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The role of intravenous glutamine administration in critical care patients with acute kidney injury: a narrative review

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Abstract

The kidneys are complex organs responsible for waste removal and various regulatory functions. Critically ill patients often experience acute kidney injury (AKI). Although renal replacement therapy is used to manage AKI, nutritional therapy is crucial. Glutamine, an amino acid involved in cellular functions, has potential benefits when administered intravenously to critically ill patients. This administration is associated with reduced mortality rates, infectious complications, and hospitalization duration. However, its use in patients with AKI remains controversial. Glutamine is used by various organs, including the kidneys, and its metabolism affects several important pathways. Intravenous glutamine supplementation at specific doses can improve blood marker levels and restore plasma glutamine concentrations. Moreover, this supplementation reduces infections, enhances immune responses, decreases disease severity scores, and reduces complications in critically ill patients. However, caution is advised in patients with multiple organ failure, particularly AKI, as high doses of glutamine may increase mortality rates. Hyperglutaminemia can have adverse effects. Monitoring and appropriate dosing can help to mitigate these risks. Kidneys rely on glutamine for various essential functions. Thus, the use of intravenous glutamine in critically ill patients with AKI remains controversial. Despite its potential benefits in terms of infection reduction, immunomodulation, and improved outcomes, careful consideration of the patient's condition, dosage, and treatment duration is necessary. Further research is needed to establish optimal guidelines for glutamine administration in this patient population.

Keywords: Acute kidney injury, Critical illness, Glutamine, Parenteral nutrition

Introduction

The kidneys are second only to the heart in energy and oxygen consumption and require abundant healthy mitochondria for proper function.[1,2] Thus, the kidneys are easily damaged by ischemia or exposure to nephrotoxic substances.[3]

Acute kidney injury (AKI) is defined as a serum creatinine increase of >0.3 mg/dL in <48 hours, a serum creatinine elevation exceeding 1.5 times the normal limit within 7 days, or a urine production <0.5 mL/kg per hour for 6 hours.[4] From an epidemiological perspective, Southeast Asia ranks first in the incidence rate of acute kidney disorders worldwide (31%).[5] The overall incidence of AKI in intensive care units (ICUs) in Indonesia is 43%.[6]

The treatment of AKI includes blood pressure regulation and fluid and electrolyte maintenance and renal replacement therapy (RRT), especially in critically ill patients.[7] Different modalities of renal support, such as continuous renal replacement therapy (CRRT), intermittent hemodialysis (IHD), and prolonged intermittent renal replacement therapy, can be used to treat critically ill patients with AKI.[8]

Critical illness is the life-threatening failure of 1 or more organs requiring intensive care. AKI is the most common complication in patients with critical illness.[9] Critically ill patients may experience energy intake and usage disturbances due to systemic inflammatory responses and impaired organ function.[10] In these cases, nutrition supplementation is an essential supportive care measure.[11]

Glutamine is the most prevalent and valuable amino acid used in metabolic processes in the body.[12] Glutamine comprises as much as 20% and 60% of the free amino acids in plasma and body tissues, respectively, with an estimated endogenous production of up to 65–85 g/d and a daily glutamine intake of as much as 10 g (Fig. 1).[13] Glutamine plays a role in the body's metabolic processes, encompassing the facilitation of nitrogen exchange between organs via ammonia transport within tissues; maintenance of optimal body pH levels; active involvement in nucleotide synthesis (including purines and pyrimidines); and facilitation of NADPH synthesis, antioxidant synthesis, and other biosynthetic pathways involved in maintaining cellular integrity and function.[14]

Glutamine can be synthesized de novo as a product of protein hydrolysis (a nonessential amino acid).[15] Critically ill patients receiving parenteral glutamine nutrition show a significant reduction in mortality rates, infection complication rates, and duration of hospitalization.[16] Thus, critically ill patients may benefit from glutamine through its effects to reduce infectious complications, hospitalization time, and ICU treatment duration.[17] However, the use of high

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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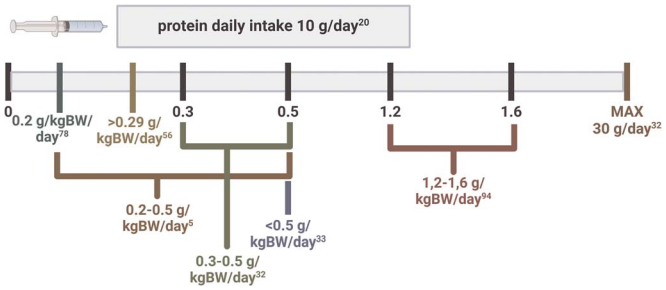

Figure 1. Dosage for intravenous glutamine administration. Image created using BioRender.com. Different intravenous glutamine dosage recommendations across different research findings with positive outcomes on the kidneys.

doses of intravenous glutamine in critically ill patients with AKI has been associated with potential risks.

Therefore, the use of intravenous glutamine in patients with AKI remains controversial, despite the long-standing recommendation of glutamine as routine parenteral nutrition for critically ill patients. This article aimed to summarize the risks and benefits of intravenous glutamine administration in critically ill patients with AKI to provide future clinical considerations.

Glutamine

Glutamine is an L-α amino acid with concentrations 10–100 times higher than other amino acids.[18] The 2 amino groups, namely, an α-amino group and a hydrolyzable amide chain group, allow glutamine to act as a nitrogen transporter and NH_3 carrier (Fig. 2).[19] Several primary organs, including the lungs, liver, brain, skeletal muscles, adipose tissue, intestinal mucosa, leukocytes, and kidney tubular cells, consume glutamine due to their high glutaminase (GLS) activity and cofactor levels for glutamine degradation.[20]

Endogenous glutamine is produced at a rate of 50–70 g/d and 5 μmol/kg of body weight (BW) per minute.[13] Each day, approximately 1.2 g of glutamine is excreted.[21] Two main intracellular enzymes are involved in glutamine metabolism: glutamine synthetase (GS), located in the cytosol, and GLS, located in the mitochondria (Fig. 3). GS initiates glutamine synthesis from ammonium ions (NH_4^+) and glutamate through adenosine triphosphate consumption, whereas GLS hydrolyzes and converts glutamine into glutamate and NH_4^+.[22] Glutamine enters the cell via the solute carrier family 1 (neutral amino acid transporter), member 5 (SLC1A5) transporter and plays a role in the glutathione synthesis and nucleotide synthesis cycles.[23] The glutathione cycle originates from glutamate transformed by glutamate cysteine ligase into glutathione. Glutathione acts as an antioxidant, reducing oxidative stress, aiding metabolic detoxification, and regulating immune system function.[24] The nucleotide cycle originates from glutamine transformed by carbamoyl-phosphate synthetase 2 (CAD) into cytidine triphosphate as a nucleic acid precursor, carrying genetic information and forming proteins.[25] CAD forms uridine diphosphate N-acetylglucosamine as a protein glycosylation precursor, modulating inflammatory responses, regulating apoptosis, and contributing to kidney filtration function in glomerular endothelial cells.[26] Ultimately, the nucleotide cycle synthesizes pyrimidine, which plays a significant role in cell proliferation.[27]

Compared with enteral glutamine administration, intravenous glutamine administration has a more significant effect on plasma concentration because it bypasses first-pass metabolism in enterocytes and more effectively improves body parameter values such as leukocyte, lymphocyte, albumin, and lactate levels.[28] Glutamine is unstable in its free form in fluids as parenteral nutrition; therefore, supplementation is provided as alanyl-glutamine or glycyl glutamine dipeptides.[29] Although parenteral glutamine administration is considered to have higher advantages, no definitive conclusions have been reached regarding the correct dose and duration of glutamine therapy as supplementation.

Parenteral glutamine doses of 0.2–0.5 g/kg per day restore plasma glutamine concentrations to normal ranges,[30] with >0.29 g/kg of BW per day showing the greatest benefit.[31] In critical illness, 0.3–0.5 g/kg of BW per day, up to 30 g/d, is administered (Fig. 1).[32]

A systematic review by Wischmeyer et al. reported that intravenous glutamine supplementation at doses of 0.3–0.5 g/kg per day in critically ill patients was associated with significant reductions in hospital mortality, treatment duration, and infectious complications; however, caution is required in patients with shock and organ failure. In these patients, the treatment aim is to maintain stability with doses <0.5 g/kg of BW per day (Fig. 1).[33] In addition to the dose and patient condition, the duration of the administration of

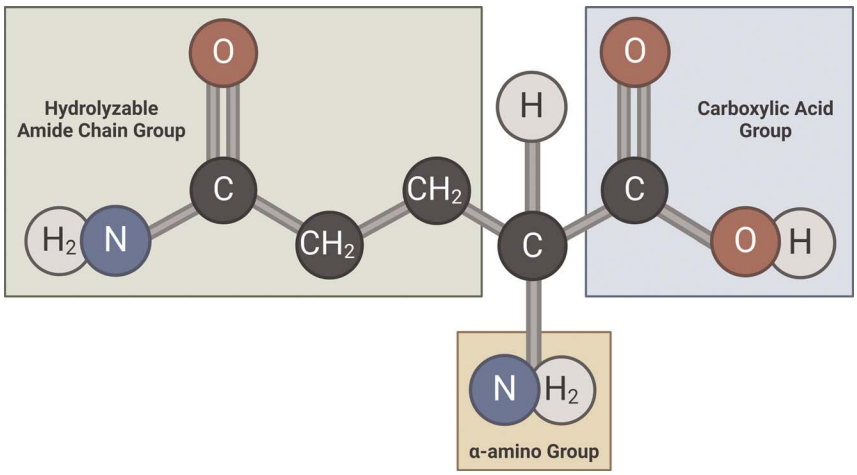

Figure 2. Glutamine structure. Image created using BioRender.com.

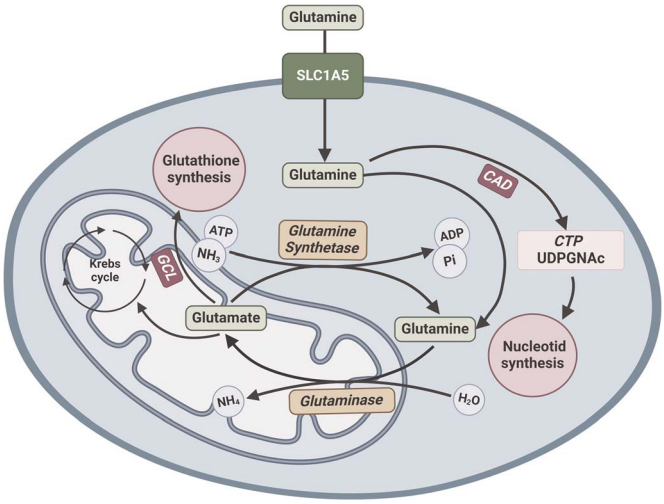

Figure 3. Glutamine metabolism. Image created using BioRender.com. The 2 main intracellular enzymes in glutamine metabolism are glutamine synthetase (GS), which is located in the cytosol, and glutaminase (GLS), which is located in the mitochondria. GS initiates glutamine synthesis. GLS hydrolyzes and converts glutamine to glutamate. The solute carrier family 1 (neutral amino acid transporter), member 5 (SLC1A5) transporter facilitates glutamine uptake into cells and plays a role in glutathione and nucleotide synthesis cycles. The glutathione cycle transforms glutamate into glutathione via glutamate cysteine ligase (GCL). The nucleotide cycle transforms glutamine into cytidine triphosphate (CTP) via carbamoylphosphate synthetase 2 (CAD), a nucleic acid precursor. CAD transforms glutamine to uridine diphosphate *N*-acetylglucosamine (UDPGlcNAc). The nucleotide cycle synthesizes pyrimidines.

parenteral nutrition of glutamine has an effect. Bendavid et al. reported that glutamine could improve cure rates if administered at the beginning of treatment of critically ill patients.[34] In addition, large amounts of protein in the early phase of critical illness can only be provided in parenteral nutrition.[35]

Critical illness is a state of organ dysfunction with a potentially reversible risk of high mortality without appropriate treatment. Therefore, critical illness requires critical care for monitoring, supporting vital functions, and substituting essential body needs.[36] Although most patients receiving intensive critical care can experience improvement (reversibility), a few may enter a prolonged catabolic phase. Increased catabolism leads to low plasma glutamine and is associated with low albumin levels, triggering severe inflammation and malnutrition.[37,38]

The increased metabolic rate during this catabolic phase leads to elevated glutamine utilization. Stress conditions in critical illness can increase cortisol levels, ultimately stimulating the GS enzyme.[39] Hsu et al. reported a 72% decrease in glutamine concentration in critically ill patients.[40] This decline can result in increased endogenous glutamine production that may surpass normal production levels. If endogenous glutamine production does not meet the body's needs, the potential benefits of exogenous glutamine supplementation should be considered. This is supported by research indicating that the relative safety of glutamine use in critically ill patients, including the lack of evidence of hospital mortality, decreased 6-month mortality rates, and reduced risk of nosocomial infection.[41] Although glutamine is a nonessential amino acid, in specific conditions such as extreme stress as in critically ill patients, glutamine can become conditionally essential and require supplementation.[42]

Patients with critical illnesses require amino acids to support healing. Moreover, critically ill patients with complications of AKI need more amino acids than those without such complications.[43] AKI increases kidney glutamine usage.[44] Glutamine is a necessary parenteral nutrient in critically ill patients as it helps maintain intestinal integrity, provide immune responses, and balance antioxidant levels.[45] Excessive glutamine degradation and inadequate glutamine supply can impact several glutamine-dependent metabolic pathways and mechanisms. One such mechanism occurs within immune cells, which require sufficient glutamine as a substrate for leukocyte function, cell proliferation, tissue repair, and intracellular pathogen recognition pathways. If these needs are not met, they can lead to worse outcomes, increased mortality risk, and immunosuppression in critically ill patients.[46]

Low plasma glutamine levels result in a 59% increase in interleukin 6 (IL-6) levels and immunosuppression in 23% of critically ill patients.[47] Low plasma glutamine levels can be predicted by 2 indicators: infection and inflammation markers (increased C-reactive protein [CRP] and decreased serum albumin levels) and disease severity scores (increased Acute Physiology and Chronic Health Evaluation [APACHE-II] and Sequential Organ Failure Assessment [SOFA] scores).[48] A meta-analysis by Gholamalizadeh et al. reported that glutamine supplementation significantly reduced CRP levels in critically ill patients. Higher CRP levels correspond to lower glutamine levels; thus, glutamine supplementation is beneficial in patients with critical illness.[49] Patients receiving parenteral glutamine nutrition experience reduced infection rates, immunomodulatory effects, decreased APACHE-II scores, and fewer disease complications such as multiple organ dysfunction syndrome.[50]

However, glutamine use requires strict monitoring under certain patient conditions. Mundi et al. indicated the need for further investigation of glutamine supplementation for amino acid deficiency in critical care patients.[51] Studies such as SIGNET (Scottish Intensive care Glutamine or seleNium Evaluative Trial), REDOX (Reducing Deaths due to Oxidative Stress), and MetaPlus reported harmful effects of glutamine supplementation in critically ill patients with organ failure, especially AKI. These harmful effects included increased mortality rates; moreover, glutamine use did not reduce infection rates. However, these studies used higher doses of glutamine than recommended.[52] Routine glutamine supplementation is not recommended for critically ill patients with organ failure.[53] Thus, administration must be performed carefully according to the patient's condition. Hill et al. suggested that intravenous glutamine is not recommended in unstable patients undergoing a series of critical care procedures, especially those with liver and kidney failure, but may be considered for patients requiring exclusive parenteral nutrition.[54]

Excessive glutamine administration can lead to hyperglutaminemia. Hyperglutaminemia in critical care patients is associated with a high mortality risk, making glutamine administration a crucial consideration in critically ill patients.[55] Hyperglutaminemia can lead to hyperammonemia; however, adhering to proper dosage guidelines, as suggested in recent recommendations, can mitigate this effect.[56] Therefore, although critical care patients can still take glutamine, its use requires intensive monitoring.

Mechanism of action of glutamine in the kidneys

The kidneys require glutamine for acute protein synthesis, optimization of the cellular immune response, improvement of antioxidant function, maintenance of cellular structure, and reduction of kidney damage.[57] The kidneys use glutamine for gluconeogenesis and ammoniagenesis.[58] The process of ammonia excretion begins with the transport of NH_3 from glutamine to the renal collecting tubules to bind to H^+ to form NH_4^+ in urine. The kidneys convert H_2CO_3 to HCO_3^- to regulate the blood pH.[59] In cases of acidosis, the kidneys produce more HCO_3^-, which can lead to coagulation disorders, decreased enzyme function, increased glutamine intake, and catabolism in the proximal renal tubules.[60]

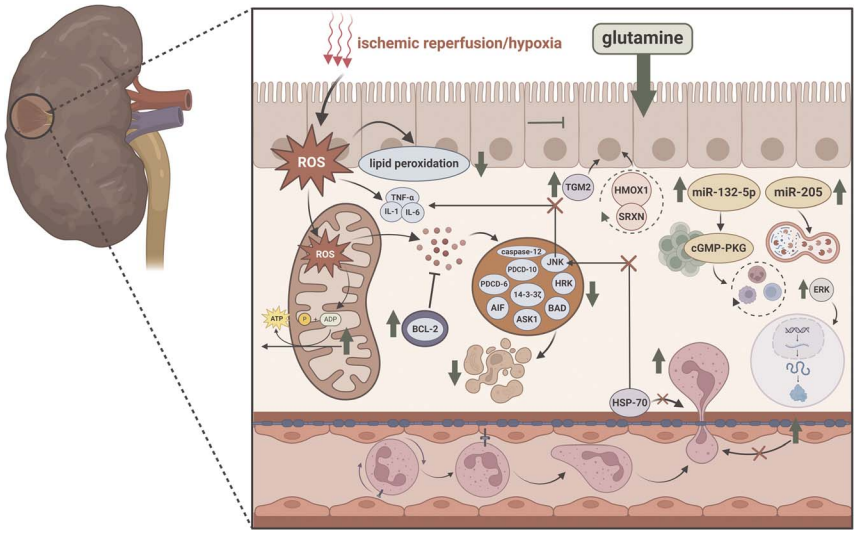

Figure 4. Mechanism of action of glutamine in the kidneys. Image created using BioRender.com. Glutamine administration improves reperfusion ischemia in acute kidney injury (AKI) by upregulating microRNA (miRNA)-132-5p (a miRNA subtype) to increase $CD4^+$ cell levels of immunoregulator cyclic guanosine 3′,5′-monophosphate–protein kinase G (cGMP-PKG). Upregulated miR-205 expression reduces oxidative stress and autophagy. The activation of extracellular signal–regulated kinase (ERK)–dependent proteins for cell proliferation and gene transcription regulation has anti-inflammatory properties. Reduced caspase-12 expression in glomerular epithelial cells, deactivated Jun N-terminal kinase (JNK), and halted synthesis of proinflammatory cytokines (tumor necrosis factor α [TNF-α], interleukin 1 [IL-1], and interleukin 6 [IL-6]) reduce lipid peroxidase production and increase tight junction gene expression in kidney cell walls to reduce macrophage-neutrophil infiltration and inflammation pathways. Glutamine reprograms transcriptomic and proteomic programs in kidney tubular epithelial cells, reducing epithelial apoptosis by inhibiting apoptotic proteins (programmed cell death protein [PDCD]-6 and PDCD-10 and 14–3-3ζ), reducing neutrophil recruitment, and improving mitochondrial function and oxidative phosphorylation. The main targets of glutamine are transglutaminase 2 (TGM2) and apoptosis signal-regulating kinase (ASK1). TGM2 catalyzes glutamine and lysine, which play important roles in maintaining cell integrity, particularly under stressful conditions. Heat shock protein-70 (HSP-70) regulates the mitigation of inflammatory responses and neutrophil infiltration in kidneys. HSP-70 deactivates Jun N-terminal kinase (JNK) and prevents the activation of BCL-2 associated agonist of cell death (BAD) and BCL-2–associated X protein (BAX) in intrinsic apoptosis signaling. Glutamine inhibits the expression of apoptosis inducing factor (AIF) (an apoptotic protein) and increases the expression of B-cell lymphoma-2 (BCL-2) (an antiapoptotic protein) in human kidney-2 (HK-2) cells.[61] At the transcriptional level, glutamine downregulates proapoptotic genes (Harakiri [HRK] and BAD) and regulates cytoprotective genes (sulfiredoxin 1 [SRXN1] and heme oxygenase 1 [HMOX1]) in kidney tubular epithelial cells. ATP, adenosine triphosphate.

Glutamine can reduce reperfusion ischemia incidents in AKI (Fig. 4).[62] This is marked by differential miRNA expression in kidney histocytes in vitro.[63] The regulation of miRNA subtype miR-132-5p leads to increased cyclic guanosine 3′,5′-monophosphate-protein kinase G (cGMP-PKG) processes, an immunoregulator in $CD4^+$ cells.[64] Glutamine administration enhances the activity of these $CD4^+$ immune cells, resulting in more stimulated cGMP-PKG processes. Additionally, miRNA subtype miR-205 is a target for oxidative stress and autophagy treatment in AKI (Fig. 4).[65]

Intravenous glutamine can reduce caspase-12 expression in glomerular epithelial cells.[66] Glutamine has anti-inflammatory effects, activating extracellular signal–regulated kinase–dependent proteins for cell proliferation and gene transcription regulation.[67] Glutamine deactivates Jun N-terminal kinase (JNK), an apoptotic signaling activator, and the synthesis of proinflammatory cytokines such as tumor necrosis factor α, IL-1, and IL-6.[67] Glutamine is assumed to have nephroprotective effects.[68] Intravenous glutamine can reduce lipid peroxidase production and increase tight junction gene expression in kidney cell walls to reduce macrophage-neutrophil infiltration and inflammation pathways.[69] A mouse trial of gentamicin-induced nephrotoxicity observed that glutamine supplementation provided a protective effect on the kidneys (Fig. 4).[70]

Thomas et al. reported that glutamine ameliorated kidney damage in vivo and kidney tubular epithelial cells in vitro under inflammatory or hypoxic conditions. Glutamine can reprogram the transcriptomic and proteomic programs in kidney tubular epithelial cells, reducing epithelial apoptosis.[71] Glutamine works by inhibiting apoptotic proteins (programmed cell death protein [PDCD-6 and PDCD-10] and 14–3-3ζ), reducing neutrophil recruitment, and improving mitochondrial function and oxidative phosphorylation.[72] The main targets of glutamine are transglutaminase 2 (TGM2) and apoptosis signal-regulating kinase (ASK1) proteins. TGM2 is a multifunctional enzyme that catalyzes glutamine and lysine and plays a role in maintaining cell integrity, especially under stressful conditions.[73]

In addition to TGM2 and ASK1, glutamine has protective effects on the kidneys through the activation of heat shock protein-70 (HSP-70), which regulates the mitigation of inflammatory responses and neutrophil infiltration in the kidneys.[74] HSP-70 deactivates JNK and prevents the activation of B-cell lymphoma-2 (BCL-2)–associated agonist of cell death (BAD) and BCL-2–associated X protein (BAX) in intrinsic apoptosis signaling,[50] and it is a therapeutic target in AKI.[75]

Glutamine inhibits the expression of apoptosis-inducing factor, an apoptotic protein, and increases the expression of BCL-2, an antiapoptotic protein in human kidney-2 cells.[61] Therefore, glutamine plays a role in inhibiting oxidative stress and reducing inflammation in kidney tubular cells. At the transcriptional level in kidney tubular epithelial cells, glutamine supplementation can downregulate proapoptotic genes (Harakiri [HRK] and BAD) and regulate cytoprotective genes (sulfiredoxin 1 [SRXN1] and heme oxygenase 1 [HMOX1]).[76] In summary, glutamine has anti-inflammatory and cytoprotective properties.

The kidney is a central organ in glutamine metabolism, implying that the loss of renal functional capacity in ammonia elimination, such as in AKI without RRT, poses a risk to additional glutamine

metabolism.[77] Patients in the injury phase of AKI, with creatinine levels <25 mL/min and not receiving RRT, should be excluded from glutamine supplementation. This is because ongoing RRT can eliminate 21% of the amino acids, 30% of which are glutamine. This results in insufficient glutamine levels in the body, which can adversely affect recovery in critically ill patients.[78]

The critical illness aggravated by AKI itself can induce metabolic disturbances and reduce the ability to synthesize nonessential amino acids. The condition worsens when the patient has stage 3 AKI and requires RRT, particularly CRRT. Although crucial, CRRT can have metabolic effects due to the concurrent loss of macronutrients and micronutrients along with the elimination of uremic toxins during therapy.[21] The results of a randomized controlled trial by Song et al. showed that hypophosphatemia often occurs during CRRT, with an incidence of up to 59%. This is caused by the highly effective urea clearance ability of CRRT, which coincides with the clearance of phosphates and potassium, especially with a high effluent flow rate and a long CRRT duration. Hypophosphatemia can lead to respiratory muscle impairment, failure to wean off mechanical ventilation, myocardial dysfunction, arrhythmias, and rhabdomyolysis.[79] Furthermore, hypokalemia poses a risk of arrhythmia and muscle weakness.[80] However, this can be rectified with fluid management during CRRT with dialysate and replacement fluid containing phosphate and potassium.[81] Another condition, hypocalcemia, often emerges during CRRT initiation, increasing the risk of hypotension due to systemic vasodilation effects and a decrease in left ventricular function.[82] A case series and case report mention rare metabolic disturbances caused by CRRT and poor intake, leading to euglycemic ketoacidosis with characteristics of high-anion-gap metabolic acidosis in patients with diabetes with normal blood glucose levels.[83,84] Nevertheless, the nonselective clearance of uremic toxins can positively impact sepsis. The clearance of uremic toxins during CRRT may be accompanied by the clearance of inflammatory cytokines.[85]

Another limitation of dialysis is that it tends to contribute to amino acid deficiency by causing amino acid loss. Dialysis procedures can result in the loss of amino acids, ranging from 4 to 13 g.[86] The loss of amino acids in hemodialysis depends on the specifications of the membrane used and the hemodialysis modality itself.[87,88] Table 1 describes data from studies on this topic. An observational prospective study by Oh et al. in patients with stage 3 AKI undergoing 3 different RRT modalities, IHD, sustained low-efficiency diafiltration (SLEDf), and continuous venovenous hemofiltration (CVVH), demonstrated the highest amino acid loss for CVVH, followed by SLEDf and IHD. Their study results suggested that glutamine is the most prominently lost amino acid because of its high concentration in the plasma.[88,90] This aligns with the findings reported by Ostermann et al., using the same research methodology, in which critically ill patients with stage 3 AKI had concentrations of amino acids, vitamins, and trace elements below the reference range. This condition is exacerbated by RRT modalities such as CRRT and non-CRRT, which deplete essential micronutrients, particularly glutamine, although the 2 modalities showed no statistically significant differences.[89] In their prospective study on patients with AKI undergoing extended dialysis for 10 hours, Schmidt et al. reported a discharge of 3.2 g of glutamine out of a total of 10.5 g of amino acids.[78] Therefore, the provision of nutritional supplementation should be considered based on these risks and the fact of nutrient deficiencies, including amino acids, especially glutamine, in stage 3 AKI requiring RRT.

AKI often occurs in critically ill patients, with an incidence rate of 30%–60%, and is associated with morbidity and mortality.[91] Patients with critical illness and AKI may experience decreased levels of essential amino acids such as arginine, histidine, lysine, tryptophan, and glutamine.[89] The results of several studies suggest the need for glutamine supplementation. The administration of glutamine regulates protein expression through mitochondrial oxidative phosphorylation pathways, specifically the essential subunits of NADH and the glutathione (antioxidant-forming) system.[92] This process results in a more regulated NAD^+-binding process with its function in autophagy to decrease AKI complications.[93]

Patients with AKI are recommended to receive 1.2–1.6 g/kg of BW per day of protein (Fig. 1).[94] Those with prolonged dialysis in AKI require daily protein replacement to prevent wasting.[95] However, excessive amino acid intake, including glutamine, in patients with AKI can lead to progressive kidney damage and uremia toxicity (amino acid paradox).[96]

However, studies argue against the necessity of glutamine supplementation. Wernerman suggested that intravenous glutamine is not recommended for patients with liver or kidney insufficiency.[97] Additionally, the ESPEN guidelines state that high-dose parenteral glutamine should not be administered to critically ill patients with AKI, especially in the form of alanyl-glutamine because it can be harmful.[98]

Nutrient intake via enteral routes is generally prioritized over parenteral or intravenous methods. However, a meta-analysis by van Zanten et al. suggested otherwise. The results of their analysis of enteral glutamine supplementation in critically ill patients showed that enteral administration of glutamine was not associated with a reduction in mortality rates, infectious complications, or length of ICU stay.[99] This finding is supported by the statement that enteral glutamine supplementation at large doses has a minimal impact on plasma glutamine concentration compared with intravenous administration, which can rapidly increase plasma glutamine concentration and achieve a stable condition.[97,100] Therefore, intravenous glutamine supplementation is preferable.

Given the diverse causes of AKI, a comprehensive understanding of the etiology of AKI in critically ill patients necessitates a thorough understanding of appropriate glutamine administration. These differences occur because of variations in the underlying pathophysiology of AKI. For example, AKI related to cardiac surgery arises from ischemia-reperfusion injury to the kidneys caused by arterial clamping during surgery.

In their randomized controlled trial, Brinkmann et al. hypothesized that aortic clamping during open aortic surgery reduced arginine production. Glutamine is essential to counteract the diminished production

Table 1

Different RRT Modalities Effect on Glutamine Loss

RRT Modalities			Non-CRRT		CRRT	
Duration			**Intermittent**	**Intermediate**	**Continuous (24 h)**	***P* Value**
Reference	Oh et al.[88] 2019	Plasma glutamine loss (μmol/L)	17.7	152	84.5	0.01
	Ostermann et al.[89] 2020		352		383	0.9
	Schmidt et al.[78] 2014			121.5		-

CRRT, continuous renal replacement therapy; RRT, renal replacement therapy.

of arginine in the kidneys because citrulline, which acts as an arginine precursor, is formed from glutamine. The authors demonstrated that supplementation with alanyl-glutamine at a dose of 0.5 g/kg of BW per day, starting before the surgical procedure and continuing for 1 day postoperatively, could compensate for the inhibitory effects on arginine production resulting from ischemia-reperfusion injury to the kidneys.[101] Although their study was not aimed at assessing the benefits of glutamine supplementation in AKI resulting from cardiac surgery, their findings provide insights into strategies for glutamine supplementation in cardiac surgery that are beneficial for preserving glutamine whole-body flux. A slightly different supplementation approach was employed in another randomized controlled trial by Weiss et al. Their results indicated that intravenous glutamine administration for 12 hours post–cardiac surgery in patients at high risk of AKI resulted in a significant reduction in the levels of the markers of kidney damage.[102]

In cases of AKI stemming from different etiologies, distinct strategies for glutamine supplementation have been reported. In a randomized controlled trial by Xiangdong of critically ill patients experiencing AKI due to sepsis, intravenous supplementation of glutamine at a dosage of 0.67 g/kg of BW per day for 7 days led to a reduction in the SOFA score related to kidney function in patients with severe sepsis.[103] However, clinical trials on glutamine supplementation in sepsis, especially in sepsis-induced AKI, are limited.

Clinical trials in patients with critical illnesses resulting from burns and AKI have been actively pursued. Glutamine supplementation strategies have been reported in studies of critically ill patients with burns (with unknown kidney function). A randomized controlled trial by Wang et al. demonstrated satisfactory outcomes following additional supplementation of intravenous glutamine (alanyl glutamine) at a dosage of 0.5 g/kg of BW for 14 days in patients with severe burns. These patients showed improvement with a reduction in hypermetabolic response. Moreover, the levels of a specific kidney function marker, β2-microglobulin, decreased significantly.[104] Contrary outcomes emerged from a large-scale multicenter study involving more than 1200 subjects. Heyland et al. investigated enteral glutamine supplementation in patients with severe burns. The intervention group received enteral glutamine supplementation starting at 72 hours postadmission until reaching the predetermined criteria set by the researchers. According to the authors, these results were unexpected, especially considering that previous studies yielded positive outcomes. Their study findings demonstrated that enteral glutamine supplementation in patients with severe burns did not result in significant differences in time to discharge, mortality rates, length of stay, bacteremia, elevation of urea levels, or the incidence of AKI requiring RRT.[105] This unexpected outcome might be attributed to the rapid impact on the intestine and kidneys in patients with severe burns. The intestine is susceptible to various disturbances caused by burn injuries, particularly a decline in nutrient absorption.[106] This provides insights into the crucial strategy of glutamine administration in severe burns that can prevent the deterioration of kidney function before the development of AKI.

In critically ill patients with multiorgan failure, careful consideration is needed regarding glutamine supplementation. The use of glutamine and omega-3 fatty acids reportedly confers no benefits to critically ill patients with multiple organ failure and high APACHE-II scores.[107] Individualized glutamine replacement based on patient requirements is essential, and enhancing kidney function parameters, including plasma creatinine and urea levels, can serve as a proactive approach owing to its negative prognostic role in parenterally nourished patients. Elevated creatinine levels within 2 weeks in patients are associated with adverse outcomes.[108]

Combination glutamine therapy in critically ill patients with AKI has not yielded promising results. A randomized controlled trial comparing intravenous glutamine and selenium supplementation showed that their combination had no significant effect on mortality rates or the occurrence of infection in critically ill patients. Similar results were observed for the administration of either glutamine or selenium alone.[109] The limitations of this study include the lack of precise consideration of the protein and calorie needs of patients, the inability to assess long-term effects, inappropriate initiation timing of parenteral nutrition, and failure to account for presupplementation glutamine levels.

When critically ill patients progress to AKI stage 3, a suitable combination of CRRT and nutritional supplementation should be considered as AKI is accompanied by metabolic and physiological disturbances and CRRT leads to the loss of micronutrients and macronutrients. In such cases, the addition of glutamine (alanyl-glutamine dipeptide) at a dose of 0.3–0.6 g/kg per day to the total parenteral nutrition provided is advised.[110]

Unstable metabolic conditions resulting from CRRT-exacerbated AKI require precise monitoring. Alterations in carbohydrate and lipid metabolism coupled with electrolyte imbalances are likely to occur. Continuous glucose monitoring is necessary to anticipate dysglycemia, whereas triglyceride level monitoring is essential to anticipate filter clotting, and electrolyte correction should be performed according to patient needs.[110]

Table 2

Effects of Intravenous Glutamine Administration in Critical Care Patients with AKI

No.	Effects of Intravenous Glutamine Administration	References
Positive Effects		
1.	Immunomodulatory effects (pathogen recognition, cytokine production, carrying out immune responses, reducing inflammation)	[14],[16],[17],[32],[53],[94],[95]
2.	Decreased apoptosis in glomerular epithelial cells (transcriptomic and proteomic reprogramming, decreased expression of AIF, caspase-12, and apoptotic cells)	[21],[60],[61]
3.	Specific role in inhibiting oxidative stress in renal tubule cells	[26],[53],[111]
4.	Reduce hospitalizations	[16],[17],[40],[56]
5.	Maintain antioxidant balance	[26],[32]
6.	Nephroprotective effect	[60],[62]
7.	Activates cell proliferation and tissue repair	[14]
8.	Repairs kidney damage in vivo and renal tubular epithelial cells in vitro under inflammatory or hypoxic conditions	[71]
9.	Reduces the production of lipid peroxidase by improving the condition of close link gene expression in the kidneys	[65]
Negative Effects		
1.	Increased mortality rate in critical care patients with multiorgan failure, especially acute renal impairment	[26],[40]
2.	Alanyl-glutamine is harmful in patients with renal impairment	[44]

AIF, apoptosis-inducing factor; AKI, acute kidney injury.

Correcting glutamine deficiency is more beneficial than excessive glutamine supplementation in patients without deficiency. Therefore, establishing normal limits for glutamine and identifying glutamine deficiency before initiating glutamine supplementation are essential. The presence of both positive and negative effects of intravenous glutamine use, as presented in Table 2, emphasizes the need for careful consideration of all aspects of each therapeutic decision to ensure positive effects and minimize negative effects. In the practical management of critically ill patients with AKI, appropriate timing, dosage, and administration of glutamine supplementation can optimize the overall clinical outcomes.

Conclusion

Due to its essential functions, glutamine plays a pivotal role in the management of critically ill patients with AKI. Despite the adverse effects associated with intravenous glutamine, it has substantial potential benefits, including immunomodulation, reduction in apoptosis within glomerular epithelial cells, inhibition of oxidative stress, and provision of tissue and cytoprotective effects. The effects of intravenous glutamine to potentially decrease mortality and hospitalization rates make it a viable option in clinical practice.

For effective implementation, glutamine administration should align with established guidelines and recognize the diverse etiologies of AKI, which necessitate distinct therapeutic strategies. Moreover, adherence to guidelines ensures a tailored approach that optimizes the therapeutic benefits of glutamine by considering specific patient conditions.

Understanding glutamine depletion across various etiologies is crucial, especially in patients with AKI stage 3 undergoing RRT. RRT modalities can exacerbate glutamine loss, highlighting the need for supplementation to address potential deficiencies. This underscores the importance of a nuanced guideline-driven approach to determine the appropriate dosage, timing, and duration of intravenous glutamine administration based on the underlying cause of AKI.

However, the administration of intravenous glutamine requires careful consideration of multiple factors including the patient's condition, dosage, and timing and requires prolonged observation. This cautious approach is essential to ensure the success of the therapeutic process and optimize clinical outcomes. Thus, observational studies are needed to clinically assess glutamine toxicity in critically ill patients with AKI to provide a basis for informed recommendations in the field.

Conflict of interest statement

The authors declare no conflict of interest.

Author contributions

Jonny J and Pasiak TF participated in conception and design. Jonny J contributed to data analysis and interpretation. All authors contributed to provision of study materials or patients, collection and assembly of data, manuscript writing, and final approval of manuscript.

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