Strategies for Intestinal Rehabilitation

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Today’s specials

• Characterizing Intestinal Rehabilitation
• Understanding outcomes
• Available therapies
• Choices
• Algorithm for personal use
Intestinal Rehabilitation

• Active process of improving residual intestinal function in intestinal failure, using any combination of nutritional, medical and surgical measures, with the goal of achieving enteral autonomy from PN.
Intestinal Rehabilitation

- Is not the same as stable HPN
- May be complete or partial
- May be predictable based on anatomy
- May be de-railed by complications
- May be achieved by intestinal transplant
Intestinal failure (short bowel) treatment

Intestinal Rehab Candidate
- Full
- Partial
- None

Transplant Candidate

TPN Weaning Potential Decreases

TPN Complications
Surgical Approach

Intestinal Failure

Specific disease

Slow Transit

Rapid Transit

Dilated Bowel

Normal Bowel caliber

Adequate length

Short
Complex fistulae & intestinal failure
The Bianchi Procedure
- splits the bowel lengthwise
- 2 hemi-loops
- puts the 1/2 loops end to end
The Bianchi Procedure
STEP Enteroplasty

Kim et al, 2003

Figure 8.6  STEP Enteroplasty
Experience With Bianchi Procedure

• Bianchi’s reported experience:
  – 32 children over about 24 years
  – long term survival of 55%, majority of survivors off TPN
  – Survivors
    • > 40 cm small bowel
    • minimal or no liver disease

• Extended application of the Bianchi procedure
  • Patients with advanced liver disease
  • Patients awaiting transplantation
  • N = 31 procedures in 11 years

Iyer et al, 2003
Take home - Bianchi v STEP

- Median length 45 cm (11-150) to 68 (B) or 65(S)
- 58% patients weaned off tpn
- Trend toward longer time to wean after Bianchi
- Resolution of jaundice* after lengthening in 83%
  - Even if TPN not weaned*
- ? Bianchi as primary, STEP as salvage
- Intestinal transplant in 9 patients in this series

Sudan et al, Ann Surg, 2007:246; 593-604;
Survival with Home PN*

• North American HPEN Registry
  – SBS: 1 & 4 year survival 94% and 80%

• UCLA, Alabama, Omaha, Denver, Paris
  – similar

uncomplicated*
Intestinal Transplant: Indications

- Irreversible intestinal failure with TPN dependence
  - PLUS

- TPN failure*
  - Impending or overt liver failure
  - Thrombosis of ≥2 central veins

* As defined by Center for Medicare and Medicaid Services

<table>
<thead>
<tr>
<th>Blood stream infections</th>
<th>≥2 line sepsis w/ hospitalization in a yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver dysfunction</td>
<td>1 fungemia</td>
</tr>
<tr>
<td>Loss of vascular access</td>
<td>1 line sepsis with shock or ARDS</td>
</tr>
<tr>
<td>Recurrent dehydration despite TPN/IVF</td>
<td>Metastatic infection</td>
</tr>
</tbody>
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Outcomes are binary

• What does 80% survival at 1 year mean?
  – Outcomes for a cohort
  – Risk factors differ
  – Individual outcomes in the cohort differ
  – The cohort outcomes are a composite of the individual risks and outcomes
Can we predict TPN failure?


Intestinal Transplantation?

I'd like to buy a bowel.
Isolated Small Bowel Transplant

- Reversible/no liver disease
- Venous access
- Recurrent sepsis
- Fluid/electrolyte
Reversal of Parenteral Nutrition–Associated Liver Disease in Two Infants With Short Bowel Syndrome Using Parenteral Fish Oil: Implications for Future Management

Kathleen M. Gura, PharmD, Christopher P. Duggan, MD, MPhPh, Sharon B. Coller, MS, RCP, Russell W. Jennings, MD, Judith Falkman, MD, Bruce R. Biettram, MD, and Mark Puder, MD, PhD

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ABSTRACT

Here we report the reversal of cholestasis in 2 infants with intestinal failure and parenteral nutrition–associated liver disease. Treatment involved the substitution of a conventional intravenous fat emulsion with one containing primarily omega-3 fatty acids. Biochemical tests of liver function improved significantly. One child was removed from the liver transplantation list because of improved hepatic function, and the second child had complete resolution of cholestasis while solely on parenteral nutrition. This suggests that fat emulsions made from fish oils may be an effective means of treating and preventing this often-fatal condition. A randomized, controlled trial is necessary to study the efficacy of this new approach to parenteral nutrition–associated liver disease.

Changing the Paradigm: Omegaven for the Treatment of Liver Failure in Pediatric Short Bowel Syndrome

Ivan R. Diamond, Anca Sterescu, Paul B. Pencharz, Jae H. Kim, and Paul W. Wales

Group for Improvement of Intestinal Function and Treatment, The Hospital for Sick Children, Toronto, Canada
Omegaven 1g/kg/day

Intralipid 1g/kg + Omegaven 1g/kg

Liposyn Minimization 1g/kg twice weekly

SMOFlipid 2g/kg/d

Gura, 2008
Cober, 2010
Diamond, 2009
Rafeeq, 2009

Slide courtesy Paul Wales, MD, Toronto.
Evolution of Intestinal Transplant

1997-2003
- Isolated Intestinal Tx
- Multiorgan Tx
N=61

2003-2009
- Isolated Intestinal Tx
- Multiorgan Tx
N=22
Actuarial Survival By Era

![Graph showing survival probability over years by era]

- 1: 1985 - 1989
- 2: 1990 - 1994
- 3: 1995 - 2000
- 4: 2000 - 2004
- 5: 2005 - 2009

Logrank p < .001

Survival Probability

Years

1 23
2 128
3 387
4 728
5 922

1 4
2 128
3 137
4 187
5 0

1 24
2 38
3 60
4 11
5 0

1 1
2 11
3 0
4 0
5 0

Overall Data
Pre-Transplant Status and Survival (Cases 04-09)

Logrank p < .001

Survival Probability

pYears

1: Home

2: Hospital

Overall Data
Transplant vs. TPN: Survival

Fig. 4. Actuarial survival probability of adult short bowel syndrome patients ($n = 268$), according to HPN dependence or independence.
STEPS trial - Teduglutide

- Multicenter, placebo-controlled, phase III study

- Primary objective: to evaluate whether teduglutide 0.05 mg/kg/day could reduce PN/IV volume

- ≥ 20% reduction defined as clinically meaningful

Study Design

**Stage 1**
- **Screening**: 1–7 days
- **PN/IV Optimization**: 0–8 weeks (Urine volume 1–2 L/day)
- **PN/IV Stabilization**: 4–8 weeks

**Stage 2**
- **Teduglutide**: 0.05 mg/kg/day (n=43)
- **Placebo**: (n=43)
- **PN/IV volume reductions (up to 30%) if urine volume >10% higher than baseline**

*Parenteral support (PS) is parenteral nutrition and/or intravenous [PN/IV] fluids*
Primary Responder Rate

\[ P=0.002 \]
Cochran-Mantel-Haenszel test

- **Teduglutide** (n=43): 63%
- **Placebo** (n=43): 30%
Secondary endpoint – mean absolute reduction in PN/IV volume

Teduglutide vs placebo, *P≤0.05, ** P≤0.01, *** P≤0.001
Phase 3, STEPS 020 study: Fluid Composite Effects at Week 24

- Placebo: FCE=153 ml/day
- Teduglutide 0.05 mg/kg/day: FCE=768 ml/day

***p<0.001 vs placebo
Safety population
Jeppesen et al. Gastroenterology 2012
Teduglutide & enteral autonomy from TPN

• Phase III clinical studies of teduglutide in SBS-IF
  – Daily SC injection (0.05 mg/kg/day) significantly reduces PN/IV volume requirements and number of infusion days\(^1\)\(^-\)\(^3\)
  – Some patients achieve complete independence from PN/IV\(^3\)

Teduglutide & enteral autonomy from TPN

• 15/134 patients with SBS-IF achieved enteral autonomy and independence from PN/IV support with 0.05 mg/kg/day teduglutide therapy
  – 10/15 patients after >1 year of teduglutide treatment
  – 8/15 had been PN/IV dependent for >5 years
  – 6/15 patients had ≤50 cm of remnant small bowel
Short Bowel Syndrome

Unfavorable anatomy

No colon/Ultra short/High stoma

Yes

Complications

No

Enteral nutrition/diet

Yes

dilated bowel/stomata

Yes

Surgery

Intestinal transplant

NO

NO

HPN

Gattex
The future is here!?

*Yogi Berra*