Medicine and Health Sciences
Geneeskunde en Gesondheidswetenskappe
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METABOLIC DYSREGULATION IN CRITICAL CARE: HOW TO OVERCOME?

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UNIVERSITEIT STELLENBOSCH UNIVERSITY

PN Critical Care Webcast: December 2016

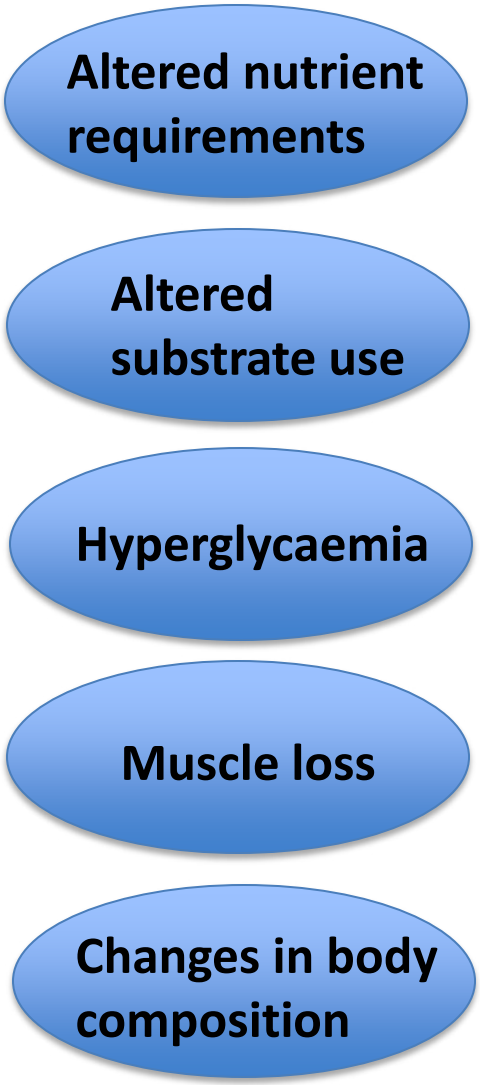
CONFLICT OF INTEREST

- I regularly give lectures that are organized by Fresenius Kabi and Nestlé Nutrition Institute Africa
- I serve on the Advisory Board for Fresenius Kabi, South Africa
- I provide consultancy work for ASPEN, Future Life, Fresenius Kabi and Nestlé Nutrition Institute Africa
- I received an unconditional grant for research from Fresenius Kabi
- I declare no conflict of interest which might have interfered with the scientific validity of this presentation

INTRODUCTION

Metabolic response to stress in critical illness:

- Phased response
- Acute phase effects
  - Changes in energy expenditure
  - Changes in substrate utilization
  - Anabolic resistance
  - Increased protein breakdown
- Persistent inflammation

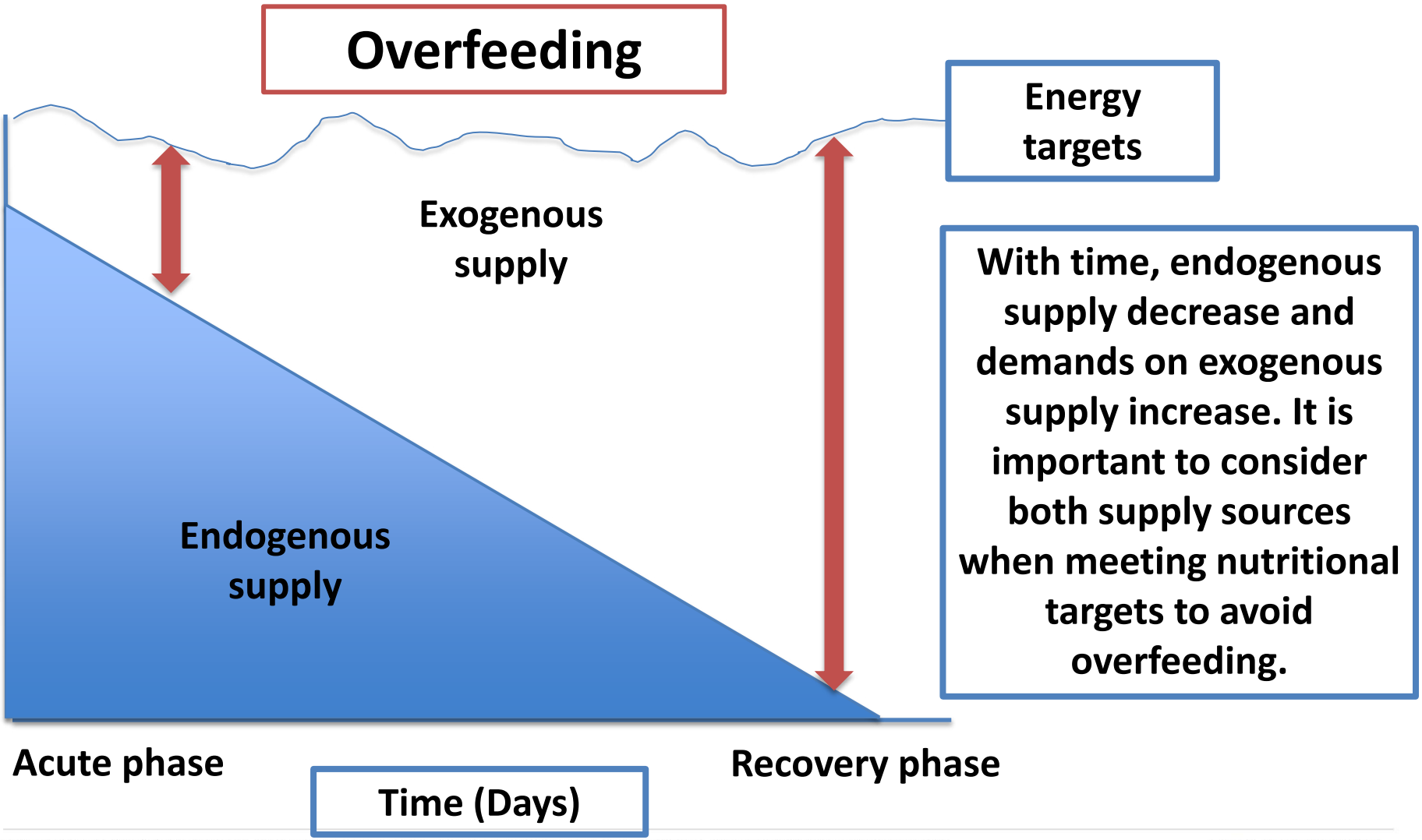


DIETARY MANIPULATION OF DYSREGULATION

- Altered nutrient requirements
- Altered substrate use
- Hyperglycaemia
- Muscle loss
- Changes in body composition

- Energy requirements
- Specific nutrient needs
  - Protein/ Amino acids
    - Glutamine
  - Lipids
    - Omega-3 fatty acids
  - Micronutrients
    - Vitamins and trace elements
    - Antioxidants

SUBSTRATE SUPPLY



ENERGY REQUIREMENTS

- Indirect calorimetry vs Predictive equations vs Simplistic equations
- **ESPEN[1,2]**
  - Acute and initial phase: 20 – 25 kcal/kg/day
  - Recovery phase: 25 – 30 kcal/kg/day
- **ASPEN[3]**
  - High risk or severely undernourished: ≤20 kcal/kg/day
  - 25 – 30 kcal/kg/day (normal BMI)
  - 11-14 kcal/kg actual body weight/ day for BMI = 30-50
  - 22-25 kcal/kg ideal body weight/ day for BMI >50

1 Singer P et al. Clin Nutr 2009 **2** Singer P et al. Clin Nutr 2014 **3** McClave S et al. JPEN 2016

Re-evaluate continuously

PROTEIN REQUIREMENTS

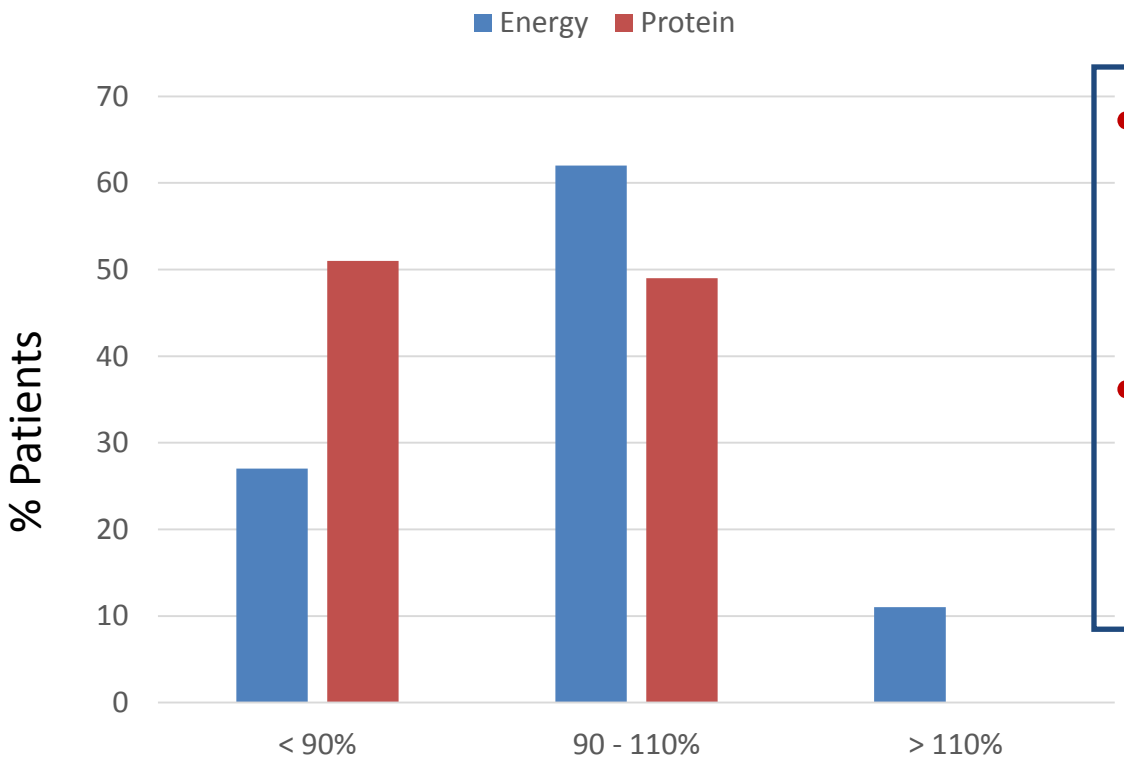
- **ESPEN[1,2]**
  - 1.3 -1.5 g/kg ideal / actual body weight / day
- **ASPEN[3]**
  - 1.2 – 2.0 g/kg actual body weight/day for BMI <30
  - ≥ 2.0 g/kg ideal body weight/ day for BMI 30-40
  - ≤ 2.5 g/kg ideal body weight/ day for BMI ≥40

Disease-specific

1 Singer P et al. Clin Nutr 2009 **2** Singer P et al. Clin Nutr 2014 **3** McClave S et al. JPEN 2016

PERCENTAGE TARGETS ACHIEVED

- N=71 mixed ICU patients, Johannesburg, South Africa
- Median Energy intake = 26 kcal/kg/day
- Protein intake = 1.1 g/kg/day



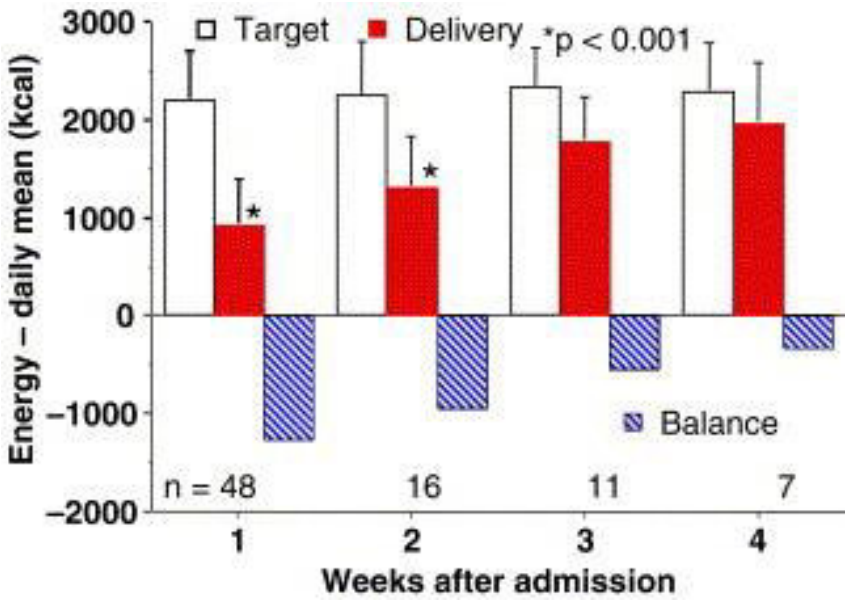
- **1 in 2 patients not meeting protein targets**
- **1 in 4 patients not meeting energy targets**

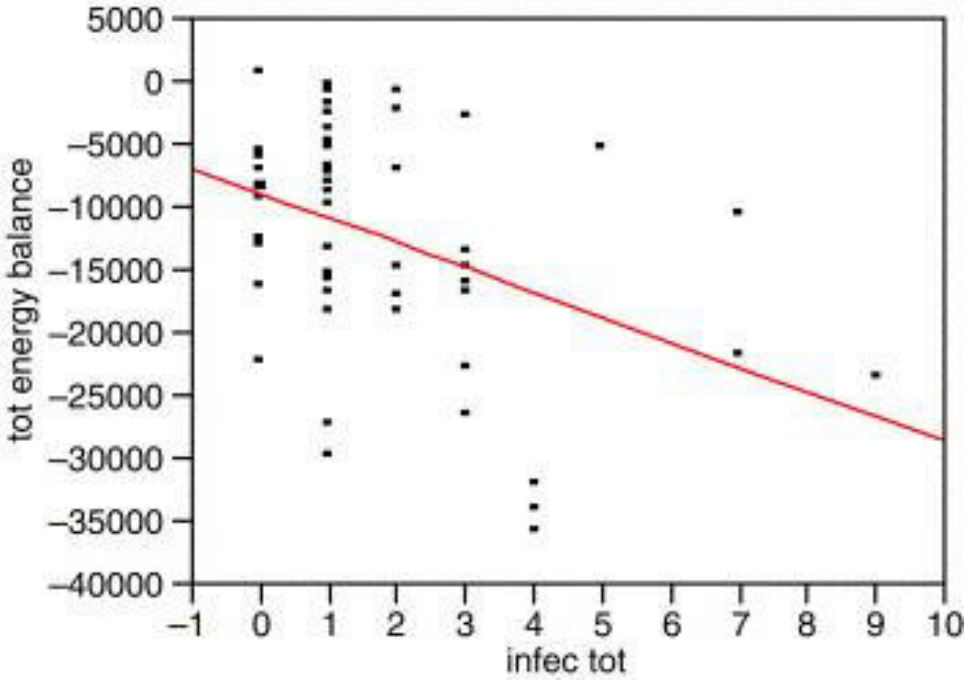
Veldsman et al, Nutr J 2016

Correlation between nutritional intake and clinical ICU outcome

- Prospective study in surgical ICU
- N = 48
- Average energy requirements:
- 29 ± 7 kcal/kg/d

- Largest deficit during first week
- Cumulated deficits correlated with complications
- Cannot be compensated for





Villet et al. Clin Nutr 2005

Correlation between nutritional intake and clinical ICU outcome

- N=886 mechanically-ventilated patients admitted to ICU
- Energy requirements = Indirect calorimetry
- Protein requirements: > 1.2 g/kg/d

Table 3. Relationship Between Nutrition Therapy and Intensive Care Unit, 28-Day, and Hospital Mortality[a]

	Protein and Energy Target	Energy Target
Model 0[b]		
Intensive care unit	0.91 (0.64–1.31), P = .626	1.03 (0.86–1.25), P = .733
28 d	0.59 (0.40–0.88), **P = .010**	0.90 (0.74–1.09), P = .291
Hospital	0.76 (0.58–0.99), **P = .041**	0.93 (0.81–1.08), P = .339
Model 1[c]		
Intensive care unit	0.79 (0.54–1.17), P = .242	0.99 (0.81–1.20), P = .886
28 d	0.51 (0.33–0.78), **P = .002**	0.84 (0.68–1.03), P = .085
Hospital	0.70 (0.53–0.94), **P = .017**	0.91 (0.79–1.06), P = .233
Model 2[d]		
Intensive care unit	0.72 (0.48–1.09), P = .116	0.98 (0.80–1.19), P = .834
28 d	0.40 (0.26–0.64), **P < .001**	0.79 (0.64–0.97), **P = .024**
Hospital	0.62 (0.46–0.84), **P = .002**	0.89 (0.77–1.04), P = .137

Weijs et al. JPEN 2012

Correlation between nutritional intake and clinical ICU outcome

- N=886 mechanically-ventilated patients admitted to ICU
- Energy requirements = Indirect calorimetry
- Protein requirements: > 1.2 g/kg/d

Not meeting Protein <u>and</u> Energy targets were significantly correlated with:

- **28 day mortality**
- **Hospital mortality**

Weijs et al. JPEN 2012

ENERGY AND PROTEIN COMBINATION

Clinical Nutrition 35 (2016) 968–974

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Opinion paper

Protein-energy nutrition in the ICU is the power couple: A hypothesis forming analysis

Taku Oshima [a, 1], Nicolaas E. Deutz [b, 2], Gordon Doig [c, 3], Paul E. Wischmeyer [d], Claude Pichard [e, *]

INFLAMMATORY RESPONSE

An appropriate response

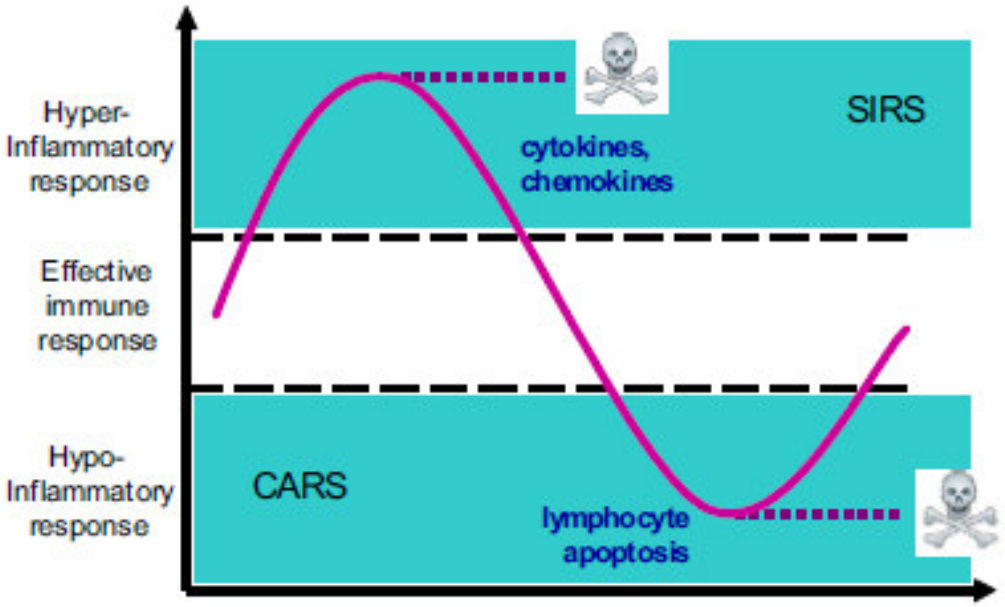
- Fights infection
- Coordinates metabolic response
- Supports wound healing

An inappropriate response

- Exaggerated inflammation
- Excessive production of free radicals

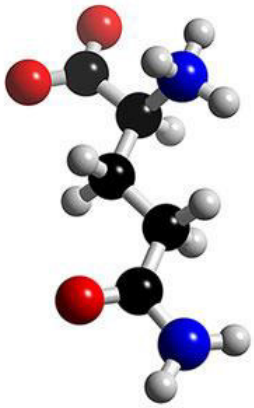
  and / or

- Immunosuppression
  - Increased risk of superinfection



Ott et al, Prostagl Leukotr Ess FA 2011

GLUTAMINE

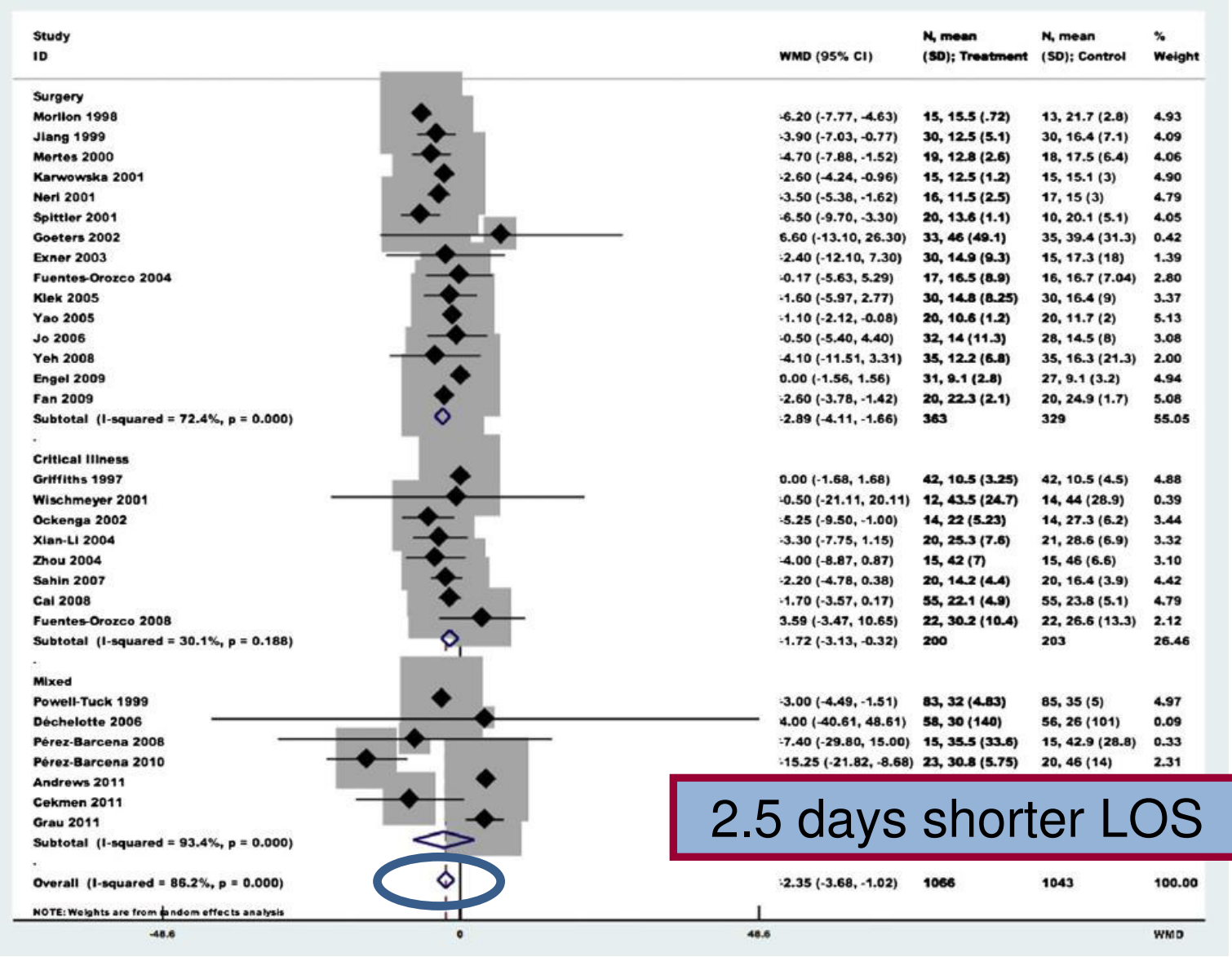


- Non essential amino acid
- Most abundant free amino acid
- Conditionally essential during periods of stress
  - Increased requirements
  - Adequate stores for 24-48 hr
- Major surgery / critical illness

↓ plasma levels →

- Immune dysfunction
- Increased mortality
- Indicator of poor outcome

Parenteral GLN and Hospital LOS in critically ill and patients undergoing major surgery



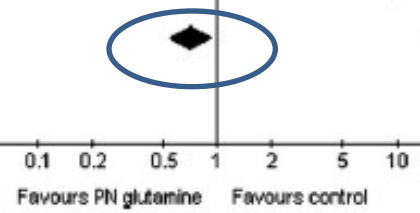
Bollhalder et al 2013

Parenteral glutamine and overall mortality in critically ill patients

Table 4
Effect of parenteral glutamine on mortality

Study or Sub-category	PN Glutamine (n/N)	Control (n/N)	Weight (%)	RR (Random) (95% CI)	Year
Griffiths	18/42	25/42	35.43	0.72 (0.47, 1.11)	1997
Powell-Tuck	14/83	20/85	17.40	0.72 (0.39, 1.32)	1999
Wischmeyer	2/15	5/16	2.98	0.43 (0.10, 1.88)	2001
Fuentes-Orozco	2/17	3/16	2.39	0.63 (0.12, 3.28)	2004
Xian-Li	0/20	3/21	0.77	0.15 (0.01, 2.73)	2004
Dechelotte 2006	2/58	2/56	1.76	0.97 (0.14, 6.62)	2006
Palmese	6/42	8/42	6.96	0.75 (0.28, 1.97)	2006
Sahin	2/20	6/20	3.00	0.33 (0.08, 1.46)	2007
Cai	17/55	20/55	23.44	0.85 (0.50, 1.44)	2008
Duska	2/10	0/10	0.77	5.00 (0.27, 92.62)	2008
Estivariz	1/32	6/31	1.54	0.16 (0.02, 1.27)	2008
Fuentes-Orozco 2008	2/22	5/22	2.79	0.40 (0.09, 1.85)	2008
Luo 2008	0/11	0/9		Not estimable	2009
Perez-Barcena	3/15	0/15	0.79	7.00 (0.39, 124.83)	2009
Total (95% CI)	442	440	100.00	0.71 (0.55, 0.92)	

Total events: 71 (PN glutamine), 103 (control)
Test for heterogeneity: $\chi^2 = 9.84$, $df = 12$ ($P = .63$), $I^2 = 0\%$
Test for overall effect: $z = 2.63$ ($P = .008$)

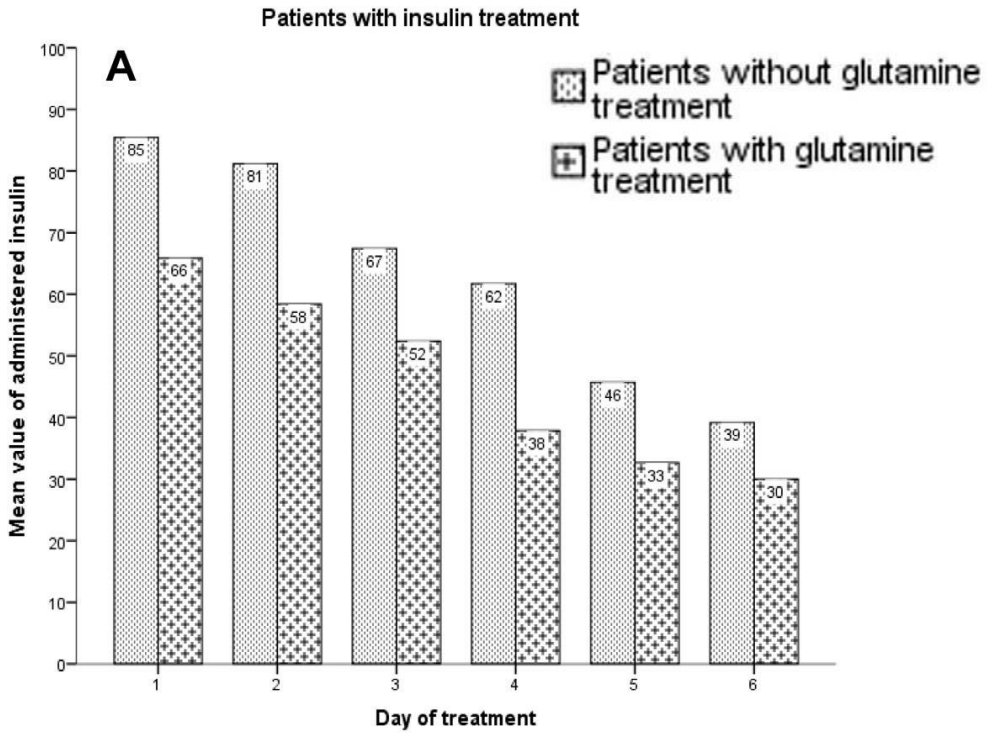


29% reduction in mortality

Weitzel et al 2010

Parenteral glutamine in critically ill patients
Glucose control

- N=82 critically ill trauma patients
- i.v. Ala-Gln (0.5 g/kg/d) supplemented vs. isocaloric, isonitrogenous standard nutritional support



Gln group:

- Only 37% vs. 51% in the control group **required exogenous insulin**
- Glucose levels, though not significantly lower than in the control group, showed less variability

Grintescu et al, 2015

- Lowering mean daily insulin requirements (63 vs 44 U/d, p = 0.0407)

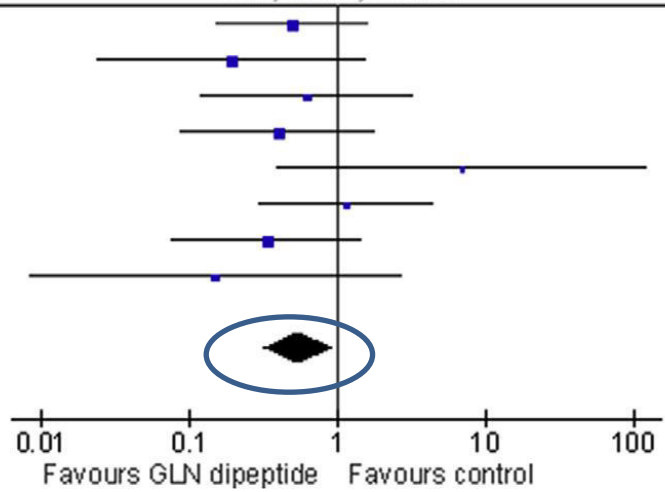
Parenteral glutamine in critically ill patients

- Lower total infectious complication rate (RR 0.70, p<0.0001)
- ~1.5 days shorter LOS in the ICU (MD -1.61, p=0.04)
- 1.5 days shorter duration of mechanical ventilation (MD -1.56, p=0.02)
- Lower hospital mortality (RR 0.55, p=0.03)

	Glutamine dipeptide		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Cekmen et al. 2011	3	15	6	15	18.6%	0.50 [0.15, 1.64]
Estivariz et al. 2008	1	30	5	29	15.7%	0.19 [0.02, 1.56]
Fuentes-Orozco et al. 2004	2	17	3	16	9.6%	0.63 [0.12, 3.28]
Fuentes-Orozco et al. 2008	2	22	5	22	15.5%	0.40 [0.09, 1.85]
Perez-Barcena et al. 2008	3	15	0	15	1.5%	7.00 [0.39, 124.83]
Perez-Barcena et al. 2010	4	23	3	20	9.9%	1.16 [0.29, 4.57]
Sahin et al. 2007	2	20	6	20	18.6%	0.33 [0.08, 1.46]
Xian-Li et al. 2004	0	20	3	21	10.6%	0.15 [0.01, 2.73]
Total (95% CI)		**162**		**158**	**100.0%**	**0.55 [0.32, 0.94]**
Total events	17		31			

Heterogeneity: $Chi^2 = 6.52$, df = 7 (P = 0.48); $I^2 = 0\%$

Test for overall effect: Z = 2.20 (P = 0.03)



Stehle et al, 2016, Clinical Nutrition

FATTY ACIDS

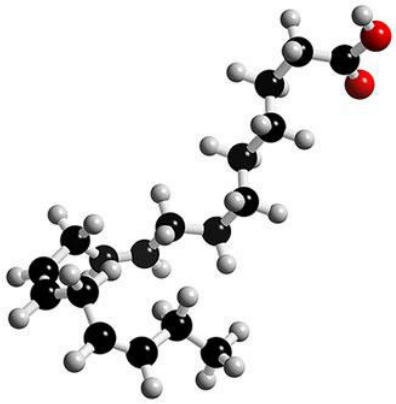
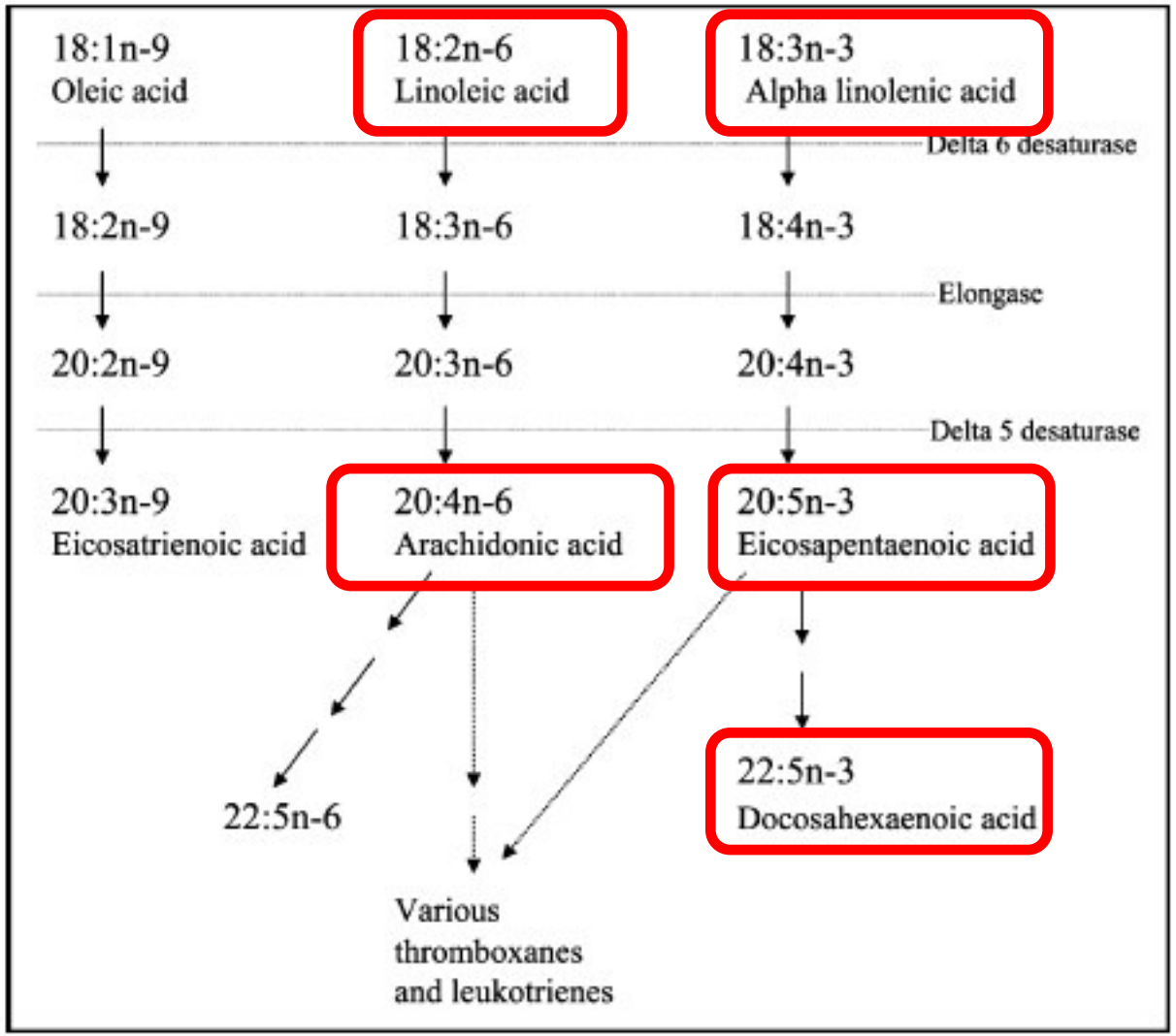


Figure 1. Parallel pathways of polyunsaturated fatty acid metabolism



McCowen & Bistrian 2005

OMEGA-3 FATTY ACIDS

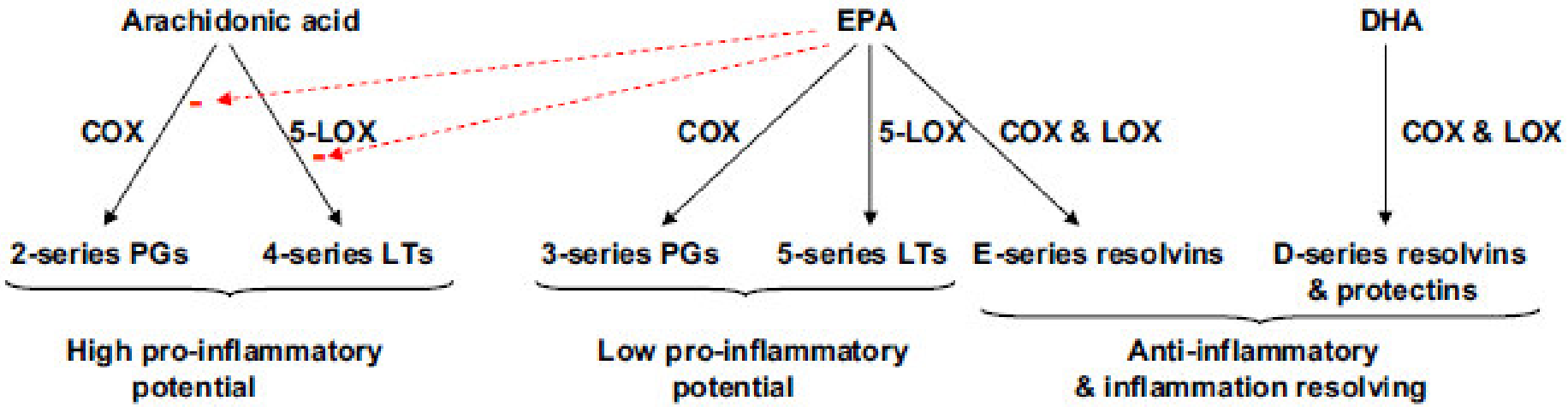


Fig. 4. General overview of the synthesis of lipid mediators from arachidonic acid, EPA and DHA and of their effects on inflammation.

Calder, 2010

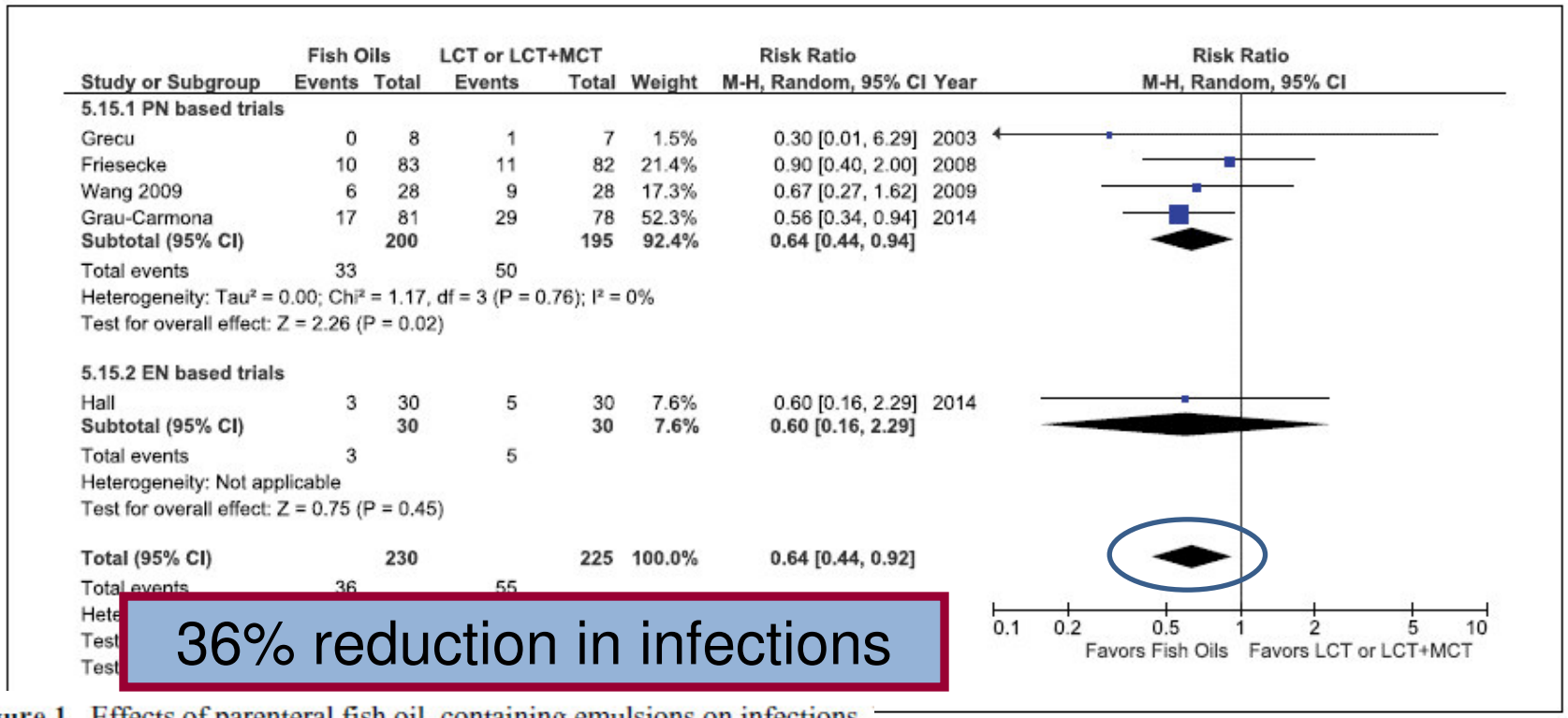
Manzanares et al. Critical Care (2015) 19:167
DOI 10.1186/s13054-015-0888-7

CRITICAL CARE

RESEARCH Open Access

Intravenous fish oil lipid emulsions in critically ill patients: an updated systematic review and meta-analysis

William Manzanares[1*], Pascal L Langlois[2], Rupinder Dhaliwal[3], Margot Lemieux[3] and Daren K Heyland[3,4]



36% reduction in infections

Figure 1. Effects of parenteral fish oil–containing emulsions on infections.

N-3 FATTY ACID ENRICHED LIPID EMULSIONS

n-3 fatty acid-enriched parenteral nutrition regimens in elective surgical and ICU patients: a meta-analysis

Lorenzo Pradelli[1*], Konstantin Mayer[2], Maurizio Muscaritoli[3] and Axel R Heller[4]

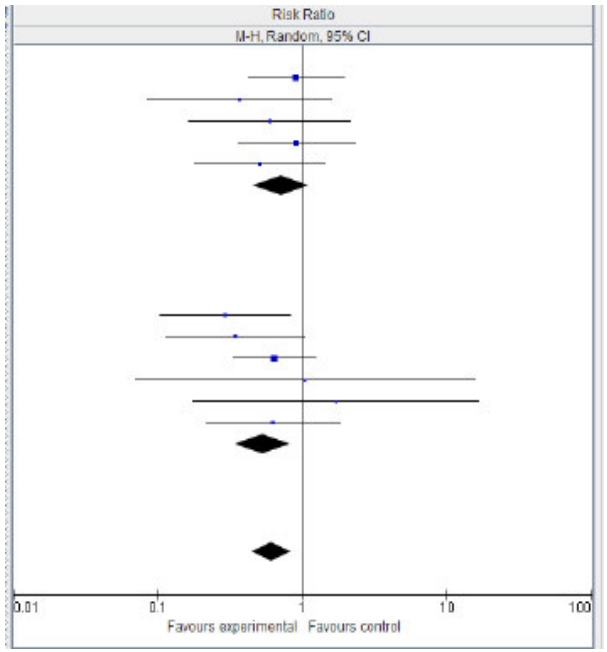
Critical Care 2012, **16**:R184

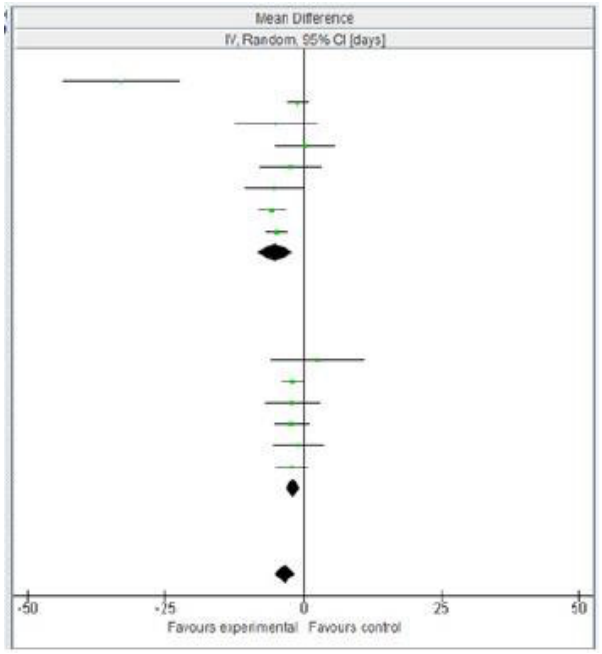
- Meta-analysis on 23 RCT's to evaluate omega-3 enriched PN regimens in elective surgery and ICU patients
- n=1502 patients
- Parenteral omega-3 containing lipid emulsions vs other lipid emulsions without omega-3 fatty acids from fish oil

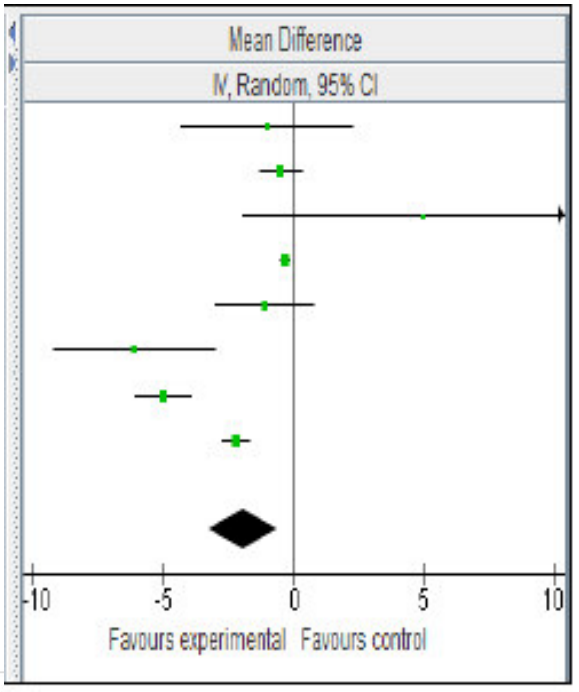
N-3 FATTY ACID ENRICHED LIPID EMULSIONS

Omega-3 fatty acid enriched lipid emulsions associated with significant reductions in:

Infection rate (39%)	Hospital LOS (3.29 days)	ICU LOS (1.92 days)







Pradelli et al, 2012

IVFE RECOMMENDATIONS

- **Recommended Dosage and Expert Opinions**
  - 0.7 – 1.5 (2) g lipids/kg/day[1,2]
  - Omega-6 : 3 FA ratio = 2:1 to 3:1[3]
  - Fish oil: 0.1 – 0.2 g/kg/day[4]
  - Infusion time: 12-24 hours

1 Singer P et al. Clin Nutr 2009 2 Vanek VW et al Nutr Clin Pract 2012 **3** Mayer K. et al. 2006 **4** Heller et al Crit Care 2006

MICRONUTRIENTS

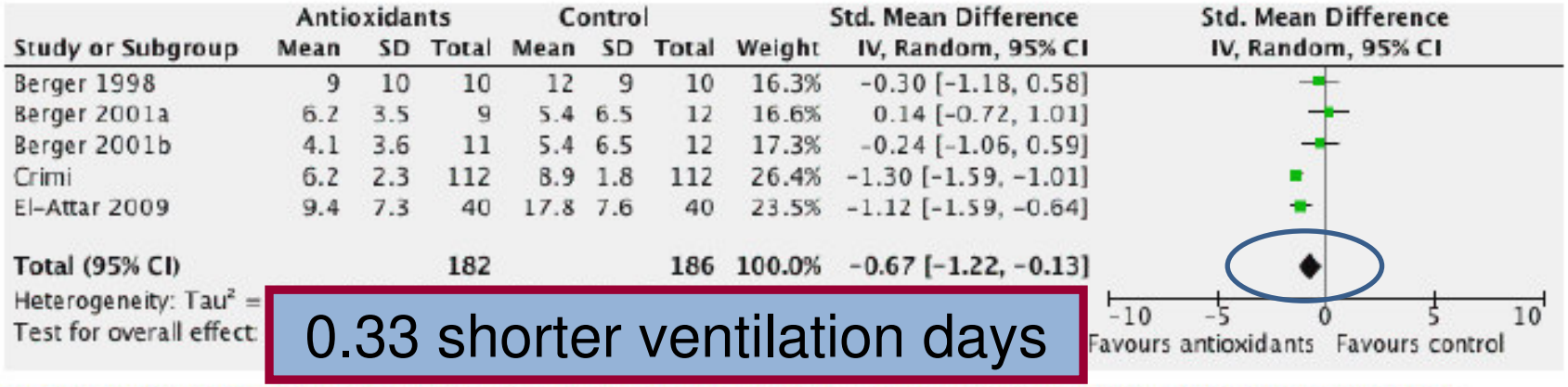
Manzanares *et al. Critical Care* 2012, **16**:R66
http://ccforum.com/content/16/2/R66

CRITICAL CARE

RESEARCH Open Access

Antioxidant micronutrients in the critically ill: a systematic review and meta-analysis

William Manzanares[1], Rupinder Dhaliwal[2], Xuran Jiang[2], Lauren Murch[2] and Daren K Heyland[2,3*]



Study or Subgroup	Antioxidants Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Berger 1998	9	10	10	12	9	10	16.3%	-0.30 [-1.18, 0.58]
Berger 2001a	6.2	3.5	9	5.4	6.5	12	16.6%	0.14 [-0.72, 1.01]
Berger 2001b	4.1	3.6	11	5.4	6.5	12	17.3%	-0.24 [-1.06, 0.59]
Crimi	6.2	2.3	112	8.9	1.8	112	26.4%	-1.30 [-1.59, -1.01]
El-Attar 2009	9.4	7.3	40	17.8	7.6	40	23.5%	-1.12 [-1.59, -0.64]
Total (95% CI)			182			186	100.0%	-0.67 [-1.22, -0.13]

Heterogeneity: Tau² =
Test for overall effect:

Std. Mean Difference IV, Random, 95% CI

-10 -5 0 5 10
Favours antioxidants Favours control

0.33 shorter ventilation days

Figure 3 Effect of combined antioxidant therapy on ventilation days (n = 4). RR, risk ratio; 95% CI, 95% confidence intervals.

Nutrition 27 (2011) 745–758

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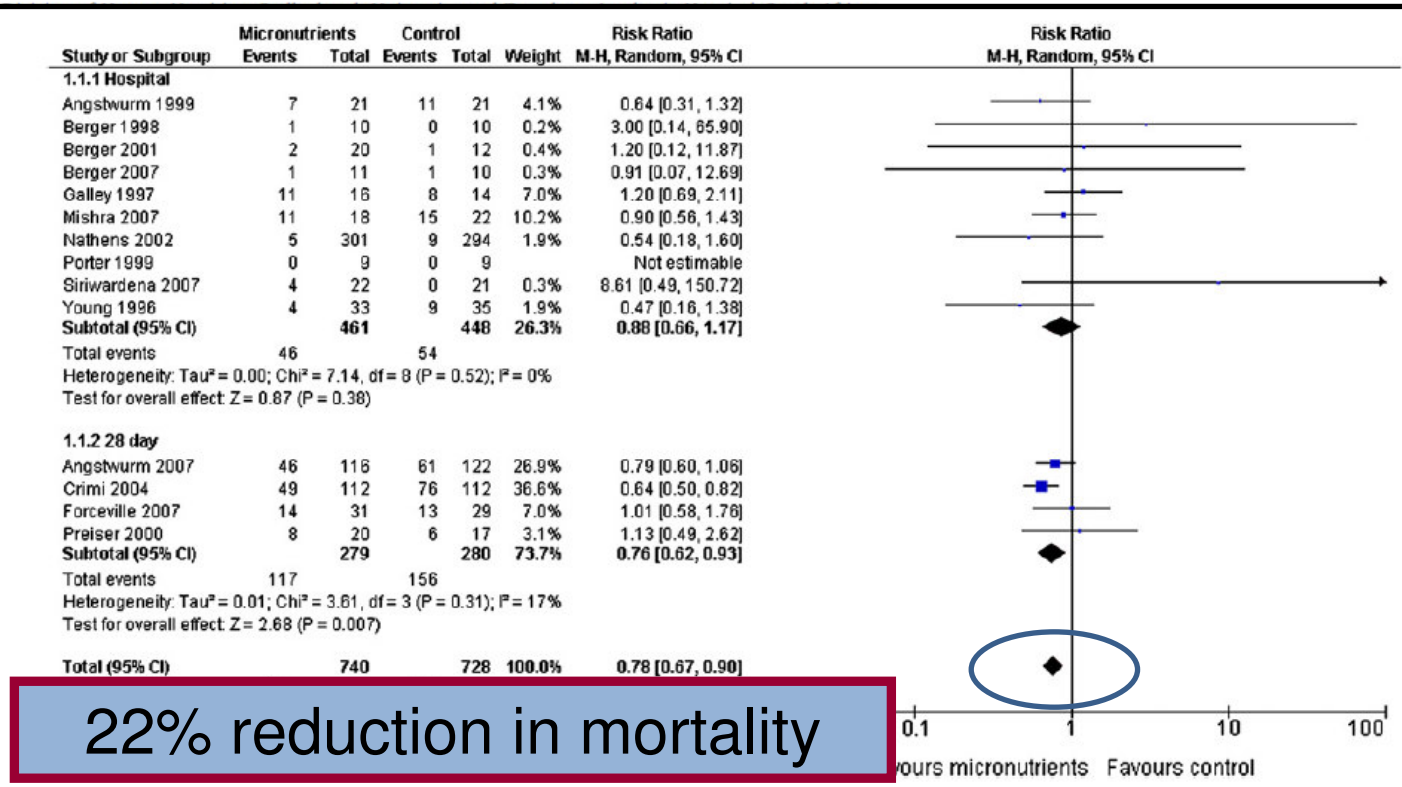
journal homepage: www.nutritionjrnl.com

Review

Micronutrient supplementation for critically ill adults: A systematic review and meta-analysis

Janicke Visser M.Nutr. [a,*], Demetre Labadarios M.B.Ch.B., Ph.D. [b], Renée Blaauw Ph.D. [a]



22% reduction in mortality

Fig. 3. Effect of micronutrient supplementation on overall mortality in critically ill patients. CI, confidence interval; M-H, Mantel-Haenszel method.

MICRONUTRIENT RECOMMENDATIONS

- **Recommendations**
  - All PN prescriptions should include a daily dose of multivitamins and trace elements[1]
  - Combinations of antioxidant vitamins and trace elements should be provided to patients requiring specialized nutrition therapy[2]

1 Singer P et al. Clin Nutr 2009, 2 McClave S et al. JPEN 2016

TAKE HOME MESSAGES

1. Nutrition is dynamic and exciting
2. Metabolic dysregulation can be altered through nutrition.
3. Nutrition prescription should be adapted according to patient needs and clinical condition.
4. *One size does not fit all* – Individualize approaches are needed