Published in final edited form as:

Curr Opin Clin Nutr Metab Care. 2011 January ; 14(1): 75–82. doi:10.1097/MCO.0b013e328341235a.

Amino acid composition in parenteral nutrition: what is the evidence?

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Abstract

Purpose of review—Complete parenteral nutrition solutions contain mixed amino acid products providing all nine essential amino acids and a varying composition of nonessential amino acids. Relatively little rigorous comparative efficacy research on altered parenteral nutrition amino acid composition has been published in recent years.

Recent findings—Limited data from randomized, double-blind, adequately powered clinical trials to define optimal doses of total or individual amino acids in parenteral nutrition are available. An exception is the growing number of studies on the efficacy of glutamine supplementation of parenteral nutrition or given as a single parenteral agent. Parenteral glutamine appears to confer benefit in selected patients; however, additional data to define optimal glutamine dosing and the patient subgroups who may most benefit from this amino acid are needed. Although some promising studies have been published, little data are available in the current era of nutrition support on the clinical efficacy of altered doses of arginine, branched chain amino acids, cysteine, or taurine supplementation of parenteral nutrition.

Summary—Despite routine use of parenteral nutrition, surprisingly little clinical efficacy data are available to guide total or specific amino acid dosing in adult and pediatric patients requiring this therapy. This warrants increased attention by the research community and funding agencies to better define optimal amino acid administration strategies in patient subgroups requiring parenteral nutrition.

Keywords

amino acids; arginine; cysteine; glutamine; taurine

Introduction

Studies over many decades show that the blood amino acid profile is disturbed, lean body mass is lost, and body protein requirements are generally increased in a variety of illnesses and catabolic conditions warranting amino acid supplementation in all patients who require parenteral nutrition [1[•],2[•],3–6]. Mixed amino acid formulations that provide both essential and nonessential amino acids are thus a standard component of complete parenteral nutrition

prescriptions to support cell, organ and skeletal, cardiac and respiratory muscle functions, and wound healing [3,4,6].

All commercially available amino acid formulations for parenteral nutrition provide the nine essential amino acids (histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine) in amounts varying between 38 and 57% of total amino acids (Table 1). Commonly used amino acid mixtures also provide nonessential amino acids comprising 43–62% of total amino acids. Alanine, arginine, glycine, proline, serine, and tyrosine are present in all commonly used products and other nonessential amino acids differ by manufacturer (e.g. glutamate and aspartate are present in some, but not all commercial formulations). Commercial amino acid formulations also contain varying amounts of classically nonessential amino acids that may become conditionally essential under certain circumstances (e.g. cysteine, as acetyl-cysteine or cysteine HCL, taurine, and, in one formulation, glycyl-glutamine and glycyl-tyrosine dipeptide) (Table 1). L-Cysteine HCL (50 mg/ml as a 5% solution) and L-alanyl-L-glutamine dipeptide (200 mg/ml as a 20% solution; of which approximately two-thirds comprises the glutamine moiety) are also commercially available in many countries for admixture into cysteine-free or glutamine-free complete parenteral nutrition.

Amino acid mixtures for parenteral nutrition that are enriched in branched chain amino acids and low in aromatic amino acids (intended for use in hepatic encephalopathy) and a variety of other ‘designer’ products are also available for clinical use; examples of these include specially designed formulas for individuals with inborn errors of metabolism and the addition of L-glutamine to otherwise glutamine-free parenteral nutrition solutions by commercial pharmacies (glutamine dipeptide is not FDA approved in the USA) [4,6]. This review will focus on recent evidence from human studies and clinical practice guidelines, generally published within the past 5 years, concerning the utility and efficacy of amino acid dosing in patients requiring parenteral nutrition and the impact of alteration of specific amino acids in this clinical setting.

Total amino acid dosing

Rigorous data on the comparative efficacy of various formulations of parenteral nutrition, the optimal timing of administration, and the role of specific clinical factors (e.g. blood glucose control) on clinical outcomes with different parenteral nutrition formulations are lacking [7,8]. Unfortunately, few well designed, double-blind, randomized, controlled clinical trials (RCTs) have been published, particularly in recent years, on the clinical impact of different daily total amino acid doses per kg body weight or different concentrations of specific amino acids in parenteral nutrition [7,8]. Further, the relevance of earlier clinical studies to guide current parenteral nutrition amino acid dosing is uncertain given the significant changes that have occurred in common practices of parenteral nutrition administration worldwide over the past decade, including tighter blood glucose control, use of lower caloric doses, and commercial availability of alternative lipid emulsions in many countries (e.g. medium chain triglycerides, olive oil, fish oil, etc.) [3]. Given the relative lack of high-quality RCTs and comparative effectiveness research, current practices of amino acid use in parenteral nutrition are largely based on uncontrolled or observational studies, expert opinion, and clinical practice guidelines by academic societies [1[•],2[•],3,5,6].

Studies performed in the 1980s in nonburned intensive care unit (ICU) patients indicated that protein loads of more than approximately 2.0 g/kg/day are not efficiently utilized for protein synthesis and the excess is oxidized and contributes to azotemia [3]. Clinical practice guidelines published by the American Society for Parenteral and Enteral Nutrition (ASPEN) and the Society of Critical Care Medicine, the European Society for Clinical Nutrition and

Metabolism (ESPEN), and the German Association for Nutritional Medicine in 2009 recommend a parenteral nutrition amino acid dose range of between 1.2 and 1.5 g/kg/day for most adult catabolic patients with normal renal and hepatic function (e.g. 50–100% above the RDA of 0.8 g/kg/day). Some guidelines suggest that lower amino acid intake may be appropriate for patients without significant catabolic stress [4]. Administration of adequate nonamino acid calories is essential to allow amino acids to be effectively utilized for protein synthesis and to minimize the amount that is oxidized as fuel (e.g. nitrogen to calorie ratio of 1 : 130 to 1 : 170) [3,4,6].

The optimal dosing of amino acid for patients with acute or chronic renal and/or hepatic failure who require parenteral nutrition is unknown [8,9[•],10[•],11,12[•]]. Recent guidelines have suggested that adult patients with chronic hepatic failure and cirrhosis do not need to have protein restriction, but may benefit from amino acid/protein doses of 1.2–1.5 g/kg/day given the high rate of protein wasting in this patient population [2[•],9[•]]. However, these recommendations have not been based on evidence from rigorous studies in hospital patients, who may exhibit acute, severe hepatic decompensation, with or without encephalopathy; in such patients, short-term parenteral nutrition amino acid restriction may be indicated on an individual basis depending on hepatic function and other clinical factors (also not evidence-based) [3]. Specific parenteral nutrition amino acid dosing recommendations for patients with acute and chronic renal failure (largely based on nitrogen balance estimates and data on amino acid losses during renal replacement therapies) have been recently published by professional societies and others [2[•],10[•],11,12[•]]. Recent European and American clinical practice guidelines suggest that requirements for protein/amino acid be provided as a combination of adequate essential amino acids plus non-essential amino acids in adults with renal failure, combined with adequate nonprotein energy [10[•],12[•]]. Suggested protein/amino acid dosing in adult patients with chronic renal failure receiving hemodialysis or peritoneal dialysis is between 1.2 and 1.5 g/kg/day [10[•],12[•]]. Suggested protein/amino acid dosing in adult patients with acute renal failure in the European guidelines is from 0.6 to 1.0 g/kg/day in patients with mild catabolism, 1.0–1.5 g/kg/day in patients on dialytic therapy with moderate catabolism, to a maximum of 1.7 g/kg/day in patients on continuous renal replacement therapy with severe hypercatabolism [10[•]]. The recent American guidelines suggest that standard parenteral nutrition amino acid formulations be used in acute kidney injury, while the lack of clinical outcome data does not support the use of intradialytic parenteral nutrition as a nutritional supplement in malnourished patients with chronic kidney disease [12[•]]. These guidelines cite metabolic studies showing that doses of protein/amino acid between 1.8 and 2.5 g/kg/day may be optimal to support lean body mass during continuous renal replacement therapy; those with acute kidney injury treated with hemodialysis may require protein/amino acid doses of 1.5–2.5 g/kg/day to achieve positive nitrogen balance [2[•],11,12[•]]. A common, but not evidence-based, clinical practice in hospital patients receiving parenteral nutrition is to adjust the total amino acid dose downward depending on the degree and tempo of azotemia (in the absence of renal replacement therapy) [3,6].

Recent guidelines for parenteral nutrition support in children, with or without critical illness, have been recently published by professional societies from Europe and America [13,14]. As noted in the American guidelines for critically ill children, there are insufficient data to make evidenced-based recommendations for macronutrient intake in this population [14]. However, based on limited data, estimated protein/amino acid requirements for critically ill children are a function of the child's age, as follows: 0–2 years, 2.0–3.0 g/kg/day; 2–13 years, 1.5–2.0 g/kg/day; and 13–18 years, 1.5 g/kg/day [14].

Glutamine

Over the past 20 years, a large and growing number of clinical investigations have explored the clinical and metabolic efficacy of parenteral nutrition supplemented with glutamine, either as L-glutamine or as water soluble and heat-stable glycyl-glutamine or alanyl-glutamine dipeptide (reviewed in Refs. [15–17,18*]). These clinical trials, supported by translational studies in animal models, strongly suggest that glutamine becomes a conditionally essential amino acid in severe stress conditions such as critical illness, surgery, and trauma, when endogenous utilization exceeds endogenous glutamine production [3,15–17,18*]. Glutamine added to parenteral nutrition at doses up to 0.57 g/kg/day in adults also appears to be safe. For example, recent studies in head trauma patients show that intravenous alanyl-glutamine dipeptide at doses equivalent to 0.34 g/kg/20 h did not alter cerebral glutamate (a product of amino acid metabolism and a potential neurotransmitter) or brain amino acid exchange [19,20]. In addition to the large number of clinical trials summarized in recent reviews [15–17,18*], several additional trials of intravenous glutamine have recently been published [21–35]. In these studies, glutamine was either admixed in parenteral nutrition formulations or infused as the alanyl-glutamine dipeptide through central or peripheral veins. Two relatively small but rigorous RCTs from France [21] and the USA [22], respectively, showed that glutamine-supplemented parenteral nutrition (providing 0.5 g/kg/day of alanyl-glutamine) decreased nosocomial infections in ICU patients [21,22]; however, in the latter trial, patients admitted to the ICU after pancreatic surgery for severe pancreatitis showed no difference in outcomes versus patients who received standard glutamine-free parenteral nutrition [22]. In an unblinded study of 109 patients, enterally fed patients requiring colorectal cancer resection surgery and given 1.0 g/kg/day alanyl-glutamine for 11 days perioperatively ($n = 57$) showed a significant decrease in wound infection, intra-abdominal abscess and wound dehiscence [23]. Two recent small, unblinded controlled studies suggested that patients with acute pancreatitis may clinically benefit from glutamine-supplemented parenteral nutrition in terms of a reduction in total complications [24] and infectious morbidity [25], without any effect on length of hospital stay or mortality, but rigorous RCTs of glutamine-supplemented parenteral nutrition in this disorder are lacking.

Results of studies over the past two decades on the clinical efficacy of glutamine-supplemented parenteral nutrition in various forms of cancer and cancer treatment have been mixed to date; however, when taken together with results of enteral glutamine trials and animal studies, glutamine administration appears to be safe and potentially efficacious with regard to some clinical outcomes in cancer [18*]. A recent Cochrane review concluded that bloodstream infections with glutamine-supplemented parenteral nutrition are significantly reduced but length of stay is not altered in bone marrow transplant (BMT) recipients [26]. In a 2006 pilot double-blind RCT from Argentina, peripherally infused alanyl-glutamine dipeptide was given as intermittent daily doses in patients undergoing chemoradiotherapy for head and neck malignancy; patients receiving glutamine ($n = 14$) demonstrated a significantly lower incidence of mucositis, less oral pain, and a reduced need for feeding tube placement than saline-treated controls ($n = 15$) [27]. A small unblinded study of peripherally infused alanyl-glutamine dipeptide (30 g/day) versus mixed amino acid infusion in acute myeloid leukemia patients showed that neutrophil phagocytosis and superoxide generation were improved in the glutamine group [28]. A double-blind trial from Brazil in 53 patients undergoing allogeneic BMT for hematologic malignancies showed that patients receiving parenteral nutrition supplemented with 0.3–0.4 g/kg/day alanyl-glutamine dipeptide ($n = 27$) had a significantly lower mortality rate at day 100 and 180 post-BMT versus glutamine-free parenteral nutrition-treated controls ($n = 26$), with a nonsignificant trend for less infectious complications and no change in intestinal permeability to sugar markers [29].

Several of the recently conducted trials do not show clinical benefits with parenteral glutamine administration [30–35]. A randomized, unblinded, multicenter Italian study in 428 patients undergoing major abdominal surgery for cancer showed no significant difference in surgical complications, morbidity, incidence of infection or length of stay between patients who received parenteral alanyl-glutamine supplementation (0.40 g/kg/day of dipeptide solution, equal to 0.25 g/kg/day of free glutamine) or no treatment beginning 1 day preoperatively and continued for at least 5 days postoperatively (mean = 7 days) [30]. Patients in this study were not given specialized nutritional support unless enteral feeding was not possible at day 7 postoperatively [30]. In a double-blind RCT from Germany, Engel *et al.* [31] studied 78 patients undergoing cardiopulmonary bypass and cardiac surgery received either alanyl-glutamine dipeptide (0.5 g/kg/day), isonitrogenous glutamine-free mixed amino acids or normal saline for the initial 3 postoperative days. Glutamine administration did not alter T cell cytokine responses or clinical parameters of recovery compared to the other two groups [31]. Jo *et al.* [32], in South Korea, in a double-blind RCT of 60 patients requiring pancreati-coduodenectomy for periampullary tumors, randomized patients to complete parenteral nutrition supplemented with glycyl-glutamine (Table 1) or isonitrogenous parenteral nutrition without glutamine given perioperatively for 7 days (2 days preoperatively and 5 days postoperatively). No differences in length of hospital stay and complication rates were observed between the study groups [32]. An unblinded study of perioperative parenteral nutrition with or without glutamine in 70 gastrointestinal surgical patients in Taiwan did not show differences between groups in clinical outcomes, although indices of inflammation were decreased in the glutamine group [33]. In a double-blind study of critically ill patients receiving identical conventional tube feedings, Luo *et al.* [34] found no metabolic differences during 8 days of treatment in the study groups given alanyl-glutamine dipeptide (0.5 g/kg/day) either enterally or intravenously and when compared with a group not receiving glutamine supplementation. Very little information is available on the efficacy of glutamine-supplemented parenteral nutrition in home patients. In the first such trial, Culkin *et al.* [35] performed a 12-month cross-over study in 22 home parenteral nutrition patients who received 6 months of parenteral nutrition containing glycyl-glutamine during either the first or second 6-month study period (0.14–0.15 g/kg/day dipeptide). No differences were observed between study periods in nutritional status, intestinal permeability, plasma glutamine concentrations, or quality of life [35].

The mixed results of these clinical trials could be due to the fact that parenteral glutamine may be beneficial in only certain patient subgroups (e.g. those with significant body glutamine depletion or increased glutamine needs, or in those with specific medical or surgical characteristics or conditions) [22]. Completion of large ongoing RCTs of glutamine supplemented parenteral nutrition in postoperative surgical ICU patients (ClinicalTrials.gov identifier NCT00248638), combined enteral and parenteral glutamine plus high-dose selenium with antioxidants in medical/surgical ICU patients (ClinicalTrials.gov identifier NCT00133978), and parenteral glutamine as a single agent (ClinicalTrials.gov identifier NCT00922714), or in combination with high-dose selenium [36] will better define adult patient subgroups who may benefit from parenteral glutamine [16,37,36]. Of interest, the 2009 clinical practice guidelines of ESPEN and the German Association for Nutritional Medicine each recommend that ICU patients requiring parenteral nutrition routinely receive glutamine supplementation (ranging from 0.2 to 0.4 g/kg/day) [1^{**},4]. In contrast, the American ICU guidelines do not recommend that glutamine be routinely administered in ICU patients requiring parenteral nutrition or a specific dose, but that its use should be considered if the product is available [2^{**}].

Studies on glutamine-supplemented parenteral nutrition in pediatrics are limited to four earlier trials, including one large multicenter American study, in preterm, very low birth weight infants requiring ICU care [38]. A recent Cochrane report concluded that glutamine

supplementation in such infants does not have a statistically significant effect on mortality invasive infection, necrotizing enterocolitis, time to achieve full enteral nutrition, or duration of hospital stay [38].

Despite inconsistent study results across diverse patient groups, parenteral glutamine supplementation in adults has been shown to significantly increase plasma glutamine concentrations, improve nitrogen retention and upregulate various immune functions [15–17]. Also, in catabolic adults, parenteral glutamine also decreased indices of insulin resistance [21,39] and upregulated the cytoprotective molecules heat shock protein 70 [40] and glutathione in plasma [41] and skeletal muscle [42]. In sum, parenteral glutamine appears to confer benefit in selected patients; however, additional data to define optimal glutamine dosing strategies in patient subgroups who may most benefit from this amino acid are needed.

Arginine

Arginine is present in relatively high doses in all common amino acid formulations for parenteral nutrition used in both children and adults (Table 1). Arginine is thought to be a conditionally essential amino acid in neonates and infants and possibly in catabolic states. Arginine's functions and metabolic roles in health and disease have been comprehensively reviewed [43,44]. Although enteral arginine supplementation in patients requiring specialized nutrition support has been extensively studied, little clinical research on clinical or metabolic effects of arginine dosing in parenteral nutrition has been performed. A recent review speculated on the rationale for combined administration of glutamine and arginine in pathologic states [45]. Arginine is the substrate for the production of nitric oxide (a potent vasodilator), and there is some speculation that, given the low plasma arginine levels observed in preterm neonates, arginine supplementation may serve to prevent necrotizing enterocolitis (NEC). In 2002, a double-blind RCT was published in 152 premature infants randomized to receive either supplemental L-arginine ($n = 75$) or placebo ($n = 77$) with oral feeds (as tolerated) and in any required parenteral nutrition during the first 28 days of life [46]. Arginine supplementation was well tolerated and resulted in a significant decrease in the incidence of NEC [46]. To our knowledge, no further study of arginine efficacy in pediatrics has subsequently been published, but further study on the issue of NEC is clearly needed.

Cysteine

Cysteine is commonly believed to be a conditionally essential amino acid in preterm neonates, who have a relative inability to enzymatically convert methionine (the essential sulfur amino acid precursor to cysteine), in the liver [47]. As noted in Table 1, small amounts of acetyl-cysteine or cysteine HCL are present in some mixed amino acid formulas for parenteral nutrition use and larger doses of an approved cysteine HCL product can be admixed into parenteral nutrition on the day of administration. Commercial mixed amino acid formulas do not contain appreciable cysteine because of instability in solution, but methionine, as an essential amino acid, is present in all mixed amino acid formulas (Table 1).

Cysteine has dynamic effects in metabolism and systemic redox control. The metabolism and roles of cysteine (and its disulfide cystine) in physiologic and pathophysiologic states, including as a precursor for the synthesis of glutathione (GSH), have been recently summarized [48,49]. Cysteine is used in protein synthesis and, in critically ill patients receiving conventional parenteral nutrition, GSH levels fall; thus, increased cysteine utilization may exceed endogenous production and decreased plasma cysteine. In humans, plasma cysteine levels and the redox potential of the cysteine/cystine redox pool have been

recently shown by our group to be dynamically affected by oral dietary intake of cysteine and methionine [50,51]. In a rat model of short-bowel syndrome, we showed that supplementation of enteral diets with cysteine and methionine improved gut mucosal and plasma cysteine/cystine redox potential and enhanced adaptive ileal mucosal growth [52]. Although no studies, to our knowledge, have been published on the clinical or metabolic effects of cysteine added to parenteral nutrition in adults, L-cysteine HCL at doses of 500 mg to 1.5 g/day is empirically added to parenteral nutrition by some clinicians in patients with parenteral nutrition-associated liver disease.

As noted, cysteine is approved for addition to parenteral nutrition in preterm infants. A 2006 Cochrane review evaluated five small trials of short-term cysteine supplementation of cysteine-free parenteral nutrition [53]. The authors concluded that growth was not significantly affected by cysteine supplementation (evaluated in one quasi-randomized trial), but that nitrogen retention was significantly increased by cysteine supplementation (studied in four trials); no data were available on clinical outcomes [53]. Riedijk *et al.* [47] concluded that there was no evidence for limited endogenous cysteine synthesis in 4-week-old low birth weight infants using exhaled breath methods after oral cystine loads, while Courtney-Martin *et al.* [54] found that the methionine requirement to achieve adequate cysteine plasma levels in postsurgical human neonates requiring parenteral nutrition is lower than the methionine dose currently provided in commercial parenteral nutrition solutions (Table 1). Te Braake *et al.* [55] found that administration of high-dose cysteine (81 mg/kg/day) via parenteral nutrition to preterm infants was safe but did not increase plasma cystine or GSH concentrations or synthesis rates. Parenteral cysteine supplementation did not increase erythrocyte GSH in a recent study using tracer methodology in five parenteral nutrition-fed neonates [56]. Mager *et al.* [57] report that addition of N-acetyl-cysteine (NAC) to parenteral nutrition or parenteral hydration fluid at doses of 20–50 mg/kg/day decreased liver enzyme elevations and tended to increase blood GSH levels in children requiring home parenteral nutrition. RCTs on the clinical and metabolic efficacy of either L-cysteine or NAC added to parenteral nutrition in adults or children requiring this therapy are needed.

Taurine

Taurine, which can be synthesized via its amino acid precursor cysteine, is believed to be conditionally essential in premature neonates. As shown in Table 1, taurine is present in some commercial amino acid formulas for use in parenteral nutrition, particularly in formulas designed for infants. Taurine supplementation in enteral nutrition has been studied in premature neonates without any conclusive effect on growth rate, morbidity and mortality, similar to the one trial of taurine added to parenteral nutrition in this setting, according to a Cochrane report [58]. One observational study suggested that taurine supplementation of parenteral nutrition may decrease the occurrence of parenteral nutrition-associated cholestasis in neonates [59], but a small pilot study failed to reproduce this effect in adults requiring long-term parenteral nutrition for short-bowel syndrome [60].

Branched chain amino acids

Earlier studies, primarily in the 1980s, showed that plasma concentrations of the essential branched chain amino acids (BCAA) isoleucine, leucine, and valine were decreased in patients with severe liver disease and encephalopathy, while levels of aromatic amino acids (phenylalanine, histidine, tryptophan, and tyrosine) were elevated in this setting. Given that this amino acid pattern was associated with encephalopathy, parenteral nutrition amino acid formulas designed to correct this metabolic abnormality became commercially available (enriched in BCAA and with decreased amounts of aromatic amino acids). Numerous studies of various levels of rigor were conducted (primarily in the 1980s and 1990s) to test

the clinical and metabolic efficacy of these amino acid solutions. While a review of these studies is beyond the scope of this paper, the results on clinical outcomes were overall inconclusive and such amino acid formulations are no longer routinely used. However, the recent European clinical practice guidelines do suggest that these BCAA-enriched amino acid formulations may be useful in selected patients with liver failure-induced encephalopathy [9**], and these are sometimes used by clinicians in the USA and elsewhere in malnourished patients with hepatic encephalopathy who cannot clinically tolerate higher doses of parenteral nutrition amino acids. In more recent, relatively small, nonblinded studies, patients given BCAA-enriched parenteral nutrition after gastrointestinal surgery demonstrated improved nitrogen balance compared to patients receiving conventional amino acid formulations in parenteral nutrition [61,62], while one of these studies demonstrated a decreased overall morbidity rate [62]. Rigorous RCTs on the potential utility of BCAA supplementation in specific catabolic patient groups are needed.

Conclusion

Administration of mixed essential and nonessential amino acids in parenteral nutrition is a routine aspect of clinical nutrition support. Although current paradigms of parenteral nutrition amino acid administration are clearly safe and efficacious in patients receiving parenteral nutrition, surprisingly little clinical outcome data are available to more specifically guide total amino acid dosing in adult and pediatric patients. In addition, with the exception of glutamine, comparatively little rigorous clinical outcome data are available in the current era of nutritional support on the effects of adding specific amino acids or adjusting their dose in parenteral nutrition. Thus, more high-quality research is critically needed to better define optimal amino acid administration in patient subgroups requiring parenteral nutrition.

Acknowledgments

Funding for this work was received from National Institutes of Health grants U01 DK069322, K24 RR023356 (to T.R.Z.), and UL1 RR025008 (Atlanta Clinical and Translational Science Institute).

References and recommended reading

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Table 1
Amino acid composition of some commonly used commercial products for parenteral nutrition

Product (% amino acids) (manufacturer)						
	ProSol (20%) (Baxter)	Aminoven (15%) (Fresenius Kabi)	Amino-plasmal (15%) (B. Braun)	Travasol (10%) (Baxter)	Troph-Amine (10%) ^a (B. Braun)	Glamin (13.4%) ^b (Fresenius Kabi)
Amino acid (g or mg/100 g amino acid)						
EAA						
Valine	7.20 g	3.66 g	4.80 g	5.80 g	7.80 g	5.45 g
Lysine	6.75 g	7.39 g	5.29 g	5.80 g	8.20 g	6.71 g
Histidine	5.90 g	4.86 g	3.50 g	4.80 g	4.80 g	5.07 g
Isoleucine	5.40 g	3.46 g	3.90 g	6.00 g	8.20 g	4.18 g
Leucine	5.40 g	5.92 g	7.59 g	7.30 g	14.00 g	5.89 g
Phenylalanine	5.00 g	3.66 g	3.80 g	5.60 g	4.80 g	4.36 g
Threonine	4.90 mg	5.73 g	3.60 g	4.20 g	4.20 g	4.18 g
Methionine	3.80 mg	2.53 g	3.80 g	4.00 g	3.40 g	4.18 g
Tryptophan	1.60 mg	1.07 g	1.40 g	1.80 g	2.00 g	1.42 g
EAA (%)	46%	38%	38%	45%	57%	41%
NEAA						
Alanine	13.80 g	16.65 g	14.89 g	20.07 g	5.40 g	11.94 g
Glycine	10.30 g	12.32 g	12.79 g	10.30 g	3.60 g	See footnotes
Arginine	9.80 g	13.32 g	10.69 g	11.50 g	12.00 g	8.43 g
Proline	6.70 g	11.32 g	4.90 g	6.80 g	6.80 g	5.07
Glutamic acid	5.10 g	0	10.79 g	0	3.20 g	4.18 g
Serine	5.10 g	6.39 g	2.00 g	5.00 g	3.80 g	3.36
Aspartic acid	3.00 mg	0	5.29 g	0	3.20 g	2.54 g
Tyrosine	250 mg	266 mg	333 mg	400 mg	2.4 g (as tyrosine and acetyl-L-tyrosine)	See footnotes
Taurine	0	1.33 g	0	0	250 mg	0
Cysteine	0	0	244 mg (as acetyl-L-cysteine)	0	240 mg (as cysteine HCL)	0
Glycyl-glutamine ^c	0	0	0	0	0	22.58 g
Glycyl-tyrosine ^d						2.57 g
NEAA (%)	54%	62%	62%	55%	43%	59%

EAA, essential amino acids; NEAA, nonessential amino acids.

^a Designed for infants and young children (including those of low birth weight).

^b Dipeptide-containing formula.

^c Glycyl-glutamine dipeptide composition corresponds to 7.66 g glycine and 14.92 g glutamine.

^d Glycyl-tyrosine dipeptide composition corresponds to 701 mg glycine and 1.70 g tyrosine.