"NUTRIZIONE ARTIFICIALE IN OSPEDALE E SUL TERRITORIO:
ATTUALITA' CLINICHE E TECNICO-FARMACEUTICHE"

Milano, c/o AC HOTEL
Evento 313- 93078
21 maggio 2014

Up to date
"Immunonutrizione e farmaco-economia"

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Ospedale San Gerardo
Monza

Indicazioni alla Nutrizione Artificiale

Farmaconutrizione

A mano a mano che si identificano difetti metabolici propri di diverse condizioni di malattia o si riconosce il ruolo essenziale di determinati nutrienti per il supporto metabolico di organi e/o apparati cruciali per la sopravvivenza dell'ospite, la NA trova impiego in condizioni che prescindono dallo stato di malnutrizione e secondo moduli quantitativi e qualitativi che non corrispondono necessariamente ai fabbisogni fisiologici.

Con il termine di farmaconutrizione si intende la possibilità di modulare alcune risposte biologiche, fisiologiche e/o patologiche attraverso la somministrazione, orale o parenterale, di dosi farmacologiche di singoli principi nutritivi. I benefici ottenuti dalla somministrazione di tali substrati sono in parte o in tutto indipendenti dal miglioramento dello stato nutrizionale, ma appaiono legati alle loro proprietà chimiche e fisiologiche intrinseche.

I substrati che sono entrati a far parte del novero dei farmaconutrienti, o nutraceutici, sono gli aminoacidi a catena ramificata, invero già noti da tempo, la glutamina, l'arginina, i chetoacidi, gli acidi grassi ω-3, i nucleotidi, i frutto-oligosaccaridi (FOS). La farmaconutrizione rappresenta certamente una delle più interessanti sfide del prossimo decennio.

Nutrición Hospitalaria

Nutr Hosp. 2011;26(1):56-67
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S.V.R. 318

Revisión

Revising concepts of artificial nutrition in contemporary surgery: from energy and nitrogen to immuno-metabolic support

L. Gianotti[1] and M. Braga[2]

[1]Department of Surgery. Milano-Bicocca University. S. Gerardo Hospital. Monza. Italy. [2]Deparment of Surgery. S. Raffaele University. Milan. Italy.

Switching philosophy

Nutritional therapy
“ the classic concept”

↓

Nitrogen and calorie support

↓

Indications:
- **Malnourished patients or with nutritional risk**

Immuno-nutrition

↓

Immuno-metabolic support

↓

Indications :
- **Patients candidate to major surgery independently from nutritional status**

Postoperative complications in gastrointestinal cancer patients: The joint role of the nutritional status and the nutritional support

Federico Bozzetti[a,*], Luca Gianotti[b], Mario Braga[c], Valerio Di Carlo[c],

Clinical Nutrition (2007) **26**, 698–709

1410 pts

Table 1. Systematic Reviews and Meta-Analyses Examining the Effectiveness of Immunonutrition in Surgery.

Author	RCTs	Control Group	Patients	Short-Term Outcome	Patients Who Benefit
Waitzberg et al, 2006[13]	17	Standard EN/parenteral	2305	Lower infections Shorter LOS	GI cancer
Marik and Zaloga, 2010[15]	21	Standard EN	1908	Lower morbidity Shorter LOS	Malnourished and well nourished
Cerantola et al, 2011[14]	21	Standard EN	2730	Lower morbidity Shorter LOS	Upper GI Lower GI
Drover et al, 2011[18]	35	Standard EN	3445	Lower morbidity Shorter LOS	GI and non-GI Upper/lower GI Receiving Impact[a]
Marimuthu et al, 2012[21]	26	Standard EN	2496	Lower morbidity Shorter LOS	GI cancer

Meta-analysis

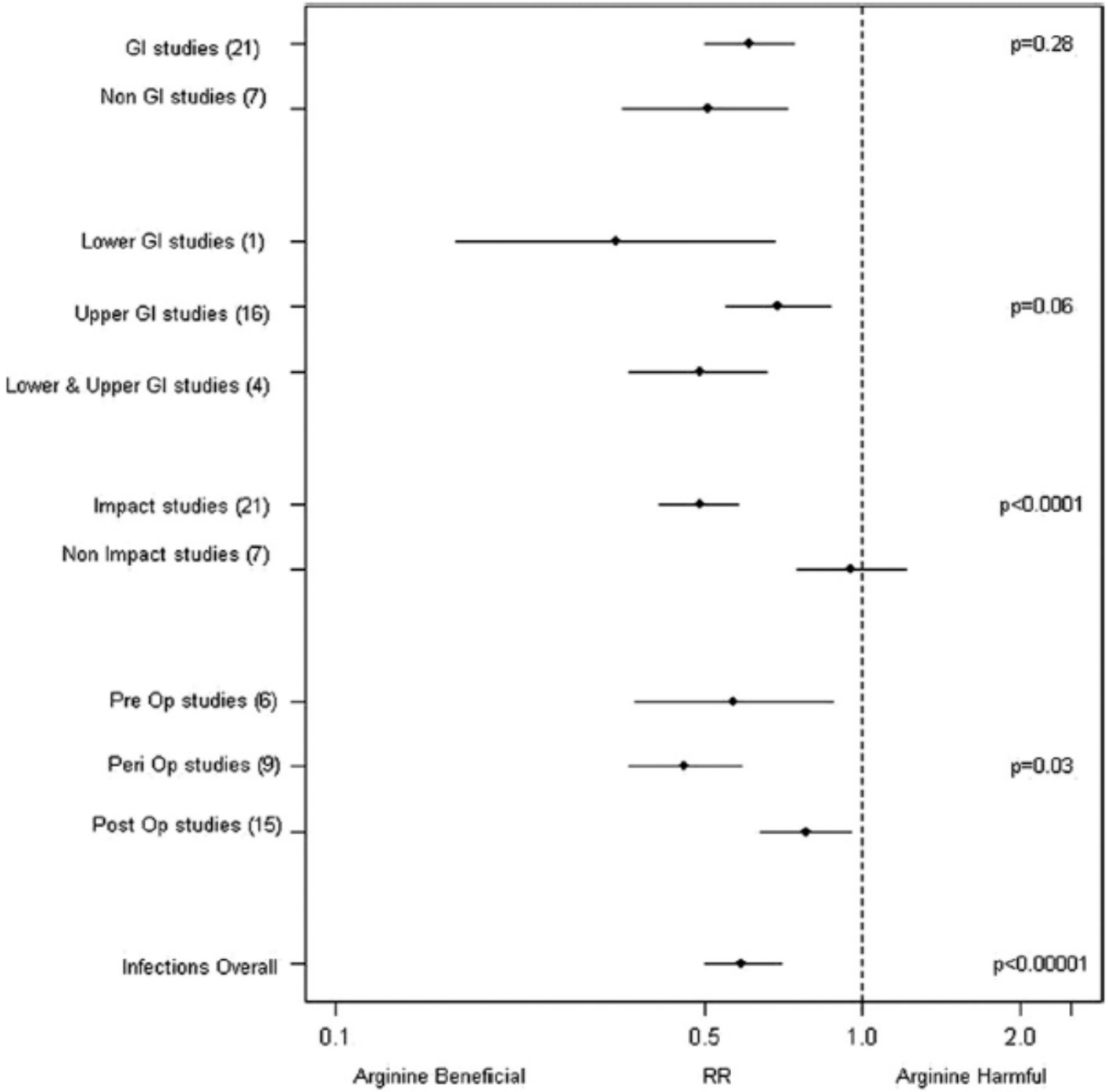
Immunonutrition in gastrointestinal surgery

Y. Cerantola, M. Hübner, F. Grass, N. Demartines and M. Schäfer

Department of Visceral Surgery, University Hospital Vaudois (CHUV), Bugnon 46, 1011 Lausanne, Switzerland
Correspondence to: Professor N. Demartines (e-mail: Demartines@chuv.ch)

Table 3 Pooled data for high-quality studies only

Outcome measure	Rate		Odds ratio
	IN	Control	
Complications[2,7,10,12–19,28]	338 of 956	495 of 957	0·46 (0·38, 0·57)
Infections[2,7,10,12–19,28]	177 of 956	306 of 957	0·47 (0·38, 0·59)
Length of hospital stay[2,7,10,12–18,28] (1837 patients)	—	—	−2·26 (−2·65, −1·88)*
Mortality[7,10,12–14,16–18,28]	13 of 797	13 of 803	1·01 (0·46, 2·23)


GI studies (21)
Non GI studies (7)
Lower GI studies (1)
Upper GI studies (16)
Lower & Upper GI studies (4)
Impact studies (21)
Non Impact studies (7)
Pre Op studies (6)
Peri Op studies (9)
Post Op studies (15)
Infections Overall
p=0.28
p=0.06
p<0.0001
p=0.03
p<0.00001
0.1
0.5
1.0
2.0
Arginine Beneficial
RR
Arginine Harmful

A Meta-Analysis of the Effect of Combinations of Immune Modulating Nutrients on Outcome in Patients Undergoing Major Open Gastrointestinal Surgery

Kanagaraj Marimuthu, MRCS, Krishna K. Varadhan, MSc, MRCS,* Olle Ljungqvist, MD, PhD,† and Dileep N. Lobo, MS, DM, FRCS, FACS**

(*Ann Surg* 2012;255:1060–1068)

TABLE 3. Subgroup Analysis Based on Timing of Initiation of the Enteral Feed

Outcomes	Preoperative Feed	Perioperative Feed	Postoperative Feed
Infectious complications RR (M-H, Fixed, 95% CI)	0.48 [0.31, 0.74] $P = 0.001$	0.53 [0.38, 0.76] $P = 0.0004$	0.68 [0.58, 0.80] $P < 0.00001$
Noninfectious complications RR (M-H, fixed, 95% CI)	1.53 [0.83, 2.83] $P = 0.17$	0.68 [0.43, 1.07] $P = 0.09$	0.81 [0.70, 0.94] $P = 0.006$
Length of hospital stay MD (IV, fixed, 95% CI)	−1.46 [−2.41, −0.50] $P = 0.78$	−2.71 [−3.82, −1.59] $P < 0.00001$	−2.44 [−2.88, −2.01] $P = 0.009$

M-H indicates Mantel-Haenszel method, IV Inverse Variance.
P value based on test for overall effect in the meta-analysis (Z test).

GASTROENTEROLOGY 2002;122:1763–1770

A Randomized Controlled Trial of Preoperative Oral Supplementation With a Specialized Diet in Patients With Gastrointestinal Cancer

LUCA GIANOTTI,* MARCO BRAGA,* LUCA NESPOLI,* GIOVANNI RADAELLI,† ALDO BENEDUCE,* and VALERIO DI CARLO*

*Department of Surgery, San Raffaele University, Milan; and †Department of Informative Systems, University of Milan, Milan, Italy

Table 2. Surgical Parameters

	Conventional (n = 102)	Preoperative (n = 102)	Perioperative (n = 101)
Gastroesophageal resections	44	48	46
Pancreatic resections	26	28	27
Colorectal resections	32	26	28
Operative time (*min*)	220 ± 90	226 ± 92	237 ± 107
Operative blood loss (*mL*)	435 ± 350	470 ± 370	520 ± 410
Transfused patients	32	34	37
Transfusion (*mL*)	495 ± 265	430 ± 160	550 ± 305

NOTE. Values are means ± SD or number of patients.

Table 3. Outcome Variables

	Conventional (n = 102)	Preoperative (n = 102)	Perioperative (n = 101)
Death	1	1	2
Patients with infectious complications	31	14[a]	16[b]
Patients with noninfectious complications	36	30	28
Patients with any complication	49	36	34
Length of hospital stay (*days*)	14.0 ± 7.7	11.6 ± 4.7[c]	12.2 ± 4.1[d]

NOTE. Values are means ± SD or number of patients.
[a]$P = 0.006$ vs. conventional.
[b]$P = 0.02$ vs. conventional.
[c]$P = 0.008$ vs. conventional.
[d]$P = 0.03$ vs. conventional.

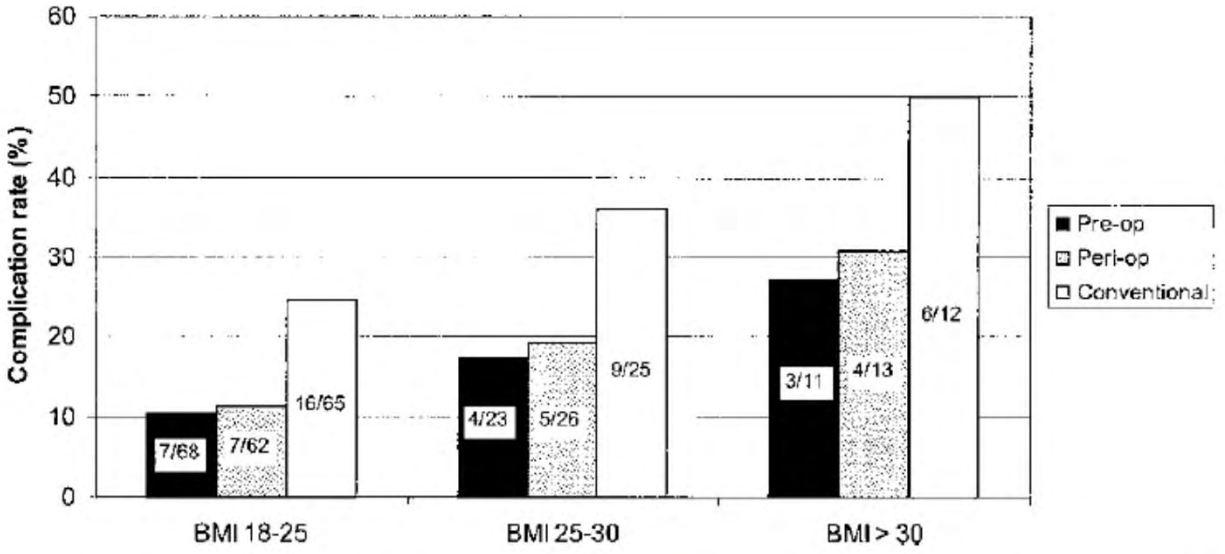


Figure 2. Rate of infectious complications in the 3 groups according to different BMI values.

TABLE 4. Postoperative Complications

Type of Complication	SEN (n = 53)	IMEN (n = 52)	SPN (n = 49)	IMPN (n = 51)
Infectious complications	15	13	13	12
Pneumonia	14	12	13	10
Urinary tract infection	2	1	2	1
Surgical wound infection	2	4	2	1
Intra-abdominal abscess	2	2	1	2
Bacteremia	8	5	4	6
Infection of venous catheter	1	0	2	2
Sepsis	2	3	2	1
Surgical complications	7	6	7	7
Wound dehiscence	0	1	0	1
Pancreatic fistula	4	4	3	4
Duodenal fistula	2	3	2	2
Jejunal fistula	0	1	0	1
Biliary fistula	0	1	1	0
General complications	5	4	2	2
Pulmonary thrombosis	0	0	1	0
Myocardial infarct	0	1	0	0
Peripheral veins thrombosis	0	0	0	1
Neurological complications	0	0	0	0
Mortality	1	1	1	1
Overall morbidity	19	19	17	18
Postoperative hospital stay (d), mean (SD)	12.4 (3.9)	13.1 (4.1)	12.9 (4.9)	12.5 (3.3)
Enteral nutrition complications				
Diarrhea	3	3	0	0
Tube obstruction	1	0	0	0

Preoperative oral arginine and n-3 fatty acid supplementation improves the immunometabolic host response and outcome after colorectal resection for cancer

Marco Braga, MD, Luca Gianotti, MD, ScD, Andrea Vignali, MD, *and* **Valerio Di Carlo, MD,** *Milan, Italy*

Table I. Baseline and surgical variables

	Peri-op (n = 50)	*Pre-op (n = 50)*	*Control (n = 50)*	*Conventional (n = 50)*
Age (y)	60.5 ± 11.5	63.0 ± 8.1	61.8 ± 9.9	62.2 ± 10.4
Male:female	28:22	30:20	31:19	29:21
Albumin (g/L)	41.5 ± 4.1	41.8 ± 5.0	42.2 ± 4.8	40.9 ± 4.3
Prealbumin (g/L)	0.23 ± 0.06	0.24 ± 0.05	0.23 ± 0.10	0.22 ± 0.07
Hemoglobin (g/L)	127 ± 21	124 ± 18	130 ± 19	126 ± 15
Arginine (μmol/L)	63 ± 13	61 ± 18	64 ± 11	59 ± 16
Weight loss >10%	5	6	4	5
ASA score	2.1 ± 1.0	1.9 ± 1.1	2.0 ± 1.3	2.1 ± 1.4
Procedure				
Rectal resection	19	22	21	20
Left colectomy	18	15	16	14
Right colectomy	11	9	10	13
Transverse colon resection	1	2	1	2
Abdominoperineal amputation	1	2	2	1
Operative time (min)	190 ± 63	202 ± 46	188 ± 65	197 ± 55
Blood loss (mL)	385 ± 288	377 ± 383	342 ± 351	403 ± 374
Homologous transfusion	11	9	8	9

Data are means ± SD or number of patients.

Table II. Outcome variables

	Peri-op (*n* = 50)	*Pre-op* (*n* = 50)	*Control* (*n* = 50)	*Conventional* (*n* = 50)
Death	1	0	0	1
Patients with infectious complications	5*	6†	16	15
Patients with noninfectious complications	5	4	3	4
Anastomotic leak	3	3	6	5
Antibiotic therapy** (d)	6.2 ± 1.9‡	6.5 ± 1.3§	8.9 ± 2.0	8.4 ± 1.8
Length of stay (d)	9.8 ± 3.1‖	9.5 ± 2.9¶	12.0 ± 4.5	12.2 ± 3.9

ORIGINAL ARTICLE

Nutritional Approach in Malnourished Surgical Patients

A Prospective Randomized Study

Marco Braga, MD; Luca Gianotti, MD, ScD; Luca Nespoli, MD; Giovanni Radaelli, PhD; Valerio Di Carlo, MD

Table 5. Surgical Variables in 150 Participants

Variable	Control Group (n = 50)	Preoperative Group (n = 50)	Perioperative Group (n = 50)
Gastric resection, No.	19	19	18
Pancreatic resection, No.	18	20	21
Colorectal resection, No.	11	8	10
Esophageal resection, No.	2	3	1
Operative time mean (SD), min	244 (110)	258 (90)	263 (97)
Operative blood loss, mean (SD), mL	452 (330)	485 (312)	493 (291)
Transfused patients, No.	17	16	18
Transfusion, mean (SD), mL	555 (310)	570 (255)	480 (190)

Table 6. Outcome Variables

Variable	Control Group (n = 50)	Preoperative Group (n = 50)	Perioperative Group (n = 50)
Patients with major complications, No.	12	9	6
Patients with infectious complications, No.	12	8	5
Patients with noninfectious complications, No.	11	10	6
Patients with complications, total No.	21	14	9*
Length of hospital stay, mean (SD), d	15.3 (4.1)	13.2 (3.5)†	12.0 (3.8)‡

*P = .02 vs the control group.
†P = .01 vs the control group.
‡P = .04 vs the preoperative group and P = .001 vs the control group.

Clinical Nutrition (2006) 25, 224–244

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Clinical Nutrition

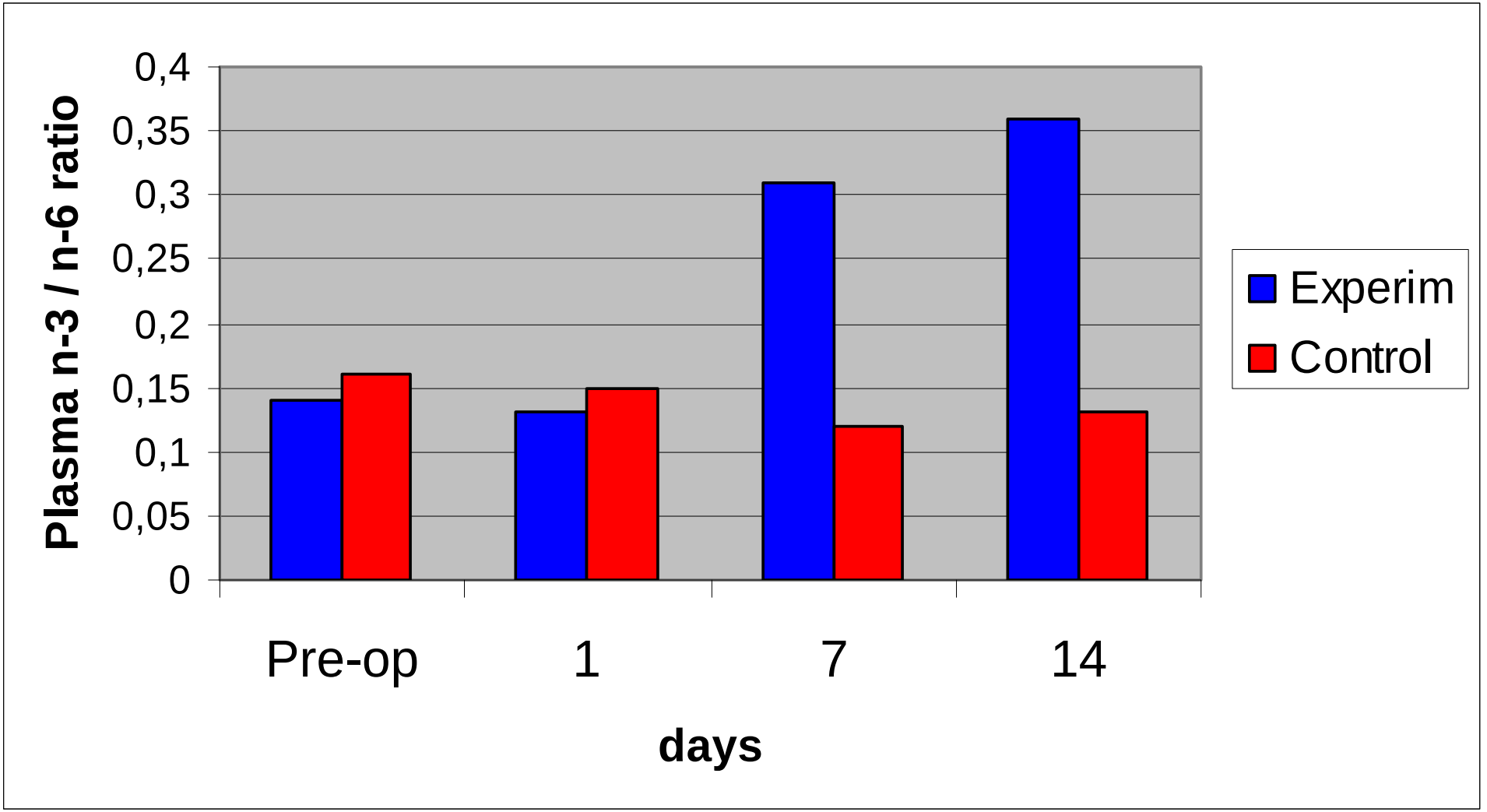
http://intl.elsevierhealth.com/journals/clnu

ESPEN GUIDELINES

ESPEN Guidelines on Enteral Nutrition: Surgery including Organ Transplantation ☆

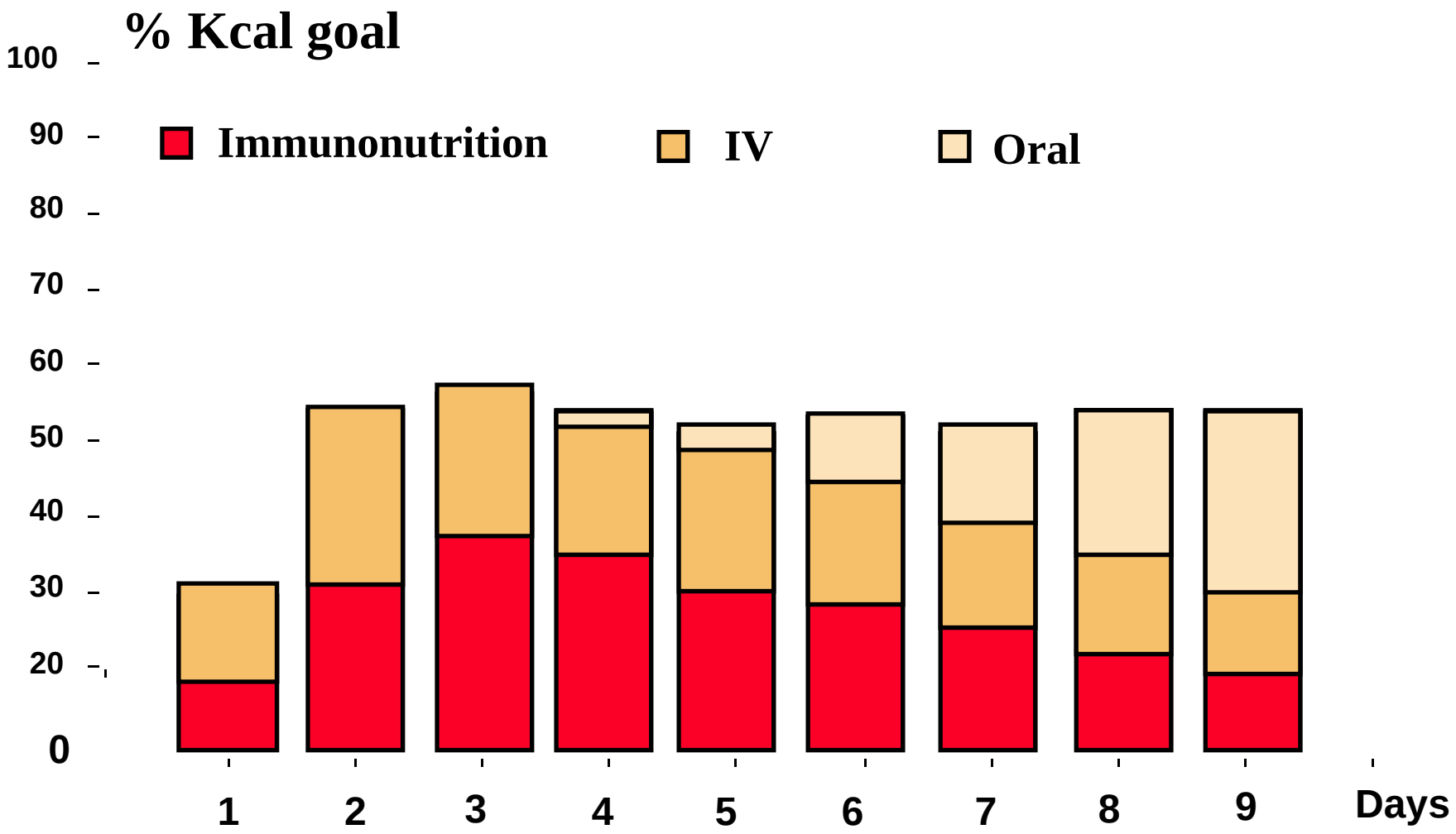
A. Weimann[a,*], M. Braga[b], L. Harsanyi[c], A. Laviano[d], O. Ljungqvist[e], P. Soeters[f],

Post-operative Immunonutrition (Daly, Ann Surg 1995)

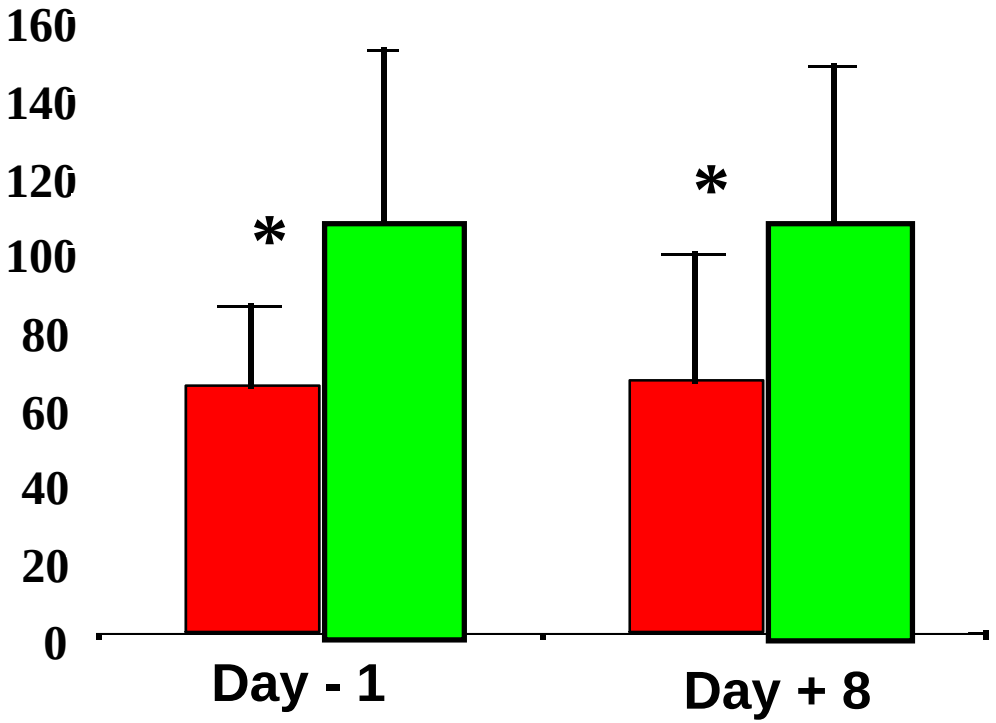


Post-operative Immunonutrition (Elective surgery)

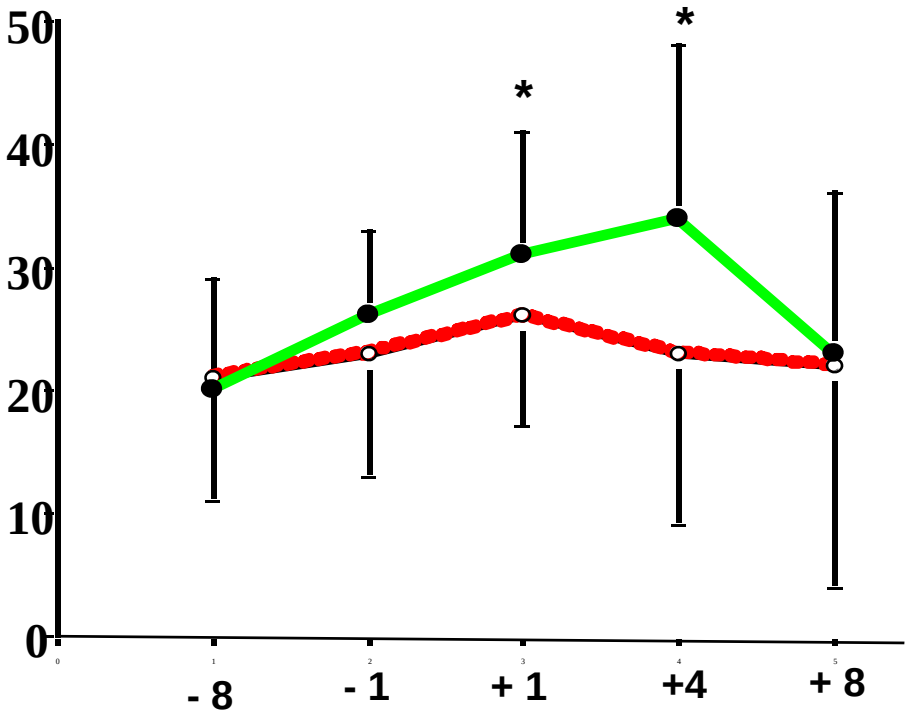
Heslin MJ, et al. Ann Surg 226: 567-580; 1997



Plasma Arginine (mmol/L)



Plasma NO (mmol/L)



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Control

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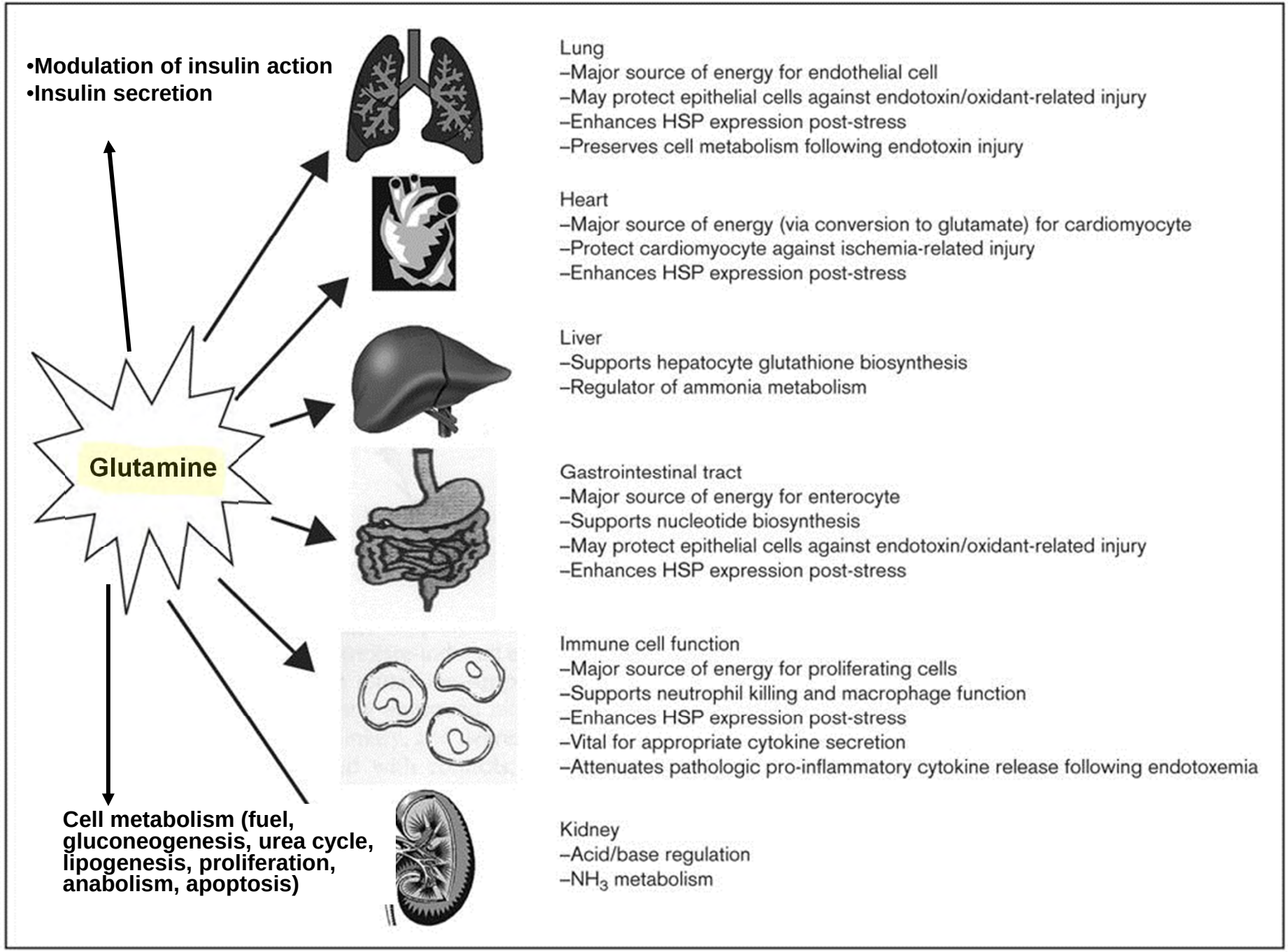
Summary Points and Consensus Recommendations From the North American Surgical Nutrition Summit

Stephen A. McClave, MD[1]; Rosemary Kozar, MD, PhD[2]; Robert G. Martindale, MD, PhD[3]; Daren K. Heyland, MD, FRCPC[4]; Marco Braga, MD[5]; Francesco Carli, MD[6]; John W. Drover, MD[4]; David Flum, MD[7]; Leah Gramlich, MD[8]; David N. Herndon, MD[9]; Clifford Ko, MD[10]; Kenneth A. Kudsk, MD[11]; Christy M. Lawson, MD[12]; Keith R. Miller, MD[1]; Beth Taylor, MS, RD, CNSC[13]; and Paul E. Wischmeyer, MD[14]



Kelly D & Wischmeyer PE, Curr Opin Clin Nutr Metab Care 6:217-222, 2003

Glutamine supplementation in serious illness: A systematic review of the evidence*

Frantisek Novak, MD; Daren K. Heyland, MD, FRCPC, MSc;
Alison Avenell, MD, MRCP, MRCPath, MB BS, MSc; John W. Drover, MD, FRCSC; Xiangyao Su, PhD

Crit Care Med 2002; 30: 2022-29

ORIGINAL ARTICLE

The impact of glutamine dipeptides on outcome of surgical patients: systematic review of randomized controlled trials from Europe and Asia

Zhu-Ming Jiang[a,*], Hua Jiang[b], Peter Fürst[c]

Clinical Nutrition Supplements (2004) 1, 17–23

Glutamine dipeptide for parenteral nutrition in abdominal surgery: A meta-analysis of randomized controlled trials

Ya-Min Zheng, Fei Li, Ming-Ming Zhang, Xiao-Ting Wu

World J Gastroenterol 2006 December 14; 12(46): 7537-7541
World Journal of Gastroenterology ISSN 1007-9327

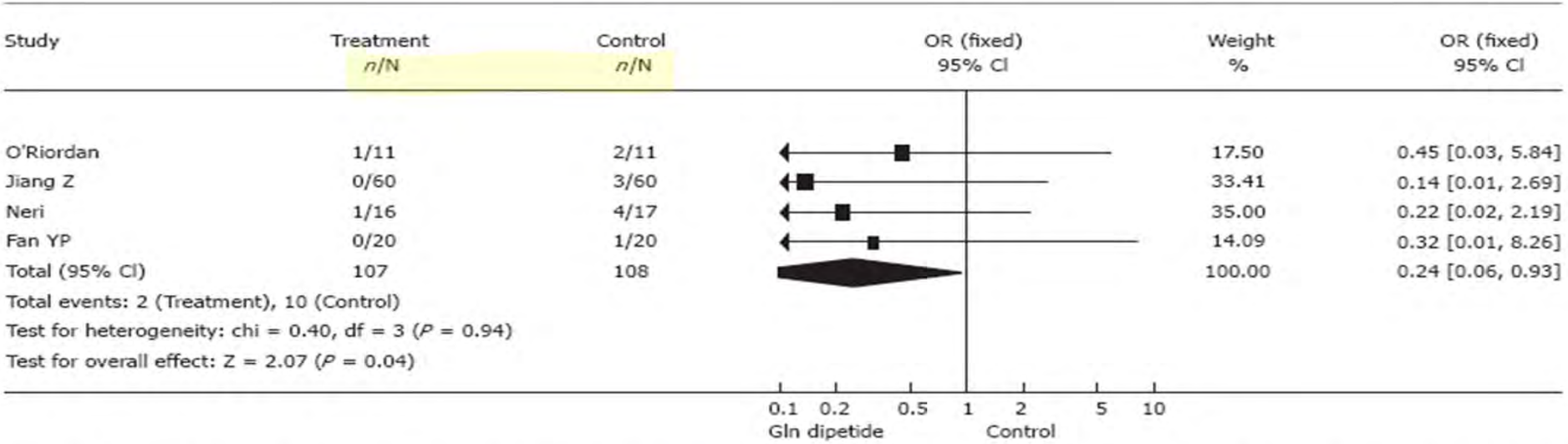


Figure 2 Effect of glutamine dipeptide on postoperative morbidity of infection for abdominal surgery. Review: Clinical evidence of glutamine dipeptide for abdominal surgery; Comparison: Gln dipetide *vs* control; Outcome: Postoperative infective morbidity.

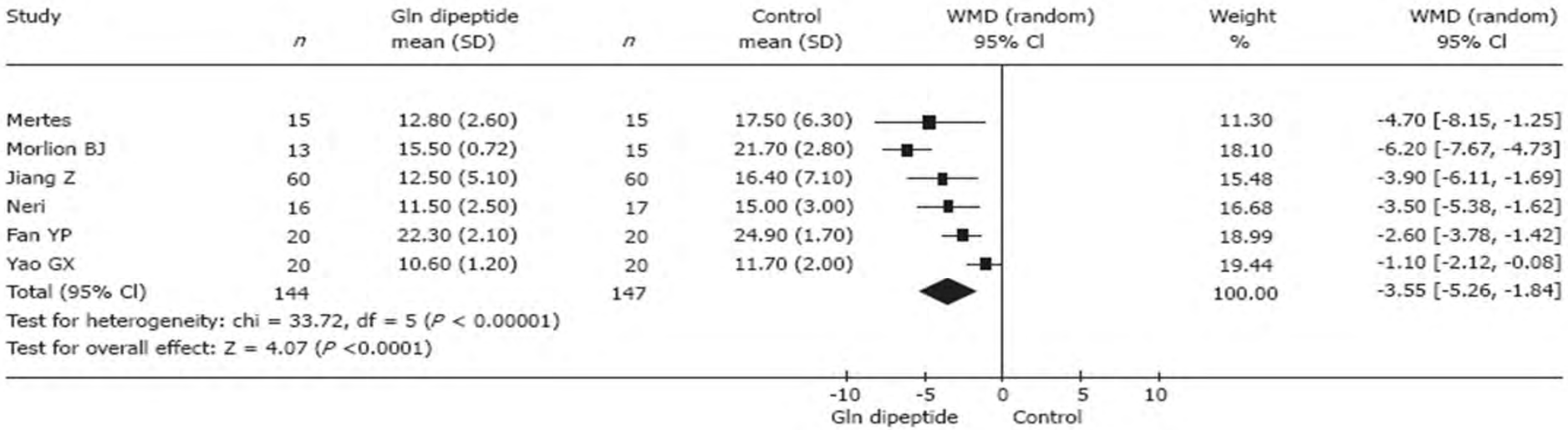


Figure 3 Effect of glutamine dipeptide on length of hospital stay for abdominal surgery. Review: Clinical evidence of glutamine dipeptide for abdominal surgery; Comparison: Gln dipeptide *vs* control; Outcome: Length of hospital stay.

Perioperative Intravenous Glutamine Supplemetation in Major Abdominal Surgery for Cancer

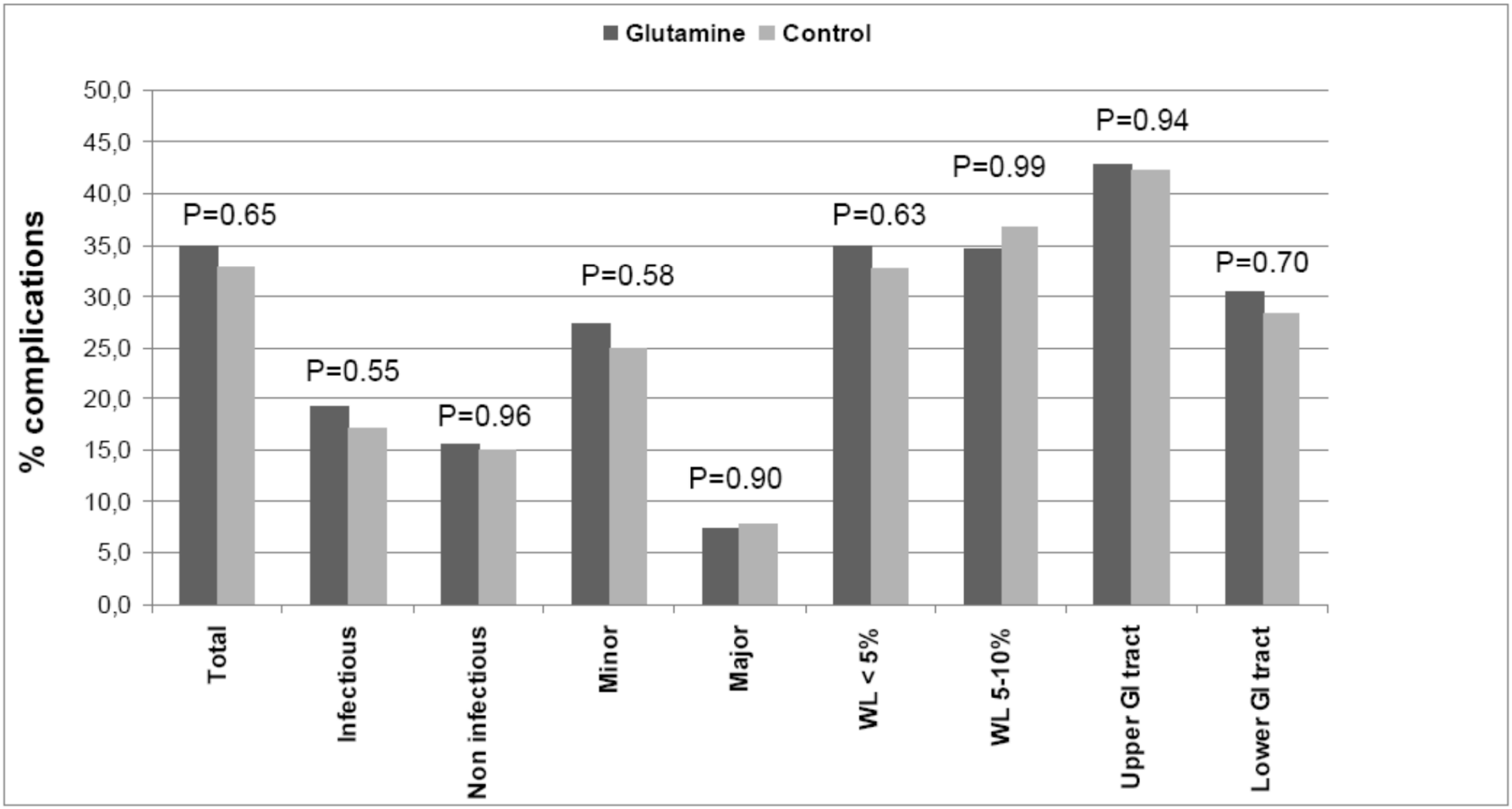
A Randomized Multicenter Trial

Luca Gianotti, MD, ScD, Marco Braga, MD,† Roberto Biffi, MD,‡ Federico Bozzetti, MD,§ and Luigi Mariani, PhD,¶ for the GlutamItaly Research Group of the Italian Society of Parenteral, and Enteral Nutrition*

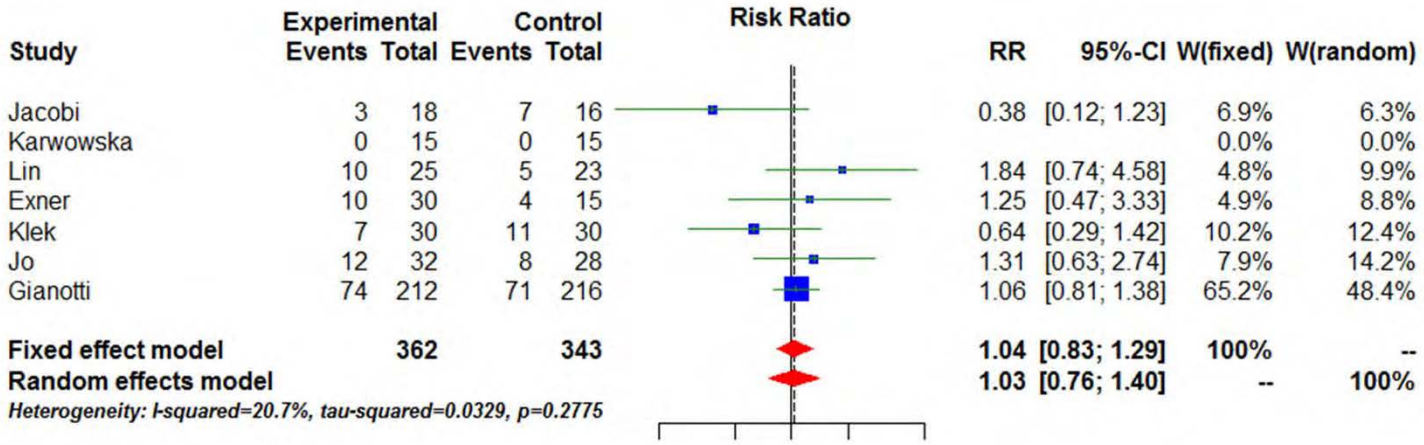
(*Ann Surg* 2009;250: 684–690)

Treatment Protocol

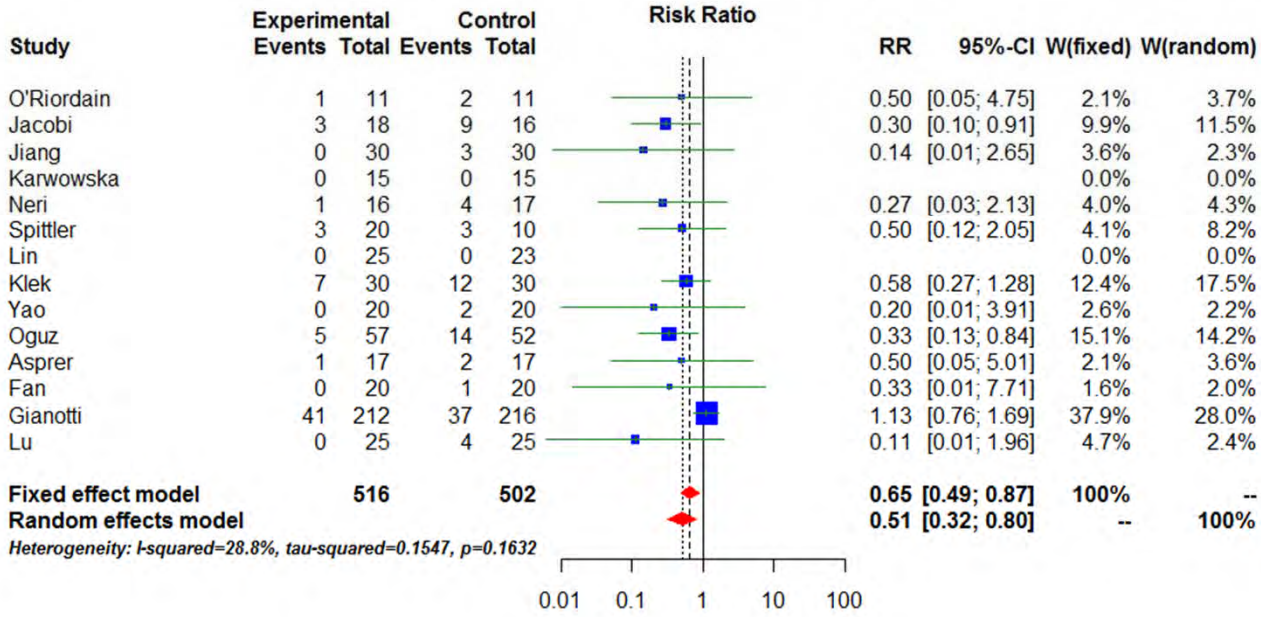
- Parenteral L-alanine-L-glutamine dipeptide (0.40 g/kg/day; equal to 0.25 g of free glutamine).
- The first dose of Ala-Glu given the afternoon before the operation.
- Infusion through a peripheral or central catheter, mixed in 5% glucose solution (vehicle) .
- Continuous infusion over a period of 20 hours
- Ala-Glu given for a minimum of 6 days
- No other artificial nutritional support given unless the patient could not start a progressive oral feeding within 7 days after surgery (SINPE – ESPEN - ASPEN guidelines)

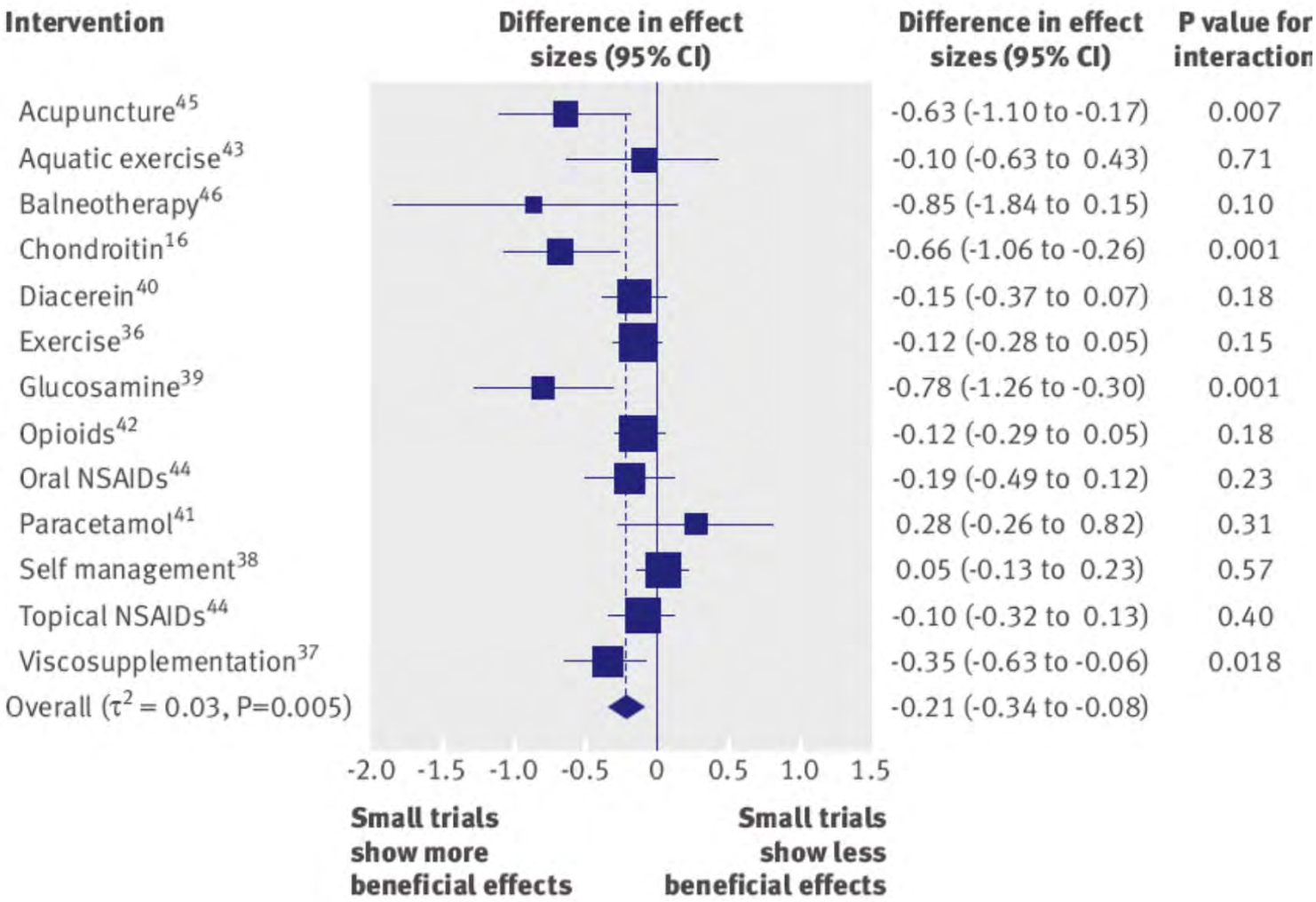

Glutamine
Control
% complications
50,0
45,0
40,0
35,0
30,0
25,0
20,0
15,0
10,0
5,0
0,0
P=0.65
P=0.55
P=0.96
P=0.58
P=0.90
P=0.63
P=0.99
P=0.94
P=0.70
Total
Infectious
Non infectious
Minor
Major
WL < 5%
WL 5-10%
Upper GI tract
Lower GI tract

Elective surgery: Overall morbidity



Elective surgery: Infectious morbidity





Conclusions Small study effects can often distort results of meta-analyses. The influence of small trials on estimated treatment effects should be routinely assessed.

Position Paper

A.S.P.E.N. Position Paper: Parenteral Nutrition Glutamine Supplementation

Vincent W. Vanek, MD, FACS, CNSP; Laura E. Matarese, PhD, RD, LDN, FADA, CNSD; Malcolm Robinson, MD, CNSP; Gordon S. Sacks, PharmD, BCNSP, FCCP; Lorraine S. Young, RD, MS, CNSD; and Marty Kochevar, MS, RPh, BCNSP, Novel Nutrient Task Force, Parenteral Glutamine Workgroup and the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors

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- Parenteral glutamine may be beneficial in certain other adult surgical patients, such as patients undergoing major abdominal surgery, or critically ill non-ventilated patients requiring PN; however, due to the heterogeneity of these patient populations more research is needed regarding which patients may benefit from PN glutamine supplementation.

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Summary Points and Consensus Recommendations From the North American Surgical Nutrition Summit

Stephen A. McClave, MD[1]; Rosemary Kozar, MD, PhD[2]; Robert G. Martindale, MD, PhD[3]; Daren K. Heyland, MD, FRCPC[4]; Marco Braga, MD[5]; Francesco Carli, MD[6]; John W. Drover, MD[4]; David Flum, MD[7]; Leah Gramlich, MD[8]; David N. Herndon, MD[9]; Clifford Ko, MD[10]; Kenneth A. Kudsk, MD[11]; Christy M. Lawson, MD[12]; Keith R. Miller, MD[1]; Beth Taylor, MS, RD, CNSC[13]; and Paul E. Wischmeyer, MD[14]

- Glutamine supplementation for the patient requiring postoperative PN cannot be recommended for lack of outcome benefit (and actually may cause net harm for the patient who has renal or hepatic failure). Whether supplemental parenteral glutamine benefits the cancer patient undergoing a major operation who remains on PN for a prolonged period postoperatively (and is thus at risk for glutamine depletion) has yet to be proven.

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DECISION MAKING IN EVIDENCE-BASED MEDICINE

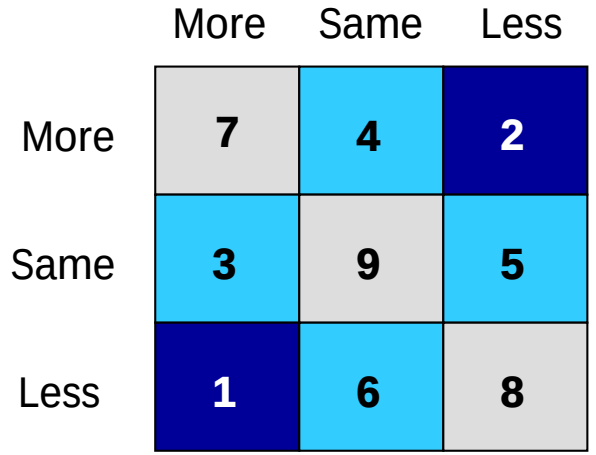
1) Benefits of treatment X

2) Risks of treatment X

3) Economic (cost-benefit / effectiveness) analysis of treatment X

DOMINANCE FOR DECISION

(resolution of the clinical scenario)



Strong dominance for decision:

1 = Accept treatment
2 = Reject treatment

Weak dominance for decision:

3 = Accept treatment
4 = Reject treatment
5 = Reject treatment
6 = Accept treatment

Non dominance: No obvious decision.

7 = Is added effect worth added cost to adopt treatment ?
8 = Is reduced effect acceptable given reduced cost to accept treatment ?
9 = Neutral on cost and effect. Other reasons to accept treatment ?