Novel Therapies in Intestinal Failure

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Disclosures

- Investigator initiated protocol "Patient Outcomes of Stopping Teduglutide (POST)," Compher PI
- "A 24-Week Study of the Efficacy and Safety of Teduglutide in Subjects with Parenteral Nutrition-Dependent Short Bowel Syndrome (STEPS)," Compher, Site PI
  - Active research funding by NPS Pharmaceuticals

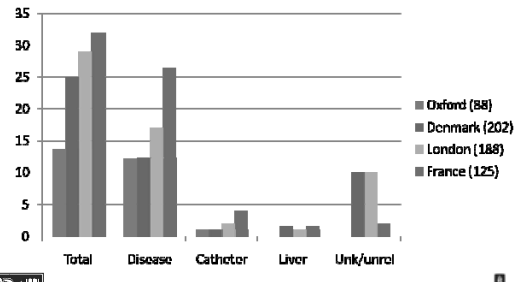
Learning Objectives

1. Discuss long-term complications of home PN (HPN)
   - Mortality
   - Bloodstream infection
   - Bone disease
   - Liver disease
2. Delineate desirable clinical outcomes in PN-dependent short bowel syndrome
3. Describe outcomes from clinical trials with growth hormone and glucagon-like peptide II in adults with short bowel syndrome

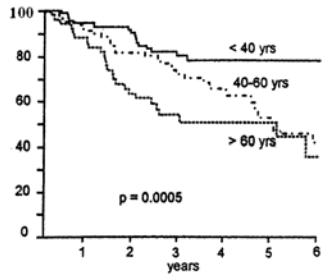
Learning Assessment Questions Pre Test

1. Use of PN for > 1 y has no downsides.
   - True
   - False
2. Growth hormone therapy results in permanent independence from PN in most patients.
   - True
   - False
3. A glucagon-like peptide II prodrug is currently available for clinical use in the U.S. & Europe.
   - True
   - False

10-y HPN Mortality

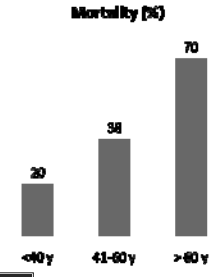


Age of HPN Onset vs Survival



Messing, 1998

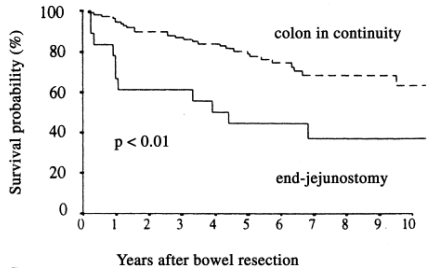
Age at HPN Onset vs Mortality



- Age > 50 y, RR 1.24
  - Jeppesen, 1998
    - Age > 60 y RR 2.5 (95% CI=1.2-5.8)
    - Messing, 1995

Scolapio, 1999

Remaining Intestine vs Survival



Messing, Gastro 1999

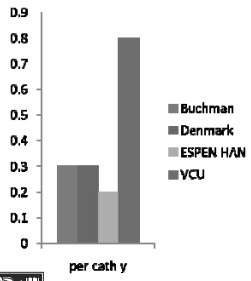
SB Length vs Mortality

- <200 cm
  - Scolapio, 1999
- <100 cm RR=1.15
  - Jeppesen, 1998
    - <50 cm RR 4.1 (95% CI=2.3-8.1)
- End jejunostomy
  - RR 4.9 (95% CI=2.2-10.7)
    - Messing, 1995

Summary Mortality

- Mortality risk > healthy population
- Greatest risk due to underlying disease
  - NOT controllable by pt
- PN-related risk a concern to patients

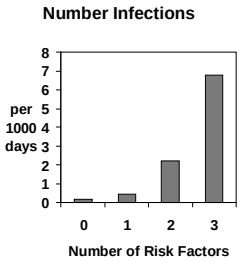
Catheter Related Bloodstream Infection (CRBSI)



- 53% of patients do NOT have CRBSI over 10 y
  - Jeppesen
- Minority have many CRBSI
  - 3/cath y
    - Opilla JPEN 2007

Risk Factors for CRBSI

- Prospective data from 827 pts; 69,532 catheter d
- PN
  - RR= 4.1 (CI = 2.3-7.2)
- Multi-lumen catheter
  - RR= 2.8 (CI = 2.3-7.2)
- Previous CRBSI
  - RR= 2.5 (CI = 1.5-4.2)
    - Tokars, 1999



Summary CRBSI

- Risk includes 1-3% mortality
- Considerable lifestyle disruption for treatment

Bone Disease in HPN

- Osteopenia in 54-84%
- Osteoporosis in 33-67%
  - Pironi, Clin Nutr, 2002; Cohen-Solal, J Bone Min Res, 2003; Haderslev , Gut, 2000

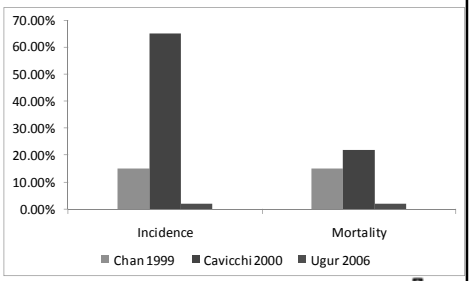
Risk Factors for Bone Disease

- Young age to start PN
- Female
- Steroid hx
- Excess amino acids → calciuresis
- Long PN duration
- Crohn's disease
  - Pironi, Clin Nutr, 2002;
  - Cohen-Solal, J Bone Mineral Res, 2003
- Metabolic acidosis
- Nutrient, mineral deficiencies
- Medications (steroids, heparin, warfarin)
  - Ferrone, NCP 2008; 22:329-339.

Summary Bone Disease

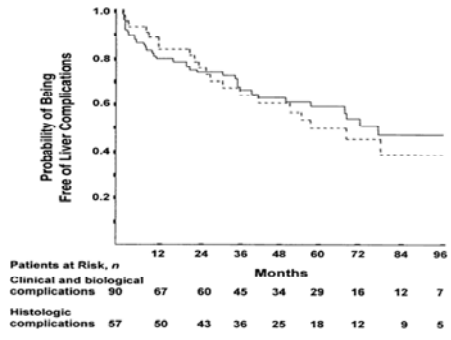
- Risk for bone disease is substantial
- Physical disability, fracture risk, bone pain

PN-Associated Liver Disease (PNALD)

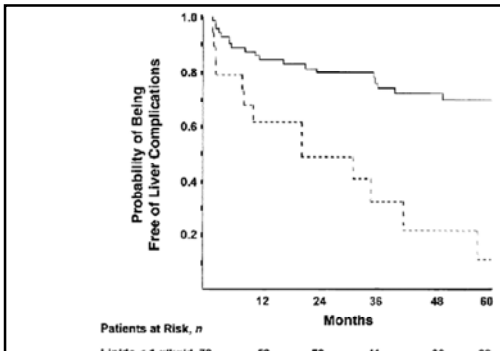


Risk of PNALD

- SB < 50 cm
  - RR=2.1 (95% CI=1.2-3.7)
- PN lipid > 1 g/kg/d
  - RR=2.3 (95% CI=1.6-5.9)
    - Cavicchi, Ann Intern Med 2000; 132:525-532
- SB < 50 cm
- Inflammatory disease
  - Chan 1999
- Inflammation
- Carb kcal
  - Reimund, Nutr 2001



90 HPN pts in France, 1985-1996;
Cavicchi, M. et. al. Ann Intern Med 2000;132:525-532



Cavicchi, M. et. al. Ann Intern Med 2000;132:525-532

Summary

- Risk of PNALD considerable
- Patients and medical professionals fear patient's death by PNALD

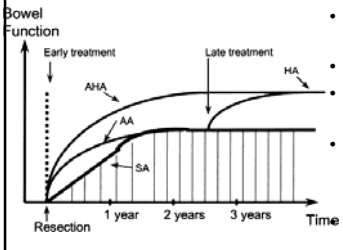
Quality of Life

- Illness & bowel disease scores worse in 57 HPN patients than healthy subjects
  - Jeppesen, Gut 1999
- Physical, role, and social function;
- Body pain, general health worse in 31 HPN than healthy subjects
  - Pironi, Transpl Proc 2004.

Desirable Outcomes of Novel Therapies

- ↓ disease complications, mortality
- ↓ need for catheter
- ↓ bone disease
- ↓ PNALD risk
- ↑ quality of life
  - ↓ PN dependence
  - ↓ infusion days ↑sleep
  - ↓ fear of death to PNALD

Gut Adaptation



- Spontaneous adaptation (SA)
- Hyper adaptation (HA) > SA
- Accelerated adaptation (AA), faster than SA
- Accelerated hyperadaptation (AHA)

Goal of growth factors is to enhance adaptation

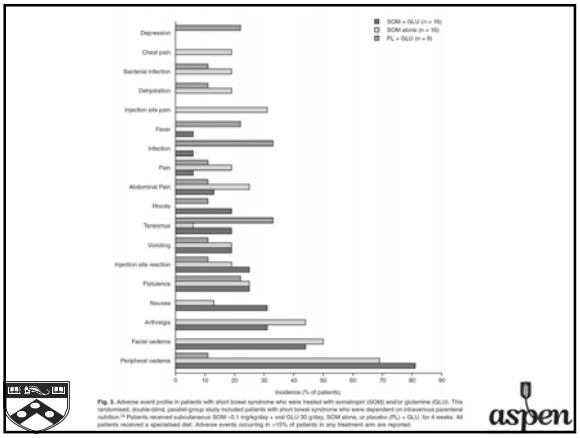
Jeppesen, Gastroenterol 2006; 130:S127-S131

Absorption Studies

- SBS pts have unique anatomy
- Random order treatment arms with washout between – patient as own control
- 4-d admission to CRC for collection of all stool, urine output
- Measurement or calculation of nutrient absorption
- Nutrient intake – fecal nutrient output = absorption

Somatropin

- Growth hormone (Zorbtive ®)
- Approved by FDA for use in adult SBS
- Course is 4 weeks, dose 0.14 mg/kg/d
- Intestinotrophic
- May benefit bone disease
- Not advised for patients with cancer hx
- Open label studies suggest drug enables ↓PN dependence



Somatropin vs Absorption

Scolapio, JPEN 1999

- Random controlled crossover, n=8, 3 wk
- 0.14 mg/kg/d GH + 0.6 g/kg/d oral gln + HCLF diet
- No difference in stool volume, absorption of fat
- 3 kg wt gain
- ↑ lean mass, ↓ % fat by DXA

Jeppesen, Gut 2000

- Random controlled crossover, n=8, 4 wk
- 0.14 mg/kg/d GH + 30 g oral gln + usual diet
- Nutrient balance 5 d after treatment ended
  - No difference in absorption of kcal, carb, fat, nitrogen, wet weight, Na, K, Ca, Mg
- AE in all pts on GH, peripheral edema, severe hand pain

Low Dose Somatropin vs Absorption

Ellegard, Ann Surg, 1997

- Random controlled crossover, n=10, 8 wk
- 0.024 mg/kg/d GH + no oral gln + usual diet
- Absorption of fluid, kcal, nitrogen, K, Na, Ca, Mg unchanged
- Improved body composition by BIA
- Mild AEs

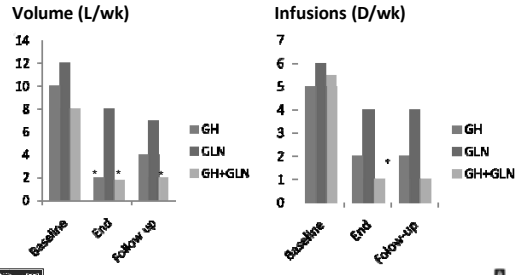
Seguy, Gastro 2003

- Random controlled crossover, n=12, 3 wk
- 0.05 mg/kg/d GH + no gln + usual diet
- Nutrient absorption
  - Kcal ↑ 15%
  - Nitrogen ↑ 14%
  - Carb ↑ 10%
- Body weight ↑ 15%
- No AE

Somatropin

- PRCT, n=41 adult PN-dependent SBS
- 4 wk treatment arms
  - 0.1 mg/kg/d GH vs
  - 0.1 mg/kg/d GH+ 30 g/d oral gln vs
  - 30 g/d oral gln
- Endpoints
  - Change in PN volume, kcal, number infusions at 4 wk, 12 wk after drugs stopped
    - Byrne, Ann Surg 2005; 242:655

Somatropin

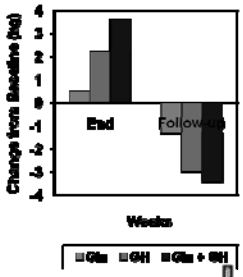


Somatropin

- Somatropin permitted significantly more weaning than Gln
- Only GH + Gln + diet maintained reduction for 12 wk
- AE
  - 94% w peripheral edema, 44% musculoskeletal complaints
    - Byrne, Ann Surg 2005; 242:655

Weight Change

- No significant change in weight during study
- Weight change after study end attributed to fluid shifts
  - Byrne, Ann Surg 2005; 242:655



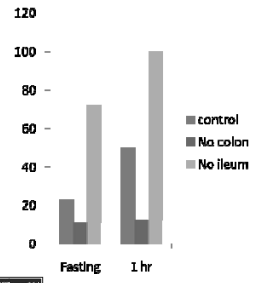
Summary Somatropin

- Data available only in adults, usually 4 wk treatment
- Most studies show reduced benefit when drug stopped
- Fewer side-effects with lower doses, but also less improvement in absorption

Glucagon Like Peptide 2 (GLP2)

- Intestinotrophic
- Antisecretory
- ↑ mesenteric blood flow
  - Brenholm, Scand J Gastro 2008
- ↓ bone resorption
  - Henrickson, J Bone Min Res 2003

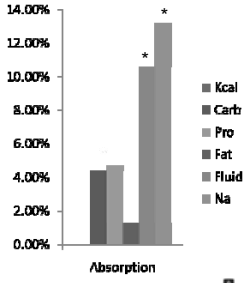
GLP2 in SBS



- Secreted by L cells of ileum, colon
- High GLP2 may be mechanism of adaptation in SBS + colon
  - Jeppesen, 2000
- Lack of GLP2 may limit adaptation in SBS no colon
  - Jeppesen 2001

GLP2 in SBS + Colon

- Nutrient balance pre and 35 d post twice daily SC 400 mcg GLP2
- No serious adverse effects
  - Jeppesen 2001



GLP-2 Analog

- Half-life GLP-2= 7 min
  - Rapid renal clearance
  - Proteolytic degradation by dipeptidyl peptidase 4 (DPP4)
- Glycine 2- GLP2 lacks DPP4 cleavage site
  - Half-life increased to 120 min
  - Teduglutide (Gattex ®)

GLP-2 Analog

15 SBS pts, 10 end J, 5 ≥50% colon in continuity

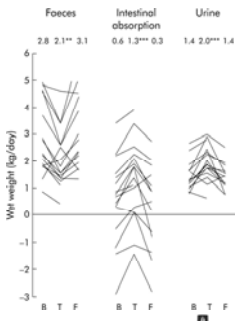
B=baseline, T=treatment, F=follow-up

No deaths, no withdrawal for AE

Most common AE, swelling of jejunostomy nipple

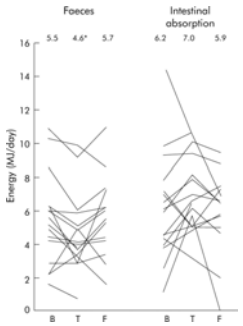
Similar effects colon or not

Jeppesen 2001



Jeppesen, P B et al. Gut 2005;54:1224-1231

GLP-2 Analog



- Energy excretion ↓1453 kcal/d
- Energy absorption ↑ 10% with treatment
- Reversed with stopping drug

Jeppesen, P B et al. Gut 2005;54:1224-1231

GLP-2 Analog

- Phase II/III PRCT
- 25 sites
  - 9 U.S.
  - 11 European
  - 3 Canadian
- 83 patients with PN-dependent SBS

RCT Criteria

Included

- Adults
- ≥12 m PN dependent SBS
- PN ≥ 3 infusions/week
- Urinary output > 1 L/d
- Urine sodium >20 mmol/d
- Serum Cr, BUN <1.5 × ULN
- LFTs < 2 × ULN

Excluded

- Pregnancy, lactation
- Cancer
- Clinical trial within 30 d
- GLP2 in past 3 m

Endpoints

- Primary Endpoint
  - ≥ 20% ↓PN volume
- Secondary Endpoints
  - Fluid balance
  - Plasma citrulline concentrations
  - Body composition by DXA
  - Safety

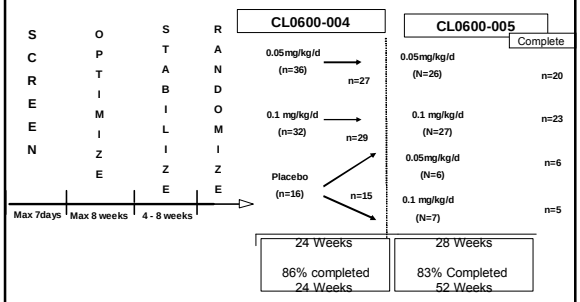
PN Adjustment Algorithm

Urine Output	PN Action
< 1.0 L/d	↑ PN to previous volume
> 1.0 L/d but < Baseline	Maintain PN volume If dehydrated or malnourished, ↑ PN
100-110% of baseline	Maintain PN volume
>110% baseline & ≤ 2.0 L/d	↓ PN by 10% baseline volume
> 2.0 L/d	↓ PN by 10-20% baseline volume Evaluate subjects with PN > 4L/d for negative fluid balance.

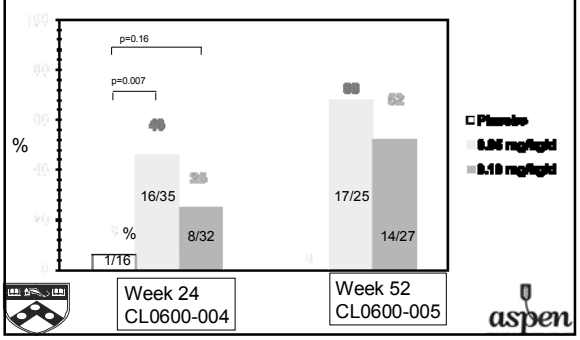
Baseline Characteristics

	Placebo	Low Dose	High Dose	Total
PN Consumption Level n (%)				
Level 1:IV Fluids 3-5x weekly (18.1%)	4 (25.0%)	8 (22.9%)	3 (9.4%)	15
Level 2:PN 3-5x weekly (54.2%)	8 (50.0%)	19 (54.3%)	18 (56.3%)	45
Level 3:PN 5-7x weekly (27.7%)	4 (25.0%)	8 (22.9%)	11 (34.4%)	23
BMI at Screening				
Mean (SD)	22.0 (2.90)	21.2 (2.97)	21.7 (2.55)	21.5 (2.79)
Median	21.3	20.8	21.0	21.0
Range	(17, 28)	(16, 27)	(17, 26)	(16, 28)

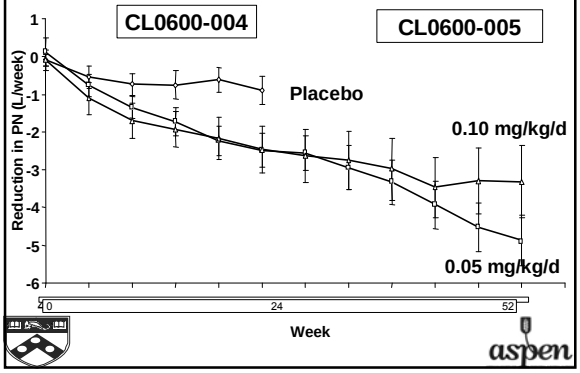
Study Flow Chart
CL0600- 004 And CL0600- 005



20% PN Reduction



Reduction in PN



Patients who Came Off PN

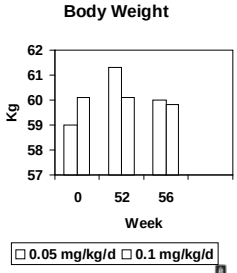
PN (L;d/wk)	PN Hx (y)	SB (cm)	ICV	Colon
12; 6	2	48	+	+
5.4; 3	25	28	+	+
3.5; 4	6	80	-	+
4.5; 3	4	75	-	-
7.2; 4	15	75	-	+

Anatomy of Patients who Came Off PN

PN (L/;d/wk)	PN Hx (y)	SB (cm)	ICV	Colon
12; 6	2	48	+	+
5.4; 3	25	28	+	+
3.5; 4	6	80	-	+
4.5; 3	4	75	-	-
7.2; 4	15	75	-	+

Body Weight

- No change from baseline weight
- <4% ↑ by wk 52
- <1% ↑ from baseline by 30-d follow up (wk 56)



Adverse Event Number (%)	Placebo (n=16)	0.05 mg/kg/d (n=41)	0.10 mg/kg/d (n=39)
Headache	1 (6.3%)	11 (26.8%)	13 (33.3%)
Abdominal pain	2 (12.5%)	9 (22.0%)	12 (30.8%)
Nasopharyngitis	2 (12.5%)	9 (22.0 %)	7 (17.9%)
Catheter sepsis	2 (12.5%)	8 (19.5%)	5 (12.8%)
Abdominal distension	0 (0.0%)	7 (17.1%)	5 (12.8%)
Nausea	4 (25.0%)	7 (17.1%)	12 (30.8%)
Urinary tract infection	3 (18.8%)	6 (14.6%)	6 (15.4%)
Vomiting	2 (12.5%)	6 (14.6%)	8 (20.5%)
Abdominal pain – upper	0 (0.0%)	5 (12.2%)	3 (7.7%)
Pyrexia	1 (6.3%)	5 (12.2%)	4 (10.3%)

Conclusions

- GLP-2 analogue is **safe** for 52 wk
  - Adverse events not > placebo
- GLP-2 analogue is **effective**
  - > 50% of patients with SBS had> 20% ↓ in PN volume over 52 wk
  - 5/82 patients came off PN

Further Research

- Study protocol did not supply drug after study end
  - Descriptive study of patient outcomes of stopping study drug (POST) underway
- Study protocol may have limited number of subjects coming off PN or extent of PN reduction
  - 28-wk replication study underway (STEPS)
  - Will be followed by 2-y extension w study drug

- Clearly, growth factors may have important contributions for patient care
- Studies at earlier points after SBS (hyperadaptation) are needed
- Trials in children

Learning Assessment Questions
Post Test

1. Which of the following outcomes are a risk for PN dependent patients?
   - CRBSI
   - Bone disease
   - Liver disease
   - All of the above
   - None of the above
2. Growth hormone therapy results in permanent independence from PN in most patients.
   - True
   - False
3. A glucagon-like peptide II prodrug is currently available for clinical use in the U.S. & Europe.
   - True
   - False