

# Clinical Evidence for Enteral Nutritional Support With Glutamine: A Systematic Review

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**OBJECTIVE:** The purpose of this systematic review was to locate and assess the quality of scientific evidence to establish a graded recommendation based on the effectiveness of glutamine-enriched enteral nutrition in different medical and surgical conditions. We were concerned with the following topics: 1) benefits of enteral administration of glutamine in different pathologic conditions, and 2) dose, duration, and time of initiation of glutamine-enriched diets.

**METHODS:** The sources consulted for the search were MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Healthstar and HSTAT. Ninety-one studies were assessed; after a methodologic review (primary review), only 16 studies met the inclusion criteria for analysis by a group of experts (secondary review). The coordinators supervised all data, and a final consensus was reached among the coordinators, experts, and methodologists.

**RESULTS AND CONCLUSIONS:** Glutamine-enriched diets showed good overall tolerance, improvement of immunologic aspects in multiple trauma patients, cost reduction in critically ill patients, and improvement of mucositis in post-chemotherapy patients (grade B recommendations). The doses given and the duration of therapy varied widely depending on the pathologic condition. Intake of 20 to 30 g/d, early initiation of diet, and maintenance for 5 d or longer are recommended (grade C recommendations). *Nutrition* 2003; 19:805–811. ©Elsevier Inc. 2003

**KEY WORDS:** nutrition, diet, glutamine, critically ill, chemotherapy, short bowel, surgery, Crohn's disease, immunonutrition, systematic review

## INTRODUCTION

Glutamine, a non-essential amino acid widely distributed throughout the body, can behave as an essential amino acid in certain clinical settings. Its metabolism and kinetics have been studied over the past three decades in diseases characterized by the presence of significant metabolic stress and in postsurgical patients, septic patients, critically ill patients, and patients with multiple trauma and have been extended to other diseases such as inflammatory bowel disease, short bowel syndrome, and bone marrow transplantation, in which the trophic actions of glutamine on rapid-turnover cells (lymphocytes, mastocytes, and enterocytes) could have certain beneficial effects on the illnesses of these patients.

Different mechanisms of action of glutamine in the body have been proposed:

- Improves trophism of enterocytes and colonocytes
- Enhances the immunologic barrier due to its trophic action on the immune system

- Involved in the acid–base balance
- Substrate for glutathione and thus involved in its antioxidant and scavenging actions on free radicals
- Decreases bacterial translocation

In this systematic review, we present the possible benefits of enteral administration of glutamine and its dose, duration, and time of initiation in different pathologic conditions to address the recent increased interest in the effectiveness and safety of glutamine supplementation in humans.

## MATERIALS AND METHODS

### Objective

We evaluated the best scientific evidence on the use of nutritional supplements that base their effects on the inclusion of glutamine in their composition. Seven possible clinical settings where its use has been reported to have beneficial effects were considered. The eligibility criteria follow:

- Critically ill and septic patients
- Multiple-trauma patients
- Postsurgical patients

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TABLE I.

LEVEL OF QUALITY OF EVIDENCE AND DEGREES OF RECOMMENDATION		
Level of quality of scientific evidence	Degree of recommendation	Recommendation
I: randomized trials with large samples and well defined results (and a low risk of types I or II statistical errors)	A	There is adequate scientific evidence to support a recommendation for or against the adoption of the technology
II: randomized trials with small samples (and a moderate to high risk of type I or II statistical errors)		
III: non-randomized studies, concurrent controls	B	There is some scientific evidence to support a recommendation for or against the adoption of the technology
IV: non-randomized studies, historic controls		
V: uncontrolled studies, clinical series	C	There is insufficient scientific evidence to support a recommendation for or against adoption of the technology and its use should be based on other criteria

- Post-chemotherapy patients
- Bone marrow transplantation
- Short bowel syndrome
- Crohn's disease

- 7. explode CLINICAL-TRIALS
  - 8. CROSSOVER in ti,ab,mesh
  - 9. SYSTEMATIC\* NEAR (REVIEW OR OVERVIEW\*) in ti,ab,mesh
- 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9

### Search Strategy and Eligibility Criteria

TARGET POPULATION. Male and female patients older than 18 y.

TYPES OF STUDIES. Systematic reviews and clinical trials.

DATABASES. The following databases were consulted:

- MEDLINE, from 1990 to 2002
- EMBASE, from 1995 to 2002
- Healthstar, from 1990 to 2002
- HSTAT databases of the National Library of Medicine

CONTROLLED LANGUAGE (MeSH).

- explode "Glutamine"/all subheadings
- explode "Short-Bowel-Syndrome"/all subheadings
- explode "Burns"/all subheadings
- explode "Crohn-Disease"/all subheadings
- explode "Critical-Illness"/all subheadings or explode "Critical-Care"/all subheadings
- explode "Postoperative-Care"/all subheadings or explode "Postoperative-Period"/all subheadings
- explode "Enteral-Nutrition"/all subheadings
- explode "cost/all subheadings" or "cost-benefit analysis"
- explode "quality of life" or "quality-adjusted life years"

FREE TEXT.

- (glutamine) in ti,ab
- (short near bowel) in ti,ab
- (burn\*) in ti,ab
- (crohn) in ti,ab
- (severe near illness) in ti,ab
- (postoperat\*) in ti,ab
- (enteral near nutrition) in ti,ab

To locate articles having the highest quality of evidence, we used the methodologic filters listed below, provided on-line by the Cochrane Library:

1. RANDOMIZED-CONTROLLED-TRIAL in PT
2. META-ANALYSIS in PT
3. CONTROLLED-CLINICAL-TRIAL in PT
4. CLINICAL-TRIAL in PT
5. Random\* in TI,ab,mesh
6. (meta?anal\* or meta analy\*) in ti,ab,mesh

### Assessment of Quality of Evidence

Most of the literature located falls into the levels of evidence corresponding to groups II to IV of the Agencia d'Avaluació de Tecnologia Médica classification<sup>1</sup> (Table I).

Subsequently, based on the analysis and evaluation of the evidence collected and the experts' experiences, we developed recommendations to whether appropriate conditions were met for adoption or use of a health technology. Grade A recommendations were classified as conclusive and were derived from the conclusions of meta-analyses and well-designed clinical trials with small or large samples. (We consider large-sample clinical trials to be those in which the study sample exceeds 50 patients.) Grade B recommendations were considered inconclusive based on the results of non-randomized controlled clinical trials, cohort studies, or case control studies. Grade C recommendations were classified as inconclusive because the scientific evidence was considered insufficient by being based on publications having a lower level of scientific evidence (descriptive studies, uncontrolled clinical series, expert committees, and anecdotal reports), so the use of the technology should be based on other criteria. This type of recommendation was used for educational proposals and clinical research. The correlation between levels of quality of evidence and the grade of recommendation is shown in Table I.

There are more than 25 measurement scales to assess the quality of a clinical trial. For its clarity, speed, and ease of use, we adopted the scale proposed by Jaddad et al.<sup>2</sup> (Fig. 1), described below, which is also one of the most widely accepted scales.

### Inclusion Criteria

Patients older than 18 y with any of the following conditions:

- Critical illness (Acute Physiology and Chronic Health Evaluation score > 10 or Injury Severity Score > 20)
- Burns
- Major abdominal surgery
- Short bowel syndrome
- Inflammatory bowel disease
- Bone marrow transplantation and antitumor chemotherapy
- Multiple trauma (Injury Severity Score > 20 or Acute Physiologic and Chronic Health Evaluation II > 10)

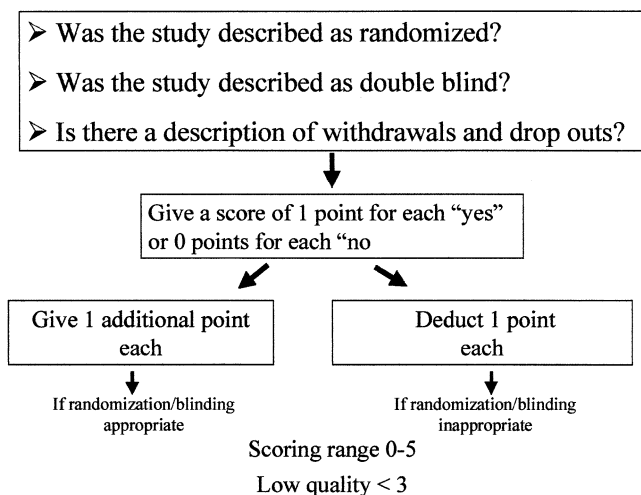


FIG. 1. The Jaddad Scale.

**Exclusion Criteria**

- Multiorgan failure
- Prior immunologic disease
- Prior steroid therapy

**Type of Intervention**

- Enteral nutrition with glutamine supplements
- Total parenteral nutrition versus enteral nutrition with glutamine

**Measurement of Results**

- Nutrition status
- Immunologic function
- Body fluid distribution
- Intestinal mucosa atrophy
- Intestinal mucosa permeability
- Nitrogen balance
- Sepsis, clinical infection, or positive cultures
- Mortality rate
- Costs
- Length of hospitalization

**Search Results**

Ninety-one articles were located, 16 of which met our eligibility criteria. The distribution of the 16 articles according to underlying disease is shown in Table II.

**RESULTS**

**Current Evidence on the Efficacy of Enteral Nutritional Supplementation With Glutamine in Different Pathologic Conditions**

Of the 91 articles located in the search, only 16 (Table III) met the eligibility criteria used.

Patient distribution grouped by studies was as follows:

- Bone marrow transplantation: two studies (259 patients)<sup>3,4</sup>
- Non-intensive chemotherapy: one study (24 patients)<sup>5</sup>
- Short bowel syndrome: seven studies (61 patients)<sup>6-12</sup>
- Crohn's disease: one study (14 patients)<sup>13</sup>
- Critical illness: four studies (208 patients)<sup>14-17</sup>

TABLE II.

NUMBER OF STUDIES FOUND FOR EACH PATHOLOGIC CONDITION	Enteral	Enteral/Parenteral
	Glutamine	Glutamine
BMT	2	
Multiple trauma	3	
Critically Ill	1	
Postsurgical		1
Short-bowel	4	3
Crohn's Disease	1	
Postchemotherapy	1	

- Intestinal permeability: one study (17 patients)<sup>18</sup>

Level of evidence:

- Twelve studies: level III (75%)
- Four studies: level II (25%)

Jaddad Scale:

- Five studies: score of 5
- Two studies: score of 4
- Six studies: score of 3
- Three studies: score of 2

**Tolerance**

Glutamine was given by the enteral route in all studies, and parenteral nutrition also was used in four cases.<sup>6,10,11,18</sup> All studies confirmed the good clinical tolerance of enteral and parenteral glutamine, with no adverse effects occurring even in patients with intolerance due to short bowel syndrome or mucositis. No restrictions or contraindications were indicated for any of the diseases reviewed.

**Post-Chemotherapy in Tumor Patients**

Although mucositis is a very common side effect of chemotherapy, until now few treatments have shown effectiveness for its treatment or prophylaxis. Treatments include oral cryotherapy during administration of 5-fluoracyl (5-FU) and the use of granulocyte-macrophage colony-stimulating factor after the administration of cisplatin, 5-FU, and leucovorin.

In one study, glutamine also limited mucositis.<sup>5</sup> The data showed a statistically significant decrease in the number of days of mucositis and a decrease in the severity of the condition (assessed by the degree of dysphagia, which is related to a decrease in pain; grade B recommendation). The results of that study showed that the use of oral glutamine is a simple and effective way to treat or prevent mucositis after chemotherapy in high-risk subjects such as those who have had mucositis in previous cycles (especially if they contained anthracyclines). However, any recommendations based on one study must be considered speculative.

**Bone Marrow Transplantation**

These studies indicated a trend toward decreased mortality, which was not statistically significant, in bone marrow transplant patients who received a glutamine-supplemented diet. They also suggested a reduction in the need for total parenteral nutrition, indicating a greater availability of the digestive tract for nutrient administration due a protective effect of glutamine on the intestinal mucosa. No differences were found in length of hospital stay, sepsis, or rejection rates.<sup>3</sup> Glutamine supplementation was started at admittance

TABLE III.

## SUMMARY OF STUDIES USED

AUTHOR	DESIGN	POPULATION	INTERVENTION	RESULTS	CONCLUSIONS	LEVEL OF EVIDENCE	CT QUALITY
Jensen et al. <sup>14</sup>	Randomized, double blind	Multiple trauma (APACHE II > 10; 10 experimental, 9 control)	ENT 126–146 k J · kg <sup>-1</sup> · d <sup>-1</sup> Gln 180 g/d v. 60 g/d 10 d	T4/T8 > BCAAs < N balance =	Changes in aminogram and immunological function	III	5
Houdijk et al. <sup>15</sup>	Randomized, double blind	Multiple trauma (ISS > 20; 35 experimental, 37 control)	ENT 30.5 g/d Gln v. 3.5 g/d 7 d	Infection rate < TNF < Gln = at 7 d	Decreased infectious morbidity; improved immunological and metabolic function	II	5
Long et al. <sup>16</sup>	Randomized, double blind	Multiple trauma (ISS > 20; 30)	ENT 3 d 25.8 g/d Gln Exp 3.6 g/d Control AlitraQ	Nitrogen balance, essential serum amino acids, non-essential serum amino acids	Similar nitrogen balance in both groups; both formulas improved concentration of essential amino acids; only control diet improved non-essential amino acid concentration	III	3
Schloerb et al. <sup>3</sup>	Randomized, double blind	BMT (35 experimental, 31 control)	ENT/50% TPN 30 g/d p.o./39.9 g/d Gln vs. 30 g/d Glycine p.o./TPN standard	Sepsis 3 (gln)/3 mucositis 12(gln)/11 Gln (5), BMT rejection (1/10 Gln versus 3/8 Gly), survival, <i>P</i> = 0.57, hospital stay	Possible increase in survival with Gln; no differences in hospital stay; rejection; mucositis and diarrhea	II	5
Anderson et al. <sup>5</sup>	Randomized, crossover, double blind	Tumor chemotherapy (24)	ENT 14 d; 2 g/m <sup>2</sup> Gln twice daily; control with Gly	Duration of oral pain, pain severity	Decreased duration and severity of chemotherapy-induced mucositis	III	3
Anderson et al. <sup>4</sup>	Randomized, double blind	BMT (193)	ENT 28 d, 1 g/m <sup>2</sup> Gln 4 times daily; control with Gly	Duration of pain, use of TPN, disease progression, use of antibiotics, transplant rejection, hospital stay	Gln decreased duration of pain and severity of mucositis in autologous but not in allogenic BMT	II	5
Fish et al. <sup>18</sup>	Randomized, unblinded	Upper GI surgery; TPN (10), ENT (7)	ENT/TPN 5 d; 0.3 g · kg <sup>-1</sup> · d <sup>-1</sup> Gln	Nitrogen balance, aminogram, cholesterol, lymphocytes	Identical levels of circulating amino acids; similar nitrogen balances	III	3
Byrne et al. <sup>6</sup>	Crossover, unblinded	SBS (15), intestinal rehabilitation (42)	TPN+ENT+ GH; 3–4 wks with 0.6 g · kg <sup>-1</sup> · d <sup>-1</sup> Gln TPN or ENT+GH; control 7 d	Weight, Na, protein absorption, stool output	Gln improved protein absorption, reduced TPN requirements by 40%, and 40% of patients were maintained without TPN	III	2

Scolapio et al. <sup>7</sup>	Crossover, double blind	SBS (8)	6 wk, GH + Gln + high-carbohydrate, low-fat diet; Gln: 0.63 g · kg <sup>-1</sup> · d <sup>-1</sup>	Weight, BMR, nutrient and electrolyte balance, IGF-1, D-xylose, enterocyte, DNA proliferation, intestinal transit	Modest increases in electrolyte absorption and gastric emptying; does not improve intestinal morphology, macronutrient absorption or fecal losses	III	4
Beaugerie et al. <sup>8</sup>	Randomized, crossover	SBS (6)	Control: standard solution of 20 g glucose; 18 g maltodextrin + 14.6 g Gln	Intestinal sodium absorption, glucose absorption	Decreased Na absorption in diets with Gln; no differences in glucose absorption	III	2
Scolapio et al. <sup>8</sup>	Randomized, double blind	SBS (8)	ENT 6 wk, GH + Gln + high-carbohydrate, low-fat diet; Gln: 0.63 g · kg <sup>-1</sup> · d <sup>-1</sup>	Body composition by DEXA	Increase in lean body mass and total body weight with decreased body fat, increased extracellular fluid	III	3
Szkudlarek et al. <sup>10</sup>	Randomized, crossover, double blind	SBS (8)	28 d, ENT + TPN + GH; 30 g/d Gln + 17% protein N from TPN with Gln + GH 0.14 mg · kg <sup>-1</sup> · d <sup>-1</sup>	Intestinal absorption of nitrogen, carbohydrates, and fats; ion absorption; serum IGF-1; weight gain; same parameters 5 d after treatment	No increase in absorption of macronutrients, energy, or micronutrients; no evidence of increased intestinal absorption 5 d after treatment in SBS patients	III	4
Jeppsen et al. <sup>11</sup>	Randomized, double blind, crossover	SBS + HPN (4 experimental, 4 control)	GH + Gln (oral 30 g/d + parenteral; 17% N as Gln), 4 wk	Body weight, body composition, fatty acid absorption, lean body mass, extracellular fluids	No improvement in fatty acids or fat absorption, Increase in lean body mass related to water retention	III	3
Scolapio et al. <sup>12</sup>	Randomized, double blind	SBS crossover study (8)	ENT 0.45 Gln g · kg <sup>-1</sup> · d <sup>-1</sup> 8 wk, no washout period	D-Xilose test, fecal fat, morphologic analysis, GI transit	No differences in morphologic analysis, fat or carbohydrate absorption, or GI transit	III	2
Den Hond et al. <sup>13</sup>	Randomized, double blind	Crohn's disease with disturbed intestinal permeability (7 experimental, 7 control)	ENT 28 d, 21 g/d Gln	Plasma glutamine, serum ammonium, Crohn's disease activity index, protein C, nutrition status	Gln-supplemented diet does not restore intestinal permeability in Crohn's disease	III	3
Jones et al. <sup>17</sup>	Randomized in blocks, double blind	Critically ill patients (APACHE II > 11; 26 experimental, 24 control)	ENT 6-mo follow-up, 20 g/d Gln	Mortality, cost/TESS, length of ICU stay, cost/survival	No differences in mortality, significant reduction in costs in Gln group, 30% reduction in cost per survivor	II	5

\* Treatment (number of patients).

† Affected patients/all patients.

AATM, Agencia d'Avaluació de Tecnologia Médica classification; APACHE II, Second Acute Physiology and Chronic Health Evaluation; BMR, ??; BMT, bone marrow transplant; DEXA, dual x-ray absorptiometry; ENT, enteral nutrition; GH, growth hormone; GI, gastrointestinal; Gln, glutamine; Gly, glycine; HPN, home parenteral nutrition; ICU, intensive care unit; IGF-1, insulin-like growth factor-1; N, nitrogen; ISS, injury severity score; Na, sodium; SBS, short bowel syndrome; TPN, total parenteral nutrition

to the hospital for bone marrow transplantation and continued for 3 to 5 wk.

Overall, there were no differences in mucositis. However, administration of oral glutamine caused a statistically significant improvement in mucositis in patients receiving an autologous bone marrow transplant due to leukemias and solid tumors (grade B recommendation). This difference was noted in the duration and severity of the mucositis, with severity being assessed by opioid requirements to treat associated pain.<sup>5</sup>

In patients receiving an allogeneic bone marrow transplant, this difference did not reach statistical significance (grade C recommendation). This finding likely was due to the use of methotrexate for prophylaxis of graft-versus-host disease (84% versus 0% in autologous patients), because coadministration of glutamine and methotrexate can inhibit renal clearance of methotrexate, thereby exposing the patient to higher concentrations of methotrexate and, hence, to a greater risk of developing mucositis.<sup>4</sup>

### Short Bowel Syndrome

Seven studies were analyzed (three by Scolapio et al.,<sup>7,9,12</sup> one by Byrne et al.,<sup>6</sup> one by Jeppsen et al.,<sup>11</sup> one by Szkudlarek et al.,<sup>10</sup> and one by Beaugerie et al.<sup>8</sup>). Beaugerie et al. compared six patients with short bowel syndrome who were treated alternatively for 2 d with two oral isotonic rehydration solutions, with or without glutamine, with unfavorable results with respect to fluid and sodium absorption, and no other notable changes for the solution of glutamine and maltodextrin.<sup>8</sup> Byrne et al. compared a high-carbohydrate, low-fat diet supplemented with glutamine and growth hormone (GH) with the same diet supplemented with glutamine or GH,<sup>6</sup> and Scolapio et al.<sup>7,9</sup> and Jeppsen et al.<sup>11</sup> used similar experimental groups but included a standard treatment control group (these studies had a crossover design). Byrne et al. found increased absorption of calories, proteins, and carbohydrates and decreased stool output in the group receiving the diet supplemented with glutamine and GH.<sup>6</sup> This resulted in a shorter length of parenteral nutrition, a larger percentage of patients on enteral nutrition, and a marked reduction in costs, despite the differences in the higher cost of the treatment (diet + glutamine + GH). These investigators analyzed a patient subset that received glutamine in addition to a standard diet and found only increased sodium absorption.

Scolapio et al., whose experimental diets were supplemented with GH and glutamine, confirmed an increase in lean body mass and modest increases in electrolyte absorption and gastric emptying.<sup>7,9</sup> For the experimental diet supplemented with glutamine, they found a decrease in body fat and an increase in extracellular fluid with the development of edema.<sup>12</sup> As in the studies by Szkudlarek et al.<sup>10</sup> and Jeppsen et al.,<sup>11</sup> who added GH and glutamine, no improvement in intestinal morphology, nutrient absorption, or reduction in diarrhea was observed.

These studies presented controversial results with regard to the usefulness of glutamine and GH in short bowel syndrome. The level of evidence was similar across the four studies (level III), with a larger patient sample in the study by Byrne et al.<sup>6</sup> (favorable to the study therapy) but a higher quality of the studies by Scolapio et al.<sup>7,9</sup> (III versus II). The latter studies supported the use of a diet enriched with glutamine and GH based on an increase in lean body mass and a decrease in body fat. The weight gain could be explained by retention of extracellular fluid. The doses of glutamine used were 0.6 g/kg per day given orally for 3 wk.

At present, there are no conclusive data favoring exclusive use of glutamine in short bowel syndrome. Therefore, there is a need to perform other controlled studies in a larger number of patients to clarify the current situation. In any case, no harmful effects have been shown from the administration of glutamine.

In most of these studies, glutamine was given in combination with GH and a high-carbohydrate, low-fat diet, which made it

difficult to assess the effect of glutamine per se on specific parameters such as its ability to promote small bowel adaptation, improve intestinal absorption, and decrease the dependence on total parenteral nutrition in this syndrome (grade C recommendation).

### Crohn's Disease

We found only one well-designed study that did not report that glutamine, given in oral doses of 21 g/d for 28 d in addition to a standard diet, improves intestinal permeability as assessed by <sup>51</sup>Cr ethylene-diamine-tetraacetic acid. The study included a small number of patients, and this may have been the reason significant results were not detected. Of the seven patients administered glutamine, four showed improvement in intestinal permeability, two remained practically stable, and one worsened. In the placebo group, one patient showed improved permeability, and the other six patients remained stable or worsened.<sup>13</sup>

Therefore, it cannot be concluded that glutamine has a positive effect in Crohn's disease. Larger studies over longer periods are needed to evaluate other parameters such as its ability to promote intestinal adaptation, antioxidant and immune effects, and effect on bacterial translocation.

No analyses of costs or length of hospital stay were performed, which should be included as factors for future assessment (grade C recommendation).

### Critical Illness

Four studies were analyzed.

Jensen et al.<sup>14</sup> found changes in the aminogram and immunologic function that were not confirmed in the studies by Long et al.<sup>16</sup> Both studies found no differences in nitrogen balance between the experimental and control groups.

In a study conducted in a population of 78 critically ill patients who received an enteral diet or an enteral diet enriched with glutamine, Jones et al. found a significant reduction in the median duration of stays in the hospital and intensive care unit and a significant reduction in total costs per survivor.<sup>17</sup> The benefits associated with cost savings from shorter stays in the intensive care unit (less parenteral nutrition) were particularly notable in patients requiring more than 5 d of nutrition support.

Houdijk et al. evaluated the effect of glutamine-enriched enteral nutrition on infection in 72 critically ill patients with multiple trauma and demonstrated a statistically significant reduction in the number of infections (pneumonia, bacteriemia, and sepsis).<sup>15</sup> This study suggested that the effects of glutamine protect against especially enteric infections and found that plasma levels of glutamine and arginine increase starting from day 3 of administration with respect to the control group. A decrease in soluble tumor necrosis factor receptors also was found, starting from day 3 of enteral administration of glutamine, which suggested a decrease in the systemic inflammatory response. There were no significant differences in mechanical ventilation requirements or length of hospitalization.

The administration of glutamine-enriched enteral diets has beneficial effects on certain parameters relating to the course of the critically ill patients (shorter stays in the hospital and intensive care unit and lower costs). In addition, in the subset of critically ill trauma patients, there was a significant reduction in pneumonia, sepsis, and bacteriemia (grade B recommendation).

### Intestinal Permeability: Efficacy of Glutamine in Enteral Versus Parenteral Administration

The route of administration was not a controversial issue in any of the studies. However, in the study by Den Hond et al., the analysis of results of a prognostic test of intestinal permeability in Crohn's disease raised some questions about the effectiveness of either

route, in favor of the parenteral route.<sup>13</sup> No other clinical results were provided in that study.

A study in postoperative patients who underwent elective upper gastrointestinal tract surgery analyzed the effects of glutamine in terms of the plasma amino acid pattern in enteral versus parenteral administration. The results showed no differences in the plasma aminogram between these artificial routes for administration of nutrients.<sup>18</sup> Differences in the nutrition parameters evaluated also were not found. Enteral administration of glutamine was accompanied by a lower reduction in cholesterol level, whereas serum albumin was maintained within better ranges when nutrition was given by the parenteral route. Effects on intestinal structure or possible effects on the intestinal mucosal barrier were not analyzed.

## CONCLUSIONS

### *Benefits of Enteral Administration of Glutamine for Nutritional Therapy in Different Pathologic States*

- Glutamine-enriched diets are well tolerated.
- Glutamine improves immunologic function by decreasing the inflammatory response and infectious morbidity in patients with multiple traumas.
- Glutamine-enriched diets reduce costs and hospital stays in critically ill patients.
- Glutamine improves mucositis in tumor patients after chemotherapy and in patients receiving an autologous bone marrow transplant, resulting in an improved quality of life and a reduced perception of severity.
- Controversy exists on the usefulness of high-carbohydrate, low-fat diets supplemented with glutamine and GH in patients with short bowel syndrome, making it difficult to draw conclusions on their effectiveness.
- There are no marked differences in nutrition status or plasma aminogram between the enteral and parenteral administrations of glutamine.

### *Dose, Duration, and Time of Initiation*

- The dose and duration of treatment vary widely depending on the disease. These variations may be related to the use of this nutrient in pharmacologic doses.
- Bone marrow transplantation: 6 to 12 g/d for longer than 15 d
- Trauma/critically ill patients: 15 to 25 g/d for longer than 5 d
- Crohn's disease: 21 g/d for 28 d
- Short bowel syndrome: 42 g/d for 21 d
- Based on the conditions involved, early initiation of therapy with glutamine administration is indicated.

### *Recommendations for Clinical Practice and Research (Grade C Recommendations)*

- The average intake of glutamine should be 20 to 30 g/d or account for 20% to 30% of grams of protein; however, this can be increased in certain diseases (for a trophic effect?) provided that its effects are monitored (clinical trial, observational study, etc.).
- Because of the positive effects of the administration of glutamine observed starting 3 d after administration, administration of this amino acid should be prolonged for 5 d or longer.

- An analysis of costs and length of hospital stay should be performed to allow the effects of glutamine to be evaluated in different disease states.
- The effect of orally administered glutamine needs to be demonstrated over longer periods.
- There are no studies on the effect of glutamine in patients with short bowel syndrome not dependent on total parenteral nutrition. Its capacity to reduce the time required for intestinal recovery and adaptation to an oral diet in these patients should be evaluated.
- Research is needed not only on the plasma amino acid pattern, protein kinetics, and nitrogen balance but also on infectious morbidity and overall mortality. Sequential measurements of the amino acid profile during weeks 1 and 2 nutrition should be performed, and the effects on intestinal structure, intestinal permeability, and bacterial translocation should be determined. Studies should include larger numbers of patients.

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