

## 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

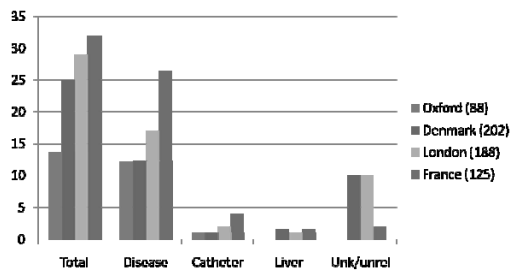


## Learning Assessment Questions Pre Test

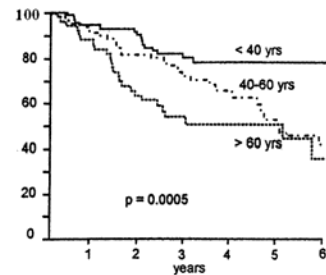
1. Use of PN for > 1 y has no downsides.
  - True
  - False
2. Growth hormone therapy results in permanent independence from PN in most patients.
  - True
  - False
3. A glucagon-like peptide II prodrug is currently available for clinical use in the U.S. & Europe.
  - True
  - False



## 10-y HPN Mortality



## Age of HPN Onset vs Survival

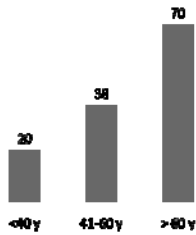


Messing, 1998



## Age at HPN Onset vs Mortality

### Mortality (%)

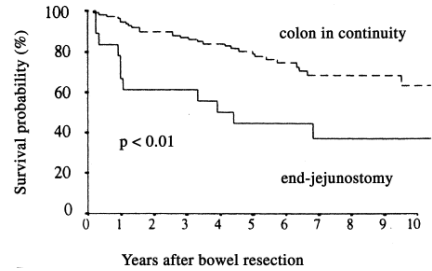


- Age > 50 y, RR 1.24
  - Jeppesen, 1998
- Age > 60 y RR 2.5 (95% CI=1.2-5.8)
- Messing, 1995

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

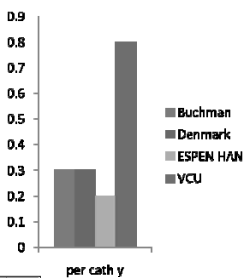


## Summary Mortality

- 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)

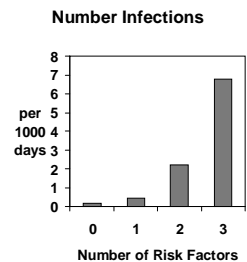


- 53% of patients do NOT have CRBSI over 10 y
  - Jeppesen
- Minority have many CRBSI
  - 3/cath y
  - Opilla JPEN 2007



## 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.

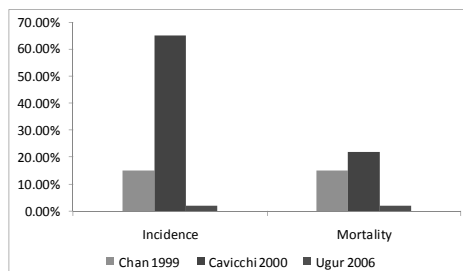


## Summary Bone Disease

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



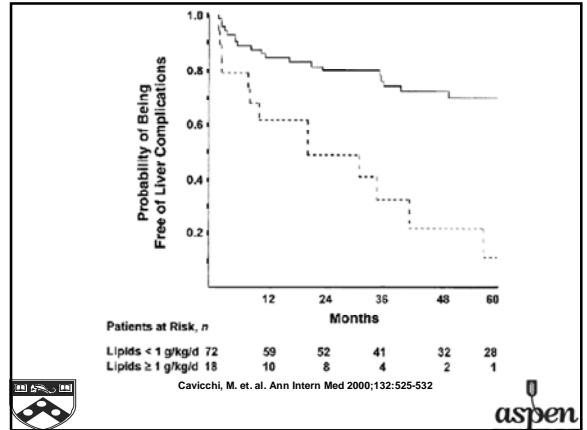
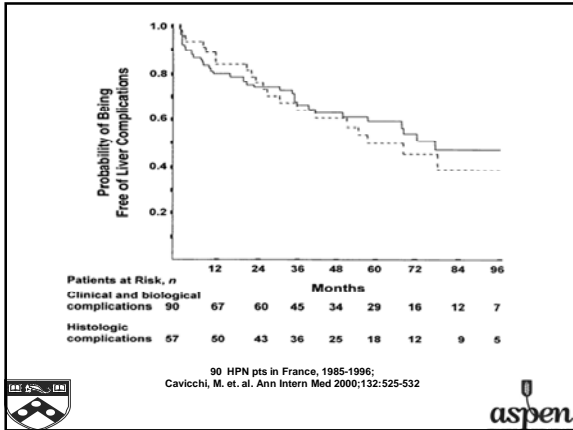
## PN-Associated Liver Disease (PNALD)



## 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
- Inflammatory disease
  - Chan 1999
- Inflammation
- Carb kcal
  - Reimund, Nutr 2001





## Summary

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

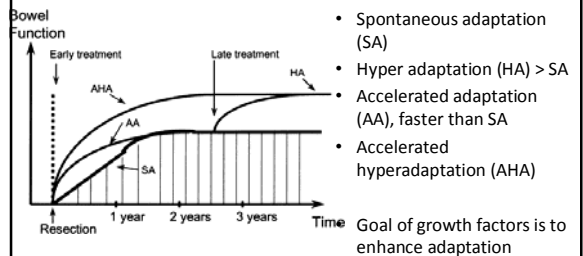
## Quality of Life

- 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



Jeppesen, Gastroenterol 2006; 130:S127-S131

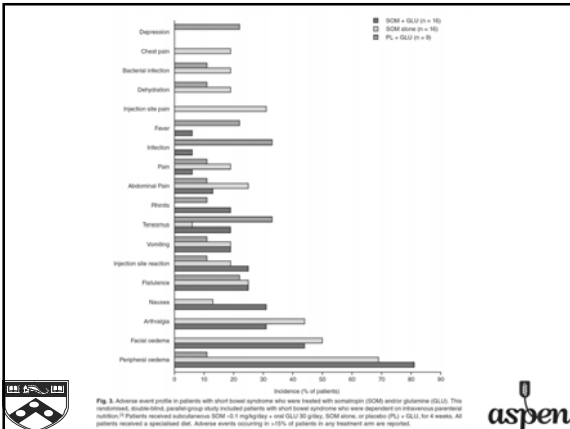
## Absorption Studies

- 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<sup>®</sup>)
- 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

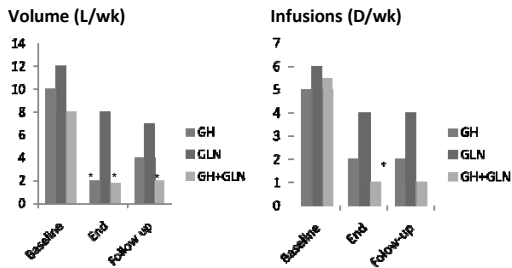


## Somatropin

- 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



## Somatotropin



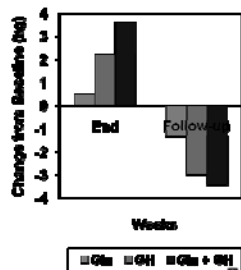
## Somatotropin

- 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

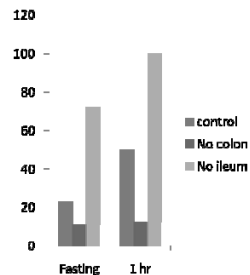


## Glucagon Like Peptide 2 (GLP2)

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



## GLP2 in SBS

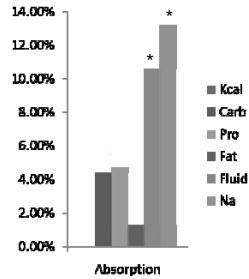


- Secreted by L cells of ileum, colon
- High GLP2 may be mechanism of adaptation in SBS + colon
  - Jeppesen, 2000
- Lack of GLP2 may limit adaptation in SBS no colon
  - Jeppesen 2001



## GLP2 in SBS + Colon

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



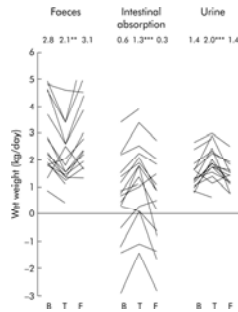
## GLP-2 Analog

- 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®)



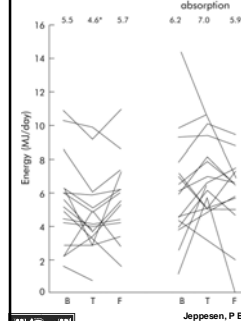
## GLP-2 Analog

- 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



## GLP-2 Analog

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



## 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
  - $\geq 20\%$   $\downarrow$  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	$\uparrow$ PN to previous volume
> 1.0 L/d but < Baseline	Maintain PN volume If dehydrated or malnourished, $\uparrow$ PN
100-110% of baseline	Maintain PN volume
>110% baseline & $\leq 2.0$ L/d	$\downarrow$ PN by 10% baseline volume
> 2.0 L/d	$\downarrow$ PN by 10-20% baseline volume Evaluate subjects with PN > 4L/d for negative fluid balance.

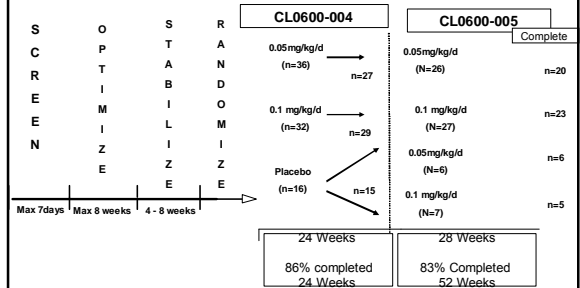


## Baseline Characteristics

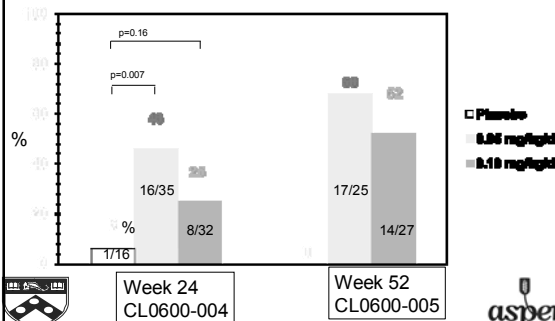
	Placebo	Low Dose	High Dose	Total
<b>PN Consumption Level n (%)</b>				
Level 1: IV Fluids 3-5x weekly (18.1%)	4 (25.0%)	8 (22.9%)	3 (9.4%)	15
Level 2: PN 3-5x weekly (54.2%)	8 (50.0%)	19 (54.3%)	18 (56.3%)	45
Level 3: PN 5-7x weekly (27.7%)	4 (25.0%)	8 (22.9%)	11 (34.4%)	23
<b>BMI at Screening</b>				
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)



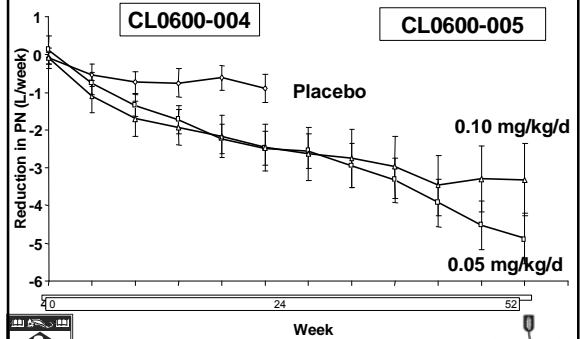
## Study Flow Chart CL0600- 004 And CL0600- 005



## 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	-	+



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## Anatomy of Patients who Came Off PN

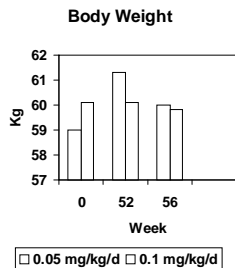
PN (L;d/wk)	PN Hx (y)	SB (cm)	ICV	Colon
12; 6	2	48	+	+
5.4; 3	25	28	+	+
3.5; 4	6	80	-	+
4.5; 3	4	75	-	-
7.2; 4	15	75	-	+



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## Body Weight

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



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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%)



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## 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



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## 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



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



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## 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



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Thank  
You



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