Position Paper

Nutrition in Clinical Practice
Volume 26 Number 4
August 2011 479-494

10.1177/0884533611410975
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A.S.P.E.N. Position Paper: Parenteral Nutrition Glutamine Supplementation

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A.S.P.E.N. Position Statement

The position of The American Society of Parenteral and Enteral Nutrition (A.S.P.E.N.) is that specific patient populations can benefit from the use of parenteral nutrition (PN) glutamine supplementation when indicated. A beneficial effect of this therapy has been demonstrated in critically ill postoperative or ventilator dependent patients. Parenteral nutrition glutamine supplementation may be advantageous in certain other adult surgical patients or critically ill non-ventilated patients requiring PN. A positive impact of PN glutamine supplementation in adult hematopoietic stem cell transplant recipients, burn patients, and patients with severe acute pancreatitis remains unclear and warrants large, well designed, randomized control trials. Currently, access to parenteral glutamine in the United States is limited. It is the position of A.S.P.E.N. that a United States (U.S.) Food and Drug Administration (FDA)–approved commercial parenteral glutamine dipeptide solutions should be available for clinical use in the United States based on the professional judgment of prescribers.

Introduction/Background

Glutamine is the most abundant amino acid in the blood and the free amino acid pool in the body.[1,2] It is considered a nonessential amino acid.[1,3] In normal healthy individuals, glutamine can be produced in sufficient amounts *in vivo* and does not need to be supplied in the diet.[1,3] The majority of glutamine is synthesized in skeletal muscle with some being produced in the brain and possibly the lungs.[3] Cells that utilize glutamine are immune competent cells, enterocytes, and hepatocytes.[2,3] During certain pathological conditions, such as critical illness, the body is unable to produce sufficient amounts of glutamine causing profound depletion in plasma and tissue glutamine levels making it a conditionally essential amino acid.[1-4] Low plasma and tissue levels of glutamine have been associated with poor clinical outcomes.[5] Some studies have demonstrated beneficial effects of glutamine supplementation while significant reports of negative or adverse effects have not been published.[3] A systematic review of glutamine supplementation demonstrated that parenteral glutamine supplementation was more beneficial than enteral supplementation in terms of reduced mortality and hospital length of stay (LOS). High-dose supplementation (i.e., > 0.2 g/kg/day) lowered infectious complications in surgical patients compared to low-dose (i.e., < 0.2 g/kg/day).[6] Several other published clinical guidelines have recommended parenteral glutamine supplementation along with PN when indicated in specific patient populations, including the critically ill, surgical patients, burn patients, hematopoietic stem cell transplantation patients, and acute pancreatitis patients.[7-13]

All enteral nutrition (EN) formulations contain some glutamine with several commercially available formulas containing additional supplemental glutamine. Oral glutamine products are available for oral supplementation or use with EN formulations. Parenteral free L-glutamine has limited stability in aqueous solutions compared to the currently manufactured crystalline amino acid solutions therefore it is not included in the standard amino acid solutions used to compound PN. Appropriate compounding of free L-glutamine for administration alone or admixed in PN requires a strict aseptic environment and storage at 4 °C when cold membrane sterilization is performed. Because of the risk of precipitation, final concentrations of free L-glutamine solutions should not exceed 1.5%.[1,3,14] Parenteral glutamine dipeptide products (i.e., L-Alanyl-L-glutamine and Glycyl-L-glutamine) are available outside

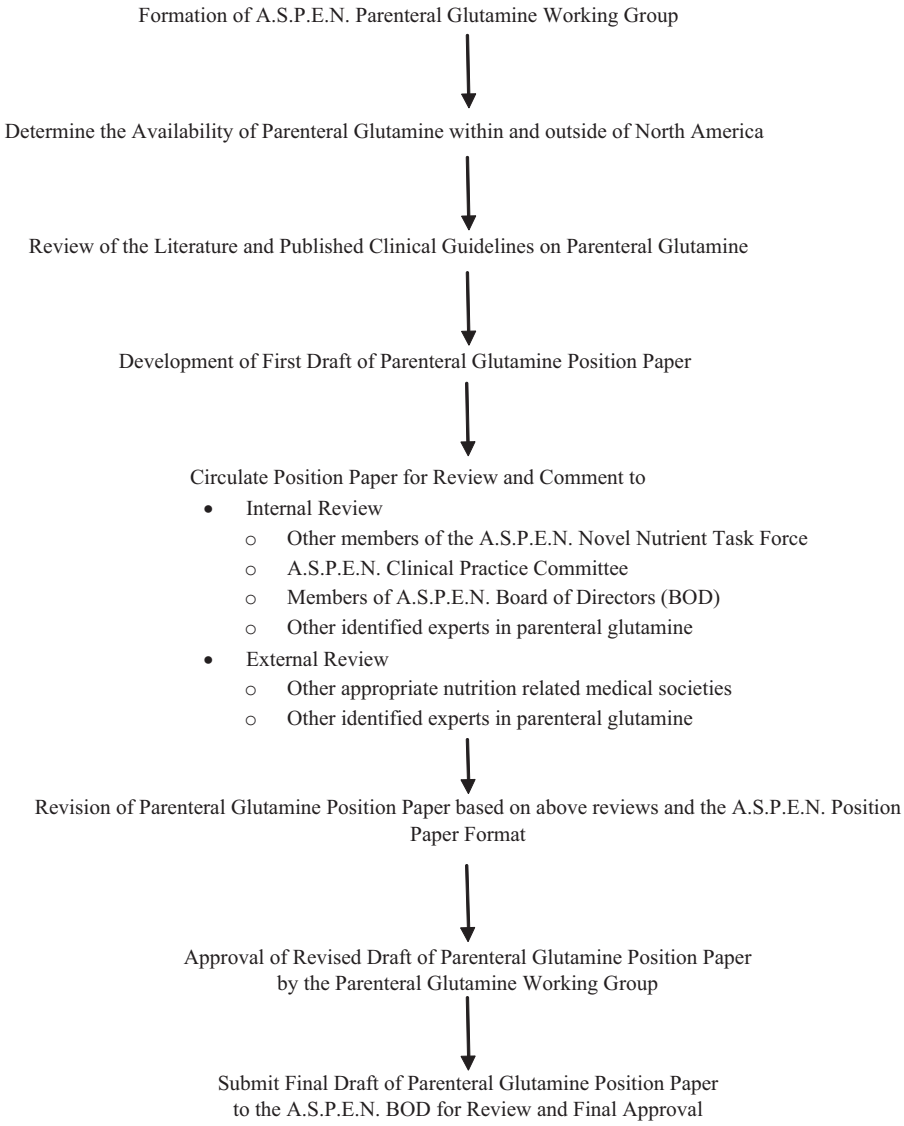

Figure 1. Procedure for the development of A.S.P.E.N. position paper on the clinical use of parenteral glutamine.

of the United States.[1,3] In contrast to free L-glutamine, dipeptide formulations with glutamine residues at the C-terminal position confer high water solubility, stability during heat sterilization, and the capability for prolonged shelf life (e.g., 2 years). When given intravenously (IV), the dipeptide is hydrolyzed by peptidase on the surface of the endothelium releasing free L-glutamine within 3 to 10 minutes of administration.[3]

In May 2009, the A.S.P.E.N. Novel Nutrient Task Force was formed and charged to assess the level of scientific evidence for the clinical use of several different parenteral nutrients and develop position papers for the Society in regards to the use of that nutrient in clinical practice and the need for any modifications in the availability of that nutrient in the U.S. Working Groups were formed for each of these nutrients, one of which was the Parenteral Glutamine Working Group, to review the literature on PN glutamine supplementation and develop a position paper that would then be reviewed and approved by the A.S.P.E.N. Board of Directors.

Issue/Problem Definition

Methods

The Parenteral Glutamine Working Group agreed upon a procedure for the development, review and approval for the A.S.P.E.N. Parenteral Glutamine Position Paper (Figure 1). A PubMed search using the key word "parenteral glutamine" resulted in 613 references, 165 were classified as "clinical trials," 114 were classified as "randomized controlled trials" (RCT), 12 were classified as

"meta-analyses" and 267 were classified as "reviews." Search results for this position paper only included parenteral glutamine alone in the PN study group(s). There were several published clinical guidelines that recommend the use of PN glutamine supplementation in specific clinical settings. The Working Group decided to base their recommendations for the use of PN glutamine supplementation on the published meta-analyses and published clinical guidelines as well as the review of selected review articles and original articles in the case of discrepancies between the meta-analyses and/or clinical guidelines.

In addition to the 12 meta-analyses identified from the PubMed search,[15-26] five other meta-analyses were subsequently discovered.[6,27-30] Seven of these meta-analyses were excluded for the following reasons: two[15,16] were Cochrane Reviews that were later updated so only the updated meta-analyses were included, two involved enteral glutamine supplementation instead of PN glutamine supplementation,[19,20] and three were excluded because the article was not available in English.[21-23] Table 1 summarizes the findings of the remaining 10 meta-analyses/Cochrane Reviews.

Discussion of Evidence

Use of PN glutamine supplementation in critically ill patients. Three meta-analyses have been published including this patient population (Table 1). The first was published in 2002[6] and was a combination of surgical patients (8 studies) and critically ill patients (6 studies). Three of the 6 studies on critically ill patients involved enteral glutamine supplementation where as all of the other studies involved in the meta-analysis involved PN glutamine supplementation. The meta-analysis showed trends toward improved mortality and incidence of infections in the glutamine supplemented patients but these differences were not statistically significant. Glutamine supplementation patients had a significantly shorter hospital LOS. In subgroup analysis, the critically ill study patients still had trends towards reduced mortality (Relative Risk (RR) 0.77; 95% CI 0.57 to 1.03) and reduced infections (RR 0.86; 95% CI 0.68 to 1.08) but no significant difference in hospital LOS (Mean Weighted Difference (MWD) 0.9 days; 95% CI −4.9 to 6.8). Another subgroup analysis examined the effects of route and dose of glutamine supplementation. PN glutamine supplementation had a significant reduction in mortality (RR 0.71; 95% CI 0.51 to 0.99) whereas there was no significant difference with enteral glutamine supplementation (RR 1.08; 95% CI 0.57 to 2.01). In regards to hospital LOS, PN glutamine supplementation resulted in a significant decrease (MWD −2.8 days; 95% CI −4.8 to −0.7) whereas enteral glutamine supplementation showed no significant difference (MWD −1.09 days; 95% CI −5.4 to 3.2). Higher doses of glutamine supplementation (>0.2 g/kg/day) were associated with a reduction in mortality (RR 0.71; 95% CI 0.51 to 0.99), infectious complications (RR 0.58; 95% CI 0.43 to 0.80), and hospital LOS (MWD −2.67 days; 95% CI −4.4 to −0.9). However, lower doses resulted in no significant differences in mortality (RR 1.02; 95% CI 0.52 to 2.01), infectious complications (RR 0.57; 95% CI 0.08 to 3.90), or hospital LOS (MWD −2.70 days; 95% CI −9.93 to 4.26). Several reviews of the literature suggested that the ideal dose of glutamine supplementation may be even closer to 0.5 g/kg/day.[31,32]

The second meta-analysis was published in 2006[26] and divided the studies into those involving critically ill patients alone, those involving surgical patients alone, and those with a combination of critically ill and surgical patients. The meta-analysis on the studies involving critically ill patients alone showed no significant differences in mortality or incidence of infections. The third meta-analysis was presented as a part of the Canadian critical care guidelines released in 2009.[25] This included 13 studies involving 798 critically ill, mechanically ventilated patients receiving PN glutamine supplementation and demonstrated a significant decrease in hospital mortality, infectious complications, and hospital LOS. There was no significant difference in intensive care unit (ICU) LOS. A subgroup of studies included patients who were primarily fed via the enteral route and parenteral glutamine supplementation had no significant effect on mortality in patients receiving mainly enteral nutrition.

Published clinical guidelines from 3 different organizations recommend the use of PN glutamine supplementation in critically ill adult patients but the grade of these recommendations vary (Table 2).[7-9]

Use of PN glutamine supplementation in surgical patients. Five meta-analyses have been published using PN glutamine supplementation in surgical patients (Table 1). The first[6] was a combination of surgical and critically ill patients that was previously discussed. In subgroup analysis of studies only involving surgical patients, glutamine supplementation had no significant effect on mortality (RR 0.99; 95% CI 0.27 to 3.58). However, it did result in a significant decrease in infectious complications (RR 0.36; 95% CI 0.14 to 0.92) and hospital LOS (MWD −3.54; 95% CI −5.3 to −1.76). There was no difference in mortality in the other 2 meta-analyses in surgical patients that reported this outcome but the number of patients included in these analyses were very low (50 to 87 patients) so these analyses are under powered to detect any difference in this variable. All 5 meta-analyses showed significant decreases in infectious complications with PN glutamine supplementation. All 4 meta-analyses reported shortened hospital LOS in PN glutamine supplemented patients with the difference being statistically significant in 3 of the 4 analyses. One meta-analysis[24] showed a significant decrease in hospital costs in the PN glutamine supplemented patients.

Table 1. Summary of Seven Published Meta-Analyses and Three Cochrane Reviews for PN Glutamine in the English Literature

Author (Year) Journal	Patient Population Study Groups	No. Studies (No. Patients)	Findings/Conclusions
Novak (2002) Crit Care Med[6]	Critically Ill and Surgical Patients PN+Glu or EN+Glu vs. STD nutrition support	14 studies (737 Pts)	3 studies involved enteral glutamine supplementation and 11 studies PN glutamine supplementation 6 studies involved critically ill patients and 8 studies surgical patients (all surgical patient studies used PN glutamine supplementation; Exclusions: studies of pediatric or neonatal patients or studies of adults undergoing bone marrow transplantation or chemotherapy.) Trend towards decreased mortality (RR 0.78, CI 0.58 to 1.04) Trend towards lower rate of infectious complications (RR, 0.81;CI 0.64 to 1.00)—7 studies (326 pts) Significant decrease in hospital LOS (−2.6 days; CI −4.5 to −0.7)—10 studies (541 pts)
Avenell (2006) Proceedings Nutrition Society[26]	Critically Ill PN+Glu vs. STD PN	8 Studies (537 pts)	No significant difference RR of Hosp mortality (0.75, 95% CI 0.52 to 1.07) No significant difference in RR of infection (0.71, 95% CI 0.49 to 1.05)—7 studies (367 pts)
	Surgical Patients PN+Glu vs. STD PN	6 Studies (248 pts)	Significantly reduced RR of infection (0.45, 95% CI 0.26 to 0.78) No significant difference RR of Hosp mortality (1.00, 95% CI 0.07 to 15.12)—1 study (50 pts)
	Critically Ill and Surgical Patients PN+Glu vs. STD PN	5 Studies (460 pts)	No significant difference RR of Hosp mortality (0.72, 95% CI 0.39 to 1.32)—1 study (168 pts) No significant difference in RR of infection (0.1.00, 95% CI 0.71 to 1.40)—1 study (168 pts) Significantly reduced RR of multiorgan or renal failure (0.67, 95% CI 0.46 to 0.98)—4 studies (292 pts)
Heyland (2009) Canadian Critical Care Guidelines[25]	Critically Ill Mechanically Ventilated Patients PN+Glu vs. STD PN	13 Studies (798 pts)	Significant decrease in RR Hosp mortality (0.71, 95% CI 0.55 to 0.92) Significant decrease in RR infectious complications (0.76, 95% CI 0.62 to 0.93)—9 Studies (504 pts) Significant decrease in mean difference of Hosp LOS (−3.14 days, 95% CI −6.03 to −0.24)—9 studies (439 pts) No significant difference in mean difference of ICU LOS (−0.30, 95% CI −1.45 to 0.85)—6 studies (321 pts)
Jiang (2004) Clinical Nutrition Suppl[24]	Elective Surgical Patients in Europe and Asia PN+Glu dipeptide vs. STD PN	10 Studies (355 pts)	Significant decrease in RR infectious complications (0.42, 95% CI 0.24 to 0.72) Significant decrease in mean difference of Hosp LOS (−3.25 days, 95% CI −4.87 to −1.62)—8 studies (273 pts) No significant difference in mean difference of cost of hospitalization (−1913.26, 95% CI −4996.60 to 1170.03)
Zheng (2006) World Journal Gastroenterology[27]	Adult abdominal surgery patients PN+Glu vs. STD PN	9 Studies (3737 pts)	Significantly higher mean difference in cumulative nitrogen balance (8.35, 95% CI 2.98 to 13.71)—5 studies (238 pts) Significantly reduced OR of infections (0.24, 95% CI 0.06 to 0.93)—4 studies (215 pts) Significantly lower mean difference in Hosp LOS (−3.55, 95% CI −5.26 to −1.84)

(*continued*)

Table 1. (continued)

Author (Year) Journal	Patient Population Study Groups	No. Studies (No. Patients)	Findings/Conclusions
Wang (2010) JPEN[28]	Surgical Patients PN+Glu dipeptide vs. STD PN	14 Studies (587 pts)	Significant decrease in postoperative infectious complications (RR 0.69; CI 0.5 to 0.95) Subgroup analysis, alanyl-glu PN yielded lower infection-related complication rates than glycyl-glu PN (RR 0.71; CI 0.51-0.99) LOS was significantly reduced by alanyl-glu dipeptide (WMD −3.84;CI −5.40 to −2.28) and glycyl-glu dipeptide supplemented PN (WMD −5.40; CI −8.46 to −2.33) No difference in mortality rate (RR 0.38; CI 0.09 to 1.53)—only 2 studies (87 pts.)
McClave (2006) JPEN[30]	Acute Pancreatitis pts PN+ Glu vs. STD PN	3 Studies (82 pts.)	Trend towards reduction in overall complication rate (RR 0.68;CI 0.42 to 1.09)
Murray (2009) Cochrane Review[17]	Bone Marrow Transplant Patients PN+Glu vs. STD PN	4 Studies (147 pts)	No significant mean difference in duration of nutritional intervention (0.36, 95% CI −1.63 to 2.35) Trend towards lower OR for positive blood cultures (0.46, 95% CI 0.20 to 1.04)No significant mean difference in Hosp LOS (0.22 days, 95% CI −1.29 to 1.72)—143 pts No significant mean difference in cumulative mucositis score (−0.02, 95% CI −0.48 to 0.45)—143 pts No significant difference in OR for line infections (0.0, 95% CI 0.0 to 0.0)—110 pts No significant mean difference in % change in BW (−0.34, 95% CI −1.40 to 0.72)—107 pts No significant difference in OR for developing > grade 2 graft vs. host disease (0.57, 95% CI 0.18 to 1.83)—109 pts No significant mean difference in days to achieve normal neutrophil level (0.57, 95% CI −1.63 to 2.76)—106 pts No significant difference in OR for completing study and surviving for 100 days (0.69, 95% CI 0.16 to 2.97)—109 pts
Grover (2007) Cochrane Review[29]	Infants up to 3 months old with "severe GI disease" Glu supplementation vs. no supplementation or placebo by the parenteral or enteral route.	1 Study (79 pts)	No significant difference RR of Hosp mortality (4.64, 95% CI 0.23 to 93.71) Underpowered study and insufficient data
Tubman (2008) Cochrane Review[18]	Pre-term infants PN+Glu vs. STD PN	3 Studies (1523 pts)	No significant difference RR of Hosp mortality (0.98, 95% CI 0.79 to 1.23) No significant difference in RR of invasive infection (1.07, 95% CI 0.94 to 1.21) No significant difference in RR for necrotizing enterocolitis (0.94, 95% CI 0.69 to 1.29) No significant mean difference in Hosp LOS (1.95, 95% CI −3.25 to 7.15)—2 studies (1210 pts) No significant mean difference in time to full EN (−1.11 days, 95% CI −3.40 to 1.18)—2 studies (1197 pts) No significant mean difference in rate of weight gain (1.3 g/kg/day, 95% CI −1.66 to 4.26)—1 study (28 pts)

BW, body weight; CI, confidence interval; EN, enteral nutrition; GI, gastrointestinal; Glu, glutamine; Hosp, hospital; ICU, intensive care unit; LOS, length of stay; OR, odds ratio; pts, patients; PN, parenteral nutrition; RR, relative risk; STD, standard ; WMD, weighted mean difference.

Table 2. Summary of Published Clinical Guidelines on Parenteral Nutrition Glutamine Supplementation

Organization	Clinical Guidelines	Guideline Statement	Grade
Critically Ill Patients			
A.S.P.E.N./ SCCM	Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.)[7]	G5. When PN is used in the critical care setting, consideration should be given to supplementation with parenteral glutamine.	Grade: C[a]
CCCN	Canadian Clinical Practice Guidelines for Nutrition Support in the Mechanically Ventilated, Critically Ill Adult, 9.4 Composition of PN: Glutamine[8]	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.**	strongly recommended[b]
		There are **insufficient data** to generate recommendations for intravenous glutamine in critically ill patients receiving enteral nutrition.	insufficient data[b]
ESPEN	ESPEN Guidelines on Parenteral Nutrition: Intensive care[9]	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[c]
Hematopoietic Stem Cell Transplantation Patients			
A.S.P.E.N.	A.S.P.E.N. Clinical Guidelines: Nutrition Support Therapy During Adult Anticancer Treatment and in Hematopoietic Cell Transplantation[10]	B4. Pharmacologic doses of parenteral glutamine *may benefit* patients undergoing hematopoietic cell transplantation.	Grade: C[a]
ESPEN	ESPEN Guidelines on Parenteral Nutrition: Non-surgical Oncology[11]	HSCT [Hematopoietic Stem Cell Transplantation] patients may benefit from glutamine-supplemented PN	Grade: B[c]
Inflammatory Bowel Disease			
ESPEN	ESPEN Guidelines on Parenteral Nutrition: Gastroenterology[33]	Although there are encouraging experimental data, the present clinical studies are insufficient to permit the recommendation of glutamine, n-3 fatty acids or other pharmaconutrients [in PN] in CD.	Grade: B[c]
		The value of specific substrates (n-3 fatty acids, glutamine) [added to PN] is not proven [in UC patients].	Grade: B[c]
Other Patient Populations			
ESPEN	ESPEN Guidelines on Parenteral Nutrition: Gastroenterology[33]	Currently, the use of growth hormone, glutamine or GLP-2 [in PN] cannot be recommended [for intestinal failure patients].	Grade: B[c]
ESPEN	ESPEN Guidelines on Parenteral Nutrition: Hepatology[34]	Currently, no recommendations can be made regarding [liver] donor or organ conditioning by use of i.v. glutamine or arginine with the object of minimizing ischaemia/reperfusion damage.	Grade: C[c]
ESPEN	ESPEN Guidelines on Parenteral Nutrition: Pancreas[12]	When PN is indicated [for acute pancreatitis patient], parenteral glutamine supplementation (>0.30 g/kg Ala-Gln dipeptide) should be considered.	Grade: B[c]
ESPEN	ESPEN Guidelines on Parenteral Nutrition: Surgery[13]	"Another modification of the PN regimen that may be of benefit [in surgical patients] consists of the addition of extra glutamine and arginine."	NR[d]

ala, alanine; A.S.P.E.N., American Society for Parenteral and Enteral Nutrition; CCCN, Canadian Critical Care Nutrition group; CD, Crohn's Disease; ESPEN, European Society for Clinical Nutrition and Metabolism; Gln, glutamine; GLP, glucagon-like peptide; NR, not reported; PN, parenteral nutrition; SCCM, Society for Critical Care Medicine; UC, Ulcerative Colitis.

[a]Grade of Recommendation ranges from A (highest level) to E (lowest level)

[b]Grade of Recommendation ranges from "strongly recommend" (highest) to "recommend" to "should consider" to "insufficient data" (lowest)

[c]Grade of Recommendation ranges from A (highest level) to C (lowest level)

[d]This was not an official guideline statement but was a statement in the introduction section of the clinical guidelines. There is no mention of glutamine in the guideline statements for this paper.

It should be noted that in some of the studies included in these meta-analyses, PN was often administered to patients after uncomplicated elective surgery when PN may not have been indicated. Also, there may be significant publication bias in that small trials with positive results were more likely to be published.

Even though the evidence supporting the use of PN glutamine supplements seems strongest in surgical patients, there are no published clinical guidelines that made a statement about its use in this patient population other than the European Society for Clinical Nutrition and Metabolism (ESPEN) PN guidelines that simply stated "Another modification of the PN regimen that may be of benefit [in surgical patients] consists of the addition of extra glutamine and arginine" (Table 2). This recommendation was not graded regarding the level of evidence.

Use of PN glutamine supplementation in bone marrow transplant (BMT) patients. A Cochrane Review[17] showed no clinical significant benefit with the use of PN glutamine supplementation in BMT Patients; however, both the A.S.P.E.N.[10] and ESPEN[11] guidelines on this topic state that PN glutamine supplementation "may benefit" these patients. In order to reconcile these findings and recommendations, all of the studies references in these three publications were reviewed (Table 3). The differences in these findings and recommendations may be explained by variation in the studies used for these analysis and differences in interpretation of some of these study findings.

There were actually two Cochrane reviews performed on this subject and Murray was the first author for both. The first review, entitled "Nutrition Support for Bone Marrow Transplant Patients," was published in 2008.[15] It involved 4 subgroup analyses as follows:

1. Oral glutamine vs. oral placebo
2. PN with and without parenteral glutamine supplementation
3. PN vs. IV hydration
4. PN vs. EN

There were only 3 studies[35-37] included in the PN with and without PN glutamine supplementation meta-analysis. This meta-analysis showed a decrease in hospital LOS by 6.62 days (95% CI, 3.47-9.77; $P < 0.0001$) and a decreased number of positive blood cultures with PN glutamine supplementation but no difference in the other clinical outcomes (Table 3). A revised Cochrane Review was published in 2009[17] that added 1 more study[38] to the meta-analysis (Table 3), which negated the benefits in hospital LOS and minimized the difference in the number of positive blood cultures. The addition of data from this study resulted in a non-significant increase of 0.22 days in hospital LOS in PN glutamine supplementation vs. glutamine-free PN. Conclusions drawn from these results should be made with caution as the new study differed in several ways from the earlier studies, including the use of alanyl-glutamine dipeptides vs. free L-glutamine, a lower dose of free glutamine (0.25 g/kg/day vs. 0.57 g/kg/day) and exclusion of allogeneic bone marrow transplants, which have significantly different treatment protocols. Addition of the new data set did not change findings from the first Cochrane review in that PN glutamine supplement had no effect on the severity grading of mucositis, days of PN required, occurrence of graft versus host disease (GVHD) ratings, incidence of >2 days of neutropenia, and survival rates at 100 days post transplant. Four RCT[39-42] were excluded from both Cochrane reviews because these were "duplicate reports" of the original Ziegler[37] study.

Despite the findings of the above Cochrane reviews, both the A.S.P.E.N.[10] and ESPEN[11] guidelines stated that BMT patients "may benefit" from "pharmacologic doses of parenteral glutamine" or "glutamine-supplemented PN," respectively (Table 2). Both organizations gave this recommendation a mid-level grade of evidence, C (on a scale from A to E) for A.S.P.E.N. and B (on a scale of A to C) for ESPEN. Table 3 compares the studies cited in the Cochrane review to the studies used to base the recommendations in the A.S.P.E.N. and ESPEN guidelines.

In addition to the studies included in the Cochrane Review, there were 4 other RCT[43-46] that were cited in the A.S.P.E.N. or ESPEN Guidelines and some of these studies showed some benefit to PN glutamine supplementation. For reasons not clearly explained, none of the latter 4 RCT was included in the Cochrane review. There were five other publications cited in the ESPEN clinical guidelines supporting the use of PN glutamine supplement and these included reviews,[47,48] a case report,[49] and 2 non-English publications[50,51] that could not be obtained for independent review.

When reviewing the rationale section for the A.S.P.E.N. Clinical Guidelines, PN glutamine supplementation in BMT patients was reported to improve nitrogen balance (NB), decrease hospital LOS, and decrease morbidity. The evidence for improved NB was based on Ziegler's study (Table 3).[37] The decrease in the hospital LOS was based on the Ziegler[37] and Young[39] studies. However, these 2 studies involved the same group of patients. There have been 7 independent RCT in BMT patients reporting hospital LOS, two reported a decrease in LOS,[36,37] one a trend towards increased LOS,[38] and four found no differences.[35,43,45,46] The A.S.P.E.N. Clinical Guidelines also reported a "decreased morbidity," citing 4 studies.[17,37-39] One of these, the Pytlik[38] study, did find a decreased incidence of diarrhea but also showed an increased severity of mucositis, use of narcotics, relapses, and mortality (Table 3). The second and third studies, Ziegler[37] and Young,[39] reported on the same group of patients and found a

Table 3. Comparison of the Studies Cited and Used for Recommendations in the Most Recent Murray Cochrane Review[17] as Well as the A.S.P.E.N.[10] and ESPEN[11] Clinical Guidelines Regarding Glutamine-Supplemented Parenteral Nutrition (PN) in Bone Marrow Transplant (BMT) Patients

Author (Ref) Year	Type of Study/ No. Pts	Findings (Glutamine Group vs. Control Group)	Murray Cochrane Review[17]	A.S.P.E.N. Guidelines[10]	ESPEN Guidelines[11]
Pytlik[38]2002	RCT 40 pts	Decreased diarrhea ($P<0.05$) Increased severity of oral mucositis ($P<0.05$) Trend towards increase LOS ($P=0.06$) Increased use of narcotics ($P<0.05$) More relapses ($P<0.05$) Trend towards more deaths ($P=0.06$)	X	X	X
Brown[35] 1998	RCT 34 pts	No difference in LOS[a] No difference in graft vs. host disease[a] No difference in mortality	X		X
Schloerb[36] 1993	RCT 29 pts	No difference in mucositis score No difference in infections No difference in mortality Decreased LOS ($P<0.05$)	X	X	
Ziegler[37] 1992	RCT 45 pts	Improved nitrogen balance (-1.5 ± 0.5 vs. -4.2 ± 1.2 g/d, $P<0.01$) Decreased infections ($P<0.05$) Decreased LOS ($P<0.05$) No difference in mortality	X	X	
Young[39,b] 1993	RCT 23pts	Decreased no. positive blood cultures ($P<0.05$) Decreased LOS ($P<0.05$) Trend towards less change in "vigor" score ($P=0.07$) and "anger" score ($P=0.05$)		X	
da Gamma Torres[43] 2008	RCT 53 pts	Trend towards faster neutrophil recovery ($P=0.18$) Trend towards decreased infections ($P=0.25$) No difference in LOS Decreased mortality ($P<0.05$)			X
Sykorova[44] 2005	RCT 44 pts	Trend towards decrease overall survival ($P=0.09$) Decreased disease-free survival ($P<0.05$)		X	
Scheid[45] 2004	RCT 54 pts	Faster neutrophil recovery ($P<0.05$) No difference in incidence of neutropenic fevers No difference in LOS		X	
Piccirillo[46] 2003	RCT 27 pts	Faster lymphocyte recovery ($P<0.05$) Trend towards faster neutrophil recovery ($P=0.08$) Decreased mucositis peak scores ($P<0.05$) with trend towards decrease duration of mucositis ($P=0.10$) No difference in LOS		X	
Murray[15,c] 2008	Cochrane Review	Decreased no. positive blood cultures ($P<0.05$) Decreased LOS ($P<0.001$) No difference in cumulative mucositis score No difference in incidence of line infections No difference in graft vs. host disease No difference in time for neutrophil recovery No difference in 100 day-mortality			X

(*continued*)

Table 3. (continued)

Author (Ref) Year	Type of Study/ No. Pts	Findings (Glutamine Group vs. Control Group)	Murray Cochrane Review[17]	A.S.P.E.N. Guidelines[10]	ESPEN Guidelines[11]
Murray[17,c] 2009	Cochrane Review	Trend towards decreased no. positive blood cultures No difference LOS No difference in cumulative mucositis score No difference in incidence of line infections No difference in graft vs. host disease No difference in time for neutrophil recovery No difference in 100 day-mortality	Same article	X	
Ziegler[47] 2001	Review	Enteral and parenteral glutamine in cancer patients receiving bone marrow transplant "Although not all studies demonstrate benefit, there are sufficient positive data to suggest that this nutrient [glutamine] should be considered in the metabolic support of many individuals undergoing the catabolic process of marrow transplant" RCT are needed to "further define the utility" of glutamine treatment in these pts			X
Wilmore[48] 1999	Review	Enteral or parenteral glutamine in cancer patients receiving bone marrow transplant "appears safe and efficacious" Further RCTs are needed			X
Goringe[49] 1998	Case Report (2 patients)	Two cases of hepatic veno-occlusive disease following BMT "successfully treated" with parenteral glutamine and oral vitamin E Further "formal trials" indicated			X
Mercadal[50] 2007	Unknown[d]	Unknown[d]			X
Gomez[51] 2006	Unknown[d]	Unknown[d]			X

BMT, bone marrow transplant; LOS, hospital length of stay; No., number; PN, parenteral nutrition; pts, patients; RCT, randomized controlled trial; Ref, reference number in published article; X, study cited in the publication.

NOTE: This table is designed to reconcile the differences between the Murray[17] Cochrane review's findings of no statistically significant benefit of glutamine supplemented PN to BMT patients and the recommendations in the A.S.P.E.N.[10] and ESPEN[11] clinical guidelines that this therapy "may benefit" these patients and to present the findings of the original studies cited in each of these three resources.

[a]Data not reported in published article but recorded in Murray's Cochrane Review of this study

[b]Subset of pts included in the Ziegler[37] study

[c]Cochrane Review initially published in 2008 but did not include the Pytlik[38] study, which significantly changed the conclusions of the review, so updated Cochrane Review published in 2009

[d]Articles not in English; not reviewed

decrease in infections and number of positive blood cultures with a trend towards less adverse change in "vigor" and "anger" scores. The last citation was the 2009 Cochrane review.[17] The A.S.P.E.N. guidelines stated that the Cochrane review showed "a benefit of fewer bloodstream infections" but this was a trend that did not reach statistical significance.

The ESPEN Guidelines state that "some evidence exists" that PN glutamine supplementation can improve LOS and infection risk, referencing the 2008 Murray Cochrane Review[15] and 2 review articles, Ziegler[47] and Wilmore.[48] However, when reviewing all of the RCT in Table 3 as well as the updated 2009 Murray Cochrane review,[17] there is conflicting data in this regard as previously discussed. The ESPEN Guidelines also refer to a decrease in short-term mortality with PN glutamine supplementation as reported in the da Gamma Torres[43] study but the Pytlik[38] study reported significantly more relapses (3 control vs. 10 glutamine patients, $P<0.05$) and a trend toward more deaths (1 control vs. 6 glutamine patients, $P=0.06$) in the PN glutamine supplemented group. Six trials evaluated mortality as an outcome parameter, with one showing a decrease,[43] two a trend towards increased mortality,[38,44] and three finding no differences.[35-37]

Use of PN glutamine supplementation in infants. Only 2 meta-analyses have evaluated the impact of PN glutamine supplementation on outcome variables in neonates and young infants (i.e., up to the age of 3 months) (Table 1). The first meta-analysis included only 2 studies and one of these focused on enteral glutamine supplementation leaving only 1 study with 79 neonatal or pediatric patients on PN because of either necrotizing enterocolitis, congenital bowel obstruction, anterior abdominal wall defects, or Hirschsprung disease.[29] There was no statistically significant difference in hospital mortality but the study was markedly under powered for this variable. No other clinical outcome variables were reported in the meta-analysis paper. The second meta-analysis included 1523 preterm infants from 3 different clinical trials.[18] There were no significant differences in mortality, invasive infections, hospital LOS, time to full enteral feedings, or the incidence of necrotizing enterocolitis. There are no published clinical guidelines regarding any recommendations on the use of PN glutamine supplementation in neonatal or pediatric patients.

Use of PN glutamine supplementation in acute pancreatitis patients. One meta-analysis has been published on PN glutamine supplementation in acute pancreatitis patients that included only 3 small studies for a total of 82 patients (Table 1).[30] It showed a trend towards decrease in overall complications as a result of PN supplemented glutamine. One of the studies[52] had no mortality in either study group. Another study[53] had only 1 mortality out of the 14 patients in the control group and no deaths in the 14 patients in the study group. The third study[54] had a lower mortality in the PN glutamine supplementations group (0% (0/20) vs. 14% (3/21), P=0.24) but this was not statistically significant. All 3 studies[52-54] showed a decrease in the hospital length of stay of a mean of 3 to 4 days but this difference did not reach statistical significance in any of these studies due to small number of patients and the hospital LOS data could not be combined and analyzed. One study[54] showed a significant reduction in pancreatic infection (0% (0/20) vs. 24% (5/21), P<0.05) and total complications (20% (4/20) vs. 52% (11/21), P<0.05) in the PN glutamine supplemented group.

ESPEN's published clinical guidelines recommend "When PN is indicated [for acute pancreatitis patients], parenteral glutamine supplementation (>0.30 g/kg Ala-Gln dipeptide) should be considered." This recommendation was given an intermediate grade of B (on a scale of A to C).[12] This recommendation was based on several studies including the previously discussed meta-analysis[30] and the 3 studies included in the meta-analysis.[52-54] Also, four other studies were cited to support this recommendation.

Zhao[55] showed in a RCT that PN glutamine supplementation significantly decreased the APACHE II scores at days 4, 7, and 11 of treatment compared to patients treated with standard PN. There were also significantly higher pre-albumin levels and lower tissue necrosis factor (TNF), IL-6, and C-reactive protein levels in the PN glutamine supplementation group. Sahin[56] found that PN glutamine supplementation was associated with a significantly lower overall complication rate (10% (2/20) vs. 40% (8/20), P<0.05), a trend towards lower mortality (10% vs. 30%, P=0.25), and a trend towards shorter hospital LOS (14.2 vs. 16.4 days, P=0.11). Another study[57] showed a significant reduction in infections (41% (9/22) vs. 73% (16/22), P<0.05) but no significant difference in mortality (9% (2/22) vs. 23% (5/22), P=0.41). There were also no significant differences in hospital or ICU LOS.

In a Chinese study,[58] 80 patients with severe acute pancreatitis were given 20 g alanyl-glutamine dipeptide intravenously for 10 days but the patients were randomized to start either on the day of admission (early treatment group) or 5 days after admission (late treatment group) admission. The early treatment group had a significant reduction in mortality (5.3% vs. 21.1%, P< 0.05), infection rate (7.9% vs. 26.3%, P< 0.05), operation rate (13.2% vs. 34.2%, P< 0.05), and hospital stay (28.8 ± 9.4 d vs. 45.2 ± 27.1 d, P< 0.01). Also the early treatment patients had a shorter duration of acute respiratory distress syndrome (2.7 ± 3.3 d vs. 12.7 ± 21.0 d, P< 0.01), renal failure (1.3 ± 0.5 vs. 5.3 ± 7.3 days, P< 0.01), acute hepatitis (3.2 ± 2.3 vs. 7.0 ± 7.1 days, P< 0.01), shock (1.7 ± 0.4 vs. 4.8 ± 3.1 days, P< 0.05), encephalopathy (2.3 ± 1.9 vs. 9.5 ± 11.0 days, P< 0.01) and ileus (2.2 ± 1.4 vs. 3.5 ± 2.2 days, P< 0.01) as well as a significantly lower 15-day mean APACHE II score (5.0 ± 2.4 vs. 8.6 ± 3.6, P< 0.01).

Use of PN glutamine supplementation in other patient populations. Glutamine supplementation may be beneficial in burn patients. In 2006, Windle[32] collectively reviewed the nine published RCT of glutamine supplementation in burn patients and concluded that this therapy could result in improved morbidity, mortality, and hospital LOS. However, due to the small sample sizes, the authors felt that further research is needed before definite practice recommendations could be made. Also, only 1of these studies, Wischmeyer,[59] used parenteral glutamine and this study administered free L-glutamine at a dose of 0.57 g/kg/day in conjunction with either PN or enteral nutrition. Parenteral glutamine supplementation resulted in a significant decrease in gram-negative bacteremia and C-reactive protein with a trend in decreased incidence of positive blood cultures and mortality. There are no published clinical guidelines on the use of PN glutamine supplementation in burn patients specifically although burn patients were included in some of the studies included in the previously discussed meta-analysis on critically ill and surgical patients.

PN glutamine supplementation has been studied in a variety of different gastrointestinal diseases. However, in ESPEN's published clinical guidelines, use of PN glutamine supplementation could not be recommended in patients with inflammatory bowel disease, intestinal failure, or liver transplant due to insufficient evidence for benefit (Table 2).

Assessment of the Evidence

There is strong evidence that PN glutamine supplementation has beneficial effects in certain patient populations and with further research, may have benefits in other patient populations as well. Parenteral glutamine has not been shown to be harmful and there are no absolute contraindications.[1,3] No complications related to PN glutamine supplementation was reported in any of the meta-analysis reviewed for this position paper.[6,17,18,24-30]

However, glutamine supplementation in end stage hepatic failure patients has been reported to cause elevated serum ammonia levels and other liver function tests (LFT); therefore, it could cause or aggravate hepatic encephalopathy so it should be used with caution in these patients.[1,3] In 1994, Hornsby-Lewis[60] published a report in which free L-glutamine at a dose of 0.285 g/kg was added to the PN in 7 stable home patients. The glutamine supplementation was stopped at week 2 and at week 3, respectively, in 2 patients due to elevations in LFT while a third patient had elevations in LFT at the end of the 4 weeks of supplementation. Only one of the 3 patients had any significant elevations of serum bilirubin and it was a minimal elevation (0.8 to 1.4 mg/dL). All three had mild elevations of serum alkaline phosphatase. Two patients had minimal elevation of serum glutamic oxaloacetic transaminase (AST) while the third patient had significant elevation (10 times normal). One patient had a minimal elevation of serum glutamic pyruvate transaminase (ALT) while the other 2 patients had moderate elevations (2 to 4 times normal). One patient had a minimal elevation of serum lactic acid dehydrogenase (LDH) while the other 2 patients had mild elevations (about 1.5 times normal). One patient had no change in serum ammonia levels while the other 2 patients had minimal elevations. All LFT and serum ammonium levels returned to normal within 2 weeks of cessation of the PN glutamine supplementation and no other manifestations of liver dysfunction or other side effects were reported.

Theoretically, glutamine supplementation can cause or aggravate azotemia in acute or chronic renal failure patients. However, this has not been shown to be clinically significant and is not a contraindication to PN glutamine supplementation.[3] In head injury patients, there was concern that PN glutamine could cause an increase in glutamate in the interstitium of the brain, which could cause neurotoxicity. However, in a prospective, cross-over study of severe head injury patients,[61] PN glutamine dipeptide supplementation did not increase plasma or intracerebral glutamate levels. There is no contraindication to PN glutamine supplementation in head injury patients.[1,3]

Counter Issues/Problems Definition

There are several barriers to promoting the routine clinical use of PN glutamine supplementation. Two parenteral glutamine dipeptide products are commercially available outside the U.S. (Table 4). Glamin® contains glycyl-glutamine dipeptide along with another dipeptide and free amino acids. It is designed for use as a complete amino acid solution supplemented with glutamine dipeptide to be used in compounding a PN formulation. Glamin® contains 134 g/liter of amino acids/dipeptides and, once the dipeptides are broken down in the body, the solution will provide 20 g of free L-glutamine per 1000 mL of base solution. Dipeptiven® contains only L-alanyl-L-glutamine dipeptide (200 g/liter) and can be administered IV separate from the PN or added to the PN during the compounding process. Once the dipeptide is broken down in the body, Dipeptiven® provides 134.6 g free L-glutamine per liter of base solution.

Until recently, neither of the parenteral glutamine dipeptide solutions was available in North America. However, as of 1/4/2010, Dipeptiven® became available in Canada through the Special Access Program (SAP) from Health Canada. A specific authorization process must be followed on each patient and only the quantity of product approved for that patient will be delivered. Neither of the parenteral glutamine dipeptide products is available in the U.S. However, glutamine appears on the FDA List of Bulk Drug Substances That May Be Used in Pharmacy Compounding.[68] There are several licensed pharmacies that can compound free L-glutamine either as a separate IV solution or as a part of an amino acid solution. These pharmacies compound parenteral free L-glutamine within their state statutes and compliant with USP General Chapter <797> Pharmaceutical Compounding-Sterile Preparations[69] as a High-Risk Level Compounded Sterile Preparation. For example, one of these pharmacies compounds either a 1000 mL bag of 2.5% glutamine (25 g/liter) alone or a combination of L-glutamine with a standard crystalline amino acid solution for a 10% amino acid solutions (2.5% Glutamine and 8.5% standard amino acids, which provides 25 g of glutamine and 85 g standard amino acids for a total of 110 g/L of amino acids).

Because of concern regarding the limit stability of the free L-glutamine in aqueous solution, these compounded

Table 4. Commercially Available Parenteral Glutamine Products Outside of North America[62-67]

Product Name	Glamin®	Dipeptiven®
Manufacturer/ Distributor[a]	Australia, Fresenius Medical Germany, Baxter New Zealand, Baxter Czechoslovakia, Baxter Czechoslovakia, Fresenius Kabi Italy, Fresenius Kabi Malaysia, Fresenius Kabi Netherlands, Fresenius Kabi New Zealand, Fresenius Kabi Portugal, Fresenius Kabi Spain, Fresenius Kabi Switzerland, Fresenius Kabi UK, Fresenius Kabi	Austria, Fresenius Kabi Chile, Fresenius Kabi Czechoslovakia- Fresenius Kabi Denmark, Fresenius Kabi Finland, Fresenius Kabi France, Fresenius Kabi Greece, Fresenius Kabi Hong Kong, Fresenius Kabi Hungary, Fresenius Kabi Indonesia, Fresenius Kabi Italy- Fresenius Kabi Malaysia, Fresenius Kabi Mexico, Fresenius Kabi Netherlands, Fresenius Kabi Norway, Fresenius Kabi Poland, Fresenius Kabi S. Africa, Fresenius Kabi Spain, Fresenius Kabi Sweden, Fresenius Kabi Switzerland, Fresenius Kabi Thailand, Fresenius Kabi Turkey, Fresenius Kabi UK, Fresenius Kabi
Composition and Final Concentration of Glutamine Product	Content (per 1,000 mL): -Alanine: 16.00 g -Arginine: 11.30 g -Aspartic acid: 3.40 g -Glutamic acid :5.60 g -Glycyl-Glutamine H2O: 30.27 g (corresponds to Glycine 10.27 g corresponds to Glutamine 20.0 g) -Glycyl-Tyrosine 2H2O: 3.45 g (corresponds to Glycine 0.94 g corresponds to Tyrosine 2.28 g) -Histidine: 6.80 g -Isoleucine: 5.60 g -Leucine: 7.90 g -Lysine-Acetate: 12.70 g (corresponds to Lysine 9.0 g) -Methionine 5.60 g -Phenylalanine: 5.85 g -Proline : 6.80 g -Serine: 4.50 g -Threonine: 5.60 g -Tryptophan: 1.90 g -Valine: 7.30 g Amino acids/dipeptides: 134 g/L Total nitrogen: 22.4 g/L Energy content: 2300 kJ (540 kcal)/L Citric acid: to pH 5.8 Water for injection: to 1000 mL Theoretical osmolarity: 1040 mosm/L Titration acidity to pH 7.4: approx. 60 mmol/L of NaOH pH: approx. 5.8 Density: 1.0414 g/cm^3	Content (per 1,000 mL): -N(2)-L-alanyl-L-glutamine: 200 g L-alanine: 82 g L-glutamine: 134.6 g Water for Injections: to 1,000 mL Theoretical osmolarity: 921 mosm/L pH: 5.4-6.0 Titration acidity: 90-105 mmol/L of NaOH
Shelf Life	24 months	36 months
How Supplied	250 mL, 500 mL, and 1000 mL glass bottles	50 mL, 100 mL, or 250 mL glass bottle
Comments:	Safety and efficacy has not been established in children under the age of 18 years	Safety and efficacy has not been established in children under the age of 18 years

[a]Formulations produced by Baxter and Fresenius Kabi are the same

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solutions must be kept refrigerated and used within a short period of time. One pharmacy recommends using the compounded glutamine solution within 30 days and the compounded solution cannot hang at room temperature for more than 24 hours. However, these recommendations may vary between the pharmacies that compound these free L-glutamine solutions. These solutions are prepared from L-glutamine crystalline powder which is pyrogen-free (although not sterile). Compounding must be performed in an ISO Class 5 environment and dispensed per a patient-specific prescription. These compounded glutamine solutions are cold sterilized and must undergo quality control measures to monitor for potential bacterial contamination. A 0.22 micron filter and a certificate of analysis should be used. Due to these limitations parenteral free L-glutamine has not been readily available so clinical utilization in the U.S. has been limited.

Further research on parenteral glutamine supplementation is still needed to further delineate which, if any, critically ill, non-ventilated adult medical patients would benefit from PN glutamine supplementation. While PN glutamine supplementation has been shown to be beneficial in surgical patients, the subpopulation of which surgical patients benefit most from supplementation is unknown. It appears that for PN glutamine supplementation to be effective, it needs to be given early and in pharmaceutical doses (> 0.2 g/kg/day and probably closer to 0.5 g/kg/day).[6,31,32] The effects of the timing, dose, and duration of glutamine supplementation in surgical and non-surgical patients require further investigation. The current A.S.P.E.N./SCCM critical care guidelines[7] recommend delaying initiation of PN for at least 7 days unless the patient is already malnourished. It is likely that a delay in initiation of PN and therefore glutamine supplementation would reduce the potential positive effects. Additionally, the potential benefits of parenteral glutamine supplementation in patients on a combination of enteral and parenteral nutrition or enteral nutrition alone have not been adequately evaluated. The mechanisms of action of PN glutamine supplementation must be further elucidated to provide a better understanding as to which patients may benefit from supplementation. There is no significant research regarding parenteral glutamine supplementation in various pediatric patient populations. Finally, a cost-benefit analysis for parenteral glutamine supplementation needs to be performed.

Companies may be reluctant to incur the expense of conducting the additional research and administrative costs necessary to obtain FDA approval to bring their parenteral glutamine dipeptide solutions to the U.S. market. It is especially difficult for a company to justify this expense when the same product has already gone through extensive testing and has been approved and in clinical use for over 10 years in other countries without any problems.

Summary/Recommendations

Based on a critical evaluation of the scientific literature, our summary and recommendations are:

- Parenteral glutamine administration is associated with a decrease in infectious complications, decrease in hospital length of stay, and possibly a decrease in mortality in critically ill postoperative or ventilator dependent patients requiring parenteral nutrition (PN).
- 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.
- There is a trend toward fewer positive blood cultures with the use of parenteral glutamine in adult hematopoietic stem cell transplant recipients receiving PN. The full potential benefit of PN glutamine supplementation remains unclear since there is a reduced length of hospital stay only when data from allogeneic and autologous transplants is combined vs. no effect from glutamine-supplemented PN when given post-transplant to those solely undergoing autologous transplantation.
- Parenteral glutamine may be beneficial in adult burn patients or acute pancreatitis patients who require PN.
- Due to limited available data in pediatric/neonatal patients, no recommendations regarding the use of PN glutamine supplementation can be made in these patients.
- PN glutamine supplementation should probably be given early and in doses > 0.2 g/kg/day to be effective.
- To date, there is no evidence that parenteral glutamine is harmful. There are no absolute contraindications to the use of parenteral glutamine but LFT should be monitored in all patients and it should be used with caution in end stage hepatic failure patients and patients with hepatic insufficiency.
- Further research is needed on glutamine supplemented PN in the following areas: specific adult patient populations; pediatric patients; use of glutamine supplementation in combination with parenteral and enteral nutrition or enteral/oral nutrition alone; dipeptide vs. free L-glutamine; timing and dosing; cost-benefit analysis; and further elucidation of parenteral glutamine's mechanisms of action.

- Parenteral free L-glutamine is available on an individual prescription, pharmacy-compounded basis in the U.S. However, the practicality of compounding free L-glutamine for use in or with PN should be weighed with the benefits that may be gained with its use.
- A.S.P.E.N. recommends that a FDA-approved parenteral glutamine dipeptide solution should be made available for use based on the professional judgment of prescribers.

A.S.P.E.N. Parenteral Glutamine Working Group and Board of Directors Related Disclosures

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