Glutamine supplementation – where are we heading?

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Purpose of review • There is considerable interest in glutamine in both critical care and surgery. Glutamine offers the potential to enhance host defences and may reduce subsequent infections, hospital stay and mortality. This review will consider key papers in this field and update meta-analysis of this intervention in the light of new data.

Recent findings • The current literature demonstrates that there are insufficient data to enable confident recommendations on the optimal route, timing, duration and dosage of glutamine. The Scottish Intensive care Glutamine or seleNium Evaluative Trial (known as the SIGNET trial) is the largest, critical care study of glutamine to date. This prospective, randomized controlled, factorial trial showed that glutamine administered as part of parenteral nutrition support does not decrease the number of new infections nor does it reduce mortality.

Summary • To be able to confidently establish or refute the hypothesis that glutamine improves outcome in critical care, a well designed prospective randomized controlled trial is essential. To design such a trial, we require the optimal dose and duration of the nutritional supplement (balancing efficacy and toxicity, ease of administration and cost) and subsequently conduct an adequately powered trial. Such a trial is still lacking.

Keywords • Adult; Amino Acids; Antioxidants; complications; Critical Care; diagnosis; Dietary Supplements; Dipeptides; Enteral Nutrition; etiology; Glutamine; Humans; immunology; Intensive Care; Intestinal Absorption; Length of Stay; Multiple Organ Failure; Sepsis; Trace Elements; Treatment Outcome; Vitamins

Introduction
Mortality following critical care admission is high and subsequent hospital death rate even higher. In this setting, infection and sepsis are perpetual problems that are connected with increased mortality, morbidity and resource usage. The latter are associated with illness- and drug-related impairment of the patient’s immune system.

Glutamine is the most abundant amino acid in the plasma. It has an key role in acid-base balance, nitrogen transport, maintaining muscle mass and function, and as an energy source for rapidly dividing cells - particularly those of the immune system and gut [1]. Gut associated lymphoid tissue comprises the largest collection of immune cells in the body; their turnover and the vulnerability of the gut to ischemia/reperfusion injury in shock states offers potential therapeutic targets for intervention in critical illness [2,3].

It is believed that glutamine synthesis and release is insufficient to meet the demands under severe metabolic stress; glutamine must therefore be supplied from nutritional sources if levels are to be maintained. It is thought that under conditions of severe metabolic stress glutamine becomes “conditionally essential”.

Healthcare acquired infections (HAI) on the ICU are the subject of many international surveillance programmes (for example, National Nosocomial Infections Surveillance (NNIS) in the USA, Victorian Hospital Acquired Infection Surveillance System (VICNISS) in Australia, National Surveillance of Hospital Infections (NSIH-ICU) in Belgium, Réseau d’alerte, d’investigation et de surveillance des infections nosocomiales (RAISIN) in France, Krankenhaus-Infektions-Surveillance-System (KISS-ICU) in Germany, Prevention of Nosocomial Infection through Surveillance (PREZIES), National Institute for Public Health and Environment (RIVM) and the Dutch Institute for Healthcare Improvement (CBO) in the Netherlands and in Spain the Spanish National Nosocomial Infection Surveillance Study (ENVIN-UCI) which underscores the importance placed on ICU acquired infections.

Supplementation of nutrition with glutamine offers the potential to reduce HAI. Although in general the enteral feeding route is preferred [4] to parenteral (because of reduced costs of administration and reduced risk of infectious complications), parenteral nutrition (PN) retains an important supportive role in the management of ICU patients, many of whom cannot be fed effectively by the enteral route because of gastro-intestinal dysfunction [5]. Therefore, this review will consider both contemporary enteral and parenteral studies over the last 3-4 years.

Recent Glutamine Publications

Critical Care
In 2008 Beale et al. [2] published the results of an enteral nutrition study that tested whether administering high doses of key nutrients (glutamine dipeptides, antioxidative vitamins and trace elements, and butyrate) in a low-volume enteral supplement, separated from the provision of general nutrition, could improve patient outcomes. The proposed advantage of this method of delivery was that all the supplementation could be given immediately after resuscitation and before enteral nutrition was started.
established. This group, calculated by power analysis, that 344 patients were required; however, the Data Monitoring and Safety Board (DSMB) recommended stopping recruitment after only 50 patients. This is surprising as the Usual DSMB terms of reference are that they will only recommend this if two conditions are satisfied: (1) the blinded results provide proof beyond reasonable doubt that treatment is on balance either definitely harmful or definitely favourable for all, or for a particular category of patients, in terms of the major outcome; (2) the blinded results would, if revealed, be expected to substantially change the prescribing patterns of doctors who are already familiar with any other trial results that exist. Neither conditions were met in my opinion.

After recruitment of only 50 patients, it is entirely plausible/likely that the published results occurred by the play of chance. Perhaps a more important message to come from this study is the importance of defining the role of the DSMB by developing and agreeing their character [6] well in advance of starting recruitment. The question of what should constitute the exact criteria for “proof beyond reasonable doubt” are not, and cannot be, specified by a purely mathematical stopping rule.

However, this study tested a pharmaco-nutritional support concept that was significantly different from traditional enteral nutrition, including immunonutrition; since the full volume of a supplement could be administered much earlier in the patient’s ICU stay, it had some theoretical advantages. These data showed more rapid improvements in Sequential Organ failure Scores (SOFA scores) in the pharmaconutritient group. There was also an associated improvement in many serum markers of nutrition absorption. There were no differences in the number of new infections between the groups and this may be related to the lack of treatment associated improvements in antioxidant status that were published. The methodology for description or detection of new infection is not given in this paper.

These data [2] are at odds with the much larger study by Kieft et al. [7] which had a more pragmatic design. A total of 597 adult ICU patients expected to require enteral tube feeding for more than 2 days were randomized to receive immunonutrition or an isocaloric control formula. The results of this largest randomized, controlled trial found that in the general ICU population immunonutrition has no beneficial effect on clinical outcome parameters.

These results are consistent with the existing literature including studies by Kumar [8], Luo [9,10, and Schulman et al. [11,12]. Marik et al. [13], conducted a systematic review of immune modulating (enteral) diets (IMD) in critical care patients and attempted to identify the effect of each component in the various possible diseases that contribute to critical illness. The results of this review demonstrate that with the exception of IMD containing a high concentration of fish oil, IMDs have no discernable clinical benefit in critically ill ICU, burn or trauma patients. Mortality, secondary infections and length of stay (LOS) were significantly lower only in the ICU patients (with sepsis, septic shock or Acute Respiratory Distress Syndrome) receiving the fish oil IMD. However, it should be noted that the control formula used in these studies were high in omega-6 fatty acids which may have contributed to the poor outcome in these patients as a high proportion of n–6 to n–3 fat in the diet shifts the physiological state in the tissues toward prothrombotic, pro-inflammatory and pro-vasoconstrictive states. If results are to be generalized, future studies should investigate the role of fish oil added as a supplement to a standard enteral nutrition formula to confirm the benefits of omega-3 fatty acids in critically ill patients and a standard care control group as the preferable trial design.

Standard parenteral amino acid formulations do not contain any of the amino acid glutamine, because of pharmaceutical stability problems. Several studies have shown that glutamine levels decrease markedly after major surgery and during critical illness.

Decreased serum glutamine has been associated with immune dysfunction in animal models and death or infectious complications in septic patients. A recent systematic review using random effects methods of meta-analysis [1] found that parenteral glutamine in critical illness was associated with a relative risk of mortality of 0.75 (95% CI 0.52 to 1.07) and for infection of 0.71 (95% CI 0.49 to 1.05). Recent mechanistic studies in critical care patients, show that an absence of Toll Like Receptors (TLRs) impairs the activation of host defence mechanisms such as secretion of inflammatory mediators, phagocytosis, and presentation of antigens. Perez-Barcena et al. [14], tested whether parenteral nutrition supplemented with glutamine would increase the expression of TLR-2 or TLR-4 in peripheral blood monocytes. This trial however, was neutral.

Current guidance comes in the form of nutrition guidelines from the British Association of Parenteral Enteral Nutrition (BAPEN), the European Society of Parenteral and Enteral Nutrition (ESPEN) and most recently, the Canadian Critical Care guidelines [15]. The latter were updated and published in 2009. Their recommendations are based upon four level 1 studies

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<tr>
<td>Mondello 2010</td>
<td>Immunological status in anorexia</td>
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<td>20 days</td>
<td>Increase in neopterin [p&lt;.001] and lymphocytes, clinical benefits?</td>
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<td>Gianotti 2009</td>
<td>Major abdominal surgery for cancer</td>
<td>0.25 g/kg/day IV</td>
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<td>Overall complication rate [p=.65], infectious morbidity [p=.55], LOS [p=.90]</td>
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<td>Engel 2008</td>
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<td>0.5 g/kg/day IV</td>
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<td>CRP [p=.372], SOFA [p=.439], ICU LOS [p=.436]</td>
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<td>Martin 2009</td>
<td>Oesophageal resection</td>
<td>0.5 g/kg/day IV</td>
<td>10 days</td>
<td>Morbidity and mortality [p=.807]</td>
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and 13 level 2 studies and state “When parenteral nutrition is prescribed to critically ill patients, parenteral supplementation with glutamine, where available, is strongly recommended. There are insufficient data to generate recommendations for intravenous glutamine in critically ill patients receiving enteral nutrition.” It is worth noting that the largest of the four level 1 studies is in a mixed hospital and ICU population and was published in 1999. The other reported studies were all very small, less than 100 patients, with the exception of Dechelotte’s [3] trial that recruited 114 ICU patients but showed no decrease in mortality (although the infection rate was reduced). This trial was considered of low quality, but was multicentre in design.

The Canadian Critical Care guidelines committee [15] noted that in patients receiving PN, there was a large reduction in mortality, hospital LOS and a moderate reduction in infectious complications associated with the use of parenteral glutamine. The committee stated that given the similar signals on reduced mortality and infections from the majority of the studies and from various settings, the likelihood of the results being replicated in other settings is strong. The final recommendation was that the range of glutamine of 0.2-0.57 g/kg/day, would be reasonable.

The ESPEN guideline [16] concurs with the Canadian guidelines and states that 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). This recommendation is given a “Grade A” by this writing group. What represents an appropriate endpoint for a clinical trial of nutritional supplementation is the subject of considerable debate.

The SIGNET trial [17] randomized 502 critical care patients in a double blinded, factorial, controlled trial of parenteral glutamine (20.2 g/day) and/or selenium (500 μg/day) for up to seven days. Participants and setting were United Kingdom, National Health Service, level II and III (or combined) critical care units. Primary outcomes were participants with new infection(s) in the first 14 days after randomization and mortality.

Selenium supplementation did not significantly affect participants developing a new infection (OR=0.81, 95% CI 0.57 to 1.15), except for those who had received at least five days of supplementation (OR=0.53, 95% CI 0.30 to 0.93). There was no effect of glutamine on new infections (OR=1.07, 95% CI 0.75 to 1.53), including participants who received at least five days of trial nutrition (OR=0.99, 95% CI 0.56 to 1.75). Six month mortality was not significantly different for selenium (OR 0.89, 95% CI 0.62 to 1.29) or glutamine (OR 1.18, 95% CI 0.82 to 1.70) ([BMJ, 2011, in press]) [24].

The SIGNET trial represents a substantial increase in Randomized Control Trial (RCT) evidence. When these data are added to current meta-analyses for glutamine, the random effects risk ratio for mortality of 0.71 (95% CI 0.55 to 0.92, F = 0%) becomes 0.80 (95% CI 0.62 to 1.04, F = 23%) (Figure 1), and for participants with infections changes from a risk ratio of 0.76 (95% CI 0.62 to 0.93, F = 28%) to 0.81 (95% CI 0.67 to 0.98, F = 43%) (Figure 2).

As stated by many authors, mortality is the gold standard outcome for clinical trials, but large numbers of patients (2-2500 patients) are required to show a 10-15% absolute reduction, which may be relatively optimistic. Other end points include new infection as used by Beale et al. [2], SIGNET [17], Dechelotte et al. [3], and others. Nitrogen balance, insulin resistance, and substrate oxidation [18,19], antioxidant status, plasma lymphocyte subset number, gut permeability and nitrogen balance have all been examined [9,10]. However, the majority of these proposed biomarkers do not meet the National Institute of health (NIH) (1998) definition “a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses.

Figure 1. Updated Meta-analysis of Glutamine mortality with SIGNET data, RR 0.81 (95% CI 0.58 to 1.12)
to a therapeutic intervention” or have a poorly established relationship with patient centred outcomes.

The end point, “New infection” has a significant disadvantage in clinical critical care trial data analysis. Critical care admission carries a high mortality and is one of the main reasons for investigating nutritional support. However, an ICU mortality rate of 20-30% presents a considerable challenge when analysing outcome data from an RCT that has a primary end point of new infections. Early deaths reduce the possibility of developing a new infection after starting investigational nutritional supplement(s), but do not represent a good outcome in most cases! Despite this limitation, Dechelotte et al. [3], successfully showed a reduction in infections in a glutamine supplementation group of critical care patients (although 6 month mortality was higher in the treatment group). Mondello et al., [20] investigated the effect of TPN supplemented with glutamine 0.18 g/kg/day on the immune system in 36 anorectic patients. The end points of this study were serum levels of neopterin, IGF-1, and lymphocyte count at baseline, 10 days and 20 days. They demonstrated a significant increase in neopterin levels and lymphocyte count but no clinical benefits or patient centred outcome improvement.

Surgery
Luca Gianotti et al., [21] investigated whether perioperative intravenous glutamine supplementation affected surgical morbidity. They completed a randomized, multicentre trial in 428 subjects who were candidates for elective major gastrointestinal surgery for cancer. Patients received either an intravenous infusion of L-alanine-L-glutamine dipeptide [0.40 g/kg/day, equal to 0.25 g of free glutamine] (n=212) or no supplementation (n=216). Glutamine infusion began the day before the operation and continued postoperatively for 5 days. The study showed no difference in terms of complications, LOS, or infectious morbidity. However, these studies were performed upon well-nourished patients and there was no mention of the general management of these patients. A similar study conducted by Martin et al. on patients with oesophageal resection found no beneficial effects of glutamine [22].

Cardiac surgery provokes an intense inflammatory response due to surgical trauma, hypothermia, transfusion and extracorporeal circulation. Engel et al. [23] evaluated the role of "high dose" perioperative glutamine infusion on inflammatory T-cell cytokine expression, in 78 patients undergoing elective cardiac surgery, including cardiopulmonary bypass. The primary endpoint was the intracellular pro-inflammatory T-cell cytokine accumulation on the first postoperative day; secondary end points included CRP, SOFA scores, and ICU LOS. 31 Patients received glutamine, 27 patients received iso-nitrogenous nutritional solution, and 20 patients received 0.9% saline. Perioperative glutamine had no influence on the T-cell inflammatory response or SOFA scores and ICU LOS (Table 1).

Conclusion
Current guidelines support the use of parenteral glutamine in critical care and surgical practice. Contemporary research does not to support this recommendation. However, heterogeneity of the evidence is considerable.
References