Intestinal failure

Past, present and future

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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
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
<table>
<thead>
<tr>
<th><strong>Intestinal transplantation</strong></th>
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<td><strong>Birmingham</strong></td>
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<td><strong>Boston(2)</strong></td>
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<td><strong>Xi’an</strong></td>
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</table>
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
Diagnosis, Management and Transplantation

Intestinal Failure in Children
O. Goulet

1998

2008
Intestinal failure

a medico-surgical management

Ped-GI and Nutrition
- Adaptation of PN intakes
- Prevention of complications
- Long term Home-PN/Tx follow up

Pediatric surgery
- Neonatal surgery
- Non transplant surgery
- 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
- > 2000: «Intestinal rehabilitation»
Search results
Items: 1 to 20 of 603

1. Impact of multidisciplinary teams for management of intestinal failure in children.

Belza C, Wales PW.
PMID: 28379928
Similar articles
ESPGHAN – ESPEN Guidelines on Paediatric Parenteral Nutrition

2005
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

**Onset day 1-5**

- **Persists at bowel rest**
  - Family history
  - Consanguinity
  - Abundant watery diarrhea

- **Reduced at bowel rest**
  - Family history
  - Hydramnios / prematurity
  - Watery diarrhea
  - Biological presentation

- **Disappears at bowel rest**
  - Family history
  - Extra-digestive disease
  - Protein losing enteropathy

**Family history**

- Reduced at bowel rest

**Hydramnios / prematurity**

**Watery diarrhea**

**Biological presentation**

**Family history**

**Consanguinity**

**Abundant watery diarrhea**

**Microvillous atrophy**

**MYO5B**

**Epithelial dysplasia**

**EpCam / SPINT2**

**Other « new » diseases/mutations to be founded**

**Syndromic diarrhea**

**THE syndrome**

**Mutations : TTC37, SKIV2L**

**And other candidate genes**

**Chloride diarrhea**

**Sodium diarrhea**

**SPINT2 ??**

**Consanguinity**

**SGA birth**

**Facial dysmorphia**

**Hair abnormalities**

**Liver disease**

**CDG syndrome**

**Mitochondrial disease**

**Neurogenin 3 deficiency**

**Lymphangiectasia**

**Bile salts malabsorption**

**HSPG deficiency**

**Early IPEX / AIE**

**Feeding testing**

**Lactose, glucose, galactose, fructose**

**Glucose-galactose Malabsorption**

**Primary lactase deficiency**

**CMPA and IPEX as well as sucrase deficiency are rarely of early neonatal onset**
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

< 12 mths in 80 patients (76%)

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

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>CIPOS</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self care mobility</td>
<td>96</td>
<td>79</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>School Social activities</td>
<td>94</td>
<td>68</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pain free</td>
<td>82</td>
<td>52</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Compared to both normal and JCA, CIPOS have
- Decreased self esteem
- Increased anxiety

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 type of graft

Necker 1994-2016

Years post-transplantation

53 Patients
Liver SB

58 Patients
isolated SB

< 50%
CIPOS and transplantation

long-term outcome

- Myopathy
  - No SBTX: n=29
    - Death: n=7
  - SBTX: n=3
    - Death: n=3
- Neuropathy
  - SBTX: n=3
    - Death: n=1
  - No SBTX: n=45
    - Death: n=10
- Indeterminate
  - SBTX: n=2
  - Death: n=1

62.5% post Tx death

From Home-PN to ITx

What is the most important?

Survival

QOL
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

Jejuno-colic: type II
≤ 40 - 80 cm
Atresia/gastroschisis

Jejuno-ileocolic: type III
≤ 20 - 80 cm
Mid gut volvulus Atresia

Extensive NEC
Adaptation of Remnant Intestine

**Physiological process**

Short segment

- Diminished Absorptive surfaceSA
  - Nutrients
    - Reduced Nutrient Absorption
      - Diarrhea Mucosal Inflammation
        - Dehydration
        - Electrolyte disturbance
        - Perianal excoriation

Adapted Intestine

- Increased Nutrient Absorption

- Dehydration
- Electrolyte disturbance
- Perianal excoriation

<table>
<thead>
<tr>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterostomy : type i</td>
</tr>
<tr>
<td>Jejuno-ileostomy : type ii</td>
</tr>
<tr>
<td>Jejuno-ileostomy : type iii</td>
</tr>
</tbody>
</table>

- ≤40 - 80cm
  - Aganglionosis
  - NEC, extended atresia

- ≤40 - 80cm
  - Atresia/aparoschisis
  - Extended NEC

- ≤20 - 80cm
  - Volvulus of the small intestine
  - Jejuno-ileal atresia
**Adaptation of Remnant Intestine**

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

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

Short bowel syndrome

Importance of the colon
Importance of colonic support for energy absorption as small-bowel failure proceeds\textsuperscript{1–3}

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

Fecal energy losses in MJ per day

50%

All colon left

No colon left

Small-bowel length (cm)
Role of the colon in energy salvage

Abbi Abou S……Goulet O 2017 JPGN submitted
Morphology of the colonic mucosa

SBS Controls

Crypts size
- 35% of crypts size

Epithelial cells
- 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

Role of the colon in energy salvage

Carbohydrate Salvage

Carbohydrate soluble fiber → Bacteria → Short chain fatty acids + CH₄, CO₂, H₂ → Colon

Small intestine

H₂O

Na

Jeppesen et al. JPEN 1999;23:S101-S105
Short chain fatty acids and GLP-2

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

controls

SBS

controls

Type L enterochromafin cells: ileum and colon
Evidence of SBS « specific » bacterial strain

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

<table>
<thead>
<tr>
<th>Beneficial</th>
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<tbody>
<tr>
<td>Bacterial flora</td>
</tr>
<tr>
<td>Microbiota</td>
</tr>
<tr>
<td>Intestine</td>
</tr>
<tr>
<td>Colon</td>
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<tr>
<td>Intestinal barrier</td>
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<tr>
<td>Improved</td>
</tr>
<tr>
<td>Trophic consequences</td>
</tr>
<tr>
<td>Hyperplasia</td>
</tr>
<tr>
<td>Small bowel &amp; colon</td>
</tr>
<tr>
<td>Mechanisms</td>
</tr>
<tr>
<td>SCFA</td>
</tr>
<tr>
<td>butyrate induced GLP$_2$</td>
</tr>
<tr>
<td>Outcome</td>
</tr>
<tr>
<td>Intestinal autonomy</td>
</tr>
</tbody>
</table>
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

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

REFERENCES


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 inappropriate and aggressive tube 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*

Review

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


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

- Meta-analysis of RCTs
- Randomised controlled trial (RCT)
- Observational studies (case-control, cohort)
- Observational studies (case report, case series)
- Experimental and physiological studies
Short bowel syndrome

Experience >>>>>>> evidence

- Meta-analysis of RCTs
- Randomised controlled trial (RCT)
- Observational studies (case-control, cohort)
- Observational studies (case report, case series)
- Experimental and physiological studies
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
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
± primary anastomosis
± ICV

± % alive

± % not weaned

Survival in pediatric SBS

Necker-Enfants Malades cohorts

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)

Type 1: 91%, p<0.0001

Type 2: 63%

Type 3: 29%

Perella et al JPEN submitted 2017
### Necker SBS (n = 156) : Growth follow up

<table>
<thead>
<tr>
<th></th>
<th>HPN duration (months)</th>
<th>Weight (SD)</th>
<th>Height (SD)</th>
<th>BMI</th>
<th>Calories PN/REE</th>
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<tbody>
<tr>
<td><strong>At HPN weaning</strong></td>
<td>17 ± 12</td>
<td>-0.5 ± 1</td>
<td>-0.2 ± 1.4</td>
<td>15 ± 1.6</td>
<td>0</td>
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<tr>
<td><strong>6 months after weaning off HPN</strong></td>
<td></td>
<td>-0.7 ± 0.9</td>
<td>-0.1 ± 2.1</td>
<td>15 ± 2.2</td>
<td>0</td>
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<tr>
<td><strong>Still on HPN</strong></td>
<td>56 ± 45</td>
<td>-0.4 ± 1.1</td>
<td>-0.5 ± 1.3</td>
<td>16 ± 2.3</td>
<td>1.31 ± 0.2</td>
</tr>
</tbody>
</table>

*Perella B et al 2017*
Bone Health and Growth of Children Receiving Long-term Parenteral Nutrition

ABI NADER E.1, LAMBE C.1, TALBOTECA C.1, ACRAMEL A.2, GOULET O.1,3

Poster 790
WCPGHAN 2016

According to PN indications

<table>
<thead>
<tr>
<th></th>
<th>Height, Z-score</th>
<th>Spine BMD</th>
<th>Whole body BMD</th>
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<tr>
<td></td>
<td>n</td>
<td>med [1Q;3Q]</td>
<td>p</td>
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<tr>
<td>SBS</td>
<td>24</td>
<td>-0.2 [-1.0;0.8]</td>
<td></td>
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<tr>
<td>CE</td>
<td>8</td>
<td>-1.8 [-2.3;-1.1]</td>
<td>0.02</td>
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<tr>
<td>CIPOS</td>
<td>9</td>
<td>-0.7 [-2.0;-0.4]</td>
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</table>
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

Total 307 children
20 per million < 20 years

+ 14,5%
Home parenteral nutrition in France 2016

- **143 SBS**
- **60 congenital enteropathies**
- **48 CIPOS**
- **32 LS Hirschsprung**
Home parenteral nutrition in France 2016

HPN duration in months

[Bar chart showing HPN duration in months for different locations in France, with bars for NEM, AT, RD, Lille, Lyon, Marseille, Toulouse, Moy, and Med.]
Incidence of catheter related sepsis

Necker Survey AJCN 2016

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

Plasma citrulline umol/L

* paired t test; p < 0.05

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 J PEN 2010
REVESTIVE (teduglutide)
Recombinant analogue of human GLP-2

- 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.

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

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’Keefe6

**GLP 2 analog multicenter trial in adult SBS**

**Reduction of parenteral nutrition volume**

![Graphs showing reduction of parenteral nutrition volume over weeks for placebo and two dose groups](Gut 2011; 60:902—914. doi:10.1136/gut.2010.218271)
REVESTIVE paediatric Phase 3 study design

Study objective and endpoints

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)

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.\(^2\)

The approved dose of REVESTIVE in patients aged 1 year and above is 0.05 mg/kg/day body weight.\(^3\)


\(^3\) Revestive® EMA Summary of Product Characteristics, Shire Pharmaceuticals Ireland Limited, June 2016.

* Safety data were assessed after ≥28 days of REVESTIVE treatment before the next dosing cohort could proceed.
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.e5 DOI: (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-aggressive and surgically resected cancer disease
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 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:
20. 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
21. Active or history of clinically significant pancreatic or biliary disease
22. 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
23. Presence of any of the excluded disease states described in the table below
## Patient demographics

### Patient disposition and baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Standard of care (n=5)</th>
<th>REVESTIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.0125 mg/kg/day (n=8)</td>
<td>0.025 mg/kg/day (n=14)</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (min, max)</td>
<td>2.0 (2, 3)</td>
<td>3.0 (1, 14)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>3 (60)</td>
<td>6 (75)</td>
</tr>
<tr>
<td>Median body mass index, kg/m² (min, max)</td>
<td>16.8 (14.3, 18.4)</td>
<td>15.4 (13.8, 19.4)</td>
</tr>
<tr>
<td>Reason for resection, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Necrotising enterocolitis</td>
<td>2 (40)</td>
<td>1 (13)</td>
</tr>
<tr>
<td>Midgut volvulus</td>
<td>2 (40)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Intestinal atresia</td>
<td>1 (20)</td>
<td>1 (13)</td>
</tr>
<tr>
<td>Gastrochisis</td>
<td>0</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Stoma, n (%)</td>
<td>0</td>
<td>1 (13)</td>
</tr>
<tr>
<td>Colon-in-continuity, n (%)</td>
<td>5 (100)</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Median estimated residual small intestine length, cm (min, max)</td>
<td>35 (10, 75)</td>
<td>15 (2, 75)</td>
</tr>
<tr>
<td>Median parenteral support* volume at baseline, L/week (min, max)</td>
<td>7.7 (4.4, 9.8)</td>
<td>5.4 (4.2, 13.9)</td>
</tr>
<tr>
<td>Median enteral nutrition† volume at baseline, L/week (min, max)</td>
<td>5.1 (0.9, 6.0)</td>
<td>8.1 (2.9, 12.6)</td>
</tr>
</tbody>
</table>

* 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

---

Results – Adverse events

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

* 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

Results – Treatment-emergent adverse events

• No serious treatment-emergent adverse events related to REVESTIVE occurred in the 12-week paediatric study\textsuperscript{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\textsuperscript{1}

<table>
<thead>
<tr>
<th>Serious treatment-emergent adverse events occurring in &gt;1 REVESTIVE-treated patient\textsuperscript{2}</th>
<th>Standard of care (n=5)</th>
<th>REVESTIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment-emergent adverse event by preferred term, n (%)*</td>
<td>0.0125 mg/kg/day (n=8)</td>
</tr>
<tr>
<td>Central line infection</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2 (40)</td>
<td>0</td>
</tr>
<tr>
<td>Catheter-related complications</td>
<td>1 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Parainfluenza virus infection</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* 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\textsuperscript{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\textsuperscript{2}


J Pediatr 2017 181, 102-111.e5 DOI: (10.1016/j.jpeds.2016.10.027)
Results – Weekly prescribed parenteral support volume (median)

Percentage change in prescribed weekly parenteral support* volume

![Graph showing percentage change in prescribed weekly parenteral support volume.]

- Standard of care
- REVESTIVE 0.0125 mg/kg/day
- REVESTIVE 0.025 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.


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**

- **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 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.

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

Percentage change in patient-reported weekly enteral nutrition* volume

<table>
<thead>
<tr>
<th>Week</th>
<th>Median weekly enteral nutrition volume change from baseline, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>0</td>
</tr>
</tbody>
</table>

* 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.

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
\(^*n=7; \ ^*n=14\)

Teduglutide (mg/kg/day)

- 0.0125
- 0.025
- 0.05
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.

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

Mortality

**Cause of Death**

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

<table>
<thead>
<tr>
<th>Gram-positive</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td>5 (25%)</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Coagulase-negative Staphylococci</td>
<td>3 (15%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td><em>Leuconostoc spp.</em></td>
<td>1 (5%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Gram-negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>7 (35%)</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Mixed infections</td>
<td>4 (20%)</td>
<td>3 (30%)</td>
</tr>
</tbody>
</table>

Catheter related sepsis

Age at first sepsis and affect on IFALD

Hermans et al, JPGN 2007
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
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).
Outcome of intestinal failure

- ITx
- Enteral autonomy
- Death

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

Forced ETF

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

Intraluminal Bacterial overgrowth
Phase III activity and bacterial overgrowth

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

Log$_{10}$/g

Proteus  E.coli  Clostridia

Basal  Stop  6 hours  Stop  12 hours  Back to basal

Husebeye et al 1999
Small intestine bacterial overgrowth in short bowel syndrome

**Forced ETF**

- Nausea
- Vomiting
- Abdominal pain

**Translocation**
- Enterotoxins
- Gram negative sepsis

**Portal inflammation**
- Cholestasis
- Fibrosis
- Cirrhosis

**Intraluminal Bacterial overgrowth**

- Abdominal distension
- Abundant/rare stools

**Mucosal injury**
- Villous atrophy
- Malabsorption
- Permeability

**Food allergy**
- Eating disorders
- Poor growth

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

O.Goulet 2013
Short bowel syndrome

SBS
Intestinal insufficiency
Parenteral nutrition

Grêle adapté
Intestinal sufficiency
Autonomy

SBS overload syndrome

Bacterial hypermetabolism
SIBO
Abdominal distension
Growth failure

« Intestinal abundancy »

Reduced intestinal absorption

Increased intestinal absorption

Insufficient Intestinal absorption
From cholestasis to fibrosis

Geier et al., 2006; Kosters 2010
Reversal of «fat related» cholestasis

Soy/MCT  Omegaven®  SMOF®

Colomb et al 2000  Gura et al. 2006  Muhammad et al. 2011;
## Main lipid emulsions available in Europe

<table>
<thead>
<tr>
<th></th>
<th>Intralipid®</th>
<th>Medialipid®</th>
<th>ClinOleic®</th>
<th>SMOF®</th>
<th>Omegaven®</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Soybean %</strong></td>
<td>100</td>
<td>50</td>
<td>20</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td><strong>MCT %</strong></td>
<td>0</td>
<td>50</td>
<td>0</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td><strong>Olive oil %</strong></td>
<td>0</td>
<td>0</td>
<td>80</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td><strong>Fish oil %</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>15</td>
<td>100</td>
</tr>
<tr>
<td><strong>Phytosterols mg/l</strong></td>
<td>348±33</td>
<td>200±40</td>
<td>327±8</td>
<td>47.6</td>
<td>0</td>
</tr>
<tr>
<td><strong>α-tocopherol mg/l</strong></td>
<td>38</td>
<td>&lt; 30</td>
<td>200</td>
<td>200</td>
<td>150-296</td>
</tr>
<tr>
<td><strong>ω-3</strong></td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>ω-6</strong></td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>
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 algorithm for using fish oil based ILEs in infants and children at risk of IFALD

Patient at high risk of cholestasis*

Adapt IF management**

Use FO based ILEs

Composite FO-ILE

Successful

Continue with composite FO-ILE

Unsuccessful

Cholestasis (Bili > 30 micromol/l) in a patient not receiving FO based ILE

Adapt IF management** and use FO based ILEs

Pure FO based ILEs for <2 weeks (1 g/kg/day)

Successful

Continue with composite FO-ILE

Unsuccessful

Consider non-transplant or transplant surgery if adapted

* Long term PN, repeated catheter related sepsis, ileus, aggressive 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*

<table>
<thead>
<tr>
<th></th>
<th>N = 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (mo)</td>
<td>5.5 (2-27)</td>
</tr>
<tr>
<td>Males (%)</td>
<td>9 (75)</td>
</tr>
<tr>
<td>Diagnosis (%)</td>
<td></td>
</tr>
<tr>
<td>Atresia</td>
<td>6 (50)</td>
</tr>
<tr>
<td>NEC</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Gastrochisis</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Hirschsprung disease</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Volvulus</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Indication (%)</td>
<td></td>
</tr>
<tr>
<td>Bacterial overgrowth</td>
<td>7 (58.3)</td>
</tr>
<tr>
<td>IFALD</td>
<td>5 (41.7)</td>
</tr>
<tr>
<td>Median follow-up (mo)</td>
<td>68 (7-70)</td>
</tr>
</tbody>
</table>

85%
Citrulline increase suggests mucosal recovery by resuming small intestinal bacterial overgrowth.
In turn, 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

*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

- High calorie intake
- Lipids (amount and type)
- Coline/Taurine deficiency
- Age at first infection
- Recurrent septic episodes
- Type of bacteria
- Ethanol
- Mn, Fe, Al, Zn toxicity
- Continuous/cyclical infusion
- Bacterial overgrowth (obstruction, dismotility)
- Infections
- Prematurity, birth weight
- IRL and anatomy (ileal resection)
- Enteral feeds
- Underlying disease
- Hepatotoxic medications

Supportive Family

Parenteral Nutrition

Hepatologists
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
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