Clinical Use of Glutamine Supplementation1,2

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Abstract
Endogenous production of glutamine may become insufficient during critical illness. The shortage of glutamine is reflected as a decrease in plasma concentration, which is a prognostic factor for poor outcome in sepsis. Because glutamine is a precursor for nucleotide synthesis, rapidly dividing cells are most likely to suffer from a shortage. Therefore, exogenous glutamine supplementation is necessary. In particular, when i.v. nutrition is given, extra glutamine supplementation becomes critical, because most present formulations for i.v. use do not contain any glutamine for technical reasons. The major part of endogenously produced glutamine comes from skeletal muscle. For patients staying a long time in the intensive care unit (ICU), the muscle mass decreases rapidly, which leaves a tissue of diminishing size to maintain the export of glutamine. The metabolic and nutritional adaptation in long-staying ICU patients is poorly studied and is one of the fields that needs more scientific evidence for clinical recommendations. To date, there is evidence to support the clinical use of glutamine supplementation in critically ill patients, in hematology patients, and in oncology patients. Strong evidence is presently available for i.v. glutamine supplementation to critically ill patients on parenteral nutrition. This must be regarded as the standard of care. For patients on enteral nutrition, more evidence is needed. To guide administration of glutamine, there are good arguments to use measurement of plasma glutamine concentration for guidance. This will give an indication for treatment as well as proper dosing. Most patients will have a normalized plasma glutamine concentration by adding 20–25 g/24 h. Furthermore, there are no reported adverse or negative effects attributable to glutamine supplementation. J. Nutr. 138: 2040S–2044S, 2008.

Introduction
A profound depletion of glutamine in plasma and in tissues occurs in critical illness. Glutamine is unstable in aqueous solution and therefore was not included in crystalline amino acid solutions for parenteral use until the dipeptide technique was introduced in the 1990s. It was not far fetched to hypothesize that supplementation with glutamine would counteract or attenuate metabolic catabolism during critical illness. In particular, studies of the physiology and kinetics of glutamine provided evidence that glutamine availability may be affected (1–3). Starting 20 y ago, a number of reports demonstrated beneficial effects from glutamine supplementation in various patient groups and, in parallel, virtually no reports of negative effects or adverse effects attributable to glutamine supplementation have been published. Today, glutamine supplementation is the standard of care when i.v. nutrition is given to critically ill patients (4). Glutamine supplementation in enteral nutrition is still controversial.

Physiology
Glutamine is a nonessential amino acid and the major part of the de novo synthesis in the human body is in skeletal muscle (5,6). Other organs with a net export of glutamine are the brain and there are several independent reports of a net export from the lungs (7–9). From these tissues, glutamine is transported via the blood stream to organs in the splanchnic area. Cells utilizing glutamine are immune competent cells, enterocytes, and to some extent also hepatocytes. The main use for glutamine in the basal state as well as during critical illness is as an oxidative substrate. This involves the handling of the amino groups, the major part of which ends up as urea. The endogenous production of glutamine as estimated by isotopic techniques is 40–80 g/24 h (10–12). A production of the same magnitude is also found when using pharmacokinetic techniques (1,13). Both techniques may underestimate the actual de novo glutamine synthesis, because the distribution volume of glutamine is large and the equilibration time is therefore long (14). Measurements in critically ill patients indicate that the endogenous glutamine synthesis rate or rate of appearance remains similar to that in the basal state (1).
This is also supported by the observation that the quantitative eflux of glutamine from muscle remains consistent or is only slightly elevated in critically ill subjects compared with the basal state in healthy volunteers (5,15). A major difference between healthy volunteers and critically ill subjects is that the latter group usually is constantly fed enterally or parenterally over time. This makes the amino acid balance across muscle fairly similar in terms of the proportions between the individual amino acids in the fed critically ill patients and healthy volunteers in the basal state. The situation in the fed state of healthy individuals, when there is an uptake of all amino acids except glutamine, is not seen in critically ill patients. Although the physiology is well known in general terms, there are still a number of unsorted questions. It has not been clarified whether there is a relation between plasma concentration and rate of appearance for glutamine. No correlation between the size of the export of glutamine from muscle and plasma concentration has been reported, but there may be a relation between plasma concentration and the splanchnic uptake. Although this is very likely, it has never been demonstrated, to the author’s knowledge, in critically ill subjects. For glutamate, the situation is more complicated. It has been demonstrated that the uptake in cardiac or skeletal muscle is concentration dependent, but what regulates the export of glutamate from liver and whether the export concentration dependent is not well characterized in critically ill patients.

Rationale for glutamine supplementation
The rationale for treatment with glutamine supplementation in critically ill patients is the shortage of glutamine, the clinical evidence, and the fact that it is not harmful to patients.

There were 2 single-center studies of multiple organ failure patients of total parenteral nutrition that showed a survival benefit when glutamine was supplemented at the level of 20–25 g/24 h (16,17). The survival advantage in these studies shows as a tendency within the ICU stay, which becomes significant at the 6-mo follow-up. This fact has been discussed, as there is no report of a direct relation between the glutamine depletion over time and mortality. However, a low plasma glutamine at ICU admittance is an independent predictor of mortality (4). What happens during the restoration phase following ICU discharge is still an open question. A possible hypothesis for this group of patients is that the glutamine depletion and the general muscle protein depletion go hand-in-hand and that the post-ICU mortality is comparable to the general mortality in a group of patients with severe malnutrition. In addition, there are a number of studies focusing on morbidity in terms of infectious morbidity, length of stay, or hospital economics (18–23). Such reports exist both for parenteral glutamine and enterally administrated glutamine. For enterally administrated glutamine, there is a comparatively large study of a general ICU patient group with a mixture of short stayers and long stayers that fails to demonstrate any advantage in morbidity or mortality (24). For other patient groups, such as hematological patients, oncological patients, and patients with gastrointestinal diseases, clinical studies demonstrate decreased morbidity (25,26). In summary, there is clear evidence that when critically ill patients receive parenteral nutrition, i.v. supplementation with glutamine brings a survival advantage. The clinical evidence is not yet conclusive for patients receiving enteral nutrition or combined enteral and parenteral nutrition. Several multi-center studies will be conducted in the next few years that will hopefully shed more light on this topic (27,28). The major problem with the existing evidence in these groups of patients is the mixture of ICU short stayers and long stayers, which introduces a large variability of prognosis in terms of mortality within the study group.

The shortage of glutamine as reflected by the plasma concentration is a prognostic factor (2,3,29–31). There is also a depletion in tissues such as skeletal muscle, where the concentration decreases to 25% of normal. The reason for the intracellular depletion is not fully understood. A decrease in intracellular glutamine concentration occurs during starvation in healthy subjects and also following medium-size elective surgery (32,33). In the latter case, it is normalized over a period of 2 wk, while for starved healthy subjects it is normalized over a few days (34). Both of these states represent mild catabolism, which obviously resets the gradient between extracellular and intracellular glutamine differently. In healthy volunteers and in non-malnourished patients undergoing elective surgery, there is no change of plasma glutamine concentration but only a drop in tissue concentration (32,33). Hypothetically, whatever regulates the gradient for glutamine across the cell membrane resets it in this situation. For the critically ill patients, on the other hand, the decrease occurs both in plasma and intracellularly and the latter seems to be more pronounced, also decreasing the gradient.

Of all studies involving glutamine supplementation by enteral or parenteral route, there are virtually no reports of adverse effects or harmful effects. This included patients in studies of tolerance and pharmacokinetics, who were shown to have extremely high plasma glutamine levels (>2 mmol/L) (36). The only condition known to be accompanied by very high plasma glutamine concentrations is acute liver failure, whereas chronic liver failure is not accompanied by high plasma glutamine levels (37). The pathophysiology behind these high concentrations is not well characterized. There is no literature reporting that a high glutamine concentrations are associated with any of the symptoms of acute liver failure or the prognosis.

Route of administration
Administration of glutamine containing dipeptides results in an almost immediate hydrolysis into the constituent amino acids (38,39). This peptidase activity is probably present on the surface of the endothelium. The half-life of glutamine containing dipeptides is <3 min in healthy volunteers and <10 min in ICU patients (36,38,39). In tolerance studies, dipeptides have not been accumulated or been excreted via the kidneys (36,40). So glutamine becomes readily available after administration of the dipeptide. When given i.v., the plasma concentration immediately responds to the exogenous supply. In critically ill patients, this results in a normalization of the plasma level in all patients (41). The clearance and the distribution kinetics is highly variable (36); therefore, the dosage of glutamine may be guided by determinations of plasma concentration.

When exogenous glutamine is administered i.v., the distribution is uniform throughout the body. The concentrated dipeptide, alanyl-glutamine (at 200 g/L), with an osmolality <900 mOsm, can be safely administered also in a peripheral vein (42). This means that i.v. glutamine supplementation may also be administered when central venous lines are not available. All cells in the body may utilize this glutamine and there are no restrictions in uptake, although the concentration gradient in skeletal muscle, for example, is not in favor of an uptake. Experimental studies have demonstrated that intestinal mucosal cells may have a facilitated uptake across the brush border membrane, which is the cellular surface toward the intestinal lumen (43,44). The relevance of that finding in vivo is not well documented. On the contrary, the atrophy of the intestine in animals may be attenuated by i.v. administration of glutamine.
and the translocation of bacteria is also counteracted by i.v. glutamine (45–47).

When exogenous glutamine is administered enterally, there is an immediate uptake in the upper part of the gastrointestinal tract (48). The effects of enteral glutamine supplementation on plasma concentration are highly variable and often marginal in size (20,40,48,49). The major portion of the administered glutamine is utilized in the gut itself by enterocytes and immune competent cells and the rest is utilized in the liver, and through this first pass elimination, the major part of the given dose is utilized (12,40). Still, as enterocytes and immune competent cells are the target cells, this may be sufficient for an improvement in the clinical outcome, but the uneven distribution may also be a problem. In critical illness, an additional problem may be the uncertainty concerning the absorption and utilization of any enterally administered nutrient. This may add uncertainty, in particular when the effect upon plasma concentration is only marginal. In summary, parenteral administration probably has advantages, while the disadvantage is the higher cost.

Dosage and therapeutic goals
When glutamine is administered i.v., there is a dose-response effect in the sense that the higher the dose, the higher the plasma concentration (41,50). Elimination kinetics is by the first order and even large doses are eliminated within 8 h after determination of the infusion (36). In the limited number of critically ill patients so far studied in terms of glutamine kinetics, there is no evidence of a feedback mechanism where exogenous supplemented glutamine decreased the endogenous production (1,36,51,52). There are also no studies available on the long-term effects of exogenous glutamine supplementation.

In postoperative patients, a daily i.v. glutamine dose of 20 g attenuates the decrease otherwise seen in skeletal muscle (32–34). This dose was originally chosen from a calculation of the decline in the free glutamine pool. When tested in critically ill patients, it proved to be sufficient to normalize the decreased plasma concentration in the majority of ICU patients, while it did not affect the decreased free glutamine concentration in muscle (41). Lower doses of exogenous glutamine given i.v. are not sufficient to normalize the plasma concentration in ICU patients (5). The dose response of exogenous glutamine given enterally is less well characterized. It is dependent upon the group of subjects investigated, the concomitant administration of enteral feeding, and whether the mode of feeding is bolus or continuous (12,20,40,48,53–55).

For patients staying a long time in the ICU, the export of glutamine from muscle tissue remains unaltered, at least during the initial 3 wk (5). The muscle mass decreases rapidly, which leaves a tissue of diminishing size to keep up the export (31). In vitro measurement of the capacity for glutamine synthesis indicates a priori an increased production (36). Whether ICU patients staying a very long time eventually will be depleted in their capacity for endogenous glutamine production is still an open question. The metabolic and nutritional adaptation in this group of patients is poorly studied and is one of the fields that requires more scientific evidence for clinical recommendations.

Recommendations
Solid evidence is presently available for i.v. glutamine supplementation to critically ill patients on parenteral nutrition. Existing studies are confined to ICU, and continued post-ICU glutamine supplementation together with parenteral nutrition is not supported by clinical studies but is perhaps a reasonable extrapolation of existing data. However, the distinction between ICU and post-ICU is very different between countries. The group of patients confined to parenteral nutrition is small in number, whereas the patients on combined enteral and parenteral are the majority of long stayers in the ICU. Upcoming studies will hopefully provide evidence of whether this patient group will benefit from glutamine supplementation. The costs of i.v. glutamine supplementation are sometimes regarded as a problem. By routine determinations of plasma glutamine concentration, patients who are depleted of glutamine can be defined and treatment can be monitored to restore plasma glutamine to the normal concentration interval.

There are virtually no contraindications to glutamine supplementation in any form. The only patient group with a high plasma glutamine level, those with acute hepatic insufficiency, is not a nutritional problem. Usually within a limited period of time, they will regain liver function or receive a transplant. Patients in chronic liver failure are often malnourished and should not be excluded from glutamine therapy. As for kidney failure in critical illness, this should be treated by dialysis, when exogenous glutamine supplementation becomes even more important. The losses of amino acids into the dialysate are ~10 g/hemodialysis session in intermittent dialysis and in continuous renal replacement therapy the losses of glutamine are usually 3–5 g/24 h. These losses are in addition to an insufficient endogenous glutamine production (1,57). This makes glutamine supplementation even more important, and it should be in the range of 25–35 g/24 h.

For neurosurgical patients, in particular patients with head injuries, there are concerns that the elevated level of glutamate interstitially in the brain may be influenced by exogenous glutamine supplementation. The elevated glutamate has been reported to be an indicator of an unfavorable outcome. However, these observations are perhaps more anecdotal than evidence based. Nevertheless, there are concerns that glutamine may result in an elevation of glutamate. In a safety study, elevated plasma glutamate concentration secondary to exogenous glutamine supplementation did not affect plasma glutamate or intracerebral glutamate levels, as monitored by microdialysis (58). Furthermore, the efflux of glutamine from the brain was also unaffected by exogenous glutamine supplementation (51). Theoretically, there could be an impairment of the glutamate elimination via the glutamine pathway if the efflux of glutamine from the brain was diminished. In conclusion, there is no contraindication of using glutamine to head trauma patients and studies investigating if glutamine supplementation to this patient group may have advantageous effects upon outcome are encouraged.

Unanswered questions
The most important issue for ongoing and future research is whether enterally provided glutamine will be as effective as parenterally provided. Existing studies of enteral glutamine supplementation mix patients of long and short ICU stay, which makes the results inconclusive. Another issue of importance is the role of glutamine supplementation when enteral and parenteral nutrition is combined, which often is the case in the ICU. Finally, the possible influence of exogenously provided glutamine on the endogenous production is also an issue that needs to be solved.

In summary, the clinical use of glutamine supplementation has evidence to support its use in critically ill patients in the ICU and in hematology and oncology patients. There is strong evidence for glutamine supplementation for patients on parenteral
literature this is regarded as the standard of care. For patients on enteral nutrition, more evidence is needed. To guide the administration of glutamine, measurement of plasma glutamine concentration is advocated. This will give an indication for treatment as well as proper dosing. Most patients will have a normalized plasma glutamine concentration by adding 20–25 g/24 h. For patients on continuous renal replacement therapy, a bit more (25–35 g/24 h) is recommended. In addition to clinical evidence, there is rationale for glutamine supplementation by the understanding of the role of glutamine in physiology. Furthermore, importantly, there are no reported adverse effects or negative effects attributable to glutamine supplementation. More evidence from ongoing multi-center studies will be generated during the next few years.

Other articles in this supplement include references (59–68).

**Literature Cited**


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