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ORIGINAL ARTICLE

Plasma glutamine deficiency is associated with multiple organ failure in critically ill children

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Abstract A low plasma glutamine concentration (<420 μmol/L) is an independent risk factor for mortality in critically ill adult patients. Glutamine metabolism in children is less well characterized. However, pediatric ICU (PICU) mortality is low and, therefore, mortality is difficult to use as an endpoint. Here we evaluated if plasma glutamine concentration at admission to the PICU, relates to the development of multiple organ failure, using pediatric logistic organ dysfunction score (PELOD)-score. In this observational study, consecutive critically ill children ($n = 149$) admitted to the PICU of a tertiary university hospital as well as a reference group of healthy children ($n = 60$) were included. Plasma glutamine concentration and the PELOD were determined at admission for all patients and at day 5 for those patients still in the PICU. Plasma glutamine concentration at admission was low in the PICU patients as compared to controls ($p = 0.00002$) and patients with a low plasma glutamine concentration had more organ failure as compared to patients with higher plasma glutamine concentration ($p = 0.0001$). Plasma glutamine concentration normalized in patients staying >5 days in the PICU. Plasma glutamine depletion was present in 40 % of patients at PICU admission and it was associated with the development of multiple organ failure. Furthermore, the majority of the critically ill children normalized their plasma glutamine concentration within 5 days, which is different from adult ICU patients. The study suggests that an initial plasma glutamine deficiency is associated with multiple organ failure in critically ill children.

Keywords Glutamine · Intensive care · Morbidity/mortality · Multiorgan system failure

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Introduction

A low plasma glutamine concentration (<420 μmol/L) at admission to the ICU is an independent predictive factor for mortality in adult patients (Oudemans-van Straaten et al. 2001; Rodas et al. 2012). In addition, an increased mortality is also observed in patients with high plasma glutamine (>930 μmol/L), which is seen in patients with acute fulminant liver failure (Clemmesen et al. 2000). Thus, the mortality curve in relation to admission plasma glutamine concentration seems to have a U-shape (Rodas et al. 2012).

Availability of glutamine is thought to be a critical factor during critically illness, such as sepsis, and following major trauma or surgery, since the availability of glutamine

is crucial for rapidly dividing cells, such as white blood cells including lymphocytes but also enterocytes (van der Hulst et al. 1993; Wernerman 2008a, b). Glutamine is also important for the synthesis of the amino acid citrulline which is exclusively synthesized in the gut and is suggested to be a useful indicator of enteral tolerance in children with short bowel syndrome (Rhoads et al. 2005). Furthermore, glutamine is a precursor for glutathione, (Flaring et al. 2003a) which is the quantitatively most important scavenger of reactive oxygen species (ROS), and produced at increasing rates during critical illness (Alonso de Vega et al. 2002; Flaring et al. 2003b, 2005). Plasma glutamine concentration can be restored to normal levels by supplementing the patients with intravenous glutamine (Tjader et al. 2004). However, glutamine kinetics in these patients is not sufficiently characterized and the underlying mechanisms behind glutamine depletion are not well understood.

Glutamine metabolism in critically ill children is less well characterized. There is no information available whether plasma glutamine is a predictor for mortality and morbidity as in adults.

Healthy neonates show similar plasma glutamine concentrations as adults, although the scatter is larger (Hammarqvist et al. 2010; Oladipo et al. 2011). Critically ill neonates on the other hand show low plasma glutamine concentrations (Becker et al. 2000; Oladipo et al. 2011). However, there is no information about plasma glutamine concentration in critically ill children besides the neonatal period.

Mortality is low in critically ill children as compared to critically ill adult patients and, therefore, very large studies are needed when mortality is used as an endpoint. The pediatric logistic organ dysfunction score (PELOD) is developed as a marker of the degree of organ dysfunction comparable with sequential organ dysfunction assessment score (SOFA) for adults (Leteurtre et al. 2003; Vincent et al. 1996). The PELOD-score is shown to correlate with mortality and can be used as a surrogate marker of mortality.

The primary aim of this study was to evaluate if plasma glutamine concentration within 48 h of PICU admission, relates to the development of multiple organ failure. The secondary aim was to investigate the development of plasma glutamine levels in critically ill patients and relate this to changes in organ failure. For this, the patients still in the PICU at day 5 were sampled again. Plasma glutamine concentration was also determined in a group of healthy pediatric patients undergoing minor surgical procedures under general anaesthesia to obtain age-related reference values.

Materials and methods

The study protocol was approved by the Regional Ethical Review Board in Stockholm. Patients and their parents were informed orally and in writing before obtaining their informed consent, both orally and in writing.

Consecutive patients ($n = 149$) admitted to the PICU at Astrid Lindgren Children's Hospital at Karolinska University Hospital Stockholm were included during the period September 2007–June 2008. The PICU-unit is a tertiary centre in Sweden, including ECMO with mixed surgical, (including neurosurgical and thoracic but without cardiac surgery) and medical patients.

Inclusion criteria were an expected PICU-stay >24 h, informed consent and sampling within 48 h after admittance. Exclusion criteria were absence of informed consent at 48 h after admittance, failure of sampling or age >18 years.

Sampling of blood for plasma amino acid determination and multiple organ failure scoring according to the PELOD-score was performed within 48 h after admittance according to the protocol. However, it was possible to perform sampling within 24 h in all patients and, therefore, the patients received only hypocaloric glucose and minimal enteral feeding when sampling was done. For patients still remaining in the PICU, a second sampling for plasma glutamine and determination of PELOD-score was performed at day 5. At that time point the patients received continuous enteral and/or parenteral feeding. Plasma glutamine concentration was also analyzed in a reference group of healthy children ($n = 60$) undergoing minor surgery. The reference group was recruited into 4 different age cohorts (<1, 1–5, 6–12, 13–18 years).

The nutritional routine in the PICU at the study period was hypocaloric glucose (5 mg/kg/min) during the first day, and when possible combined with minimal enteral feeding. 96 patients received glucose infusion only. The remaining 53 patients received minimal enteral feeding, in addition to glucose infusion. From day 2 until day 4, parenteral nutrition was instituted at a basal level, according to the patient's estimated energy expenditure, ensuring a protein- and glucose supply of 1.5 and 10 g/kg/day, respectively, for newborns and infants resulting in an energy supply of approximately 60 kcal/kg/day. Children >1 year were given a protein- and glucose supply of 1–1.5 and 3–8 g/kg/day depending on age resulting in an energy supply of approximately 25–50 kcal/kg/day. In parallel, enteral nutrition was increased if possible. From day 5, the nutritional support was increased if patients' stress response subsided ensuring a protein- and glucose supply of 2.5–3.0 and 13 g/kg/day, respectively, for patients up to 10 kg, resulting in an energy supply of approximately 90 kcal/kg/day. For older children, less nutritional support was given with a protein and glucose intake of approximately 1.5–2.0 and 5.0–7.0 g/kg/day depending on age, resulting in an energy supply of 30–70 kcal/kg/day. If the stress response did not resolve, limited nutritional support was given to the patients guided

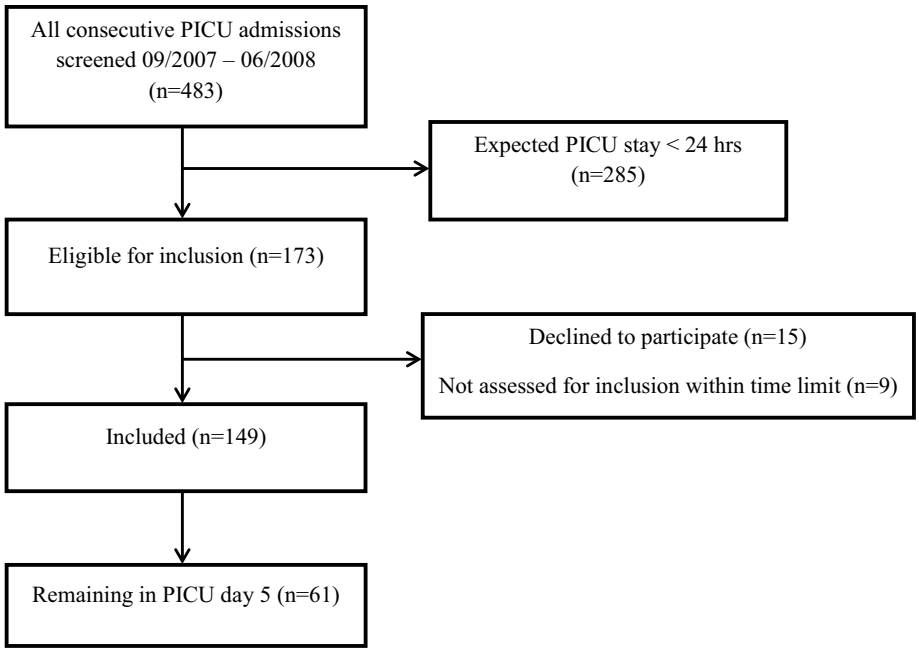

Fig. 1 A consort diagram illustrating the screening of all the admitted patients during the study period

by indirect calorimetry and C-reactive protein concentration (CRP), according to the nutritional delivery from day 2 to 4. At day 5 11/61 patients received only parenteral nutrition, 8/61 full enteral nutrition and 42/61 were given a combination of parenteral and enteral nutrition. The parenteral nutrition did not contain glutamine and no patients received glutamine supplementation. The enteral nutrition contained glutamine but was not enriched with glutamine.

The Pediatric Logistic Organ Dysfunction Score including six organ dysfunctions and 12 variables (PELOD) was used for multiorgan failure scoring and predicting mortality rate (Leteurtre et al. 2003).

Blood samples for the analysis of plasma glutamine concentration as well as the other amino acids were taken from arterial or central venous lines, taken in heparinised tubes, kept on ice and centrifuged within 30 min (2,000×*g*, 10 min. 4 °C). The plasma samples were stored at −80 °C pending analysis using HPLC. The analyses were performed by automated on-line HPLC after pre-column derivatization using *o*-phthalaldehyde/3-mercaptopropionic acid. Norvaline was used as internal standard (Vesali et al. 2002).

Statistics

The Kolmogorov–Smirnov test was used to assess normality. Data normally distributed are given as mean ± SD. Nonparametric data are given as median (quartiles). Student's *t* test, Wilson matched pair test, ANOVA followed by Tukey post hoc test, Fisher's exact test and Pearson's linear regression analysis were used when applicable. (Statistica Statsoft, Tulsa, Okla, USA).

Results

Out of 483 consecutive screened admissions, 173 patients were eligible for participation, and 149 patients were included in the study (Fig. 1). Out of the 149 included patients, 62 patients remained in the PICU on day 5 and were then reassessed for plasma glutamine and multiorgan failure scoring. The characteristics of the patients are given in Table 1.

The plasma glutamine concentrations of the reference group are given in Fig. 2. There was no relation between plasma glutamine concentration and age cohort or gender. The concentrations of the other amino acids according to age cohorts for patients at admission, at day 5 and for the reference group are provided as online supplemental Tables 1, 2 and 3, respectively. The results from the reference group demonstrated that a plasma glutamine concentration of 420 μmol/L was at 2 SD below the mean. Therefore, 420 μmol/L was used as the cutoff concentration for plasma glutamine when the patients were dichotomised for low plasma glutamine concentration or not.

The plasma glutamine concentration was low at PICU admittance as compared with the reference group ($p = 0.00002$). Patients with a plasma glutamine concentration of <420 μmol/L at admittance ($n = 61$) had a higher median PELOD-score and, therefore, more organ failures, as compared to patients with a plasma glutamine concentration of >420 μmol/L ($n = 88$); 20 (11–22) versus 11.0 (10–20), respectively ($p < 0.0001$) (Fig. 3). In addition, there was a tendency for an increased risk of staying >5 days in the PICU for the patients with a low glutamine value as compared to patients with plasma glutamine concentration

Table 1 Patient characteristics

	Admission ($n = 149$)	Day 5 ($n = 61$)
Male/female	90/59 (60/40 %)	$n = 37/24$ (61/39 %)
Age (years)		
0–1	$n = 65$ (44 %)	$n = 26$ (43 %)
1–5	$n = 54$ (36 %)	$n = 23$ (38 %)
6–12	$n = 19$ (13 %)	$n = 10$ (16 %)
13–18	$n = 11$ (7 %)	$n = 2$ (3 %)
PELOD-score	12 (10–21)	11 (10–12)
Mechanical ventilation	$n = 95$ (64 %)	$n = 52$ (85 %)
ECMO	$n = 19$ (13 %)	$n = 15$ (25 %)
CRRT	$n = 8$ (5 %)	$n = 6$ (10 %)
LOS PICU (median, IQR)	4.9 (2.1, 8.0) days	8.8 (6.6, 17.9)
LOS (median, IQR)	35.4 (12.0, 34.0) days	29 (21, 58) days
Mortality PICU	$n = 6$ (4 %)	$n = 3$ (5 %)
Mortality 6 months	$n = 9$ (6 %)	$n = 6$ (10 %)
PICU stay <24 h	$n = 6$ (4 %)	

Characteristics of the patients at admission and at day 5

ECMO extracorporeal membrane oxygenation, *CRRT* continuous renal replacement therapy, *LOS* length of stay, *IQR* inter quartile range

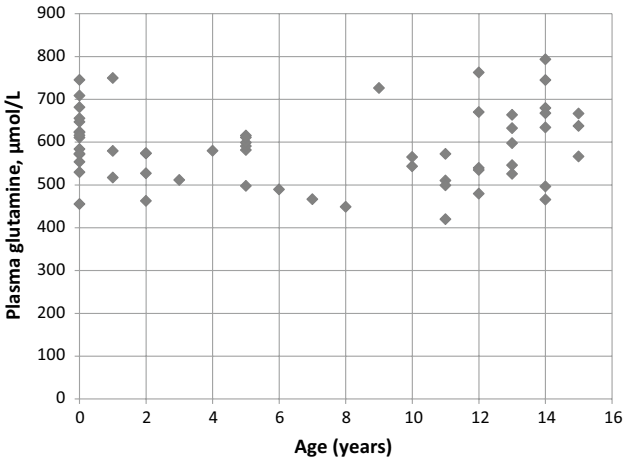

Fig. 2 Relationship between the plasma glutamine concentration and age in the control group, consisted of healthy children ($n = 60$) undergoing minor surgery

>420 µmol/L ($p = 0.07$). The admission plasma glutamine concentration for patients still in the PICU on day 5 as well as the plasma glutamine concentration on day 5 showed statistical correlations to the PELOD-score; $r = 0.43$ at admission and $r = 0.27$ at day 5 ($p < 0.05$). The admission plasma glutamine concentration was not related to age (Fig. 4).

Plasma glutamine concentration in the patients staying >5 days in the PICU, was higher at day 5 as compared to

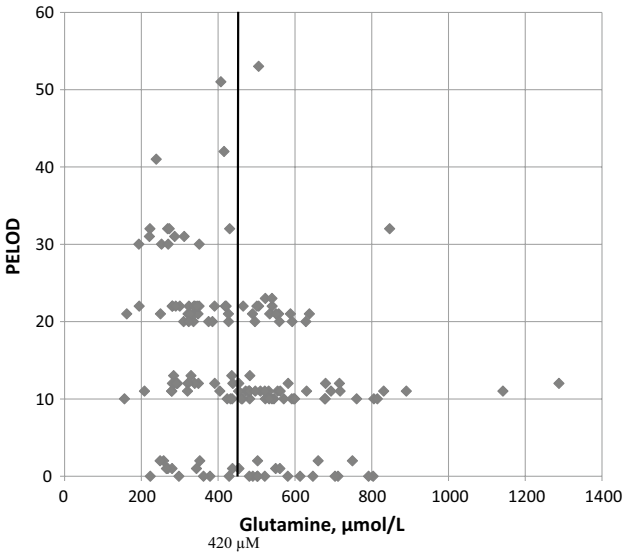

Fig. 3 Relationship between pediatric logistic organ dysfunction score (PELOD) and glutamine concentration at admission of consecutive patients ($n = 149$) admitted to the pediatric ICU. PELOD score significantly higher among patients with a plasma glutamine concentration >420 µmol/L. $p < 00001$. Mann–Whitney test

admission; 528 ± 167 and 464 ± 183 µmol/L, respectively ($p = 0.03$). Indeed at day 5 there was no difference in mean plasma glutamine concentration between the patients and the reference group; 528 ± 167 and 588 ± 86 µmol/L, respectively ($p = 0.10$). The whole group of patients staying >5 days in the PICU improved in PELOD-score ($p < 0.0001$) and the majority of these patients increased in plasma glutamine concentration as compared to admission, ($n = 46/61$). However, a subgroup of these patients (15/61) showed a decrease in glutamine concentration. For this subgroup of patients, the decrease was associated with a non-improvement in PELOD-score during this period as compared to the group of patients with an increase in plasma glutamine concentration ($p = 0.04$).

All-cause 6-month mortality rate was 6.0 %, and the PICU mortality was 4.0 % in all the included patients. This low mortality rate makes comparisons between groups not meaningful (Table 1).

The plasma total amino acid concentration was low at admission but was normalized at day 5; 1,706 (1,307–2,215) versus 2,411 (1,962–2,917) µmol/L, respectively ($p < 0.0001$). The results of the reference group were used to calculate the total amino acid concentration at −2 SD as a cutoff concentration. Hence, the patients were dichotomised for low plasma total amino acid concentration as in the calculation of low plasma glutamine concentration. The cutoff concentration was 1,509 µmol/L. Patients with a plasma total amino acid concentration of <1,509 µmol/L at admittance ($n = 51$) had higher PELOD-score as compared

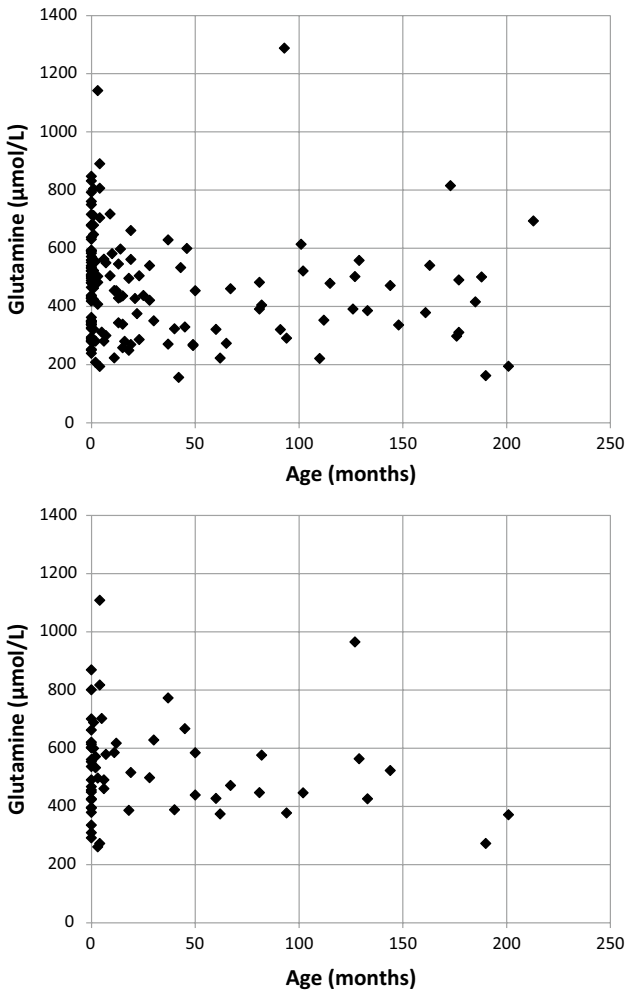

Fig. 4 Relationship between plasma glutamine concentration and age at admission to the pediatric ICU (on *top*) and at day 5 (*below*). No significant difference is seen between different ages

to patients with a plasma total amino acid concentration of >1,509 µmol/L ($n = 98$); 16.5 (10.2–22) versus 11.0 (10.0–21), respectively ($p = 0.01$). When the same calculations are performed with plasma total amino acids minus plasma glutamine a cutoff concentration of 1,037 µmol/L was seen. No difference in PELOD-score was seen between patients with a plasma total amino acid concentration minus plasma glutamine of <1,037 µmol/L as compared with patients >1,037 µmol/L ($p = 0.07$). The concentrations of all the amino acids are given in Table 2.

Discussion

To the best of our knowledge, this is the first study that longitudinally characterizes plasma glutamine concentration in relation to the severity of illness in pediatric intensive care patients from neonates up to 18 years of age. The primary aim of the study was to investigate if a low plasma glutamine concentration is related to organ failure. The results showed that a low plasma glutamine concentration (<420 µmol/L) was associated with the development of multiple organ failure (higher PELOD-score in patients with low plasma glutamine concentration) and a correlation was also seen between plasma glutamine concentration and the degree of multiple organ failure as reflected by the PELOD-score. In addition, there was a tendency for a longer stay in the PICU seen in patients with low plasma glutamine ($p = 0.07$).

Why use a cutoff point of plasma glutamine concentration at <420 µmol/L? This lower limit has been used in two adult ICU studies where it was shown to be an independent risk factor for ICU mortality (Oudemans-van Straaten et al. 2001; Rodas et al. 2012). In the study by Rodas et al. (2012) ROC analysis showed that this cutoff point was optimal. Furthermore, in the reference group of the present study, mean −2 SD was 420 µmol/L. It must be underlined that the background for all data regarding this cutoff point is empirical.

In general, the plasma glutamine concentration at admission to the PICU was low as compared to healthy children. This confirms earlier reports in which plasma glutamine concentration in newborns has been investigated. The present study adds information up to 18 years of age. In the previous adult studies, 30–40 % of the included patients had a low plasma glutamine concentration (<420 µmol/L) which is in accord with the results of the present study in which 41 % of the pediatric subjects had low glutamine values at admission. (Oudemans-van Straaten et al. 2001; Rodas et al. 2012). In the present study, only a few patients showed high plasma glutamine concentration. Plasma glutamine depletion seems to occur in critically illness to similar extent regardless of age. The reference group in our study had a similar plasma glutamine concentration as reported in healthy adults (Gamrin et al. 1996). In addition, also the pediatric critically ill patients showed that plasma glutamine concentration does not change with age which is comparable with data in adult critically ill patients (Fig. 4). There is a tendency for adolescent patients to have a somewhat lower plasma glutamine concentration (Fig. 4), which might be due to a higher protein requirement for this group of patients (Verbruggen et al. 2011). An original finding of the present study is that most critically ill children normalize their plasma glutamine concentration within 5 days, as opposed to adult ICU patients, where glutamine concentration is reported to stay low if not supplemented with intravenous glutamine (Tjader et al. 2004; Vesali et al. 2002). Indeed, at day 5 there was no difference between the patients and the reference group. However, there was a subgroup of individuals in whom plasma glutamine concentration was unaltered or decreased between admission and day

Table 2 Plasma amino acid concentration in patients and a reference group consisting of healthy children undergoing elective surgery

Amino acid	Reference group ($n = 60$)	Patients at admission ($n = 149$)	Patients at day 5 ($n = 61$)	Statistical difference
Glutamate	58 (47–74)	45 (25–70)	102 (61–140)	a c
Asparagine	40 (35–44)	31 (24–42)	34(27–45)	b
Serine	120 (102–137)	88 (61–123)	140 (109–191)	a
Glutamine	580 (526–645)	446 (323–556)	507 (424–610)	a b
Histidine	192 (150–223)	58 (46–72)	76 (55–92)	b c
Glycine	82 (72–88)	201 (136–257)	247 (207–318)	a b c
Threonine	93 (82–120)	80 (47–114)	150 (113–259)	a c
Citrulline		11 (7–15)	13 (10–18)	a
Arginine	67 (55–79)	40 (25–60)	70 (48–98)	a b
Alanine	234 (188–305)	163 (114–244)	257 (181–318)	a
Taurine	40 (34–46)	28 (16–42)	24 (12–43)	ns
Tyrosine	22 (18–27)	11 (7–17)	14 (10–19)	b
Valine	176 (157–199)	137 (102–181)	176 (143–238)	a b
Methionine	17 (15–19)	18 (13–25)	25 (20–32)	ns
Tryptophan	28 (25–33)	24 (16–31)	32 (24–39)	a
Phenylalanine	41 (37–44)	50 (42–66)	64 (50–85)	a b c
Isoleucine	45 (41–53)	29 (20–42)	44 (35–63)	ns
Ornithine	31 (25–39)	33 (23–48)	49 (39–69)	a c
Leucine	89 (78–104)	66 (50–99)	106 (85–124)	ns
Lysine	125 (108–141)	108 (75–155)	165 (132–223)	a c
BCAA	310 (278–358)	238 (176–314)	329 (279–434)	a
Total	2,095 (1,926–2,347)	1,706 (1,307–2,215)	2,411 (1,962–4,293)	a

Values (in μmol/L) are given as median and interquartile range. BCAA: branched chained amino acids. Online alphabets denote statistical significant difference (<0.05) using one-way ANOVA followed by Turkey's post hoc test; (a) between the patients at admission and at day 5 (b) between the patients at admission and the reference group (c) between the patients at day 5 and the reference group. ns denotes not significant

5. These patients had a less rapid recovery from multiple organ failure as compared to patients where the plasma glutamine concentration increased.

Most neonatal and pediatric studies have not shown conclusive results from glutamine supplementation, despite evidence from animal data and adult ICU studies where glutamine supplementation have resulted in preservation of the gut mucosal barrier, less infectious complications and also reduced mortality (Dechelotte et al. 2006; Goeters et al. 2002; Houdijk and van Leeuwen 2000; van der Hulst et al. 1993; Ziegler et al. 1992). Studies investigating possible outcome benefits of parenteral glutamine supplementation in very low birth weight-, low birth weight- and newborns after major surgery have failed to show a beneficial effect (Albers et al. 2005; Vaughn et al. 2003). In none of these studies an increased survival rate or a reduced onset of sepsis was seen. Unfortunately, the plasma glutamine concentration was not measured in any of these studies, which makes interpretation of the results difficult.

Glutamine supplementation to ICU patients has been controversial for many years. The Scandinavian glutamine trial showed a reduced ICU mortality in patients supplemented with intravenous glutamine, but the positive effect was not sustained after the patients were discharged from the ICU (Wernerman et al. 2011). Recently, however, glutamine supplementation with very large doses to critically ill adult patients with multiple organ failures was associated with harm (Heyland et al. 2013). It may still be possible that glutamine supplementation to glutamine-depleted individuals will result in more favorable outcomes and, therefore, interventional studies should focus on depleted individuals. However, it remains to be investigated when to start supplementation and how to identify patients with persistent glutamine depletion.

A high plasma glutamine concentration can also be associated with poor outcome. A high glutamine concentration is typically seen in patients suffering from severe liver failure (Clemmesen et al. 2000; Rodas et al. 2012; Ytrebo et al. 2006). In addition, plasma glutamine concentration has been shown to be higher in children who died with malaria as compared to those that survived (Planche et al. 2002). From the present study, a plasma glutamine concentration at mean +2 SD of 760 μmol/L was obtained from the reference group as a high cutoff value. Only a few patients (10/149) had a plasma glutamine concentration above 760 μmol/L. The median PELOD-score for these patients

was 10.5. One of these patients died. Because of the limited number of patients showing the high plasma glutamine concentration, it was not possible to make any conclusion regarding either morbidity or mortality.

Glutamine is related to the other amino acids and must be put into that perspective. In the present study, the plasma total amino acid concentration showed a similar pattern as glutamine but the total amino acid minus glutamine did not. The plasma total amino acid concentration was low at admission and normalized at day 5. Patients with a low plasma total amino acid concentration showed a higher PELOD-score as did the patients with low plasma glutamine concentration. However, the difference was less pronounced and less significant as compared with patients who showed low plasma glutamine concentration and the correlation at admission between the absolute values of the plasma total amino acids and plasma glutamine was low ($R^2 = 0.02$). In addition, there was no difference in PELOD-score between patients with low total plasma amino acid concentration minus the plasma glutamine concentration as compared to patients with normal and high total plasma amino acid concentration minus the plasma glutamine concentration. These results supports that the large contribution by glutamine to the plasma total amino acid concentration, approximately 25 %, might have influenced that plasma total amino acid concentration is associated with higher PELOD-score.

The strengths of the present study are that the results are based upon consecutive patients and that a reference group of healthy children in cohorts from newborns to the age up to 18 years was included. The latter adds new information on the age distribution as well as being a reference group. Furthermore, it is the first study presenting temporal results of plasma glutamine concentration in relation to the development of multiple organ failure in pediatric patients.

The limitation of the present study is the observational design, which means that the results only represent the patients investigated. We included 149 consecutive patients and the dropouts including the parental refuse rate was low ($n = 15$) and patients not assessed within time limited ($n = 9$). The majority of the patients were <3 years, especially newborns/infants. This is typical for Scandinavian PICU: s, where approximately >70 % of the patients are <3 years of age. This limits the extrapolation of the results. However, the plasma glutamine concentration was not age dependent. The question is to what extent can our results be generalized? Our PICU is mixed surgical (including thoracic but without major cardiac surgery) and medical. Since the outcome of our patients is similar to other PICU: s, the results should be possible to extrapolate.

In conclusion, this study shows that (1) plasma glutamine depletion at PICU admission is associated with the severity of multiple organ failure as compared to patients with normal plasma glutamine and (2) that critically ill children in general normalize plasma glutamine concentration within 5 days in contrast to adults. A remaining question is, should glutamine supplementation be given to PICU patients? According to our results, glutamine normalizes spontaneously in the majority of the patients. However, in the subgroup of patients who did not increase their glutamine concentration over time, a less favorable development of organ failure was seen. The possible benefit of supplementing this group of patients with glutamine needs to be investigated in future studies.

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Conflict of interest Nothing to disclose.

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