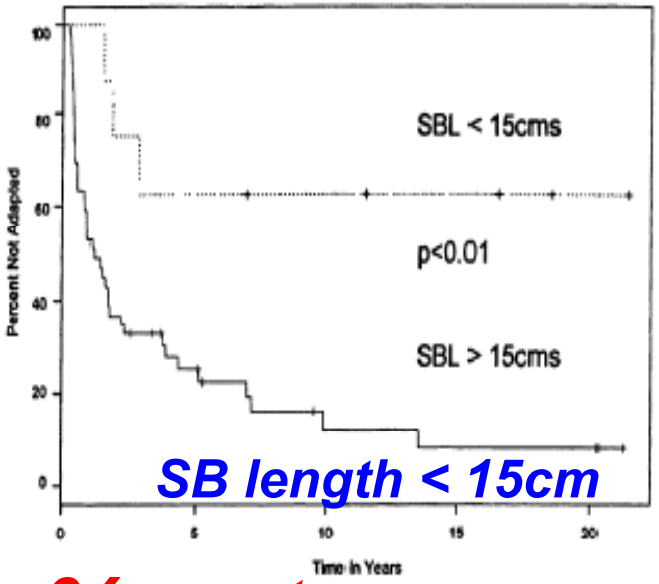


Helmrath MA et al Surgery 1998

Pronostic factors in pediatric SBS

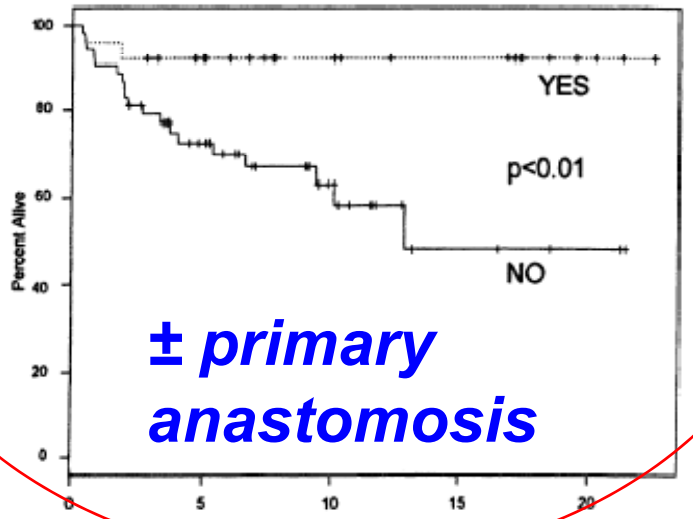


± *cholestasis*



SB length < 15cm

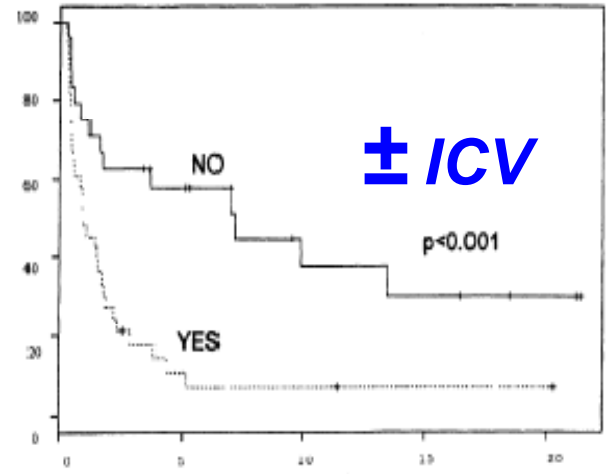
% alive



± *primary anastomosis*

% not weaned

B

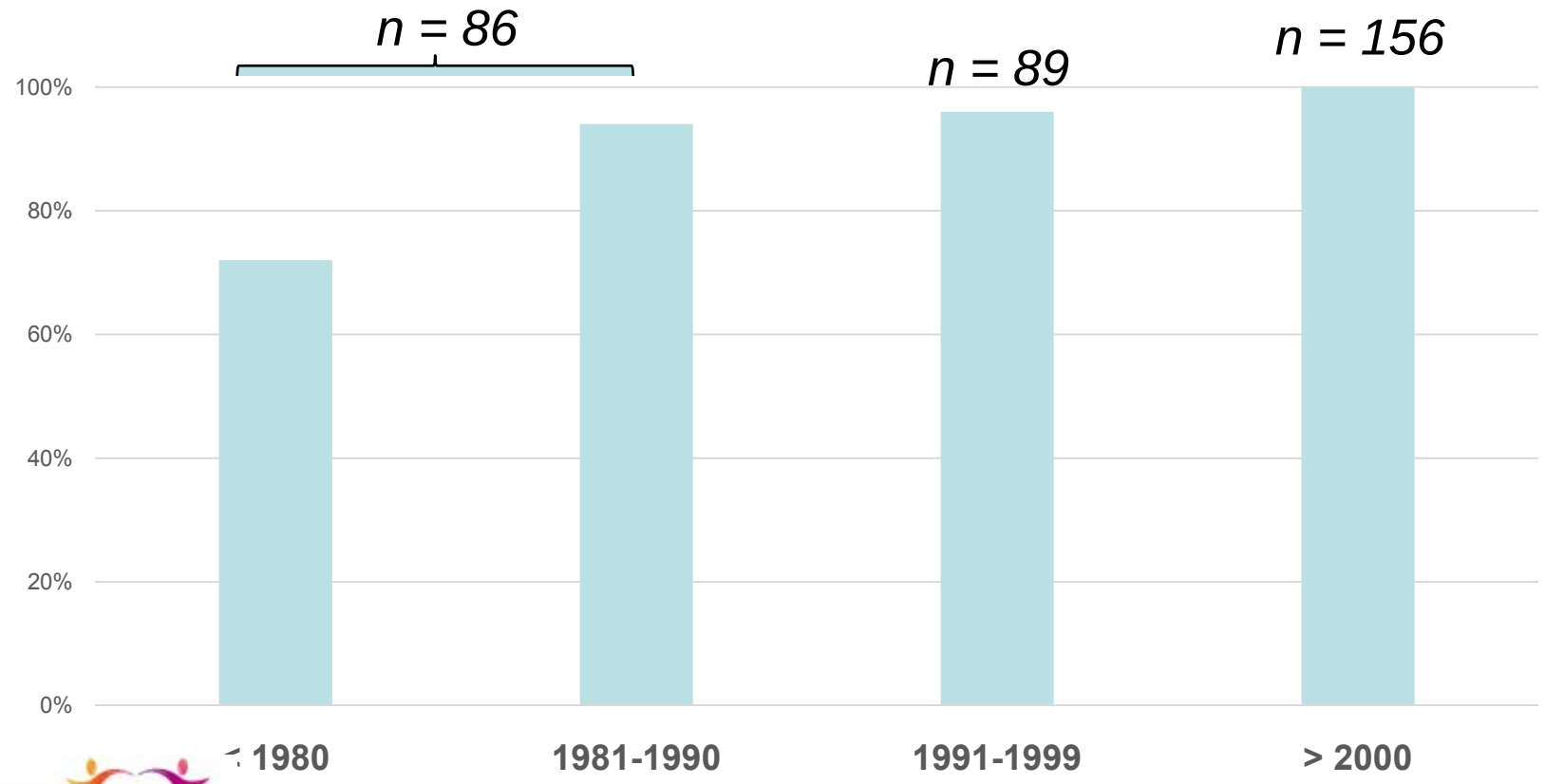


± *ICV*

Quiros-Tejera et al J Pediatr 2004; 145:157-63

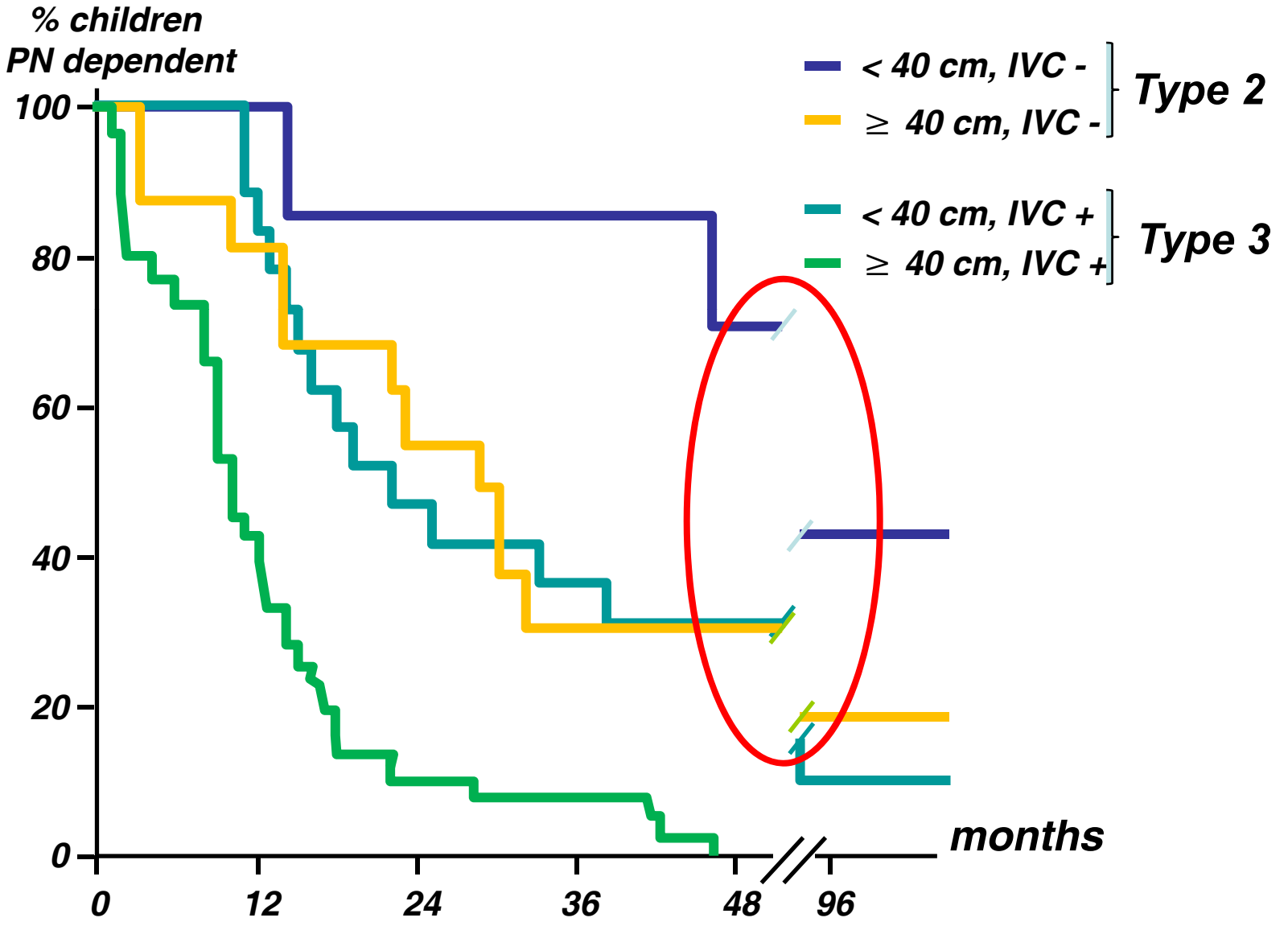
Survival in pediatric SBS

Necker-Enfants Malades cohorts



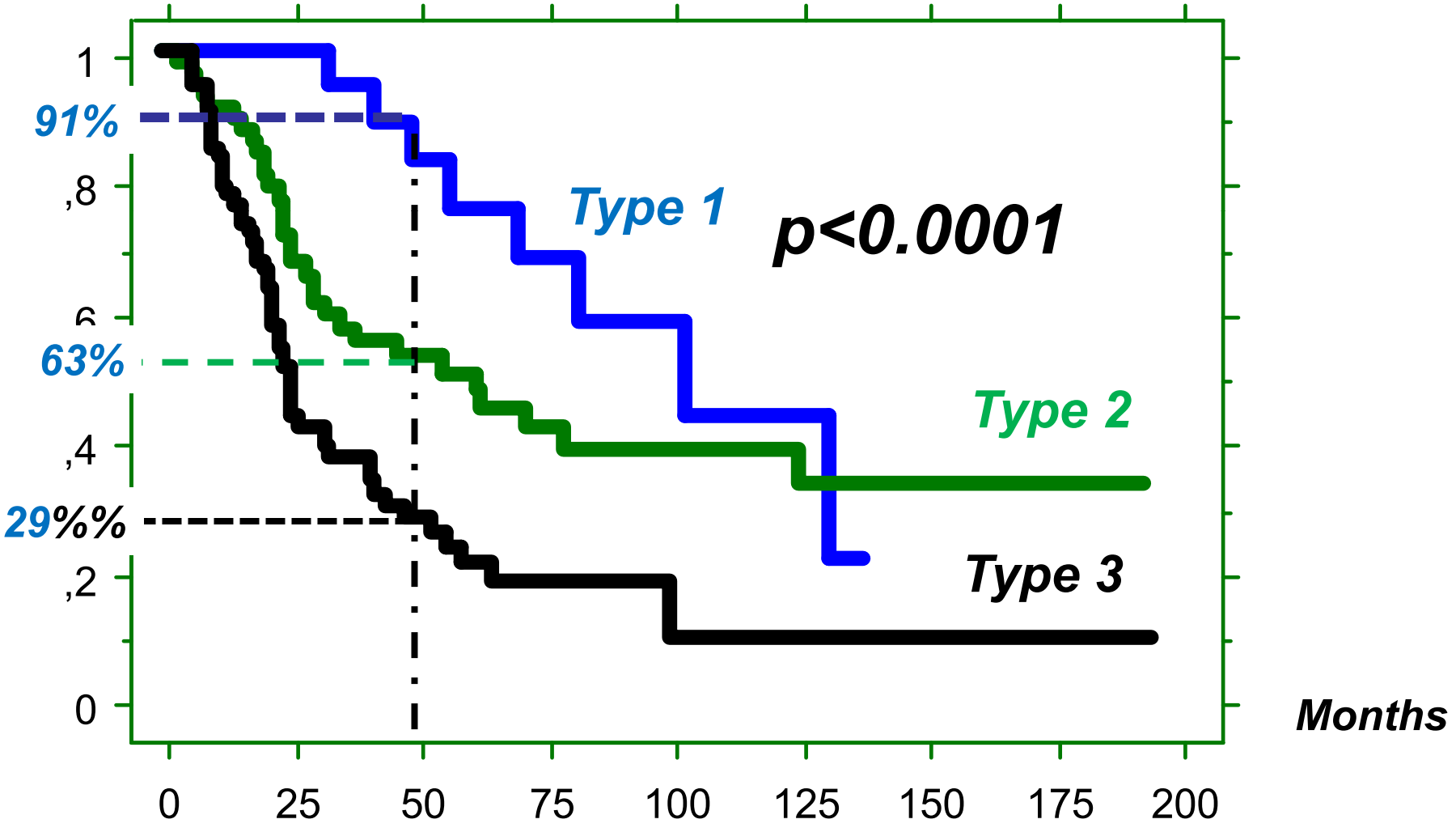
Goulet et al J Pediatr 1991
Goulet et al Eur J Pediatr Surg 2005
Perella et al JPEN submitted 2017

Delay for PN weaning in 89 patients



Goulet et al Eur J Pediatr Surg 2005

Duration of PN dependency according to SBS type (n= 156)



Perella et al JPEN submitted 2017

Necker SBS (n = 156) : Growth follow up

	HPN duration (months)	Weight (SD)	Height (SD)	BMI	Calories PN/REE
At HPN weaning	17±12	- 0.5 ±1	-0.2±1.4	15 ±1.6	0
6 months after weaning off HPN		- 0.7±0.9 *p=0.23*	-0.1±2.1 *p=0.16*	15 ±2.2	0
Still on HPN	56 ±45	- 0.4±1.1	-0.5±1.3	16 ±2.3	1.31±0.2

Necker ENFANTS MALADES HÔPITAL UNIVERSITAIRE

Perella B et al 2017

Bone Health and Growth of Children Receiving Long-term Parenteral Nutrition

ABI NADER E.[1], LAMBE C.[1], TALBOTEC C.[1], ACRAMEL A.[2], GOULET O.[1,3]

Poster 790
WCPGHAN 2016

According to PN indications

		Height, Z-score		Spine BMD		Whole body BMD	
	n	med [1Q;3Q]	p	med [1Q;3Q]	p	med [1Q;3Q]	p
SBS	24	-0,2 [-1,0;0,8]		-0.9 [-1.6;-0.3]		-0.7 [-1.3;0.2]	
CE	8	-1.8 [-2.3;-1.1]	0.02	-2.2 [-3.9;-1.5]	0.02	-3.1 [-4.2;-0.7]	0.04
CIPOS	9	-0.7 [-2.0;-0.4]		-0.8 [-2.4;-0.5]		-1.4 [-1.8;'-0.4]	

Home parenteral nutrition in France

National network
Necker Reference center

- ***Official bylaw 18/12/1984***

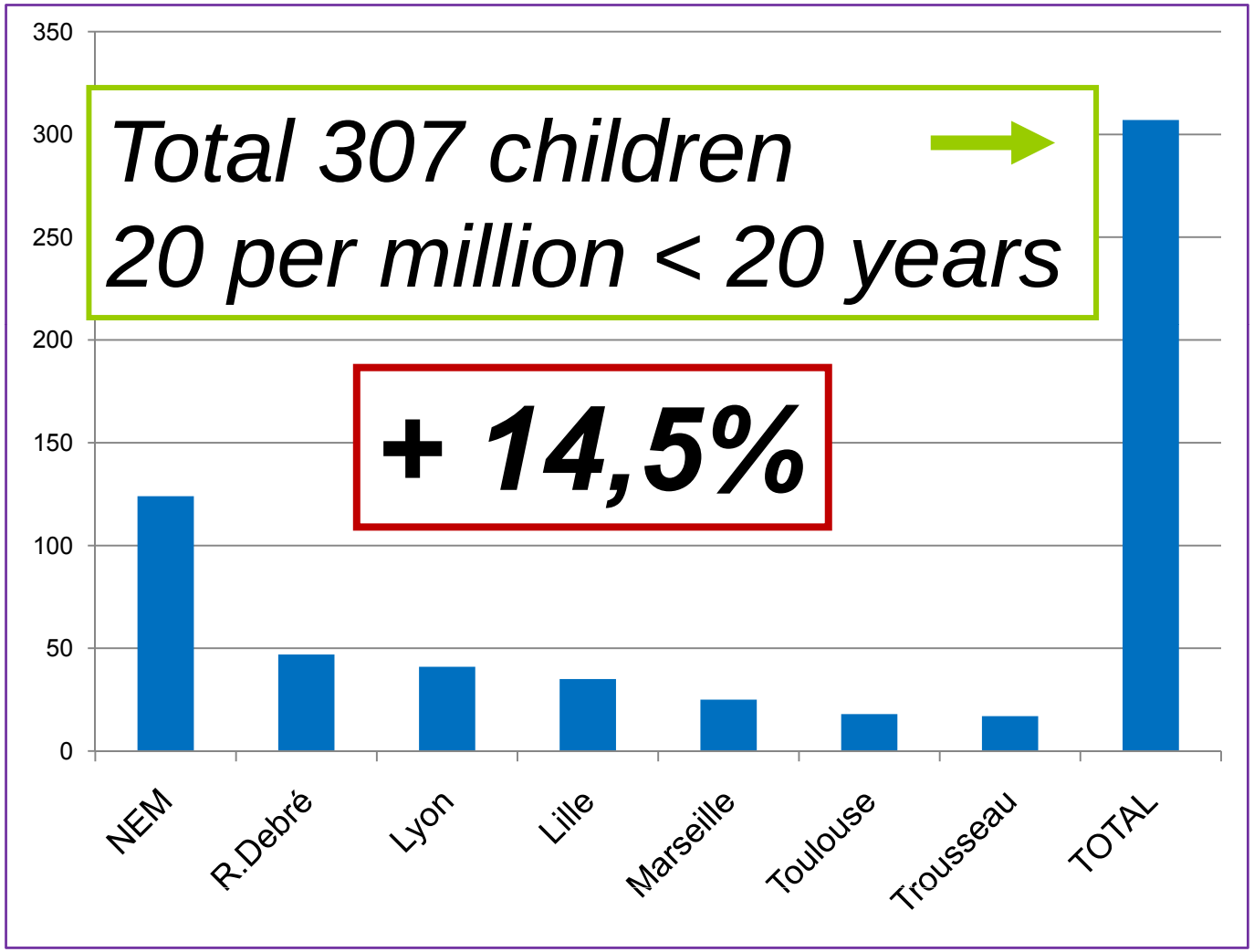
- ***National Heath System:***

Only 7 HPN expert centers are recognized by the Social Security

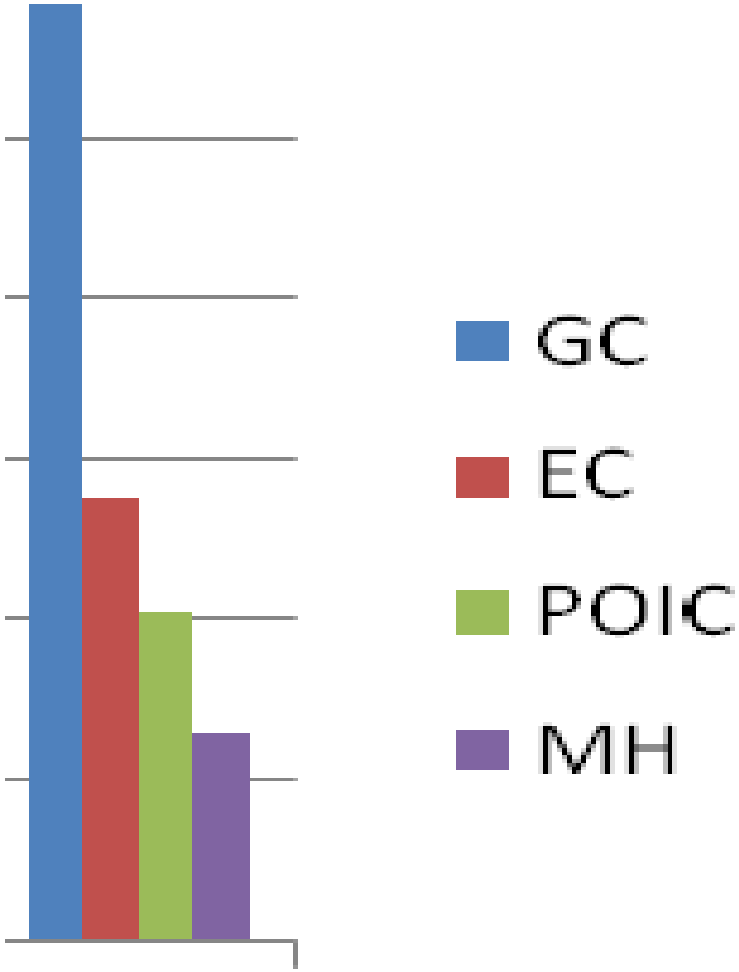
- ***Yearly report***

All HPN expert centers report pooled data for the year

Home parenteral nutrition in France 2016



Home parenteral nutrition in France 2016



143 SBS

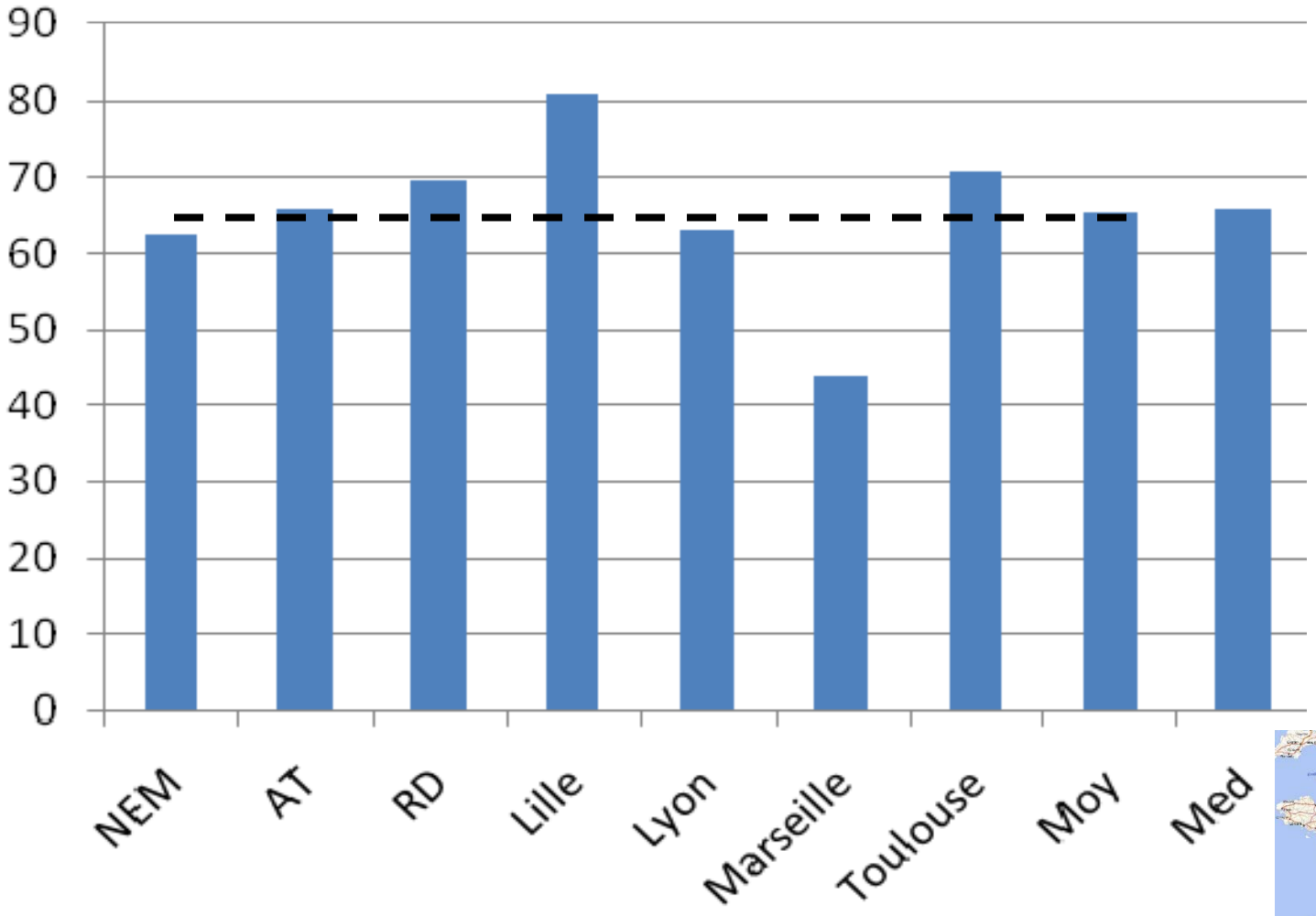
60 congenital enteropathies

48CIPOS

32 LS Hirschsprung

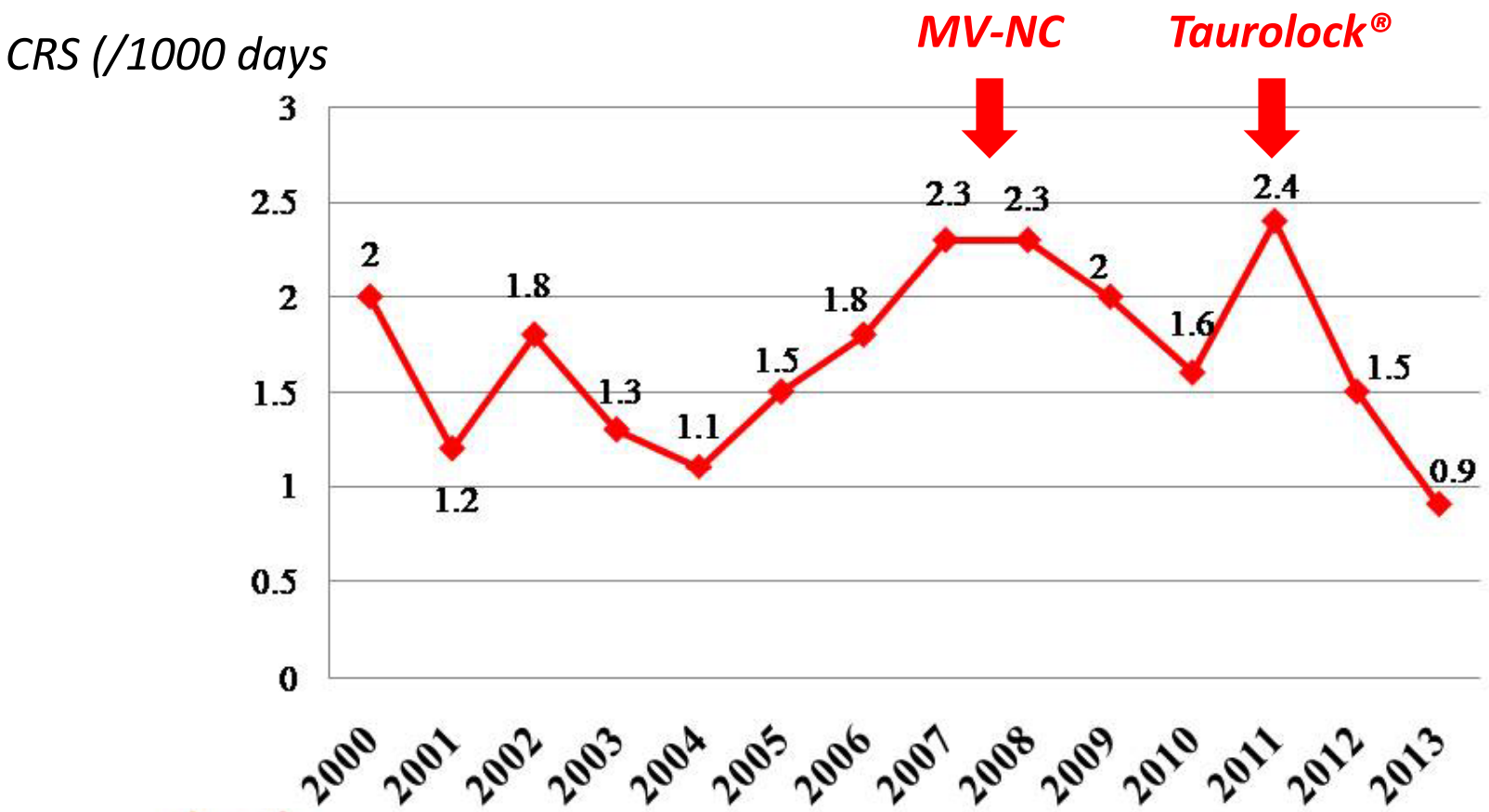
Home parenteral nutrition in France 2016

HPN duration in months



Incidence of catheter related sepsis

Necker Survey AJCN 2016



Necker ENFANTS MALADES HÔPITAL UNIVERSITAIRE

PARIS DESCARTES

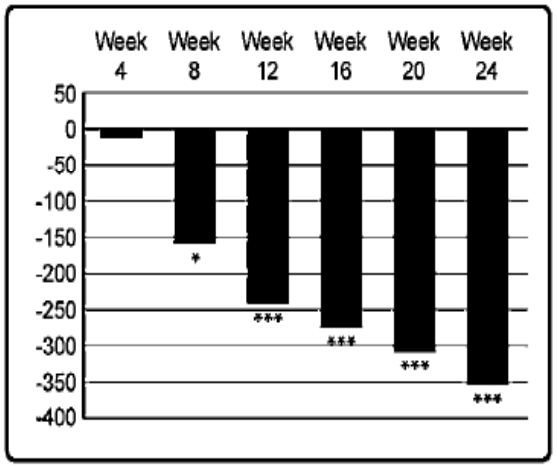
Abi Nader et al Am J Clin Nutr 2016

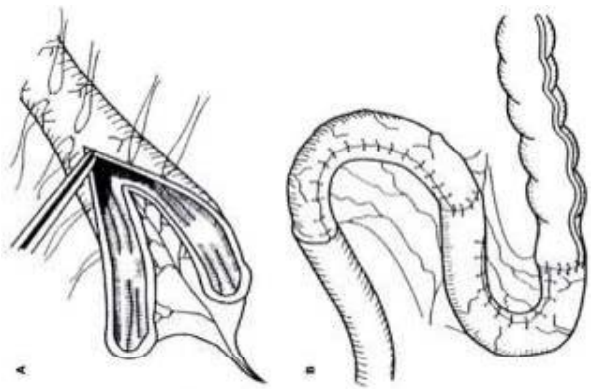
Long term PN dependency

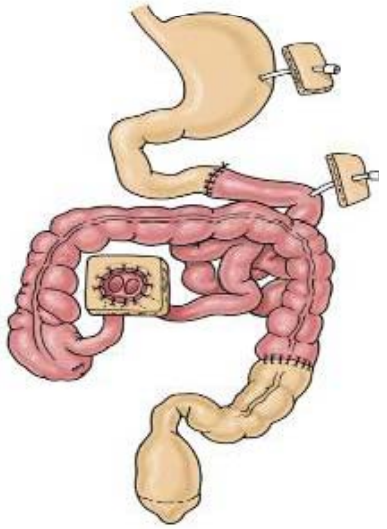
- By using hormonal therapy (GH, GLP-2)

- By performing autologous bowel surgery

- By performing intestinal transplantation







Recombinant human GH in SBS

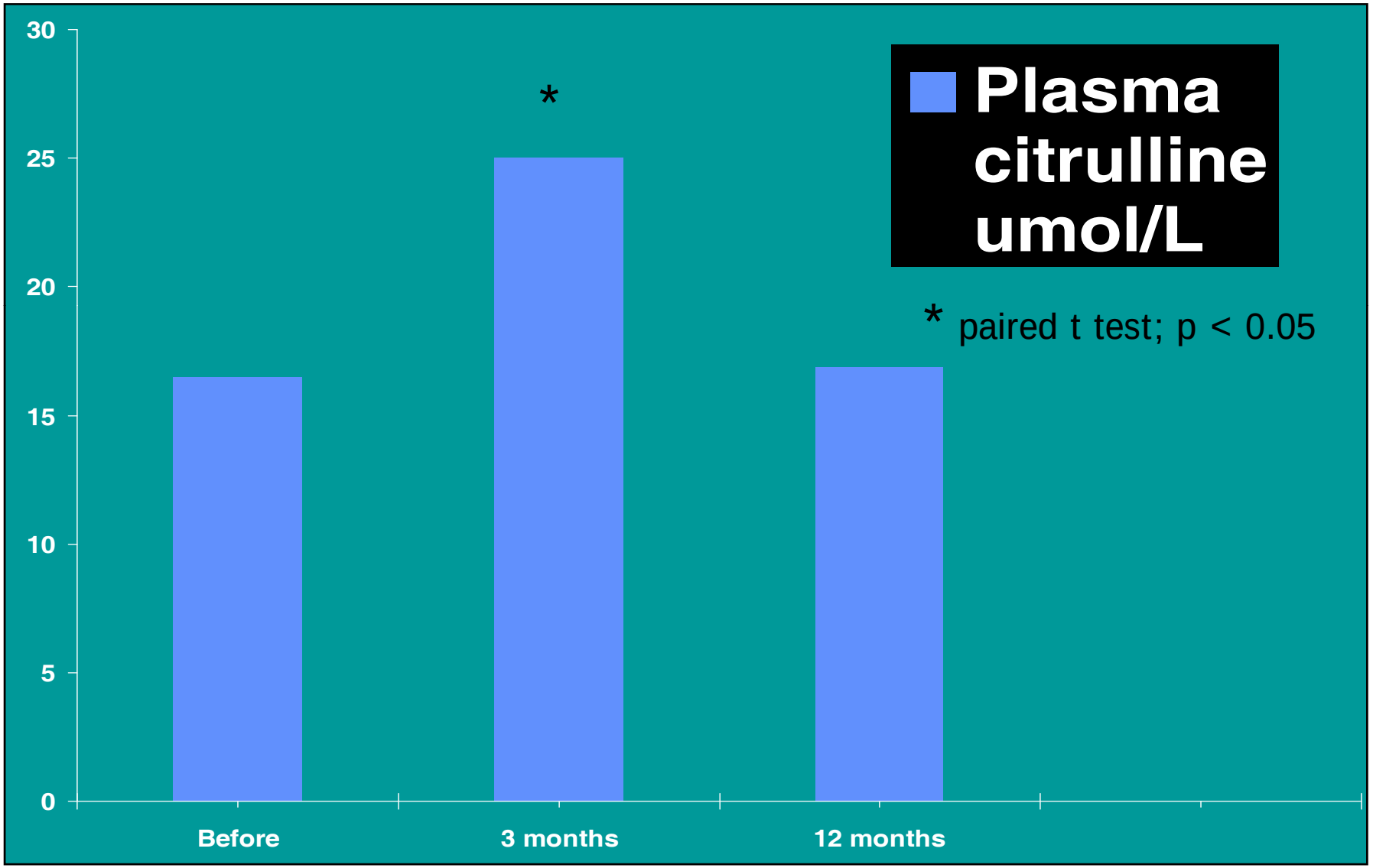
Open trial in children

- 8 children, aged: 3.8 – 11.6 years (med; 8.5)
- Remaining SB length: 20 cm (5-40 cm)
- Long-term parenteral nutrition from birth
- PN dependency: 52% (50-65%) of RDA for age
- Oral intake: 100% (45-159%) of RDA for age

  - rhGH (Umatrope®) : 0.4 IU/kg/day
  - Duration : 12 weeks-treatment

Goulet et al JPEN 2010

Recombinant human GH in SBS



Goulet et al JPEN 2010

Recombinant human GH in SBS

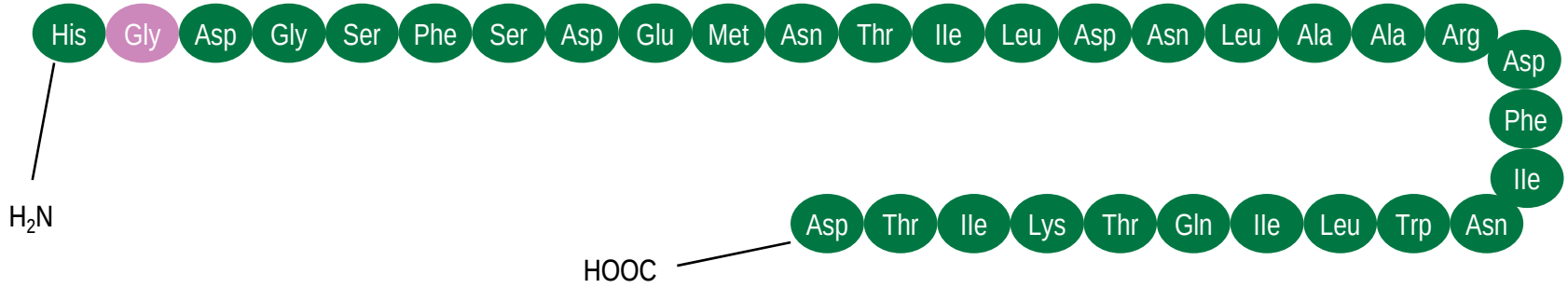
Long-term follow up

- 25% remain off parenteral nutrition
- 50% restarted 50% of previous PN
- 25% restarted about the same PN

Goulet et al JPEN 2010

REVESTIVE (teduglutide) Recombinant analogue of human GLP-2[1]

- Teduglutide is a 33-amino acid peptide identical to endogenous human glucagon-like peptide-2 (GLP-2) except for the replacement of an alanine with glycine at position 2, which blocks degradation by dipeptidyl peptidase-IV enzyme[1,2]



- Teduglutide has a longer terminal half-life ($t_{½}$) than GLP-2[1,3]
  - Mean $t_{½}$ ~2 hours versus ~7 minutes, respectively[3]

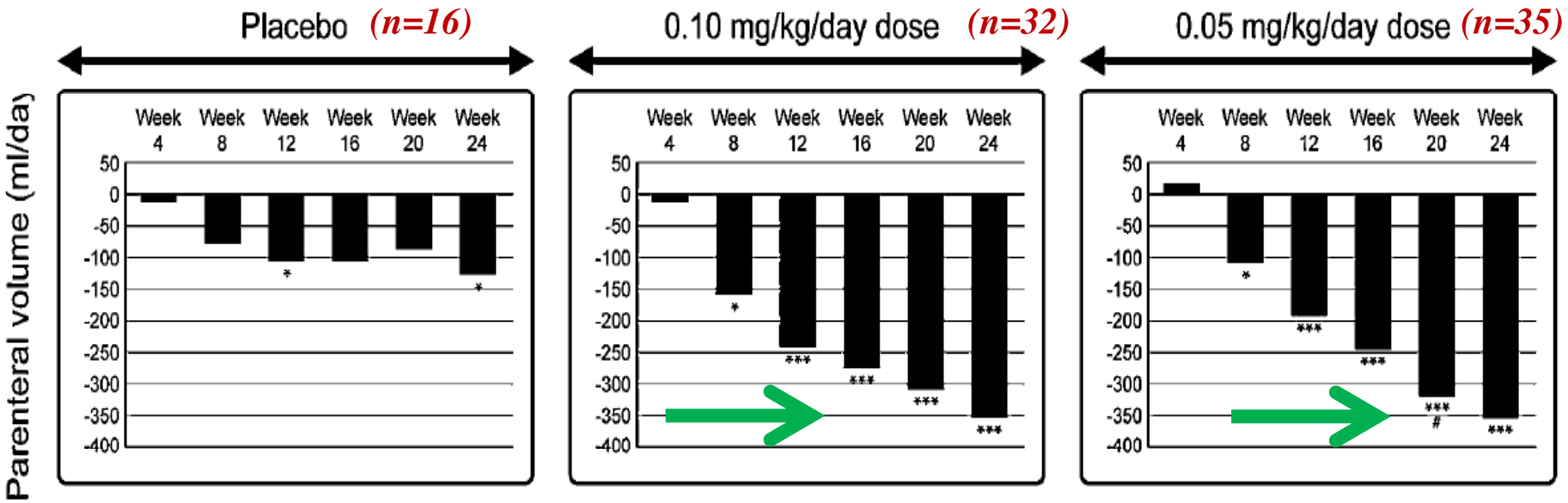
1. *Revestive® EMA Summary of Product Characteristics, Shire Pharmaceuticals Ireland Limited, June 2016.* ***2.*** *Tavares W, Drucker DJ, Brubaker PL. Am J Physiol Endocrinol Metab 2000; 278(1): E134-9.* ***3.*** *Jeppesen PB. Curr Opin Endocrinol Diabetes Obes 2015; 22(1): 14-20.*

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]

GLP 2 analog multicenter trial in adult SBS

Reduction of parenteral nutrition volume



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

REVESTIVE paediatric Phase 3 study design[1]

Study objective and endpoints

Objective:
to evaluate the safety, tolerability and efficacy of REVESTIVE compared to standard of care in children with SBS-IF.[1,2]

Endpoints included:[2-7]

- Adverse events
- Changes in PN* (volume, calories)
- Changes in EN† (volume, calories)
- Changes in clinical and nutritional status
- Changes in plasma citrulline

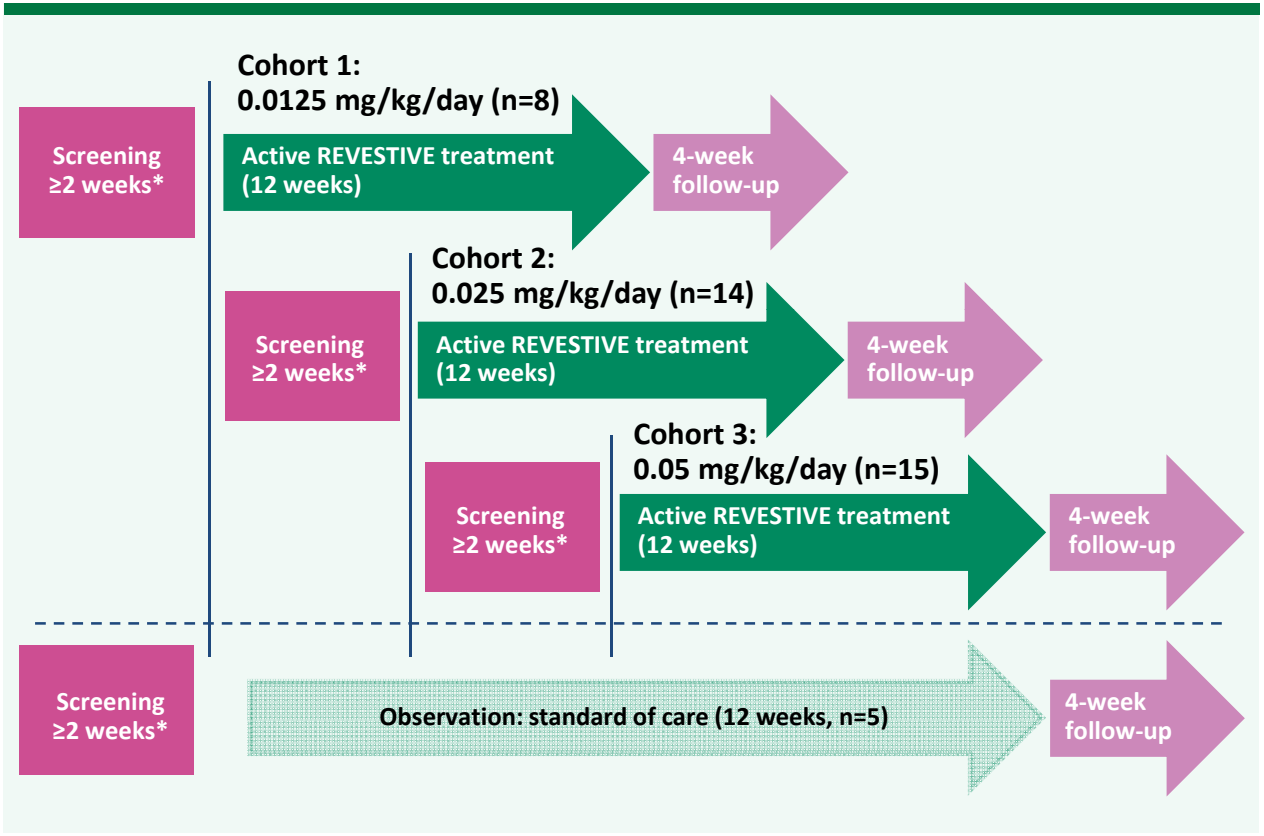
Data were assessed by descriptive statistics and no between comparisons were undertaken because of the small sample size, therefore no p values are reported

* Parenteral nutrition/intravenous fluids; † Oral and/or tube feeding.

J Pediatr 2017 181, 102-111.e5DOI: (10.1016/j.jpeds.2016.10.027)

1. Revestive® EMA Summary of Product Characteristics, Shire Pharmaceuticals Ireland Limited, June 2016. 2. Kocoshis S, Carter B, Hill S, et al. J Parenter Enteral Nutr 2016; 40(1): 132-3. 3. Hill S, Venick R, Carter B, et al. Poster presented at the 37th European Society for Clinical Nutrition and Metabolism Congress. Lisbon, Portugal; 2015. 4. Carter B, Hill S, Horslen S, et al. Poster presented at the 37th European Society for Clinical Nutrition and Metabolism Congress. Lisbon, Portugal; 2015. 5. Venick R, Horslen S, Carter B, et al. Poster presented at the 37th European Society for Clinical Nutrition and Metabolism Congress. Lisbon, Portugal; 2015. 6. ClinicalTrials.gov. Identifier: NCT01952080. A Pharmacokinetic, Safety, and Pharmacodynamic Study of Teduglutide in Pediatric Subjects With Short Bowel Syndrome. 7. Venick R, Carter B, Horslen S, et al. Poster presented at the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Annual Meeting. Washington DC, USA; 2015.

REVESTIVE paediatric Phase 3 study design[1]



A 12-week, open-label, multicentre, evaluation of safety, pharmacokinetics and pharmacodynamics in children aged 1–17 years with a history of SBS ≥12 months before screening.[2]

* Safety data were assessed after ≥28 days of REVESTIVE treatment before the next dosing cohort could proceed.

The approved dose of REVESTIVE in patients aged 1 year and above is 0.05 mg/kg/day body weight.[3]

J Pediatr 2017 181, 102-111.e5DOI: (10.1016/j.jpeds.2016.10.027)

1. Carter B, Horslen S, Hill S*, et al.* Poster presented at the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Annual Meeting. Washington DC, USA; 2015. **2.** Hill S, Venick R, Carter B*, et al.* Poster presented at the 37th European Society for Clinical Nutrition and Metabolism Congress. Lisbon, Portugal; 2015. **3.** Revestive® EMA Summary of Product Characteristics, Shire Pharmaceuticals Ireland Limited, June 2016.

Inclusion Criteria

1. Informed consent +/- assent

2. Current history of SBS as a result of major intestinal resection, (eg, NEC, midgut volvulus, intestinal atresia, gastroschisis) 12 months prior to screening

4. PN/IV support > 30% of caloric and/or fluid/electrolyte needs

5. Stable PN/IV support > 3 months prior to enrolment

J Pediatr 2017 181, 102-111.e5DOI: (10.1016/j.jpeds.2016.10.027)

Exclusion Criteria

1. Any bowel lengthening procedure performed within the past 3 months
2. Evidence of untreated intestinal obstruction or active stenosis
3. Unstable absorption due to cystic fibrosis, untreated Hirschsprung's disease or known DNA abnormalities
4. Radiographic or manometric evidence of pseudo-obstruction or severe known

dysmotility syndrome, including gastroschisis-related motility disorders

5. Evidence of obstruction on upper gastrointestinal (GI) series done within 6 months prior to screening
6. Major gastrointestinal surgical intervention within 3 months prior to screening

(insertion of feeding tube or endoscopic procedure is allowed)

7. Unstable cardiac disease, congenital heart disease or cyanotic disease, with the exception of subjects who had undergone ventricular or atrial septal defect repair
8. History of cancer or clinically significant lymphoproliferative disease within 5 years,not including resected cutaneous basal or squamous cell carcinoma, or in situ non aggressiveand surgically resected cancer
9. Pregnant or lactating female subjects
10. Participation in a clinical study using an experimental drug within 1 month or an experimental antibody treatment within 3 months prior to screening, or concurrent participation in any clinical study using an experimental drug that would affect the safety of teduglutide
11. Previous use of native glucagon-like peptide-2 (GLP-2) and glucagon-like peptide-1 analog or human growth hormone within 3 months prior to screening
12. Previous use of oral or IV glutamine, octreotide, or dipeptidyl peptidase IV (DPP-IV)

inhibitors within 3 months prior to screening

13. Previous use of teduglutide Pediatric Study
14. Subjects with active Crohn's disease who had been treated with biological therapy (eg, antitumor necrosis factor [anti-TNF] or natalizumab) within the 6 months prior to screening
15. Subjects with inflammatory bowel disease (IBD) who required chronic systemic

immunosuppressant therapy that had been introduced or changed during the last 3 months

16. More than 3 SBS-related or PN-related hospital admissions (eg, catheter sepsis, clots,bowel obstruction, severe water-electrolyte disturbances) within 3 months prior to screening visit
17. Hospital admission, other than scheduled, within 1 month prior to screening
18. Body weight < 5 percentile for age or < 10 kg
19. Signs of severe hepatic impairment:
21. Parent(s) and/or subjects who are not capable of understanding or not willing to adhere to the study visit schedule and other protocol requirements
22. Active or history of clinically significant pancreatic or biliary disease
23. Any condition or circumstance that in the investigator's opinion puts the subject at any undue risk, prevented completion of the study, or interfered with analysis of the study results
24. Presence of any of the excluded disease states described in the table below

J Pediatr 2017 181, 102-111.e5DOI: (10.1016/j.jpeds.2016.10.027)

Patient demographics

Patient disposition and baseline characteristics[1]

	Standard of care (n=5)	REVESTIVE		
		0.0125 mg/kg/day (n=8)	0.025 mg/kg/day (n=14)	0.05 mg/kg/day (n=15)
Age, years Median (min, max)	2.0 (2, 3)	3.0 (1, 14)	4.0 (1, 14)	4.0 (1, 14)
Male, n (%)	3 (60)	6 (75)	11 (79)	8 (53)
Median body mass index, kg/m^2 (min, max)	16.8 (14.3, 18.4)	15.4 (13.8, 19.4)	16.2 (14.8, 18.2)	15.9 (14.3, 18.4)
Reason for resection, n (%)				
Necrotising enterocolitis	**2 (40)**	**1 (13)**	**2 (14)**	**3 (20)**
Midgut volvulus	**2 (40)**	**2 (25)**	**4 (29)**	**7 (47)**
Intestinal atresia	**1 (20)**	**1 (13)**	**4 (29)**	**2 (13)**
Gastroschisis	**0**	**2 (25)**	**7 (50)**	**3 (20)**
Other	**0**	**2 (25)**	**0**	**1 (7)**
Stoma, n (%)	0	1 (13)	1 (7)	1 (7)
Colon-in-continuity, n (%)	**5 (100)**	**7 (100)**	**12 (86)**	**14 (100)**
Median estimated residual small intestine length, cm (min, max)	**35 (10, 75)**	**15 (2, 75)**	**68 (15, 45)**	**26 (0, 68)**
Median parenteral support* volume at baseline, L/week (min, max)	7.7 (4.4, 9.8)	5.4 (4.2, 13.9)	8.1 (4.4, 16.0)	5.6 (4.0, 13.1)
Median enteral nutrition† volume at baseline, L/week (min, max)	5.1 (0.9, 6.0)	8.1 (2.9, 12.6)	7 (1.9, 13.4)	3.4 (0.3, 6.3)

* Parenteral nutrition/intravenous fluids; † Oral and/or tube feeding.

The approved dose of REVESTIVE in patients aged 1 year and above is 0.05 mg/kg/day body weight.[2]

1. Carter B, Horslen S, Hill S*, et al.* Poster presented at the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Annual Meeting. Washington DC, USA; 2015.
2. Revestive® EMA Summary of Product Characteristics, Shire Pharmaceuticals Ireland Limited, June 2016.

Results – Adverse events

Adverse events occurring in ≥10% of REVESTIVE-treated paediatric patients[1]

Adverse event by preferred term, n (%)*	Standard of care (n=5)	REVESTIVE			
		0.0125 mg/kg/day (n=8)	0.025 mg/kg/day (n=14)	0.05 mg/kg/day (n=15)	Total (n=37)
Vomiting	0	0	5 (36)	7 (47)	12 (32)
Upper respiratory tract infection	2 (40)	2 (25)	4 (29)	4 (27)	10 (27)
Catheter-related complications	1 (20)	3 (38)	4 (29)	2 (13)	9 (24)
Pyrexia	2 (40)	0	2 (14)	7 (47)	9 (24)
Cough	1 (20)	1 (13)	2 (14)	4 (27)	7 (19)
Abdominal pain	1 (20)	1 (13)	1 (7)	4 (27)	6 (16)
Headache	0	1 (13)	2 (14)	2 (13)	5 (14)
Nausea	0	1 (13)	2 (14)	2 (13)	5 (14)
Fatigue	0	0	1 (7)	4 (27)	5 (14)
Blood bicarbonate decreased	2 (40)	1 (13)	1 (7)	3 (20)	5 (14)
Diarrhoea	1 (20)	0	1 (7)	3 (20)	4 (11)
Faecal volume increased	0	1 (13)	1 (7)	2 (13)	4 (11)
Central line infection	0	0	3 (21)	1 (7)	4 (11)
Gastrointestinal stoma complication†	0	0	0	1 (100)	1 (25)

* Percentages based on number of patients in each treatment group; † Percentages based on number of patients with a stoma in each treatment group.

The approved dose of REVESTIVE in patients aged 1 year and above is 0.05 mg/kg/day body weight.[2]

1. Venick R, Carter B, Horslen S, *et al.* Poster presented at the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Annual Meeting. Washington DC, USA; 2015.
2. Revestive® EMA Summary of Product Characteristics, Shire Pharmaceuticals Ireland Limited, June 2016.

J Pediatr 2017 181, 102-111.e5DOI: (10.1016/j.jpeds.2016.10.027)

Results – Treatment-emergent adverse events

- No serious treatment-emergent adverse events related to REVESTIVE occurred in the 12-week paediatric study[1]
- Although serious treatment-emergent adverse events were experienced by both patients in the REVESTIVE and standard of care groups (46% [n=37] and 60% [n=5], respectively), none were considered related to the study treatment[1]

Serious treatment-emergent adverse events occurring in >1 REVESTIVE-treated patient[2]

Treatment-emergent adverse event by preferred term, n (%)*	Standard of care (n=5)	REVESTIVE			
		0.0125 mg/kg/day (n=8)	0.025 mg/kg/day (n=14)	0.05 mg/kg/day (n=15)	Total (n=37)
Central line infection	0	0	3 (21)	1 (7)	4 (11)
Pyrexia	2 (40)	0	1 (7)	3 (20)	4 (11)
Catheter-related complications	1 (20)	0	2 (14)	1 (7)	3 (8)
Parainfluenza virus infection	0	0	1 (7)	1 (7)	2 (5)

* Percentages based on number of patients in each treatment group.

- All patients experienced at least one treatment-emergent adverse event but most were mild or moderate in severity[1]
- No patient developed neutralising antibodies to teduglutide; however, one patient receiving REVESTIVE 0.025 mg/kg/day developed a transient non-neutralising anti-teduglutide antibody[2]

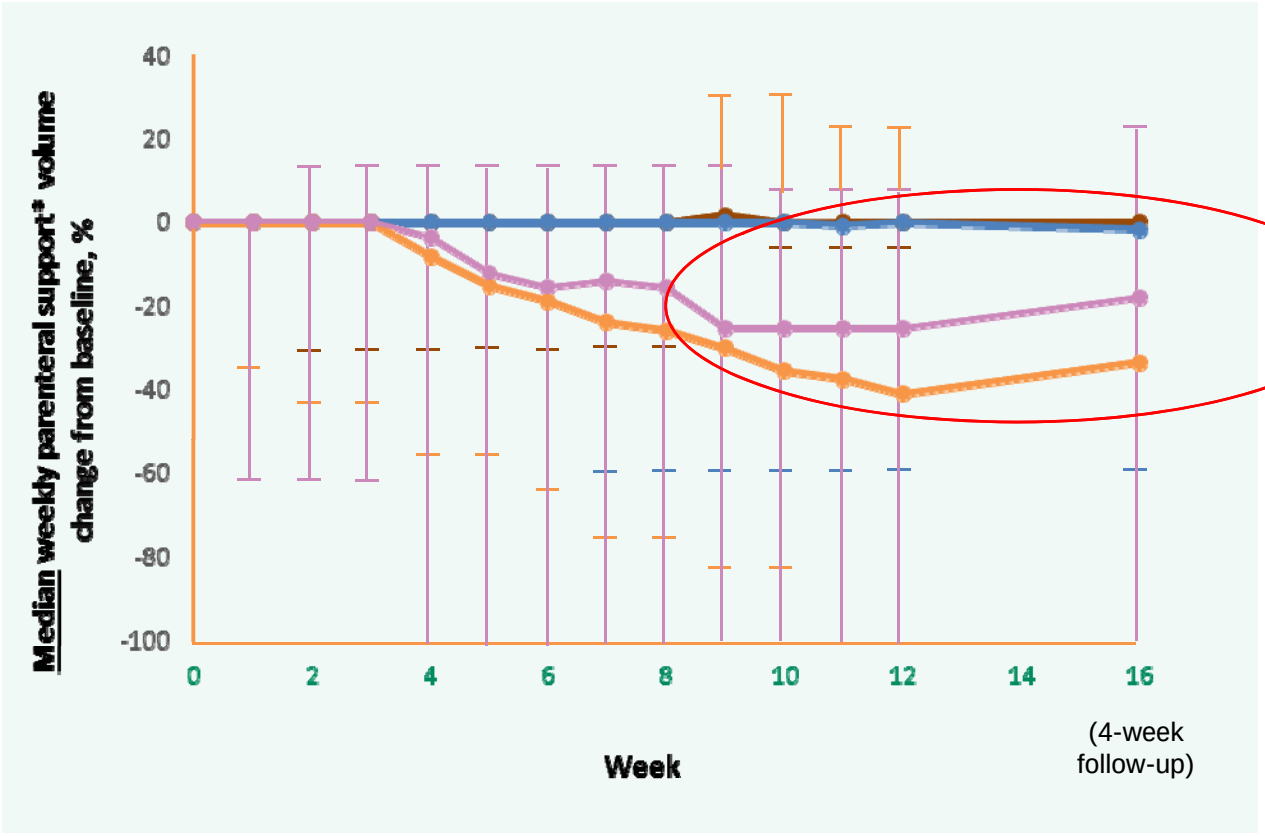
The approved dose of REVESTIVE in patients aged 1 year and above is 0.05 mg/kg/day body weight.[3]

1. Kocoshis S, Carter B, Hill S, et al. J Parenter Enteral Nutr 2016; 40(1): 132-3. 2. Carter B, Horslen S, Hill S, et al. Poster presented at the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Annual Meeting. Washington DC, USA; 2015. 3. Revestive® EMA Summary of Product Characteristics, Shire Pharmaceuticals Ireland Limited, June 2016.

J Pediatr 2017 181, 102-111.e5DOI: (10.1016/j.jpeds.2016.10.027)

Results – Weekly prescribed parenteral support volume (median)

Percentage change in prescribed weekly parenteral support* volume[1]



Standard of care†
REVESTIVE 0.0125 mg/kg/day‡
REVESTIVE 0.025 mg/kg/day § REVESTIVE 0.05 mg/kg/day¶

* Parenteral nutrition/intravenous fluids.
† n=5 (except n=4 at Week 5).
‡ n=8 (except n=6 at Week 11 and n=7 at Weeks 1, 4–10, 12 and 16).
§ n=14 (except n=13 at Week 12).
¶ n=15 (except n=14 at Weeks 7, 9–12 and 16).

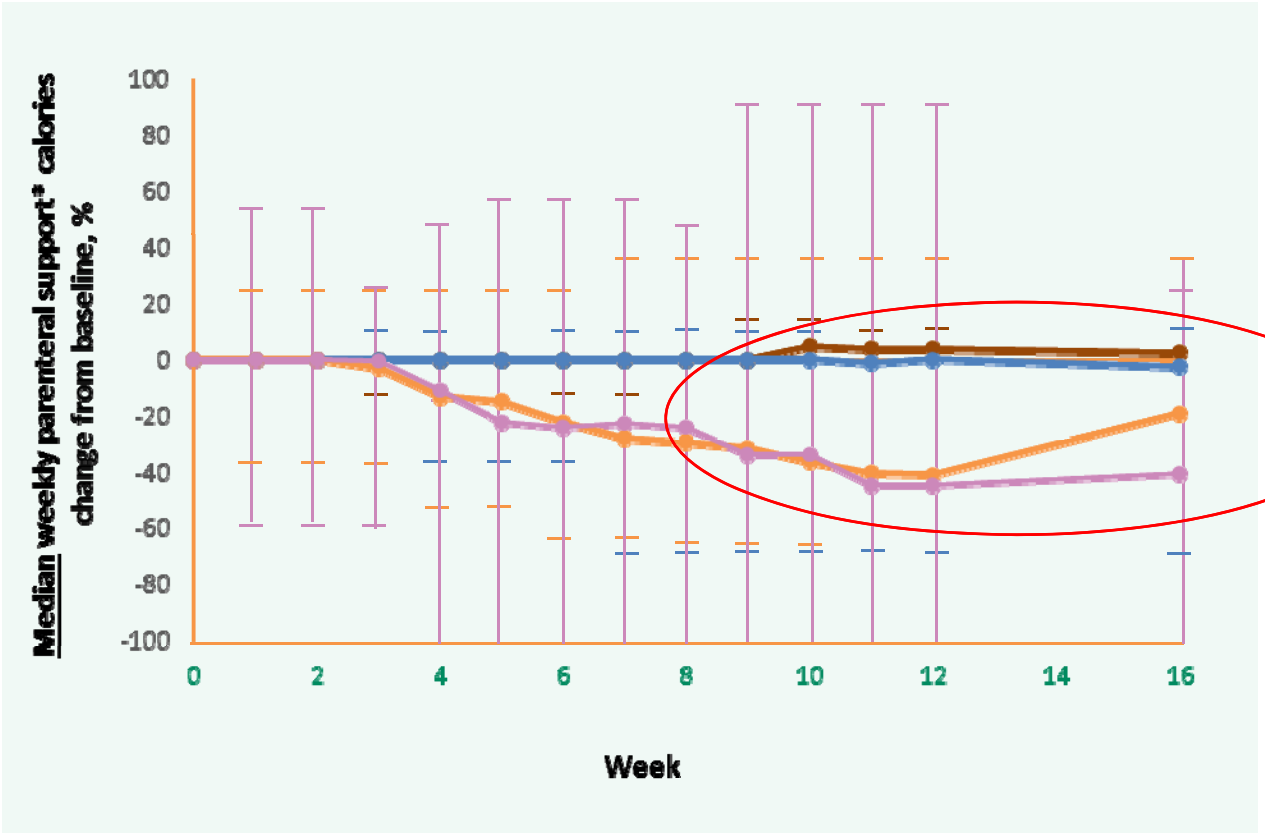
The approved dose of REVESTIVE in patients aged 1 year and above is 0.05 mg/kg/day body weight.[2]

1. Carter B, Horslen S, Hill S, et al. Poster presented at the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Annual Meeting. Washington DC, USA; 2015.
2. Revestive® EMA Summary of Product Characteristics, Shire Pharmaceuticals Ireland Limited, June 2016.

J Pediatr 2017 181, 102-111.e5DOI: (10.1016/j.jpeds.2016.10.027)

Results – Weekly prescribed parenteral support calories (median)

Percentage change in prescribed weekly parenteral support* calories[1]



* Parenteral nutrition/intravenous fluids.
† n=5 (except n=4 at Week 5).
‡ n=8 (except n=6 at Week 11 and n=7 at Weeks 1, 4–10, 12 and 16).
§ n=14 (except n=13 at Weeks 12 and 16).
¶ n=15 (except n=14 at Weeks 7, 9–12 and 16).

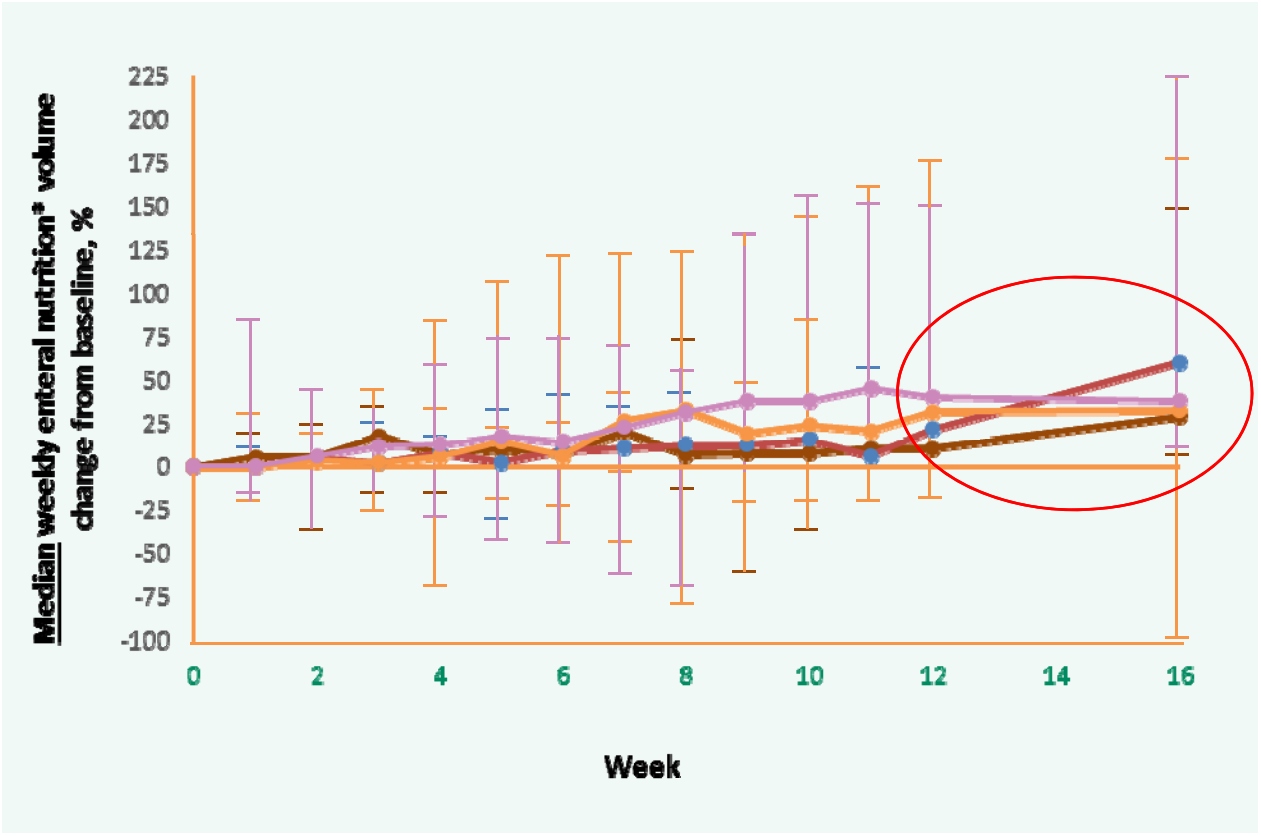
The approved dose of REVESTIVE in patients aged 1 year and above is 0.05 mg/kg/day body weight.[2]

1. Carter B, Horslen S, Hill S, et al. Poster presented at the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Annual Meeting. Washington DC, USA; 2015.
2. Revestive® EMA Summary of Product Characteristics, Shire Pharmaceuticals Ireland Limited, June 2016.

J Pediatr 2017 181, 102-111.e5DOI: (10.1016/j.jpeds.2016.10.027)

Results – Weekly patient-reported enteral nutrition volume (median)

Percentage change in patient-reported weekly enteral nutrition* volume[1]



* Oral and/or tube feeding.
† n=4 (except n=3 at Weeks 5, 11 and 12).
‡ n=4 (except n=1 at Week 16 and n=3 at Weeks 1–3, 5 and 11).
§ n=13 (except n=11 at Week 16 and n=12 at Weeks 4, 7, 8 and 12).
¶ n=10 (except n=8 at Weeks 1 and 12 and n=9 at Weeks 2–4, 9–11 and 16).

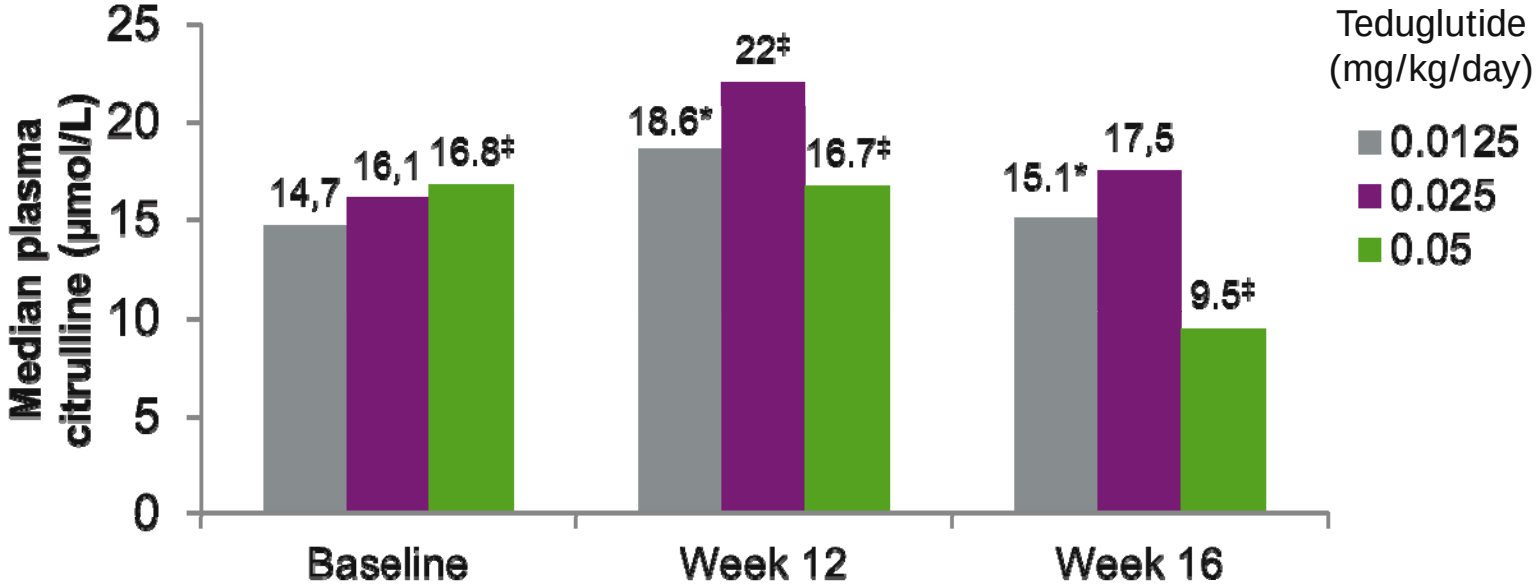
The approved dose of REVESTIVE in patients aged 1 year and above is 0.05 mg/kg/day body weight.[2]

1. Carter B, Horslen S, Hill S, et al. Poster presented at the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Annual Meeting. Washington DC, USA; 2015.
2. Revestive® EMA Summary of Product Characteristics, Shire Pharmaceuticals Ireland Limited, June 2016.

J Pediatr 2017 181, 102-111.e5DOI: (10.1016/j.jpeds.2016.10.027)

Citrulline plasma levels

- Levels of plasma citrulline correlate with remnant bowel mass in pediatric patients with SBS and may predict independence from PS[1,2]
- The observed changes in PS and EN volumes was accompanied by an increase in plasma citrulline levels from baseline while on treatment[3]
- **Following discontinuation of teduglutide, citrulline levels decreased toward baselines[3]**



EN=enteral nutrition; PS=parenteral support
*n=7; ‡n=14

1. Bailly-Botuha C, et al. Pediatr Res. 2009;65:559-563
2. Fitzgibbons S, et al. J Pediatr Surg. 2009;44:928-932
3. Hill S, et al. ESPEN 2015

Results – Independence from parenteral support

- At Week 12, three of 15 children receiving REVESTIVE 0.05 mg/kg/day (20.0%) gained independence from parenteral support*[1]

- At Week 16, after a four-week wash-out period, two of these patients had reinitiated parenteral support*[1]

Some children treated with REVESTIVE achieved independence from parenteral support.*[1]

* Parenteral nutrition/intravenous fluids.

1. Revestive® EMA Summary of Product Characteristics, Shire Pharmaceuticals Ireland Limited, June 2016.

J Pediatr 2017 181, 102-111.e5DOI: (10.1016/j.jpeds.2016.10.027)

Revestive / Teduglutide in pediatric SBS

Messages

- Teduglutide can assist intestinal adaptation in children who have reached a plateau in intestinal function if
  - Used in an intestinal rehabilitation setting
  - Multidisciplinary team support

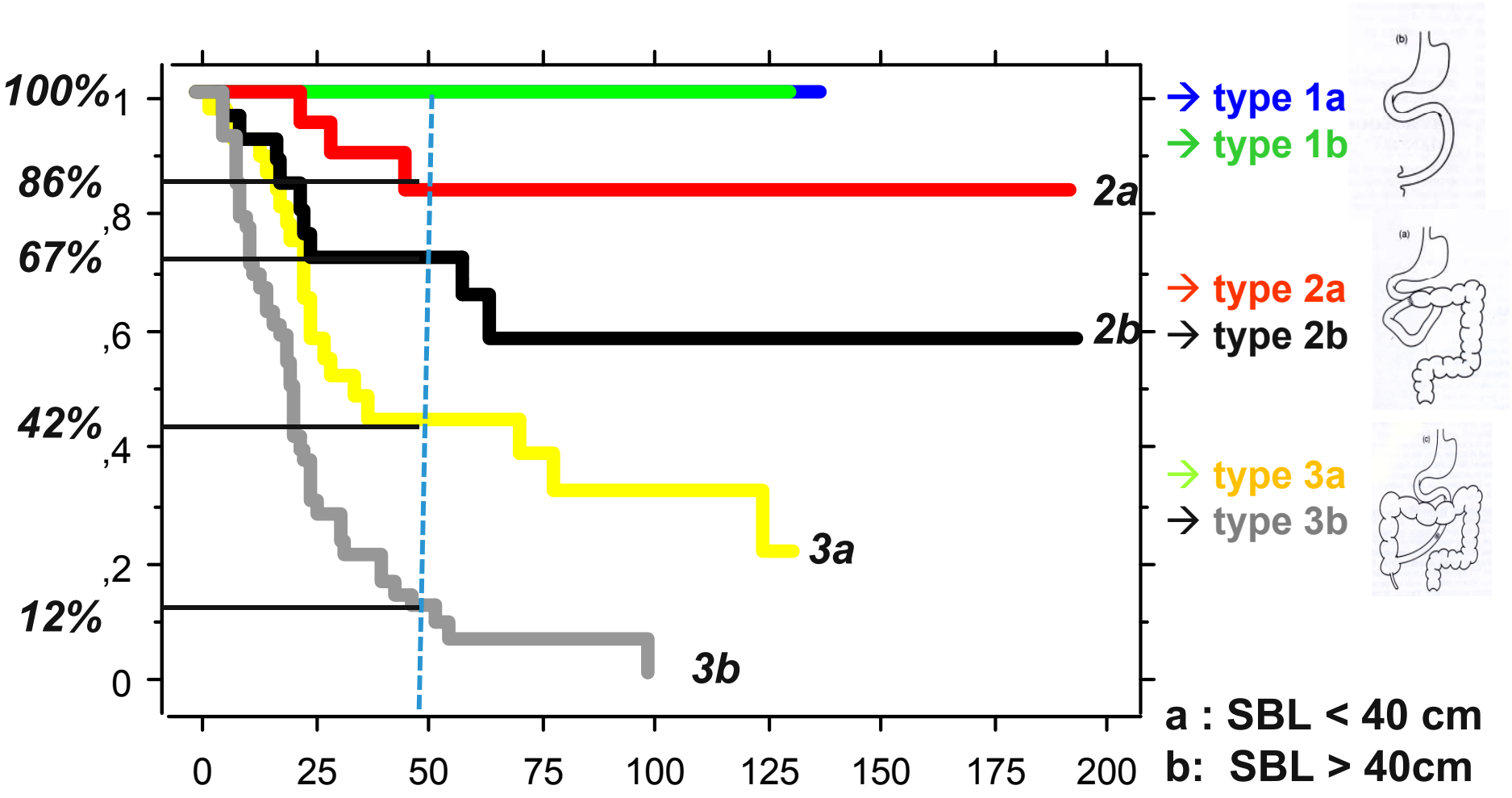
Long term use appears to be beneficial

Revestive / Teduglutide in pediatric SBS

Questions

- Would expect children to wean dose with age as adaptation continues
- Are indications in neonates before the plateau
  - Early use
  - Neonatal use
- On the long term
  - Cost / effectiveness
  - Long term effects

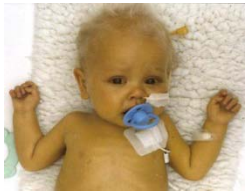
Duration of PN dependency according to anatomical variants of SBS (data from 156 patients)

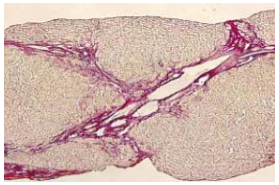


Goulet et al 2017

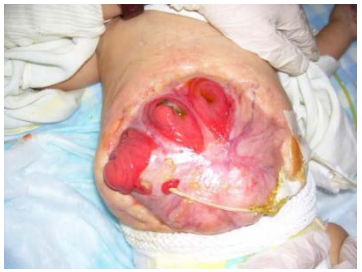
Intestinal failure and liver disease

- While receiving identical PN regimens, patients with Short Bowel Syndrome developed liver disease (Stanko et al, 1987)





- Mechanisms
  - *Negative impact of fasting on bile flow*
  - *Impaired enterohepatic circulation*
  - *Increased risk for translocation/sepsis*
  - *Pro-inflammatory state (Aprahamian et al., 2007)*



Intestinal failure and liver disease

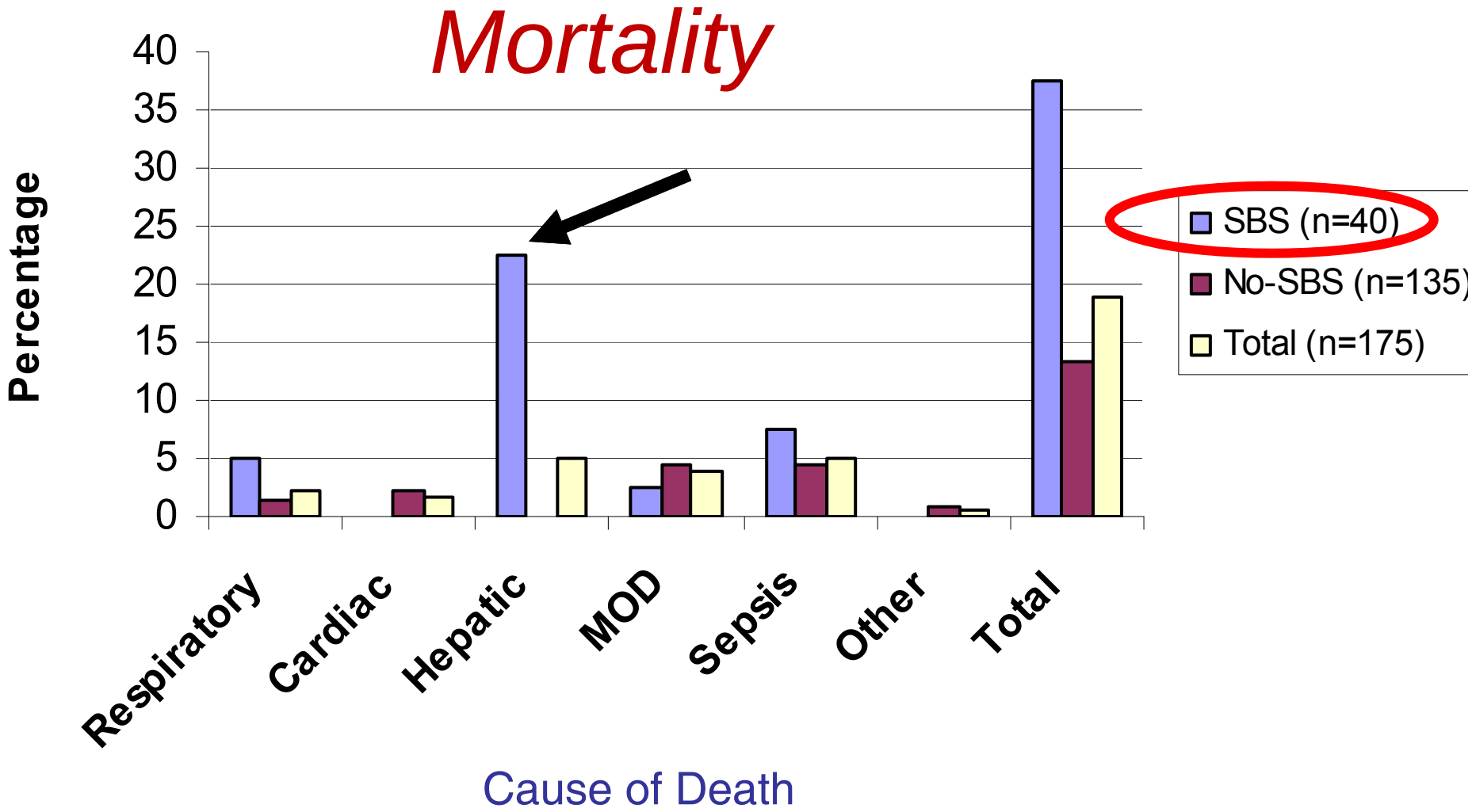
- Incidence not known

- Risks factors

- Prematurity
- Loss of mucosal integrity (*intestinal permeability)*
- SBS *(< 25cm and ICV-)*
- Lack of enteral stimulation (oral feeding)
- Catheter related sepsis
- ***Small intestinal bacterial overgrowth***
- Intravenous fat emulsion
- Unappropriate staff training

O.Goulet; Transplant Proc 1998
O.Goulet; World Rev Nutr Diet. 2015;112:90-114
O.Goulet, C.Lambe Cur Op Org Transplant 2017

Intestinal failure and liver disease



Wales et al, J Pediatr Surg; 40: 755-762

The rate of bloodstream infection is high in infants with short bowel syndrome: Relationship with small bowel bacterial overgrowth, enteral feeding and inflammatory and immune responses

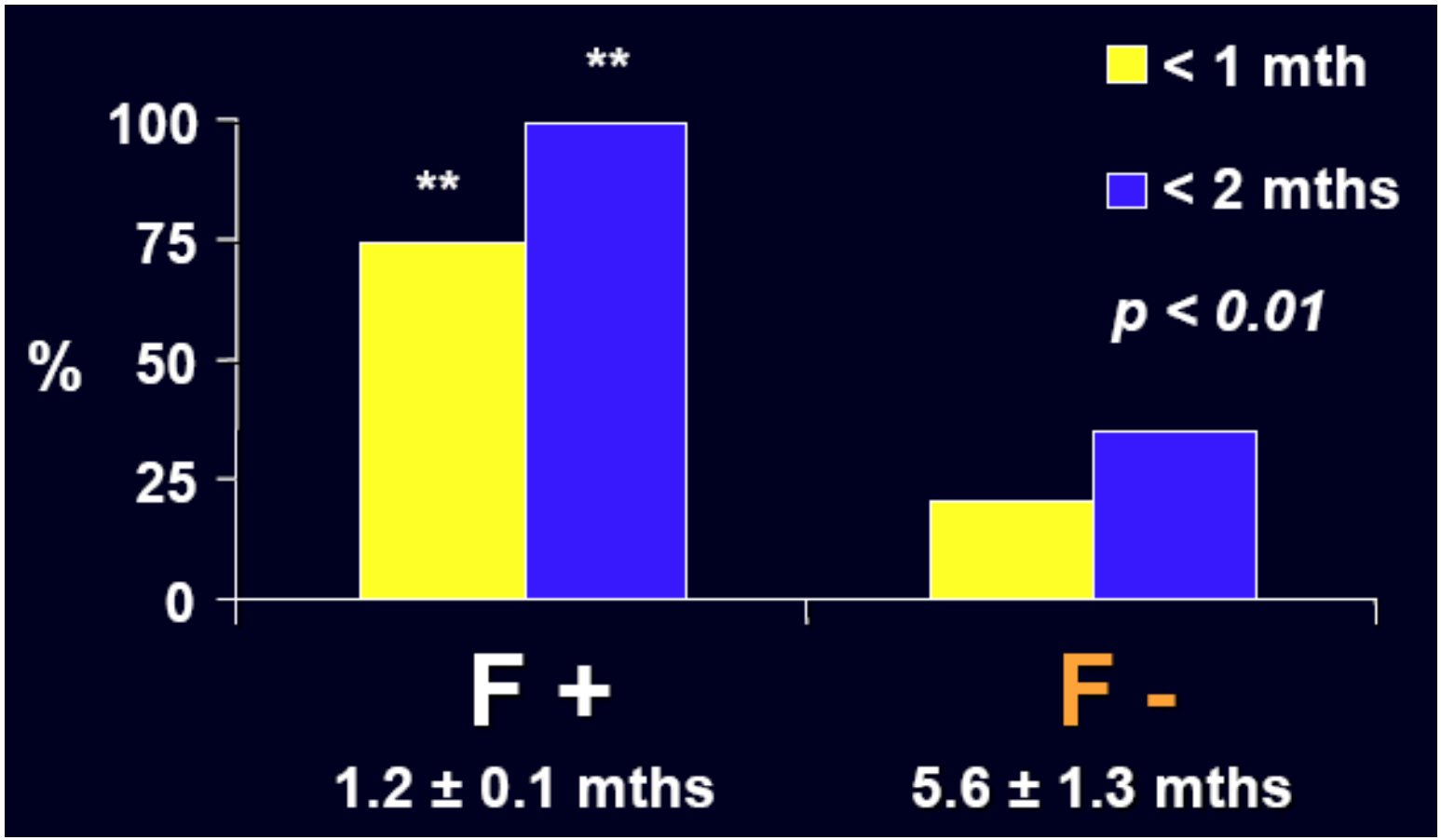
High incidence of fecal origin of bacteria causing sepsis in pediatric patients with short bowel syndrome

Gram-positive		
Enterococcus faecalis	5 (25%)	4 (40%)
Coagulase-negative Staphylococci	3 (15%)	3 (30%)
Leuconostoc spp.	1 (5%)	1(10%)
Gram-negative		
Klebsiella pneumoniae	7 (35%)	4 (40%)
*Mixed infections	4 (20%)	3 (30%)

J Pediatr. 2010 June ; 156(6): 941–947.

Catheter related sepsis

Age at first sepsis and affect on IFALD



Hermans et al, JPGN 2007

Necker
ENFANTS MALADES
HÔPITAL UNIVERSITAIRE

Natural History of Pediatric Intestinal Failure: Initial Report from the Pediatric Intestinal Failure Consortium

J Pediatr . 2012 October ; 161(4): 723–728.e2. doi:10.1016/j.jpeds.2012.03.062.

USA collaborative study

- Multi-center cohort of infants with IF (n=14 IRC)
- Retrospective analysis (5 years study period)
- Clinical and outcome data
- Entry criteria included
  - *Infants <12 months*
  - *PN for > 60 continuous days.*
  - ***Enteral autonomy :***

discontinuation of PN for >3 consecutive months

Natural History of Pediatric Intestinal Failure: Initial Report from the Pediatric Intestinal Failure Consortium

J Pediatr . 2012 October ; 161(4): 723–728.e2. doi:10.1016/j.jpeds.2012.03.062.

Results

- **272 infants in the data base**
  - *gestational age of 34 wks (30, 36)*
  - *birth weight of 2.1 kg (1.2, 2.7)*
  - *followed for 25.7 mo (11.2, 40.9)*

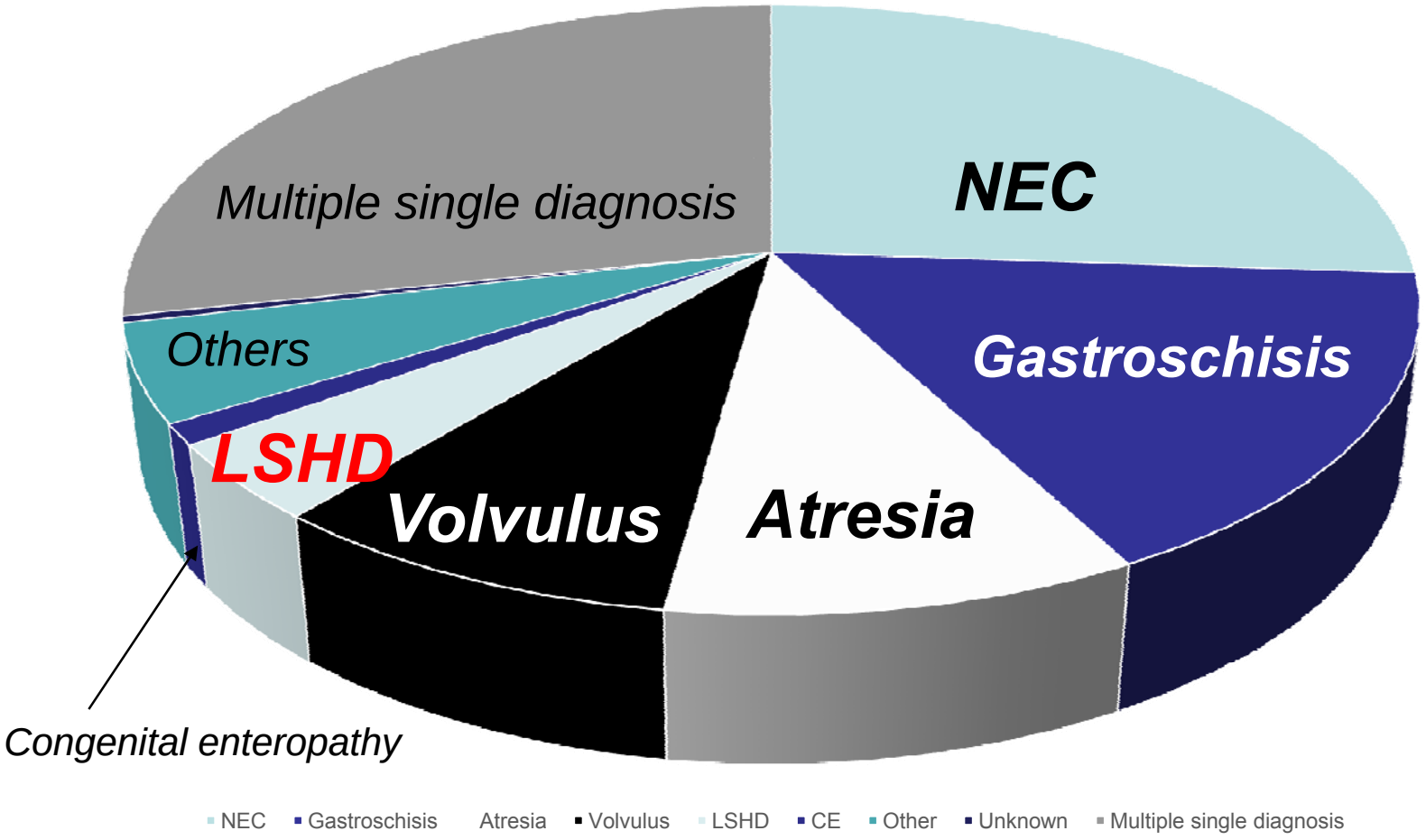
- **Residual small bowel length**

in only 144 patients: 41 cm (25.0, 65.5).

Natural History of Pediatric Intestinal Failure: Initial Report from the Pediatric Intestinal Failure Consortium

J Pediatr . 2012 October ; 161(4): 723–728.e2. doi:10.1016/j.jpeds.2012.03.062.

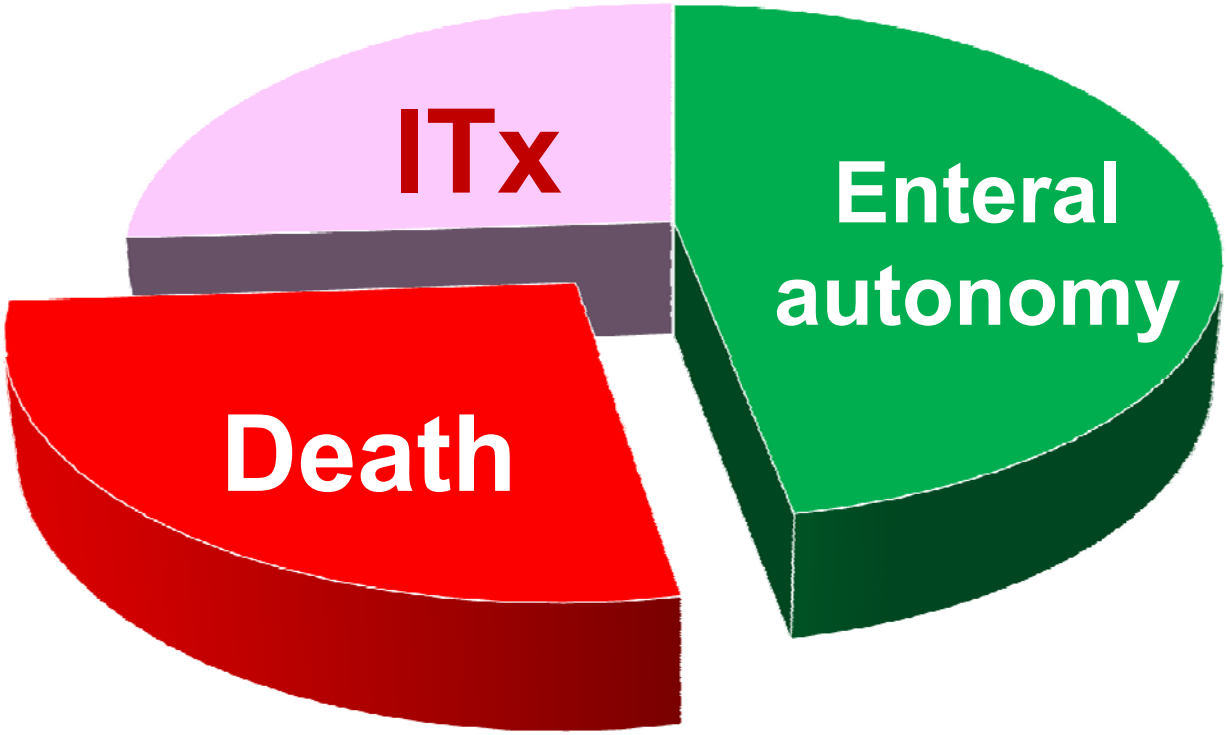
Causes of intestinal failure



Natural History of Pediatric Intestinal Failure: Initial Report from the Pediatric Intestinal Failure Consortium

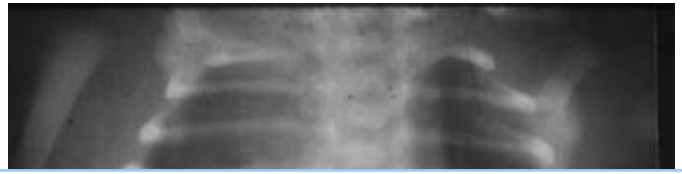
J Pediatr . 2012 October ; 161(4): 723–728.e2. doi:10.1016/j.jpeds.2012.03.062.

Outcome of intestinal failure

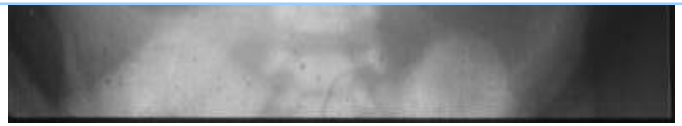
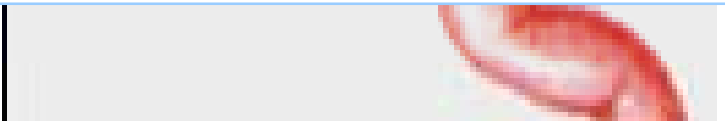


8.9 new catheter-related blood stream infections per 1,000 catheter days.

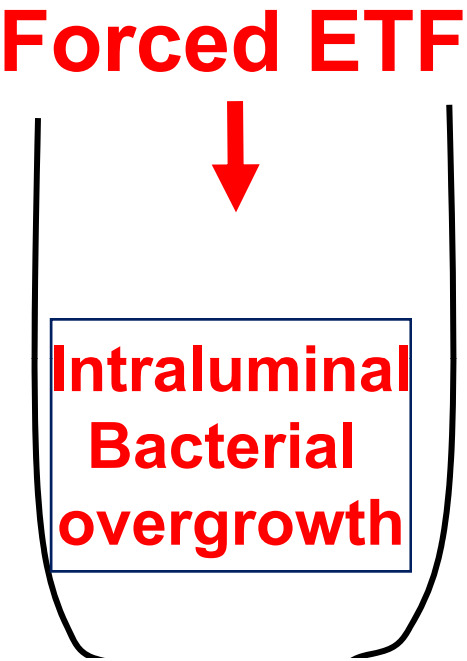
Small intestine bacterial overgrowth in short bowel syndrome




- Motility: *atresia, gastroschisis, NEC*
- Bacterial overgrowth
  - *Mucosal injury*
  - *Bacterial translocation*
- Cholestatic liver disease

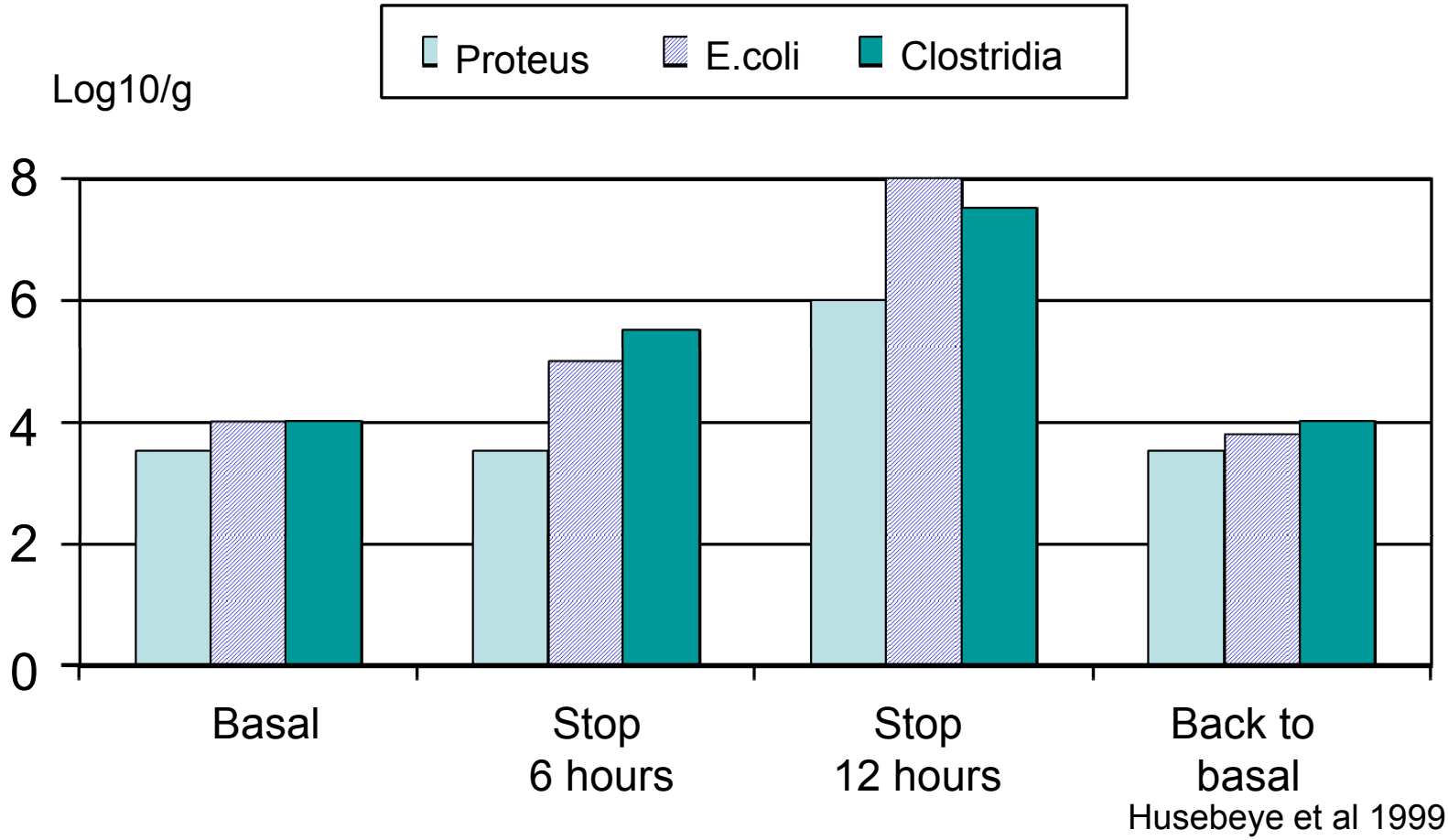
Agressive tube feeding and bacterial overgrowth



- *Interruption of fasting phase III MMC*
- *Loss of bacterial clearance*
- *Intestinal contamination (ICV-)*

Phase III activity and bacterial overgrowth

By suppressing inter-prandial phase III activity
continuous tube feeding
impairs intestinal bacterial clearance



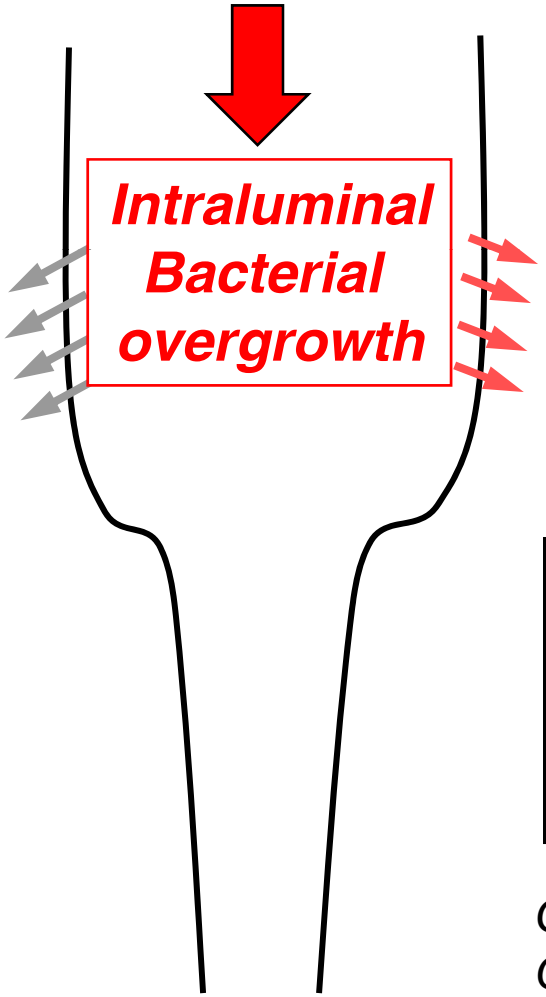
Husebeye et al 1999

Small intestine bacterial overgrowth in short bowel syndrome

Forced ETF

Nausea
Vomiting
Abdominal pain

Abdominal distension
Abundant/rare stools



Translocation
Enterotoxins
Gram negative sepsis

Mucosal injury
Villous atrophy
Malabsorption
Permeability

Portal inflammation
Cholestasis
Fibrosis
Cirrhosis

Food allergy
Eating disorders
Poor growth

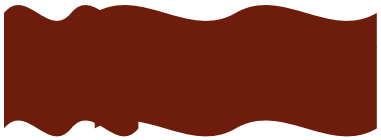
O.Goulet 2013

PARIS DESCARTES

Goulet et al Clin Nutr 2013
O.Goulet in Karger : 2015

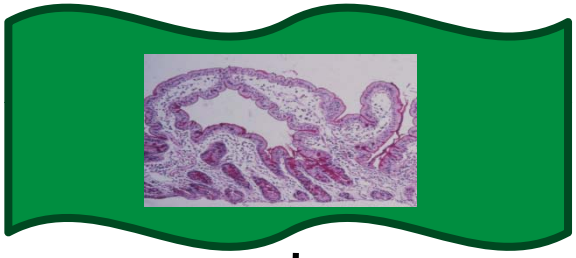
Short bowel syndrome

SBS
Intestinal insufficiency
Parenteral nutrition



Reduced intestinal absorption

Grêle adapté
Intestinal sufficiency
Autonomy



Increased intestinal absorption

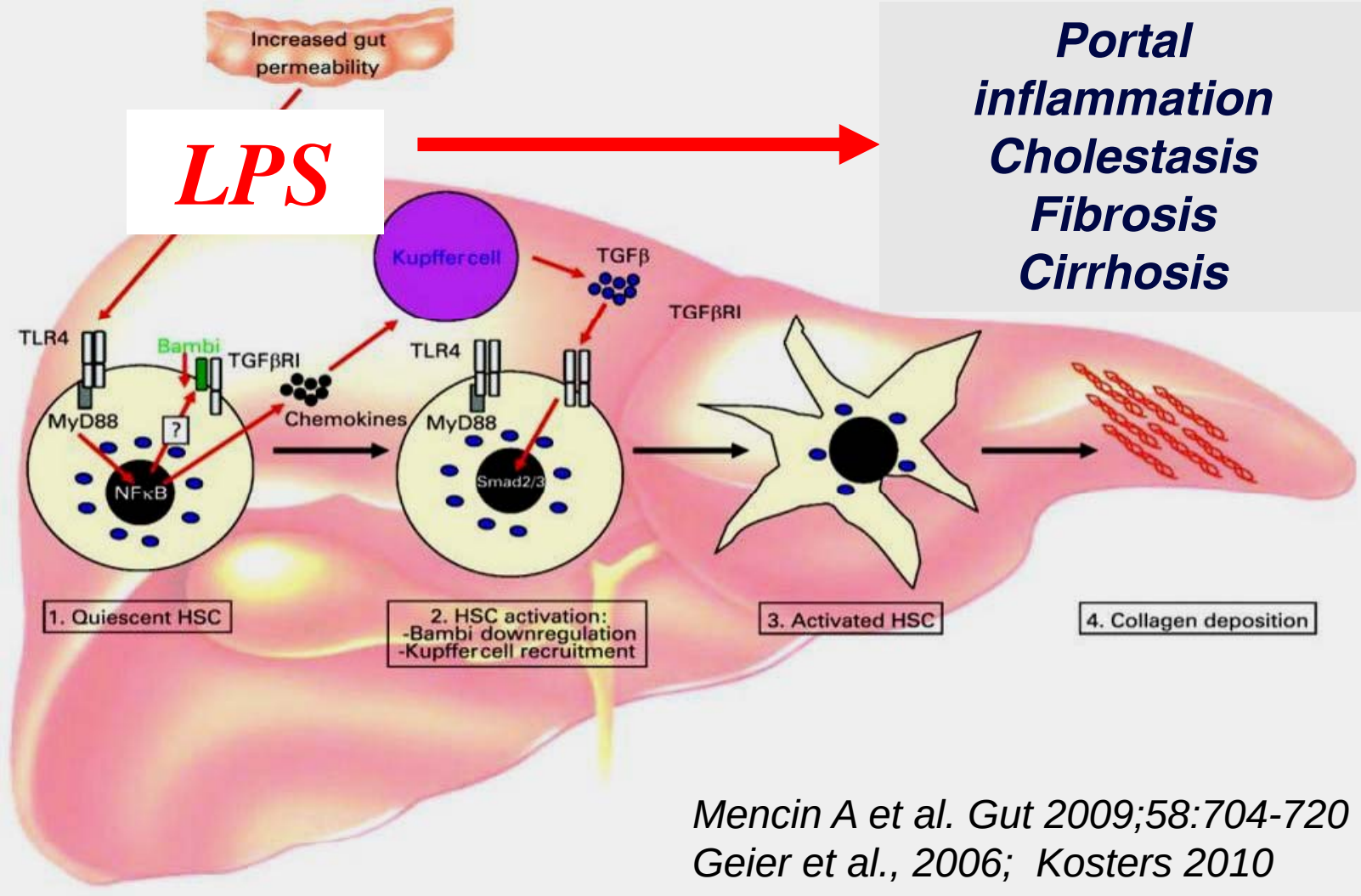
SBS overload syndrome

Bacterial hypermetabolism
SIBO
Abdominal distension
Growth failure

Insufficient Intestinal absorption

« Intestinal abundancy »

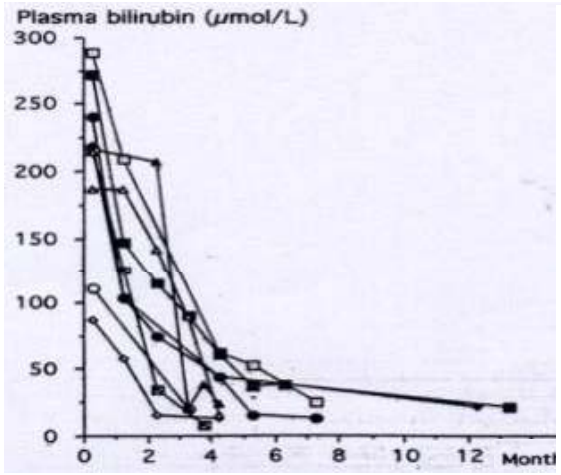
From cholestasis to fibrosis



Mencin A et al. Gut 2009;58:704-720
Geier et al., 2006; Kosters 2010

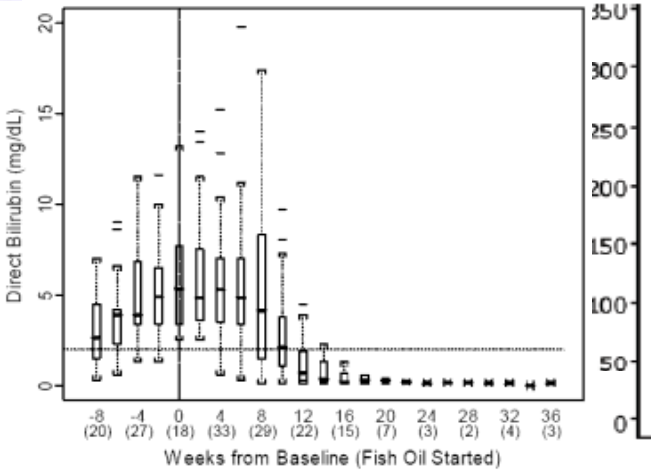
Reversal of «fat related» cholestasis

Soy/MCT



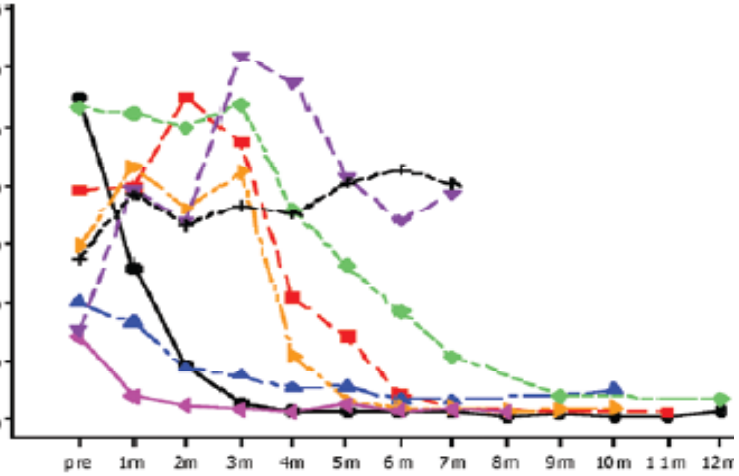
Colomb et al 2000

Omegaven®



Gura et et al. 2006

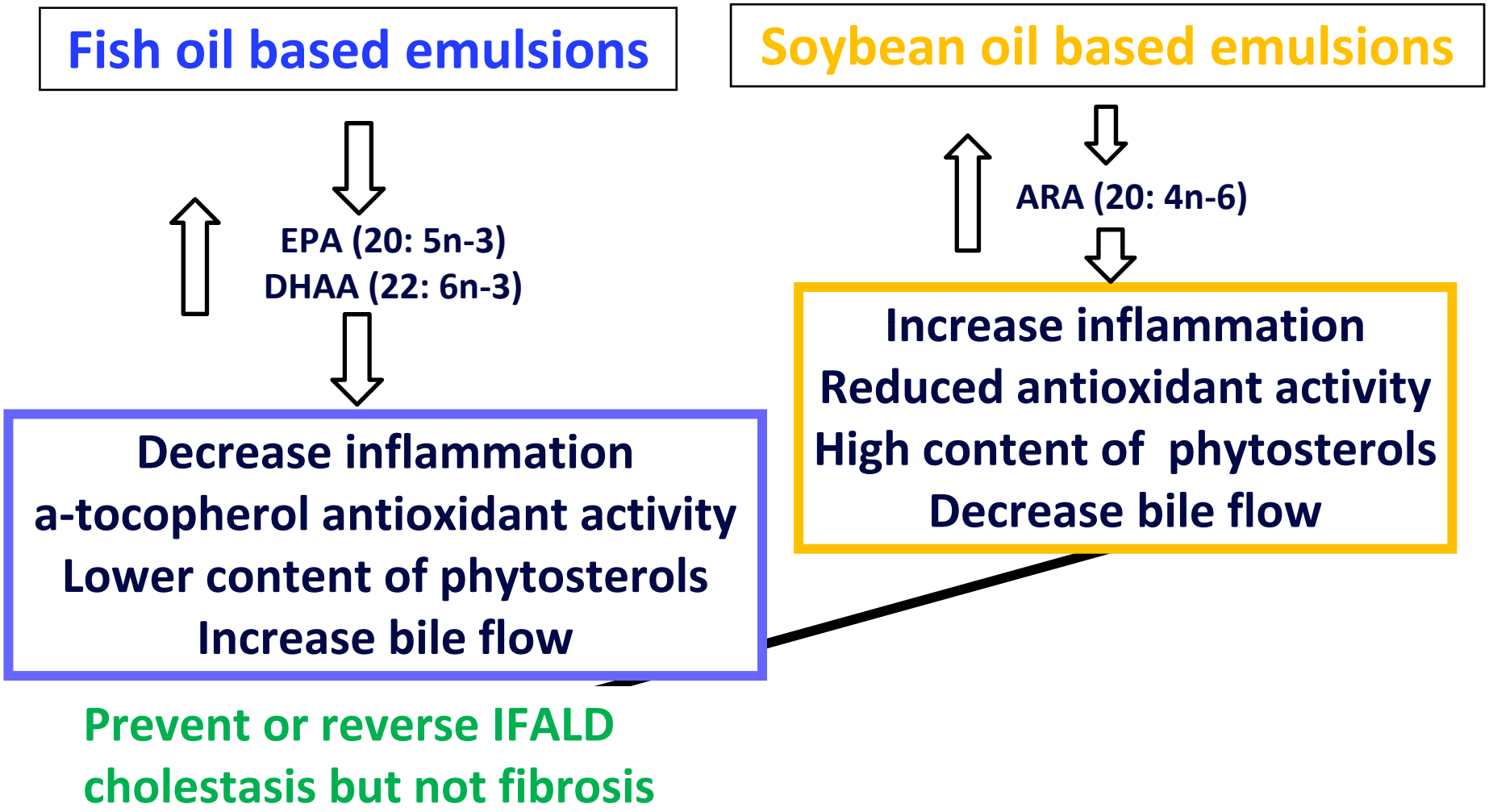
SMOF®



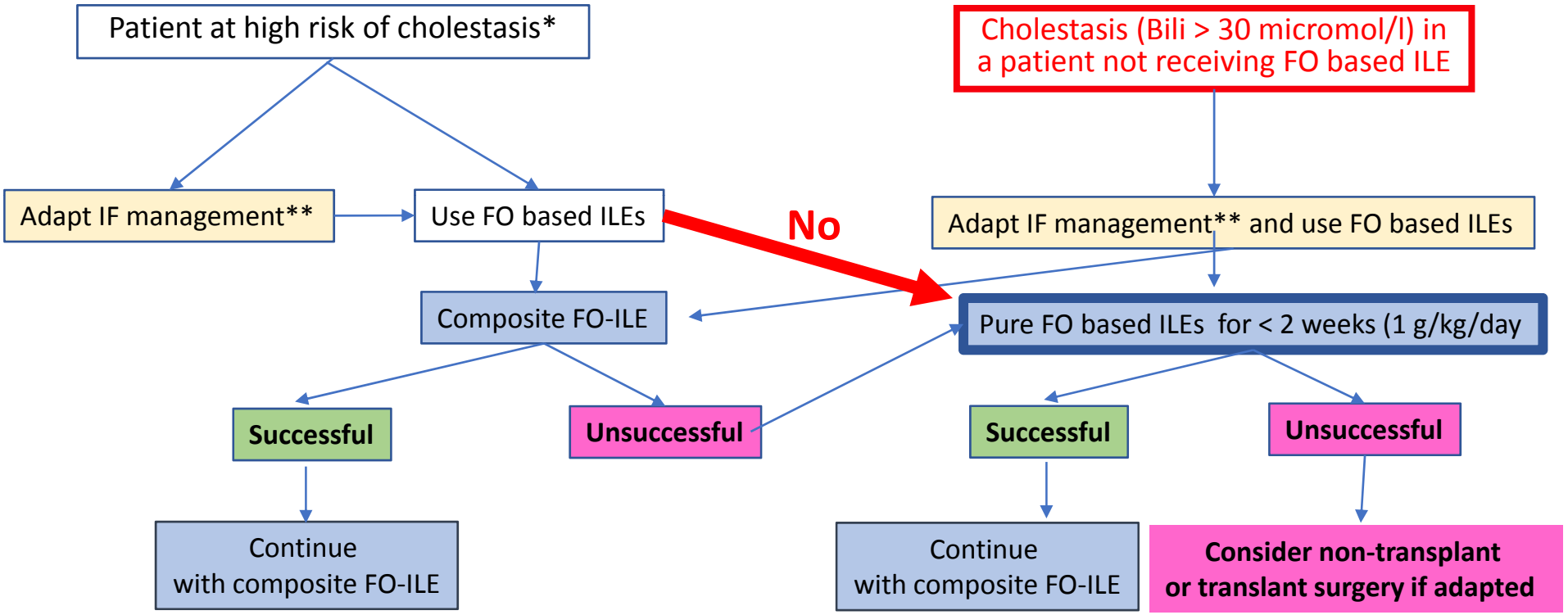
Muhammad et al. 2011;

Main lipid emulsions available in Europe

	Intralipid®	Medialipid®	ClinOleic®	SMOF®	Omegaven®
Soybean %	100	50	20	30	0
MCT %	0	50	0	30	0
Olive oil %	0	0	80	25	0
Fish oil %	0	0	0	15	100
Phytosterols mg/l	348±33	200±40	327±8	47.6	0
α-tocopherol mg/l	38	< 30	200	200	150-296
ω-3	+	±	+	++	+++
ω-6	+++	++	+	++	+


Fish oil based emulsions
EPA (20: 5n-3)
DHAA (22: 6n-3)
Decrease inflammation
a-tocopherol antioxidant activity
Lower content of phytosterols
Increase bile flow
Soybean oil based emulsions
ARA (20: 4n-6)
Increase inflammation
Reduced antioxidant activity
High content of phytosterols
Decrease bile flow
Prevent or reverse IFALD
cholestasis but not fibrosis

Suggested algorythm for using fish oil based ILEs in infants and children at risk of IFALD



* Long term PN, repeated catheter related sepsis, ileus, agressive tube feeding, SIBO, lack of entero-hepatic cycle….

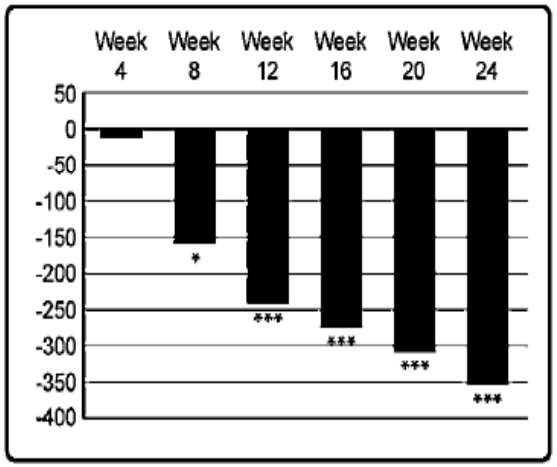
** Prevent sepsis and SIBO, reconstructive surgery, promote oral feeding……

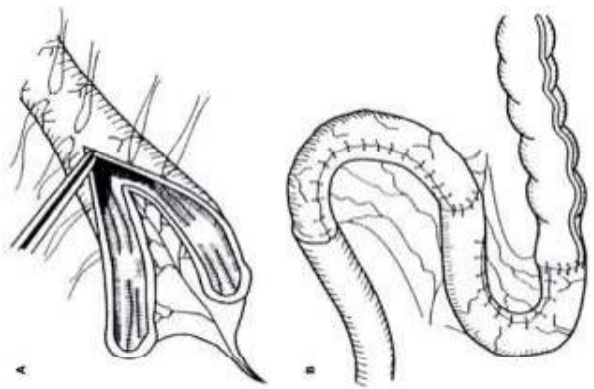
Long term PN dependency

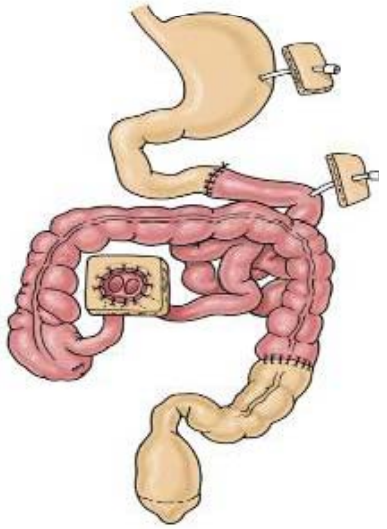
- By using hormonal therapy (GH, GLP-2)

- By performing autologous bowel surgery

- By performing intestinal transplantation

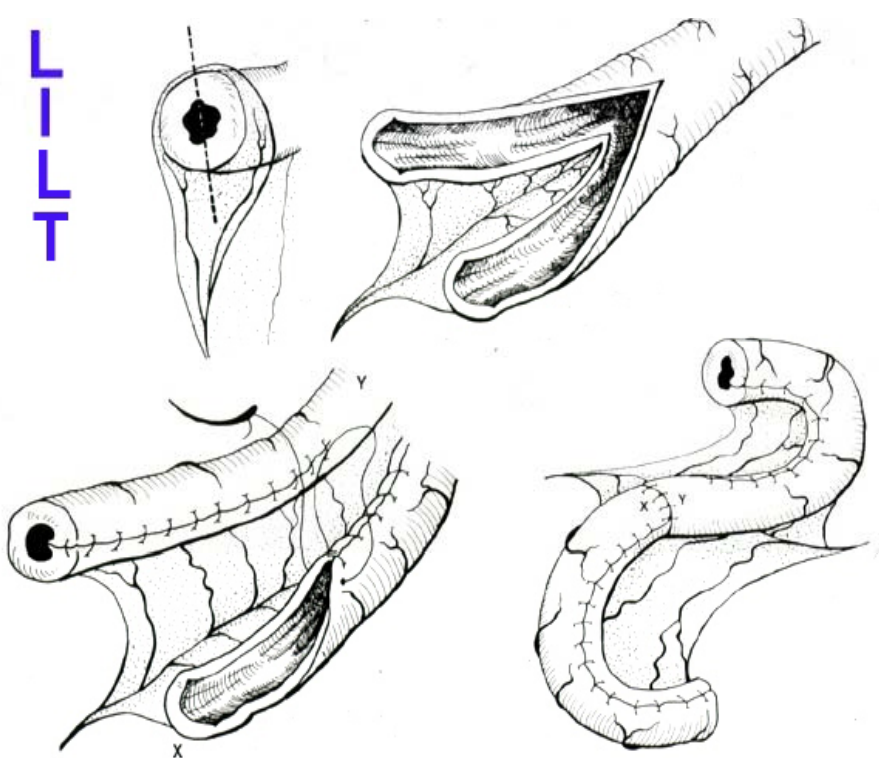


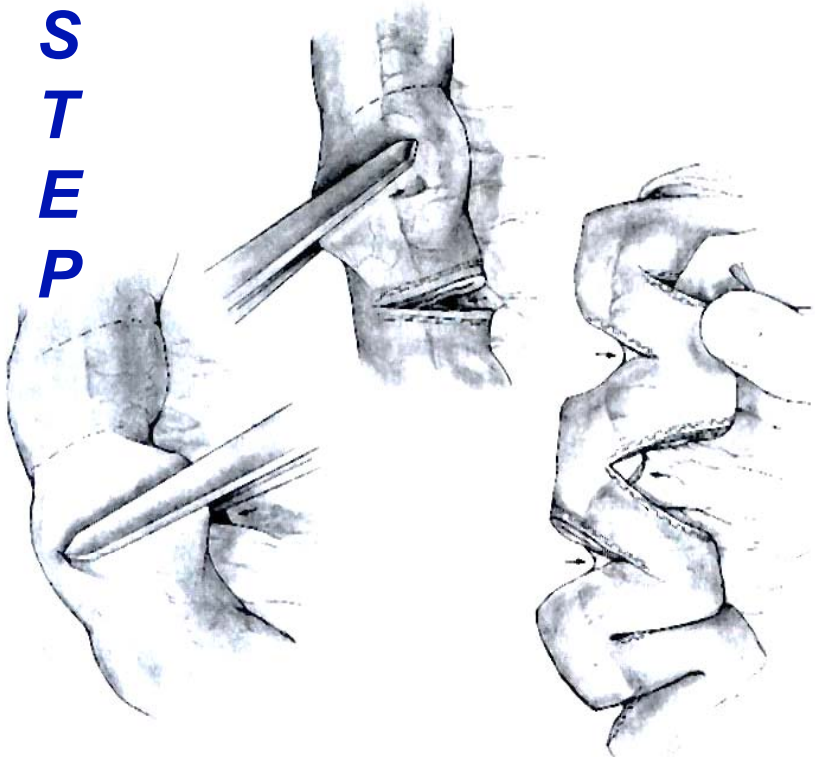




Short bowel syndrome

Autologous bowel surgery





Five-year outcomes after serial transverse enteroplasty in children with short bowel syndrome

Carol Oliveira, Nicole de Silva, Paul W. Wales*

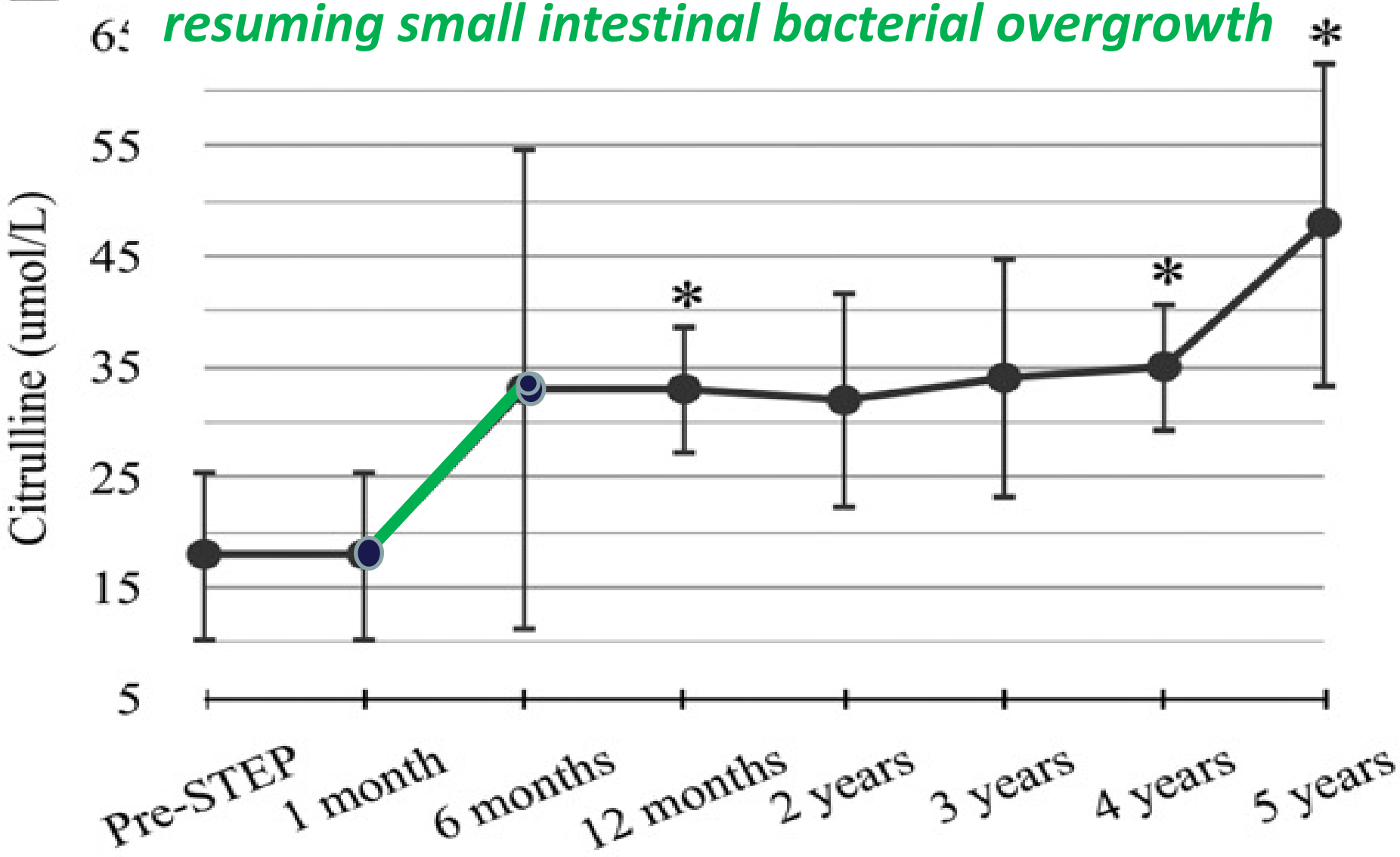
Journal of Pediatric Surgery (2012) 47, 931–937

	N = 12
Median age (mo)	5.5 (2-27)
Males (%)	9 (75)
Diagnosis (%)	
Atresia	6 (50)
NEC	3 (25)
Gastroschisis	1 (8.3)
Hirschsprung disease	1 (8.3)
Volvulus	1 (8.3)
Indication (%)	
Bacterial overgrowth	7 (58.3)
IFALD	5 (41.7)
Median follow-up (mo)	68 (7-70)

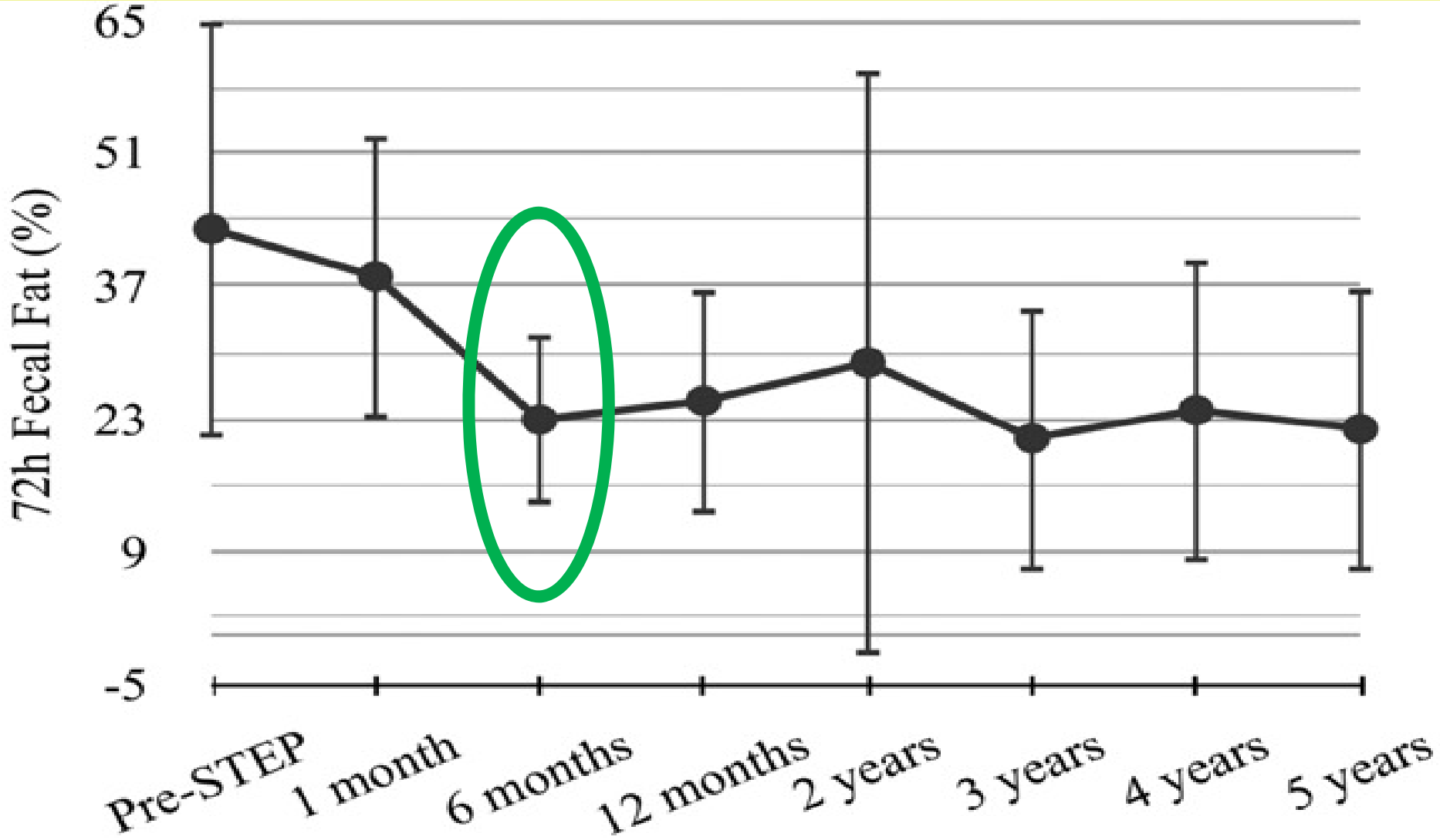
85%

E

Citrulline increase suggests mucosal recovery by resuming small intestinal bacterial overgrowth



In turm, improving intestinal absorption, reducing fecal fat and improving liver condition (decreased cholestasis)



Necker home-PN data base
Intestinal transplantation

- 140 children (56%) weaned off HPN.
- Mean HPN duration : 1.9 ± 0.4 years.
- 87 children (34%) : ongoing HPN.

12 have been transferred to adult units

9 children restarted HPN after weaning

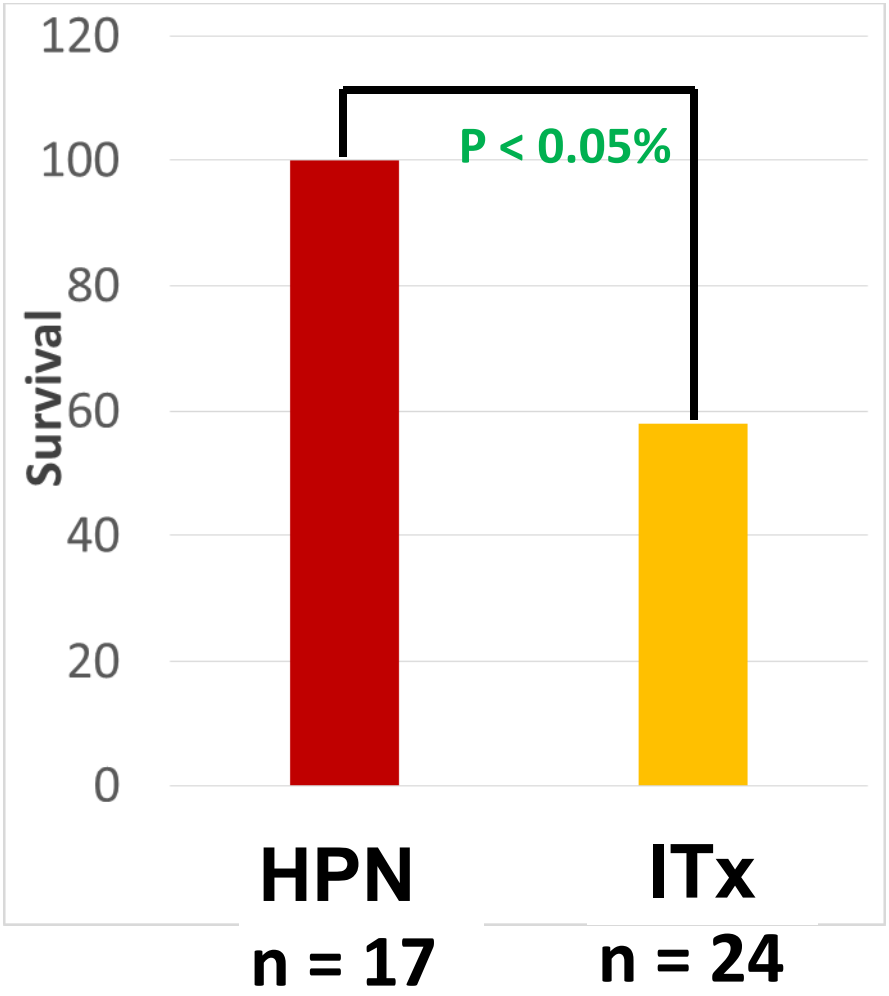
19 have been transplanted ITx or liver-ITx

Necker ENFANTS MALADES HÔPITAL UNIVERSITAIRE

PARIS DESCARTES

Abi Nader et al Am J Clin Nutr 2016

Ultra Short Bowel Syndrome in children: Long term Home-PN *versus* intestinal transplantation



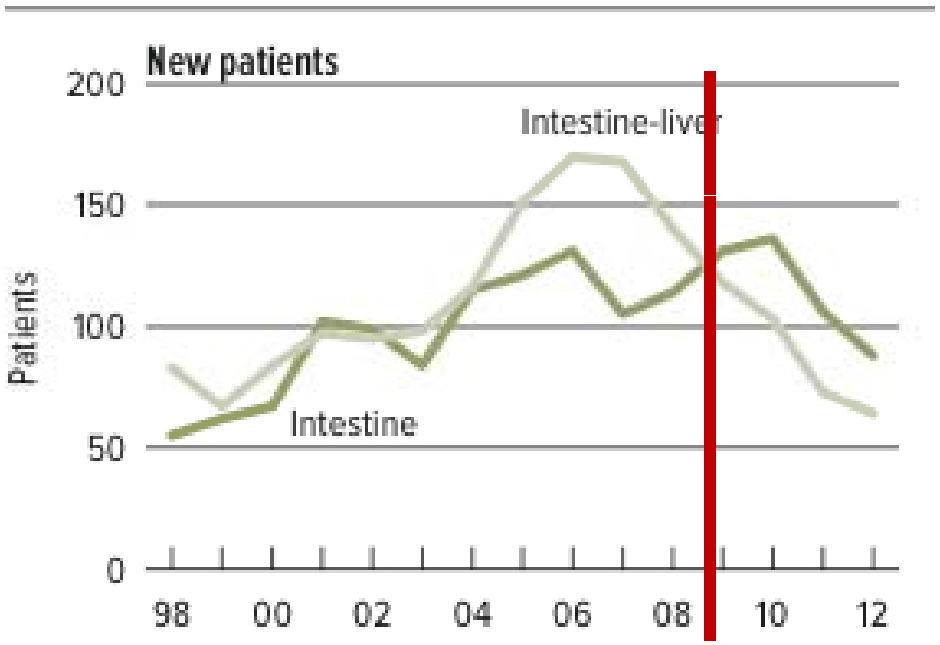
Long term management of IF patients should prevent any associated complications leading to **« nutritional failure »**

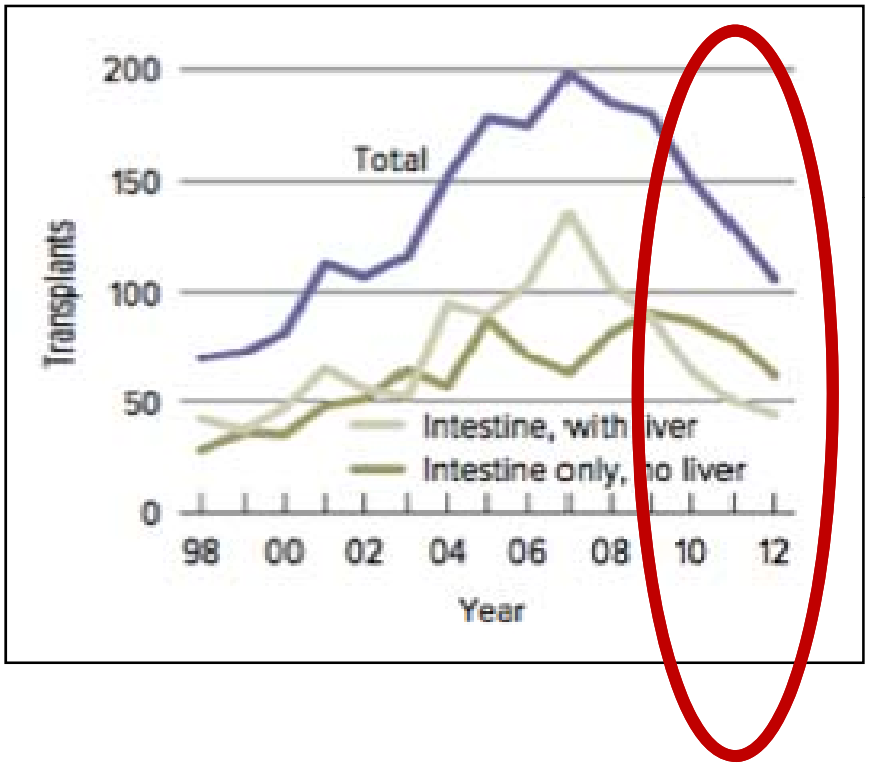
- Finally, intestinal Tx should be avoided as much as possible

Intestinal failure

- HPN remains the first line treatment for children with protracted or irreversible intestinal failure
- Home-PN programme requires medical expertise and logistic for reducing complication's rate **(Taurolock®…, SMOF®** *vs* **Intralipid®,….Oral feeding…)**
- A multidisciplinary management and decisions for the best therapeutic strategy in case of irreversible intestinal failure with consideration for children behavior and quality of life

Preventing IFALD
Multidisciplinary team approach





Intestinal failure

In the future

- Prenatal diagnosis of inherited diseases
- Hormonal therapy in SBS
- Intestinal Tx improvement *(immune approach)*
- Tissue engineering (SBS)
- Stem cell transplantation (CE, HD)
- Intestinal pace maker insertion
- Intestinal microbiome science

Necker intestinal rehabilitation team

Ped GI-Hep-Nutrition

Cécile Lambe
Bénédicte Pigneur
Frank Ruemmle
Cécile Talbotec
Florence Lacaille
Olivier Goulet

Specialized nurses

Christelle Alliot
Djamila Fezaa
Catherine Poisson
Amelia Rocha

Surgery & ICU

Yves Aigrain
Carmen Capito
Christophe Chardot

Laurent Dupic
Fabrice Lesage

Muchas gracias por su atención

olivier.goulet@nck.aphp.fr

Muchas gracias por su atención

olivier.goulet@nck.aphp.fr