

Glutamina

en la Terapia Nutricional

Prof. Dr. Abelardo García de Lorenzo y

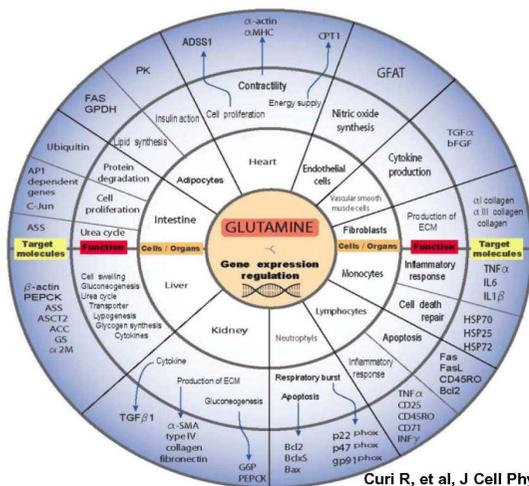
Mateos

Cátedra de Medicina Crítica



Glutamina

funciones metabólicas

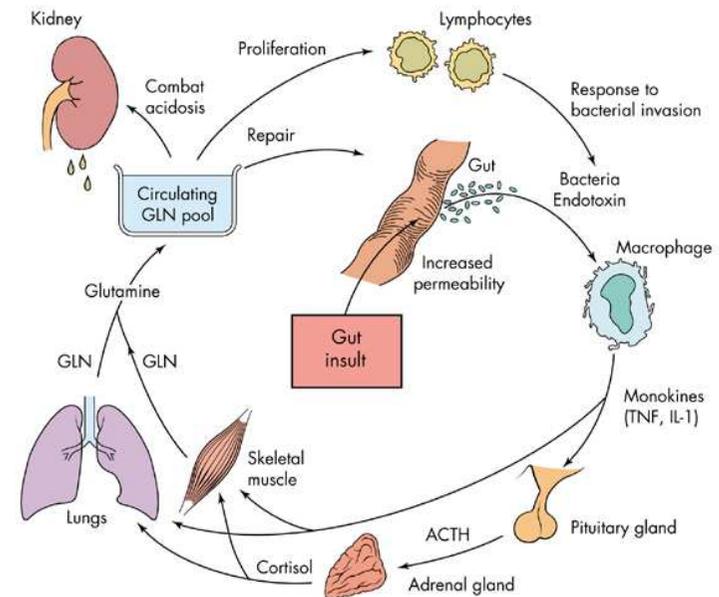


Curi R, et al, J Cell Physiol, 2005

- Transporte de N inter-órganos
- Amoniogénesis renal (EAB)
- HSP
- Resistencia a la insulina
- Precursor en la síntesis de
 - Glutation
 - Nucleótidos
- Regulador en:
 - Síntesis de glucógeno
 - Turnover proteico
- Productor de :
 - Orn, Cit, Arg, Tau y Ala,

Substrato primordial para:

- enterocitos
- linfocitos, macrófagos
- otros:
 - Páncreas
 - Pulmón
 - Cerebro
 - Endotelio
 - Hígado (ADP, ATP)
 - Corazón (cardiomiocitos)



- ¿ El aporte *intravenoso* de Glutamina se acompaña de efectos beneficiosos clínicamente demostrables ?

1. En todas las situaciones clínicas
2. En los pacientes muy graves
3. En los pacientes quirúrgicos
4. Depende



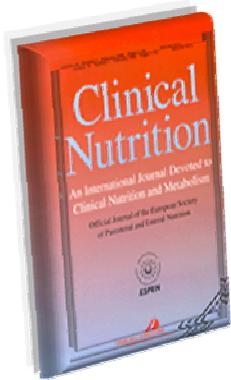
Glutamine Supplementation in Serious Illness: A Systematic Review of the Evidence

Novak F, Heyland DK, Avenell A, Drover J, Su X.

Crit Care Med 2002; 30:2022-9

Pacientes Quirúrgicos:

- Estancia ($p < 0,05$)
- Complicaciones ($p < 0,05$)



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

Jiang Z-M, Jiang H, Furst P

Clin Nutr 2004; S1:17-23

Reducción de:

- **Complicaciones infecciosas** ($p < 0,002$)
- **Estancia hospitalaria en 3,86 d** ($p < 0,00001$)

PO Box 2345, Beijing 100023, China
www.wjgnet.com
wjg@wjgnet.com



World J Gastroenterol 2006 December 14; 12(46): 7537-7541
World Journal of Gastroenterology ISSN 1007-9327
© 2006 The WJG Press. All rights reserved.

RAPID COMMUNICATION

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

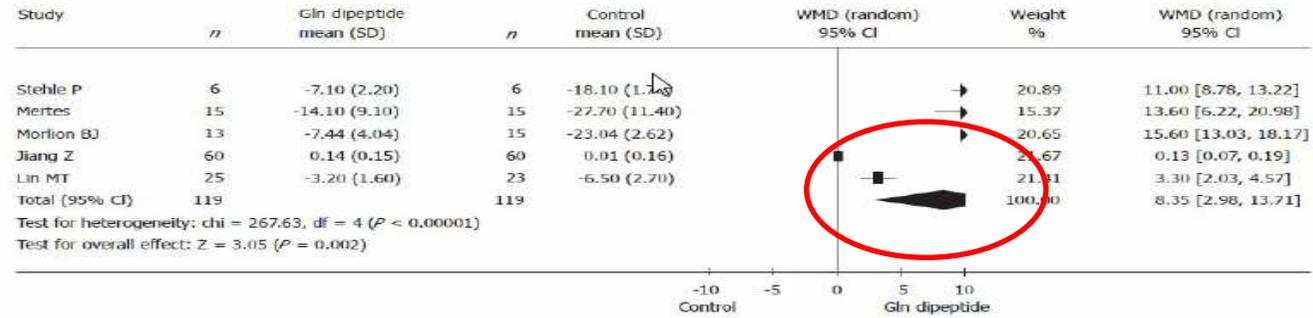
Ya-Min Zheng, Fei Li, Ming-Ming Zhang, Xiao-Ting Wu



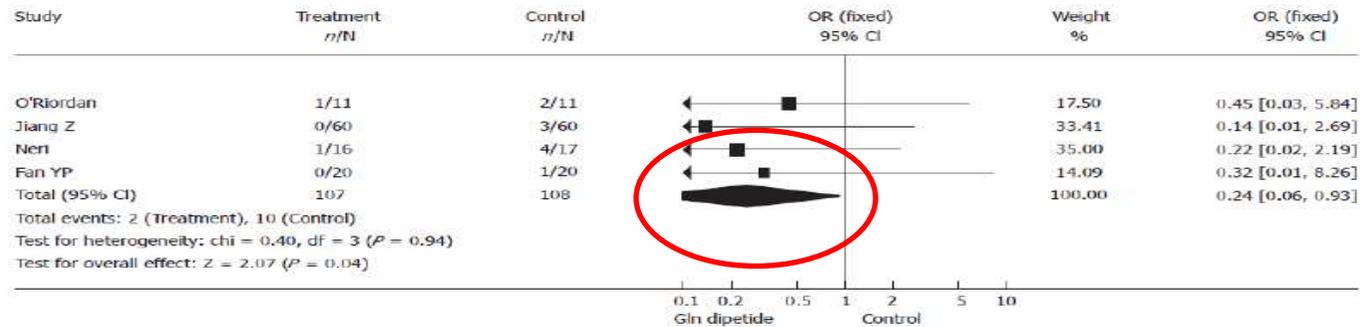
Cátedra de Medicina Crítica



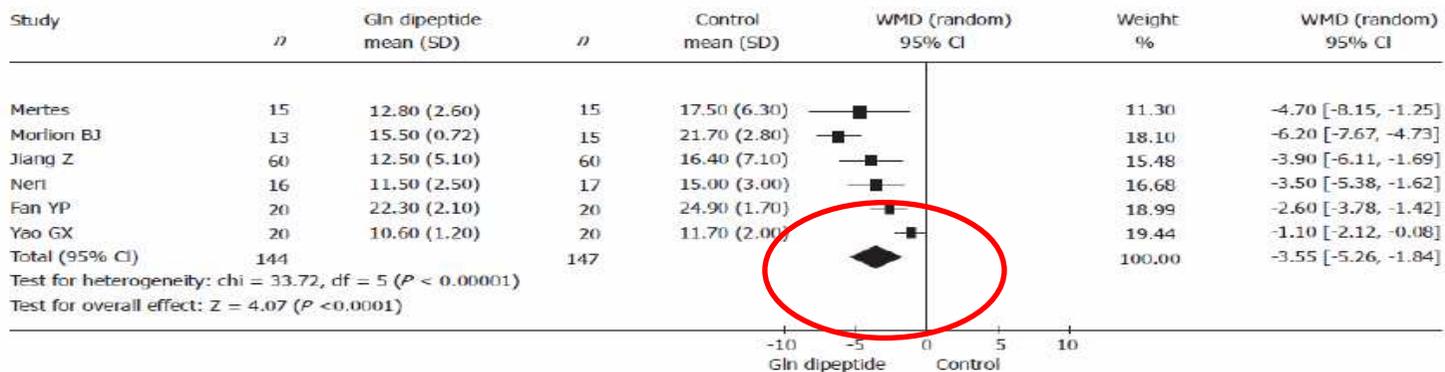
Glutamine dipeptide increases postsurgical cumulative nitrogen balance

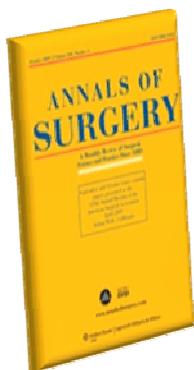


Glutamine dipeptide decreases postsurgical infection rate



Glutamine dipeptide decreases length of postsurgical hospital stay





Perioperative intravenous glutamine supplementation in major abdominal surgery for cancer: A randomized multicenter trial

Gianotti L, Braga M, Bozzetti F, et al

Ann Surg 2009 250:684-90

428 Pacientes neoplásicos: NO VENTAJAS

- Pérdida de peso < 10 % en 6 meses
- NP perioperatoria con Gln [0,4 -> 0,25 g/kg/d]
- Evolución a corto plazo



L-Alanyl-L-glutamine-supplemented parenteral nutrition improves infectious morbidity in secondary peritonitis

Clotilde Fuentes-Orozco^a, Roberto Anaya-Prado^{a,b,c},
Alejandro González-Ojeda^{a,b}, Humberto Arenas-Márquez^{b,*},
Carlos Cabrera-Pivaral^a, Gabino Cervantes-Guevara^d,
Luis M. Barrera-Zepeda^b

Clin Nutr 2004; 23:13-21

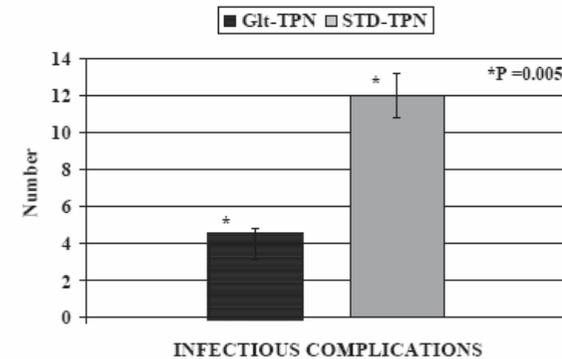


Figure 1 The patients in the study group had fewer ($n=4$) complications than those in the control ($n=12$). Difference between both groups was statistically significant ($P<0.005$).

Conclusion: L-alanyl-L-glutamine-supplemented TPN improved the infectious morbidity of patients with secondary peritonitis. Gln supplementation to parenteral nutrition may be an alternative for enhancing host defenses and improving infectious morbidity.

© 2003 Elsevier Ltd. All rights reserved.

L-alanyl-L-glutamine dipeptide-supplemented total parenteral nutrition reduces infectious complications and glucose intolerance in **critically ill patients**: The French controlled, randomized, double-blind, multicenter study

Dechelotte P, Hasselmann M, Cynober L, et al

Crit Care Med 2006;34:598-604

El aporte de Gln (iv, Ala-Gln a 0,5 g/kg/d) se asocia a:

- **menor incidencia de complicaciones infecciosas** (neumonía; $p < 0,05$)
- **mejor tolerancia metabólica** (menor hiperglucemia y mas bajos requerimientos de insulina; $p < 0,05$)



Applied nutritional investigation

Glutamine as a modulator of the immune system of critical care patients: Effect on Toll-like receptor expression. A preliminary study

Jon Pérez-Bárcena, M.D.^{a,*}, Verónica Regueiro^b, Pedro Marsé, M.D.^a,
 Joan María Raurich, Ph.D.^a, Alberto Rodríguez, M.D.^a, Jordi Ibáñez, Ph.D.^a,
 Abelardo García de Lorenzo Mateos, Ph.D.^c, and José Antonio Bengoechea, Ph.D.^b

Of 30 consecutive patients who met the inclusion criteria, 15 were randomly assigned to receive a daily glutamine supplement of 0.35 g/kg of body weight as N2-L-alanyl-L-glutamine ($0.5 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$; Dipeptiven, Fresenius Kabi España, Barcelona, Spain) for 5 d. The treatment period of

Complications during ICU hospitalization

	PN + GI (n = 15)	PN – GI (n = 15)	P
Septic shock*	1	1	1.0
Respiratory infection [†]	4	2	0.65
Urinary infection [‡]	1	0	1.0
Blood culture [§]	3	2	1.0
Catheter infection	2	5	0.39
Other infections [¶]	1	4	0.47
Total infections	11	13	0.51
Days on MV	14 ± 10	14 ± 10	0.94
ICU length of stay (d)	22.9 ± 20.6	20.5 ± 16.0	0.87
Hospital length of stay (d)	35.5 ± 33.6	42.9 ± 28.8	0.39
Hospital mortality (d)	3	0	0.22

The effects of supplemental glutamine dipeptide on gut integrity and clinical outcome after major escharectomy in **severe burns**: a randomized, double-blind, controlled clinical trial

Zhou Y, Jiang Z, Sun Y.

Clin Nutr 2004; S1:55-60

- Aumenta la concentración plasmática de Gln ($p < 0,001$)
 - Disminuyen los niveles de endotoxina ($p < 0,043$)
 - Se acorta el tiempo de curación de las heridas ($p < 0,012$)
 - Reducción en el coste de hospitalización ($p < 0,029$)
-
- *Menor tendencia a la infección (ns)*
 - *Mejora de la permeabilidad intestinal (ns)*



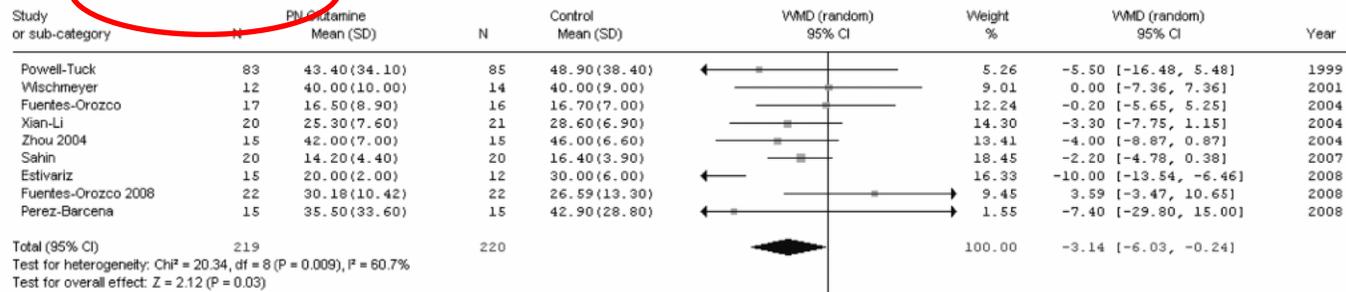
Updated Recommendations

Canadian Clinical Practice Guidelines
Summary of Topics and Recommendations

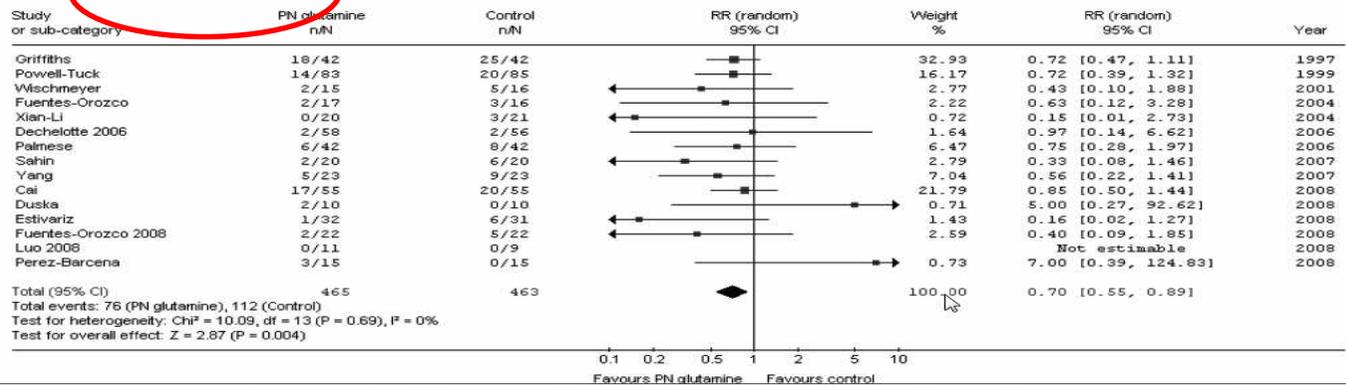
May 28th, 2009

<p>Composition of PN: Glutamine* †</p>	<p>Does glutamine supplementation of parenteral nutrition influence outcomes in the critically ill adult patient?</p>	<p>UPGRADED from 2007 Based on 4 level 1 studies and 13 level 2 studies, when parenteral nutrition is prescribed to critically ill patients, parenteral supplementation with glutamine, where available, is strongly recommended. There are insufficient data to generate recommendations for intravenous glutamine in critically ill patients receiving enteral nutrition.</p>	<p>Based on 4 level 1 studies and 5 level 2 studies, when parenteral nutrition is prescribed to critically ill patients, parenteral supplementation with glutamine, where available, is recommended. There are insufficient data to generate recommendations for intravenous glutamine in critically ill patients who are receiving enteral nutrition.</p>
--	---	--	--

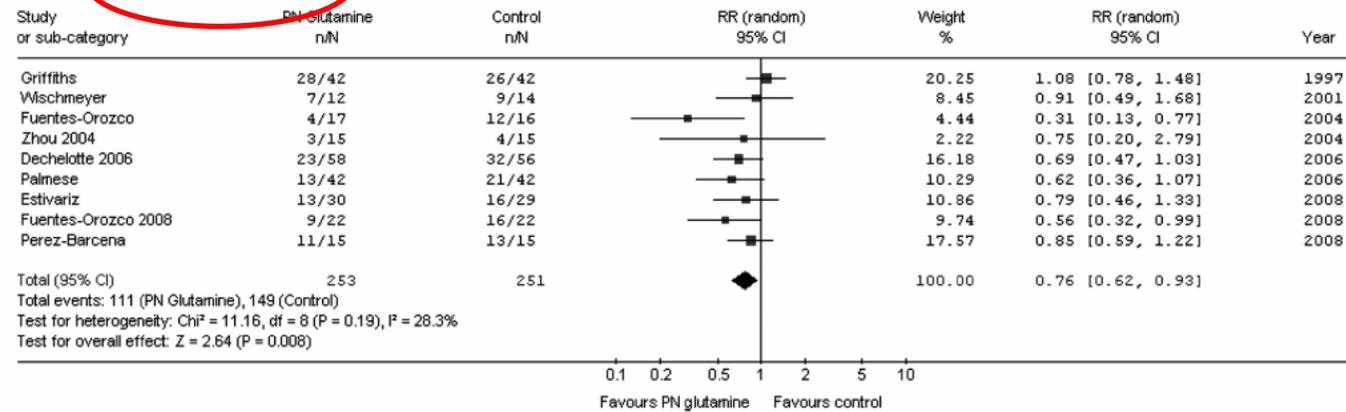
Review: glutamine New review (Version 01)
 Comparison: 02 Parenteral Glutamine vs Control
 Outcome: 02 Hospital LOS



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



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



CLINICAL THERAPEUTICS

Parenteral Nutrition in the Critically Ill Patient

Thomas R. Ziegler, M.D.

N Engl J Med 2009;361:1088-97.

Copyright © 2009 Massachusetts Medical Society.

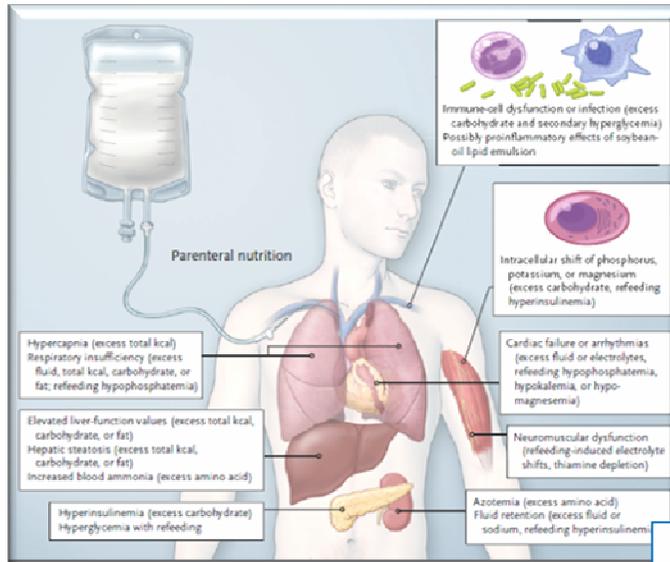


Figure 1. Potential Metabolic and Clinical Consequences of Overfeeding and the Refeeding Syndrome during Administration of Central Venous Parenteral Nutrition in Patients with Critical Illness.

Available data suggest that the body's requirement for glutamine may exceed its endogenous production in certain ICU patients.^{4,12,16,22} Several clinical trials have shown that glutamine-supplemented parenteral nutrition has protein anabolic effects, enhances indexes of immune function, and decreases the rate of hospital-acquired infections.^{12,22,68-70} However, clinical practice guidelines differ on the question of whether glutamine, if available, should be routinely added to parenteral nutrition in the ICU.^{1,4,16}

- ¿ El aporte exógeno de Glutamina - *por la vía enteral* - se acompaña de efectos beneficiosos clínicamente demostrables ?

1. No está demostrado
2. Solo en intestino corto
3. Solo en TX médula osea
4. Si

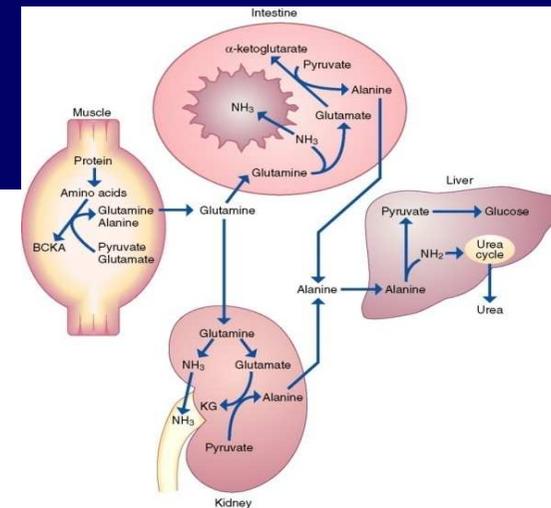
Morais AA, Santos JE, Faintuch J. Comparative study of arginine and glutamine supplements in malnourished surgical patients

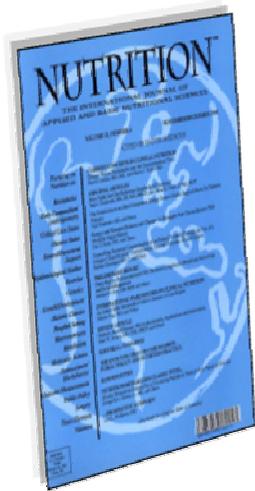
Revista do Hospital das Clínicas. 1995; 50:276-9

- La administración de Arg mejora el nivel de albúmina
- La administración de Gln reduce la morbilidad



■ Un vistazo a la MBE





Clinical Evidence for Enteral Nutritional Support with Glutamine: A Systematic Review

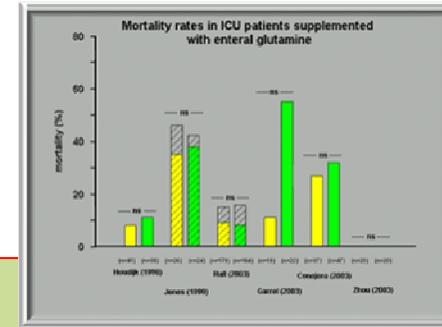
García de Lorenzo A, Zarazaga A, García-Luna PP et al.

Nutrition 2003; 19:805-11



- Buena tolerancia

- Mejoría de los aspectos inmunológicos en enfermos traumáticos críticos
- Reducción de costes y tiempo de estancia en enfermos críticos
- Mejoría de la mucositis post quimioterapia y TMO



Clinical effects by enteral glutamine:

Houdijk

Lancet 1998

Lower infectious morbidity

Jones

Nutrition 1999

Lower hospital cost

Hall

ICM 2003

No effect

Garrel

CCM 2003

Lower infectious morbidity

Conejero

Nutrition 2002

Lower infectious morbidity

Zhou

JPEN 2002

Lower hospital cost

Hall JC et al. A prospective randomised trail of enteral glutamine
in critically illness

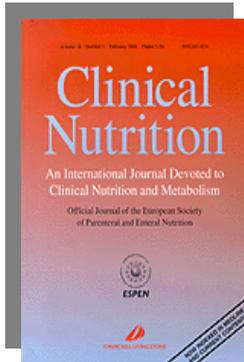
Intensive Care Med. 2003; 29:1710-6

363 pacientes críticos ¿bien nutridos?

19 g de Gln/d (0,2 g/kg/d)

NO diferencias en:

- **Mortalidad**
- **Incidencia de sepsis**



ESPEN Guidelines 2006

Glutamine should be added to standard enteral formula in

- burned patients
- trauma patients

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

A
A

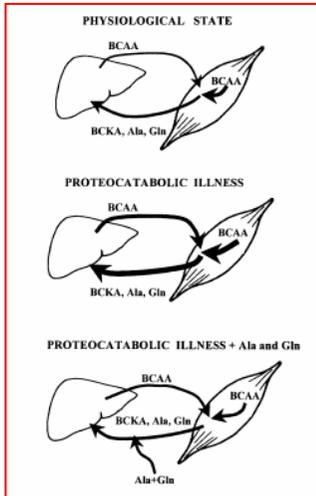
Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition: Executive Summary*

Robert G. Martindale, MD, PhD; Stephen A. McClave, MD; Vincent W. Vanek, MD; Mary McCarthy, RN, PhD; Pamela Roberts, MD; Beth Taylor, RD; Juan B. Ochoa, MD; Lena Napolitano, MD; Gail Cresci, RD; American College of Critical Care Medicine; and the A.S.P.E.N. Board of Directors

Crit Care Med 2009 Vol. 37, No. 5

- **F3.** The addition of **enteral glutamine** to an EN regimen (not already containing supplemental glutamine) should be considered in burn, trauma, and mixed ICU patients (**Grade B**)





RESUMEN: Resultados Clínicos

Trauma

- Menor incidencia de infección
- Mayor expresión de HLA-DR
- Menor resistencia a la insulina
- Menor producción de citocinas

Cirugía

- Menor incidencia de infección
- Menor estancia hospitalaria
- Mejor BN



Quemados

- Menor incidencia de infección
- Menor tasa de mortalidad

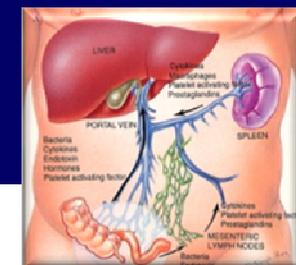
UCI

- Menos complicaciones
- Menor incidencia de mortalidad (6 meses)
- Menor hiperglucemia

- El metabolismo de la Gln depende de la vía de administración ***y es mejor la vía parenteral que la enteral***

1. Donde esté una buena vena ...
2. Solo en los pacientes muy graves
3. Solo en los pacientes quirúrgicos
4. Pueden ser similares

- El intestino capta preferencialmente Gln cuando esta se administra por vía enteral (menor nivel arterial, mayor extracción fraccional intestinal), en comparación con la administración parenteral
- Ello se debe a que los enterocitos (+ GALT) son células de división rápida y emplean la Gln como fuente de energía



- Por ello, se dispone de poca Gln a nivel de la circulación sistémica y ello justifica sus efectos limitados sobre el devenir clínico

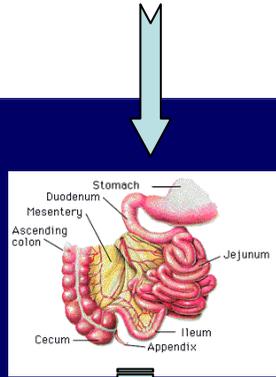
Ligthart-Melis GC, van de Poll MC, Dejong CH et al. The route of administration (enteral or parenteral) affects the conversion of isotopically labeled L-[2-15]Glutamine into Citrulline and Arginine in humans

JPEN 2007; 31:343-48

Estudio centrado en establecer el efecto de la vía de administración en la conversión de la Gln exógena en citrulina y arginina a nivel orgánico, en humanos



GLUTAMINA



ORNITINA

CITRULINA



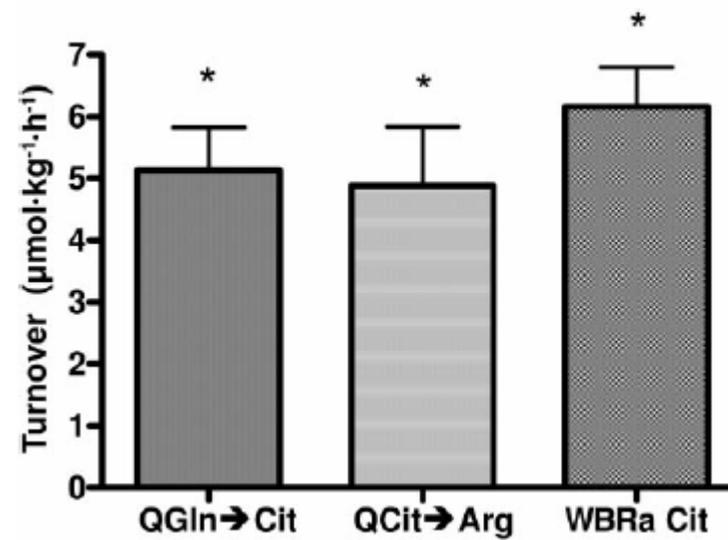
ARGININA

■ La vía de administración afecta a la conversión cuantitativa de **Gln** en **citruilina** (mayor nivel arterial si Gln enteral) y en la subsecuente síntesis renal de **arginina** (con ambas vías de administración)

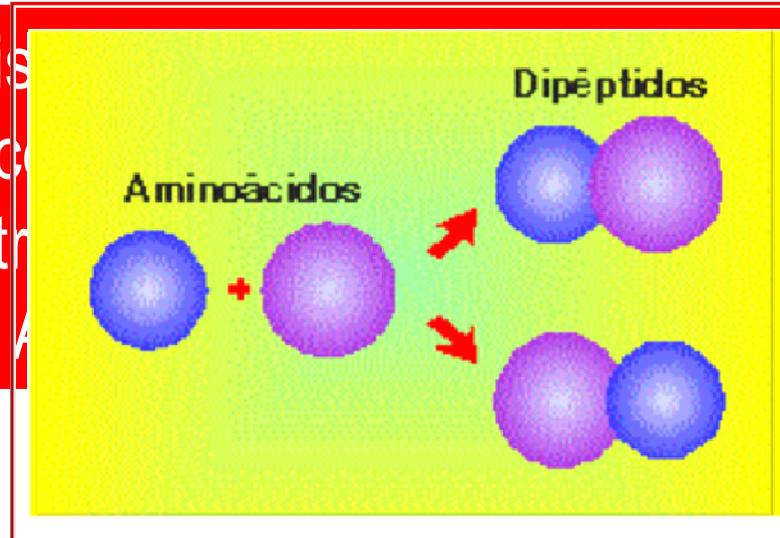
Glutamine is an important precursor for de novo synthesis of arginine in humans¹⁻⁴

Gerdien C Ligthart-Melis, Marcel CG van de Poll, Petra G Boelens, Cornelis HC Dejong, Nicolaas EP Deutz, and Paul AM van Leeuwen

Am J Clin Nutr 2008;87:1282-9.



Lighthart-Melis
(15)N]glutamine
than does intr



tion of alanyl-[2-
synthesis of arginine
otide in humans
05

El metabolismo -enteral- de la Gln
depende de la forma de administración
[mejor dipéptidos que Gln libre]

- ¿ A que *dosis*, durante cuanto *tiempo* y en que *momento* ?

1. > 0,3 g/kg/d. > 5 días. Al 5º día
2. > 0,3 g/kg/d. > 5 días. Precoz
3. > 0,3 g/kg/d. < 5 días. Al 5º día
4. > 0,3 g/kg/d. < 5 días. Precoz



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 Leverveⁱ, Claude Pichard^j

Recommendation: 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) (Grade A).



- > 0,4 g/kg/d de dipéptido o
- > 0,3 g/kg/d de glutamina

(30 % de las proteínas o 30 g/d)



Contents lists available at ScienceDirect

e-SPEN, the European e-Journal of
Clinical Nutrition and Metabolism

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



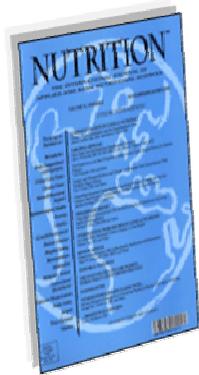
Parenteral nutrition – Guidelines of the Israeli Society for Clinical Nutrition (ISCN)

Irit Chermesh^a, Odile Azoulay^b, Efrat Alpert^c, Ronit Anbar^d, Yitshal Berner^e, Nir Barak^f,
Evgenia Chochrin^{a,g}, Mirit Cohen^a, Ruti Efargan^a, Herbert Freund^h, Miriam Ganonⁱ, Salim Hadad^j,
Moshe Hersch^k, Michal Kairi^l, Asher Korzets^m, Alon Langⁿ, Yshai Levi^o, Eva Niv^p, Irit Poraz^l,
Miryam Theilla^d, Nachum Vaisman^p, Pierre Singer^{d,*}

20.7. Indication for Glutamine in ICU

A systematic review of the evidence regarding the use of glutamine supplementation in serious illness was performed by Novak et al.¹³² and showed heterogeneous results. However, two studies^{133,134} demonstrated a 6-month outcome improvement in critically ill patients, expressed in incidence of death within six months. In addition, the addition of glutamine reduced infectious complications and glucose intolerance in critically surgical patients.¹³⁵ The recommendation of the consensus group was that glutamine supplementation (0.3 g/kg) for at least 5 days may be of benefit to ICU patients (GCPN 2B; CDC 1B).





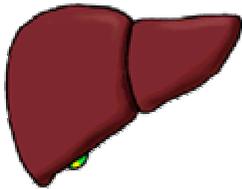
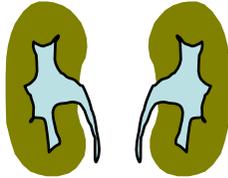
Clinical Evidence for Enteral Nutritional Support with Glutamine: A Systematic Review

García de Lorenzo A, Zarazaga A, García-Luna PP et al.
Nutrition 2003; 19:805-11

- $> 0,3 \text{ g/kg/d}$
- aporte precoz
- duración ≥ 5 días

- ¿ Existen *contraindicaciones* ?

1. Solo en el TCE
2. Solo en los EH
3. Solo en la IRA
4. En todas las anteriores

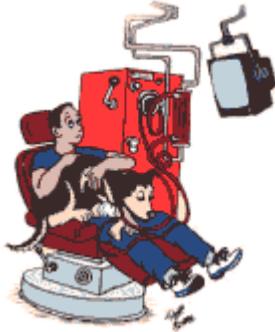


- Riñón
- Hígado
- Cerebro

Impact of new technologies on metabolic care in the intensive care unit

Corey Scurlock^a, Jayashree Raikhelkar^b and Jeffrey I. Mechanick^c

Current Opinion in Clinical Nutrition and Metabolic Care 2009, 12:196–200



Alterations in serum concentrations of amino acids are predictable with various types of kidney injury. For example, glutamine and arginine can be depleted, whereas concentrations of phenylalanine and methionine are elevated [13]. Berg *et al.* [14] studied glutamine kinetics in patients with MODS on continuous renal replacement therapy (CRRT). Glutamine clearance rates corresponded with plasma glutamine levels and effluent flow rates. Thus, Berg *et al.* [14] argued for glutamine supplementation (20 g/day) in critically ill patients on CRRT. Consistent with this, Wernerman [15] recently recommended 25–35 g/24 h of intravenous glutamine for those patients undergoing CRRT. A recent meta-analysis [13] on the use of CRRT described improved control of azotemia with a high amino acid intake. There were also improvements in nitrogen balance with high amino acid doses, up to 2.5 g/kg/day on CRRT. Unfortunately, there are still insufficient prospective, randomized, controlled trials studying amino acid dosing in ARF and clinical outcomes in patients on CRRT.

1: [Ann Hepatol.](#) 2009 Apr-Jun;8(2):95-102.

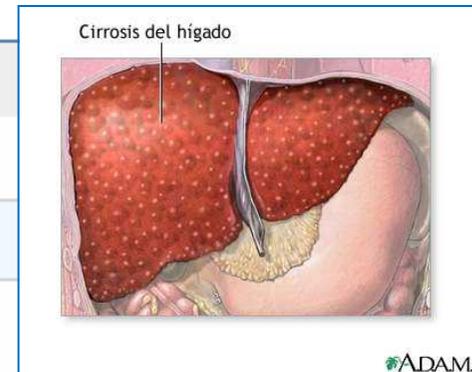
Hepatic encephalopathy, ammonia, glutamate, glutamine and oxidative stress.

[Lemberg A](#), [Fernández MA](#).

Department of Pathophysiology, School of Pharmacy and Biochemistry, University of Buenos Aires, Argentina.
allef2002@yahoo.com

This review addresses recent and not so recent works that emphasize on the mechanisms by which liver damage can induce encephalopathy. Hepatic encephalopathy constitutes an intriguing complication in severe liver acute and chronic disease, whose pathophysiology is still not completely understood. In this pathology, alterations in normal brain function are associated with morphological and functional impairments of astrocytes and neurons. A wide spectrum of psychoneurological symptoms has been described and the anatomical substratum is usually associated with brain edema and intracranial hypertension, as well as with changes in the function of brain cells. An increase in blood ammonia, toxic to the brain, depends on the activity of the enzyme glutamine synthetase, the glutamine/glutamate cycle and the brain capacity to eliminate toxic substances.

When the concentration of the excitotoxic neurotransmitter glutamate is increased, it acts as a toxic agent, especially when its specific transporters are altered and its uptake is decreased. Glutamine has also been recently considered a toxic substance when its concentration is high, and consequently contributes to brain edema. Finally, the formation of reactive oxygen species, basically produced by mitochondria, influence with their toxic action on membrane lipids, proteins and DNA. In conclusion we suggest that at least these four elements are involved directly in the mechanism of hepatic encephalopathy.





available at www.sciencedirect.com



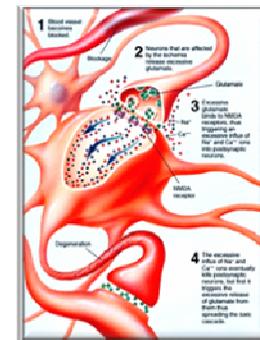
<http://intl.elsevierhealth.com/journals/clnu>

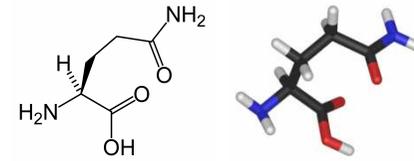


ORIGINAL ARTICLE

The pattern of amino acid exchange across the brain is unaffected by intravenous glutamine supplementation in head trauma patients

Agneta Berg ^{a,*}, Bo Michael Bellander ^b, Michael Wanecek ^b, Åke Norberg ^a, Urban Ungerstedt ^c, Olav Rooyackers ^a, Jan Wernerman ^a



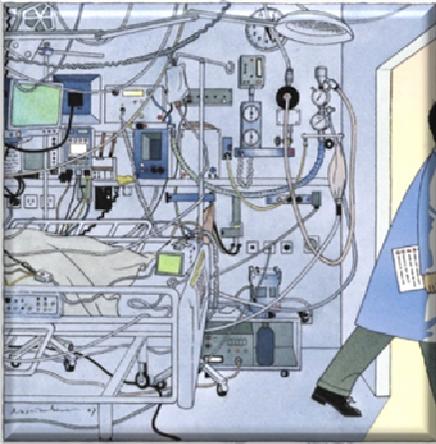


La conclusión debería ser:

¿ Existe alguna razón para no aportar
Glutamina en la nutrición de los
pacientes agredidos ?

Wernerman J, 1998





Muchas gracias por su atención

GdL



Cátedra de Medicina Crítica

