

ESPEN LL –  
Withhold of TPN for 7 days  
Pro

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# Some Rationals

# Nutrition of the Intestinal Mucosa

	Luminal Nutrition	Main Substrates
Small Bowel	30%	Glutamine
Large Bowel	80%	SCFA's

# Failure of Enteral Food Supply

- **Immunological changes and impairment of the gut associated lymphatic system (GALT)**
  - Intestine becomes source of activated cells and proinflammatory stimulants during gut starvation
  - **Secondarily permeability changes and occasionally even bacterial translocations increase the immune challenge to the GALT**

**Kudsk KA.** Effect of route and type of nutrition on intestine-derived inflammatory responses. *Am J Surg* 2003;**185**:16–21

# Recent Recognitions

## Lack of Endoluminal Supply

- PN induces intestinal epithelial cell apoptosis and villus and crypt atrophy, even if given at 100% of predicted energy needs. Changes increase with greater reduction of energy intake
- **Study supports the concept that lack of EN, rather than absolute caloric levels, is responsible for many of the adverse effects of PN**

Sun X et al. Impact of caloric intake on parenteral nutrition-associated intestinal morphology and mucosal barrier function. JPEN J Parenter Enteral Nutr. 2006;30:474-9

# Recent Recognitions

## TPN and Lymphotoxin- $\beta$ -Receptor Expression

- TPN impairs gut-associated lymphoid tissue (GALT) and mucosal immunity (Peyer's patches lymphocytes, and intestinal IgA production) by reducing lymphotoxin  $\beta$  receptor expression
  - LT- $\beta$ -R expression is critical for GALT control and intact mucosal immunity
  - Exogenous LT- $\beta$ -R stimulation reverses TPN-induced depression of gut mucosal immunity

Kang W et al. [Ann Surg.](#) 2006;244:392-399

# Recent Recognitions

## Peritoneal Host Defense

- Lack of EN impairs peritoneal defense by delaying early NFkappaB activation in peritoneal exudative cells (PECs) and cytokine responses

Chikara U. Lack of enteral nutrition delays nuclear factor kappa B activation in peritoneal exudative cells in a murine glycogen-induced peritonitis model. JPEN J Parenter Enteral Nutr. 2006;30:179-85

# Beneficial Effects of Endoluminal Substrate Supply

- Increased levels of IgA and numbers of circulating lymphocytes from GALT
  - Lymphocytes migrate to non-gut tissues (i.e. lung) and alter immune response in non-gut locales
  - Neuroendocrine system and bacteria-host-interaction of the gut also affects regulation of inflammation outside of the gut
    - Neuroendocrine system and luminal milieu is modulated by the presence of dietary constituents

Kudsk KA: Current aspects of mucosal immunology and its influence by nutrition. Am J Surg 2002, 183:390-393

Luyer MD, et al. Nutritional stimulation of cholecystokinin receptors inhibits inflammation via the vagus nerve. J Exp Med 2005, 202:1023-1029

Alverdy J. et al. Bacteria Host Interactions. Crit Care Med 2005; 33:1125-35

- The value of enteral feeding may be thus dependent on cellular neuroendocrine and milieu forming factors

How evident is luminal nutrition  
in clinical practice on

- Mucosal atrophy?
- Translocation?
- Gut barrier function?

# Evidence for nutritional Factors causing Mucosal Atrophy in Humans

- 2 weeks TPN decrease mucosal thickness by 20% in volunteers
- Mild focal villous atrophy during TPN
- Prolonged enteral starvation and severe protein calorie malnutrition induce mucosal atrophy

Buchmann et al, JPEN, 1995, Rossi et al, Dig Dis Sci, 1993, Gross et al, Submicrose Cytol Pathol, 1996, Brunser et al, Am J Clin Nutr, 1968, Martins et al, Am J Clin Nutr, 1979, Adibi and Allen, GE, 1970

# Evidence for Translocation in Humans

- Nosocomial infection are frequently caused by *E. coli*
- Septic complication are more often seen in patients with TPN than with EN

Emori and Gaynes, Clin Microbiol Rev, 1993, Moore, Yearbook of intensive care medicine, 1996, Kudsk et al, Ann Surg, 1992

# Evidence for Translocation in Humans

N=448

- Significant association between translocation and postoperative morbidity
- Translocation in 15%
  - E coli in 54%
- Septic complication 23%
  - Enteric organism 74%
  - 41% with translocation developed sepsis
  - 14% without translocation developed sepsis

# Other Issues: Early Calorie Requirements

- Absolute demand in critically ill is to avoid overfeeding
  - Critical illness induces catabolic processes for endogenous substrate production which cannot be suppressed either by exogenous enteral or parenteral nutrition

Tappy L, et al. Effects of isoenergetic glucose-based or lipid-based parenteral nutrition on glucose metabolism, de novo lipogenesis, and respiratory gas exchanges in critically ill patients. Crit Care Med 1998; 26:860–867

# Other Issues: Early Calorie Requirements

- Absolute demand in critically ill is to avoid overfeeding
  - Endogenous substrates metabolized like exogenous => have to be included in energy balance
  - ⇒ to avoid overfeeding, provide only the gap between actual energy expenditure and endogenous substrate production by EN/PN

**For this reason, even lower amounts of energy provided by (incomplete) enteral nutrition are very often sufficient**

# 1<sup>st</sup> Conclusion

- Two main reasons why (T)PN has adverse effects
  - Direct
  - Via Lack / prolonged withhold of EN
- Low calorie intake is not that important in the first week after ICU admission

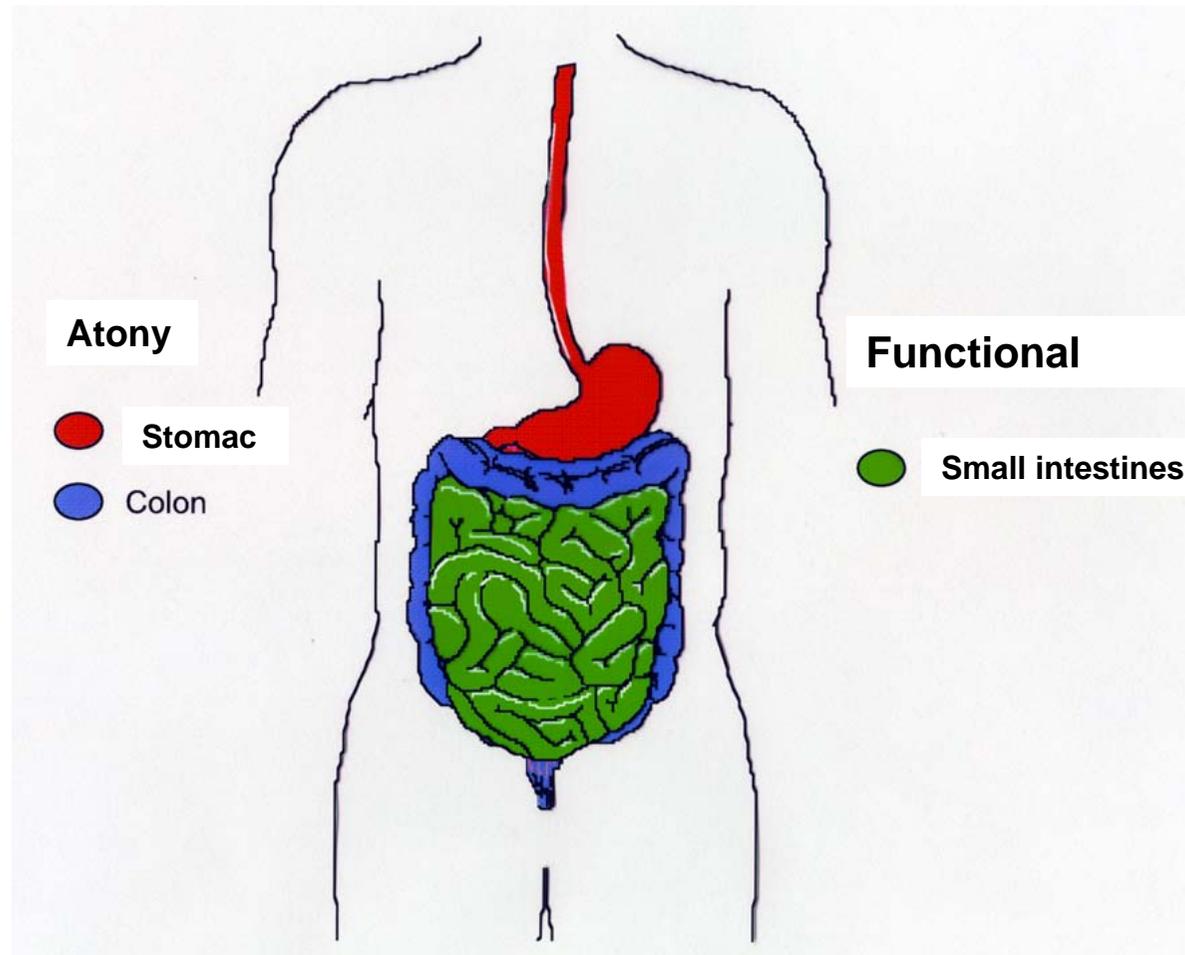
Why Do We Not Need to Provide  
TPN in the First Seven Days?

# Feasibility of EN

# Enteral Nutrition after GI Surgery

- Conventional approach
  - Starvation after bowel resection until passage of flatus, due to assumed post-operative ileus
  - Based on believe that enteral feeding not tolerated in presence of ileus and integrity of constructed anastomosis may be compromised
- But
  - Small intestinal motility recovers 6–8 hours after surgery and absorptive capacity exists even in the absence of normal peristalsis

# Postoperative „Ileus“



# Enteral Nutrition after GI Surgery: Recognitions

- Enteral feeding in patients undergoing gastrointestinal resection is safe and well tolerated even when started within 12 hours of surgery

Reissman P, et al. Is early oral feeding safe after elective colorectal surgery? A prospective randomized trial. *Ann Surg* 1995, 222:73-77, Braga M, et al. Feeding the gut early after digestive surgery: results of a nine-year experience. *Clinical Nutrition* 2002, 21:59-65

# Enteral Nutrition after GI Surgery: Recognitions

- Enteral feeding results in some specific clinical benefits
  - Reducing the incidence of post-operative infectious complications
  - Improved wound healing response

Beier-Holgersen SR, et al. Influence of postoperative enteral nutrition on post surgical infections. *Gut* 1996, 39:833-5, Schroeder D, et al. Effects of immediate postoperative enteral nutrition on body composition, muscle function and wound healing. *JPEN* 1991, 15:376-383

- Altering antigen exposure
- Improving oxygenation of the gut mucosa

Reynolds JV: Gut barrier function in the surgical patient. *Br J Surg* 1996, 83:1668-1669

## 2<sup>nd</sup> Conclusion

- Over the past decade it has been shown in the gastrointestinal surgical population that the overwhelming majority may be fed safely enterally; TPN is needed in **9%** of these patients **only**

Braga M , Giannotti L, Gentilini O, *et al.* Feeding the gut early after digestive surgery: results of a nine-year experience. *Clin Nutr* 2002;21:59–65

But to give TPN is much more  
easy.....

# Drawbacks of TPN

- TPN can contribute to the de novo development of organ dysfunction
  - Alterations in hepatic function with intrahepatic cholestasis and fatty infiltration

Grant JP, Cox CE, Kleinman LM, et al: Serum hepatic enzyme and bilirubin elevations during parenteral nutrition. Surg Gynecol Obstet 145:2398, 1977

- Aggravation of ventilatory impairment through increased CO<sub>2</sub> production potentially preventing weaning from ventilatory support

Askanazi J, Rosenbaum SH, Hyman AI, et al: Respiratory changes induced by the large glucose loads of total parenteral nutrition. JAMA 243:1444, 1980

# Drawbacks of TPN

- Higher rates of postoperative and nosocomial infections after multiple trauma

Moore FA, Feliciano DV, Andrassy RJ, et al: Early enteral feeding, compared with parenteral, reduces postoperative septic complications: the results of a meta-analysis. Ann Surg 216:172, 1992

- Predisposes to hyperglycemia => increases mortality

Hyperglycemia is associated with adverse outcomes in patients receiving total parenteral nutrition. Wah C. et al. Diabetes Care 2005;28: 2367-2371)

# Drawbacks of TPN

- More complications (primarily infections) without any demonstrable benefit in patients after major pancreatic resection receiving TPN on postoperative day 1 vs. no-TPN
- Conclusion
  - Routine postop. TPN not recommended for patients undergoing major pancreatic resection for malignancy

Brennan MF, Pisters PW, Posner M, et al: A prospective randomized trial of total parenteral nutrition after major pancreatic resection for malignancy. Am Surg 1994 220:436,

# Drawbacks of TPN

- Metaanalysis
  - 1828 patients in 27 PRCTs
- Results
  - TPN associated with a higher risk of infection compared to standard care (conventional oral diets with intravenous glucose (0.77; 95% CI: 0.65, 0.91)) and tube feeding (RR 0.64; 95% CI: 0.54, 0.76)

Braunschweig CL. et al. Enteral compared with parenteral nutrition: a meta-analysis *American Journal of Clinical Nutrition*, 2001;74:534-542

# Drawbacks of TPN

Central venous catheter through which TPN was given had a 3.3 times greater risk of becoming infected than a similar catheter not used for TPN

Beghetto MG, et al: Parenteral nutrition as a risk factor for central venous catheter-related infection. JPEN J Parenter Enteral Nutr 2006, 29:367-373.

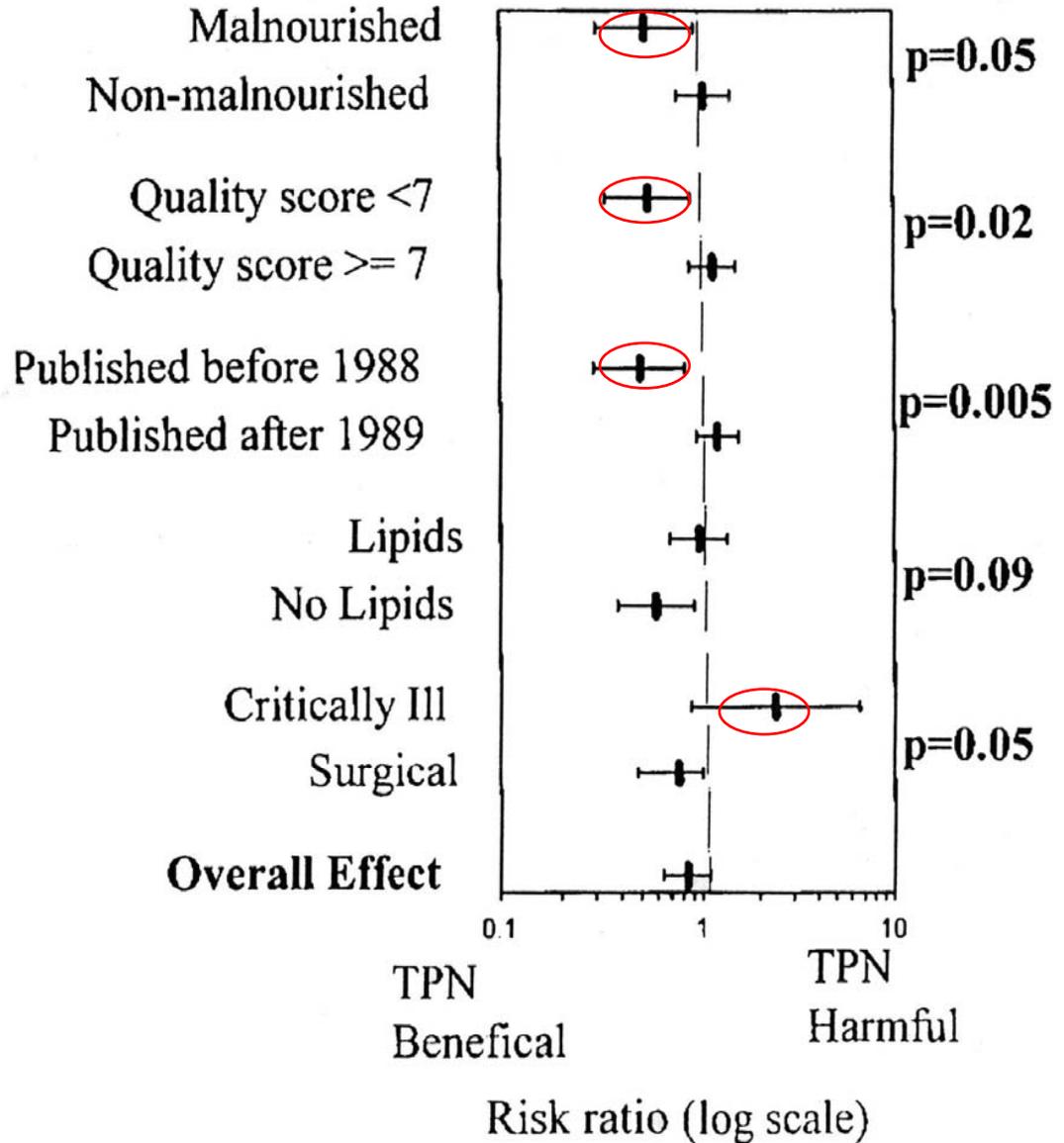
# TPN in Critically Ill Patients

## A meta-analysis

- 26 randomized trials  
N = 2221  
N per study 18-365
- TPN vs no TPN
- Endpoints
  - Complications
  - Length of stay
  - Mortality

# TPN - Subgroup Analysis

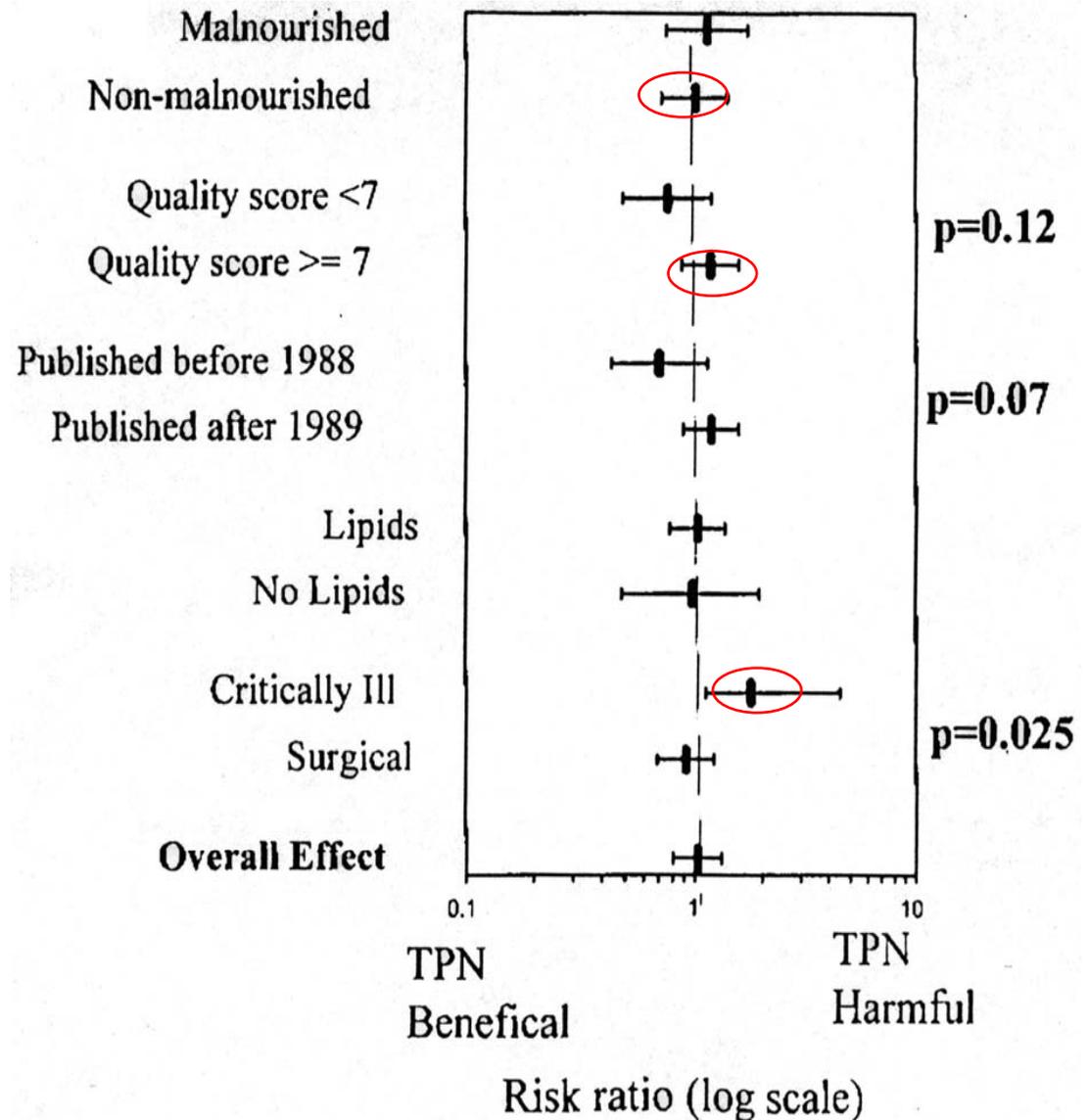
**COMPLICATIONS**



Heyland et al, JAMA, 1998

# TPN - Subgroup Analysis

**MORTALITY**



Heyland et al, JAMA, 1998

# Recent Controversy

- Another Metaanalysis
  - 9 trials (out of 465 publications reviewed) presented complete follow-up, allowing an intention to treat analysis
- Results
  - Mortality benefit in favour of TPN
  - Infectious complications were increased with TPN

Simpson F, Doig GS. Parenteral vs. enteral nutrition in the critically ill patient: a meta-analysis of trials using the intention to treat principle. *Intensive Care Med* 2005; 31:12–23

# However....

Subgroup analysis showed no survival benefit in PN if enteral nutrition was provided early => Benefit of PN confined to trials with late EN

Confirms a finding already reported in earlier metaanalyses

Peter JV, et al. A metaanalysis of treatment outcomes of early enteral versus early parenteral nutrition in hospitalized patients. Crit Care Med 2005; 33:213–220

Gramlich L, et al. Does enteral nutrition compared to parenteral nutrition result in better outcomes in critically ill adult patients? A systematic review of the literature. Nutrition 2004; 20:843–848

Braunschweig CL, et al. Enteral compared with parenteral nutrition: a meta-analysis. Am J Clin Nutr 2001; 74:534–542

## 3<sup>rd</sup> Conclusion

- The fact that delayed/inadequate delivery of EN may increase mortality compared to TPN does not justify the conclusion that early TPN should be used in patients where early EN at least to a certain amount is possible

# Why Not Supplemental PN?

- Comparison of severely injured blunt trauma patients receiving TPN or supplemental PN within the first 7 days vs. no “early” PN
- **Results**
  - Early TPN (17% out of 567) associated with greater risk of nosocomial infections
  - Early supplemental PN in enteral-tolerant subgroup (n = 249), also associated with an increase in nosocomial infections, in part increased risk of bloodstream infection
  - Mortality tended to be higher in patients receiving EN and supplemental PN versus EN alone
- **Conclusions**
  - In critically ill trauma patients who are able to tolerate at least some EN, early PN administration can contribute to increased infectious morbidity and worse clinical outcomes

Sena MJ.et al. Early Supplemental Parenteral Nutrition Is Associated with Increased Infectious Complications in Critically Ill Trauma Patients. J Am Coll Surg 2008; 207: 459-467

# EN vs EN+PN: Sytematic Review

- 5 studies; in all PN and EN started at the same time
  - No significant effect on mortality by EN + PN
  - No difference in infectious complications, length of hospital stay, or ventilator days.
- **CONCLUSIONS:** In critically ill patients who are not malnourished and have an intact gastrointestinal tract, starting PN at the same time as EN provides no benefit in clinical outcomes over EN alone

Dhaliwal R et al. Combination enteral and parenteral nutrition in critically ill patients: harmful or beneficial? A systematic review of the evidence *Intensive Care Med.* 2004; 30:1666-71

# Composition of TPN

- TPN vs. glucose and electrolyte solutions until eat and drink "freely"
  - Patients receiving glucose and electrolytes had a 5% mortality vs. 2% with TPN (not significant).
  - Similar rates of wound infections and pneumonia

Sandstrom R, et al.: The effect of postoperative intravenous feeding (TPN) on outcome following major surgery evaluated in a randomized study. *Ann Surg* 1993, 217:185-195].

Brennan MF, Pisters PWT, Posner M, Quesada O, Shike M: A prospective randomized trial of total parenteral nutrition after major pancreatic resection for malignancy. *Ann Surg* 1994, 220:436-444

- Reducing the amount of glucose and protein in the TPN admixture did not affect the infection rate in 40 patients with a variety of underlying conditions.
  - 6 of 21 hypo-caloric TPN patients developed infections as did 10 of 19 standard TPN patients (not significant; small sample size)

McCown KC, et al.: Hypocaloric total parenteral nutrition: Effectiveness in prevention of hypoglycemia and infectious complications: a randomized clinical trial. *Crit Care Med* 2000, 28:3606-3611

# Composition of TPN

- Conclusion
  - No data to support that increased delivery of nutrients intravenously alone increases the rate of non-catheter infection
  - Enteral feedings seem to protect against infection

# ASPEN Survey: Beyond Studies

- 651 responses, 90% hospital-based doctors
  - 75% processed 0 - 20 TPN orders per day
- In 78% physicians responsible for writing TPN orders, but dietitians and pharmacists had significant involvement
  - TPN base components were most often ordered against safe practice guidelines of ordering
  - No consistent method for ordering TPN electrolytes

Seres D et al. Parenteral Nutrition Safe Practices: Results of the 2003 American Society for Parenteral and Enteral Nutrition Survey\* Journal of Parenteral and Enteral Nutrition 2006; 30: 259-265

# ASPEN Survey: Beyond Studies

- 45% of responders reported adverse events directly related to TPN that required intervention
  - 25% caused temporary or permanent harm
  - 4.8% resulted in a near-death event or death

Seres D et al. Parenteral Nutrition Safe Practices: Results of the 2003 American Society for Parenteral and Enteral Nutrition Survey\* Journal of Parenteral and Enteral Nutrition 2006; 30: 259-265

# Conclusion

- Why should we not give TPN within the first 7 days?
  - The non-malnourished patient does not need it
  - Risk of overnutrition
  - Increased infectious complications
  - Delayed enteral nutrition
    - Compromised immunological function
    - Increased translocation
    - Delayed intestinal function

# Conclusion

- Why is TPN still given within the first 7 days?
  - Every idiot can prescribe it: “one bag of TPN/d”
  - Every idiot can hang it (needs a hook and an infusion line)
  - To leave it is easy (but stupid)
  - The patient cannot refuse it
  - But it is still better than to forget about nutrition

# Solution and Conclusion

- **If EN is started early, a higher proportion of ICU patients can be adequately nourished enterally after a few days**
- Reduced nutrition supply over a few days has no negative consequences in non-malnourished patients
- Adequately nourished patients who can be completely nourished orally or enterally within 5–7 days do not require PN
- For malnourished patients most probably one should start early with PN

Sandström R et al. The effect of postoperative intravenous feeding (TPN) on outcome following major surgery evaluated in a randomized study. *Ann Surg*1993;217:185-95