Dansk Selskab for Klinisk Ernæring

Initiativøde 17. januar 2012

Immunonutrition – hvad nyt?

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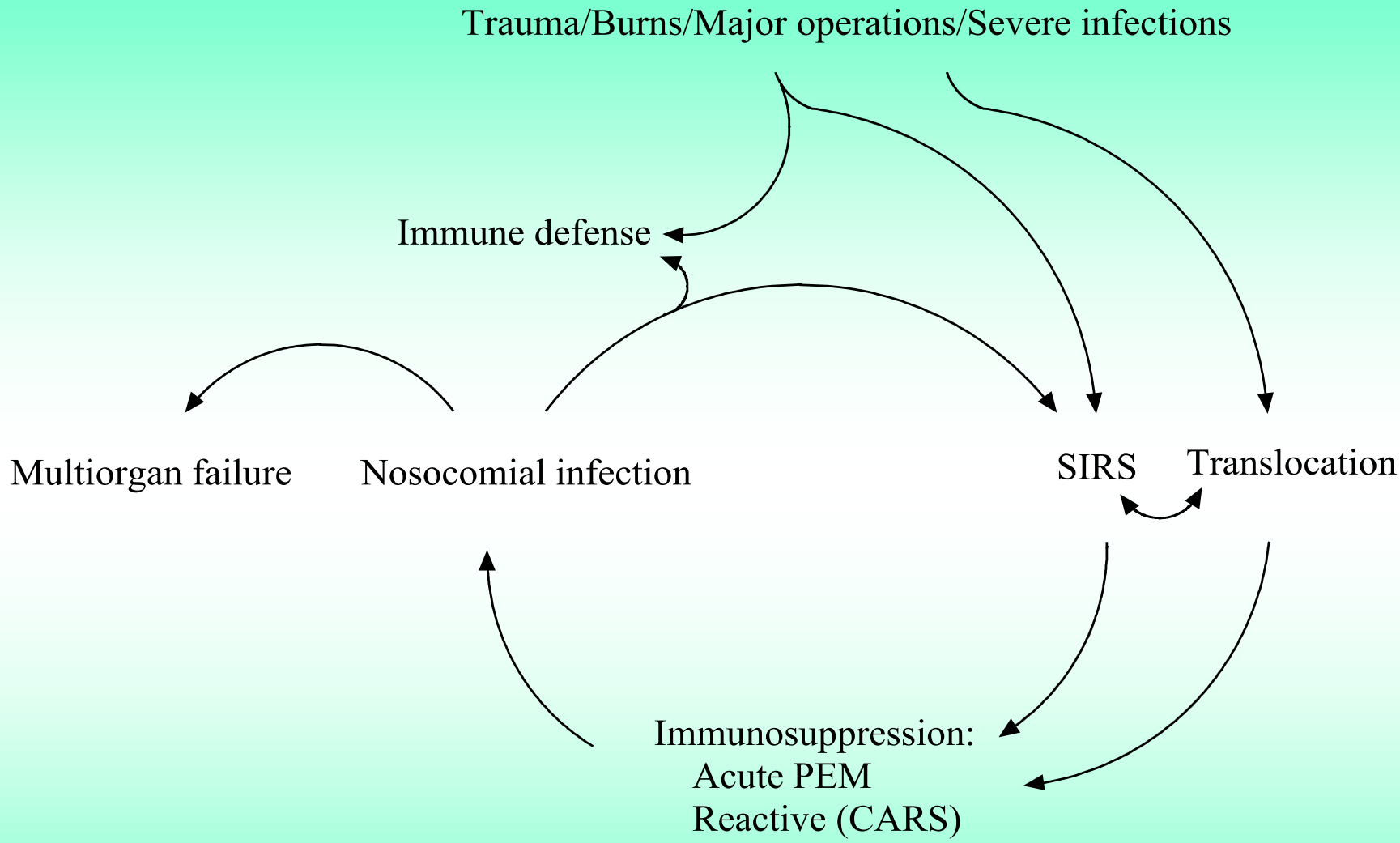
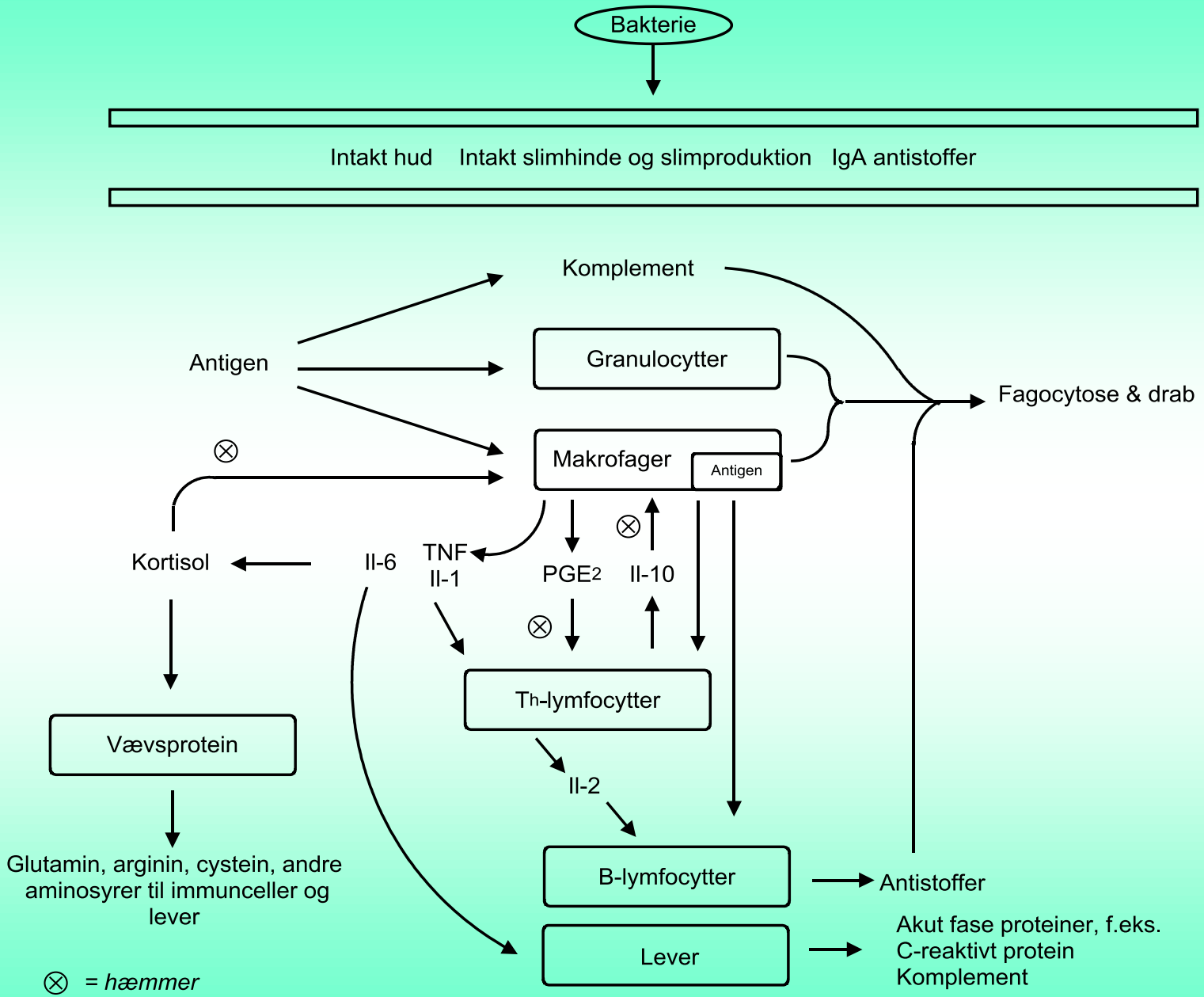
Rigshospitalet



SIRS: Systemic Inflammatory Response Syndrome
CARS: Compensatory Anti-inflammatory Response Syndrome

Bone RC. Crit Care Med 1996;24:1125-8.
Moore FA. Am J Surg 1999;178:449-53
Klinisk Ernæring 5. udg.

Fig. 2



Klinisk Ernæring 5. udg.

Plasma cytokines after trauma

Maier et al. Shock 2007;28:668-674.

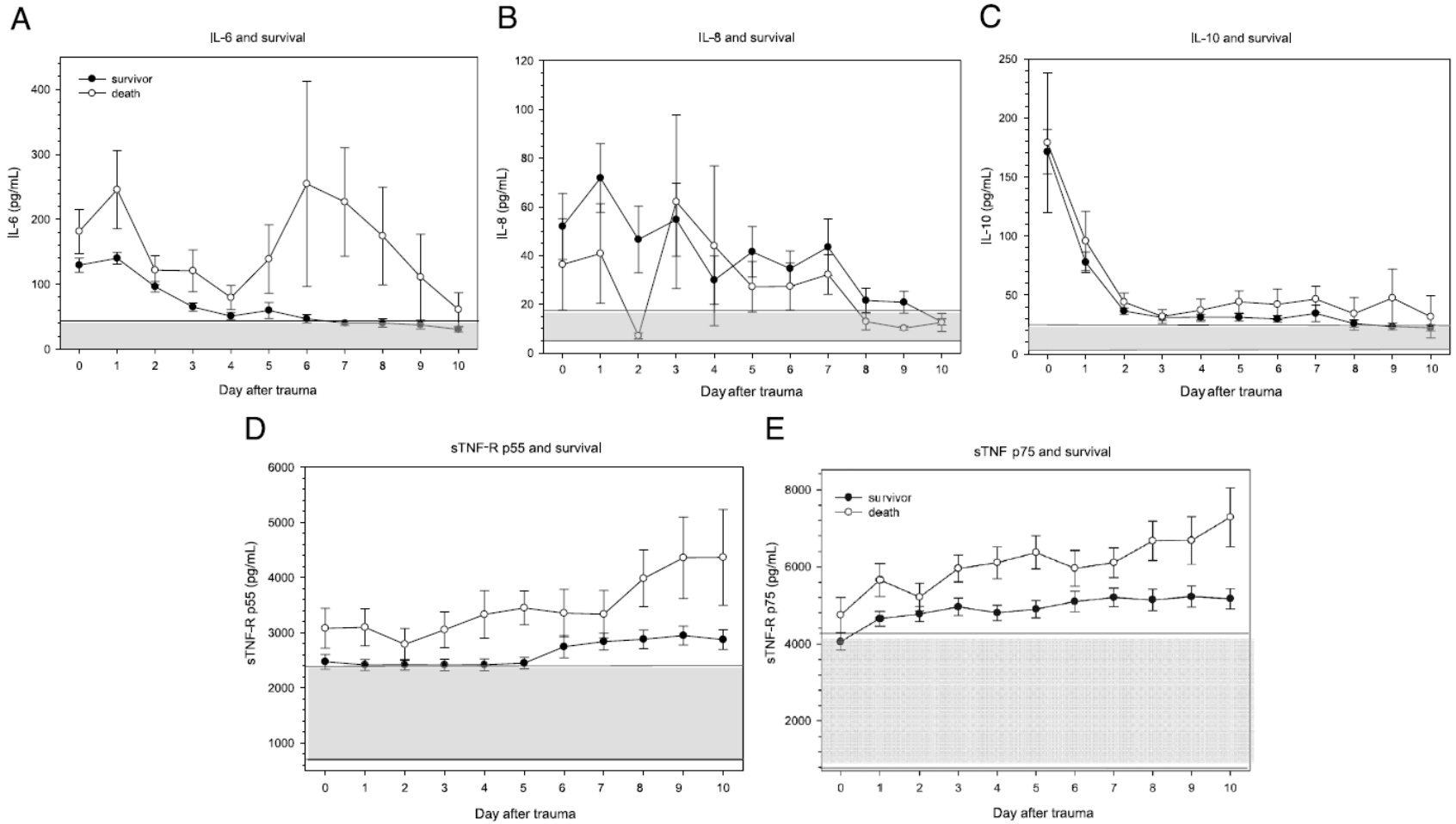


FIG. 5. **A–E, The different concentration curves of all mediator concentrations during the observation period are displayed for all MOF subgroups.** All data are expressed as mean ± SEM in picograms per milliliter. A, IL-6; B, IL-8; C, IL-10; D, sTNF-R p55; E, sTNF-R p75.

The LateMOF group showed a secondary peak for IL-6 starting on day 7 after trauma, which lasted until day 10.

TABLE 1. **The predictive value, calculated by the area under the ROC curve, of all measured cytokines and mediators for a lethal outcome or late-onset MOF are given**

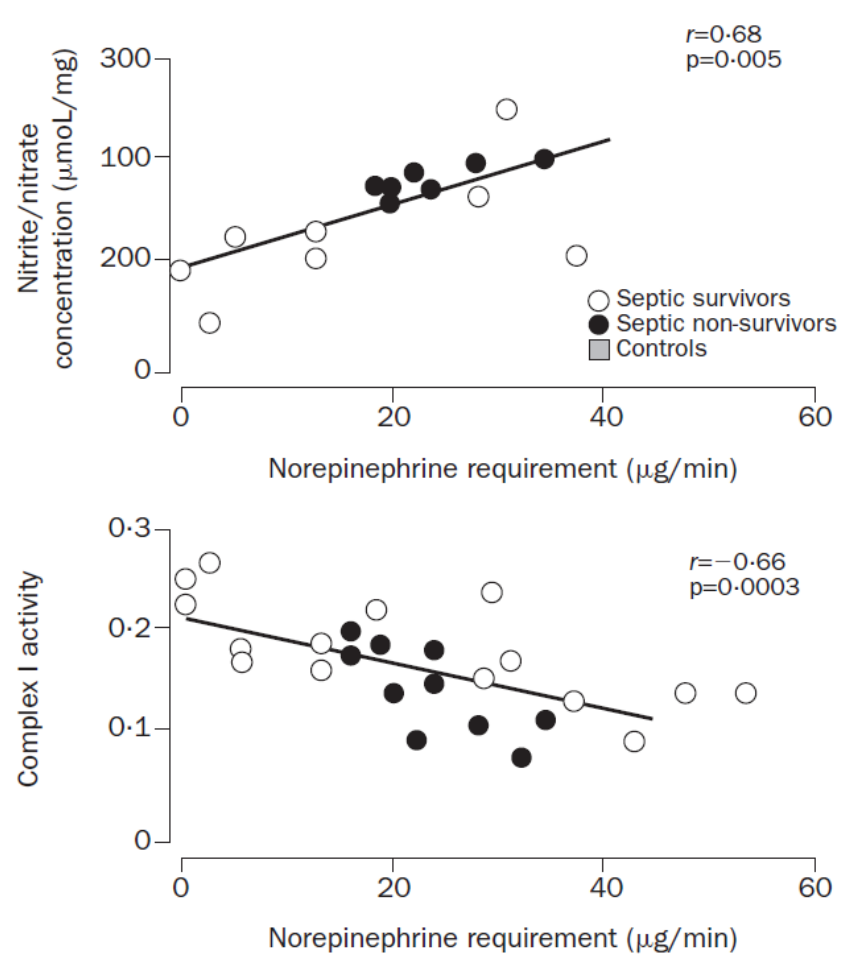
	Lethal outcome	Late-onset MOF
IL-6	0.60	0.70
IL-8	0.45	0.69
IL-10	0.51	0.60
sTNF-R p55	0.59	0.75
sTNF-R p75	0.63	0.72

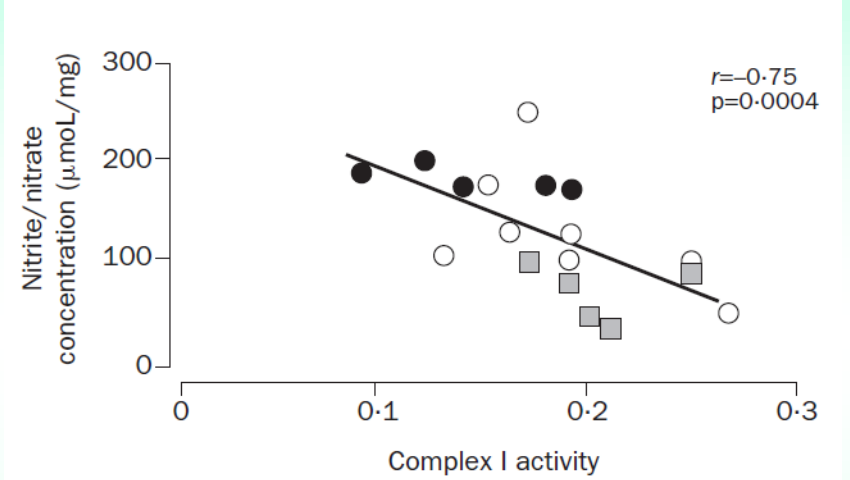
Values greater than or equal to 0.65 were accepted to have a predictive value.

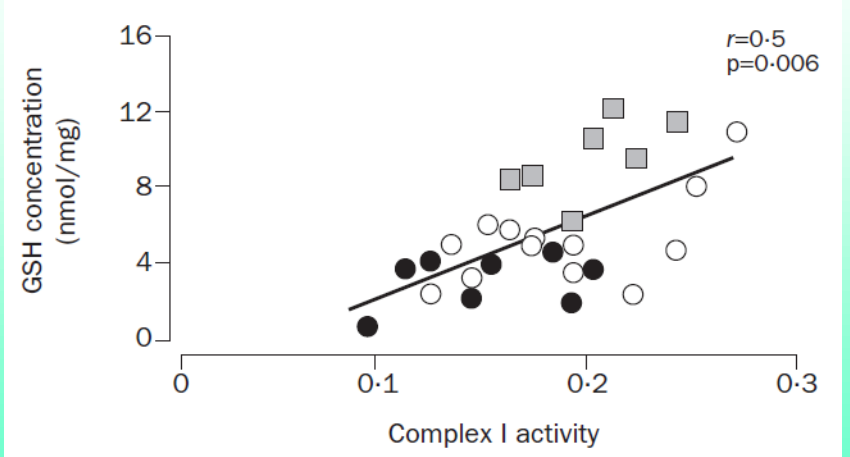
Maier et al. Shock 2007;28:668-674.

Oxidative damage in mitochondria from muscle of critically ill septic patients

Brealey et al. Lancet 2002;360:219-23







Patogenese for MOF/død

Histologi: apoptose, ikke nekrose

Oksidativ skade $\rightarrow$

Mitokondriel dysfunktion $\rightarrow$

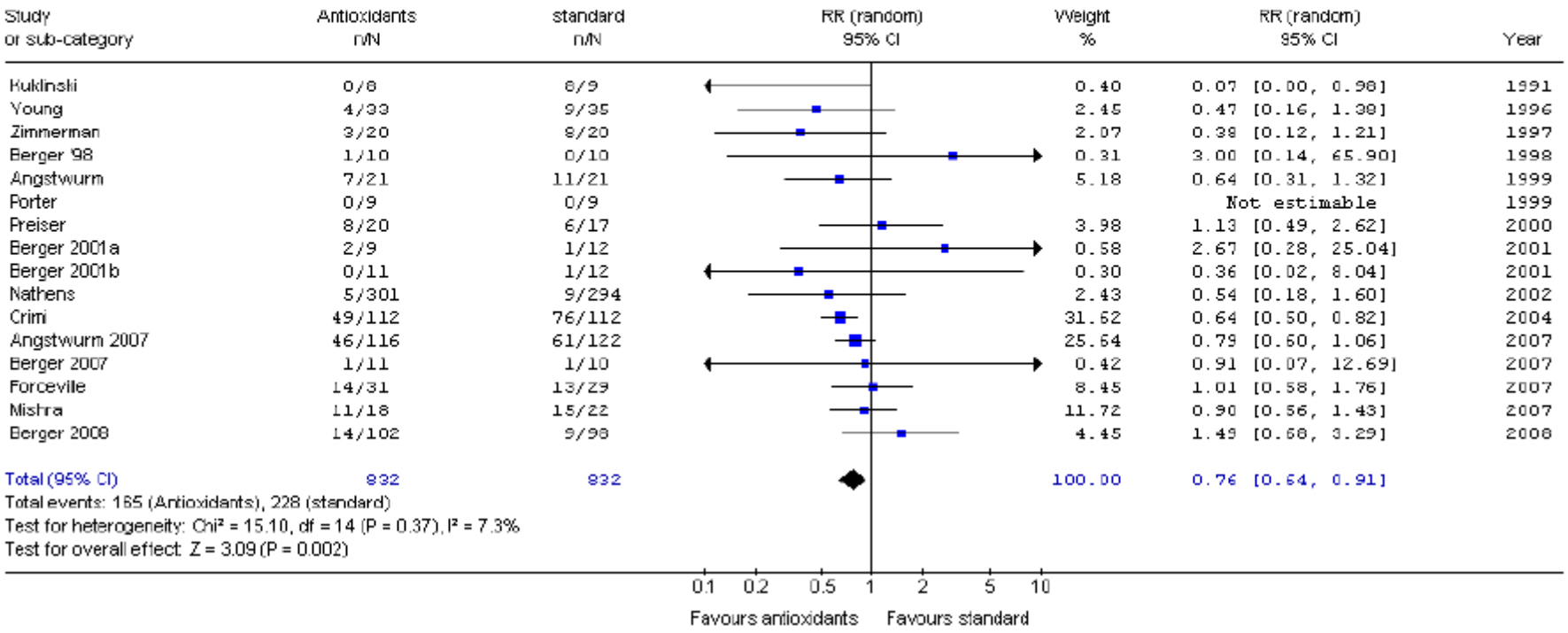
Apoptose

Antioxidants in ICU patients

As single nutrients (selenium) or as a combination of nutrients (selenium, copper, zinc, vit. A, C & E, N-acetylcysteine)
given by various routes (IV/parenteral, enteral, oral).
http://www.criticalcarenutrition.com/docs/cpg/11.1_anti_comb_FINAL.pdf January 2009

Figure 1.

Review: Antioxidants (Version 01)
Comparison: 01 Antioxidants (single + combined) vs standard
Outcome: 01 Mortality



Recommendation:
Based on 3 level 1 and 13 level 2 studies, the use of supplemental combined vitamins and trace elements should be considered in critically ill patients.

Level 1 studies

	Level 1
Randomization	Concealed randomization
Analysis	Intention to treat
Blinding	Double blinded
Co-interventions	Well-described and all equal
Outcomes	Objectively defined

Glutamine and infections in ICU patients

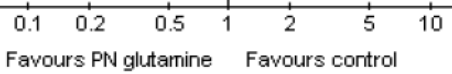
www.criticalcarenutrition.com/docs/cpg/9.4pnglu_FINAL.pdf January 2009

Figure 4

Review: glutamine New review (Version 01)
Comparison: 02 Parenteral Glutamine vs Control
Outcome: 01 Infectious Complications

Study or sub-category	PN Glutamine n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI	Year
Griffiths	28/42	26/42		20.25	1.08 [0.78, 1.48]	1997
Wischmeyer	7/12	9/14		8.45	0.91 [0.49, 1.68]	2001
Fuentes-Orozco	4/17	12/16		4.44	0.31 [0.13, 0.77]	2004
Zhou 2004	3/15	4/15		2.22	0.75 [0.20, 2.79]	2004
Dechelotte 2006	23/58	32/56		16.18	0.69 [0.47, 1.03]	2006
Palmese	13/42	21/42		10.29	0.62 [0.36, 1.07]	2006
Estivariz	13/30	16/29		10.86	0.79 [0.46, 1.33]	2008
Fuentes-Orozco 2008	9/22	16/22		9.74	0.56 [0.32, 0.99]	2008
Perez-Barcena	11/15	13/15		17.57	0.85 [0.59, 1.22]	2008
Total (95% CI)	253	251		100.00	0.76 [0.62, 0.93]	

Total events: 111 (PN Glutamine), 149 (Control)
Test for heterogeneity: Chi² = 11.16, df = 8 (P = 0.19), I² = 28.3%
Test for overall effect: Z = 2.64 (P = 0.008)



Glutamine and LOS

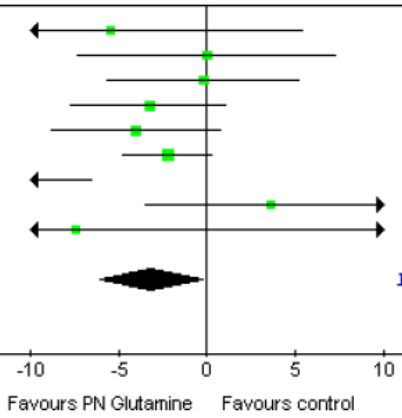
www.criticalcarenutrition.com/docs/cpg/9.4pnglu_FINAL.pdf January 2009

Figure 5. Hospital Length of Stay

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

Study or sub-category	PN Glutamine N	PN Glutamine Mean (SD)	Control N	Control Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI	Year
Powell-Tuck	83	43.40(34.10)	85	48.90(38.40)		5.26	-5.50 [-16.48, 5.48]	1999
Wischmeyer	12	40.00(10.00)	14	40.00(9.00)		9.01	0.00 [-7.36, 7.36]	2001
Fuentes-Orozco	17	16.50(8.90)	16	16.70(7.00)		12.24	-0.20 [-5.65, 5.25]	2004
Xian-Li	20	25.30(7.60)	21	28.60(6.90)		14.30	-3.30 [-7.75, 1.15]	2004
Zhou 2004	15	42.00(7.00)	15	46.00(6.60)		13.41	-4.00 [-8.87, 0.87]	2004
Sahin	20	14.20(4.40)	20	16.40(3.90)		18.45	-2.20 [-4.78, 0.38]	2007
Estivariz	15	20.00(2.00)	12	30.00(6.00)		16.33	-10.00 [-13.54, -6.46]	2008
Fuentes-Orozco 2008	22	30.18(10.42)	22	26.59(13.30)		9.45	3.59 [-3.47, 10.65]	2008
Perez-Barcena	15	35.50(33.60)	15	42.90(28.80)		1.55	-7.40 [-29.80, 15.00]	2008
Total (95% CI)	219		220			100.00	-3.14 [-6.03, -0.24]	

Test for heterogeneity: Chi² = 20.34, df = 8 (P = 0.009), I² = 60.7%
Test for overall effect: Z = 2.12 (P = 0.03)



Glutamine and mortality

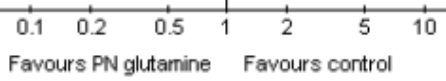
www.criticalcarenutrition.com/docs/cpg/9.4pnglu_FINAL.pdf January 2009

Figure 1 Overall Mortality

Review: glutamine New review (Version 01)
Comparison: 02 Parenteral Glutamine vs Control
Outcome: 03 Mortality

Study or sub-category	PN glutamine n/N	Control n/N	RR (random) 95% CI	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	2008
Perez-Barcena	3/15	0/15		0.79	7.00 [0.39, 124.83]	2008
Total (95% CI)	442	440		100.00	0.71 [0.55, 0.92]	

Total events: 71 (PN glutamine), 103 (Control)
Test for heterogeneity: Chi² = 9.84, df = 12 (P = 0.63), I² = 0%
Test for overall effect: Z = 2.63 (P = 0.008)



Recommendation:
Based on 4 level 1 studies and 13 level 2 studies, when parenteral nutrition is prescribed to critically ill patients, parenteral supplementation with glutamine is strongly recommended.

Avg. 2 x N per study: 63

Glutamine in the ICU (Nordic study)

2 N = 413 patients randomized to i.v. glutamine (0.3 g/kg per day) or placebo + parenteral or enteral nutrition.
Per protocol analysis (≥ 3 d glutamine; 2N = 284)

	Control	Glutamine
Infections	n.a.	n.a.
ICU LOS, d	8	9
ICU 28 d survival, %	84	91[1)]
6 months sutvival, %	69	65[NS]

[1)]P=0.046 Kaplan-Meier

Wernerman et al. Acta Anaesthesiol Scand 2011;55:812-8

Glutamine in the ICU (Signet study)

2 N = 251 patients randomized to i.v. glutamine in PN (20 g per day) or placebo + PN >50%.
Per protocol analysis (≥ 5 d glutamine; 2N = 119)

	Control	Glutamine
Infections, N	42	44
ICU LOS, d	15	16
ICU Mortality, N	14	19
6 months mortality, N	24	28

Andrews et al. BMJ 2011;342:d1542

Glutamine in the ICU (Spanish study)

2 N = 127 patients randomized to i.v. glutamine (0.3 g/kg per day) or placebo in parenteral nutrition.
Per protocol analysis (≥ 4 d glutamine; 2N = 117)

	Control	Glutamine
Infections, N	31	22[1)]
ICU LOS, d	12	12
ICU Mortality, N	11	8
6 months mortality, N	21	13

[1)] No. pneumonia per 1000 ventilator days: P =0.02

Grau et al. Crit Care Med 2011;39:1263-8.

Griffiths RD. Can the case for glutamine be proved?

Acta Anaesthesiol Scand 2011;55:769-71.

1997: an improved long-term survival that was related to duration of use and dose in those with gastrointestinal failure remaining dependent on parenteral nutrition for more than 10 days. The study design should adequately address the physiological evidence of a progressive deficiency that increases with severity and duration of illness

Wernerman et al.:
…they included many patients with a functional gastrointestinal tract on some enteral nutrition.

Andrews et al:
…the glutamine-parenteral feed could be reduced by 50% for those on enteral nutrition. It was only given for a maximum of 7 days where the median ICU stay was more than twice this.

Grau et al.:
…average of 5–6 days of glutamine provision was only about half the average ICU stay. Any potential benefit to the high-risk long stay ICU patients is effectively withdrawn.

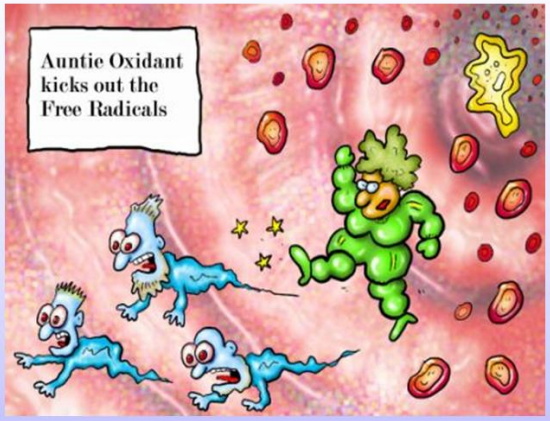
We only make it worse if we delude ourselves into thinking it is straightforward and simply a matter of size of the study.

The *REDOXS*© Study

REducing Deaths due to OXidative Stress

A randomized trial of glutamine and antioxidant supplementation in critically ill patients

It is hypothesized that these nutrients will lower morbidity and mortality in critically ill patients



What You Can Do To Help Us:

- **Identify eligible patients**
  1. Mechanically ventilated adult patients (≥18 years old) plus
  2. 2 or more of the following organ failures related to their acute illness:
     - A Pa02/Fi02 ratio of ≤300
     - Hypoperfusion
     - Renal dysfunction
     - A platelet count of ≤ 50 mm3
- **Start study supplements within 2 hours of randomization and within 24 hours from admission to ICU**
- **Optimize enteral nutrition**

CIHR IRSC A CIHR Funded Project

Study Sponsor: Dr Daren K Heyland, Clinical Evaluation Research Unit, Queen's University, Kingston ON, Canada

Supported by grants from the Canadian Institutes of Health Research (CIHR) and Fresenius-Kabi, Germany

Endorsed by the Canadian Critical Care Trials Group

Canadian Critical Care Trials Group

For Further Information:
Contact the ICU Research Team at

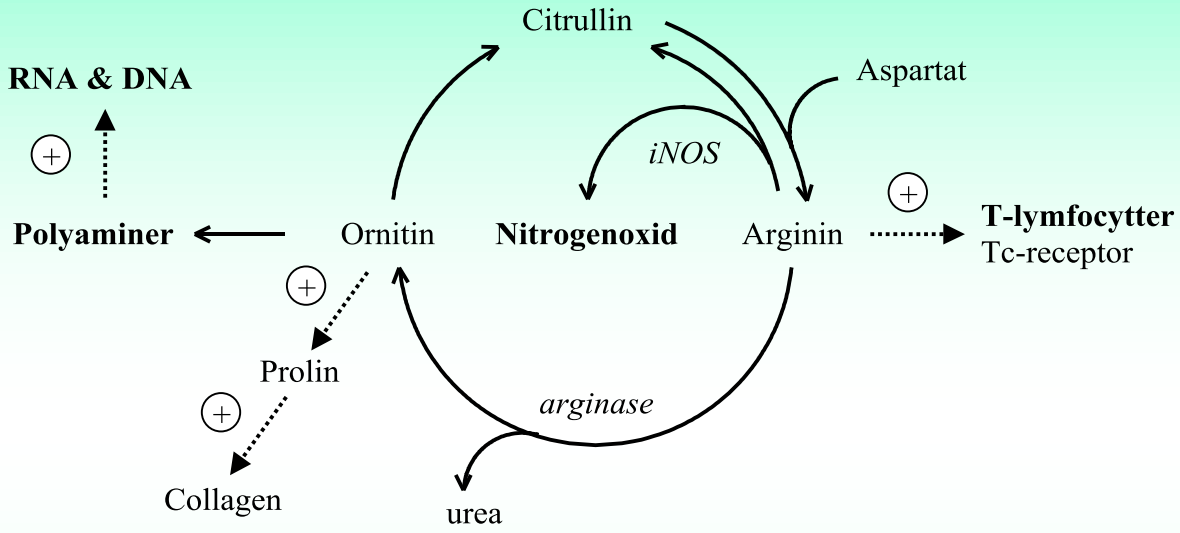
A multicenter randomized, clinical trial with a factorial 2X2 design in 1200 patients. Patients will be randomized to receive glutamine supplementation or antioxidant supplementation (or respective placebo). Glutamine will be provided parenterally at a dose of 0.35 grams/kg/day. Antioxidant supplementation: Selenium 500 µg i.v. and/or enterally: Selenium 300 µg, Beta Carotene 10 mg, Vitamin E 500 mg, and Vitamin C 1500 mg.

Outcomes: The primary outcome for this study is 28-day mortality. The secondary outcomes are duration of stay in ICU, adjudicated diagnosis of infection, multiple organ dysfunction, duration of mechanical ventilation, hospital length of stay, and survival and health-related quality of life at 3 and 6 months.

www.criticalcarenutrition.com

Arginine and immunity

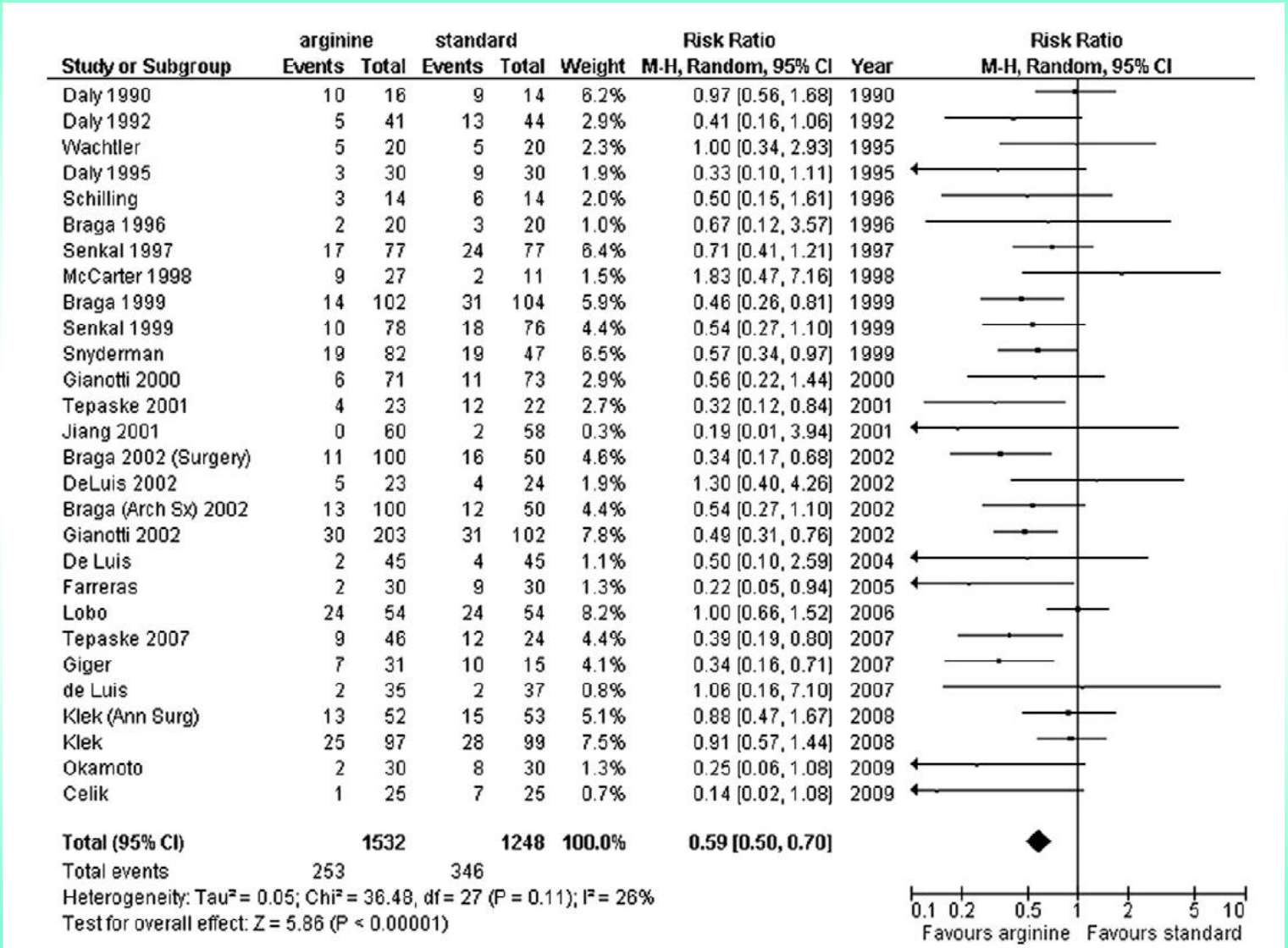
Popovic et al. Arginine and immunity. J Nutr 2007;137:1681S-1686S



Enzym	Celle	Stimulation		Effekt
iNOS	makrofag	Il-1, TNF-α, IFN-γ ($Th_1 \rightarrow$ cytotoksisk)	LPS, sepsis	Bakteriedrab, vasodilatation
arginase	granulocyt	Il-4, Il-6, Il-10, TGF-β ($Th_2 \rightarrow$ B lymf)	PGE_2 traume	Arg mangel $\rightarrow$ T-lymf suppression $\rightarrow$ NO mangel

Arginine (with other pharmaconutrients) in surgery

Drover et al. J Am Coll Surg 2011;212:385-99.



Study or Subgroup	arginine Events	Total	standard Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Daly 1990	10	16	9	14	6.2%	0.97 [0.56, 1.68]	1990
Daly 1992	5	41	13	44	2.9%	0.41 [0.16, 1.06]	1992
Wachtler	5	20	5	20	2.3%	1.00 [0.34, 2.93]	1995
Daly 1995	3	30	9	30	1.9%	0.33 [0.10, 1.11]	1995
Schilling	3	14	6	14	2.0%	0.50 [0.15, 1.61]	1996
Braga 1996	2	20	3	20	1.0%	0.67 [0.12, 3.57]	1996
Senkal 1997	17	77	24	77	6.4%	0.71 [0.41, 1.21]	1997
McCarter 1998	9	27	2	11	1.5%	1.83 [0.47, 7.16]	1998
Braga 1999	14	102	31	104	5.9%	0.46 [0.26, 0.81]	1999
Senkal 1999	10	78	18	76	4.4%	0.54 [0.27, 1.10]	1999
Snyderman	19	82	19	47	6.5%	0.57 [0.34, 0.97]	1999
Gianotti 2000	6	71	11	73	2.9%	0.56 [0.22, 1.44]	2000
Tepaske 2001	4	23	12	22	2.7%	0.32 [0.12, 0.84]	2001
Jiang 2001	0	60	2	58	0.3%	0.19 [0.01, 3.94]	2001
Braga 2002 (Surgery)	11	100	16	50	4.6%	0.34 [0.17, 0.68]	2002
DeLuis 2002	5	23	4	24	1.9%	1.30 [0.40, 4.26]	2002
Braga (Arch Sx) 2002	13	100	12	50	4.4%	0.54 [0.27, 1.10]	2002
Gianotti 2002	30	203	31	102	7.8%	0.49 [0.31, 0.76]	2002
De Luis	2	45	4	45	1.1%	0.50 [0.10, 2.59]	2004
Farreras	2	30	9	30	1.3%	0.22 [0.05, 0.94]	2005
Lobo	24	54	24	54	8.2%	1.00 [0.66, 1.52]	2006
Tepaske 2007	9	46	12	24	4.4%	0.39 [0.19, 0.80]	2007
Giger	7	31	10	15	4.1%	0.34 [0.16, 0.71]	2007
de Luis	2	35	2	37	0.8%	1.06 [0.16, 7.10]	2007
Klek (Ann Surg)	13	52	15	53	5.1%	0.88 [0.47, 1.67]	2008
Klek	25	97	28	99	7.5%	0.91 [0.57, 1.44]	2008
Okamoto	2	30	8	30	1.3%	0.25 [0.06, 1.08]	2009
Celik	1	25	7	25	0.7%	0.14 [0.02, 1.08]	2009
Total (95% CI)		**1532**		**1248**	**100.0%**	**0.59 [0.50, 0.70]**	
Total events	253		346				

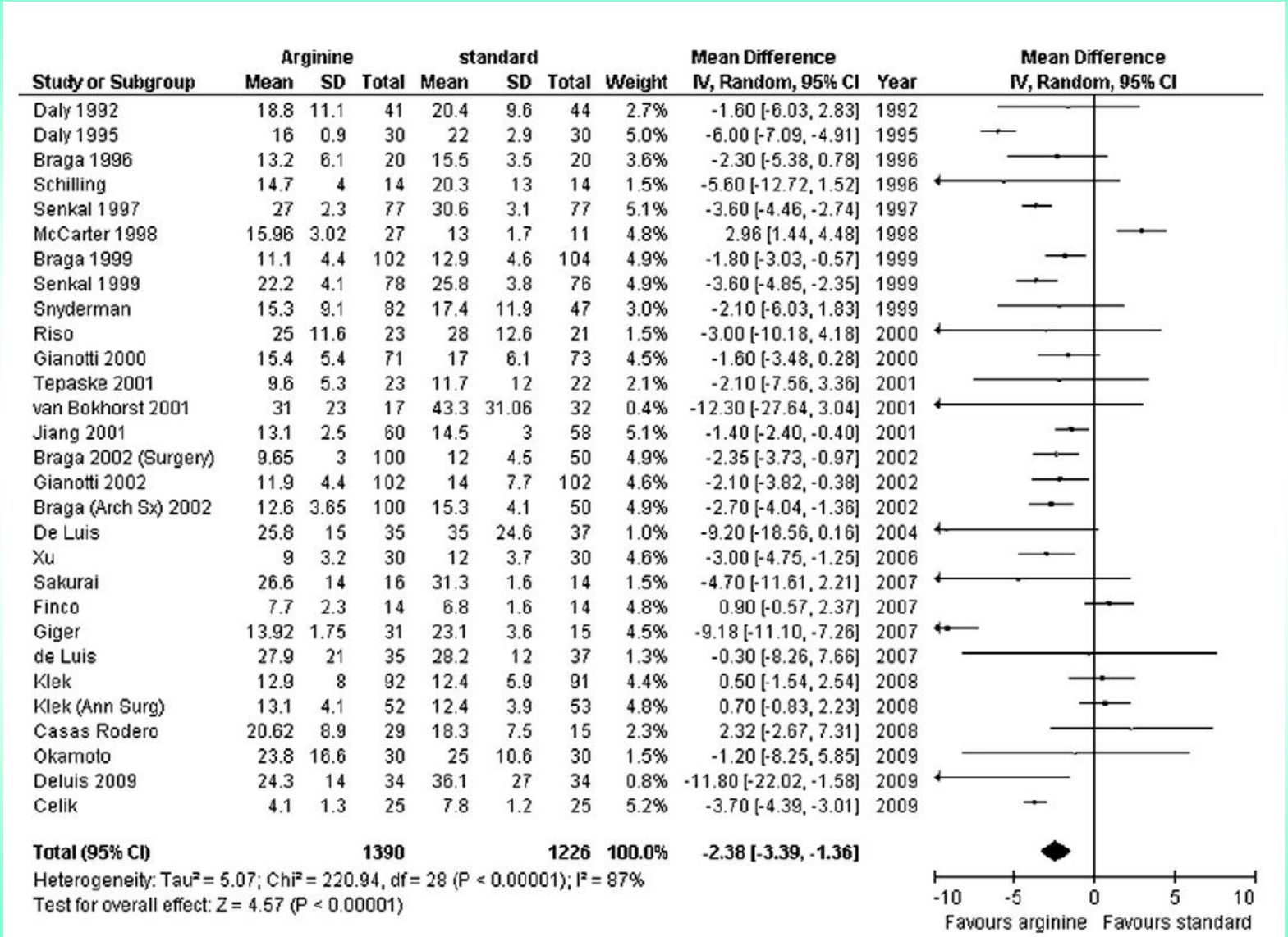
Heterogeneity: Tau² = 0.05; Chi² = 36.48, df = 27 (P = 0.11); I² = 26%

Test for overall effect: Z = 5.86 (P < 0.00001)

Figure 1. Effect of arginine-supplemented diets on infections. Events, number of patients with infections; Total, total number of patients in group; M-H, Random, Mantzel-Haenzel Random effects.

Arginine (with other pharmaconutrients) in surgery

Drover et al. J Am Coll Surg 2011;212:385-99.



Study or Subgroup	Arginine Mean	Arginine SD	Arginine Total	standard Mean	standard SD	standard Total	Weight	Mean Difference IV, Random, 95% CI	Year
Daly 1992	18.8	11.1	41	20.4	9.6	44	2.7%	-1.60 [-6.03, 2.83]	1992
Daly 1995	16	0.9	30	22	2.9	30	5.0%	-6.00 [-7.09, -4.91]	1995
Braga 1996	13.2	6.1	20	15.5	3.5	20	3.6%	-2.30 [-5.38, 0.78]	1996
Schilling	14.7	4	14	20.3	13	14	1.5%	-5.60 [-12.72, 1.52]	1996
Senkal 1997	27	2.3	77	30.6	3.1	77	5.1%	-3.60 [-4.46, -2.74]	1997
McCarter 1998	15.96	3.02	27	13	1.7	11	4.8%	2.96 [1.44, 4.48]	1998
Braga 1999	11.1	4.4	102	12.9	4.6	104	4.9%	-1.80 [-3.03, -0.57]	1999
Senkal 1999	22.2	4.1	78	25.8	3.8	76	4.9%	-3.60 [-4.85, -2.35]	1999
Snyderman	15.3	9.1	82	17.4	11.9	47	3.0%	-2.10 [-6.03, 1.83]	1999
Riso	25	11.6	23	28	12.6	21	1.5%	-3.00 [-10.18, 4.18]	2000
Gianotti 2000	15.4	5.4	71	17	6.1	73	4.5%	-1.60 [-3.48, 0.28]	2000
Tepaske 2001	9.6	5.3	23	11.7	12	22	2.1%	-2.10 [-7.56, 3.36]	2001
van Bokhorst 2001	31	23	17	43.3	31.06	32	0.4%	-12.30 [-27.64, 3.04]	2001
Jiang 2001	13.1	2.5	60	14.5	3	58	5.1%	-1.40 [-2.40, -0.40]	2001
Braga 2002 (Surgery)	9.65	3	100	12	4.5	50	4.9%	-2.35 [-3.73, -0.97]	2002
Gianotti 2002	11.9	4.4	102	14	7.7	102	4.6%	-2.10 [-3.82, -0.38]	2002
Braga (Arch Sx) 2002	12.6	3.65	100	15.3	4.1	50	4.9%	-2.70 [-4.04, -1.36]	2002
De Luis	25.8	15	35	35	24.6	37	1.0%	-9.20 [-18.56, 0.16]	2004
Xu	9	3.2	30	12	3.7	30	4.6%	-3.00 [-4.75, -1.25]	2006
Sakurai	26.6	14	16	31.3	1.6	14	1.5%	-4.70 [-11.61, 2.21]	2007
Finco	7.7	2.3	14	6.8	1.6	14	4.8%	0.90 [-0.57, 2.37]	2007
Giger	13.92	1.75	31	23.1	3.6	15	4.5%	-9.18 [-11.10, -7.26]	2007
de Luis	27.9	21	35	28.2	12	37	1.3%	-0.30 [-8.26, 7.66]	2007
Klek	12.9	8	92	12.4	5.9	91	4.4%	0.50 [-1.54, 2.54]	2008
Klek (Ann Surg)	13.1	4.1	52	12.4	3.9	53	4.8%	0.70 [-0.83, 2.23]	2008
Casas Rodero	20.62	8.9	29	18.3	7.5	15	2.3%	2.32 [-2.67, 7.31]	2008
Okamoto	23.8	16.6	30	25	10.6	30	1.5%	-1.20 [-8.25, 5.85]	2009
Deluis 2009	24.3	14	34	36.1	27	34	0.8%	-11.80 [-22.02, -1.58]	2009
Celik	4.1	1.3	25	7.8	1.2	25	5.2%	-3.70 [-4.39, -3.01]	2009
Total (95% CI)			**1390**			**1226**	**100.0%**	**-2.38 [-3.39, -1.36]**	

Heterogeneity: $Tau^2 = 5.07$; $Chi^2 = 220.94$, df = 28 ($P < 0.00001$); $I^2 = 87\%$

Test for overall effect: $Z = 4.57$ ($P < 0.00001$)

Figure 2. Effect of arginine-supplemented diets on hospital length of stay. Mean, mean hospital length of stay; SD, standard deviation; Total, total number of patients in group; IV, Random, inverse variance, random effects.

Arginine (with other pharmaconutrients) in surgery

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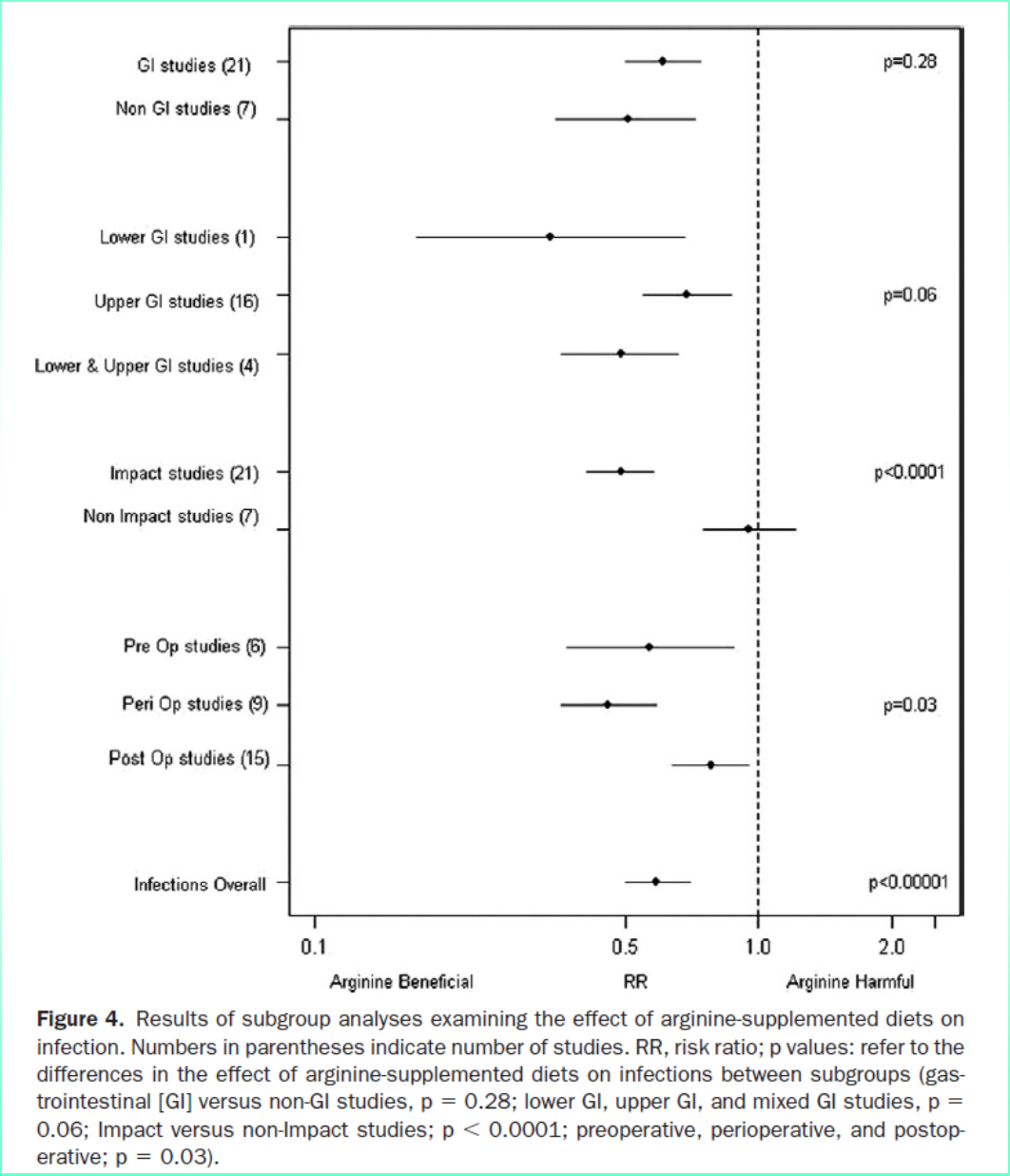

Figure 4. Results of subgroup analyses examining the effect of arginine-supplemented diets on infection. Numbers in parentheses indicate number of studies. RR, risk ratio; p values: refer to the differences in the effect of arginine-supplemented diets on infections between subgroups (gastrointestinal [GI] versus non-GI studies, $p = 0.28$; lower GI, upper GI, and mixed GI studies, $p = 0.06$; Impact versus non-Impact studies; $p < 0.0001$; preoperative, perioperative, and postoperative; $p = 0.03$).