Specific Nutritional Support in Critical Illness

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Grand Rounds September 20, 2010

Overview

- Nutritional Support
- Overview of Guidelines
- Historical Perspective
- Omega-3 Fatty Acids
- Arginine
- Glutamine
- Conclusion

Nutritional Support in Critical Illness

- Hyper-Catabolic State
- Increased Glucagon, Cortisol and Epinephrine
- <u>Supplemental Feeds:</u>
  - **1.** The patient has been without nutrition for 5 to 7 days.
  - **2.** The duration of illness is expected to exceed 10 days.
  - **3.** The patient is malnourished.
  - **4.** Burns with > 20% TBSA burn

30 kcal/kg/day generally is adequate for normal-weight patients, 35 kcal/kg/day may be targeted for underweight patients, and 25 kcal/kg/day for overweight

Harris-Benedict equations:

BEE = 66 + (13.7 × Weight) + (5 × Height) - (6.8 × Age) (Males)

BEE = 665 + (9.6 × Weight) + (1.8 × Height) - (4.7 × Age) (Females

Critical Care Nutrition Guidelines 2009, and meta analysis

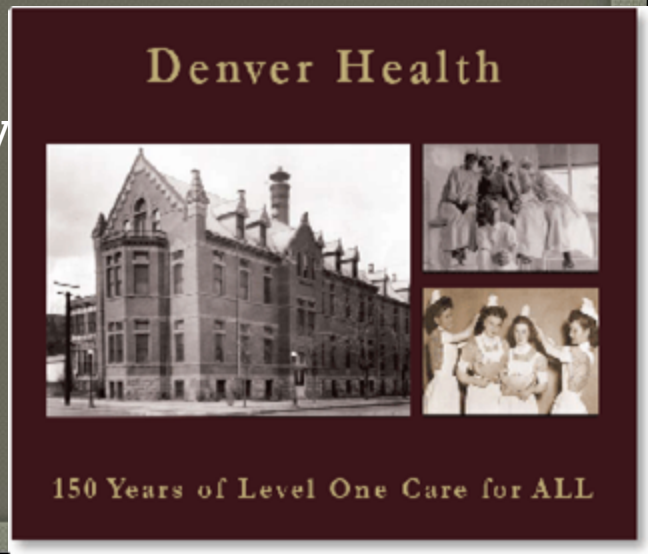
- Established by researchers at the Queens University in Ontario
- Conducted review of critical care nutrition for establishment of optimal guidelines after including over 200 studies.

- <u>Studies Included:</u>

Level 1 study: *If all of the following are fulfilled: concealed randomization, blinded outcome adjudication and an intention to treat analysis.*
Level 2 study: *If any one of the above characteristics are unfulfil*

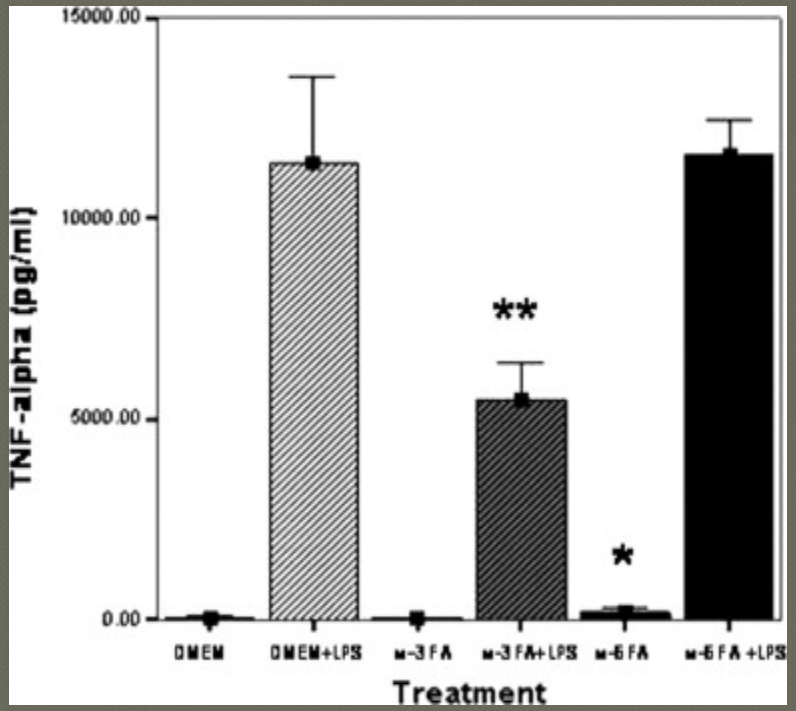
Historical Perspective

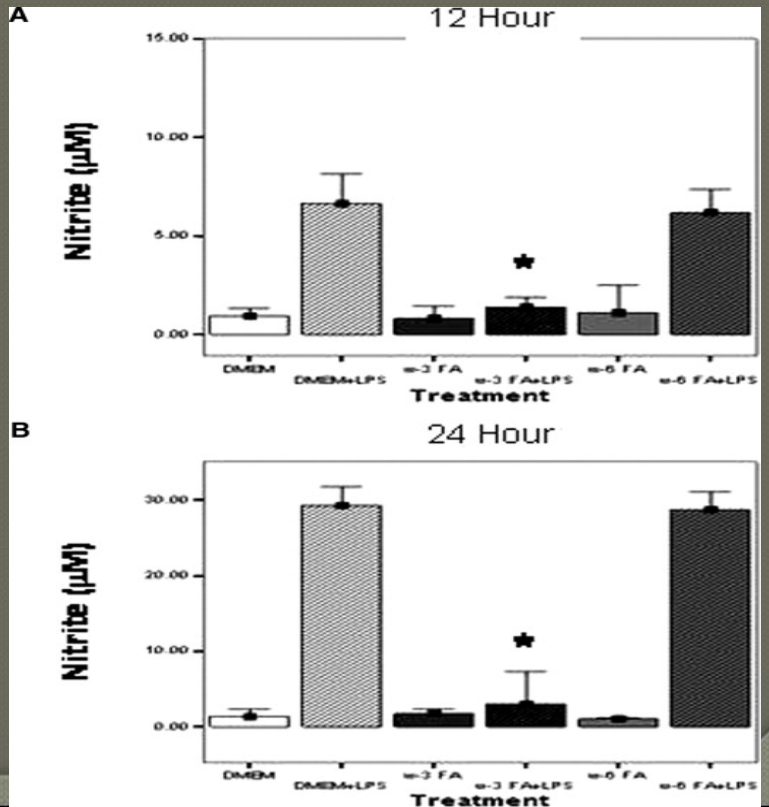
- Denver Health, Journal of Trauma, 1994
- Pts that had sustained Torso Trauma supplemented with ***"new immune-enhancing diet"*** had fewer intarabdominal abscess and decreased incidences of MOD and elevated Tcell Counts
- **Immun-Aid:** 14 g/L arginine, glutamine, BCAA, ω 3 fatty acids, nucleic acids, Vit E, selenium, zinc and 80gms protein/litre



Omega 3 Fatty Acids in Critical Care

- Proposed Mechanisms
- Attenuate pro-inflammatory cascade by down regulation of TNF-α and NOS proteins in cell cultures





Omega-3 Fatty Acids and ARDS

- Prospective, double-blinded, randomized, controlled, multi-centered trial
- 146 patients with ARDS
- Defined by the American-European Consensus Conference caused by sepsis/pneumonia, trauma, or aspiration injury in the study.
- Patients meeting entry criteria were randomized and continuously tube-fed either EPA + GLA or an isonitrogenous, isocaloric
- Pts were started on enteral feeds within 24 hrs of diagnosis

- Critical Care Medicine
- Issue: Volume 27(8), August 1999, pp 1409-1420

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- Effect of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in patients with acute respiratory distress syndrome

- Gadek, James E. MD; DeMichele, Stephen J. PhD; Karlstad, Michael D. PhD; Pacht, Eric R. MD; Donahoe, Michael MD; Albertson, Timothy E. MD, PhD, FCCM; Van Hoozen, Chi MD; Wennberg, Ann K. RD, LD; Nelson, Jeffrey L. PhD; Noursalehi, Mojtaba PhD

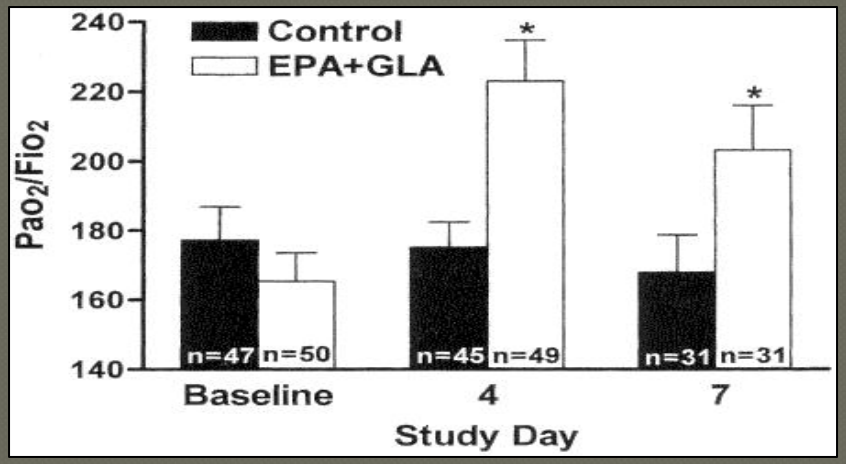
Specific Diets

Nutrient	Control	EPA+GLA
Protein		
% of total calories	16.7	16.7
g/L	62.6	62.5
Source	87% sodium caseinate	87% sodium caseinate
Carbohydrate	13% calcium caseinate	13% calcium caseinate
% of total calories	28.1	28.1
g/L	105.7	105.5
Source	46% maltodextrin	45% maltodextrin
Lipids	54% sucrose	55% sucrose
% of total calories	55.2	55.2
g/L	92.1	93.7
Source	96.8% corn oil	31.8% canola oil
	3.2% soy lecithin	25% MCT
		20% borage oil
		20% fish oil
		3.2% soy lecithin
Vitamins		
Vitamin E (IU/L)	47.6	317
Vitamin C (mg/L)	317	844
β-Carotene (mg/L)	—	5.0
Taurine (mg/L)	—	316
L-Carnitine (mg/L)	—	181
Caloric density (kcal/mL)	1.5	1.5
Osmolality (mOsm/kg/H_2O)	465	493

EPA, eicosapentaenoic acid; GLA, gamma-linolenic acid; IU, international units; MCT, medium chain triglycerides.

[a]Each liter of both formulas contained the following vitamins: 5360 IU, vitamin A; 425 IU, vitamin D; 101 mcg, vitamin K_1; 850 μg, folic acid; 3.2 mg, thiamine; 3.6 mg, riboflavin; 4.3 mg, vitamin B_6; 13 μg, vitamin B_{12}; 43 mg niacin; 635 mg, choline; 635 μg, biotin; 22 mg, pantothenic acid. [b]Each liter of both formulas contained the following trace minerals: 1310 mg, Na; 1960 mg, K; 1690 mg, Cl; 1060 mg, Ca; 1060 mg, P; 425 mg, Mg; 160 μg, I; 5.3 mg, Mn; 2.2 mg, Cu; 24 mg, Zn; 20 mg, Fe; 77 μg, Se; 130 μg, Cr; 160 μg, Mo.

Results



Variable	Intent to Treat			Evaluable		
	Control (n = 72)	EPA+GLA (n = 70)	*p* Value	Control (n = 47)	EPA+GLA (n = 51)	*p* Value
Time on supplemental oxygen[a] (days)	17.1 ± 1.6	13.6 ± 1.2	.078	20.2 ± 2.1	15.8 ± 1.5	.053
Time on ventilator[a] (days)	13.2 ± 1.4	9.6 ± 0.9	.027	16.3 ± 1.9	11.0 ± 1.1	.011
Intensive care unit stay[a] (days)	14.8 ± 1.3	11.0 ± 0.9	.016	17.5 ± 1.7	12.8 ± 1.1	.016
Hospital stay[a] (days)	31.1 ± 2.4	27.9 ± 2.1	.278	34.6 ± 3.3	29.4 ± 2.6	.07
Mortality (%)	25 (19/76)	16 (11/70)	.165	19 (9/47)	12 (6/51)	.31
New organ failures[b] (%)						
Total	25 (19/76)	10 (7/70)	.018	28 (13/47)	8 (4/51)	.015
Cardiovascular	8 (6/76)	1 (1/70)		9 (4/47)	2 (1/51)	
Renal	9 (7/76)	4 (3/70)		9 (4/47)	2 (1/51)	
Hematologic	4 (3/76)	0 (0/70)		6 (3/47)	0 (0/51)	
Hepatic	4 (3/76)	0 (0/70)		2 (1/47)	0 (0/51)	
Neurologic	5 (4/76)	0 (0/70)		6 (3/47)	0 (0/51)	
Gastrointestinal	11 (8/76)	7 (5/70)		13 (6/47)	6 (3/51)	

EPA, eicosapentaenoic acid; GLA, gamma-linolenic acid.

[a]Values are mean ± SE. [b]Percent of patients in each group, control or EPA+GLA, who developed a new failure in any organ not present at baseline.

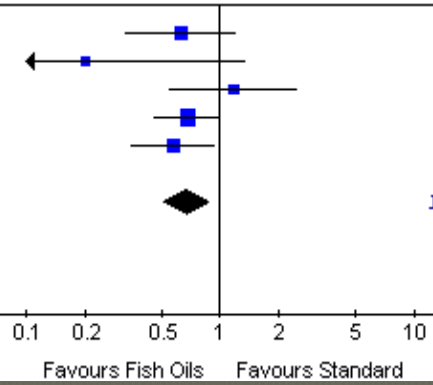
Omega-3 Fatty Acids Mortality in pts with ARDS/ALI

Critical Care Meta-analysis 2009

Review: Fish Oils vs. Standard
Comparison: 01 Mortality
Outcome: 01 28 day mortality

Study or sub-category	Fish Oils n/N	Standard n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI	Year
Gadek	11/70	19/76		15.46	0.63 [0.32, 1.23]	1999
Elamin	1/8	5/8		1.89	0.20 [0.03, 1.35]	2005
Moran	11/61	11/71		11.86	1.16 [0.54, 2.49]	2006
Pontes-Arruda	26/83	38/82		44.29	0.68 [0.46, 1.00]	2006
Singer	14/46	26/49		26.50	0.57 [0.34, 0.96]	2006
Total (95% CI)	268	286		100.00	0.67 [0.51, 0.87]	

Total events: 63 (Fish Oils), 99 (Standard)
Test for heterogeneity: $Chi^2 = 3.95$, df = 4 (P = 0.41), $I^2 = 0\%$
Test for overall effect: Z = 3.02 (P = 0.003)



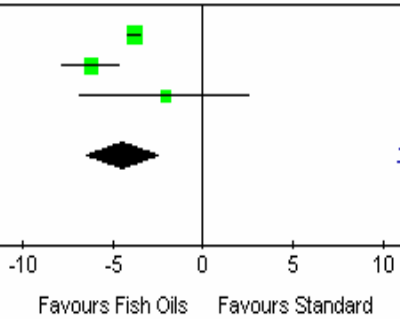
Significant Reduction in 28 day mortality RR =0.67, 95% CI 0.51, 0.87, p=0.003,

Omega-3 Effect on ICU LOS and LOV

Review: Fish oils
Comparison: 02 ICU LOS
Outcome: 01 ICU Length of Stay

Study or sub-category	N	Fish Oils Mean (SD)	N	Standard Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI	Year
Gadek	70	11.00(0.90)	72	14.80(1.30)		49.16	-3.80 [-4.17, -3.43]	1999
Pontes-Arruda	55	17.20(4.90)	48	23.40(3.50)		37.63	-6.20 [-7.83, -4.57]	2006
Singer	46	13.50(11.80)	49	15.60(11.80)		13.21	-2.10 [-6.85, 2.65]	2006
Total (95% CI)	171		169			100.00	-4.48 [-6.49, -2.47]	

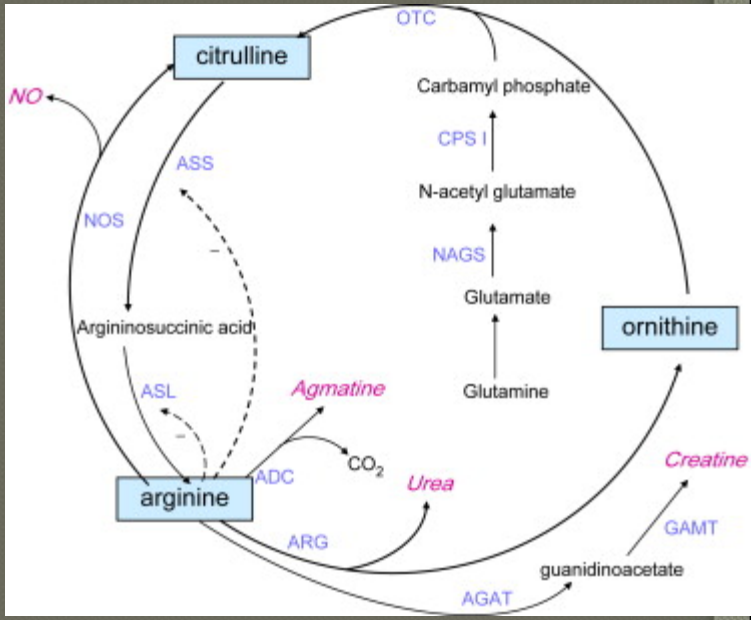
Test for heterogeneity: Chi² = 8.48, df = 2 (P = 0.01), I² = 76.4%
Test for overall effect: Z = 4.36 (P < 0.0001)



Weighted mean difference -4.48, 95 % CI -6.49, -2.47, p <0.0001

Arginine

- Conditionally essential amino acid
- Septic pts are severely depleted in arginine
- Decreased plasma levels are associated with increased mortality in sepsis
- Involved in nitrous oxide, urea and creatine pathways
- Aids in T-cell and Macrophage Proliferation
- Essential in collagen production and wound healing



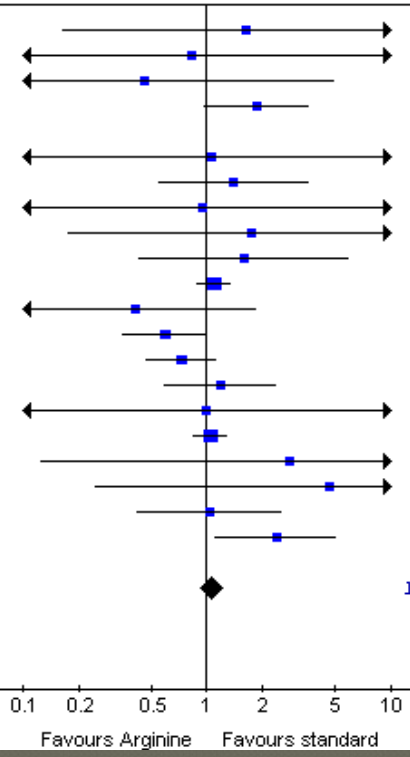
Arginine and Mortality

Critical Care Meta Analysis, 2009

Review: Immunonutrition (combined)
Comparison: 01 Diets with arginine and other vs. standard
Outcome: 01 Mortality

Study or sub-category	Diets with Arginine n/N	standard n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI	Year
Gottschlich	2/17	1/14		0.32	1.65 [0.17, 16.33]	1990
Cerra	1/11	1/9		0.24	0.82 [0.06, 11.33]	1991
Moore	1/51	2/47		0.30	0.46 [0.04, 4.92]	1994
Bower	24/153	12/143		3.91	1.87 [0.97, 3.60]	1995
Brown	0/19	0/18			Not estimable	1995
Kudsk	1/17	1/18		0.23	1.06 [0.07, 15.62]	1996
Engel	7/18	5/18		1.89	1.40 [0.54, 3.60]	1997
Mendez	1/22	1/21		0.23	0.95 [0.06, 14.30]	1997
Rodrigo	2/16	1/14		0.32	1.75 [0.18, 17.29]	1997
Saffle	5/25	3/24		0.97	1.60 [0.43, 5.97]	1997
Atkinson	95/197	85/193		33.22	1.09 [0.88, 1.36]	1998
Weimann	2/16	4/13		0.72	0.41 [0.09, 1.88]	1998
Galban	17/89	28/87		6.03	0.59 [0.35, 1.00]	2000
Capparos	27/130	30/105		8.09	0.73 [0.46, 1.14]	2001
Conejero	14/43	9/33		3.38	1.19 [0.59, 2.41]	2002
Chuntrasakul	1/18	1/18		0.23	1.00 [0.07, 14.79]	2003
Kieft 2005	114/302	106/295		34.60	1.05 [0.85, 1.30]	2005
Tsuei	1/13	0/12		0.17	2.79 [0.12, 62.48]	2005
Wibbenmeyer	2/12	0/11		0.20	4.62 [0.25, 86.72]	2006
Beale	7/27	7/28		2.05	1.04 [0.42, 2.56]	2008
Dent	20/87	8/83		2.88	2.39 [1.11, 5.11]	press
Total (95% CI)	1283	1204		100.00	1.06 [0.93, 1.20]	

Total events: 344 (Diets with Arginine), 305 (standard)
Test for heterogeneity: Chi² = 19.22, df = 19 (P = 0.44), I² = 1.1%
Test for overall effect: Z = 0.84 (P = 0.40)



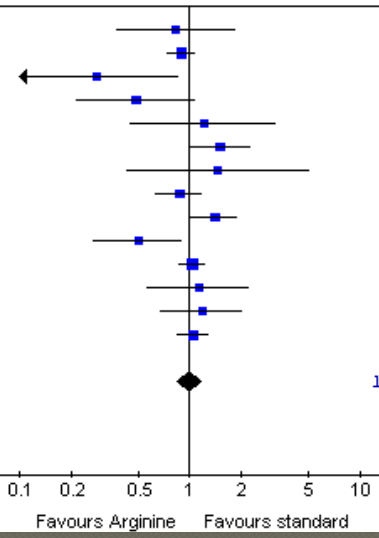
(RR = 0.75, 95 % CI 0.49, 1.15, p = 0.19

Arginine and Infection

Review: Immunonutrition (combined)
Comparison: 01 Diets with arginine and other vs. standard
Outcome: 02 Infectious complications

Study or sub-category	Diets wih Arginine n/N	standard n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI	Year
Moore	9/51	10/47		3.10	0.83 [0.37, 1.86]	1994
Bower	86/153	90/143		15.05	0.89 [0.74, 1.08]	1995
Brown	3/19	10/18		1.76	0.28 [0.09, 0.87]	1995
Kudsk	5/16	11/17		3.11	0.48 [0.22, 1.08]	1996
Engel	6/18	5/18		2.19	1.20 [0.45, 3.23]	1997
Mendez	19/22	12/21		8.34	1.51 [1.01, 2.27]	1997
Rodrigo	5/16	3/14		1.46	1.46 [0.42, 5.03]	1997
Galban	39/89	44/87		10.81	0.87 [0.63, 1.19]	2000
Capparos	64/130	37/105		10.85	1.40 [1.02, 1.91]	2001
Conejero	11/43	17/33		4.89	0.50 [0.27, 0.91]	2002
Kieft 2005	130/302	123/295		15.08	1.03 [0.86, 1.24]	2005
Tsuei	8/13	6/11		4.02	1.13 [0.57, 2.25]	2005
Wibbenmeyer	9/12	7/11		5.60	1.18 [0.68, 2.05]	2006
Dent	57/87	52/83		13.73	1.05 [0.83, 1.31]	press
Total (95% CI)	971	903		100.00	0.99 [0.85, 1.15]	

Total events: 451 (Diets wih Arginine), 427 (standard)
Test for heterogeneity: $Chi^2 = 25.16$, df = 13 (P = 0.02), $I^2 = 48.3\%$
Test for overall effect: Z = 0.15 (P = 0.88)



(RR 0.99 95% CI, 0.85,1.15, p = 0.88)

Glutamine

- Most abundant AA in human body
- Conditionally essential AA
- Released from muscle
- Preferred source on nutrition by enterocytes
- Carrier of nitrogen to intestine, kidneys and immune cells
- Pts during trauma and sepsis have decreased circulating amounts of glutamine

Proposed Methods of Glutamine

Inflammation

Attenuate the acute hyperinflammatory response. Specifically, the release of interleukin (IL)-6 and tumor necrosis factor (TNF)-α is attenuated at 6 hours post surgery or injury.

Cellular Apoptosis

- Preservations of metabolic function during stress such as sepsis, shock, ischemia by up regulation regulation of HSP'sInduces HSP 25 and HSP 72which are thought to be cytoprotetive during cellular stress

Immune Function

- Improved monocyte function and required for lympochyte receptor synthesis

Hyperglycemia

- Recent studies showing improved glucose control.

Glutamine Administration Reduces Gram-negative bacteremia in severely burned patients:

- University of Chicago
- Prospective double-blind randomized trial
- 31 patients with greater than 25% TBSA burn
- All pts were started on enteral feeds within 48hrs of admission unless unable to tolerate enteral feeds

Results

Table 4. Frequency of bacteremia and antibiotic use

	Glutamine (n = 12)	Control (n = 14)	p Value
Positive blood cultures per patient, mean ± SE	2.4 ± 1.0	4.9 ± 1.5	.10
Patients with positive blood cultures, n (%)	7 (54)	9 (63)	.76
Patients with Gram (–) bacteremias, n (%)	1 (8)	6 (43)	.04
Patients with Gram (+) bacteremias, n (%)	7 (58)	6 (43)	.43
Patients with fungemias, n (%)	2 (17)	2 (14)	.87
Antibiotic use per day, mean ± SE	1.25 ± 0.23	1.61 ± .24	.15

Table 4 . Frequency of bacteremia and anibiotic use

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Glutamine Improves 6-Month Outcome in Critically Ill Patients

- Department of Anesthesiology and Intensive Care, University of Münster, Germany
- 95 SICU pts were randomized to Glutamine supplementation or standard parenteral or enteral nutrition
- Trauma 20, Abd surgery 30, CV surgery 31 Misc Surgery 14
- All pts were treated within 3 days and greater than 5 days

- Critical Care Medicine
- Issue: Volume 30(9), September 2002, pp 2032-2037

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- Parenteral l-alanyl-l-glutamine improves 6-month outcome in critically ill patients

- Goeters, Christiane MD; Wenn, Anke MSc; Mertes, Norbert MD; Wempe, Carola PhD; Van Aken, Hugo MD, PhD; Stehle, Peter PhD; Bone, Hans-Georg MD

Results

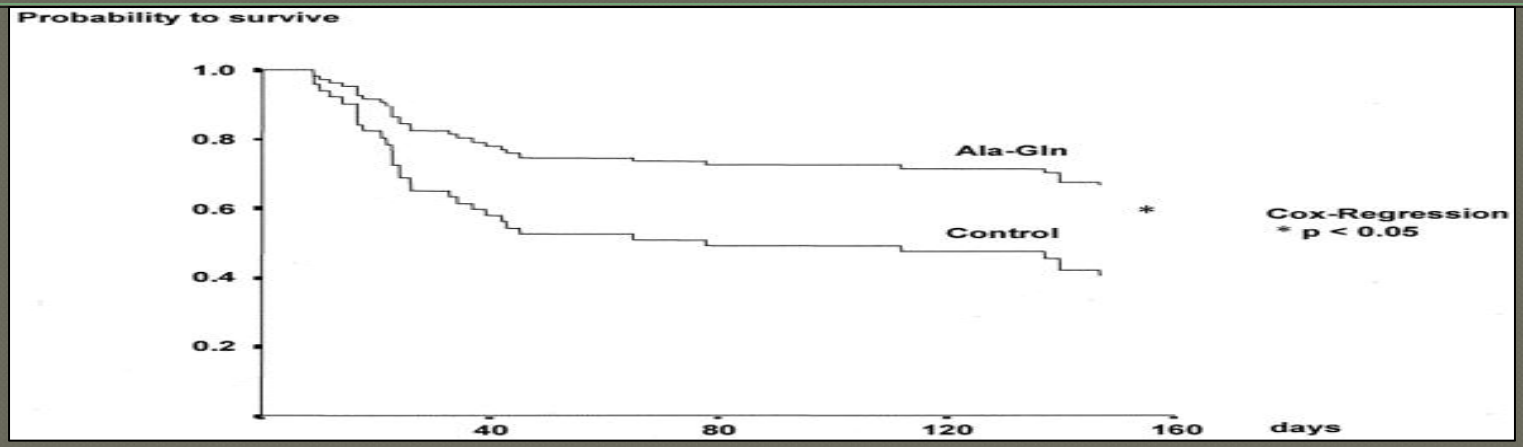


Figure 2 . Survival plot of the subgroup of patients treated for >=9 days under standardized conditions (Ala-Gln, l-alanyl-l-glutamine, the glutamine supplemented group;Control, control group)

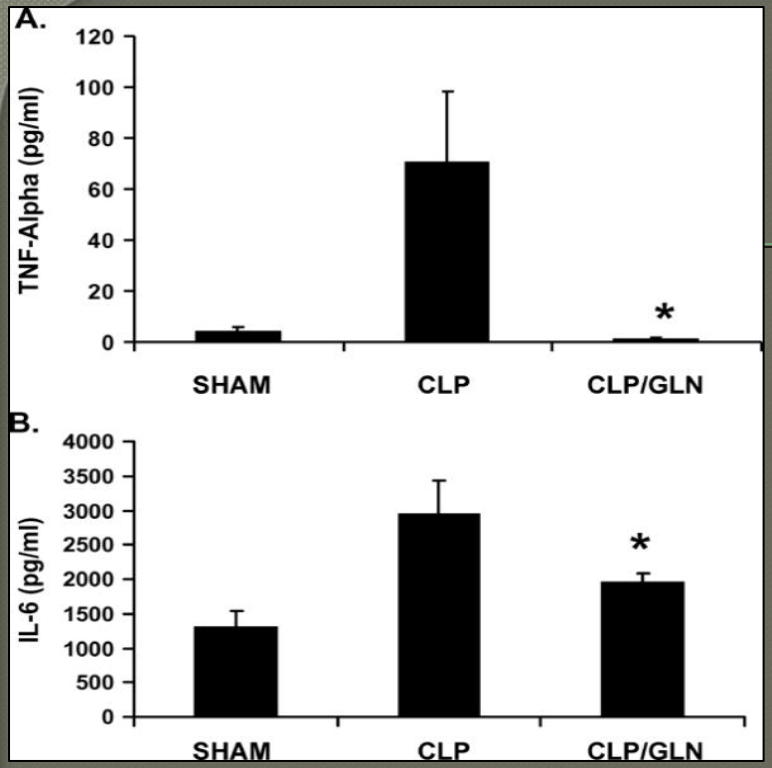
Table 6. Differences in average length of stay (ALOS) and mortality

	Ala-Gln $n = 33$	Control $n = 35$
ALOS ICU, days	21.3 ± 13.5	20.8 ± 9.1
ALOS hospital, days	46.0 ± 49.1	39.4 ± 31.1
Incidence of death in ICU	7	10
Incidence of death within 30 days	7	11
Incidence of death within 6 months	11	21[a]

Ala-Gln, L-alanyl-L-glutamine; ICU, intensive care unit; ICU, intensive care unit.
[a] $p \leq .05$.

Glutamine and ARDS

- Mice subjected to cecal ligation
- Following ligation mice were randomized to IV glutamine administration
- Mice were evaluated at 6 hour intervals for production of proinflammatory cytokine, TNF-alpha, IL-6, IL-18 and iNOS, as well and lung pathology examined
- Neutrophil accumulation, septal thickening, and hyaline membrane formation was drastically decreased
- E


A.
TNF-Alpha (pg/ml)
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100
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60
40
20
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CLP
CLP/GLN
B.
IL-6 (pg/ml)
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2000
1500
1000
500
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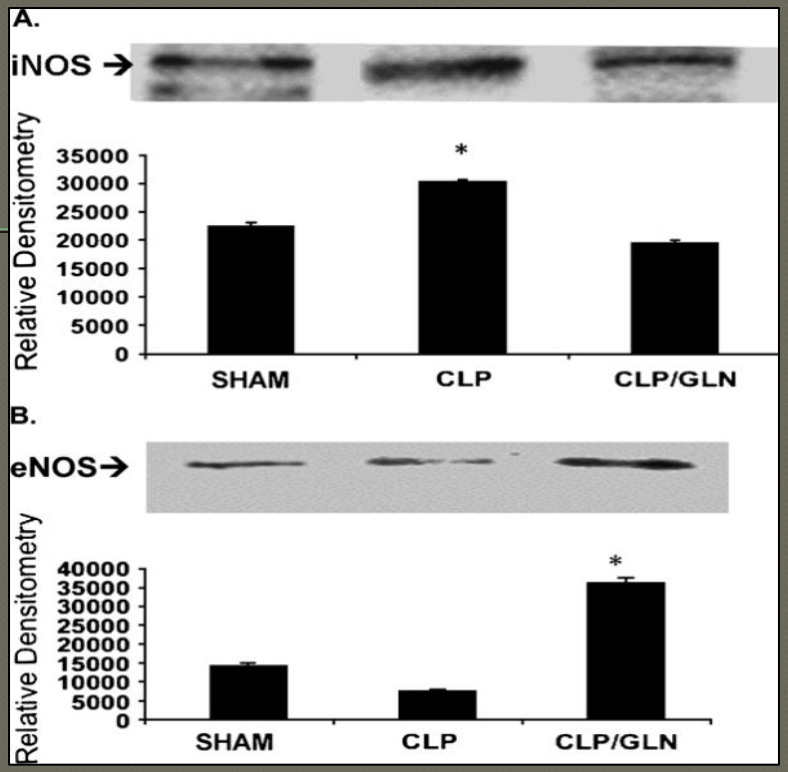
CLP
CLP/GLN


A.
iNOS →
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15000
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CLP/GLN
B.
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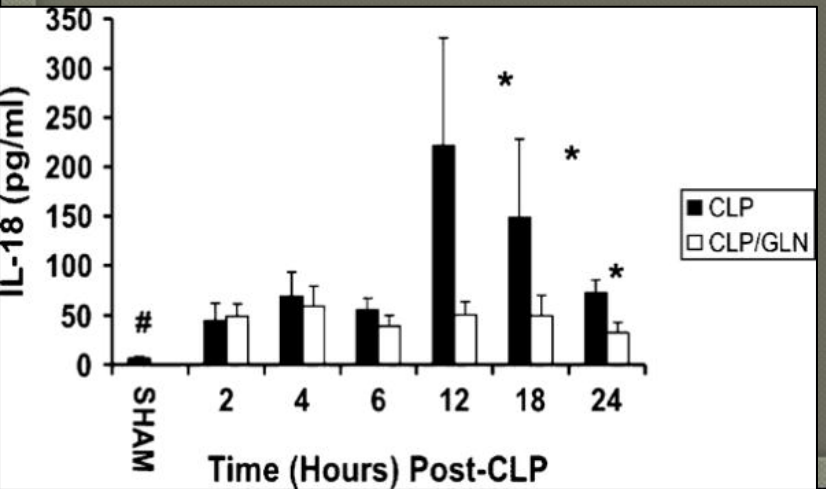
CLP
CLP/GLN


IL-18 (pg/ml)
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300
250
200
150
100
50
0
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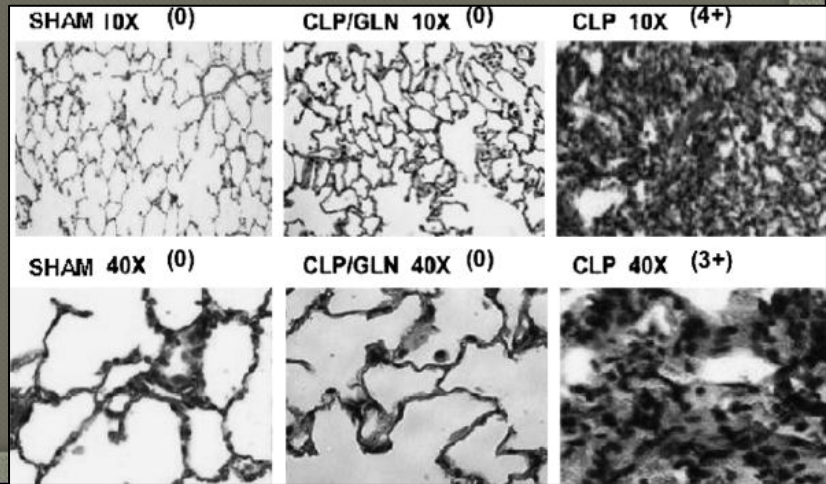
CLP
CLP/GLN
SHAM
2
4
6
12
18
24
Time (Hours) Post-CLP


SHAM 10X (0)
CLP/GLN 10X (0)
CLP 10X (4+)
SHAM 40X (0)
CLP/GLN 40X (0)
CLP 40X (3+)

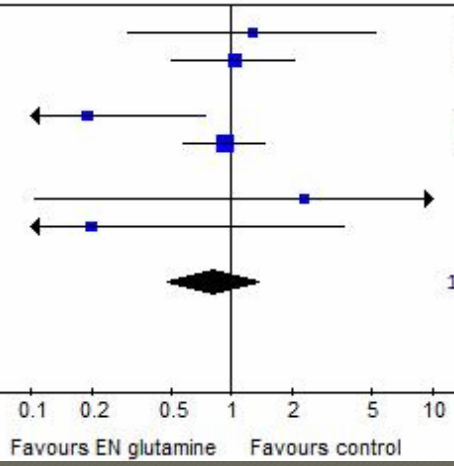
Glutamine and Mortality

Critical Care Nutrition Metanalysis, 2009

Review:
Comparison: 01 Enteral Glutamine vs Control
Outcome: 03 Mortality

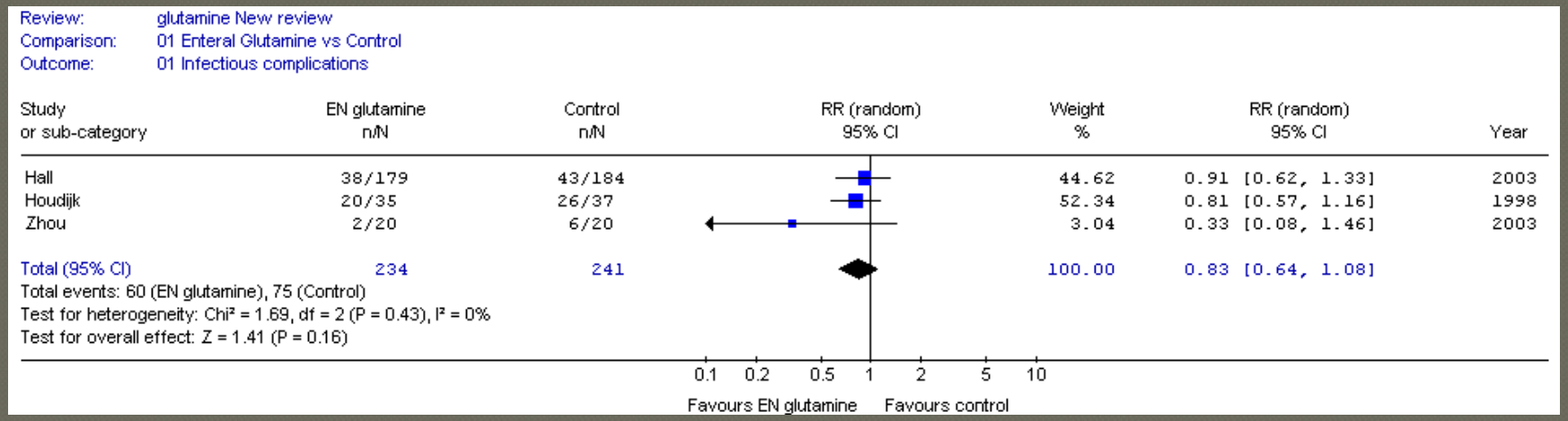
Study or sub-category	EN glutamine n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI	Year
Houdijk	4/41	3/39		10.76	1.27 [0.30, 5.31]	1998
Jones	10/26	9/24		29.48	1.03 [0.50, 2.08]	1999
Brantley	0/31	0/41			Not estimable	2000
Garrel	2/21	12/24		11.48	0.19 [0.05, 0.76]	2003
Hall	27/179	30/184		42.70	0.93 [0.57, 1.49]	2003
Zhou	0/20	0/20			Not estimable	2003
Luo	1/12	0/9		2.63	2.31 [0.10, 50.85]	2008
McQuiggan	0/10	2/10		2.94	0.20 [0.01, 3.70]	2008
Total (95% CI)	340	351		100.00	0.81 [0.48, 1.34]	

Total events: 44 (EN glutamine), 56 (Control)
Test for heterogeneity: $Chi^2 = 6.73$, df = 5 (P = 0.24), $I^2 = 25.7\%$
Test for overall effect: Z = 0.83 (P = 0.41)



(RR= 0.79, 95% CI 0.16, 3.92, p = 0.77)
3 trauma, 3 burn, 2 mixed

Glutamine and Infectious Compilations



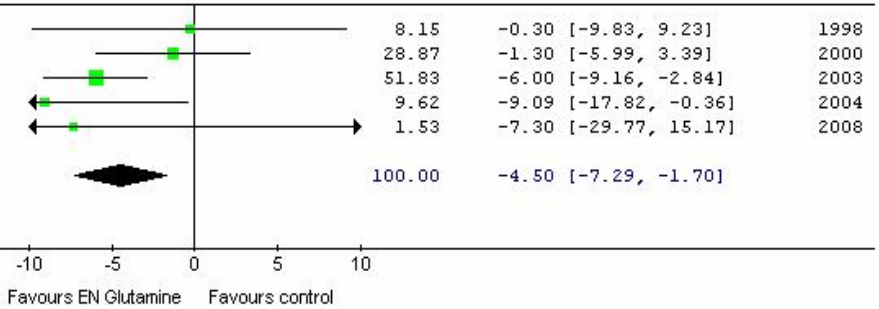
- 1 mixed ICU, 1 trauma, 1 burn

Glutamine and LOS

Review: glutamine New review (Version 01)
Comparison: 01 Enteral Glutamine vs Control
Outcome: 02 Hospital LOS

Study or sub-category	Enteral Glutamine N	Enteral Glutamine Mean (SD)	Control N	Control Mean (SD)	Weight %	WMD (random) 95% CI	Year
Houdijk	35	32.70(17.10)	37	33.00(23.80)	8.15	-0.30 [-9.83, 9.23]	1998
Brantley	31	19.50(8.80)	41	20.80(11.50)	28.87	-1.30 [-5.99, 3.39]	2000
Zhou	20	67.00(4.00)	20	73.00(6.00)	51.83	-6.00 [-9.16, -2.84]	2003
Peng	25	46.59(12.98)	23	55.68(17.36)	9.62	-9.09 [-17.82, -0.36]	2004
McQuiggan	10	32.00(13.60)	10	39.30(33.60)	1.53	-7.30 [-29.77, 15.17]	2008
Total (95% CI)	121		131		100.00	-4.50 [-7.29, -1.70]	

Test for heterogeneity: $Chi^2 = 4.51$, df = 4 (P = 0.34), $I^2 = 11.3\%$
Test for overall effect: Z = 3.15 (P = 0.002)



(WMD -4.50, 95% CI -7.29, -1.70, p= 0.002)

3 trauma, 2 burn

Critical Care Nutrition Guidelines Glutamine

Conclusions:

- 1) **Omega-3 Fatty Acids** have been shown to be effective in Pts with ARDS
- 2) **Agrinine** has no improvement on mortality, reduction of infections or length of hospital stay
- 3)**Glutamine** supplemented enteral nutrition may be associated with a reduction in mortality in burn patients
- 4) **Glutamine** supplemented enteral nutrition may be associated with a reduction in infectious complications in burn and trauma patients.
- 5) **Glutamine** supplemented enteral nutrition is associated with a significant reduction in hospital length of stay in burn and trauma patients.

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