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President of HKSPEN

UPDATE ON USE OF PARENTERAL PHARMACO-NUTRIENTS IN THE CRITICALLY ILL

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Disclosure

UNIL | Université de Lausanne

Grants:	BBraun, Fresenius Kabi
Lecturer:	Baxter, BBraun, Fresenius Kabi, Nestlé Nutrition
Advisory board:	Baxter, Fresenius Kabi, Medtronic
Bonds or other:	none

canton de vaud

CHUV

Issues to integrate in nutrition plan

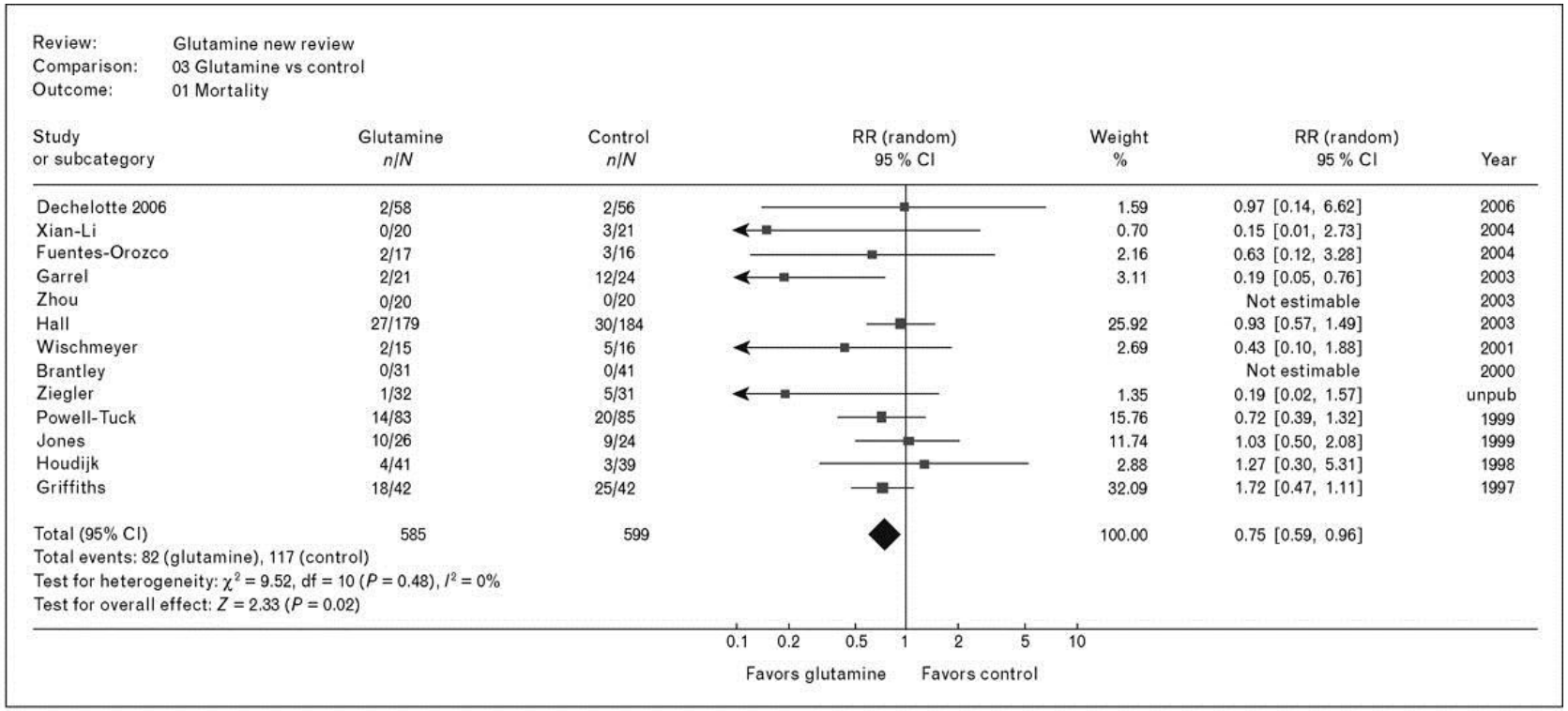
- Hemodynamic stability
- Route of feeding: enteral? … I.V.?
- Energy requirements
- Proteins: 1.3-1.5 g/d
- Fat quantity & quality
- Micronutrients

Pharmaco-nutrition?
A new paradigm? Jones & Heyland 2008

• Glutamine	PN (EN trauma burns)
• Antioxidants – particularly selenium	critically ill
• Fish oil	ARDS
• Arginine	no

Pharmaconutrition: a new emerging paradigm.

Jones & Heyland Curr. Opin. Gastroenterology. 24(2):215-222, 2008.

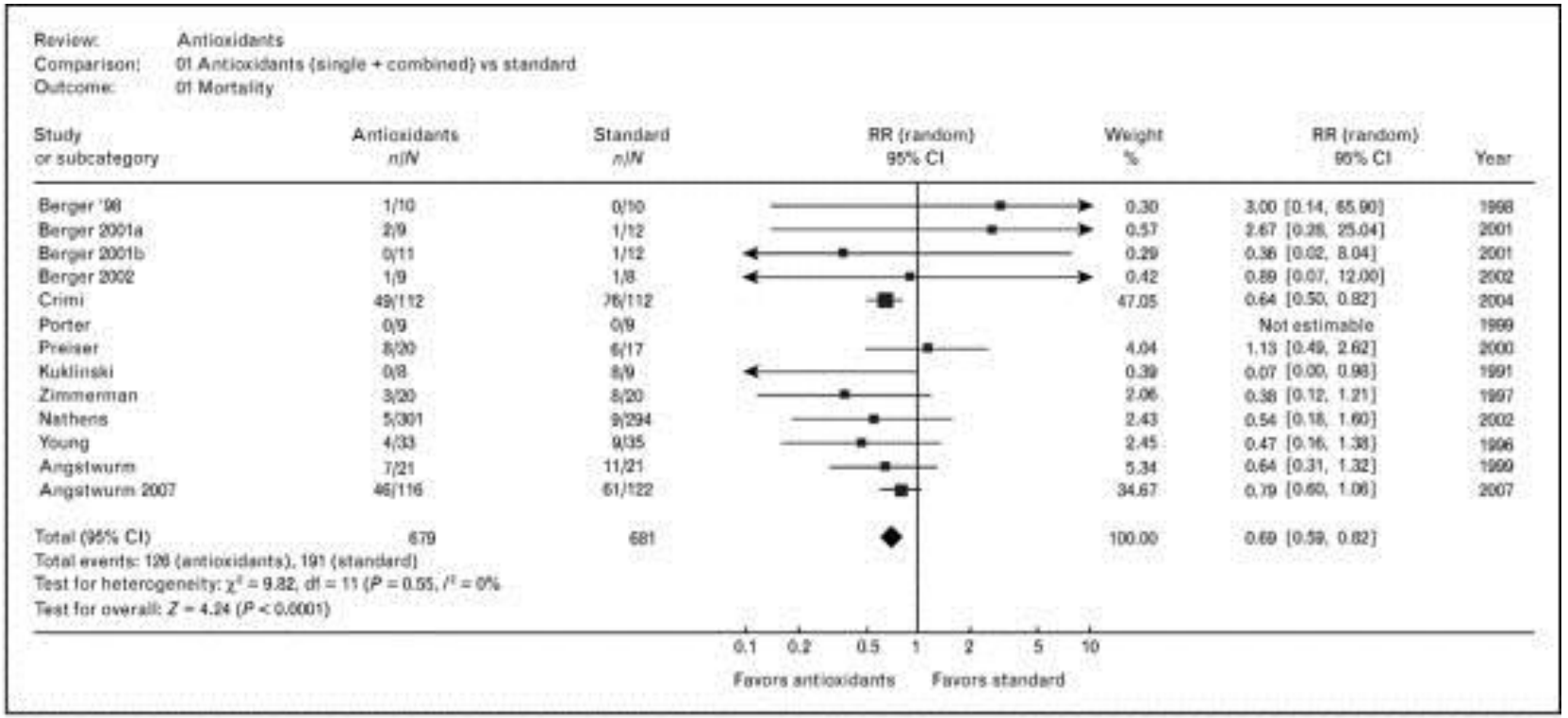


n/*N*, number of patients that die/total number of patients in group.

Figure 2 Risk ratio (RR) and associated 95% CIs for the effect of glutamine supplementation (enteral and parenteral) on mortality in critically ill patients

Pharmaconutrition: a new emerging paradigm.

Jones & Heyland Curr. Opin. Gastroenterology. 24(2):215-222, 2008.

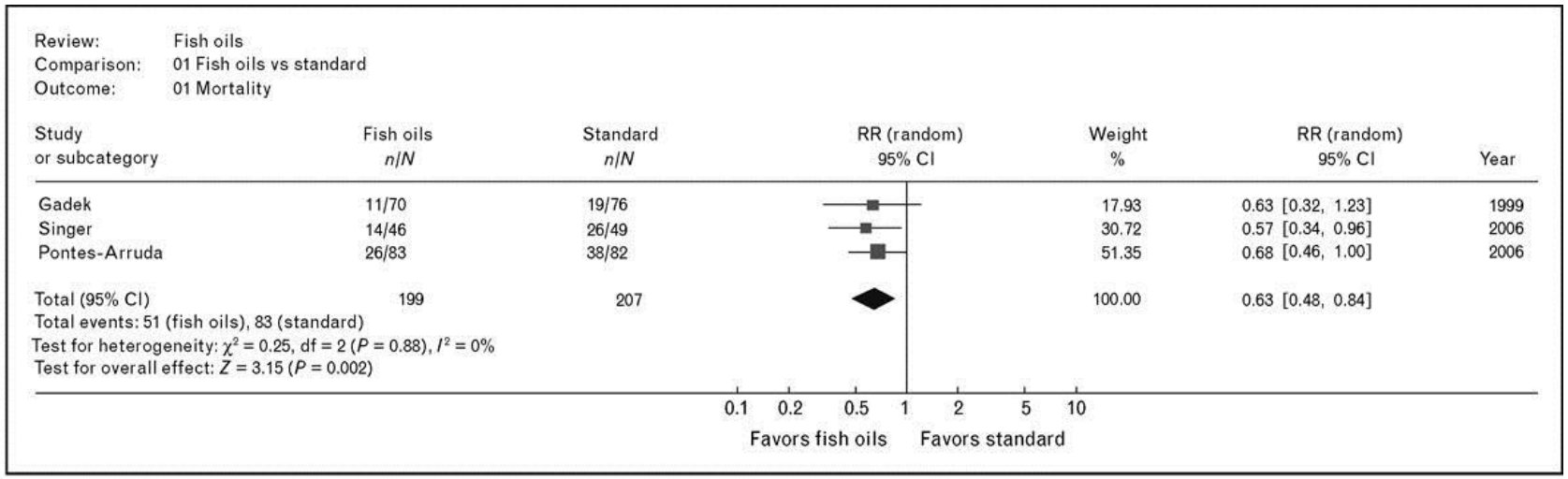


n/N, number of patients that die/total number of patients in group.

Figure 3 Risk ratio (RR) and associated 95% CIs for the effect of antioxidant supplementation on mortality in critically ill patients

Pharmaconutrition: a new emerging paradigm.

Jones & Heyland Curr. Opin. Gastroenterology. 24(2):215-222, 2008.



n/*N*, number of patients that die/total number of patients in group.

Figure 4 Risk ratio (RR) and associated 95% CIs for the effect of enteral formulas enriched with fish oils, borage oils and antioxidants on mortality in patients with acute respiratory distress syndrome

In 2008 Jones & Heyland concluded that the paradigm of immunonutrition had failed to consistently demonstrate a beneficial effect of key immunomodulating nutrients

? And where are we in ….

Confusion why?

The dogma of PRCT being the Gral

PRCTs are the only studies integrated in meta-analyses

Vincent JL Crit Care Med, 2010:38:S534

"We should abandon randomized controlled trials in the ICU and favor cohort trials, which represent real life"

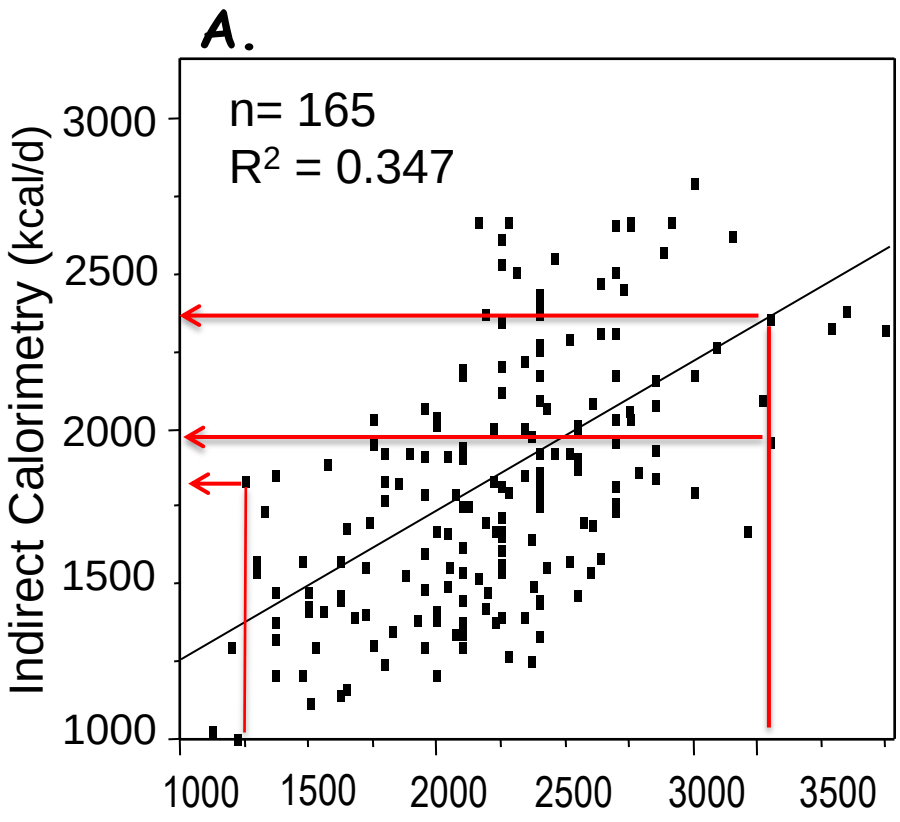
A little excessive probably ☺

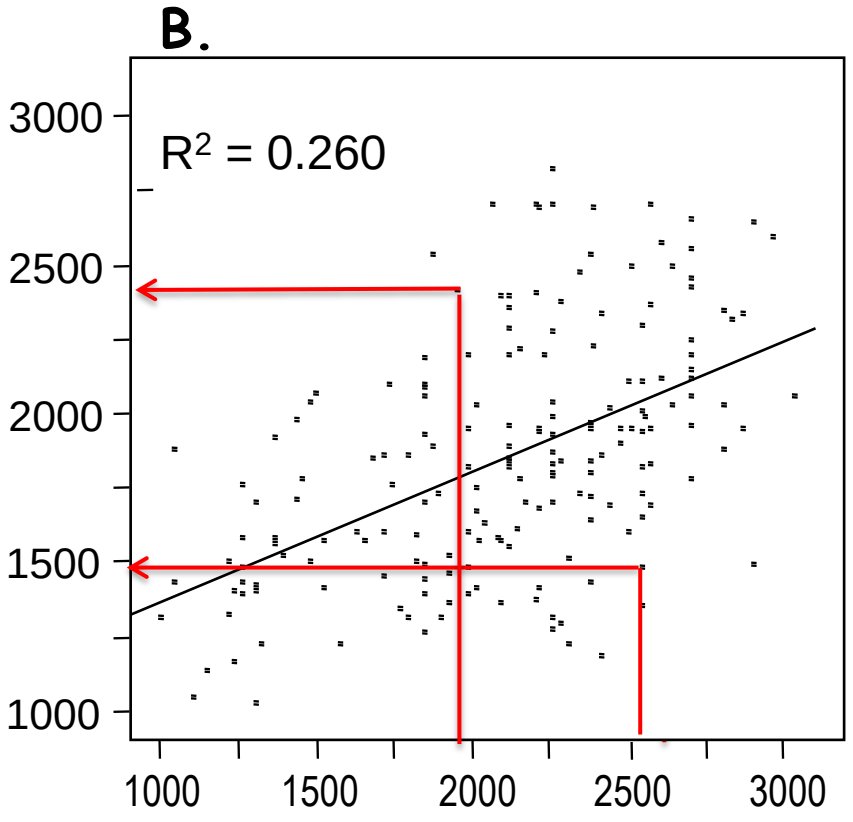
but we should consider both types of studies

Confusion from PRCT: why?

- Energy targets based on equations → favours overfeeding with PN
- PRCT → Over-selected patient population
- Practice problem (bolus…)
- Confounding nutrition & pharmacology
- Absence of monitoring → intended intervention not realized

SPN: Comparison of Energy Target set by
- Equation (25-30 kcal/kg)
- Indirect calorimetry





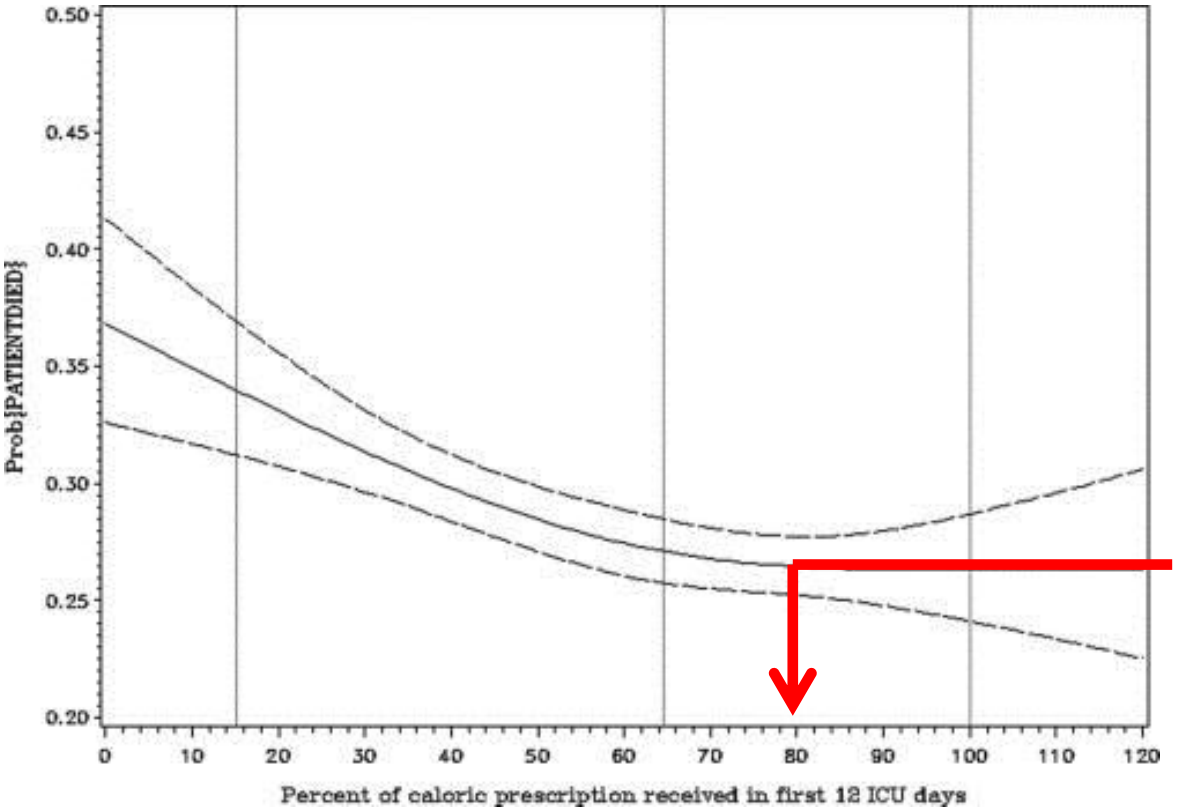
Jolliet et al 1998

Heidegger et al, Lancet 2013; 381: 385

Optimal amount of calories for critically ill patients: Depends on how you slice the cake!

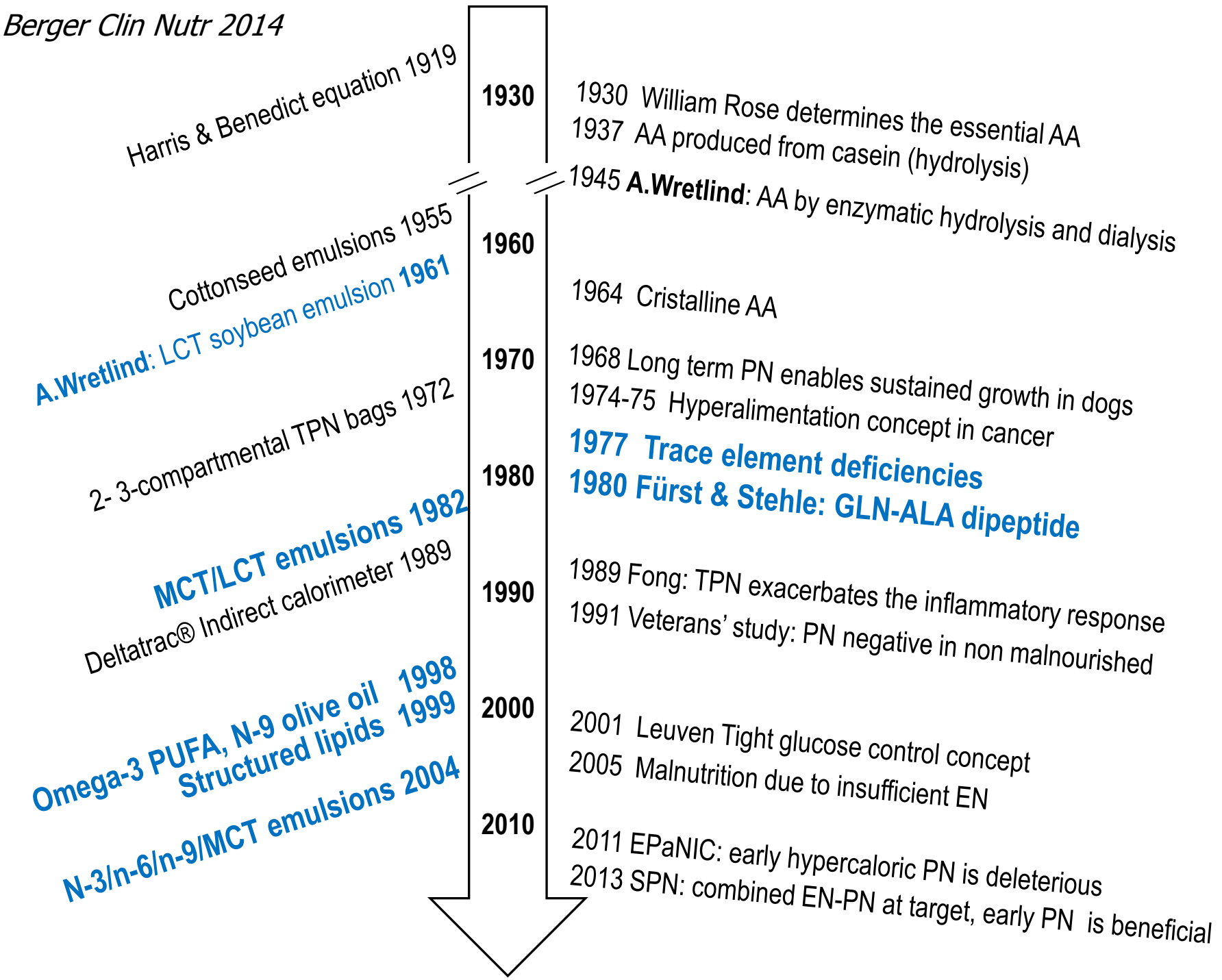
Heyland et al, CCM 2011: 39: 2619

7,872 mechanically ventilated, critically ill patients who remained in the ICU for at least 96 hrs
52 ICUs, 33 countries



Association between 12-day average % of prescribed calories received and 60-day hospital mortality using restriction C without adjustment for covariates.

Solid line is the model fit by a restricted cubic spline with knots placed at the 5th , 50th , and 95th percentiles. Dashed lines = 95% confidence bands, horizontal lines = location of the knots


Berger Clin Nutr 2014
Harris & Benedict equation 1919
1930
1930 William Rose determines the essential AA
1937 AA produced from casein (hydrolysis)
1945 A.Wretlind: AA by enzymatic hydrolysis and dialysis
Cottonseed emulsions 1955
1960
A.Wretlind: LCT soybean emulsion 1961
1964 Cristalline AA
2- 3-compartmental TPN bags 1972
1970
1968 Long term PN enables sustained growth in dogs
1974-75 Hyperalimentation concept in cancer
1977 Trace element deficiencies
MCT/LCT emulsions 1982
1980
1980 Fürst & Stehle: GLN-ALA dipeptide
Deltatrac® Indirect calorimeter 1989
1990
1989 Fong: TPN exacerbates the inflammatory response
1991 Veterans' study: PN negative in non malnourished
Omega-3 PUFA, N-9 olive oil 1998
Structured lipids 1999
2000
2001 Leuven Tight glucose control concept
2005 Malnutrition due to insufficient EN
N-3/n-6/n-9/MCT emulsions 2004
2010
2011 EPaNIC: early hypercaloric PN is deleterious
2013 SPN: combined EN-PN at target, early PN is beneficial

ESPEN Guidelines on Enteral Nutrition: Intensive care

Kreymann G et al, Clin Nutr 2006

Glutamine should be added to standard enteral formula in

- burned patients — A
- trauma patients — A

There are not sufficient data to support glutamine supplementation in surgical or heterogenous critically ill patients.

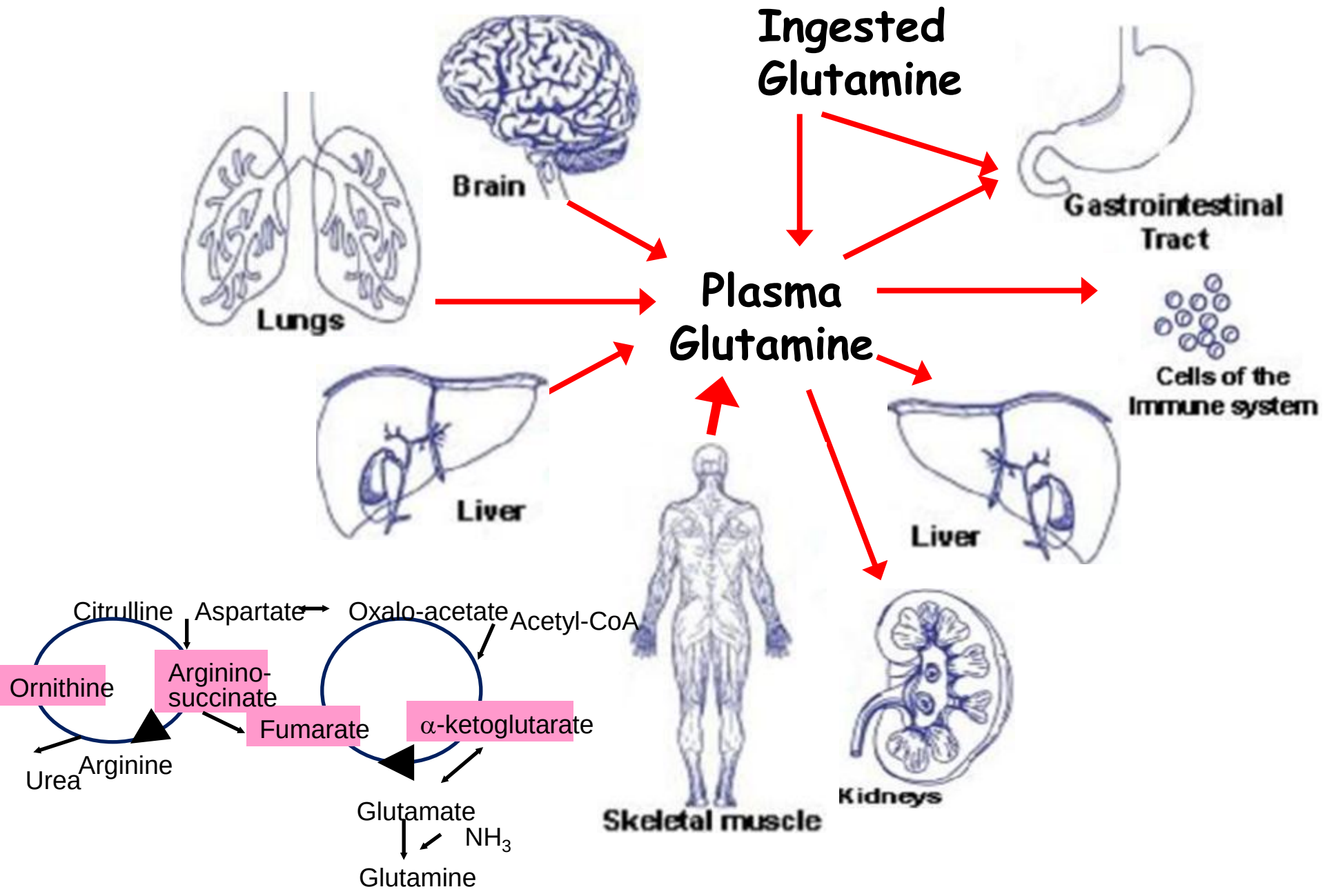
ESPEN Guidelines on Parenteral Nutrition: Intensive care

Singer P et al Clin Nutr 2009

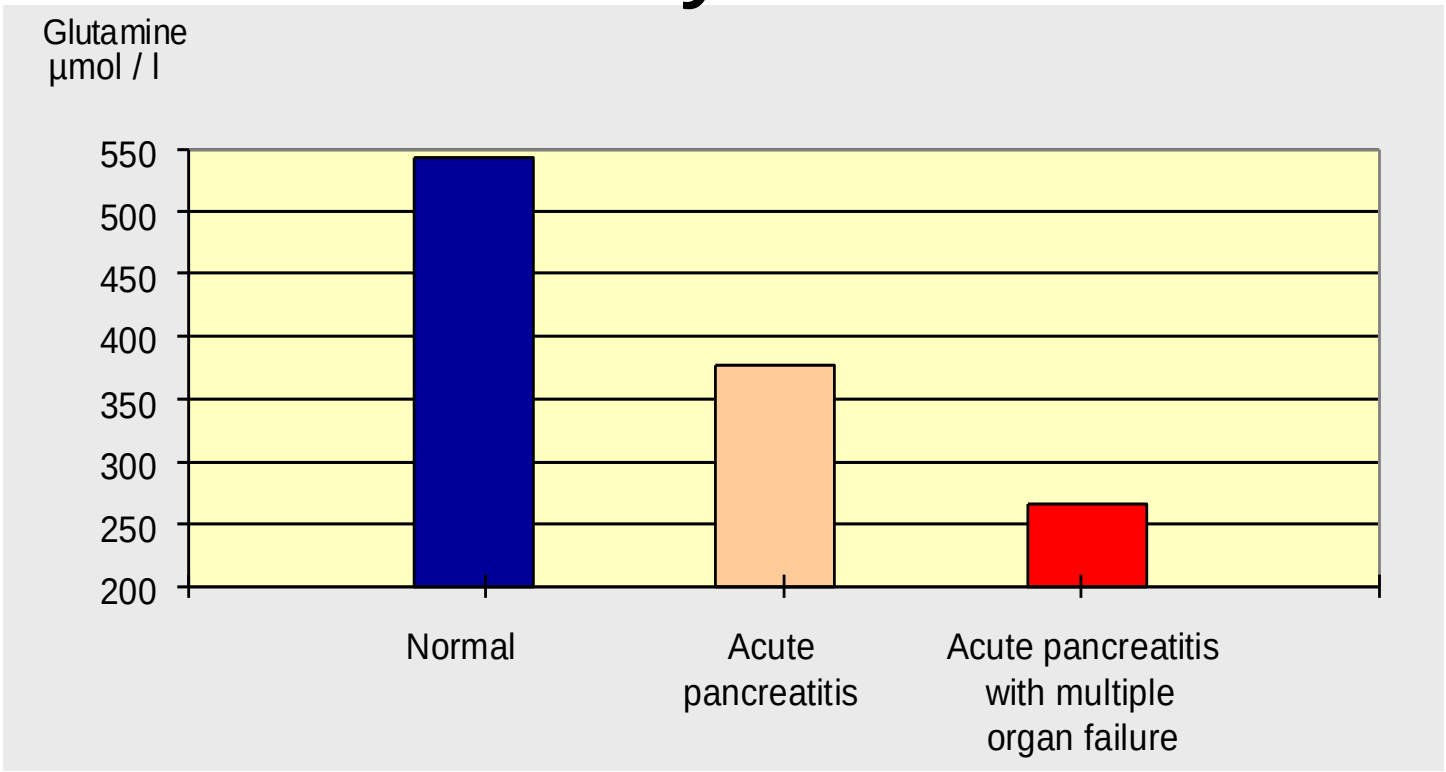
When PN is indicated, a balanced amino acid mixture should be infused at approximately 1.3–1.5 g/kg ideal body weight/day in conjunction with an adequate energy supply. — B

When PN is indicated in ICU patients the amino acid solution should contain 0.2–0.4 g/kg/day of L-glutamine (e.g. 0.3–0.6 g/kg/day alanyl-glutamine dipeptide). — A

Glutamine circuit – the most important nitrogen shuttle



Glutamine depletion in plasma – and severity of disease[1]

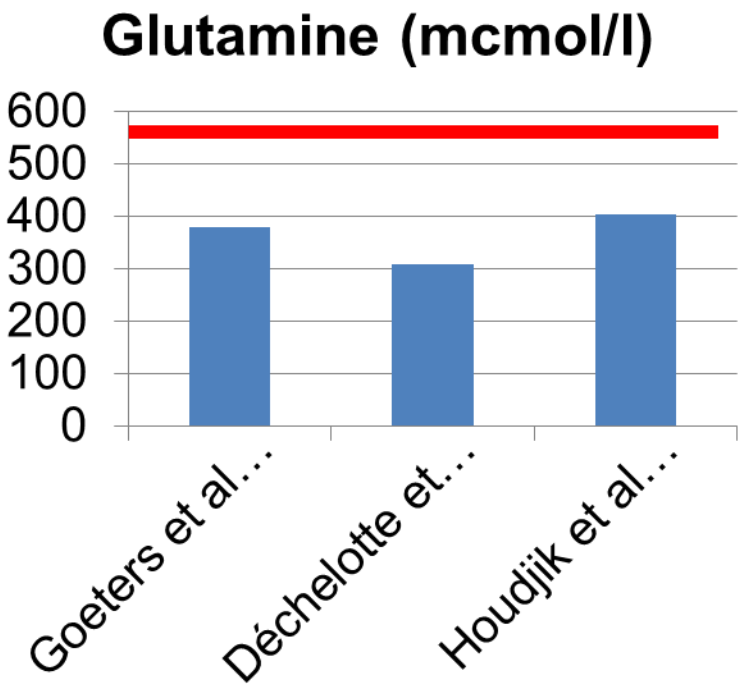


⇨ The sicker the patient the higher the glutamine demand

⇨ Low plasma glutamine at admission to ICU associated with a risk of poor outcome.[2]

[1] **Roth** et al. 1986, [2] **Oudemans-Van Straaten** et al. 2001

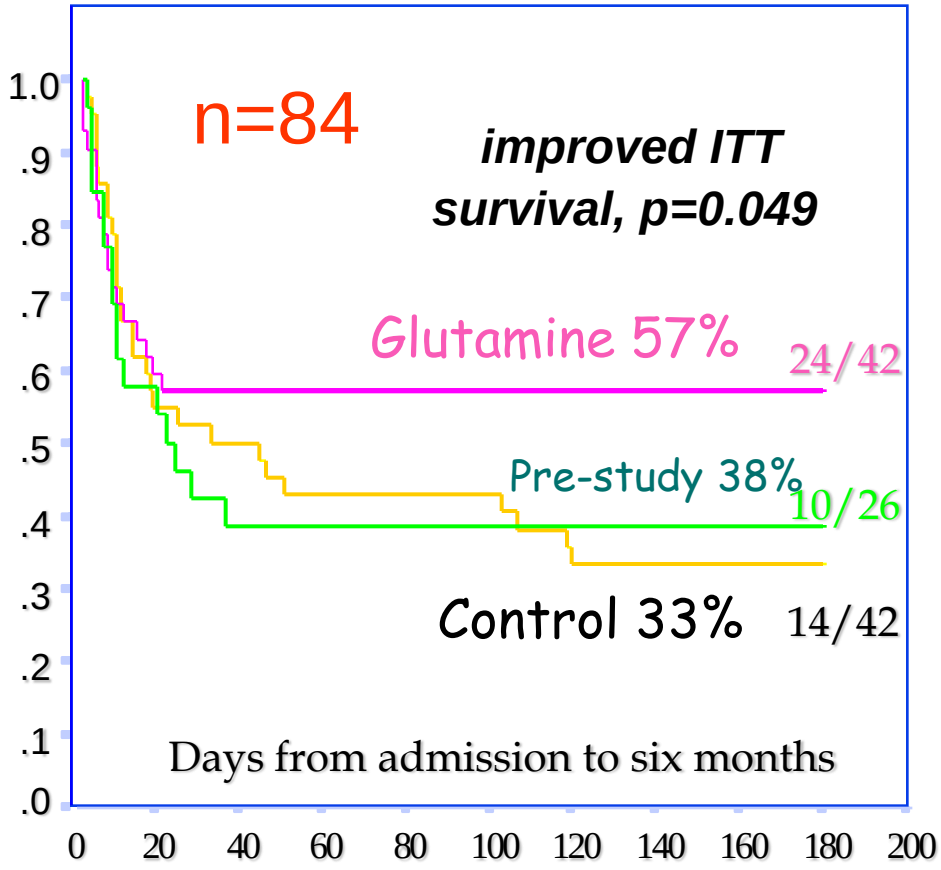
Critical illness is associated with low plasma levels in most patients



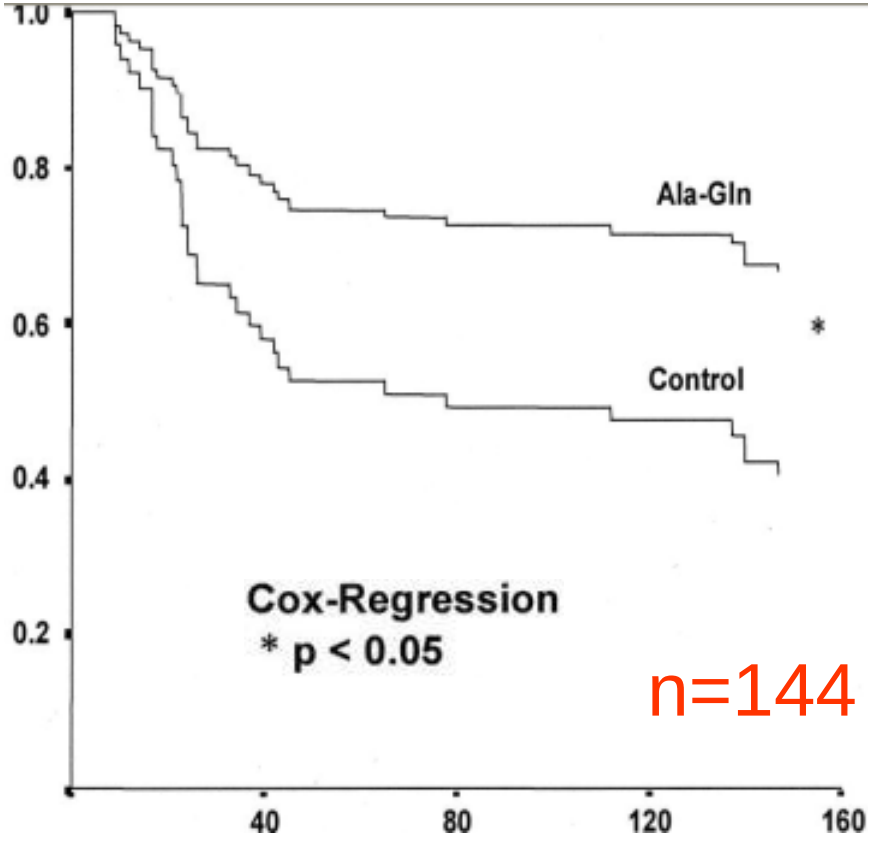
Critical illness		
Bone marrow TX	Brown et al 1998 Mc Burney et al 1994	Schloerb et al 1999 Schloerb et al 1993 Ziegler et al 1992
Sepsis Trauma Burns	Griffiths et al 1997 Houdjik er al 1998 Jensen et al 1996 Jones et al 1999 Schelting et al 1991	Newsholme et al 1987 Powell-tuck et al 1999 Rennie et al 1985 Roth et al 1990 Tremel et al 1994
Acute pancreatitis	Roth et al 1986	
Chemotherapy	Decker-Baumann et al 1989	
Surgical patients	Hammarquvist et al 1989 Jrang et al 1999 Morillon et al 1996	O'Riordin et al 1994 Stehle et al 1989

Evidence of improved survival outcome with IV glutamine

Griffiths et al. Nutrition 1997; 13:295-302
Griffiths et al. Nutrition 2002; 18:546-552



Goeters C et al
Crit Care Med 2002;30(9):2032-7



REDOXS

Critical Care Nutrition

Heyland et al, NEJM 2013

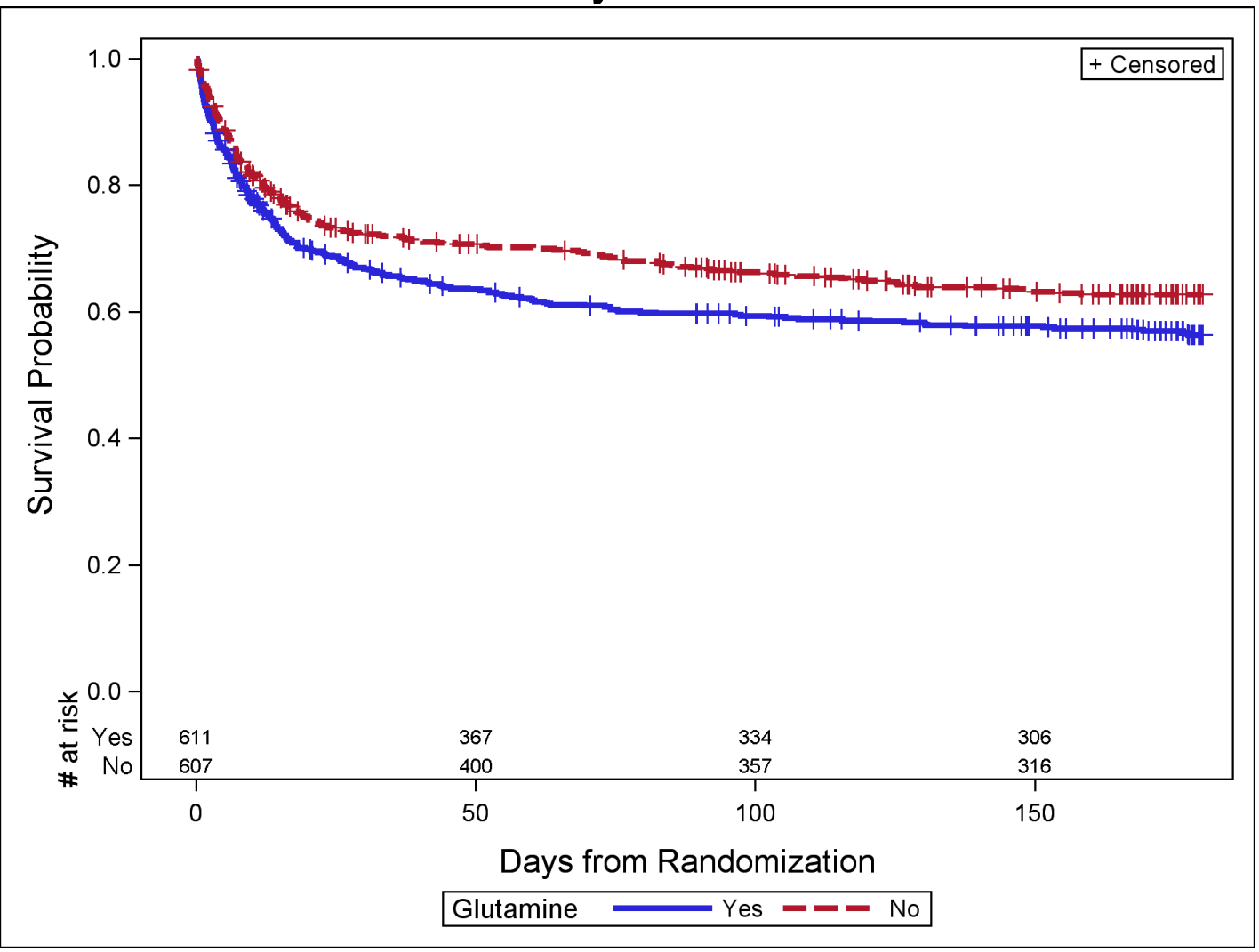
PRCT: April 2005 and December 2011 in 40 ICUs in participating countries
Factorial design

n=1218

Patient Characteristics	PLACEBO	GLN	AOX	AOX+GLN
n	**300**	**301**	**307**	**310**
Inclusion criteria				
A PaO_2/FiO_2 ratio ≤300	282 (94.0%)	285 (94.7%)	287 (93.5%)	285 (91.9%)
Clinical evidence of hypo-perfusion	277 (92.3%)	278 (92.4%)	286 (93.2%)	293 (94.5%)
Renal dysfunction	104 (34.7%)	117 (38.9%)	99 (32.2%)	122 (39.4%)
Platelet count of ≤50 x 10^9/L	16 (5.3%)	21 (7.0%)	12 (3.9%)	18 (5.8%)
Hours in ICU prior to randomization†	17.9	17.7	18.4	18.0
n	**300**	**301**	**307**	**310**
First organ dysfunction to initiation of parenteral supplements (hours)†	22.3 [16.5 to 26.5]	21.0 [14.8 to 25.0]	21.1 [16.0 to 25.5]	21.5 [16.3 to 26.0]
First organ dysfunction to initiation of EN (hours)†	22.0 [12.5 to 36.8]	21.0 [11.1 to 35.0]	20.4 [12.0 to 34.8]	20.0 [11.8 to 36.2]

REDOXS: A randomized trial of high dose Glutamine and Antioxidants in critically ill patients with MOF

Heyland et al, NEJM 2013



Kaplan-Meier 6 Month Survival curves

n=1218

Glutamine vs no-GLN 0.78 g/kg/d

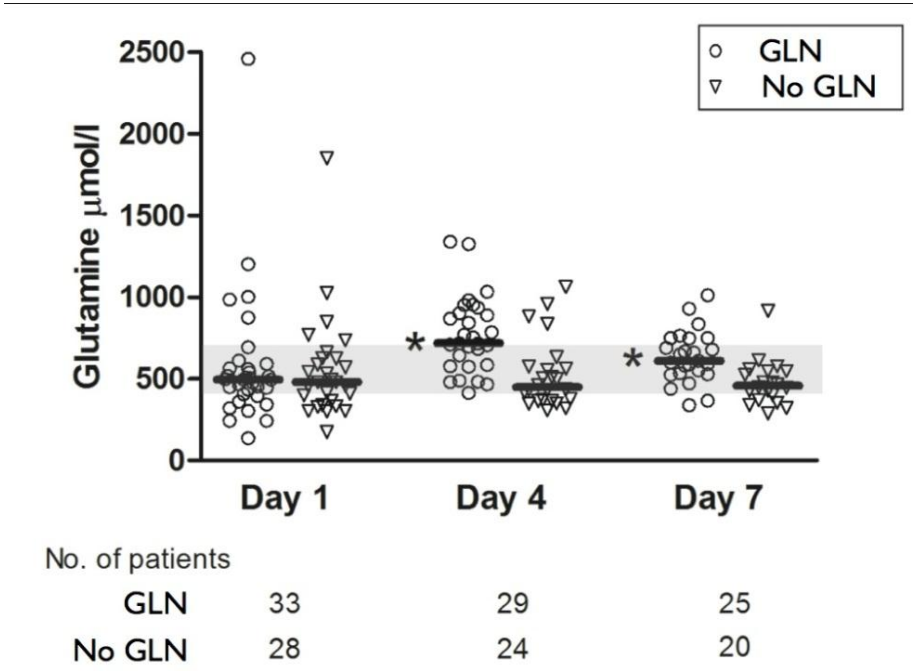
Critical Care Nutrition

Specificities of REDOXS

- Extremely sick: ≥ 2 failures , inlcuding 35 % with ARF
- Total Dose 0.78 g/kg > recommendations
- Very early administration of full GLN dose WITHOUT nutrition: mean US nutrition = 40% of target
- Predictors ofe mortality: >2 failures, renal failuree, <30% nutrition delivery, steroids, vasopressors

Glutamine: why didn't it "work"?

- SIGNET: **insufficient** GLN dose (<12g/d) for short time
- REDOXS: **highest** dose ever 0.78 g/kg/d very early (<24) during shock phase, **no deficit**
- **sickest patients ever** and not balanced



≥3 organ failures

424	187	Gln	n = 611
459	148	0 Gln	n = 607

Chi^2 P = 0.015

- No Glutamine deficit on day 1

Bollhalder et al Clin Nutr, 2013;32:213

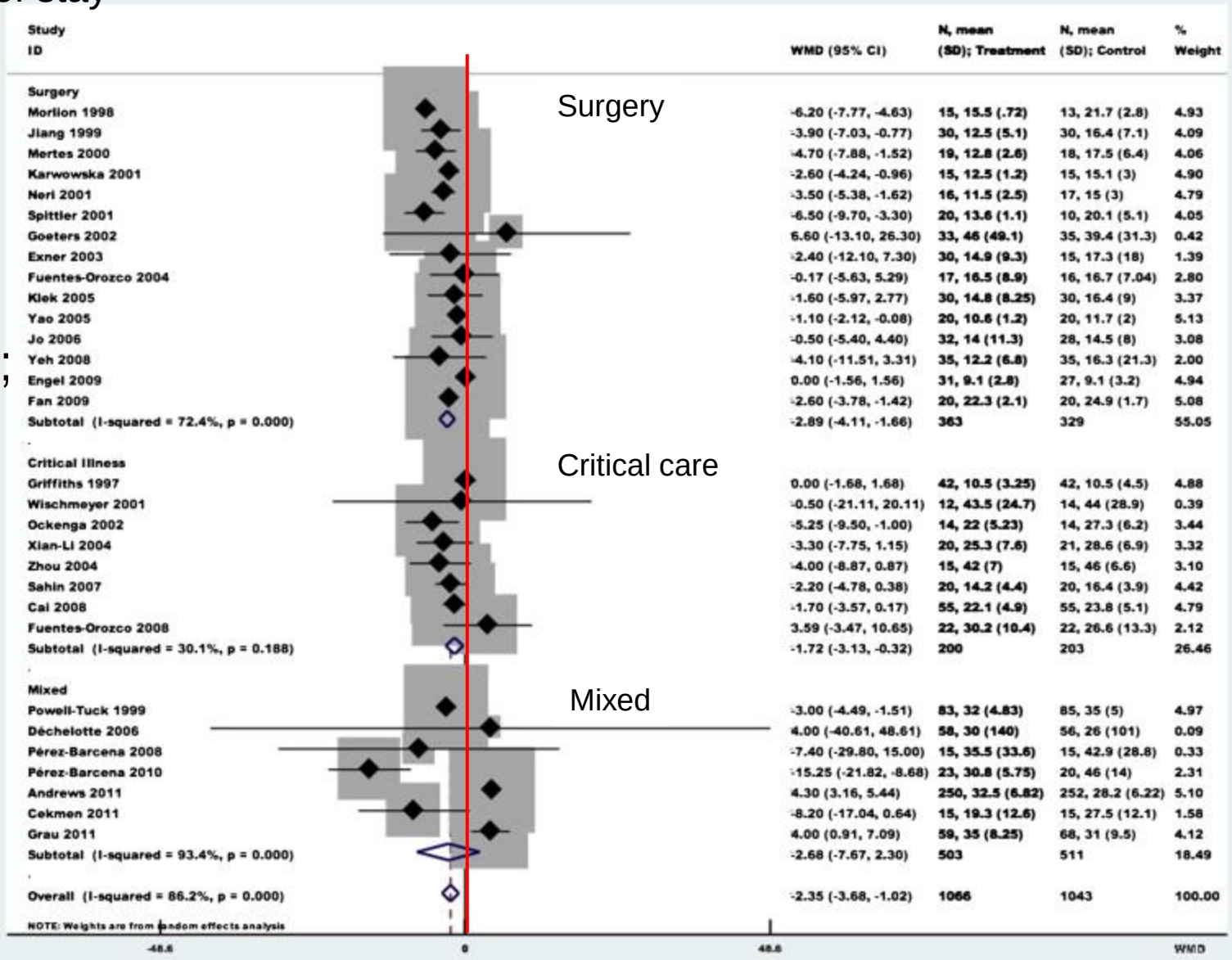
Hospital length of stay

−2.45 days

95%CI

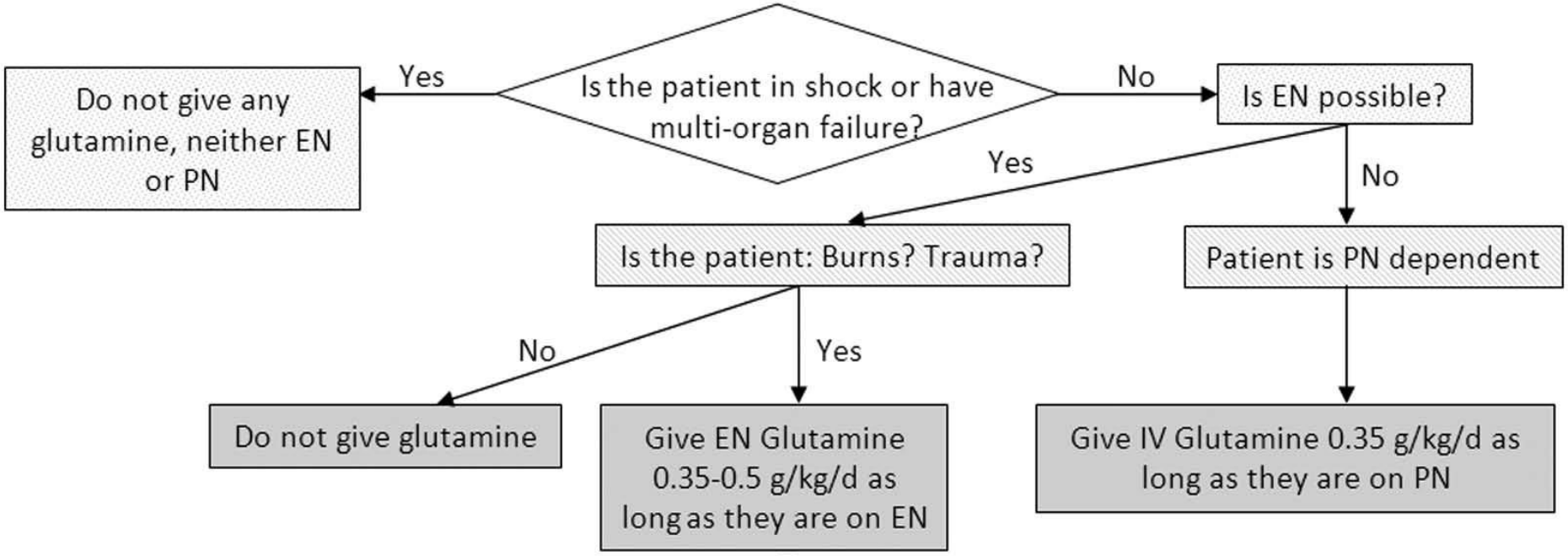
−3.85 to −1.04;

p = 0.001



Role of Glutamine Supplementation in Critical Illness Given the Results of the REDOXS Study

Heyland & Dhaliwal, JPEN 2013: in press



ESPEN ICU PN 2009: 16 statements

§ 9 - Micronutrients:

Any prescription of PN includes

1 daily dose of trace elements & vitamins

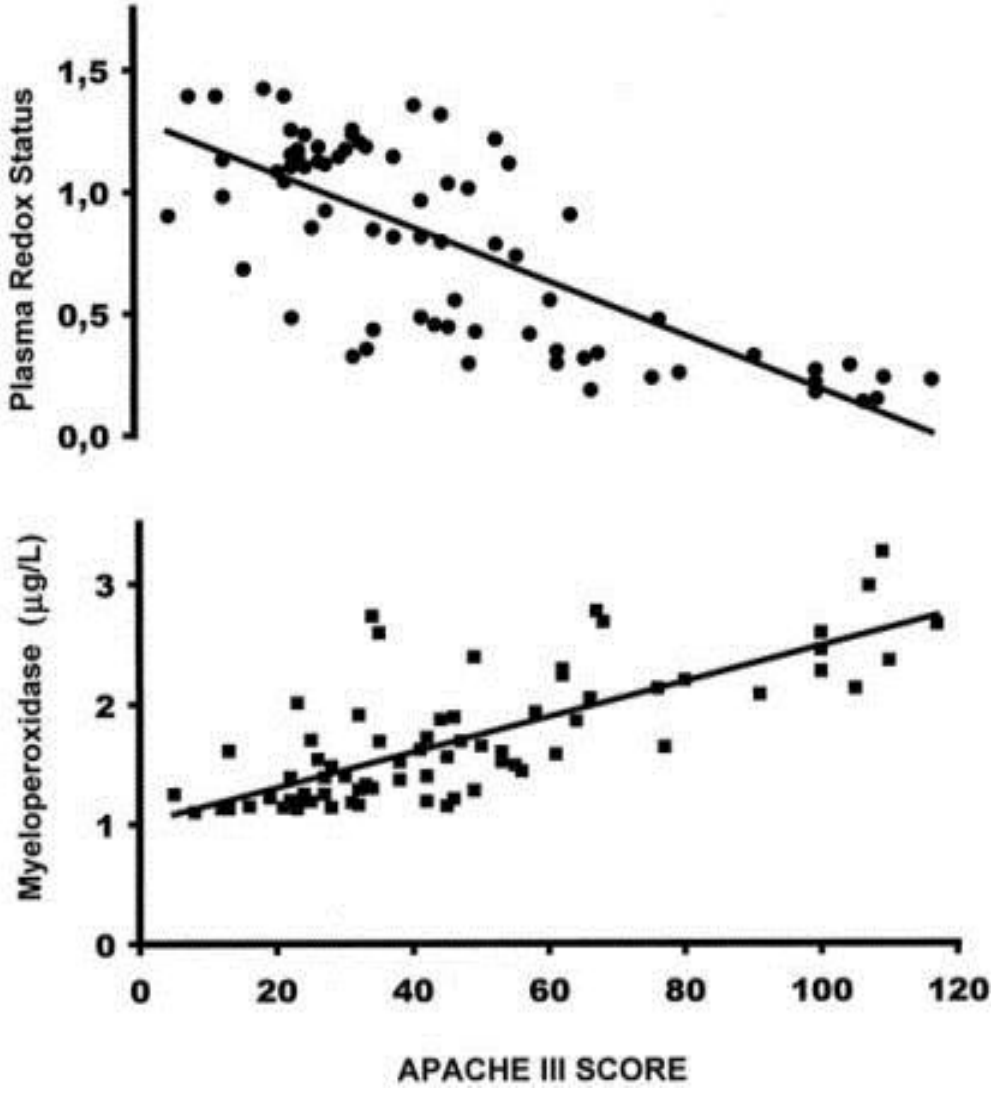
Comments: Consequences of acute deficiencies are not immediately detected as the full clinical picture requires weeks to develop, while biochemical alterations appear within 3-5 days: the biological deficiency syndrome is much earlier.

§ 9 – Micronutrients -TE: Selenium

- **Se Supplementation**: Randomised trials have tested the hypothesis that outcome in sepsis might be modulated by dosage ranges between 350 and 4000 mcg per day.
- Selenosis has been observed in the healthy population with chronic intakes > 750 mcg/day
- Therefore doses of 750-1000 mcg/day should probably not be exceeded in the critically ill, and their administration should be limited to 2 weeks.
- High dose Se supplementation is not a true part of PN, but should be considered a therapeutic intervention to reinforce antioxidant defences in defined conditions, i.e. in severe SIRS and septic conditions.

Plasma redox status relates to severity in critically ill patients

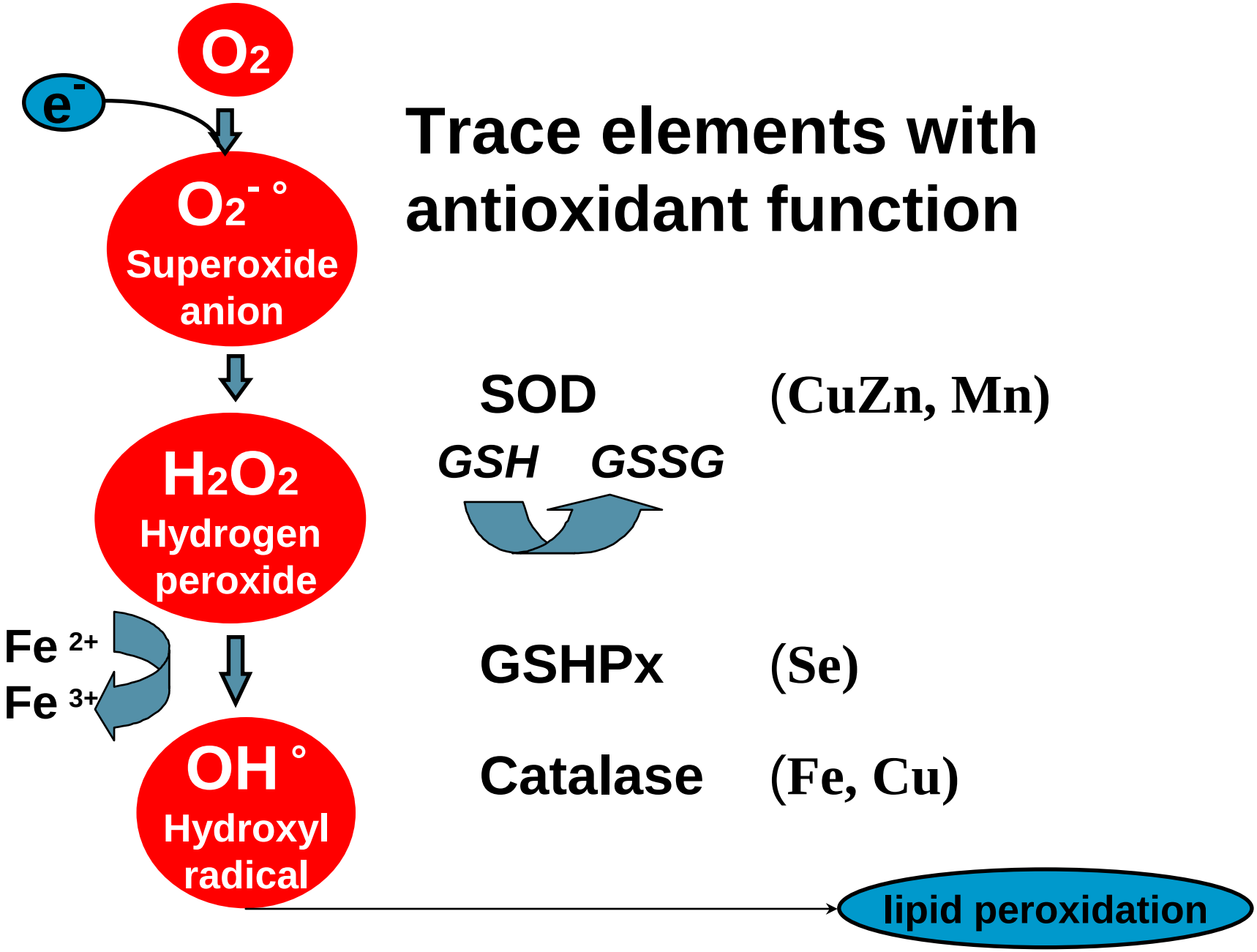
Alonso de Vega J et al, CCM 28:1812, 2000

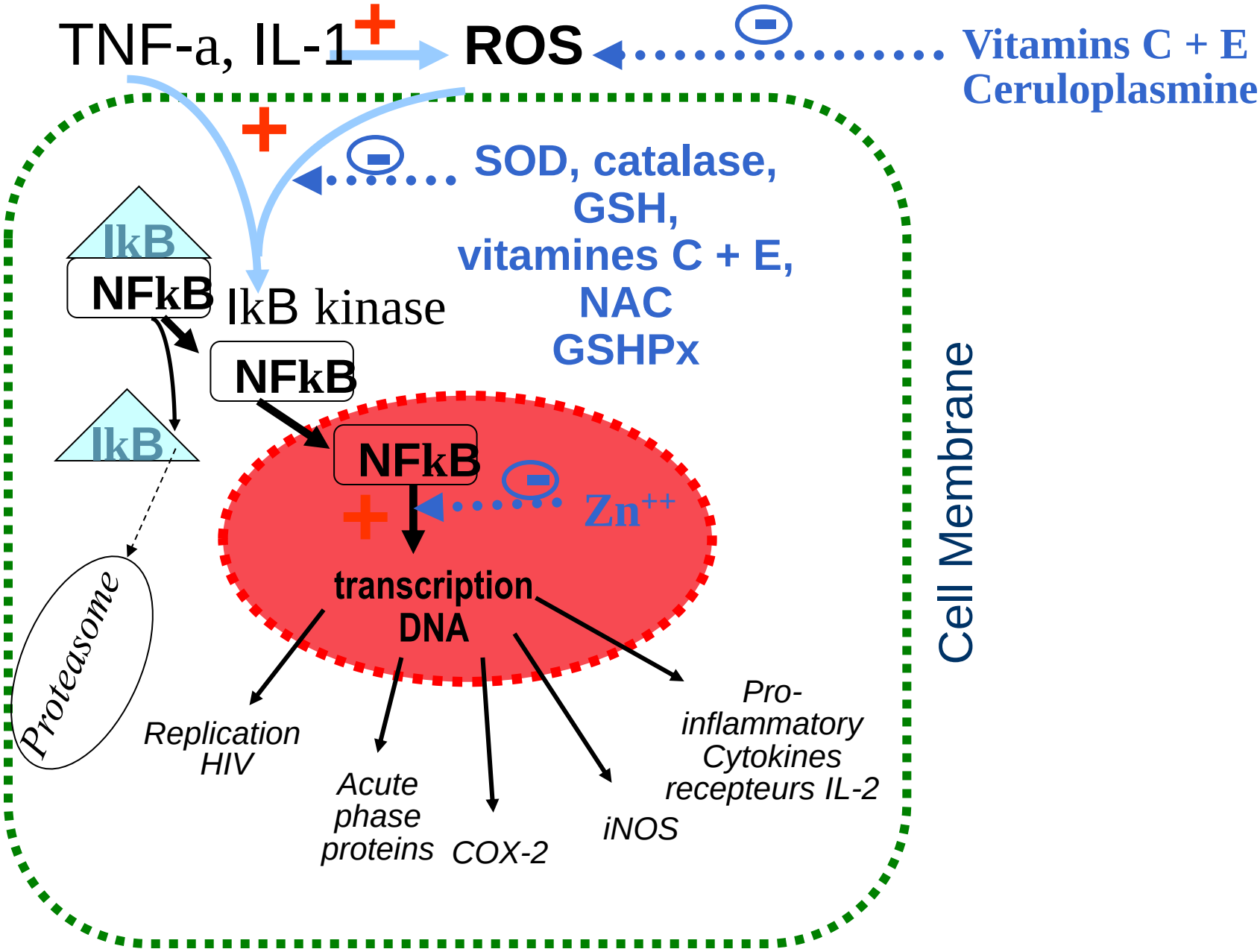


APACHE III scores and plasma redox status ($r^2 = 0.56$; $p < .001$) as defined by the ratio total antioxidant capacity (mM) / lipoperoxides (uM)

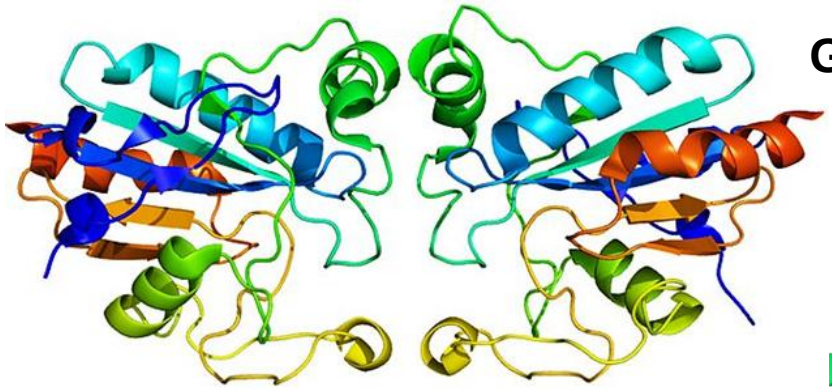
APACHE III scores and plasma myeloperoxidase concentrations ($r^2 = 058$; $p < .001$)

73 patients at admission to a mixed ICU: 8 deaths

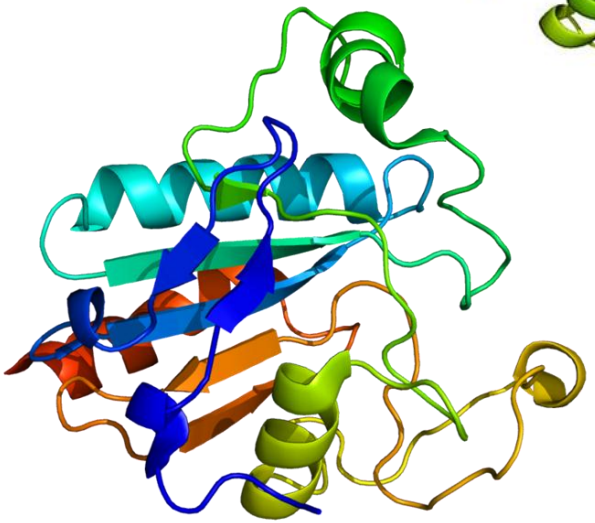

O2
e-
O2- °
Superoxide anion
H2O2
Hydrogen peroxide
Fe 2+
Fe 3+
OH °
Hydroxyl radical
Trace elements with antioxidant function
SOD (CuZn, Mn)
GSH GSSG
GSHPx (Se)
Catalase (Fe, Cu)
lipid peroxidation


TNF-a, IL-1
ROS
Vitamins C + E
Ceruloplasmine
SOD, catalase,
GSH,
vitamines C + E,
NAC
GSHPx
IkB
NFkB
IkB kinase
NFkB
IkB
NFkB
Zn++
transcription
DNA
Proteasome
Replication
HIV
Acute
phase
proteins
COX-2
iNOS
Pro-
inflammatory
Cytokines
recepteurs IL-2
Cell Membrane

SELENIUM

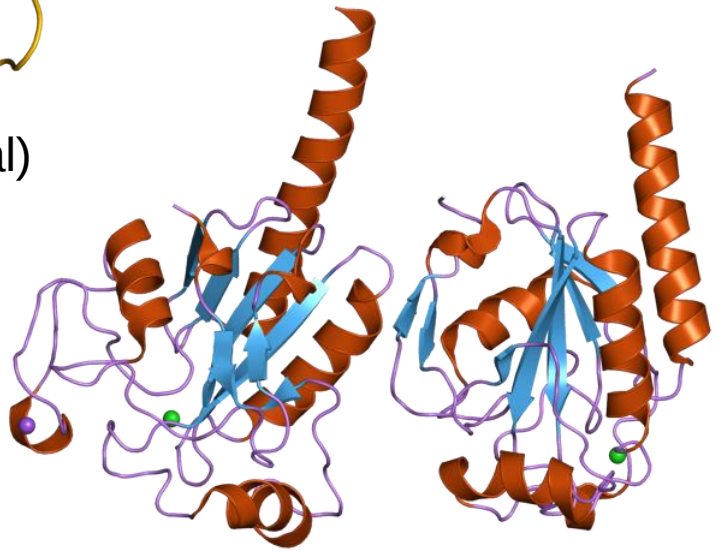


GPX1



GPX2 (gastrointestinal)

GPX4

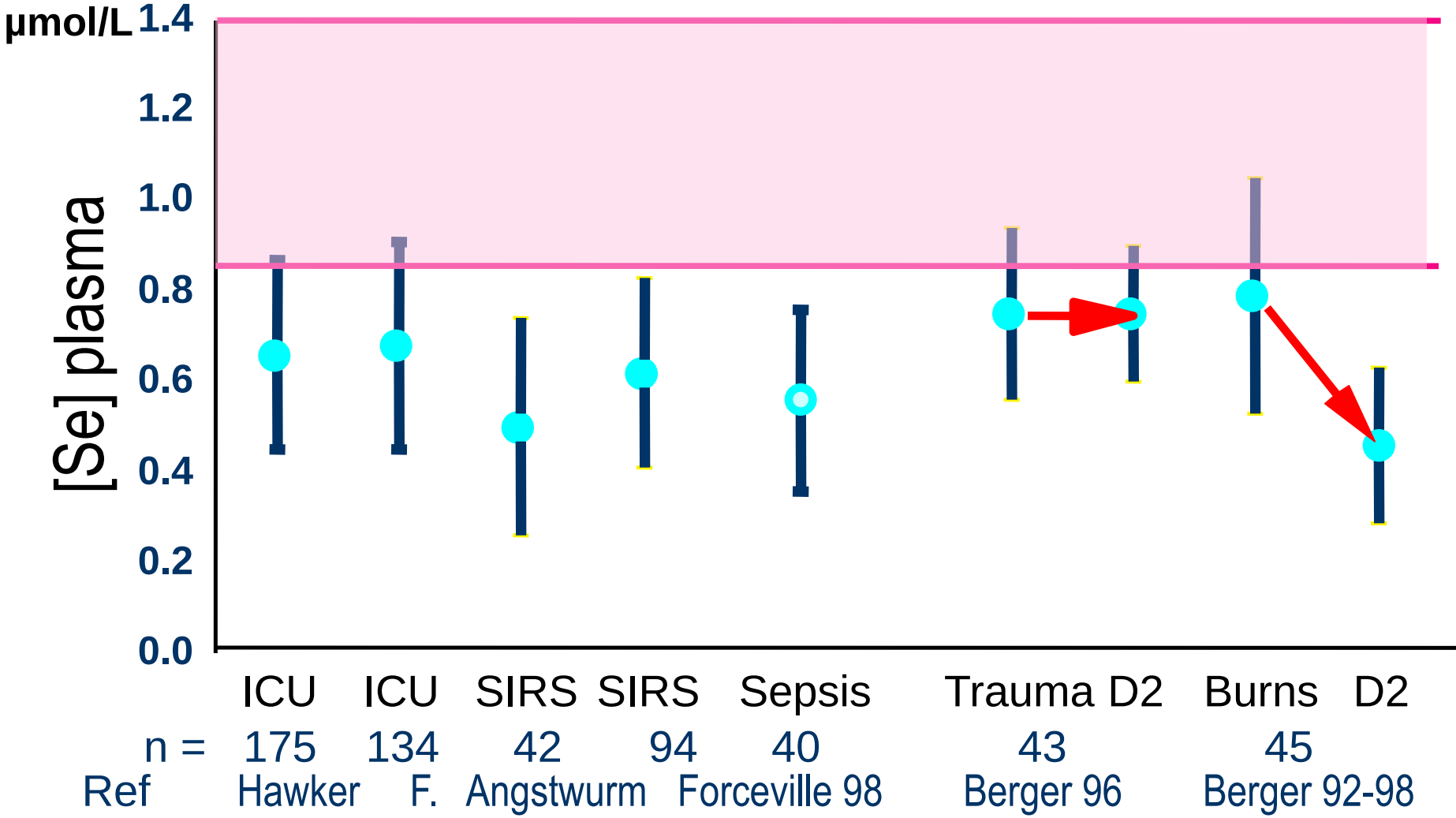


GPX3 (plasma)

Images -Wikipedia

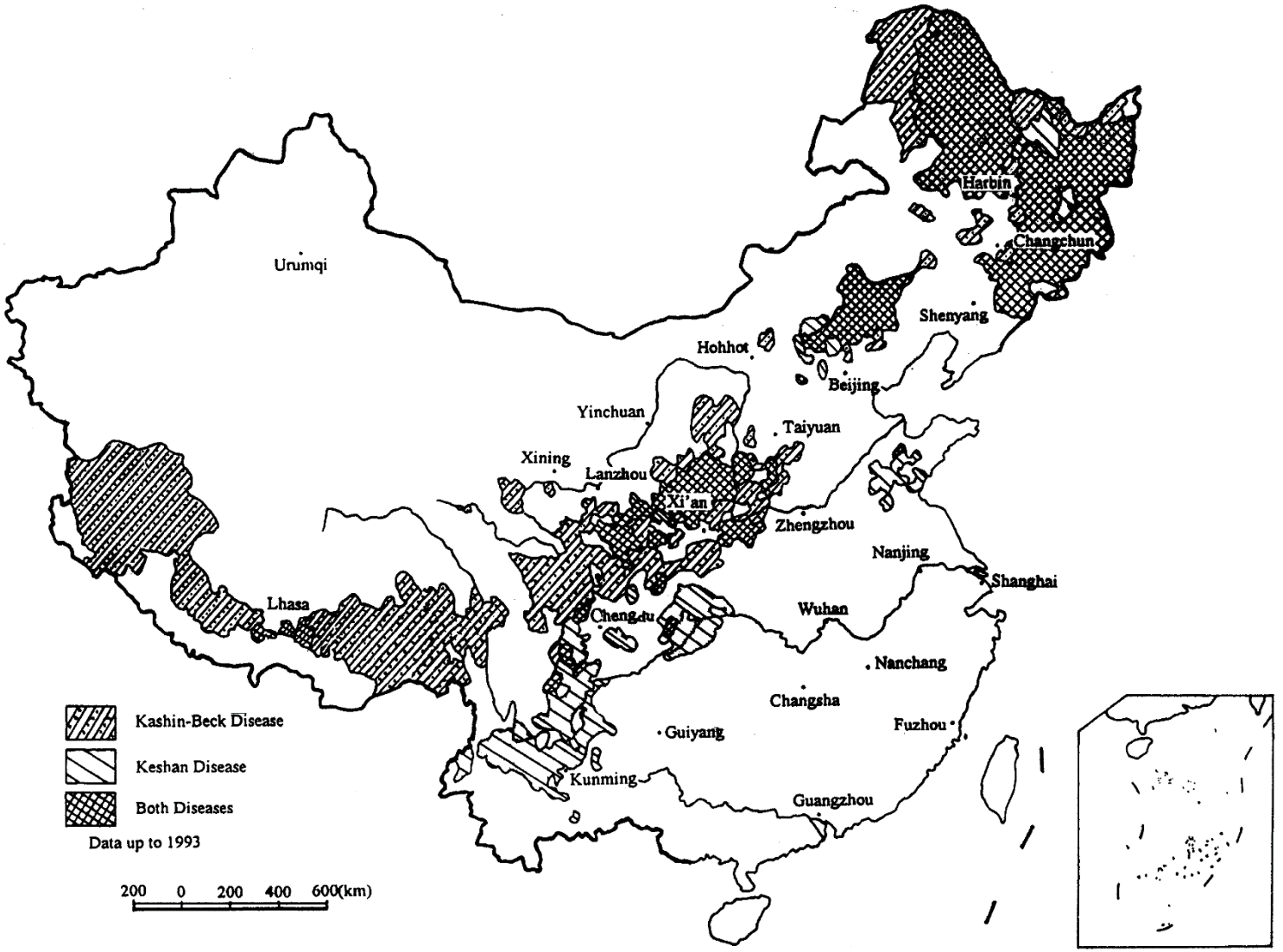
Antioxidants status in the critically ill

Selenium in plasma



Selenium in soil and endemic diseases in China

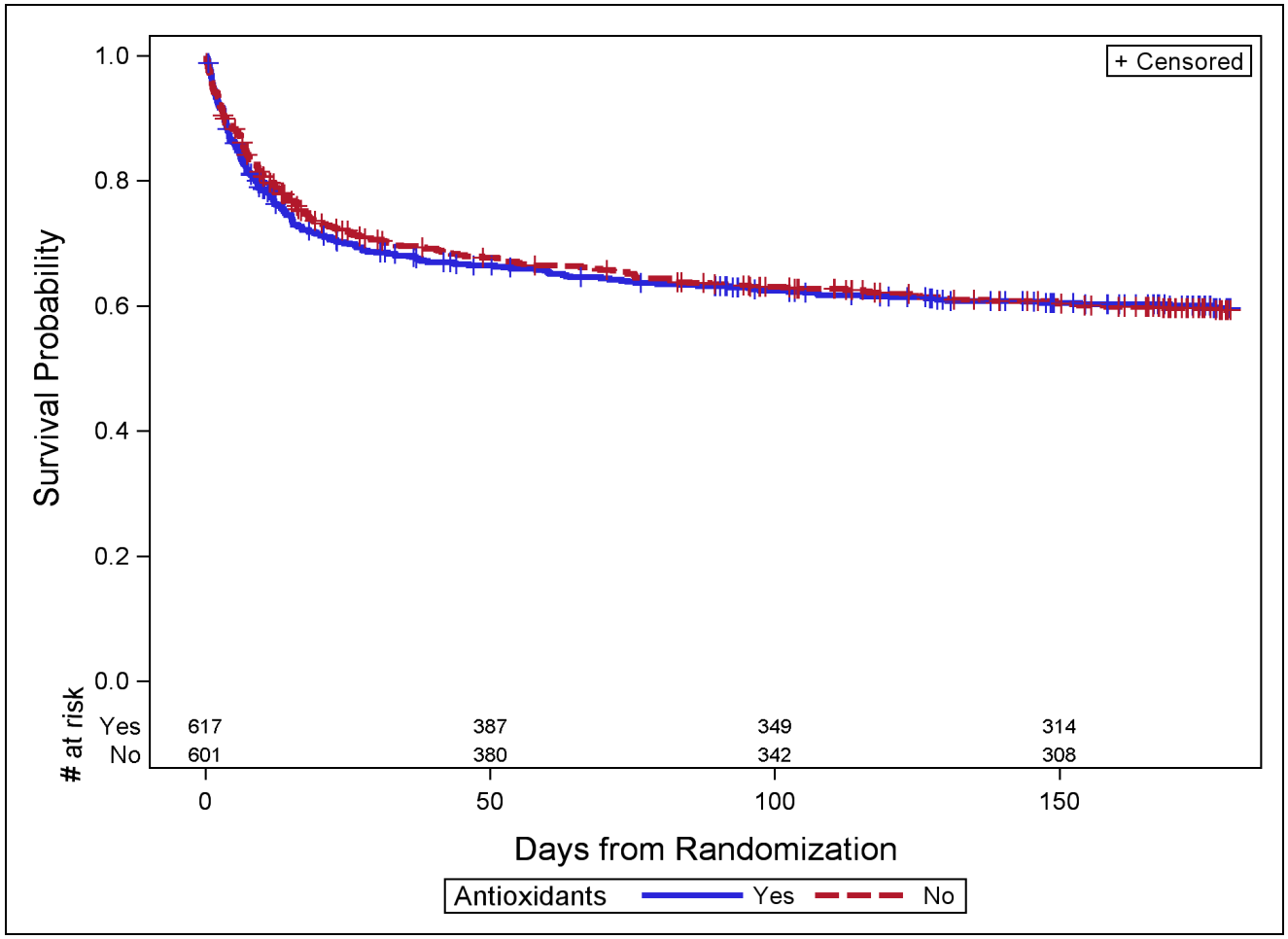
Tan et al, Science of the Total Environment 2002;842:227



REDOXS: A randomized trial of high dose Glutamine and Antioxidants in critically ill patients with MOF

Heyland et al, NEJM 2013

Antioxidant vs. no- AOX

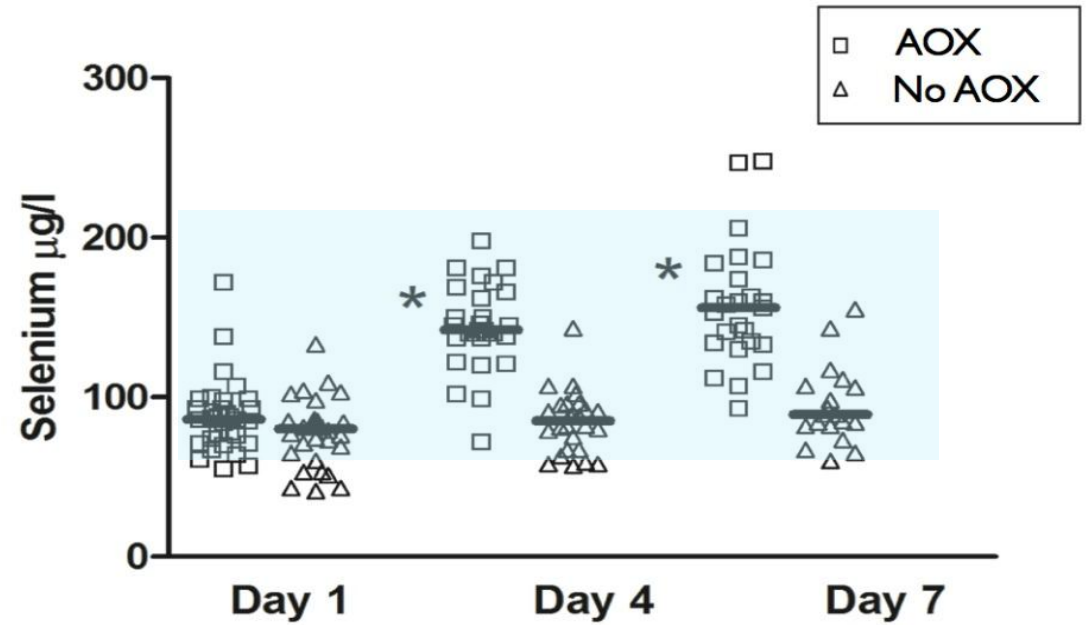


n=1218

Kaplan-Meier 6 Month Survival curves

Selenium – que passa?

- REDOXS: **no** Selenium **deficit**

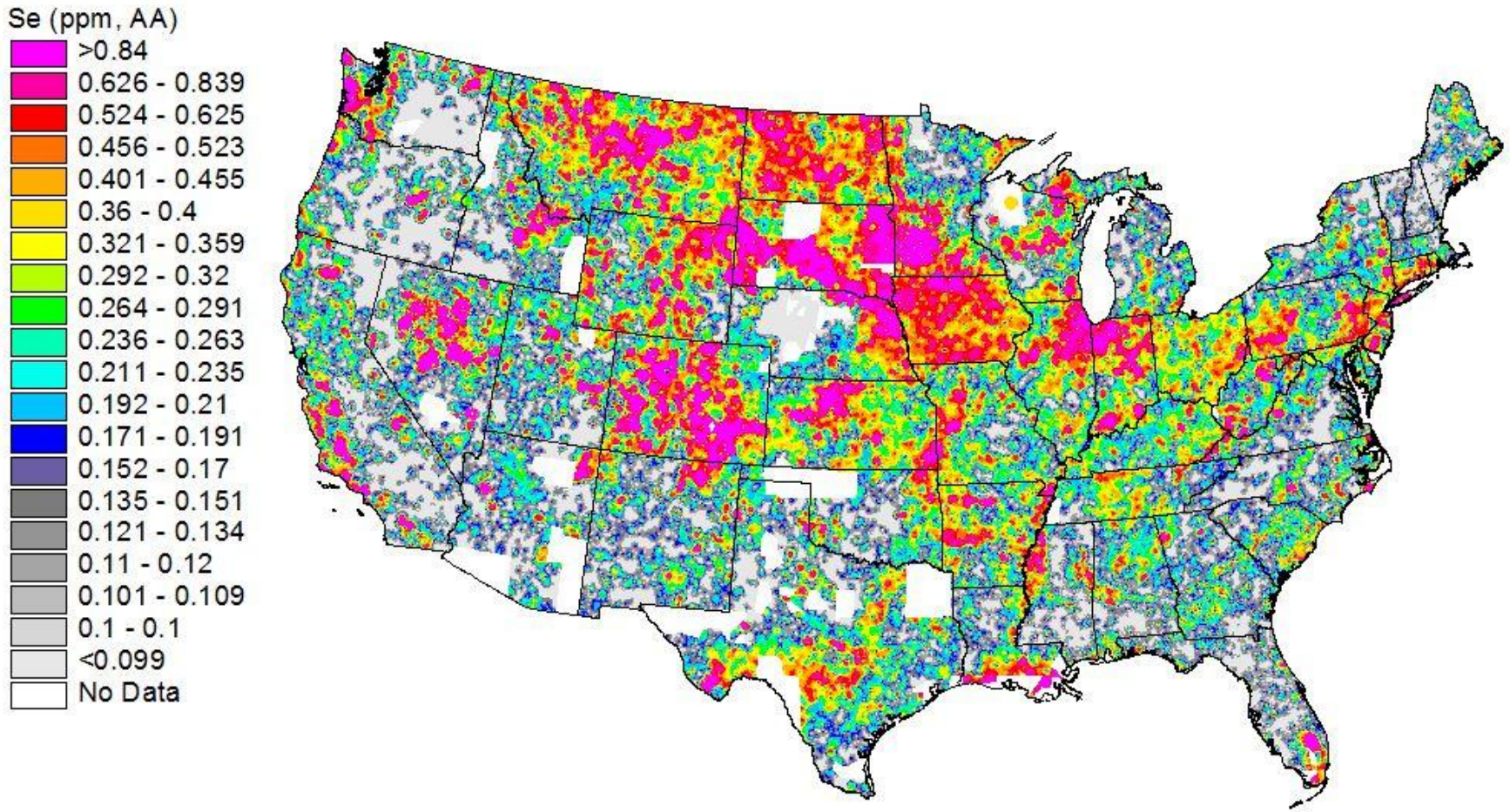


No. of patients

AOX	31	28	25
No AOX	30	26	19

Selenium, From Toxin to Essential Mineral

Dach J

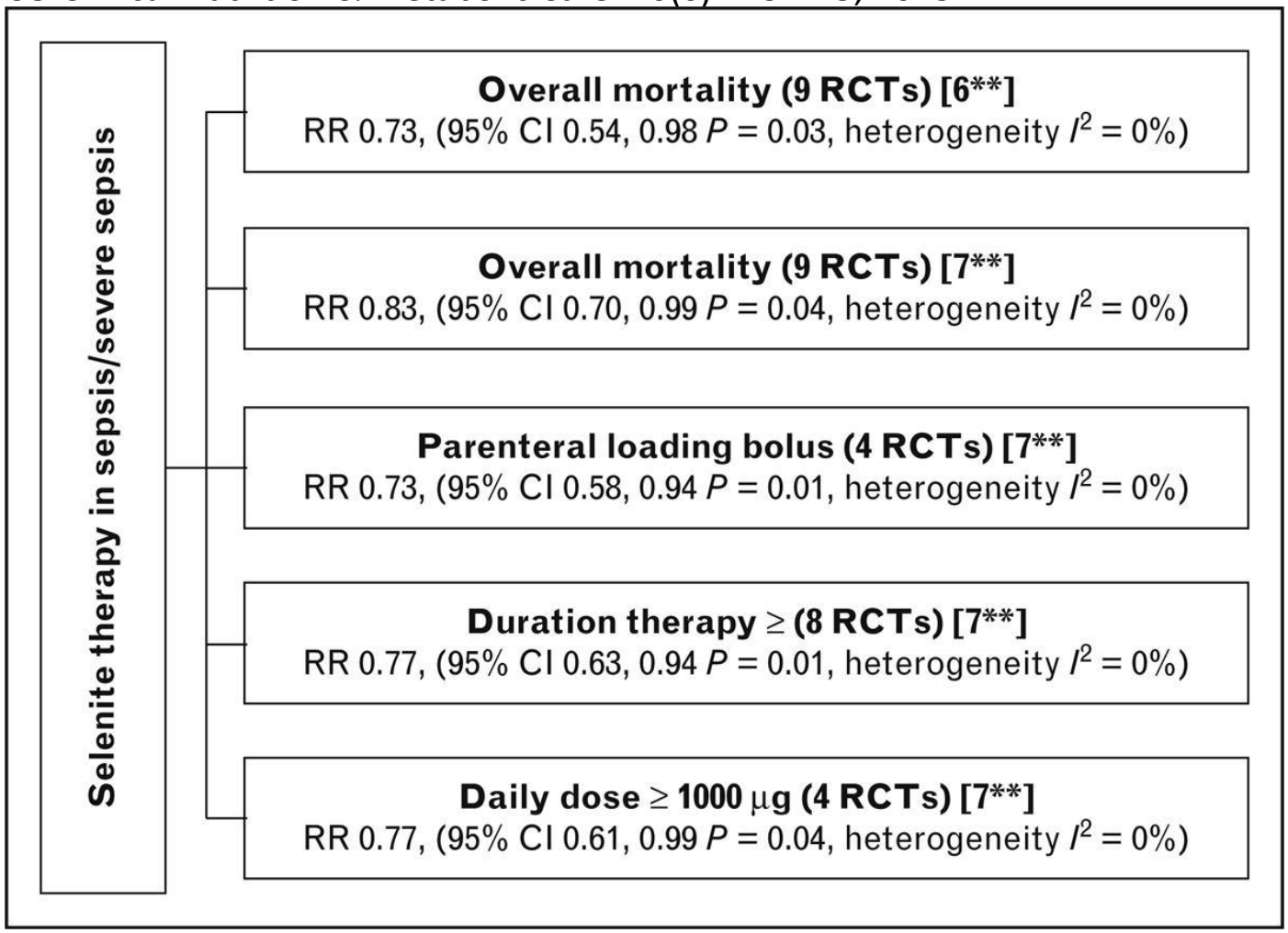


http://jeffreydach.com/2010/04/18/selenium-from-toxin-to-essential-mineral-by-jeffrey-dach-md.aspx

Update on antioxidant micronutrients in the critically ill.

Manzanares, W; Langlois, P; Hardy, G

CO Clinical Nutrition & Metabolic Care. 16(6):719-725, 2013.



high-dose micronutrient supplements such as selenium, zinc, and antioxidant vitamins are able to **decrease infections and reduce mortality**. The treatment effect may be greatest in the most seriously ill patients

Oil .. and .. oil

Fish oil
Borage n-3

Olive oil n-9

MCT
C6 - C10

Soybean oil n-6
C18

ESPEN Guidelines on Parenteral Nutrition: Intensive care

Pierre Singer[a], Mette M. Berger[b], Greet Van den Berghe[c], Gianni Biolo[d], Philip Calder[e], Alastair Forbes[f], Richard Griffiths[g], Georg Kreyman[h], Xavier Leverve[i], Claude Pichard[j]

Clinical Nutrition 28 (2009) 387–400

- **Lipids** should be an integral part of PN for energy and to ensure essential fatty acid provision. **B**
- **I.V. lipid emulsions** (LCT, MCT or mixed emulsions) can be administered safely at a rate of 0.7 g/kg up to 1.5 g/kg over 12 to 24 h. **B**

- Olive oil-based PN is well tolerated in critically ill patients. **B**
- **Addition of EPA and DHA** to lipid emulsions has demonstrable effects on cell membranes and inflammatory processes. Fish oil-enriched lipid emulsions probably decrease length of stay in critically ill patients. **B**

Choosing the lipid: A key consideration in PN

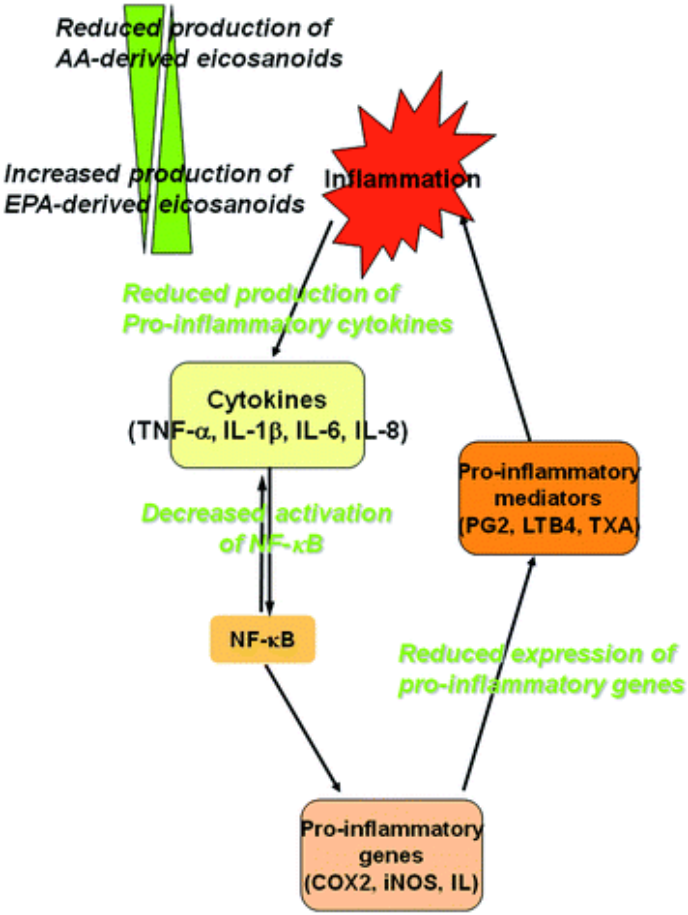
Industry proposes different levels of SFAs, PUFAs, and MUFAs[1,2]

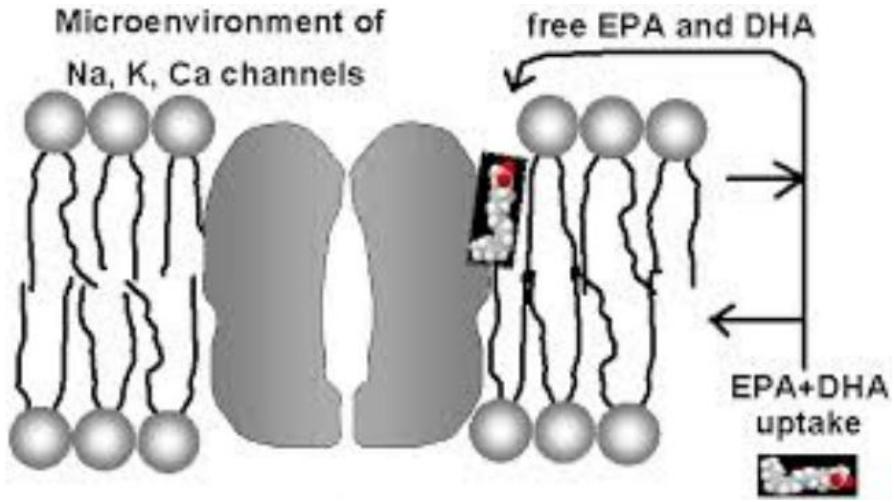
	Intralipid® 20%[1]	Lipofundin® MCT/LCT 20%[1]	Structolipid® 20%[1]	Omegaven® 10%[1]	ClinOleic® 20%[1]	Lipoplus® 20%[2]	SMOFlipid® 20%[1]
Oil source / % FA	100% soy	50% coconut 50% soy	36% coconut 64% soy	100% fish	80% olive 20% soy	50% coconut 40% soy 10% fish	30% soy 30% coconut 25% olive 15% fish
SFA	15.0	59.4	46.3	21.2	14.5	58.0	40.6
MUFA	24.0	11.0	14.0	24.3	63.7	11.5	29.3
PUFA	61.1	33.8	40.0	42.3	22.0	26.8	26.4
ω-3	8.0	4.5	5.0	35.2	2.8	5.4	7.3
ω-6	53.1	29.3	35.0	7.1	19.2	21.5	19.1
ω-9	24.0	11.0	14.0	15.1	62.3	10.6	27.7

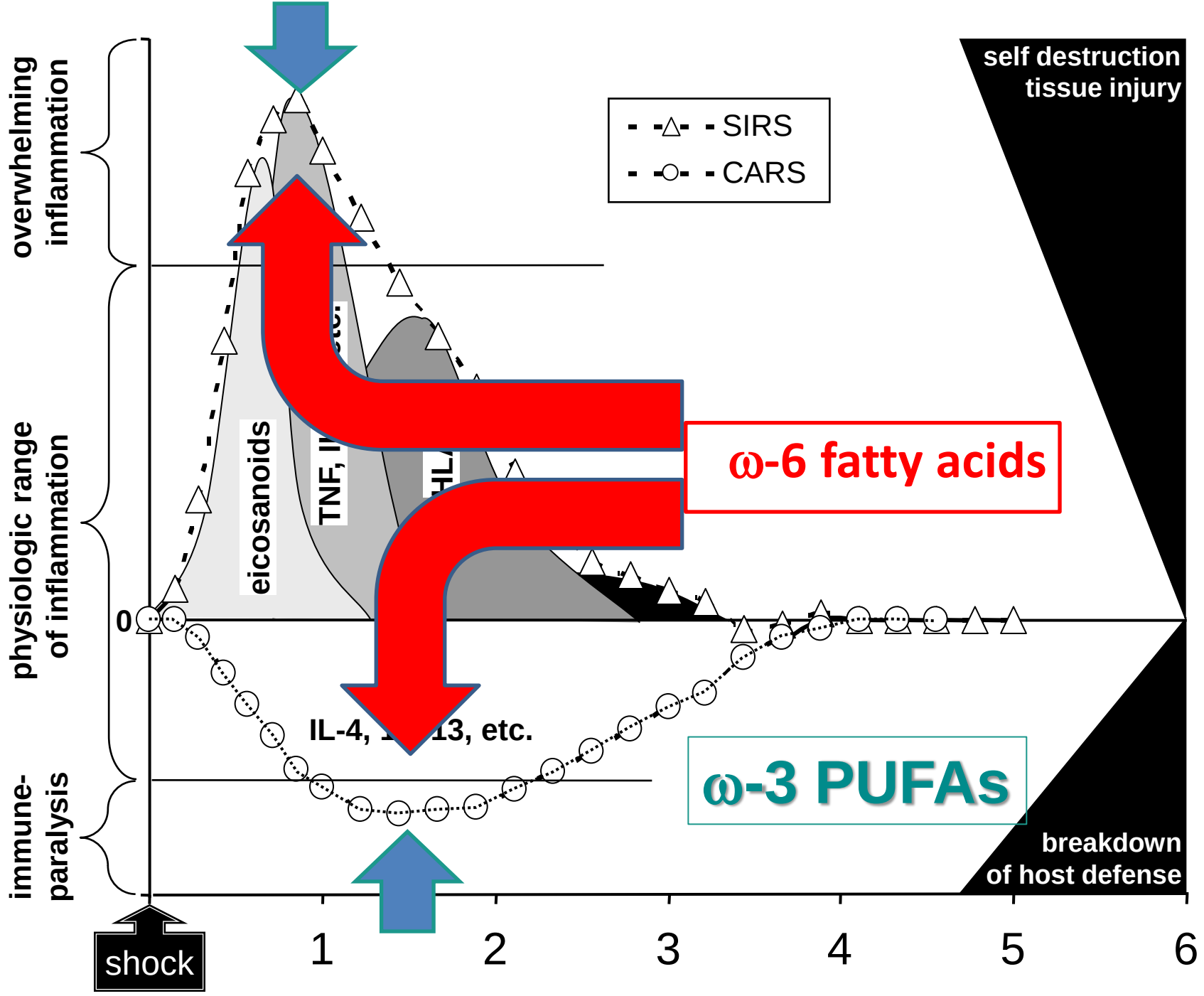
MCT, medium-chain triglyceride; LCT, long-chain triglyceride.

1. Wanten GJA, Calder PC. Am J Clin Nutr. 2007;85(5):1171-1184. 2. Driscoll DF. Nutr Clin Pract. 2006;21(4):381-386.

Ubiquitous effect of n-3 FA






overwhelming inflammation
physiologic range of inflammation
immune-paralysis
self destruction tissue injury
breakdown of host defense
SIRS
CARS
eicosanoids
TNF, I
HL
0
IL-4, 13, etc.
ω-6 fatty acids
ω-3 PUFAs
shock
1
2
3
4
5
6

Omega-3 fatty acids improve the diagnosis-related clinical outcome

Heller et al CCM,2006

Prospective, open label, multiple-centre trial.

PATIENTS : 661 patients from 82 German hospitals receiving TPN for > or =3 days were enrolled

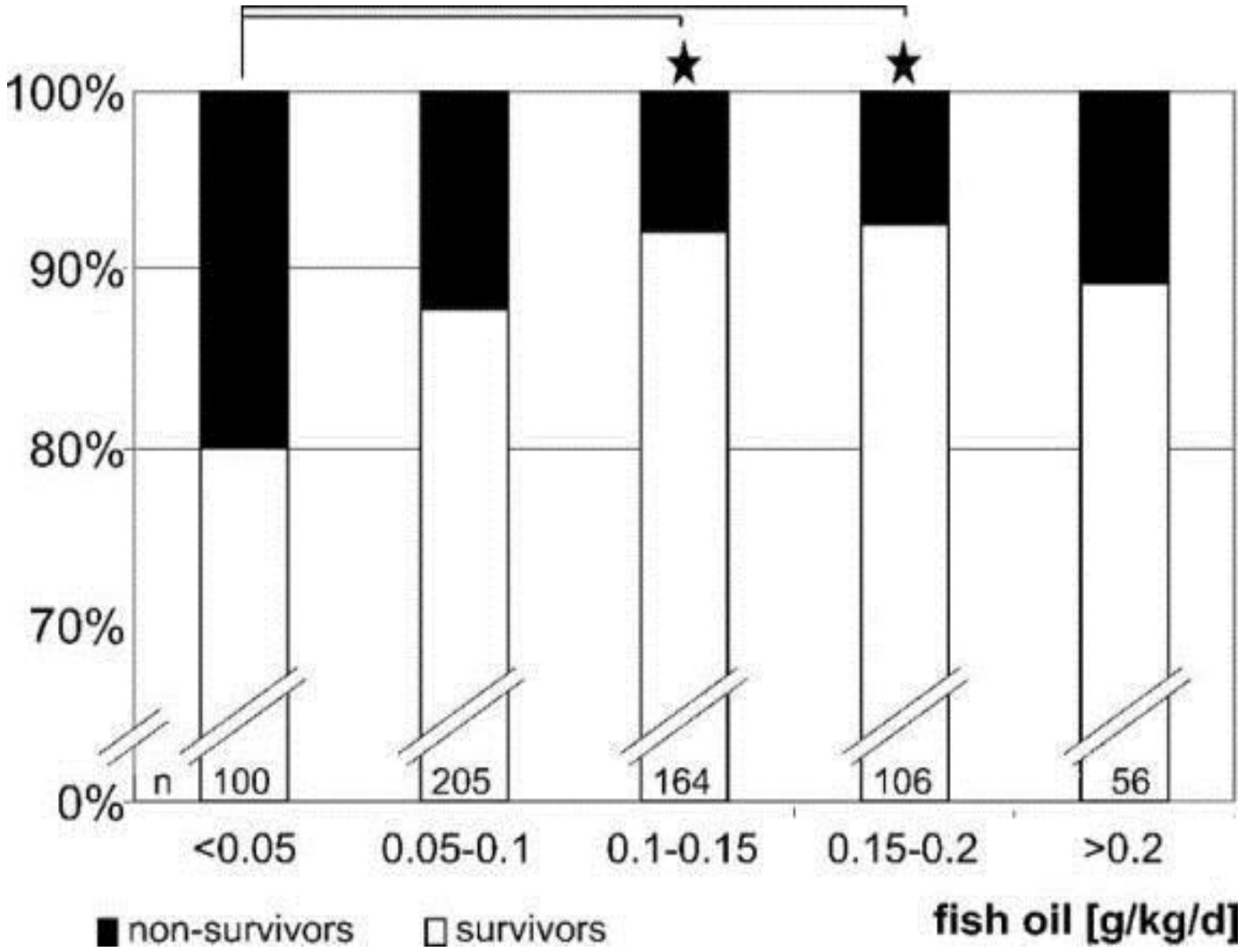
- 255 patients after major abdominal surgery
- 276 with peritonitis and abdominal sepsis
- 16 with non-abdominal sepsis
- 59 after multiple trauma
- 18 with severe head injury, and 37 other diagnoses.

Primary study end point was survival

Secondary end points: length of hospital stay, use of antibiotics with respect to the primary diagnosis and the extent of organ failure.

Omega-3 fatty acids improve the diagnosis-related clinical outcome

Heller A et al, Crit Care Med 2006 34:972



Survival in % of patients in dose-related subgroups

Safety and efficacy of fish oil-enriched PN regimen on postoperative patients undergoing major abdominal surgery

Fish-Oil enriched PN - Infections

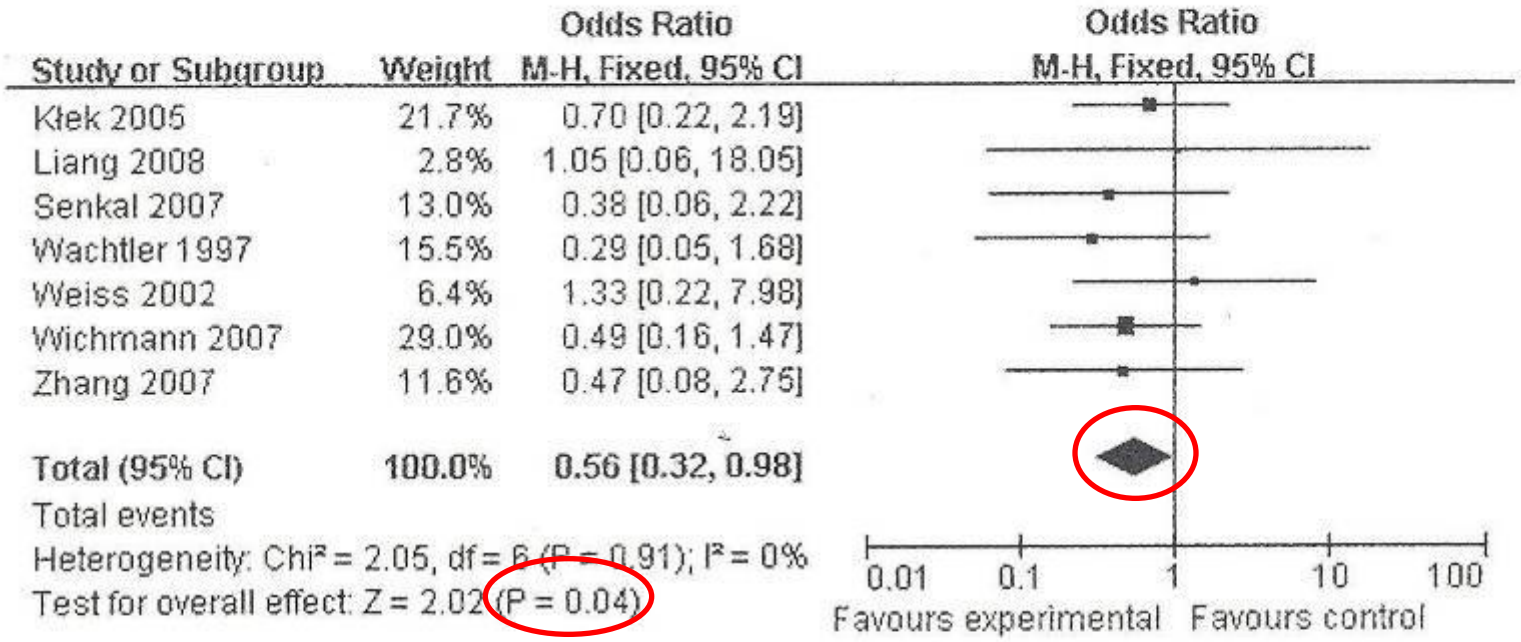


Figure 1. Forest plot for effect of fish oil on the postoperative infection rate in patients with major abdominal surgery. Abbreviation: CI, confidence interval; M-H, Mantel–Haenszel (statistical method).

Chen et al, JPEN 2010

Safety and efficacy of fish oil-enriched PN regimen on postoperative patients undergoing major abdominal surgery

Fish-Oil enriched PN - LICUS

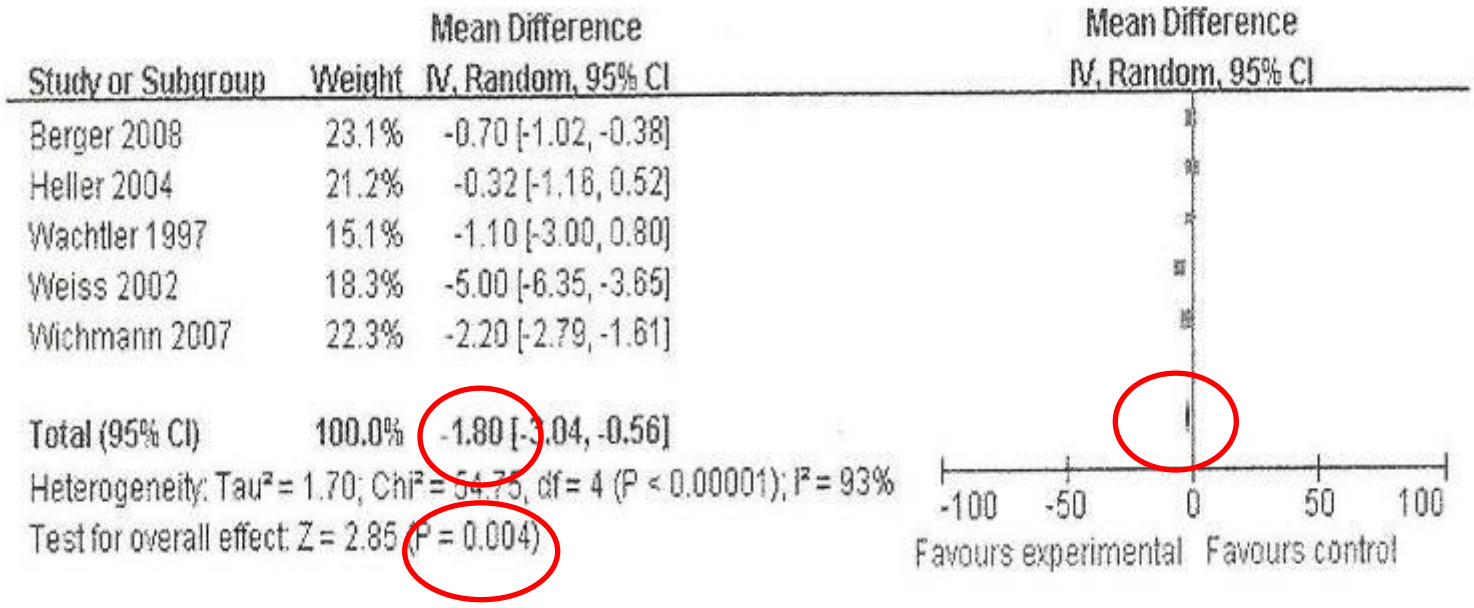
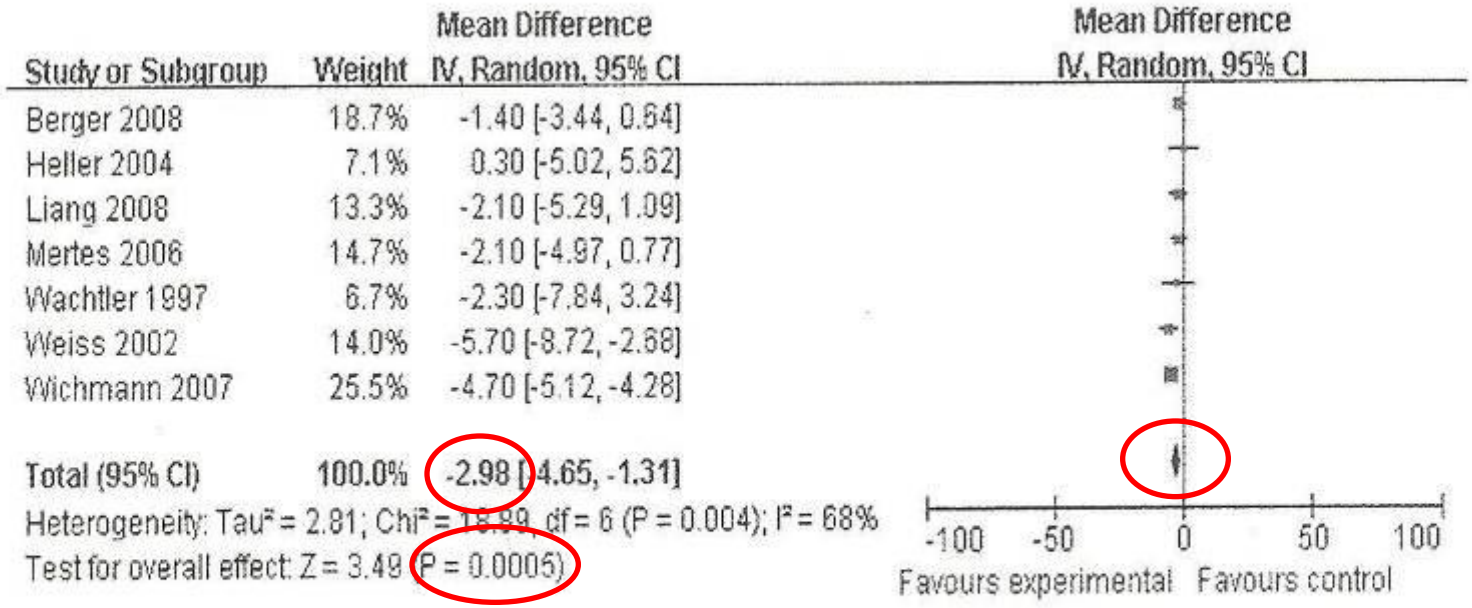


Figure 3. Forest plot for effect of fish oil on the length of intensive care unit stay in patients with major abdominal surgery. CI, confidence interval; df, degrees of freedom; IV, Inverse Variance (statistical method).

Chen et al, JPEN 2010

Safety and efficacy of fish oil-enriched PN regimen on postoperative patients undergoing major abdominal surgery

Fish-Oil enriched PN - LHOS



Study or Subgroup	Weight	Mean Difference IV, Random, 95% CI
Berger 2008	18.7%	-1.40 [-3.44, 0.64]
Heller 2004	7.1%	0.30 [-5.02, 5.62]
Liang 2008	13.3%	-2.10 [-5.29, 1.09]
Mertes 2006	14.7%	-2.10 [-4.97, 0.77]
Wachtler 1997	6.7%	-2.30 [-7.84, 3.24]
Weiss 2002	14.0%	-5.70 [-8.72, -2.68]
Wichmann 2007	25.5%	-4.70 [-5.12, -4.28]
Total (95% CI)	100.0%	-2.98 [-4.65, -1.31]

Heterogeneity: Tau² = 2.81; Chi² = 15.89, df = 6 (P = 0.004); I² = 68%

Test for overall effect: Z = 3.49 (P = 0.0005)

Figure 2. Forest plot for effect of fish oil on the length of hospital stay in patients with major abdominal surgery. CI, confidence interval; df, degrees of freedom; IV, Inverse Variance (statistical method).

Chen et al, JPEN 2010

Role of PN in etiology and pathogenesis of liver disease

- Absence of enteral feeding
  - Reduction in bile flow → cholestasis
  - Bile acid toxic to hepatocyte, inflammation mediated by cytokines from activated macrophages
  - Diminished gut motility, more bacterial overgrowth and translocation
- Excess provided by PN
  - Excess total calorie intake, CHO (>50 kcal/kg/day)
  - Excess lipid (> 1g/kg/day)
  - Excess Mn, phytosterol, methionine

Prevention of PN-associated liver disease: role of ω-3 FO

Fallon E et al, CO in Organ Transplantation. 2010, 15:334-340.

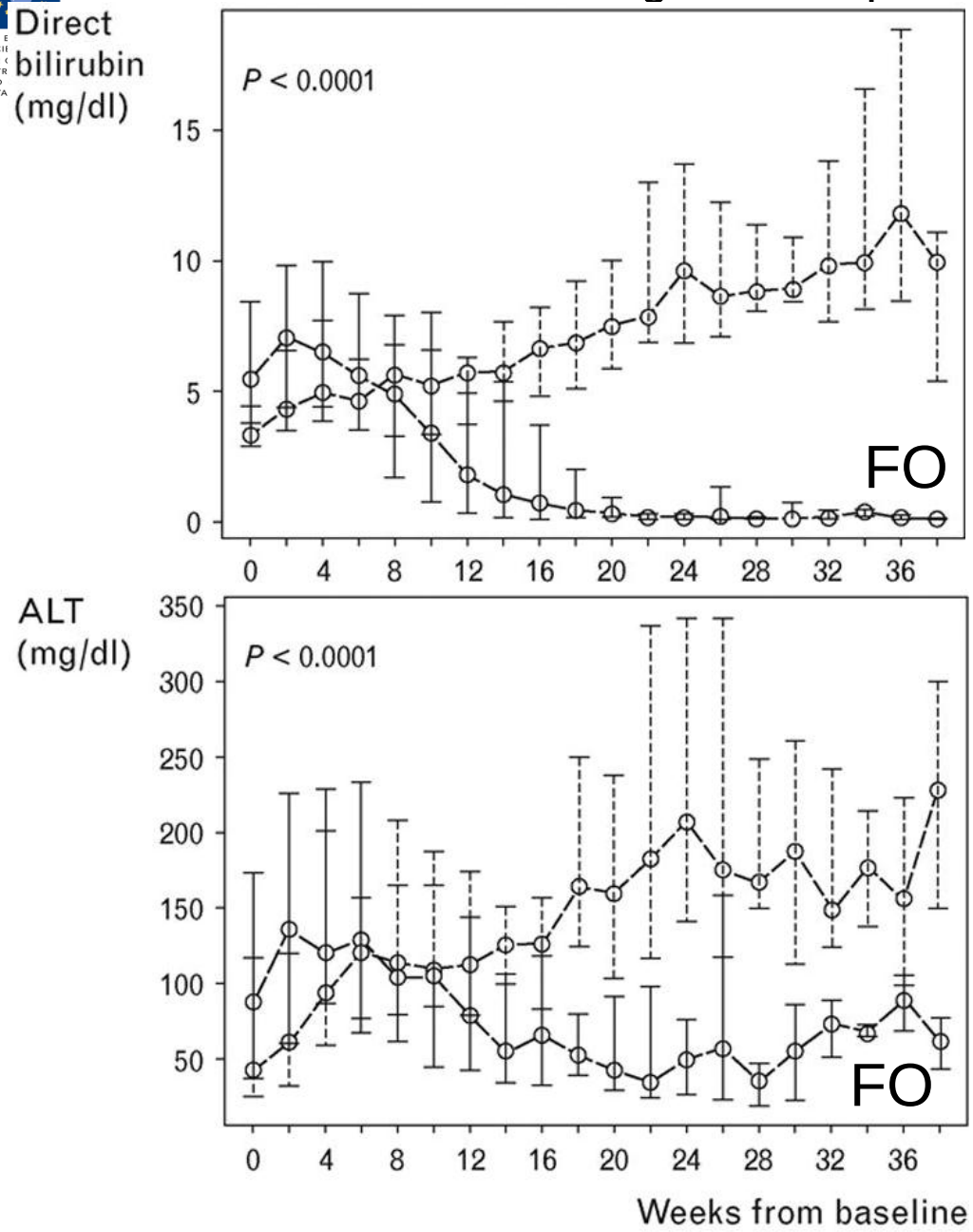


Fig. 2 Trends over time of markers of liver dysfunction in fish oil versus soybean oil cohorts

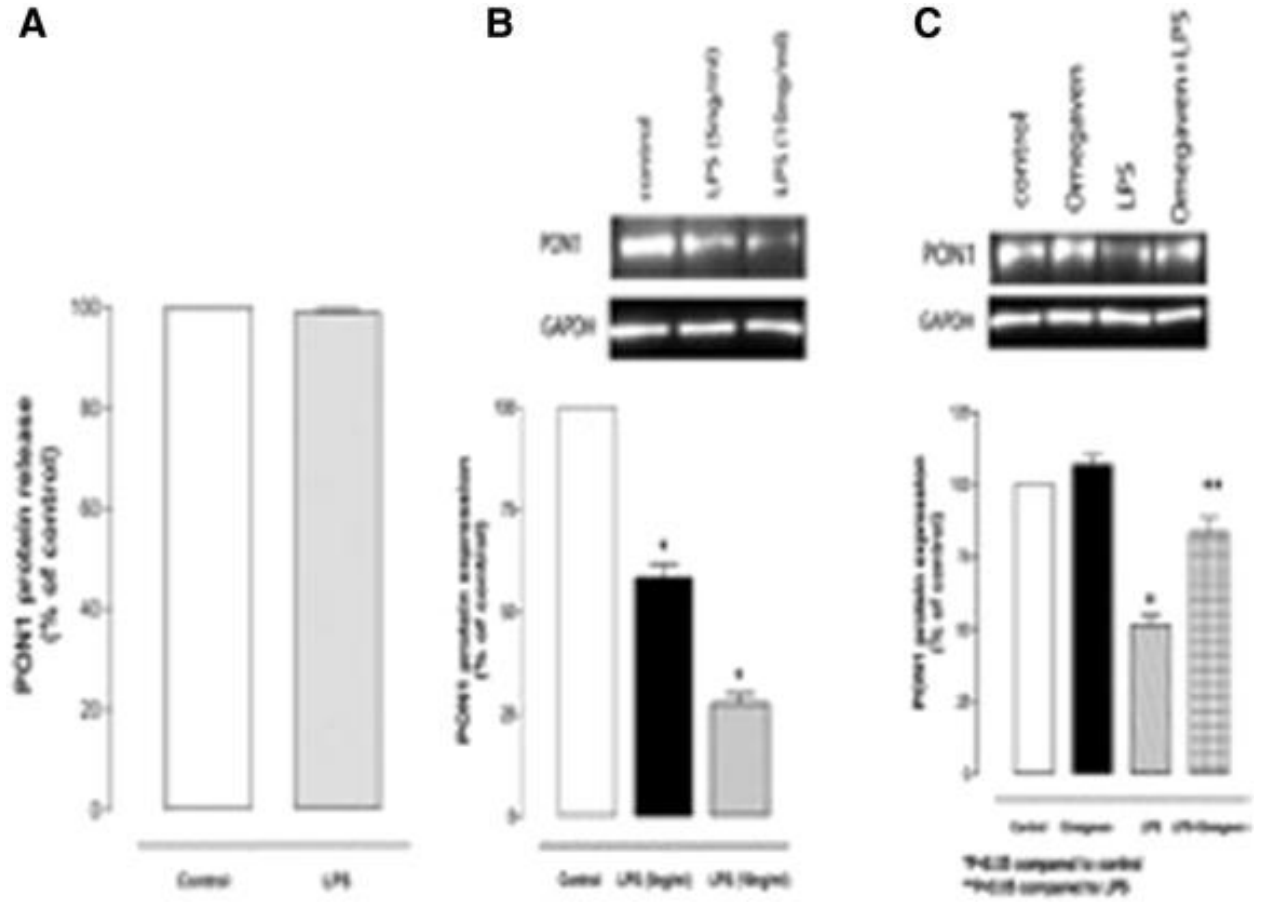
Molecular impact of omega 3 fatty acids on lipopolysaccharide-mediated liver damage

Ventro et al, J Pediatr Surg. 2016 Mar 2 epub

- Aim: study if Omegaven™ fish oil emulsion could inhibit LPS mediated liver damage
- Method: in vitro W-3 on LPS alone and synergistically on hepatic paraoxonase 1 (PON1)

A: hepatic PON1 protein expression with LPS treatment. PON1 protein level was significantly ↓ with ↑ of LPS concentration.
B: Omega-3 alone has no effect on PON1 protein expression. However, w-3 prevents LPS-mediated PON1 protein ↓.

Molecular impact of omega 3 fatty acids on LPS-mediated liver damage



Further, Omegaven blocked LPS-mediated increase in ERK1/2 activity (35% increase)

A: hepatic PON1 protein expression with LPS treatment. PON1 protein level was significantly ↓ with ↑ of LPS concentration.
B: Omegaven alone has no effect on PON1 protein expression. However, w-3 prevents LPS-mediated PON1 protein ↓.

Journal of Pediatric Surgery, 2016, Available online 2 March 2016

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

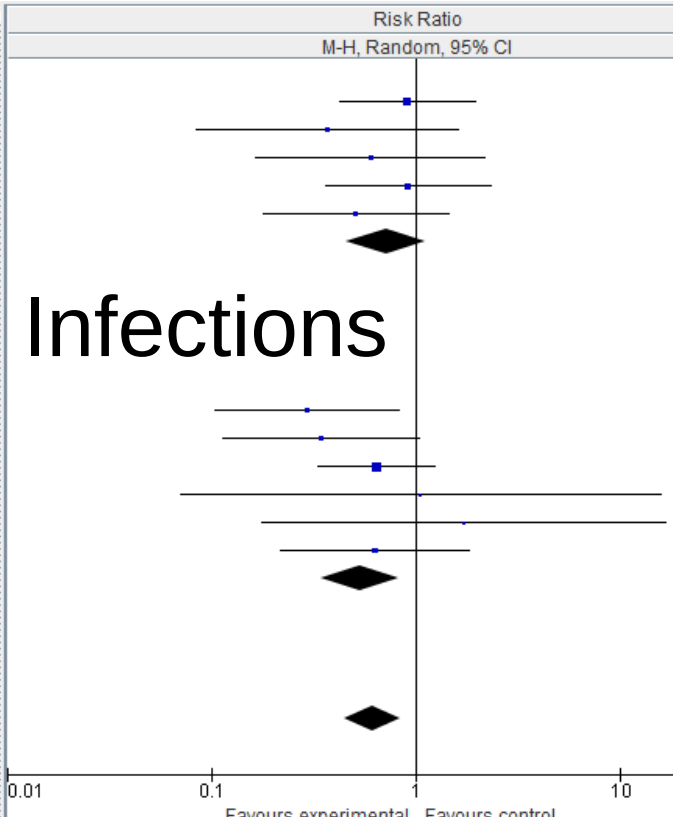
Pradelli et al, CritCare, 2012; 16:R184

Σ 23 studies (n = 1502 patients: n = 762 admitted to the ICU)

No significant ≠ in mortality rate between patients on n-3 PUFA-enriched PN vs. standard PN (RR= 0.89; 0.59, 1.33) ← low underlying mortality risk?

But …..↓ Infections, ↓ LOS, ↓ inflammation, ↑ lung gas exchange, liver function, antioxidant status, plasma FA, (↓ impairment of kidney function?)

Study or Subgroup	Omega-3 Events	Omega-3 Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 ICU patients						
Friesecke 2008	11	83	12	82	17.1%	0.91 [0.42, 1.93]
Wachtler 1997	2	19	6	21	4.5%	0.37 [0.08, 1.61]
Wang 2008	3	20	5	20	5.9%	0.60 [0.17, 2.18]
Weiss 2002	5	12	5	11	11.4%	0.92 [0.36, 2.33]
Wichmann 2007	5	127	10	129	9.0%	0.51 [0.18, 1.44]
Subtotal (95% CI)		261		263	47.9%	0.71 [0.45, 1.12]
Total events	26		38			
Heterogeneity: Tau² = 0.00; Chi² = 1.94, df = 4 (P = 0.75); I² = 0%						
Test for overall effect: Z = 1.47 (P = 0.14)						
1.2.2 Not ICU patients						
Badia-Tahull 2010	3	13	11	14	9.3%	0.29 [0.10, 0.82]
Jiang 2010	4	100	12	103	8.2%	0.34 [0.11, 1.03]
Klek 2005	9	29	14	29	22.6%	0.64 [0.33, 1.24]
Liang 2008	1	20	1	21	1.3%	1.05 [0.07, 15.68]
Makay 2011	2	14	1	12	1.9%	1.71 [0.18, 16.65]
Senkal 2007	4	19	7	21	8.8%	0.63 [0.22, 1.82]
Subtotal (95% CI)		195		200	52.1%	0.53 [0.34, 0.82]
Total events	23		46			
Heterogeneity: Tau² = 0.00; Chi² = 3.58, df = 5 (P = 0.61); I² = 0%						
Test for overall effect: Z = 2.86 (P = 0.004)						
Total (95% CI)		456		463	100.0%	0.61 [0.45, 0.84]
Total events	49		84			
Heterogeneity: Tau² = 0.00; Chi² = 6.35, df = 10 (P = 0.79); I² = 0%						
Test for overall effect: Z = 3.08 (P = 0.002)						

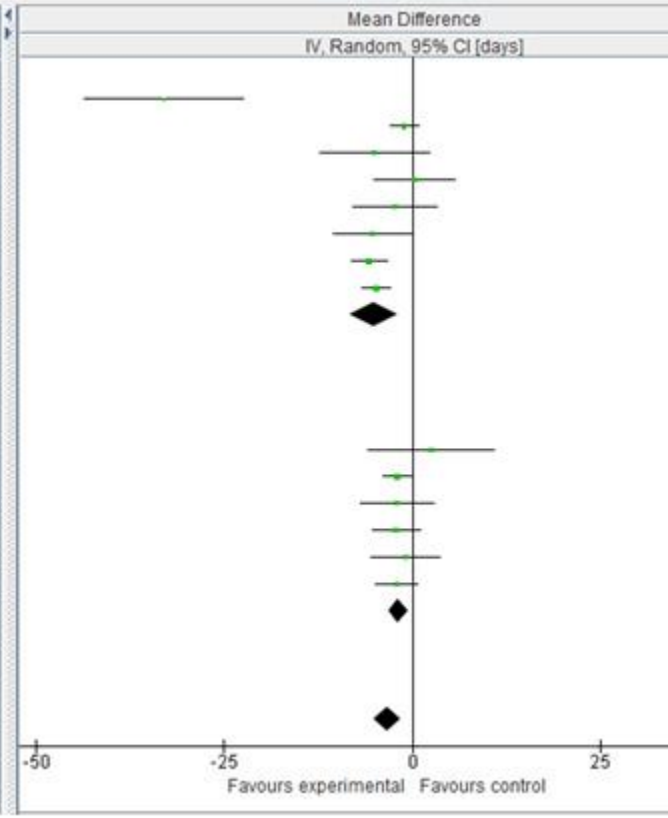


n-3 fatty acid-enriched PN regimens in elective surgical and ICU patients: a meta-analysis

Pradelli et al, CritCare, 2012; 16:R184

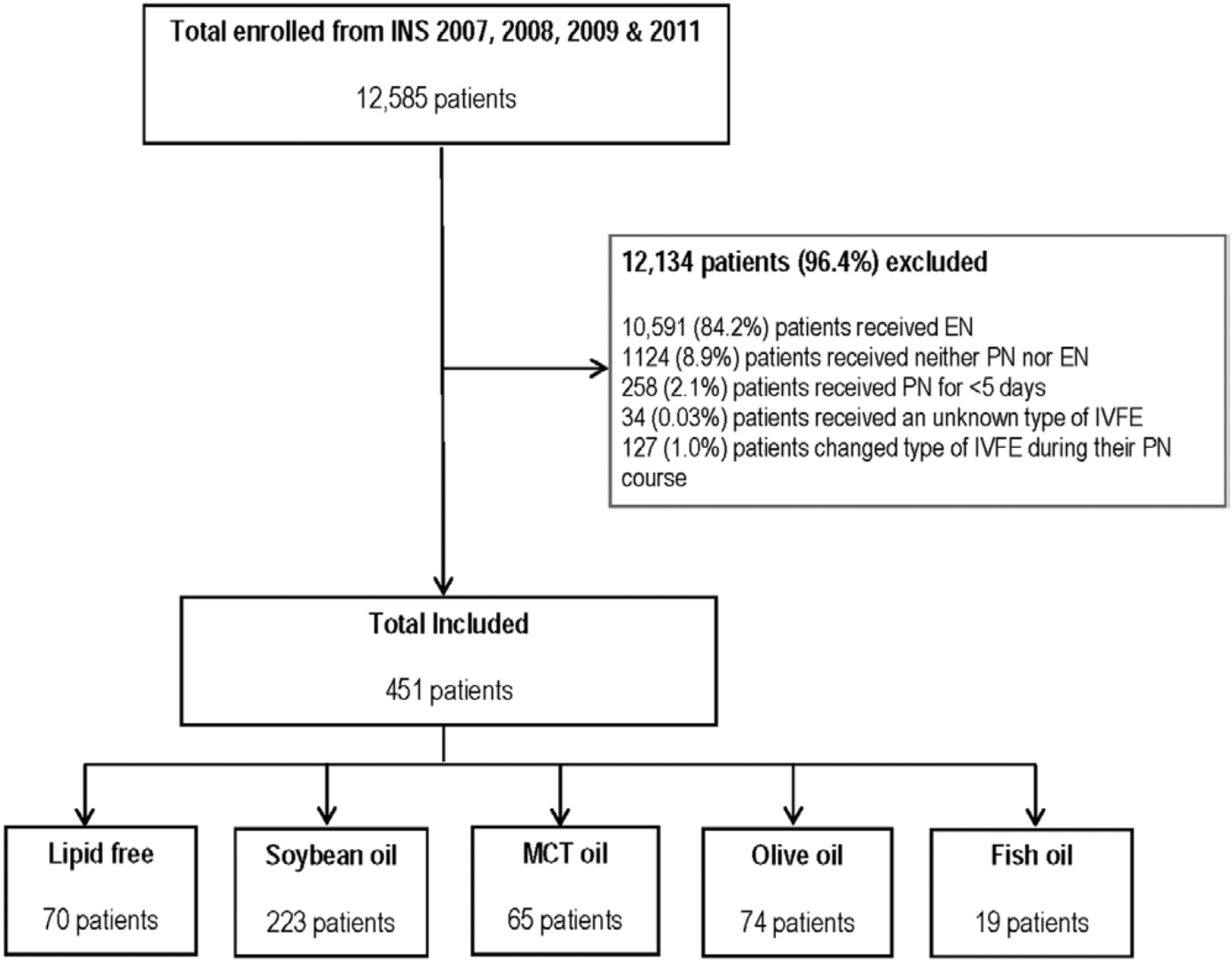
LOS

Study or Subgroup	Omega-3 Mean	Omega-3 SD	Omega-3 Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.3.1 ICU patients								
Barbosa 2010	22	7	13	55	16	10	2.4%	-33.00 [-43.62, -22.38]
Berger 2008	8.89	1.98	12	9.93	2.76	12	10.4%	-1.04 [-2.96, 0.88]
Friesecke 2008	29	21.54	83	34	26.25	82	4.1%	-5.00 [-12.33, 2.33]
Heller 2004	19.1	9.6	24	18.8	8.4	20	5.9%	0.30 [-5.02, 5.62]
Wachtler 1997	20.1	6.8	19	22.4	10.8	21	5.7%	-2.30 [-7.84, 3.24]
Wang 2008	65.2	7.3	20	70.5	9.1	20	6.2%	-5.30 [-10.41, -0.19]
Weiss 2002	17.8	3	12	23.5	3	11	9.7%	-5.70 [-8.15, -3.25]
Wichmann 2007	17.2	6.7	127	21.9	8.7	129	10.5%	-4.70 [-6.60, -2.80]
Subtotal (95% CI)			310			305	55.0%	-5.17 [-8.35, -1.99]
Heterogeneity: Tau² = 14.85; Chi² = 43.11, df = 7 (P < 0.00001); I² = 84%								
Test for overall effect: Z = 3.18 (P = 0.001)								
1.3.2 Not ICU patients								
Badia-Tahull 2010	18.65	13	13	16.1	8.7	14	3.4%	2.55 [-5.86, 10.96]
Jiang 2010	15	5	100	17	8	103	10.6%	-2.00 [-3.83, -0.17]
Klek 2005	14.4	9.28	29	16.4	9.9	29	6.4%	-2.00 [-6.94, 2.94]
Liang 2008	17.45	4.8	20	19.62	5.59	21	8.7%	-2.17 [-5.35, 1.01]
Makay 2011	13.1	6	14	14	6	12	6.8%	-0.90 [-5.53, 3.73]
Mertes 2006	15.7	6.3	99	17.8	13.2	100	9.2%	-2.10 [-4.97, 0.77]
Subtotal (95% CI)			275			279	45.0%	-1.86 [-3.13, -0.59]
Heterogeneity: Tau² = 0.00; Chi² = 1.31, df = 5 (P = 0.93); I² = 0%								
Test for overall effect: Z = 2.87 (P = 0.004)								
Total (95% CI)			585			584	100.0%	-3.29 [-5.13, -1.45]
Heterogeneity: Tau² = 7.49; Chi² = 49.36, df = 13 (P < 0.00001); I² = 74%								
Test for overall effect: Z = 3.50 (P = 0.0005)								
Test for subgroup differences: Chi² = 3.58, df = 1 (P = 0.06), I² = 72.1%								



The Effects of different IV Fat Emulsions on Clinical Outcomes in Critically Ill Patients

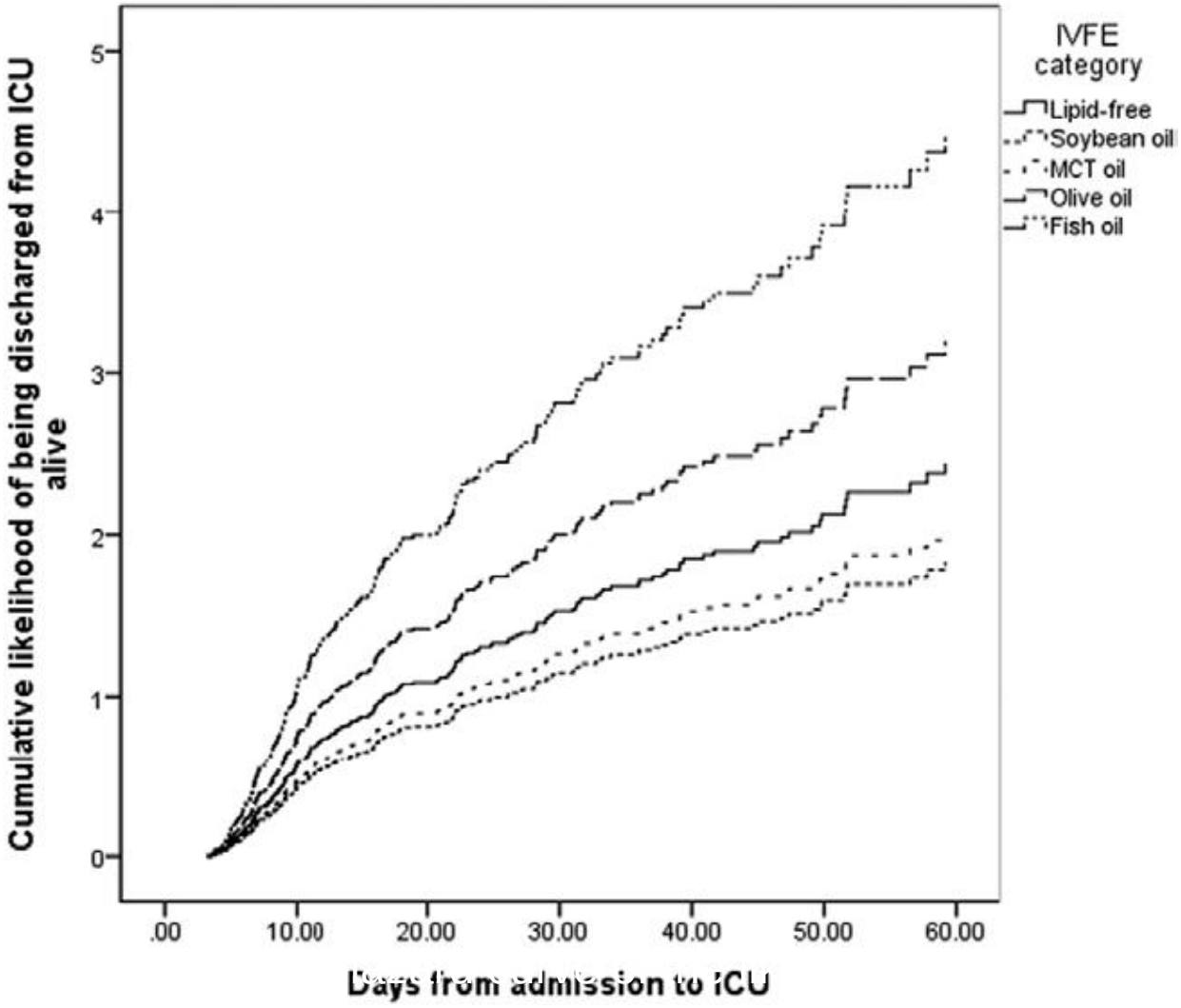
Edmunds et al CCM, 2014: 42:1168



Abbreviations: EN: enteral nutrition; INS: International Nutrition Survey; IVFE: intravenous fat emulsion; PN: parenteral nutrition

The Effects of different IV Fat Emulsions on Clinical Outcomes in Critically Ill Patients

Edmunds et al CCM, 2014: 42:1168

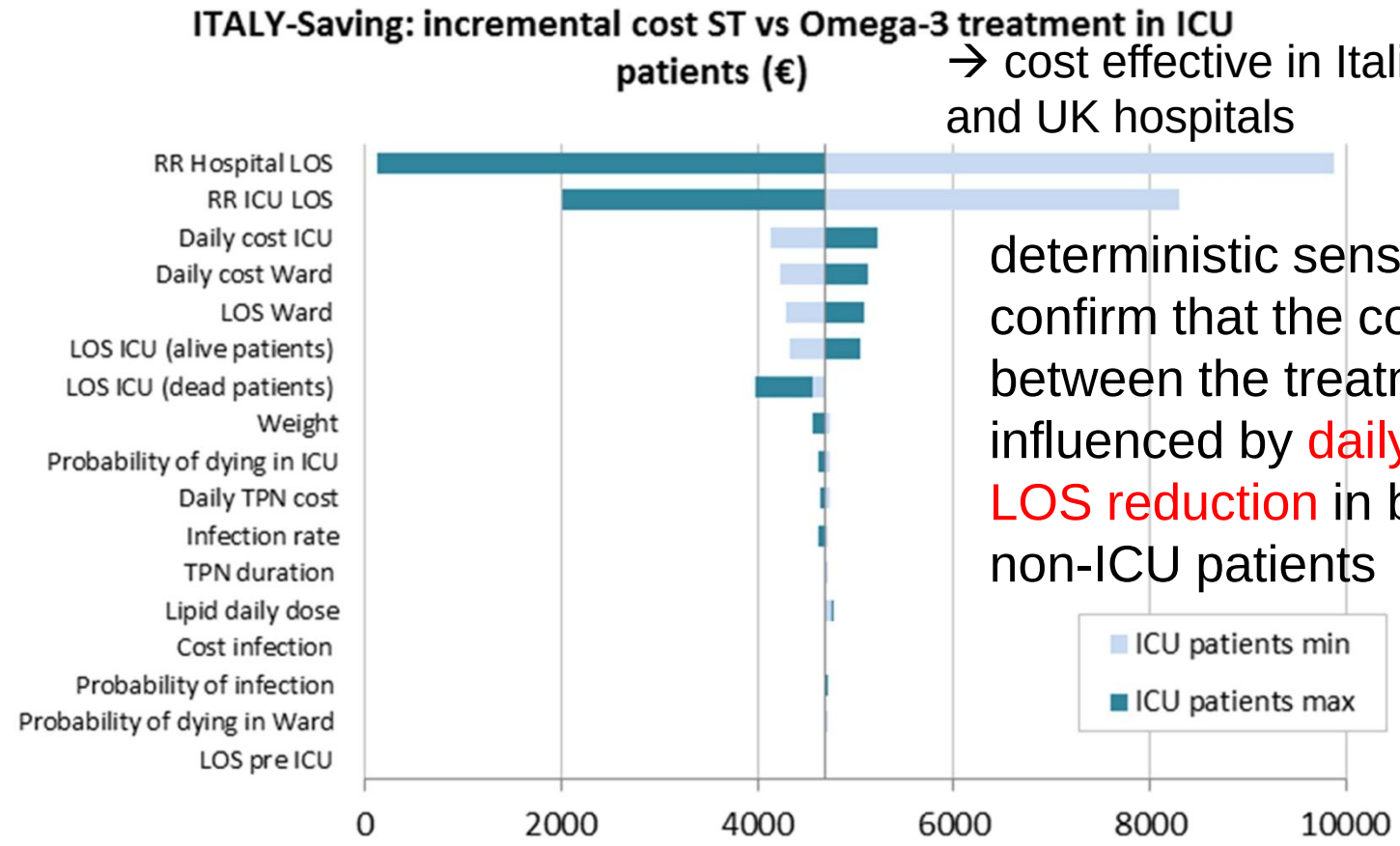


Adult patients who were admitted to the ICU for more than
72 hours, were mechanically ventilated within 48 hours, received
exclusive PN for ≥ 5 days, and
did not change IV fat emulsion type during the data collection period

Cost-effectiveness of omega-3 fatty acid supplements in PN therapy in hospitals: a discrete event simulation model

Pradelli et al, Clin Nutr 2014;33:785

n = 23 studies with a total of 1502 patients



→ cost effective in Italian, French, German and UK hospitals

deterministic sensitivity analysis confirm that the cost difference between the treatments is mostly influenced by daily ward costs and LOS reduction in both ICU and non-ICU patients

LOS, length of stay; TPN, total parenteral nutrition; RR, relative risk; ST, standard treatment.

Latest studies/meta-analyses evaluating the benefits of n-3 PUFA in PN
Klek, J Clin Med, 2016

Author	Year	Population	Intervention	Duration	Result
Jiang [117]	2010	Colectomy and rectotomy (n = 206)	LCT vs LCT+fish oil	7 days post-surgery	Significant reduction in LOS and SIRS
Wang [115]	2012	Gastrointestinal	MCT/LCT *vs.*	5 days	Amelioration of liver
Han [116]	De Miranda Torrinhas [118] 2013	Surgery for gastrointestinal cancer (n = 63)	MCT/LCT *vs.* fish oil	3 days post-surgery	Significant increase in IL-10 levels (day 3), decrease in IL-6 and IL-10 levels (day 6), less decline in leukocyte oxidative burst
Zhu [119]	Chen [123] 2010	Major abdominal surgery, meta-analysis (n = 892)	Fish oil *vs.* various control emulsions	Various	Decreased LOS in the hospital and ICU, reduced postoperative infection rate, improved liver function
Zhu [120]	Li [124] 2013	Major surgery, meta-analysis (n = 1487)	Fish oil	Various	Decreased infection rate, LOS, and liver dysfunction; no effect on mortality
Berger [121]	Pradelli [125] 2012	Subgroup analysis in patients undergoing major abdominal surgery and not admitted to ICU (n = 740)	n-3 PUFA-enriched *vs.* standard lipid emulsions	Various	Significant reduction in the infection rate and LOS
	Tian [126] 2013	Surgical patients, meta-analysis (n = 306)	Fish oil/LCT/MCT *vs.* LCT/olive oil	Various	No significant difference, fish oil less toxic to liver when compared to LCT or olive oil

Clin. Nutr. 2013, 32:503

JPEN 2010;34:387

Am J Clin Nutr

Clin. Nutr. 2014, 33, 226

Crit. Care 2012, 16, R184

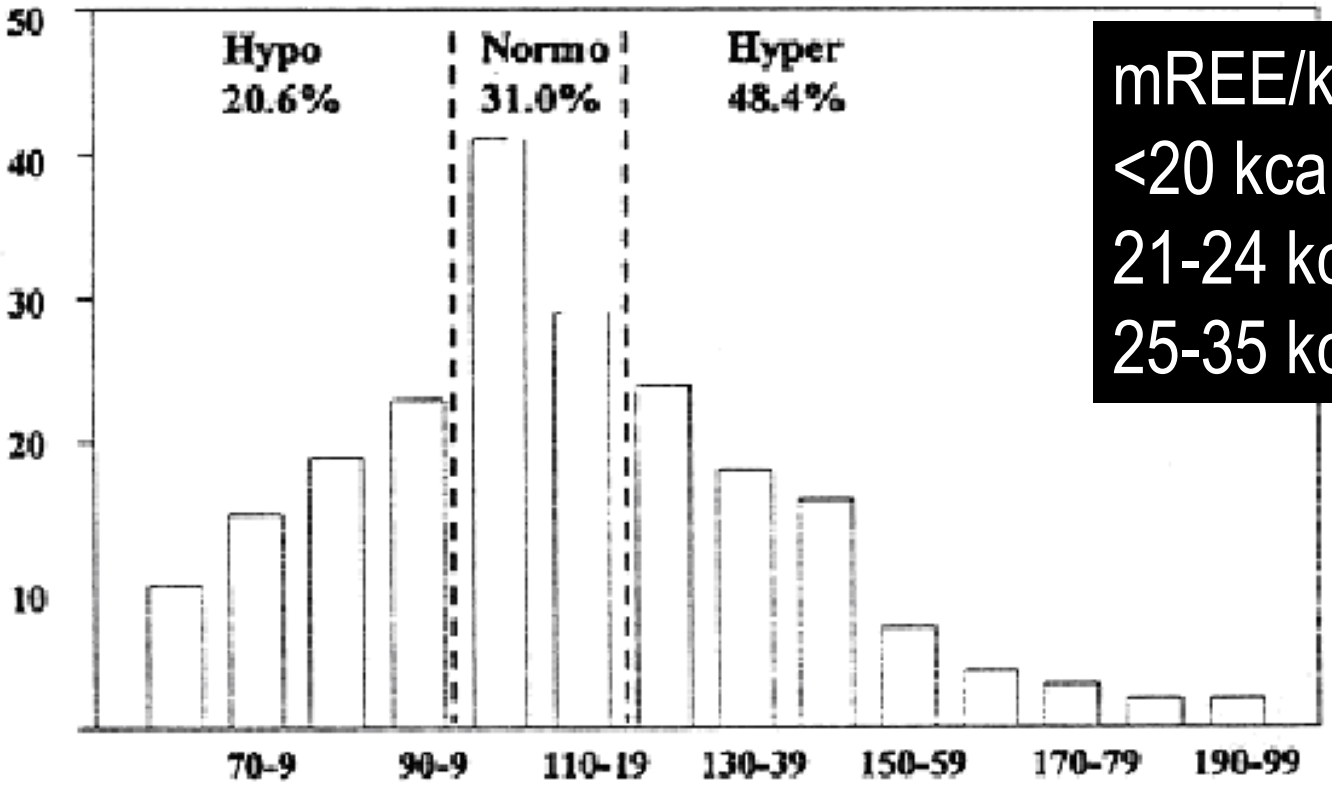
Nutr. Rev. 2013, 71, 815

Where are we standing?

- Under- and overfeeding to be avoided
- Route: not so important but enteral has non nutritional advantages
- Critically ill patients require glutamine in nutritional doses
- Micronutrients integral part of feeding – some patients have higher requirements for AOX
- Convincing evidence that PN solutions in 2016 are better balances than those available in the 90s – including a combination of fatty acids with w-3 is positive

Distribution of patients' m.E.E. by % predicted E.E.

McClave SA et al, JPEN 1998, 22:375

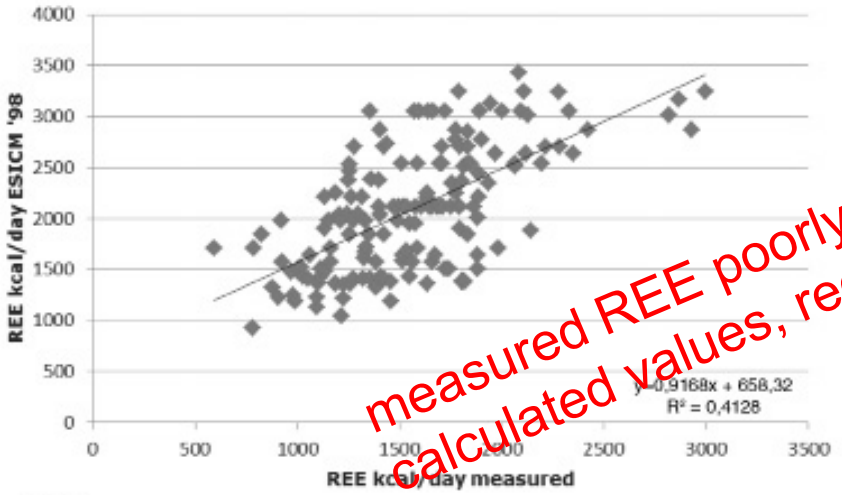


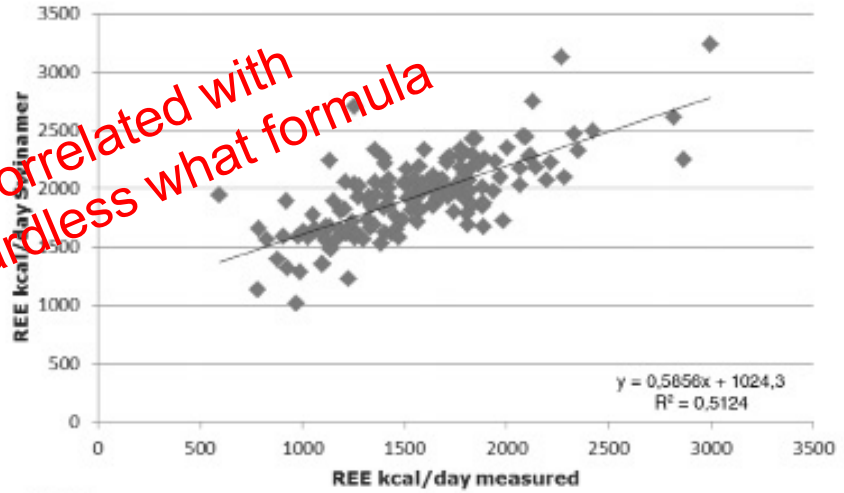
mREE/kg =
<20 kcal : 37%
21-24 kcal : 29%
25-35 kcal : 34%

% Metabolism (MREE/HB-REE x 100)

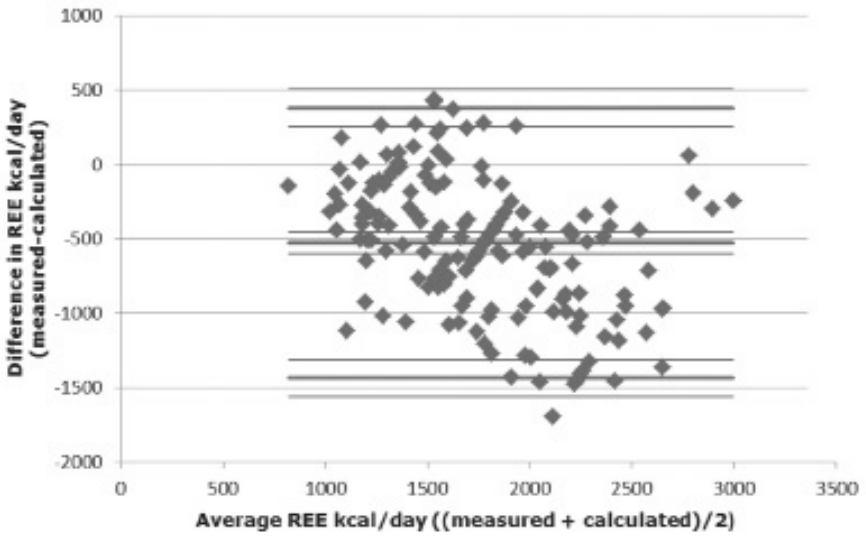
Calorimetry in 213 patients on mechanical ventilation

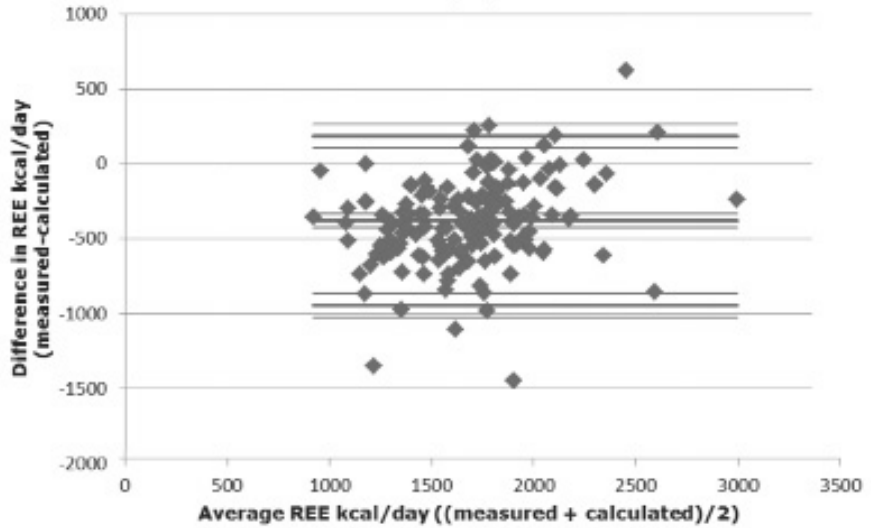
Measured *vs calculated resting EE in critically ill adult patients.* Do mathematics match the gold standard? DeWaele et al Minerva Medica 2015





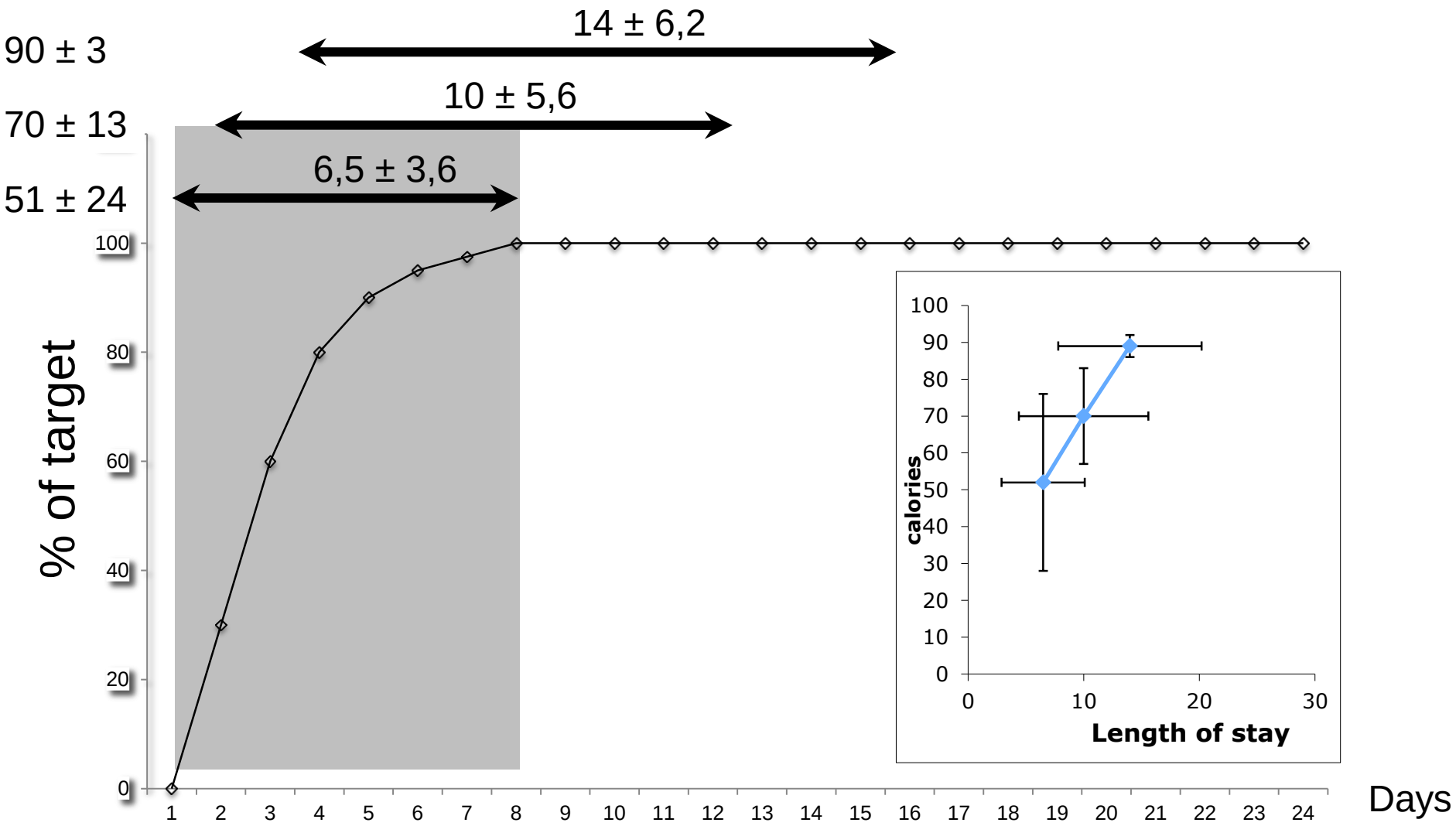
measured REE poorly correlated with calculated values, regardless what formula





Don’t get fooled

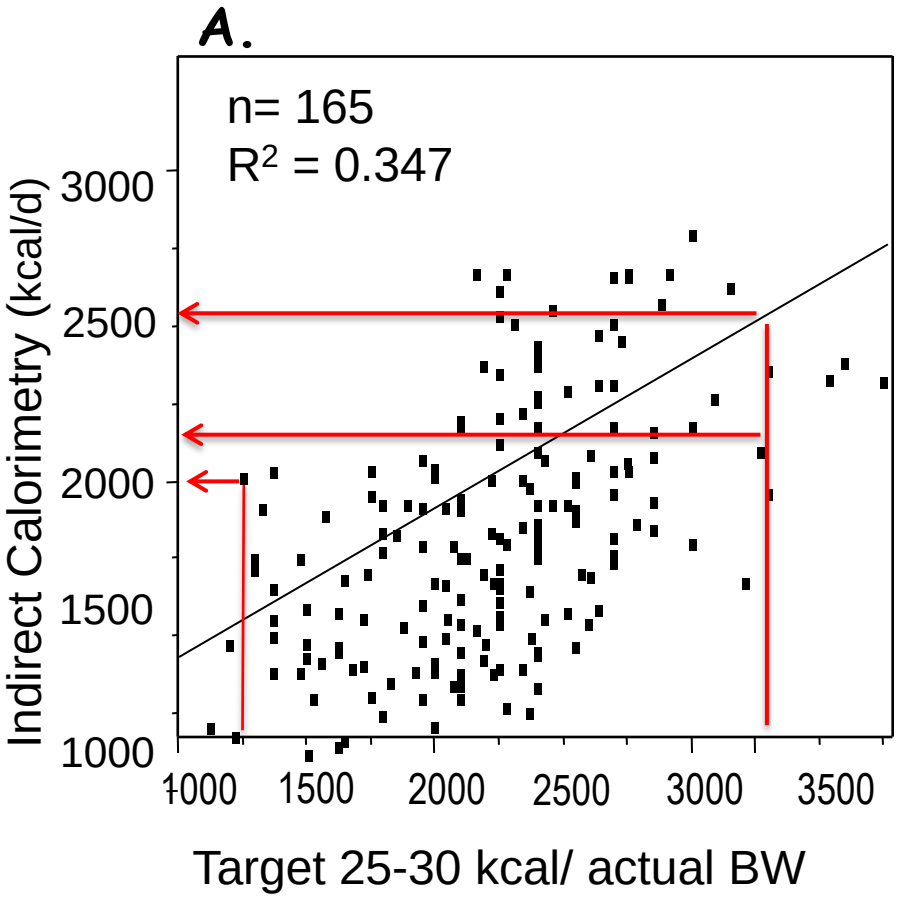
Courtesy Eric Fontaine



Why do patients stay shorter? Less severe → they do better

Development and current use of parenteral nutrition in critical care

Berger & Pichard, Crit Care 2014



Conclusion

- The debate PN versus EN is over
- Feeding «reasonably» is cost effective
- Glutamine = an essential component of nutrition that should be present at nutritional doses
  - Present normally in EN
  - Should be completed to PN
- Fatty acids: should be present in balanced proportions
- Personalized nutrition care = adapted therapy!

Geiranger fjorden - Norway

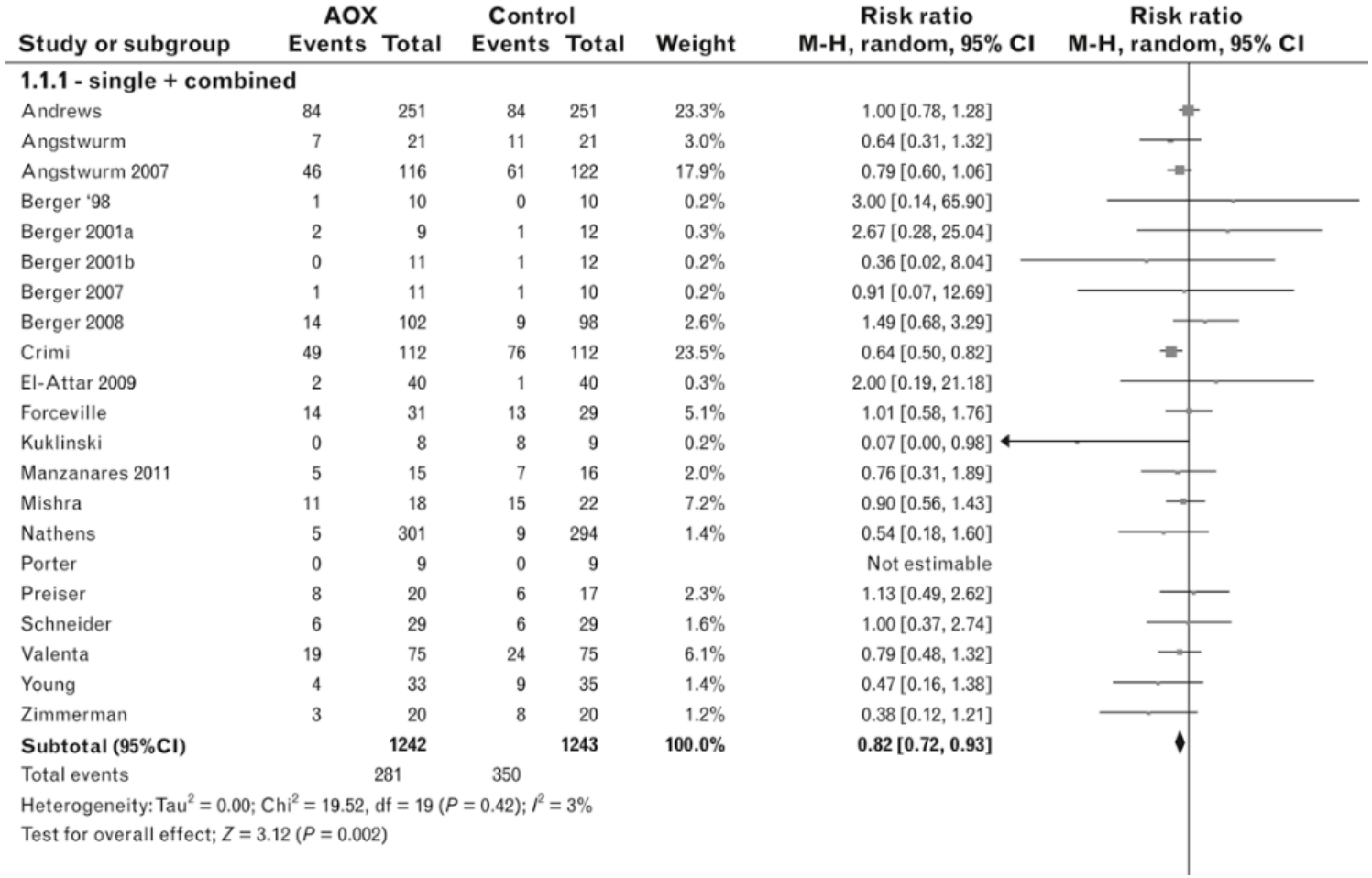
Over- Selected populations → different results between PRCT & observations trials

	Screened	Enrolled	%
EPaNIC 2011	8703	4640	53.3
SPN 2013	2555	305	11.9
REDOXS 2013	5633	1223	21.9
MetaPlus 2014	? (22 months 14 ICUs)	301	?
CALORIES 2015	11108	2400	21.6
PERMIT 2016	6400	894	14.0
PEPaNIC 2016	7519	1440	19.2

Update on antioxidant micronutrients in the critically ill.

Manzanares, W; Langlois, P; Hardy, G

CO Clinical Nutrition & Metabolic Care. 16(6):719-725, November 2013.



Study or subgroup	AOX Events	AOX Total	Control Events	Control Total	Weight	Risk ratio M-H, random, 95% CI
1.1.1 - single + combined						
Andrews	84	251	84	251	23.3%	1.00 [0.78, 1.28]
Angstwurm	7	21	11	21	3.0%	0.64 [0.31, 1.32]
Angstwurm 2007	46	116	61	122	17.9%	0.79 [0.60, 1.06]
Berger '98	1	10	0	10	0.2%	3.00 [0.14, 65.90]
Berger 2001a	2	9	1	12	0.3%	2.67 [0.28, 25.04]
Berger 2001b	0	11	1	12	0.2%	0.36 [0.02, 8.04]
Berger 2007	1	11	1	10	0.2%	0.91 [0.07, 12.69]
Berger 2008	14	102	9	98	2.6%	1.49 [0.68, 3.29]
Crimi	49	112	76	112	23.5%	0.64 [0.50, 0.82]
El-Attar 2009	2	40	1	40	0.3%	2.00 [0.19, 21.18]
Forceville	14	31	13	29	5.1%	1.01 [0.58, 1.76]
Kuklinski	0	8	8	9	0.2%	0.07 [0.00, 0.98]
Manzanares 2011	5	15	7	16	2.0%	0.76 [0.31, 1.89]
Mishra	11	18	15	22	7.2%	0.90 [0.56, 1.43]
Nathens	5	301	9	294	1.4%	0.54 [0.18, 1.60]
Porter	0	9	0	9		Not estimable
Preiser	8	20	6	17	2.3%	1.13 [0.49, 2.62]
Schneider	6	29	6	29	1.6%	1.00 [0.37, 2.74]
Valenta	19	75	24	75	6.1%	0.79 [0.48, 1.32]
Young	4	33	9	35	1.4%	0.47 [0.16, 1.38]
Zimmerman	3	20	8	20	1.2%	0.38 [0.12, 1.21]
Subtotal (95%CI)		**1242**		**1243**	**100.0%**	**0.82 [0.72, 0.93]**
Total events		281		350		

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 19.52$, df = 19 ($P = 0.42$); $I^2 = 3\%$

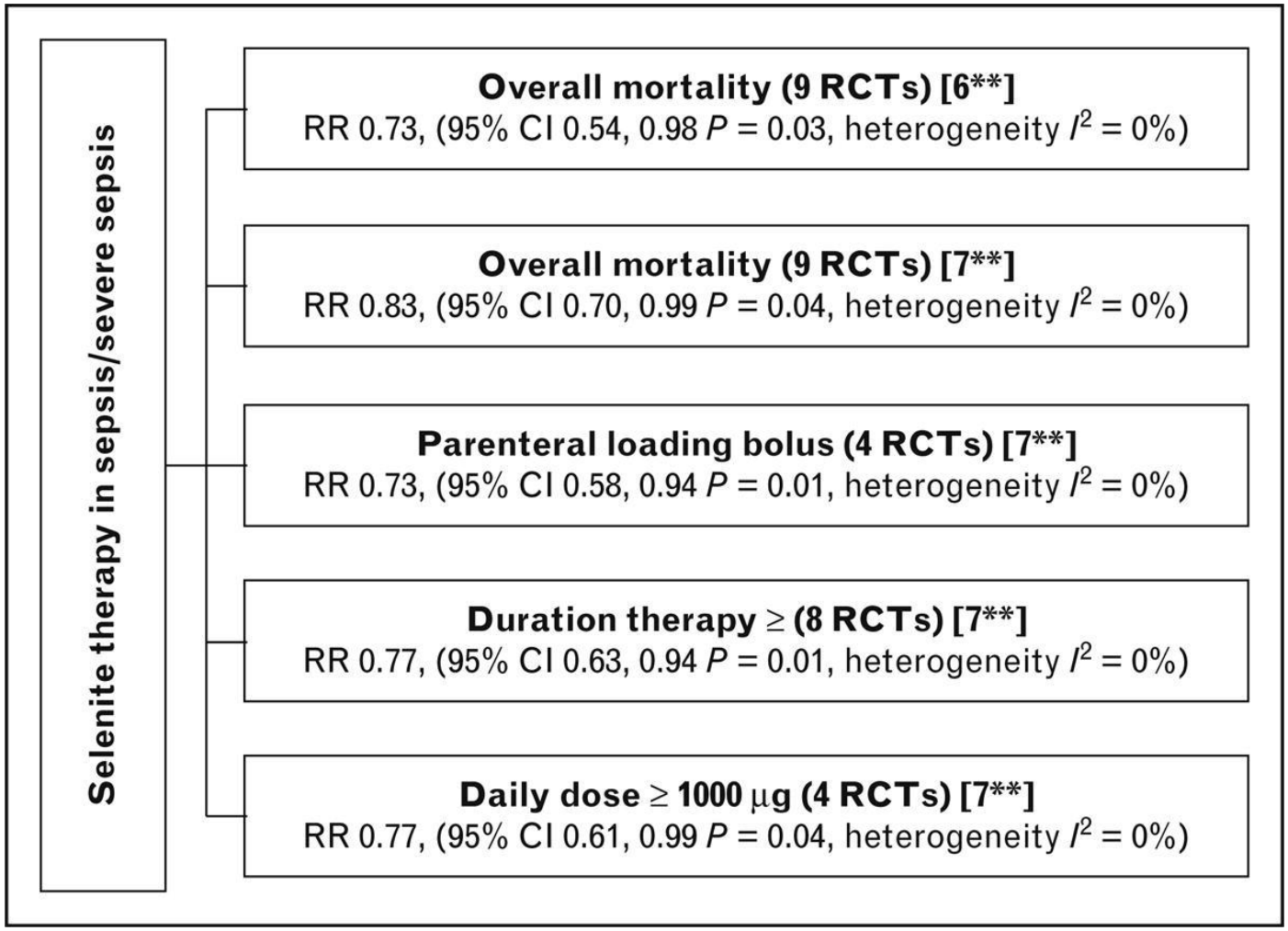
Test for overall effect; $Z = 3.12$ ($P = 0.002$)

FIGURE 1 . Overall effect of antioxidant micronutrient strategies on mortality. This Forest plot shows that after aggregating **20 randomized trials**, antioxidants may be able to significantly decrease mortality in ICU patients (RR: 0.82, 95% CI 0.72-0.93, P = 0.002; I2 = 3% P = 0.42).

Update on antioxidant micronutrients in the critically ill.

Manzanares, W; Langlois, P; Hardy, G

CO Clinical Nutrition & Metabolic Care. 16(6):719-725, November 2013.



high-dose micronutrient supplements such as selenium, zinc, and antioxidant vitamins are able to **decrease infections and reduce mortality**.

The treatment effect may be greatest in the most seriously ill patients