

Evidence for immunomodulating supplements in sepsis: A systematic review of the recent evidence

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Potential conflicts *Gordon S. Doig*

Relevant financial relationships with a commercial interest:

- **Fresenius Kabi**, Academic Research Grants (Past), Consultant and Speaker's Honoraria (Current)
- **Baxter Healthcare**, Academic Research Grant (Current), Consultant and Speaker's Honoraria (Current)
- **Nestle Healthcare**, Academic Research Grant (Current), Consultant and Speaker's Honoraria (Current)



Overview

- Arginine in sepsis
- Glutamine in sepsis
- Omega-3 fatty acids in sepsis
- Selenium in sepsis



Literature search

Intensive Care Medicine
December 2003, Volume 29, Issue 12, pp 2119-2127

Efficient literature searching: a core skill for the practice of evidence-based medicine

Gordon Stuart Doig, Fiona Simpson



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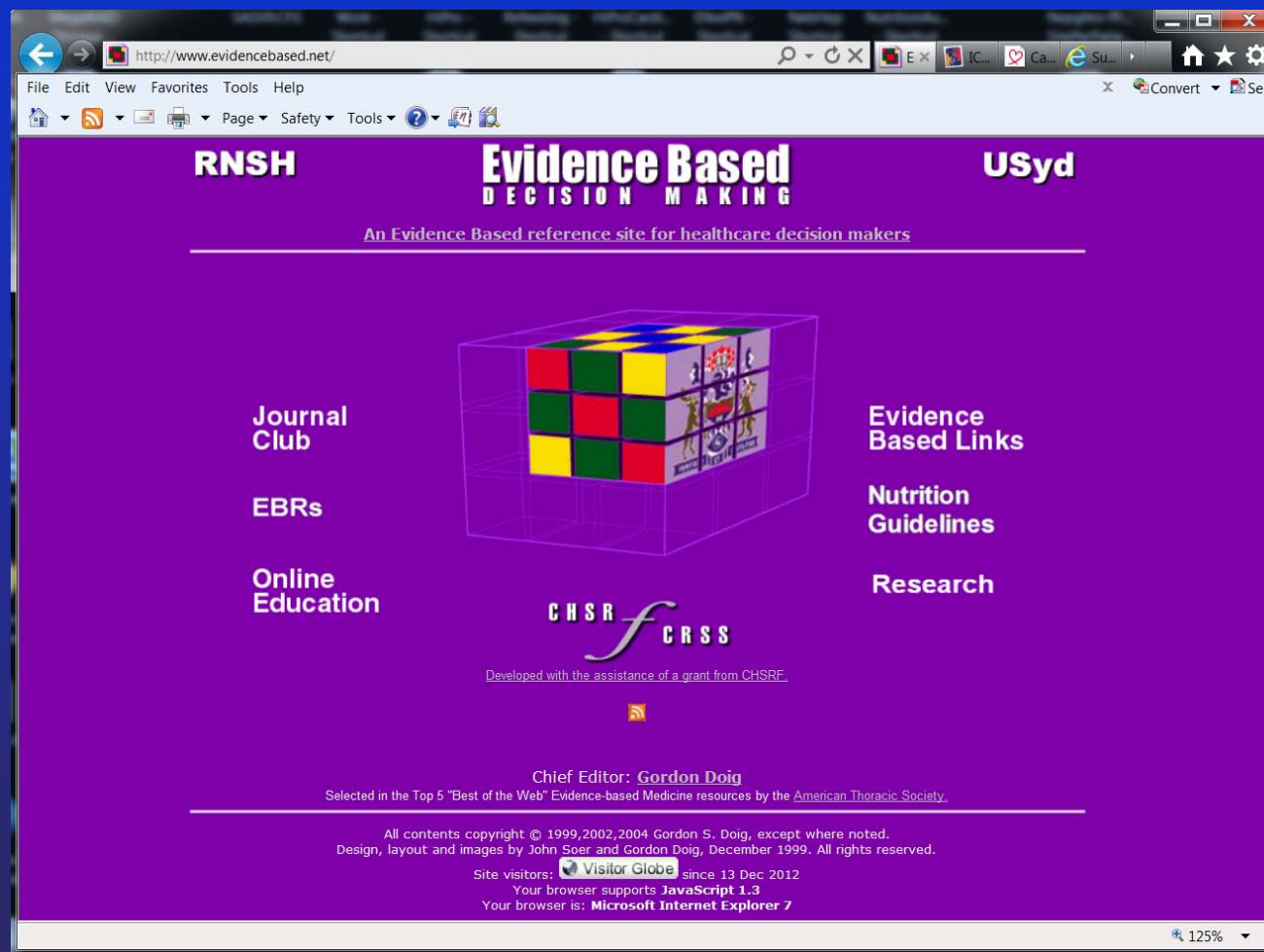
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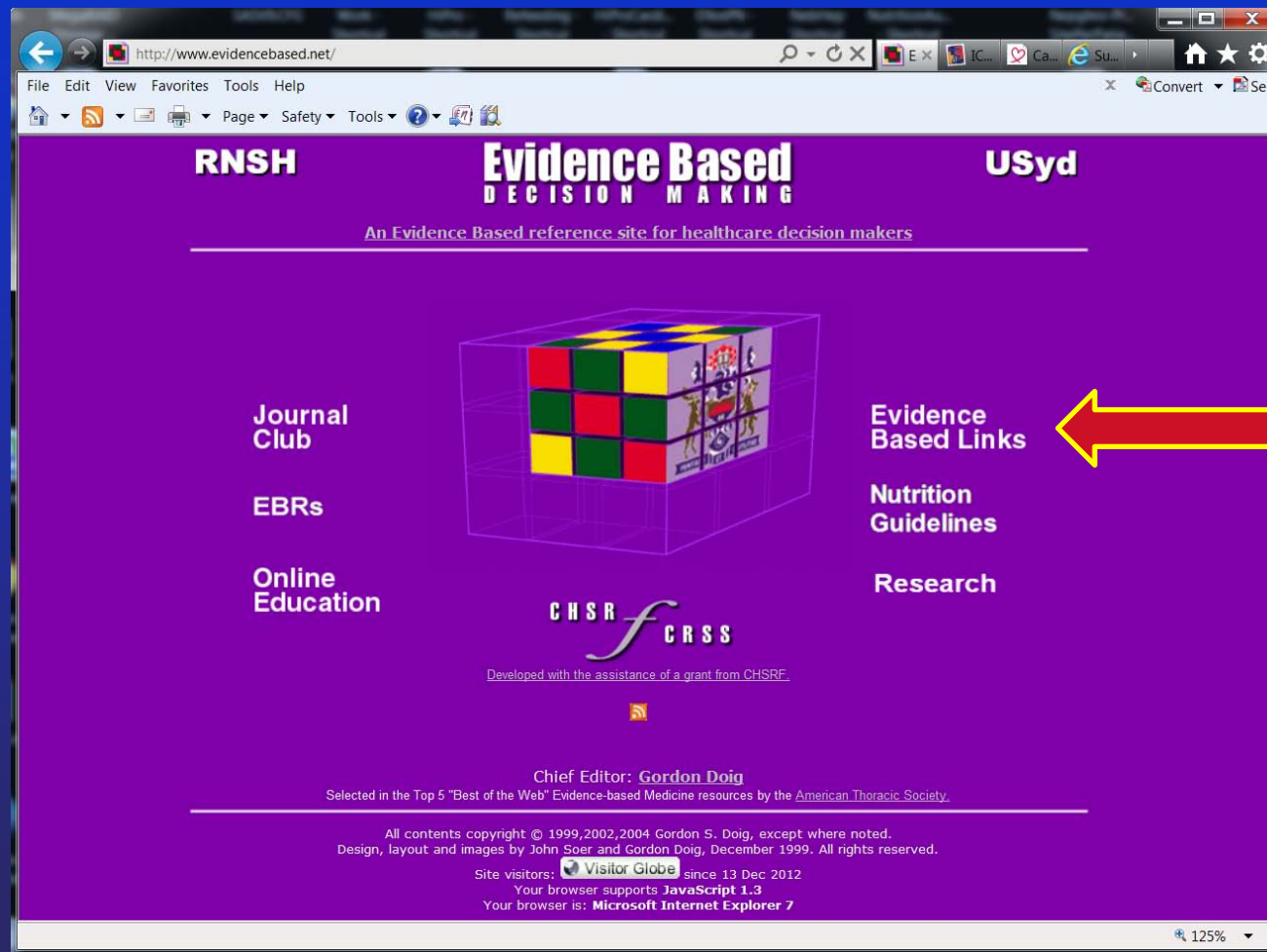
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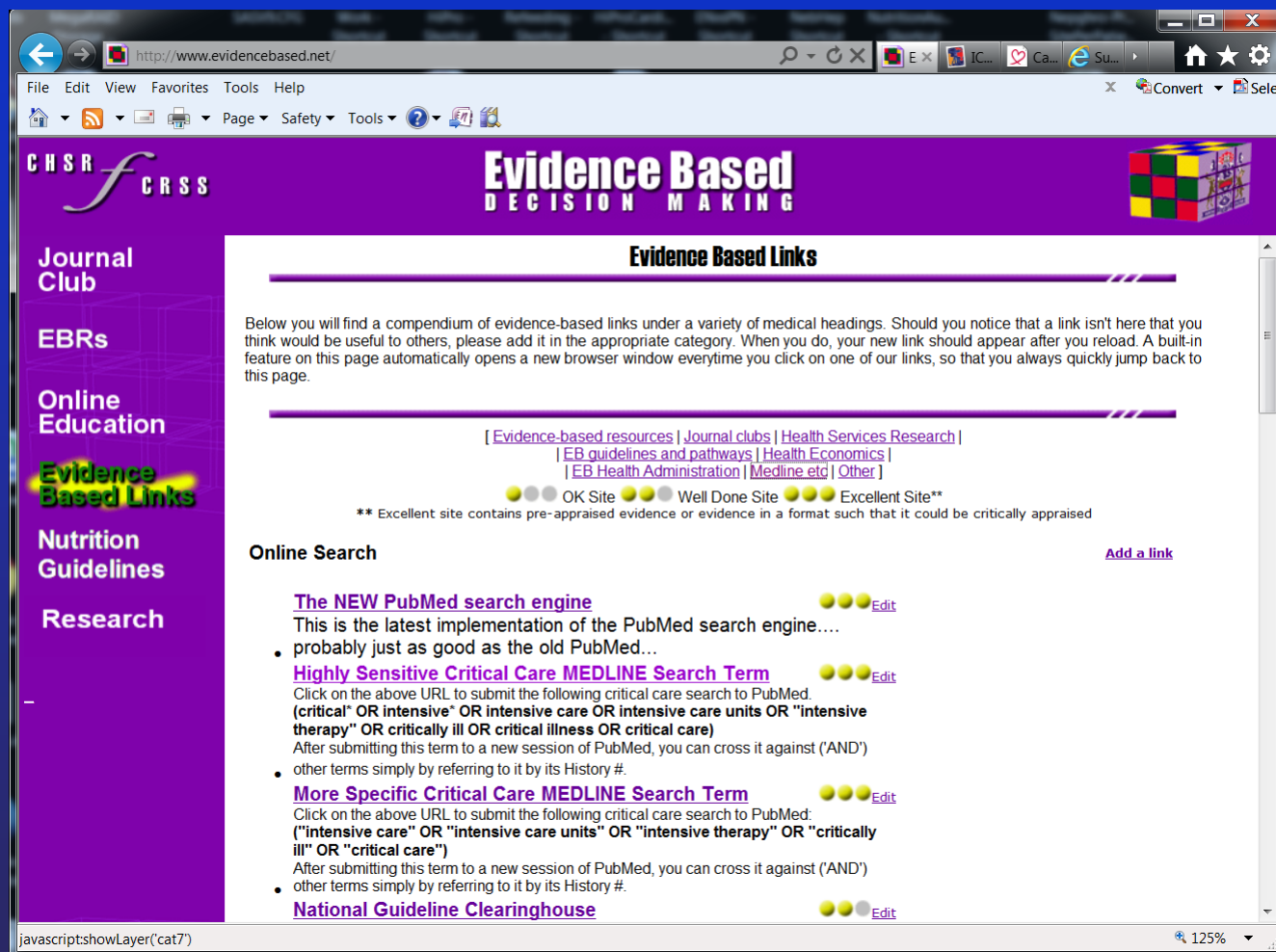
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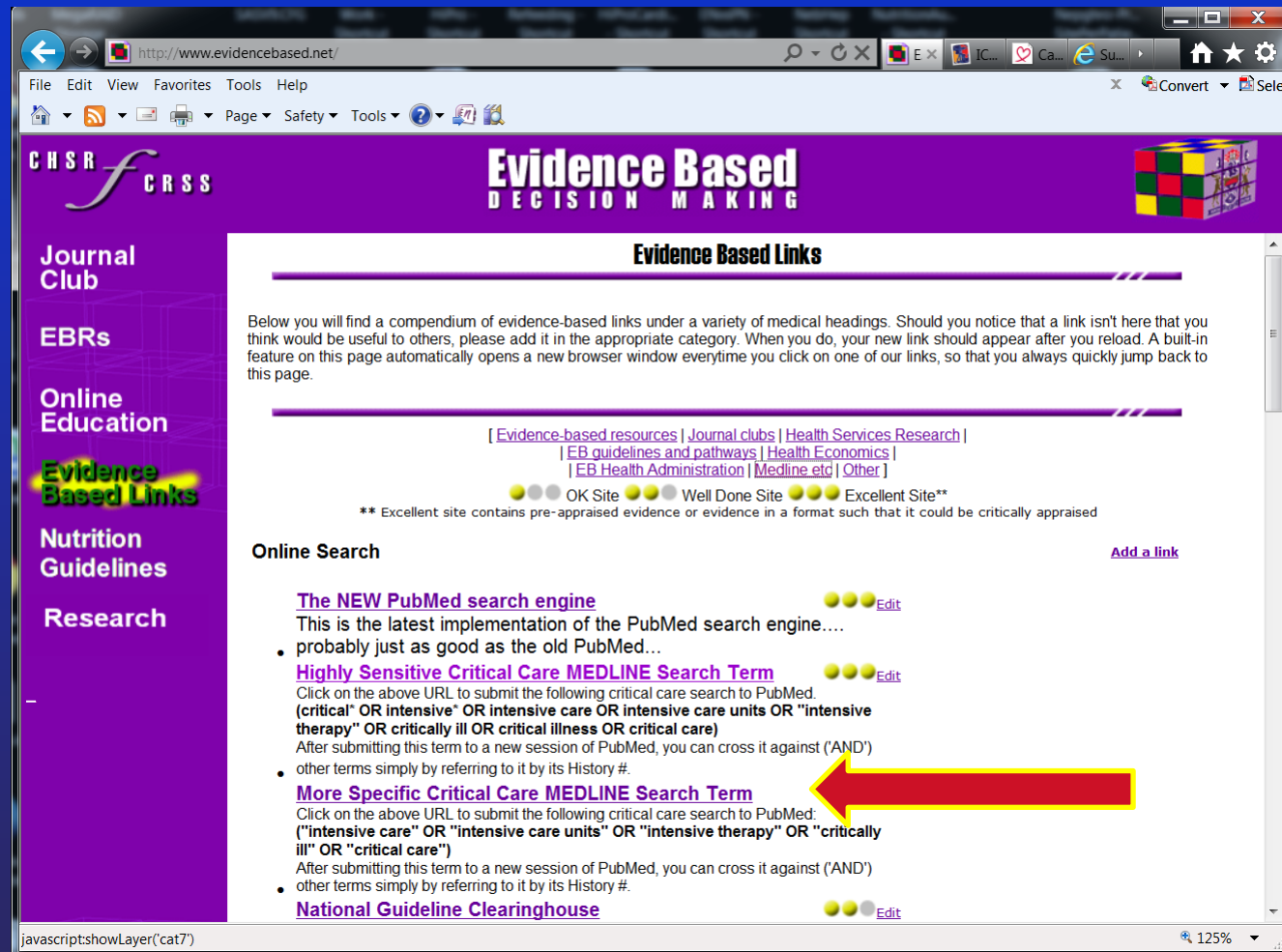
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
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#1 sepsis selenium

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Results: 5 of 38

Selenium supplementation for sepsis: a meta-analysis of randomized controlled trials.

Kong Z, Wang F, Ji S, Deng X, Xia Z.

Am J Emerg Med. 2013 Aug; 31(8):1170-5. Epub 2013 Jun 21.

The effect of selenium therapy on mortality in patients with sepsis syndrome: a systematic review and meta-analysis of randomized controlled trials.

Alhazzani W, Jacobi J, Sindi A, Hartog C, Reinhart K, Kokkoris S, Gerlach H, Andrews P, Drabek T, Manzanares W, et al.

Crit Care Med. 2013 Jun; 41(6):1555-64.

Results: 5 of 11

Selenium supplementation for sepsis: a meta-analysis of randomized controlled trials.

Kong Z, Wang F, Ji S, Deng X, Xia Z.

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Crit Care Med. 2013 Jun; 41(6):1555-64.

Results: 2 of 2

Identification of novel biomarkers for sepsis prognosis via urinary proteomic analysis using iTRAQ labeling and 2D-LC-MS/MS.

Su L, Cao L, Zhou R, Jiang Z, Xiao K, Kong W, Wang H, Deng J, Wen B, Tan F, et al.

PLoS One. 2013; 8(1):e54237. Epub 2013 Jan 23.

Low serum alpha-tocopherol and selenium are associated with accelerated apoptosis in severe sepsis.

Weber SU, Lehmann LE, Schewe JC, Thiele JT, Schröder S, Book M, Hoefft A, Stüber F.

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Literature search

- Arginine in sepsis (+ specific critical care terms, in clinical queries)
- Glutamine in sepsis (+ specific critical care terms , in clinical queries)
- Omega-3 fatty acids in sepsis (+ specific critical care terms , in clinical queries)
- Selenium in sepsis (+ specific critical care terms , in clinical queries)



Arginine in sepsis

- Arginine availability is reduced in sepsis, which can lead to reduced nitric oxide synthesis, loss of microcirculatory regulation, and enhanced production of superoxide and peroxynitrite.



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Bower RH, Cerra FB, Bershadsky B, Licari JJ, Hoyt DB, Jensen GL, Van Buren CT, Rothkopf MM, Daly JM, Adelsberg BR. Early enteral administration of a formula (Impact) supplemented with arginine, nucleotides, and fish oil in intensive care unit patients: results of a multicenter, prospective, randomized, clinical trial. *Crit Care Med*. 1995 Mar;23(3):436-49.

Bertolini G, Iapichino G, Radrizzani D, Facchini R, Simini B, Bruzzone P, Zanforlin G, Tognoni G. Early enteral immunonutrition in patients with severe sepsis: results of an interim analysis of a randomized multicentre clinical trial. *Intensive Care Med*. 2003 May;29(5):834-40.



Early enteral administration of a formula (Impact Registered Trademark) supplemented with arginine, nucleotides, and fish oil in intensive care unit patients: Results of a multicenter, prospective, randomized, clinical trial

Bower, Robert H. MD FACS; Cerra, Frank B. MD FCCM; Bershadsky, Boris PhD MSEE; Licari, Jerome J. PhD; Hoyt, David B. MD FACS; Jensen, Gordon L. MD PhD; Van Buren, Charles T. MD; Rothkopf, Michael M. MD FACP; Daly, John M. MD FACS; Adelsberg, Bernard R. MD FACCP

Patients were randomised to receive:

- 1) Arginine enhanced EN (Impact) or
- 2) standard EN

326 patients were enrolled, only 297 were included in analysis

Mortality:

15.5% (23/147) enhanced EN died vs 7.6% (10/132) standard EN

Using Fisher's Exact Test, mortality was significantly increased in patients receiving the arginine supplemented EN ($P=0.045$).

Bower RH, Cerra FB, Bershadsky B, Licari JJ, Hoyt DB, Jensen GL, Van Buren CT, Rothkopf MM, Daly JM, Adelsberg BR. Early enteral administration of a formula (Impact) supplemented with arginine, nucleotides, and fish oil in intensive care unit patients: results of a multicenter, prospective, randomized, clinical trial. Crit Care Med. 1995 Mar;23(3):436-49.



Guido Bertolini
Gaetano Iapichino
Danilo Radrizzani
Rebecca Facchini
Bruno Simini
Paola Bruzzzone
Giancarlo Zanforlin
Gianni Tognoni

Early enteral immunonutrition in patients with severe sepsis

Results of an interim analysis of a randomized multicentre clinical trial

Patients were randomised to receive:

1) Arginine enhanced EN (Perative) or 2) standard PN

Interim analysis conducted after 237 patients enrolled. Subgroup analysis planned for septic patients.

Table 3 Summary of results. (*ARD* Absolute risk difference, *ICU* Intensive care unit, *EN* Enteral nutrition, *PN* Parenteral nutrition, *MH* Mantel-Haenszel chi-squared test)

	Mortality in patients with sever sepsis				
	EN (<i>n</i> =18)	PN (<i>n</i> =21)	<i>P</i> values		
	<i>n</i> (%)		ARD (95% CI)	MH	Fisher test
ICU mortality	8 (44.4%)	3 (14.3%)	30.1 (1.5-58.7)	0.039	0.072
28-day mortality	8 (44.4%)	5 (23.8%)	20.6 (-9.4-50.6)	0.179	0.196

Bertolini G, Iapichino G, Radrizzani D, Facchini R, Simini B, Bruzzzone P, Zanforlin G, Tognoni G. Early enteral immunonutrition in patients with severe sepsis: results of an interim analysis of a randomized multicentre clinical trial. *Intensive Care Med.* 2003 May;29(5):834-40.



Glutamine in sepsis

- Glutamine levels are reduced during critical illness.
- Exogenous supplementation can improve gut mucosal atrophy and permeability, possibly leading to reduced bacterial translocation.
- Other potential benefits include enhanced immune cell function, decreased proinflammatory cytokine production, and higher levels of glutathione and antioxidative capacity.



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Fuentes-Orozco C, Anaya-Prado R, Gonzalez-Ojeda A et al. L-alanyl-L-glutamine-supplemented parenteral nutrition improves infectious morbidity in secondary peritonitis. *Clin Nutr* **2004**;23:13–21

Beale RJ, Sherry T, Lei K et al. Early enteral supplementation with key pharmaconutrients improves sequential organ failure assessment score in critically ill patients with sepsis: outcome of a randomized, controlled, double-blind trial. *Crit Care Med* **2008**;36:131–144

Heyland D, Muscedere J, Wischmeyer PE, Cook D, Jones G, Albert M, Elke G, Berger MM, Day AG; Canadian Critical Care Trials Group. A randomized trial of glutamine and antioxidants in critically ill patients. *N Engl J Med*. **2013** Apr 18;368(16):1489-97.



Glutamine in sepsis

- Two small trials (33 patients and 55 patients) conducted in septic populations failed to demonstrate mortality benefits.

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Glutamine in sepsis

- Two small trials (33 patients and 55 patients) conducted in septic populations failed to demonstrate mortality benefits.
- Due to excess mortality demonstrated in the most recent large scale trial conducted in critically ill patients, use of glutamine in patients with multiple organ dysfunction syndrome, especially renal dysfunction, is warranted.

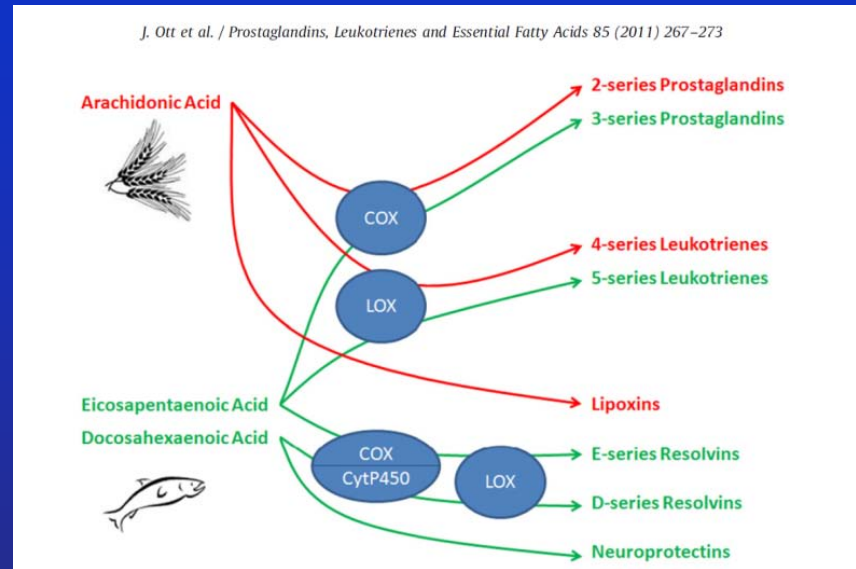
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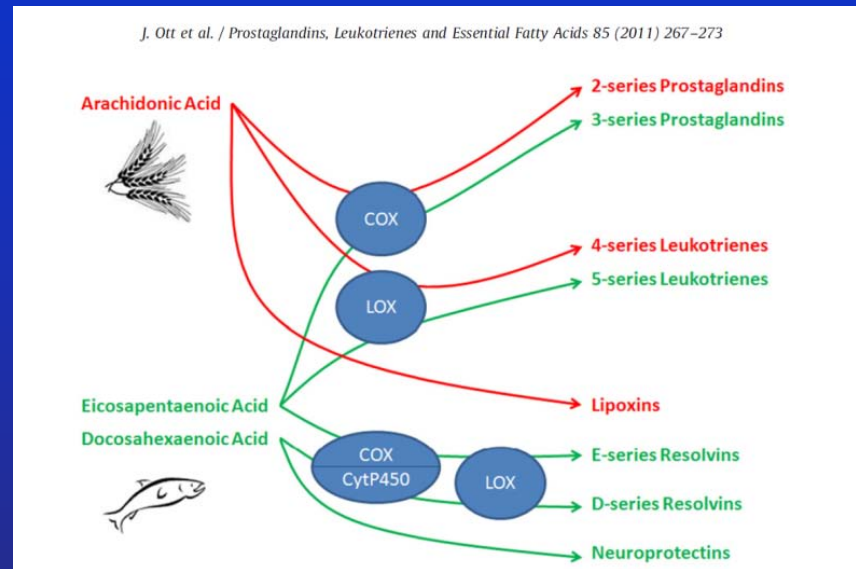
Lipids in sepsis



The omega-3 fatty acids eicosapentaenoic acid (EPA) and gamma-linolenic acid (GLA) are eicosanoid precursors.



Lipids in sepsis

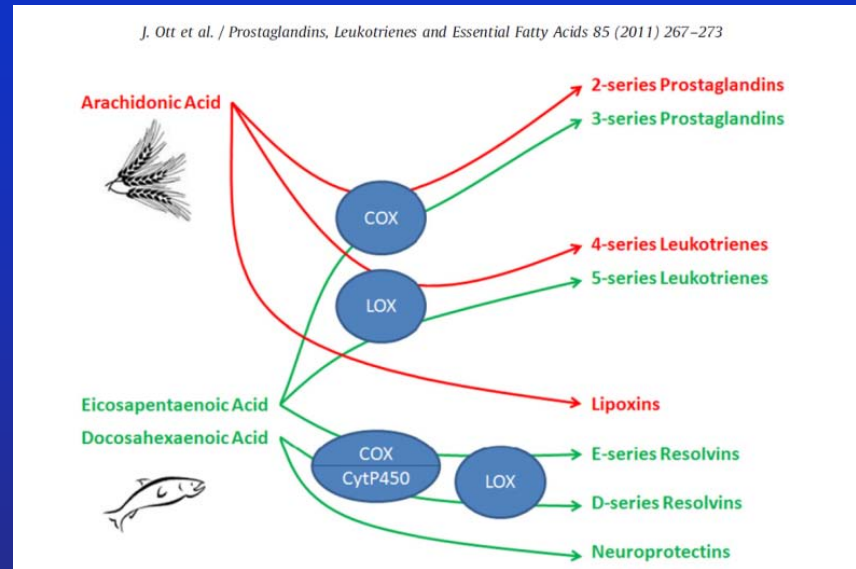


The omega-3 fatty acids eicosapentaenoic acid (EPA) and gamma-linolenic acid (GLA) are eicosanoid precursors.

The prostaglandins, leukotrienes, and thromboxanes produced from EPA/GLA are less potent than their arachidonic acid-derived equivalents, reducing the proinflammatory impact on the immune response



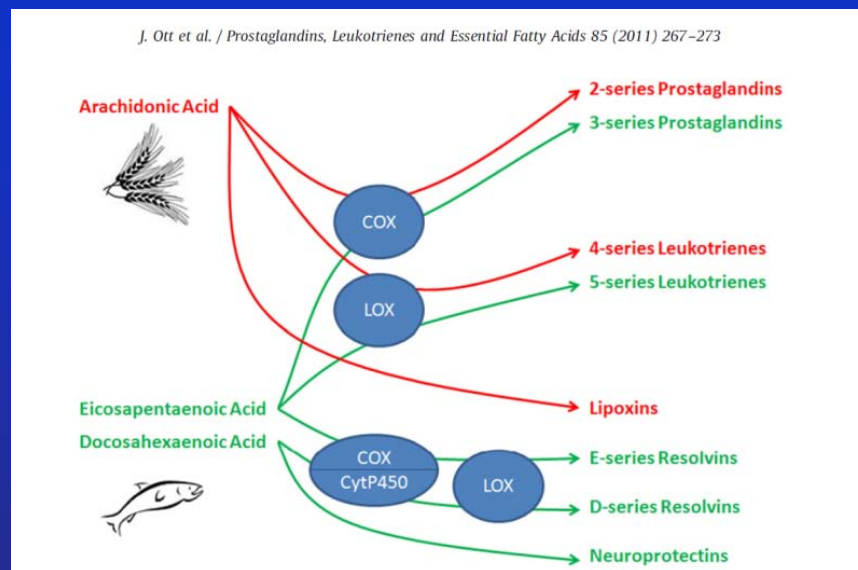
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Rangel-Huerta OD, Aguilera CM, Mesa MD, Gil A. Omega-3 long-chain polyunsaturated fatty acids supplementation on inflammatory biomarkers: a systematic review of randomised clinical trials. *Br J Nutr.* **2012** Jun;107 Suppl 2:S159-70.



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- Pontes-Arruda A, Aragão AM, Albuquerque JD. Effects of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in mechanically ventilated patients with severe sepsis and septic shock. *Crit Care Med.* **2006** Sep;34(9):2325-33.
- Pontes-Arruda A, Martins LF, de Lima SM, Isola AM, Toledo D, Rezende E, Maia M, Magnan GB; Investigating Nutritional Therapy with EPA, GLA and Antioxidants Role in Sepsis Treatment (INTERSEPT) Study Group. Enteral nutrition with eicosapentaenoic acid, γ -linolenic acid and antioxidants in the early treatment of sepsis: results from a multicenter, prospective, randomized, double-blinded, controlled study: the INTERSEPT study. *Crit Care.* **2011** Jun 9;15(3):R144.

Omega-3 long-chain polyunsaturated fatty acids supplementation on inflammatory biomarkers: a systematic review of randomised clinical trials

Oscar D. Rangel-Huerta, Concepcion M. Aguilera, Maria D. Mesa and Angel Gil*

Department of Biochemistry and Molecular Biology Molecular II, Institute of Nutrition and Food Technology, Jose Mataix Biomedical Research Centre, University of Granada, Granada, Spain

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Author (Country)	CONSORT Score	Participants/Type of Pathology/Age	RCT Type	Dose/Period	Outcome	Conclusions
Barbosa <i>et al.</i> (2010) UK	E	n 23; (Exptal = 10; Control = 13); Sepsis (32–80 years)	Randomised, single-blinded.	6.4 g/d fish oil (Average 1.6 g EPA/day + 0.7 g DHA/ day); 5 days	PGE ₂ , Leukotriene, IL-1 β , IL-6, IL-10 and TNF- α .	Inclusion of fish oil in parenteral nutrition of septic ICU patients increases plasma EPA, modifies inflammatory cytokine concentration and improves gas exchange.
Mayer <i>et al.</i> (2003) Germany	VG	n 10; (Exptal = 5; Control = 5); Septic shock (31–71 years)	Randomised, open label.	EPA = 5.2–11.2 g + DHA = 5.6–12.4 g; 10 days (See note 2)	CRP, Leukocytes.	Omega-3 and omega-6 lipid emulsions differentially influence the plasma free fatty acid profile with impact on neutrophil functions.
Mayer <i>et al.</i> (2003) Germany	VG	n 21; (Exptal = Control = 6) Sepsis (> 18 years)	Randomised, open label.	EPA = 4.55–9.8 g/d + DHA = 4.9–10.9 g/d; 5 days (See note 3)	IL-1 β , IL-6, IL-8, IL-10, TNF- α ,	Use of lipid infusions and intravenous feeding have differential impact on inflammatory events.

Rangel-Huerta OD, Aguilera CM, Mesa MD, Gil A. Omega-3 long-chain polyunsaturated fatty acids supplementation on inflammatory biomarkers: a systematic review of randomised clinical trials. Br J Nutr. 2012 Jun;107 Suppl 2:S159-70.

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Author (Country)	CONSORT Score	Participants/Type of Pathology/Age	RCT Type	Dose/Period	Outcome	Conclusions
Barbosa <i>et al.</i> (2010) UK	E	n 23; (Exptal = 10; Control = 13); Sepsis (32–80 years)	Randomised, single-blinded.	6.4 g/d fish oil (Average 1.6 g EPA/day + 0.7 g DHA/ day); 5 days	PGE ₂ , Leukotriene, IL-1 β , IL-6, IL-10 and TNF- α .	Inclusion of fish oil in parenteral nutrition of septic ICU patients increases plasma EPA, modifies inflammatory cytokine concentration and improves gas exchange.
Mayer <i>et al.</i> (2003) Germany	VG	n 10; (Exptal = 5; Control = 5); Septic shock (31–71 years)	Randomised, open label.	EPA = 5.2–11.2 g + DHA = 5.6–12.4 g; 10 days (See note 2)	CRP, Leukocytes.	Omega-3 and omega-6 lipid emulsions differentially influence the plasma free fatty acid profile with impact on neutrophil functions.
Mayer <i>et al.</i> (2003) Germany	VG	n 21; (Exptal = Control = 6) Sepsis (> 18 years)	Randomised, open label.	EPA = 4.55–9.8 g/d + DHA = 4.9–10.9 g/d; 5 days (See note 3)	IL-1 β , IL-6, IL-8, IL-10, TNF- α ,	Use of lipid infusions and intravenous feeding have differential impact on inflammatory events.

- Omega-3 FAs significantly reduced IL-6, increased IL-10 and improved gas exchange.
- No comments on mortality or other patient oriented outcomes.

Rangel-Huerta OD, Aguilera CM, Mesa MD, Gil A. Omega-3 long-chain polyunsaturated fatty acids supplementation on inflammatory biomarkers: a systematic review of randomised clinical trials. *Br J Nutr.* 2012 Jun;107 Suppl 2:S159-70.

Effects of enteral feeding with eicosapentaenoic acid, γ -linolenic acid, and antioxidants in mechanically ventilated patients with severe sepsis and septic shock*

Alessandro Pontes-Arruda, MD, PhD; Afra Maria Albuquerque Aragão, RD;
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A total of 165 patients were recruited.

- 62 patients (37.6% of all enrolled patients) were excluded from analysis due to protocol violations.
- Outcomes are not reported on these 62 patients.

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Although this trial reported a significant reduction in mortality in the 103 'evaluable' patients, due to failure to report outcomes on a large number of patients with protocol violations, confirmation in a subsequent trial was required before clinical recommendations could be made.

Pontes-Arruda A, Aragão AM, Albuquerque JD. Effects of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in mechanically ventilated patients with severe sepsis and septic shock. Crit Care Med. 2006 Sep;34(9):2325-33.

Crit Care. 2011 Jun 9;15(3):R144. doi: 10.1186/cc10267.

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Although these results were interesting, they did not confirm the findings of the 2006 trial. Due to the small size of this trial, clinical recommendations cannot be made. More research is needed.

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Selenium in Sepsis

- Selenium could be beneficial in sepsis through reversible inhibition of NF- κ B binding to DNA, cytokine production blockade, or apoptosis induction in proinflammatory cells.
- Critically ill patients with systematic inflammatory response syndrome (SIRS) and severe sepsis were found to have 40% lower selenium levels compared to critically ill patients without SIRS or severe sepsis.

Kong Z, Wang F, Ji S, Deng X, Xia Z. Selenium supplementation for sepsis: a meta-analysis of randomized controlled trials. *Am J Emerg Med.* **2013** Aug;31(8):1170-5

Alhazzani W, Jacobi J, Sindi A, Hartog C, Reinhart K, Kokkoris S, Gerlach H, Andrews P, Drabek T, Manzanares W, Cook DJ, Jaeschke RZ. The effect of selenium therapy on mortality in patients with sepsis syndrome: a systematic review and meta-analysis of randomized controlled trials. *Crit Care Med.* **2013** Jun;41(6):1555-64.



Selenium in Sepsis

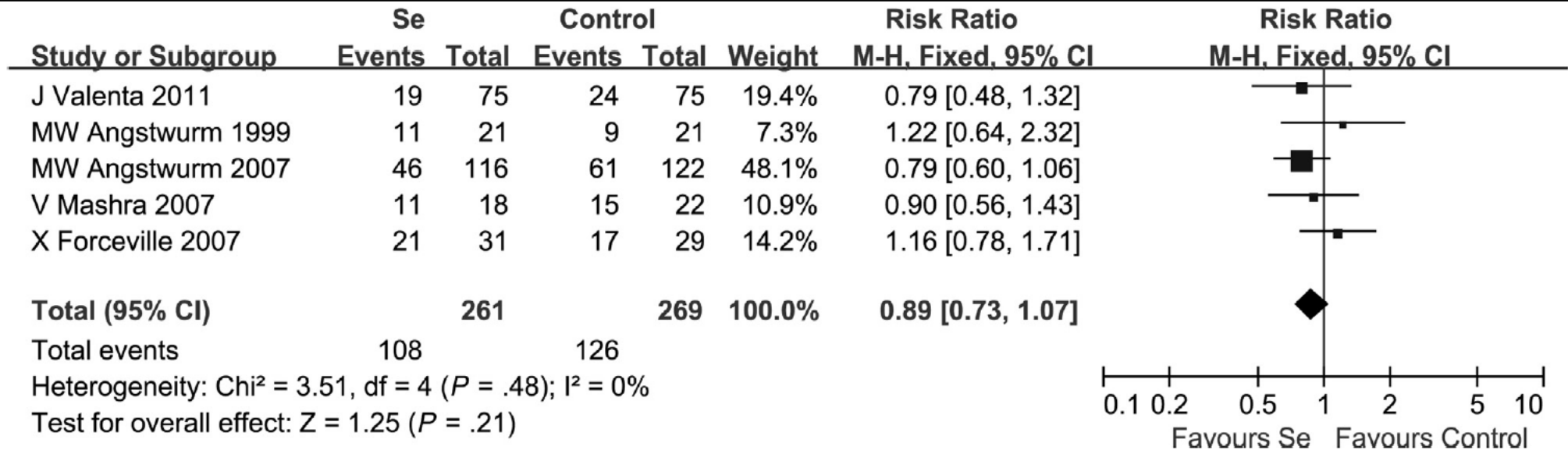


Fig. 3. Summary of relative risks of all-cause mortality in septic patients between the selenium group and the control group.

Study or Subgroup	Selenium		Placebo		Weight	Odds Ratio M-H, Random, 95% CI	Year
	Events	Total	Events	Total			
Zimmermann 1997	3	20	8	20	3.8%	0.26 [0.06, 1.21]	1997
Angstwurm 1999	7	21	11	21	5.6%	0.45 [0.13, 1.58]	1999
Angstwurm 2007	46	116	61	122	32.9%	0.66 [0.39, 1.10]	2007
Mishra 2007	11	18	15	22	5.1%	0.73 [0.20, 2.70]	2007
Forceville 2007	14	31	13	29	8.4%	1.01 [0.37, 2.80]	2007
Montoya 2009	6	34	8	34	6.2%	0.70 [0.21, 2.28]	2009
Valenta 2011	19	75	24	75	17.2%	0.72 [0.35, 1.47]	2011
Manzanares 2011	3	12	4	10	2.6%	0.50 [0.08, 3.08]	2011
Andrews 2011	30	67	27	65	18.3%	1.14 [0.57, 2.27]	2011

Figure 4. The effect of selenium versus placebo on mortality (random effects model). M-H = Mantel-Haenszel.

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Subgroup data

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The authors of two trials kindly provided us with data on the subgroup of patients with sepsis, which we included in the primary analysis (17, 26).

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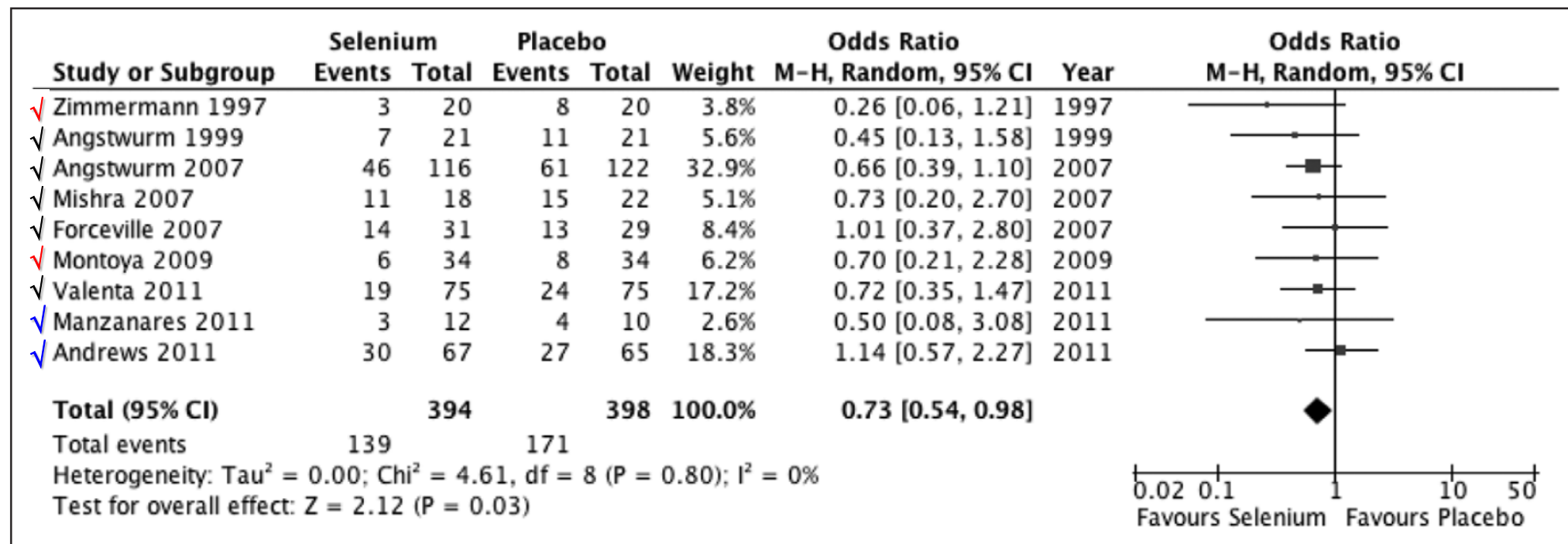
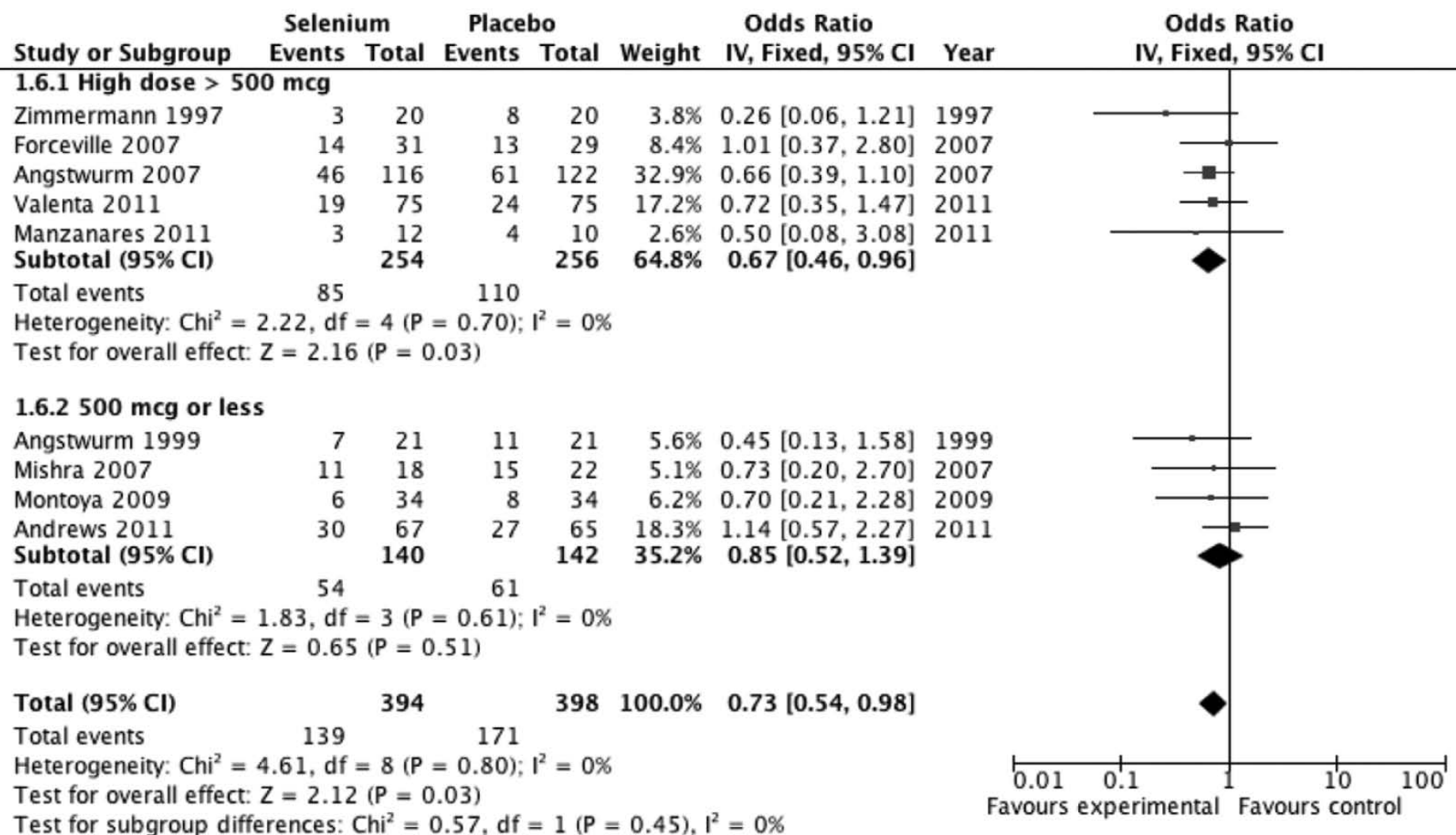


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Selenium in Sepsis

ClinicalTrials.gov

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Text Size ▾

Placebo Controlled Trial of Sodium Selenite and Procalcitonin Guided Antimicrobial Therapy in Severe Sepsis (SISPCT)

This study has been completed.

Sponsor:

Kompetenznetz Sepsis

Collaborators:

Biosyn

Brahms AG

Information provided by (Responsible Party):

Kompetenznetz Sepsis

ClinicalTrials.gov Identifier:

NCT00832039

First received: January 28, 2009

Last updated: June 28, 2013

Last verified: June 2013

[History of Changes](#)

Full Text View

Tabular View

No Study Results Posted

[Disclaimer](#)

[? How to Read a Study Record](#)

- Planned to recruit 1,180 patients.
- Recorded as 'completed' in June 2013.
- May only have recruited 380 patients?



Selenium in Sepsis

In the mean time:

- Selenium is relatively cheap.
- Sepsis carries a high risk of mortality.
- Although the authors report concerns about the analytic metrics used with the results being very close to 0.05 with Relative Risk and more significant when an Odds Ratio is used, the Odds Ratio is generally more stable and robust.
- > 500 μgm Selenium per day was associated with a significant reduction in mortality.

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Questions?

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