Chapter 16
Potential for Glutamine Supplementation in Critically Ill Children

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Key Points

- Glutamine serves as a primary fuel for rapidly dividing cells and is used as a source of nitrogen to refill the citric acid cycle.
- During critical illness, the demand for glutamine may exceed that which can be mobilised from muscle stores.
- No glutamine supplementation recommendations exist for critically ill children.
- The beneficial effect of glutamine, in experimental or animal models of sepsis, appears to be dependent on the heat-shock protein-70 response.
- In order to understand the role of glutamine supplementation in critically ill children and premature infants, future studies should address previous methodological problems within clinical studies, with the aim of investigating interrelationships between glutamine supplementation, stress-induced heat-shock protein and the inflammatory response.

Keywords Glutamine • Enteral • Parenteral • Children • Infants • Premature • Supplementation

Abbreviations

ARDS	Acute respiratory distress syndrome
ATP	Adenosine triphosphate
ASPEN	American Society of Parenteral and Enteral Nutrition
CRP	C-reactive protein

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DAMPS	Damage-associated molecular patterns
DC	Dendritic cells
ESPEN	European Society of Parenteral and Enteral Nutrition
ELBW	Extremely low birth weight
HSF-1	Heat-shock factor 1
HSP	Heat-shock protein
HSP25	Heat-shock protein 25
HSP70	Heat-shock protein 70
HBP	Hexosamine biosynthetic pathway
IL	Interleukin
IEC	Intestinal epithelial cells
IV	Intravenously
IKK	IκB kinase
LOS	Length of stay
LPS	Lipopolysaccharide
mRNA	Messenger ribonucleic acid
MAPK	Mitogen-activated protein kinase pathway
MYD88	Myeloid differentiation primary response 88
NF-κB	Nuclear factor kappa B
PICU	Paediatric intensive care unit
PRISM	Paediatric risk of mortality
PAMPS	Pathogen-associated molecular patterns
PRR	Pattern recognition receptors
RCT	Randomised controlled trial
SIRS	Systemic inflammatory response syndrome
TLR	Toll-like receptors
TNF-α	Tumour necrosis factor alpha
UK	United Kingdom
US	United States of America
VLBW	Very low birth weight

Introduction

Amino acids trigger signalling cascades, which regulate various aspects of protein synthesis and energy metabolism serving as precursors for important substrates. Glutamine is the most abundant extracellular amino acid, with a concentration of between 0.6 and 0.7 mmol/L, which becomes conditionally essential during stress, injury or illness [1]. Conversely, glutamate is usually the most abundant intracellular amino acid with a concentration of 2–20 mmol/L depending on the cell type. Glutamate facilitates de novo amino acid transamination, donating an amino group or ammonia. In some organs, e.g. liver, and cells, e.g. astrocytes, glutamate and ammonia are combined by glutamine synthetase to form glutamine, which is then exported from the cell.

Organs and skeletal muscle are the main source of endogenous glutamine with high intracellular concentrations of 20–25 mmol/L glutamine. Blood glutamine levels reflect the balance between synthesis, release and consumption by all types of cells. Glutamine serves as a metabolic intermediate and precursor, providing carbon and nitrogen for the de novo synthesis of other amino acids, nucleic acids, fatty acids, nucleotides and proteins. During times of stress, skeletal muscle is an active net exporter of free glutamine. Glutamine provides fuel source for rapidly dividing cells such as those of the immune system and gastrointestinal tract, reticulocytes and fibroblasts; it is a precursor for nucleic

acid synthesis, hexosamines, nucleotides and precursors for arginine; glutathione and helping to maintain acid–base homeostasis in the kidney and renal regulation of inter-organ glutamine flow in metabolic acidosis [2]. In the acute phase of critical illness, glutamine is released in large amounts from muscle tissue. Glutamine's functions within the cell may be broadly categorised into four main categories: (1) nitrogen transport; (2) maintenance of the cellular redox state through glutathione; (3) a metabolic intermediate and (4) a source of energy.

Nutrition support, especially in children who have limited metabolic reserves, has traditionally been seen as a means to prevent malnutrition by providing substrate e.g. protein, fat and carbohydrate [3]. Recent advances in the field of nutrition research have resulted in the realisation that specific nutrients such as glutamine may be of benefit to critically ill patients with immune modulating effects altering the host response to stress. In critically ill adults, plasma glutamine levels decrease significantly, remaining low for up to 21 days, and are associated with increased morbidity and mortality [4]. Accordingly, the American Society of Parenteral and Enteral Nutrition (ASPEN)/European Society of Enteral and Parenteral Nutrition (ESPEN) recommend that 0.3–0.5 g/kg of glutamine is added to parenteral nutrition in critically ill adults [5]. However, no such recommendations exist for critically ill children. This is because much of the work considering the use of glutamine in critical illness has been completed in adults, with little data available from paediatric critical illness.

Paediatric Sepsis

There is a growing interest into how individual nutrients particularly glutamine could influence morbidity and mortality in critical illness. Globally, sepsis and septic shock remain a leading cause of mortality in adults and children. Mortality from severe sepsis in children is reported to be between 10.3 and 14 %, which is lower than the mortality rates reported in adults of between 27 and 54 %. Recently published data shows that amongst children admitted to a paediatric intensive care unit (PICU) 82 % had evidence of systemic inflammatory response syndrome (SIRS), with 23 % of these meeting the criteria for sepsis, of which 4 % had severe sepsis and 2 % had septic shock [6].

In the USA, paediatric sepsis costs nearly $2 billion per annum and in the UK the estimated total cost of adult care was between £7,000 and £28,000 per patient per admission. The cost of healthcare during acute disease does not account for hidden costs relating to post-discharge rehabilitation following severe sepsis, especially in children and the long-term impact on cognitive abilities, executive functioning and psycho/social difficulties experienced into adulthood [7].

The Inflammatory Response

Young infants and those with underlying medical conditions (e.g. neurodevelopmental delay, chronic lung disease and primary immunodeficiency) are at particular risk of bacterial blood stream infections due to immature mucosal barriers and immune system (including macrophages, neutrophils, immunoglobulin and complement).

Many bloodstream infections in children are caused by colonising pathogenic bacteria, which are present on the skin or mucosal surfaces such as the nasopharynx. Bloodstream infections can arise when there is disruption to the mucosal-epithelia barrier allowing bacterial adherence to occur. The endothelial mucosal layer acts as an early detection system for pathogen invasion, stimulating host defence mechanisms by recruiting leukocytes to the bloodstream entry site. From bloodstream infection to the development of sepsis there is an interplay between the invading organism and the host response; the systemic inflammatory response is the body's organised response to infection promoting the

activation of the complement system and innate immune response. These mechanisms are initiated through the recognition of pathogen-associated molecular patterns (PAMPs) by receptors sites on the cell surface such as toll-like receptors (TLR) known as pattern recognition receptors (PRRs). PRRs (such as TLRs) form the first line of cellular defence, recognising and transducing signals via ligand receptors, on the host cell surface, when they come into contact with PAMPs [8].

Pathogens and the subsequent host response results in tissue and cell damage, stimulating the release of intracellular proteins, such as heat-shock protein 70 (HSP70), known as alarmins, which aim to protect tissue or cells from further damage. As alarmins and PAMPs elicit similar innate and adaptive immune responses they are broadly known as damage-associated molecular patterns (DAMPs) acting to promote an inflammatory response to infection. Inflammation, as co-ordinated by the innate immune system, is a necessary response to infection promoting increased blood flow to the injured site. In the absence of an inflammatory response the host would succumb to overwhelming infection, however, an exaggerated host response results in septic shock and increased risk of mortality [8].

During the early phase of sepsis, DAMPs are released in large amounts, both from the invading organism and the host's damaged tissue promoting the release of inflammatory cytokines (TNF-α, IL-1, IL-6, IL-12, IL-8) in addition to free radicals and enzymes in large amounts. HSP70 acts as a DAMP and signal through CD14-TLR4 complex, eliciting rapid signal transduction via MYD88–IKK/NF-κB pathway, activating NF-κB and MAPK pathways and promoting the release pro-inflammatory mediators (TNF-a, IL-1β and IL-6). In addition, the NF-κB family is capable of regulating genes associated with the inflammatory response, immunity and apoptosis, further promoting the release of inflammatory mediators such as TNF-α [9].

Heat-Shock Protein 70 and Glutamine

The beneficial effects of glutamine in critical illness are postulated to be due to increased production of HSP70. The initial response to infection results in a rapid and ubiquitous use of glutamine by immune cells, for a myriad of cell functions including the release of extracellular HSP70 (both via necrotic cell death and passive cell release), promoting high plasma levels of HSP70 [10]. In vitro glutamine supplementation upregulates HSP70 release in lung macrophages and epithelial cells protecting against sepsis related injury. The beneficial effect of glutamine appears to be HSP70 dependent, since when a knockout septic mouse model was used HSP70 (-/-) no benefit was derived from glutamine supplementation. In experimentally induced ARDS, glutamine supplementation improved ATP levels reversing lactate accumulation, by restoring HSP70 levels. HSP70 deficiency led to a decline in lung tissue metabolism, lung injury and organ failure in a rat model of sepsis. In an experimental septic mouse model glutamine administration in combination with antimicrobial significantly decreased morbidity and mortality via HSP70-mediated effects on the inflammatory response [11]. It is thought that glutamine depletion may affect the efficacy and biological activity of heat-shock factor 1 (HSF-1), HSP70, and the half-life of HSP70 mRNA levels limiting functional efficacy and activity of HSP70 during times of stress.

Glutamine Is a Pro-chaperone

A large body of literature has hypothesised a relationship between HSP70 expression and glutamine's protection in both in vitro and in vivo settings [12]. Glutamine has been shown to induce heat shock protein expression and to attenuate lipopolysaccharide (LPS)-mediated cardiovascular dysfunction. Glutamine has also been shown to exert an effect on HSP70 production relative to the upstream

influence of glutamine on HSF-1 and HSE [13]. Glutamine is metabolised via the hexosamine biosynthetic pathway (HBP), which appears to be part of an early cellular protective response to stress and is a key substrate required for optimal activity of the HBP. It has been shown that a single dose of intravenous glutamine enhances phosphorylation of nuclear HSF-1, a vital step in its transcriptional activation, causing a rapid and significant increase in HSP25 and HSP70 expression in unstressed Sprague–Dawley rat [14]. In vitro models showed that glutamine supplementation attenuated lethal heat and oxidant injury and delayed spontaneous apoptosis in neutrophils, protecting activated T cells via glutathione upregulation [15]. Recently, by inducing HSP70 in an experimental model, glutamine was also shown to attenuate LPS-induced cardiomyocyte damage [16].

Marked attenuation of tissue metabolic dysfunction was observed after glutamine administration as measured by lung tissue adenosine 5′-triphosphate/adenosine 5′-diphosphate ratio and the oxidised form of nicotinamide adenine dinucleotide. Glutamine supplementation has been shown to enhance HSP70 release, protecting intestinal epithelial cells in a dose-dependent fashion against heat stress and oxidant injury, decreasing lung injury, and improving survival [14]. Recent results demonstrated for the first time that orally administered glutamine can enhance tissue HSP70 expression [4] and improve survival following lethal hyperthermia injury [17]. In cardiac disease, oral glutamine taken for 3 days prior to coronary artery bypass graft (with a final dose given 2 h prior to surgery), promoted HSP70 release decreasing myocardial ischaemic reperfusion injury and post-operative complications [18]. It was hypothesised that glutamine may act as an HSF-1 activator and increase the entire family of HSPs after stress or injury since in HSF-1 knockout cells, glutamine's ability to generate an HSP response is lost and the protection conferred by glutamine is also completely abrogated.

Glutamine Depletion During Critical Illness

During critical illness, glutamine is released into the system to provide fuel for the accelerated metabolic functions such as RNA synthesis and perhaps as a cell primer against further injury, making it a conditionally essential amino acid during periods of severe stress [4]. The benefit of intravenous compared to enteral administration is that glutamine is available for systemic circulation benefitting immune cells in addition to those within the gut. Glutamine given intravenously (IV) mimics endogenously produced glutamine as shown by its even uptake across the splanchnic area [19]. On the other hand, enteral glutamine is rapidly metabolised within the upper part of the small bowel (jejunum) leaving little available for the remainder of the bowel. Portal circulation studies also show that little glutamine makes it across the "first-pass elimination" to the liver and for subsequent systemic circulation. Enteral administration of glutamine is not as effective at restoring plasma glutamine levels to within normal range when compared to parenteral glutamine [20].

During times of stress there is a net export of glutamine from muscle stores, which become rapidly depleted. Protein flux and turnover in rapidly growing children is considerably higher than in adults and as such the need for amino acids such as glutamine is considerably more, suggesting a preferential use by rapidly dividing cells such as enterocytes and immune cells. Protein kinetic studies using leucine isotopes have shown glutamine supplementation attenuates protein breakdown. However, glutamine supplementation is not able to increase the rate of protein synthesis, but does exert a protein-sparing effect, in very-low-birth weight infants and in surgical neonates. Increased amino acid delivery in stressed, very-low-birth-weight infants, resulted in an increase in de novo glutamine synthesis [21].

Muscle glutamine depletion occurs within hours of severe illness by up to 72 %. Griffiths et al. have shown that in adults there is a precipitous drop in plasma glutamine levels by up to 58 % with the onset of catabolism, which can last for up to 21 days, increasing mortality [22]. Up to 14 g of free glutamine is reported as being depleted from skeletal muscle, in uncomplicated critically ill adults. Furthermore, during the first few days of acute illness, nutrition support is often suboptimal which is

of concern as up to 40 % of children are malnourished on admission to PICU [23]. Plasma glutamine levels of ≤0.43 mmol are associated with increased mortality and non-surviving adult septic patients lost up to 90 % of their skeletal muscle glutamine mass [24].

Although plasma concentrations do not accurately reflect the intracellular glutamine concentration, which varies dependent on the type of cell, is currently the best proxy for glutamine depletion [25]. Low plasma glutamine levels are not necessarily due to glutamine shortage, but can be reflective of intra- and extravascular fluid redistribution in parallel with disease severity, thereby explaining controversial results in adult studies [26, 27].

One study considering glutamine levels in critically ill children, found they have early significantly glutamine depletion (glutamine 0.31 mmol/L; ±SD 0.13; range 0.05–0.64) ($p<0.001$) compared to convalescent levels (0.40 mmol/L; ±SD 0.14; range 0.07–0.64) [28]. Glutamine levels were 52 % below the lower limit of the normal reference range (i.e. 0.6 mmol/L) during the acute phase of illness, whilst in the convalescent samples levels were 26 % below, suggesting depletion rather than on going consequence of fluid shifts [22]. Importantly, HSP70 levels in critically ill children [29] were higher (26.7 ng/mL; ±SD 79.95; range 0.09–600.5) [28] than those described in adult critical illness (median 1.75 ng/mL), assuming a more rapid protective response to stress among young people.

Glutamine Supplementation in Children

In children, the use of glutamine remains largely undefined with paucity of data regarding the benefits of glutamine as a pharmacological agent in paediatric critical illness. Conflicting results with respect to the benefits of glutamine supplementation was found in preterm infants [30] infants with gastrointestinal disease and surgery, burns and malnutrition [31]. Reasons for the lack of consistent results, following glutamine supplementation in children may be as a result of the different individual study designs, heterogeneity of the populations studied [32, 33], route of enteral administration chosen, e.g. enteral or IV, dosage g/kg given (Fig. 16.1) and duration of glutamine supplementation [34].

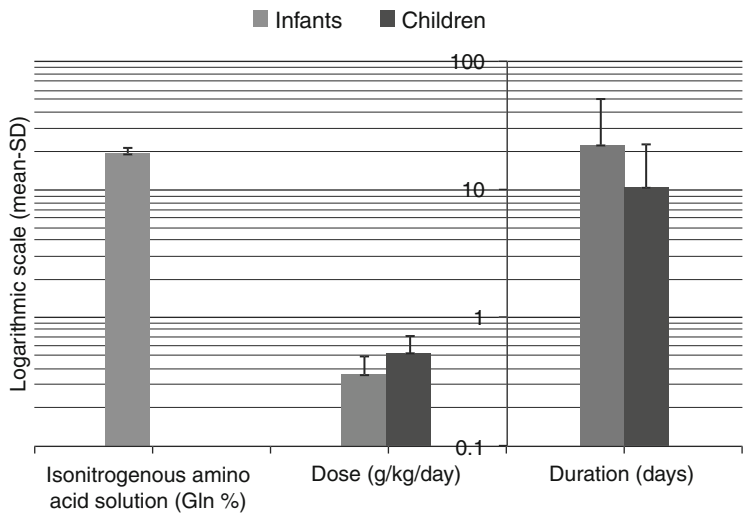

Fig. 16.1 Glutamine-dosing regimens in randomised control clinical studies in infants and children

However, beneficial effects of glutamine have been reported in children, which include decreased duration of acute diarrhoea, reduced severity of mucositis post-bone marrow transplant, decreased muscle catabolism in Duchene muscular dystrophy and improved growth in sickle cell anaemia [35].

Parenteral Supplementation of Glutamine in Preterm and Extremely Low-Birth Weight (ELBW) Infants

Glutamine is conditionally essential and safe for use in extremely low birth weight infants (ELBW) with supplementation increasing levels of plasma glutamine. In ELBW parental glutamine, given for a 2 weeks, was associated with fewer days on parenteral nutrition and length of stay in hospital, in addition to decreased hospital acquired infection episodes in premature infants [36]. Glutamine had an acute protein-sparing effect, as it suppressed leucine oxidation and protein breakdown, in parenterally fed very low birth weight infants [37], and was associated with lower whole-body protein breakdown and protein accretion in low birth weight (LBW) infants. Glutamine supplementation also improved hepatic tolerance in very low birth weight infants (VLBW) infants, suggesting a hepatoprotective effect. Although parenteral glutamine was well tolerated in ill preterm neonates, reducing the time to achieving enteral nutrition, nosocomial culture-positive sepsis or age at discharge was not reduced.

In a large multicentre, randomised clinical trial, the safety and efficacy of early parenteral nutrition (PN) supplemented with glutamine in decreasing the risk of death or late-onset sepsis were assessed in extremely low-birth weight infants. Although there were significant beneficial effects with glutamine supplementation, similar studies considering surgical neonates did not show any benefit [38]. Importantly, glutamine-enriched enteral nutrition in VLBW infants had neither beneficial nor detrimental effects on long-term cognitive, motor and behavioural outcomes of very preterm and/or VLBW children at school age, although visuomotor abilities were poorer in children that received glutamine [39].

Enteral Supplementation of Glutamine in Preterm and Extremely Low-Birth Weight (ELBW) Infants

In blinded randomised trials in VLBW infants, enteral glutamine supplementation did not decrease morbidity or mortality [40]. Preliminary results in VLBW suggest glutamine supplementation results in lower sepsis rates and a blunting of the inflammatory process [41]. Importantly, examining the effect of enteral glutamine on whole-body kinetics of glutamine in growing preterm infants, enterally administered glutamine was shown to be entirely metabolised in the gut and to have not a discernible effect on whole-body protein and nitrogen kinetics [42]. Similarly no differences between groups for plasma concentrations of glutamine, glucose or ammonia were shown during the glutamine enteral supplementation period [43].

Furthermore, the beneficial effects of glutamine supplementation especially in pre-term population may only be seen beyond the neonatal period. Follow-up studies of VLBW infants having received enteral preterm formula or breast milk supplemented with glutamine showed a lower risk of atopic dermatitis. However, there were no differences in incidence of bronchial hyperactivity, infections of upper respiratory, lower respiratory, urinary or gastrointestinal tracts [44], of intestinal microbiota, neurodevelopmental impairment or cerebral palsy. At 1 year of age intestinal (faecal) microbiota did not differ between the two groups. There was also no difference in Th1 and Th2 cytokine profiles either during the days of supplementation or at 1 year of age following in vitro whole-blood stimulation [45].

A Cochrane review concluded that glutamine supplementation confers no benefits to preterm infants and as such glutamine should not be an active research stream [30]. However, other groups argue the mode, timing, duration and type of analogue used in the randomised controlled trials included in the Cochrane review influenced the outcome measures. The use of glutamine in preterm infants has received considerable attention, with some results showing benefit with respect to infectious complications and time to full enteral feeds, and others showing no difference [46]. There are, however, inherent difficulties with trying to interpret the data from these studies as outlined below.

- Heterogeneous groups, e.g. sick versus relatively well versus surgical neonates.
- Isonitrogenous—many of the preterm studies compared the use of total parental nutrition enriched with glutamine to isonitrogenous control, the issue with this is that it potentially leads to suboptimal delivery of other essential amino acids, especially tyrosine and phenyl alanine.
- Time taken to get to goal rate—due to the delivery method some of the studies took up to 10 days to reach the goal rate of delivery, e.g. 0.3 g/kg.

Supplementation of Glutamine (Immunonutrition) in Critically Ill Children

Glutamine supplementation of 0.3–0.5 g/kg is recommended in critically ill adults [5], although no such recommendations exist for critically ill children. In critically ill children the amount of glutamine delivered enterally is often suboptimal providing only 28 % of the recommended adult intake [28], in addition to a low total protein intake of 0.88 g/kg (range 0.62–3.76 g/kg) [47]. Protein-rich feeds in critically ill children are reported to be of benefit as such protein intake should aim for the ASPEN recommendations [48].

In a multicentre randomised, double-blinded, comparative effectiveness trial, enteral zinc, selenium, glutamine and intravenous metoclopramide conferred no advantage in the immune-competent population of children requiring long-term intensive care compared with whey protein supplementation [49]. Further evaluation of these constituents' supplementation was thought to be warranted only in the immunocompromised long-term paediatric intensive care unit patient.

In another blinded, prospective, randomised, controlled clinical trial in critically ill children given an immune-enhancing formula supplemented with glutamine, nutritional indices and antioxidant catalysts showed a higher increasing trend but also higher osmolality, sodium and urea [50]. Similarly to the control group, gastrointestinal complications (diarrhoea and gastric distention) were the most frequently recorded in the immunonutrition group. Length of stay or mortality did not differ between groups, however there was a trend for fewer nosocomial infections in those receiving immunonutrition compared to conventional group. In another single-centre, randomised, blinded controlled trial in children with septic shock who received 5 days of early enteral feeding of immunonutrition, there was a decrease in pro-inflammatory cytokine IL-6 [32]. The differences in cytokines were independently correlated with PRISM, however, mortality and other paediatric intensive care unit outcome endpoints did not differ between the two groups. In two randomised studies in trauma patients (adults and children) there were no significant differences in mortality, LOS, lung infection or immunologic or biochemical parameters between the glutamine supplemented groups (enteral or parenteral) and controls [51] (Table 16.1).

Conclusions

Studies in critically ill children and in premature neonates remain inconsistent, partly because of the different effects of enteral and parenteral glutamine supplementation, different dosing and timing regimens, co-administered multi-immune-enhancing constituents, heterogeneity and pathways

Table 16.1 Outcome effect of glutamine in clinical randomised control studies in infants and children

Population	Number of studies/ patients	Mortality	Hospital-acquired infections	Length of stay	Inflammation
Extremely low-birth weight infants	1/1,433	No effect	No effect	No effect	NA
Premature or very-low-birth weight infants	12/1,359	No effect (8 studies)	3 studies (25 %) showed reduced infections/ hospital-acquired sepsis	1 (8 %) study showed reduced los	Higher lymphocyte count, blunted the rise in HLA-DR + and CD16/CD56 subsets (1 study each)
Post-surgery infants	2/215	No effect (1 study)	No effect	No effect	No effect
Ill preterm neonates, critically ill infants	2/44	No effect	No effect	No effect	No effect
Critically ill children	4/421	No effect	2 studies (50 %) showed reduced infections	No effect	Decreased IL-6, or IL-6, or Increased NB (1 study)

triggered in different stress states. Especially, findings of a number of RCTs are rather diverse and it remains unclear whether this variability is a consequence of inadequacy of innate immune heat-shock protein-response to stress or of true heterogeneity across individual trials or of the low power of many of these trials and the resulting chance effects. Since these studies are scarce and insufficient to allow safe recommendations to be made regarding immune-competent infants and children, additional large-scale, high-quality RCTs are needed.

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Conflict of Interests The authors declare that there have no conflicts of interests.

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