Severe acute pancreatitis nutrition therapy.

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Abstract

Background: Nutrition Support "crucial to the management of Acute Pancreatitis" (AP). In a significant proportion, this process causes a massive systemic inflammatory response, increasing risk for deterioration of nutritional status, septic morbidity, organ failure (OF), and prolonged hospitalization (LOS). Prevalence increased between 2002-2012 in 16.4%. Overall mortality from 5 to 20% depending on severity. Aetiology First: Biliary (decrease frequency), but there is an increase causes by alcohol consumption and Metabolic Syndrome. Obesity is related with AP severity. AP patients are normally prescribed nil per os (NPO) at admission. Although early introduction of diet has proven to shorten the length of stay, it is still not clear when and how to introduce diet. Early enteral nutrition (EEN) has shown a significative benefit over parenteral nutrition (PN) in terms of infection rates, hyperglycemia and mortality rates. To prevent pancreas auto-digestion, which leads to the release of pro-inflammatory mediators, immune system and gut barrier plays an important role in the pathogenesis of AP.

Methodology: This is a literature review.

Objectives: Review the diagnosis, pathophysiology of AP combined with timing to introduce Nutritional Support Enteral or Parenteral to try to lower the morbi-mortality and LOS.

Results/discussion: Consider the "Timing of Nutrition Intervention". Bakker Meta-Analysis EN arm of 8 RCTs (Before vs. After 24 hrs.): mortality/OF/infect necrosis: 19%* vs 45%; OF: 16% vs *42%. Petrov Meta-Analysis of 11 RCTs *p<0.05 Rx started within 48 hrs (EN vs. PN): no significant differences. Petrov in his study Early vs. Delayed EN in severe AP: EIN (enteral eco-immune nutrition) moderate's excessive immune responses (SIRS, CRP levels), EIN improves clinical outcome. Total serum Ca decrease in the first 24 hr. is as predictor of severity a risk of necrosis development in AP. Mg supplementation decrease significantly proteases activation and severity in AP and antagonist pathological Ca signaling. Have to be clear the meaning of tolerance and gastric vs jejunal feeding: pain, diarrhea and ileus. w-3 FA may be beneficial for decreasing mortality, infectious complications, and LOS in AP, when used PN delay up to 5 days in initiation of PN may be appropriate to allow for restarting oral or enteral feeding. Use PN should be considered when EN is not feasible after 1 week from onset of pancreatitis episode.

Conclusion: Nutritional status must be evaluated. When oral feeding is not tolerated EN feeding through a nasogastric/nasojejunal feeding tube should be attempted within the first 72 h. PN only if enteral route not available, optimal timing remains unclear. Antioxidants w-3 FA, vitamins and minerals (Ca, Mg, Vit C), and the role of immune-nutrients, important to be consider. The preferred route of administration was significantly (P<0.001) related to the practice type: academic physicians (52.1%, 61/117) were more likely to utilize NJ tubes compared to private practitioners (19.9%, 32/161), were most likely to use TPN/PPN than academic physicians (20.5%, 24/117). Predicting the nutritional tolerance remains challenging as current evaluation system needs to be improved.

Keywords: Acute pancreatitis, Nutritional support, Parenteral nutrition, Enteral nutrition, Proinflammatory mediators, Gut barrier.

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Introduction

Nutrition Support "crucial to the management of AP". In a significant proportion, this disease process causes a massive systemic inflammatory response, increasing risk for deterioration of nutritional status, septic morbidity, organ failure (OF), and prolonged hospitalization (LOS) [1].

Despite malnutrition high prevalence, physician's awareness of malnutrition is weak; nutritional therapy is not used routinely, and governmental policies for nutritional therapy are scarce.

Latin America is a region with extreme contrasts where most of the population lives in poverty. Accessing hospitals and health plans is limited, and malnutrition bears larger hospital length of stay (LOS).

This assertion does not only extend to Latin America but also to other continents where in spite of great efforts malnutrition and obesity still affects hospitals.

AP is a common and potentially severe disease where nutritional support does affect its development in a way it may be considered a treatment in severe cases.

In AP prevalence increased between 2002-2012 (16.4%) [2]. The Incidence 13-45 cases/100,000 populations, global estimate 33.74 cases/100,000 populations. 5% patients with Lithiasis AP and 10% can develop Chronic Pancreatitis (CP). The overall mortality ranges from 5 to 20% depending on severity [3]. Aetiology: First: Biliary (decrease frequency), but there is an increase causes by alcohol consumption and Metabolic Syndrome. Obesity is related with AP severity [4]. Patient hospitalization cost approximate 2.6 billion/annual.

In his research said AP increased in Shanghai and had a seasonal variation, with a higher frequency of events in the spring and autumn. Chinese festivals are associated with a high prevalence of AP. May be associated with alcohol consumption [5].

In pancreatitis patients are prescribed nil per os (NPO) at admission and advance diet in a progressive manner the following days. Although early introduction of diet has proven to shorten the length of stay, it is still not clear when and how to introduce diet. EEN has shown a significative benefit over PN in terms of infection rates, hyperglycemia and mortality rates.

Severe disease is a hypercatabolic situation which often appears in already malnourished patients. This benefit may be related to a decrease in bacterial intestinal translocation. Nasojejunal tube feeding is the preferred site, but there are trials supporting nasogastric tubes, a more feasible election.

The digestive enzymes are store as an inactive precursor in zymogens granules inside of acinar cells, to prevent pancreas auto-digestion. The first event premature activation of the intra-acinar digestive zymogens is one of the first characteristics of AP. The resulting autodigestion of the pancreas leads to the release of proinflammatory mediators such as tumor necrosis factor α, interleukin (IL)-1β, IL-6, which intermingle with the microcirculation, causing increased vascular permeability, edema, hemorrhage and necrosis of the pancreas. Deep acinar cell injury and amplified inflammatory responses result in SIRS and Multiple Organ Dysfunction Syndrome (MODS), ultimately responsible for AP-associated mortality. It is thought that the immune system plays an important role in the pathogenesis of AP disease.

The following lines offer an up to date review of nutritional management in AP, trying to answer the most frequent problems arising in the day to day management of this disease [6].

Objectives

1. Consider the diagnosis and pathophysiology of AP combined with Nutritional Support Therapy.
2. Show the newest nutritional interventions available for patients with AP. Health's personnel must work, first challenge: define when begin oral diet, second kind of diet and route, even EN or PN to try to lower the morbimortality and LOS.

Literature Review

Literature review of nutritional management in AP. Since 1998 there are more than 30 reviews, between 2004- 2017 a lot of studies are working to dilucidate the correct timing for the introduction and the best route for Nutritional Support: ESPEN (European Society) 2002/2006, ASPEN (American Society) 2002/2016, Meta-Analysis Marik-Zaloga 2004, Meta-analysis Cochrane Library 2006, Meta-analysis Mc Clave 2006, Meta-analysis Petrov 2008, Evidence NEG y NEY (Gastric or Jejunal), ASPEN 2009, ESPEN 2009 (NP), Cochrane 2010, Spain 2011, International 2012, IAP/AAP 2013, Cochrane 2015, Japanese 2015, Italian 2015, Canadian 2016 etc.

Sentinel AP Event- SAPE Hypothesis

1. Acinar cell stimulation [7]
2. Sentinel event [8]
   - Early pro-inflammatory
   - Late stellate cells
   - Pro-fibrotic response
1. Removal of stimulus
2. Recurrent stimulation

In the last decade gut barrier turn a very important topic in AP as we see:

- Severe AP represents septic syndrome due to failure of gut barrier, EN can modulate immune responses, improve outcome [9,10].
- Maintain gut integrity (Less bacterial challenge, endotoxemia)
- Set tone for systemic immunity (Innate, acquired responses)
- Attenuate stress response, disease severity (CRP, glucose, TAC)
- Faster resolution of disease process duration SIRS.

Determine Disease Severity

1. Mild pancreatitis [11,12]
   - Absence of OF.
   - Absence of local complications.
2. Moderately severe AP
   - Transient OF <48 hrs.
   - Local complications.
3. Severe AP

   Persistent OF lasting >48 hrs.
4. OF: Shock (Syst BP<90 mm Hg).

Pulmonary insuff (PaO_2, FiO_2<300).

Renal failure (creat>1.9 mg/dl).

5. Local complications

- Pseudocyst, abscess, necrosis

6. Unfavorable signs

- APACHE II ≥ 8, RC ≥ 3, CRP>150.

We can see the results in this Meta-analysis. Use of EN Preferred over PN [13]. Risk ratio PN vs. Post pyloric nutrition. Infection and mortality. Infection: 42.6 vs. 16.1% p<0.0001, Mortality 16.4 vs. 6.1% p=0.02 (Figures 1 and 2).

It is important to consider the "TIMING OF NUTRITION INTERVENTION".

- Bakker [14] Meta-analysis EN arm of 8 RCTs (Before vs. After 24 hrs) (Table 1)

- Petrov Meta-analysis of 11 RCTs [15] *p<0.05

Rx started within 48 hrs (EN vs. PN):

↓ MOF (RR 0.44)*

↓ Pancreatic. infections. complications. (RR 0.46)*

↓ Mortality (RR 0.46)*

Rx started after 48 hrs (EN vs. PN) No significant differences

Early vs Delayed EN in Severe AP

Local complications, OF, APACHE II>8 [16].

EEN, NJ (Naso Jejunal) feeds w/in 48 hrs vs. Delay DEN day 8 (Table 2).

EEN moderates excessive immune responses (SIRS, CRP levels). EEN improves clinical outcome.

Hot Topics

We have to consider other relevant elements as:

- Stelate cells modulation in treatment of AP, CP and Pancreatic Cancer

- Roll of the Biochemistry: Decrease Serum Calcium (Ca) it is a risk for necrosis development in AP. The total serum Ca total in the first 24 hr. as a predictor of severity [17] Mg supplementation decrease significantly proteases activation and severity in AP and antagonist pathological Ca signaling [18].

Two Aspects of Tolerance Issues with EN

1. Tolerance related to phases of stimulation of enzyme secretion. Level of EN infusion, content of EN formula, individual patient variation.

2. Tolerance related to motility and access to Gastro Intestinal tract (GI): Duration of ileus, Duodenal compression, Infusion method and institutional experience and expertise.

How do we define tolerance? [19]

Gastric vs jejunal feeding: Pain, diarrhea, energy balance.

When to advance to oral diet? Do you have to start with clear liquids? Jacobson: Clear liqs. vs. Low fat solid (no differences) [20]. Sathiariai: Clear liqs. vs. soft diet (↓ hosp LOS on soft diet

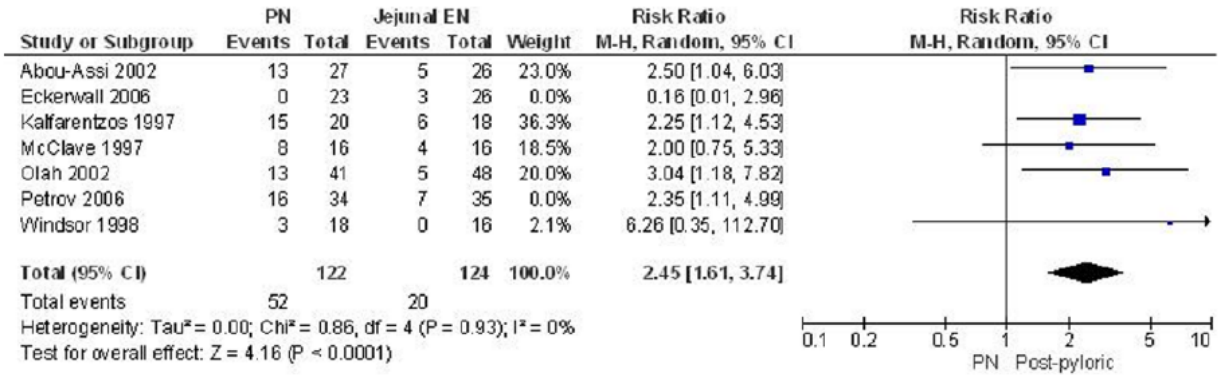

Figure 1. *Use of EN preferred over PN.*

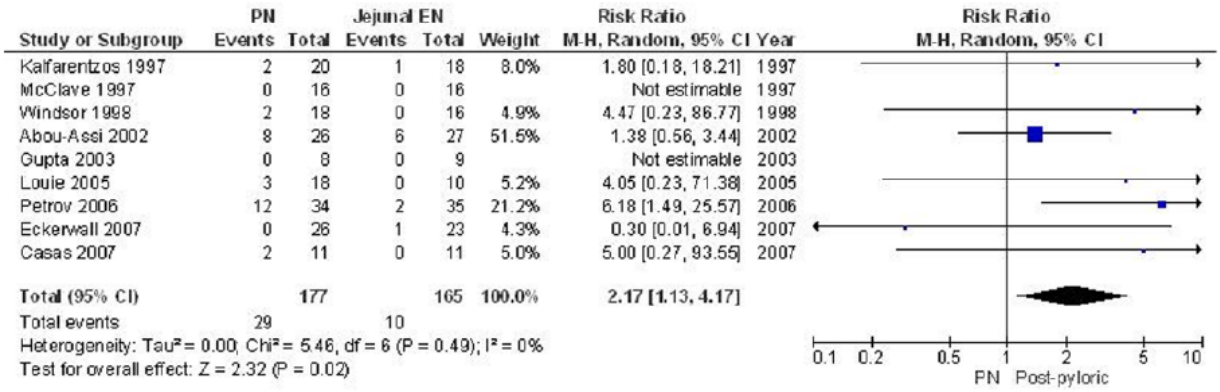

Figure 2. *Use of EN preferred over PN.*

1 d) [21]. Rajkumar: Clear liqs. vs. soft diet (↓ hosp and post-PO LOS 3 d) [22].

Should the patient decide?

Teich: Current guidelines (no pain, nl lipase) vs. pt. wishes [23].

(↓ hosp. LOS with pt. wishes)

Immune Formulas Study Pts–Control

- Pearce Arginine/Glutamine/FO formula (n=31) [24-26] (Tables 3 and 4).

↓ Pneumonia, MOF (p=NS)

↓ Hosp LOS, ICU LOS (p=NS)

- Petrov Meta-Analysis – No benefit [27], *p<0.05

Lei et al. [28] said about the role of w-3 fatty acids in AP, a meta-analysis of randomized controlled trials: The Cochrane Library, PubMed, Embase, Web of Science, and Chinese Biomedical Literature Database were searched Overall, ω-3 FA treatment resulted in a significantly reduced risk of mortality (RR 0.35; 95% CI 0.16 to 0.75, p<0.05), infectious complications (RR 0.54; 95% CI 0.34 to 0.85, p<0.05) and length of hospital stay (MD-6.50; 95% CI-9.54 to- 3.46, p < 0.05), but not length of ICU stay (MD-1.98; 95% CI-6.92 to 2.96, p>0.05).

The administration of ω-3 FA may be beneficial for decreasing mortality, infectious complications, and length of hospital stay in AP, especially when used parenterally. Large and rigorously designed RCTs are required to elucidate the efficacy of parenteral or enteral ω-3 FA treatment in AP. Should we use probiotics [29] (Table 5)?

Table 1. *Timing of nutrition intervention.*

Composite mortality, OF, infect necrosis organ failure	
Before (n=100)	**After (n=65)**
19%*	45%
16%*	42%

Table 2. *Early vs delayed EN in severe AP.*

Results	Early EN (n=30)	Delayed EN (n=30)	P value
Panc. infection	3%	10%	0.028
MOFS	5%	43%	0.024
ICU LOS (d)	9	12	0.033
SIRS	40%	73%	0.009
Surg. Operat.	7%	13%	NS
Mortality	7%	3%	NS

Table 3. *Lasztity FO (fish oil) formula (n=28).*

Lasztity FO (fish oil) formula (n=28)		
Hosp LOS	13.1 d*	19.3 d
Durat EN	10.6 d*	17.6 d
Complics	42%	64%

Table 4. *Hallay Arginine/FO formula (n=15).*

Hallay Arginine/FO formula (n=15)		
ICU LOS	8.6 d	34.8 d
Hosp LOS	27.2 d	38.4 d

Table 5. *RCT EN and Ecoimmunonutrition in Severe AP (n=183).*

Results	PN (n=60)	EN (n=61)	EN+EIN (n=62)
Panc sepsis	40.0%	21.3%*	12.9%#
Organ failure	36.7%	24.6%*	11.3%#
Mortality	11.7%	9.8%	8.1%
*p<0.05 vs PN, #p<0.05 vs EN			

RCT EN and Ecoimmunonutrition in Severe AP (n=183)

EN semi-elemental Peptisorb per NJ tube. EIN capsules *Bacillus subtilus*, *Enterococcus faecium*. As we see in Figure 3 when we combined score of severity Apache II with different formulas and days of prescription: EN decrease endotoxin, TNF, IL-6, improves outcome. Adding EIN further benefits (Figure 3).

Timing of PN

- Delay up to 5 days in initiation of PN may be appropriate to allow for restarting oral or enteral feeding [30].
- Use PN should be considered when EN is not feasible after 1 week from onset of pancreatitis episode [19].

Are clinicians becoming aware of benefits of EEN? [30] Sun E. 2013. N Amer Survey (n=406) [31]. No difference gastroenterologists (GI) vs. primary care physicians (Prim Care) (Tables 6 and 7).

Discussion

In particular, 43.1% (n=175) of respondents used TPN/PPN and 36.5% (n=148) chose NJ tube feeding. The preferred route of administration was significantly (P<0.001) related to the practice type: academic physicians (52.1%, 61/117) were more likely to utilize NJ tubes compared to private practitioners (19.9%, 32/161), were most likely to use TPN/PPN than academic physicians (20.5%, 24/117). When comparing

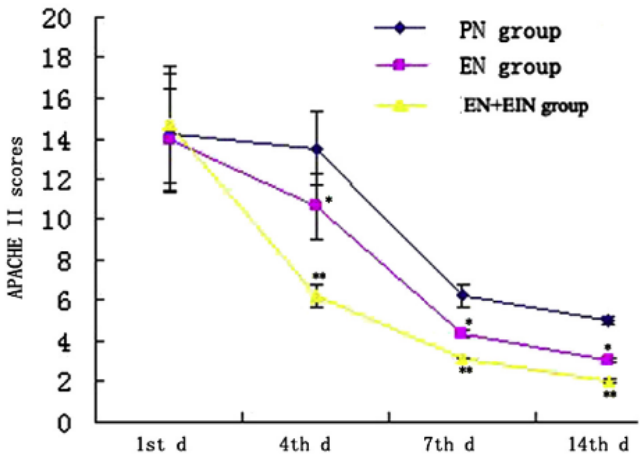

Figure 3. *[29]G Wang (J Surg Research in 2013; 183: 592-97).*

Table 6. *Timing of PN.*

Overall	PN use 43.3%
	EN use 36.5%
EN use	52.1% academic
	19.9% privpract
PN use	20.5% academic
	70.2% privpract
No diff. gastroenterologists (GI) vs. primary care physicians (Prim Care)	

Table 7. *Preferred route of nutrition by type of practice and specialty. Other includes surgical jejunostomy tube and percutaneous endoscopic jejunostomy tube.*

Overall responses	TPN/PPN	NJ tube	NG tube	Other	P value
(n=406)	175 (43.1%)	148 (36.5%)	67 (16.5%)	16 (3.9%)	<0.001
Practice type[a]					
Academic (n=117)	24 (20.5%)	61 (52.1%)	20 (17.1%)	12 (10.3%)	-
Private practice (n=161)	113 (70.2%)	32 (19.9%)	15 (9.3%)	1 (0.6%)	-
Specialty					0.151
Internal medicine (n=242)	102 (42.1%)	96 (39.7%)	38 (15.7%)	6 (2.5%)	-
Gastroenterology (n=164)	73 (44.5%)	52 (31.7%)	29 (17.7%)	10 (6.1)	-
[a] The hybrid private/academic practice class was excluded from the analysis Chi-squared test.					

gastroenterologist to primary care physicians, both groups favored PN over NJ tube feeding (P=0.151).

In this study in critically ill patients Yao et al. [32] said whether EN is superior to PN with severe AP remains unknown. The objective of this meta-analysis was to assess the effects of EN versus PN on clinical outcomes in a subgroup of pancreatitis patients. Relevant randomized controlled trials (RCTs) were searched in Scopus, PubMed and Web of Science from inception to August 2016. Ultimately, five RCTs including 348 patients were enrolled in this analysis. Compared with PN, EN was associated with a significant reduction in overall mortality risk ratio (RR)=0.36, 95% confidence interval (CI) 0.20-0.65, P=0.001) and the rate of multiple OF (RR=0.39, 95% CI 0.21–0.73, P=0.003). EN should be recommended as the preferred route of nutrition for critically ill patients with severe AP.

Conclusion and Future Perspectives

Nutritional status must be evaluated. In most patients, an oral soft or solid diet can be beneficial if tolerated. When oral feeding is not tolerated for a few days, EN feeding through a nasogastric or nasojejunal feeding tube should be attempted within the first 72 hrs. of administration. PN should be minimized for its risks of infection and other complications. Only if enteral route is not available or tolerated, PN may be considered. Overall, nutritional support plays a critical role in clinical management of severe AP, although the optimal timing remains unclear. It is important to pay attention to the antioxidants Vitamins, and the role of inmunonutrients. Inmuno Nutrition with currently mixed clinical outcomes is a subject of interest for future evaluation and may lead to promising outcomes. Predicting the nutritional tolerance of patients with AP remains challenging as the current evaluation system needs to be improved. Various nutritional supplements (s) together with PN or EN. In addition, given its heterogeneous aetiological factors and varying clinical manifestations, precision medicine, although not much applied in the condition, remains as a temping approach to optimize clinical outcomes on classified individuals based on susceptibility to the condition and its systemic complications.

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