ESPEN LL –
Withhold of TPN for 7 days
Pro
R. Stocker
Zurich, Switzerland
Some Rationals
## Nutrition of the Intestinal Mucosa

<table>
<thead>
<tr>
<th></th>
<th>Luminal Nutrition</th>
<th>Main Substrates</th>
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<tbody>
<tr>
<td>Small Bowel</td>
<td>30%</td>
<td>Glutamine</td>
</tr>
<tr>
<td>Large Bowel</td>
<td>80%</td>
<td>SCFA‘s</td>
</tr>
</tbody>
</table>
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

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.

Recent Recognitions
TPN and Lymphotoxin-β-Receptor Expression

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

Recent Recognitions
Peritoneal Host Defense

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

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


• 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

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

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

Boyle et al, GUT, 1998
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

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
  $\Rightarrow$ 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
1st 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“

- Atony
  - Stomac
  - Colon
- Functional
  - Small intestines
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

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

  - Altering antigen exposure
  - Improving oxygenation of the gut mucosa

2nd 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

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
  – Aggravation of ventilatory impairment through increased CO2 production potentially preventing weaning from ventilatory support
Drawbacks of TPN

• Higher rates of postoperative and nosocomial infections after multiple trauma

• Predisposes to hyperglycemia => increases mortality
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

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)

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

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

Heyland et al, JAMA, 1998
TPN - Subgroup Analysis

- Malnourished
- Non-malnourished
- Quality score < 7
- Quality score >= 7
- Published before 1988
- Published after 1989
- Lipids
- No Lipids
- Critically Ill
- Surgical

**Overall Effect**

- TPN Beneficial
- TPN Harmful

**Risk ratio (log scale)**

Heyland et al, JAMA, 1998
TPN - Subgroup Analysis

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

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


3rd 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

EN vs EN+PN: Systematic 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

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


• 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)

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

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

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.