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REVIEW ARTICLE

Glutamine and its use in selected oncology settings

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This review summarises the latest evidence for the use of glutamine (GLN) in oncology taking cognisance of current systematic reviews and available guidelines. Various studies in adults suggest that GLN supplementation suppresses tumour growth, by restoring the function of natural killer cells; improves protein metabolism; and, possibly enhances the effect of cancer therapy. There is insufficient data on whether GLN supplementation reduces the incidence of infection, although a trend exists towards such a reduction. GLN-supplemented enteral nutrition was superior in improving immune function, whilst oral GLN alone appeared to have no effect on: mortality; infections; time to neutrophil recovery; or, relapse. GLN significantly reduces the duration of diarrhoea, but had no effect on its prevention. Oral GLN may reduce the duration and severity of mucositis, with fewer days on opioid therapy. Oral GLN, but not intravenous GLN (IV-GLN), may decrease mucositis and graft-versus-host disease in adult bone marrow transplant patients. Currently, the evidence for reduction of severe mucositis or infection rate in children is not statistically significant, but GLN does significantly reduce parenteral nutrition use, reflecting a possible improvement in lower gut mucositis. Nevertheless, too few studies exist to either support or refute that GLN supplementation either reduces the duration of, or prevents the progression to, severe mucositis. In children, there is no significant evidence that IV-GLN supplementation reduces infection rates, hospital length of stay (LOS), graft-versus-host disease, or mortality. Children with solid tumours on chemotherapy receiving oral GLN supplementation showed significant improvements in some nutritional and immunological parameters, as well as the severity of stomatitis and need for antibiotic therapy.
Caution is recommended when considering provision of IV-GLN to oncology patients who have hepatic or renal insufficiency or failure. Monitoring of hepatic and renal function is recommended. Further studies are needed specifically on the use of glutamine in an oncology setting. Larger, multicentre, randomised placebo-controlled studies are needed in both adult and paediatric oncology populations.

Keywords: cancer, glutamine, mucositis, oncology

Introduction

Glutamine (GLN) is a non-essential branched-chain amino acid that becomes conditionally essential when demand exceeds supply during catabolic stress or periods of rapid growth.[1,2] GLN contributes 30–35% of the amino acid-based nitrogen in plasma,[3,4] plays an important role in gluconeogenesis,[4] and serves as a fuel for rapidly dividing and growing cells (e.g. enterocytes and lymphocytes).[2,5] It contains two ammonia groups: glutamate and ammonia.[3] GLN transports ammonia in a non-toxic form, from the peripheral tissue to visceral organs, where it is excreted in the urine.[4] GLN is also used by the gut and kidneys for acid-base homeostatis.[4]

Healthy subjects have an endogenous GLN production of 50–80 g/day.[6] GLN forms 25% of the free amino acid pool in the extracellular fluid and 60% in the skeletal muscle,[7] which is the main site for L-glutamine synthesis and storage.[3] It is also found in smaller amounts in the lungs and brain.[4,5] Good dietary sources of GLN are dairy, fish and green leafy vegetables.[3]

GLN depletion occurs under catabolic conditions, such as cancer, injury and infection.[8] The skeletal muscle contributes significant amounts of GLN to the GLN pool during these states, causing a marked GLN depletion in skeletal muscle over time, due to an inability to meet the body's demands.[3,9] For each gram of nitrogen lost during stress, approximately 30 g of lean tissue is broken down, thereby releasing alanine and GLN.[10] In a cancer patient, it is thought that GLN depletion, due to the side effects of chemotherapy and radiation, may lead to mucositis, lowered immunity, cachexia, increased acute-phase proteins and hyperlipidaemia.[11,12]

GLN plays an important role during the acute phase response (Figure 1), a catabolic state that leads to the increased production of counter-regulatory hormones (e.g. cortisol, glucagon) and cytokines (e.g. interleukin 1, interleukin 6, tumour-necrosis factor-α), which modulate the metabolic response. The increase in the synthesis of these mediators results in a decrease in anabolic hormones, including insulin, which leads to peripheral insulin resistance. Glycogen stores are usually depleted within the first two days of the metabolic response, resulting in lipolysis, proteolysis, and increased skeletal muscle breakdown for energy production. Immobility also contributes to further poor protein synthesis. The enzyme glutamine synthetase, present in skeletal muscle, responds to the increase in cortisol by up-regulating GLN release from skeletal muscle. Normally, GLN will be released to the glutamine pool, but, in catabolism, proteolysis leads to the *de novo* synthesis of GLN from other amino acids. When demand exceeds supply, the GLN pool is depleted and normal GLN-dependent biological functions are compromised, leading to poor wound healing, acid-base imbalance, and compromised immunity.[2,13]

During the systemic inflammatory response syndrome (SIRS), the blood concentrations of water-soluble vitamins and trace elements (e.g. selenium, zinc and iron) are compromised, leading to a decreased circulatory concentration of these antioxidants, as well as their transport proteins (e.g. transferrin and albumin). The

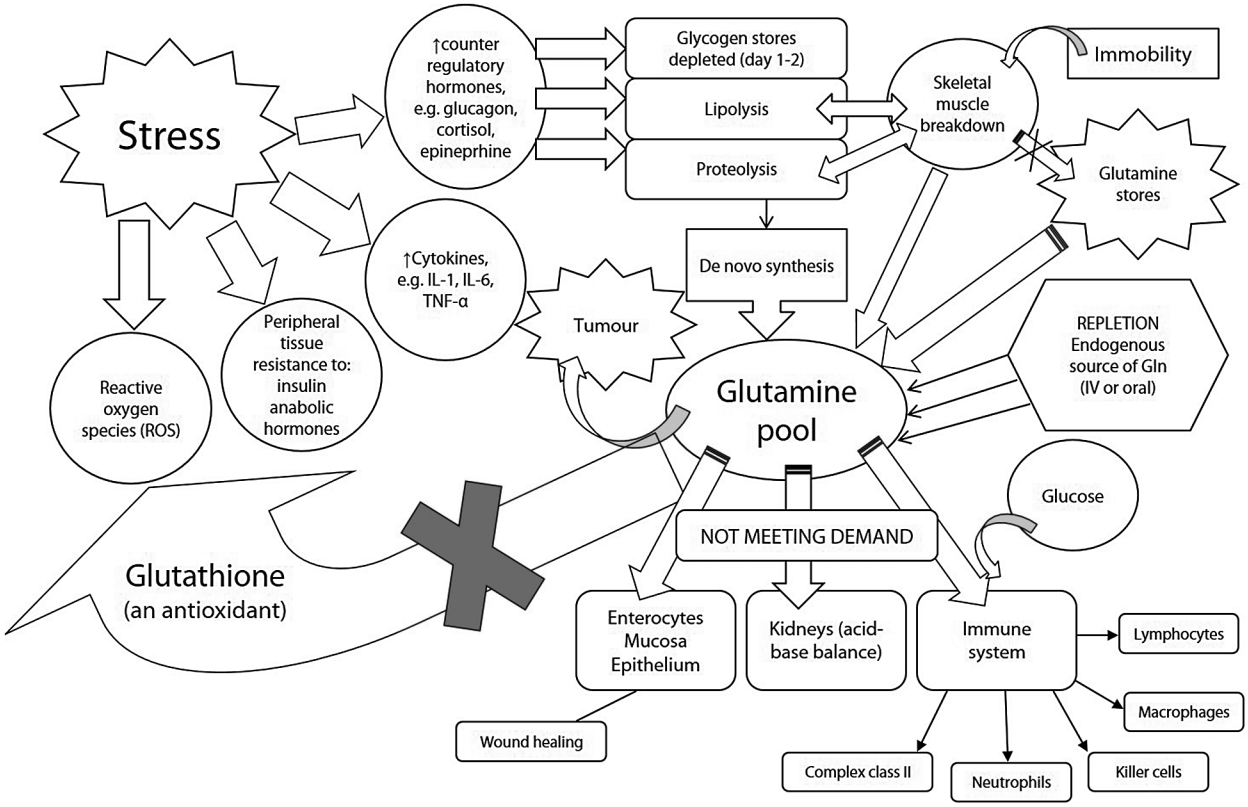

Figure 1. The depletion of GLN during stress, and its consequences[1,2,13].

deficit in circulatory antioxidants leads to oxidative stress when reactive oxygen species overcome the antioxidants' defences, leading to poor wound healing, organ dysfunction, an altered immune response and an adverse patient outcome.[1,13] GLN is also a precursor of glutathione, another antioxidant. Thus, GLN up-regulates glutathione synthesis during stress, and induces heat shock proteins (e.g. HSP 27, 70 and 72), assisting in protecting the gut and myocardium.[3,14] The GLS2 gene, which codes for glutamine enzymes (glutaminases), is regulated by tumour suppressor p53. During stress, over-expression of GLS2 reduces colony formation in tumour cells, thereby regulating tumour suppression.[1]

Therefore, supporting a patient through exogenous sources of GLN (either IV or orally), may assist in halting or reversing, in extent, the effects of GLN depletion in a catabolic patient. It is also possible that oral glutamine supplementation may increase the selectivity of anti-tumour drugs and protect against radiotherapy-induced oxidative stress, owing to increased glutathione synthesis.[3] Adequate nutrition support, which includes GLN, will meet GLN needs and spare energy reserves, thereby retarding the onset of severe complications, improving the general metabolic state of the patient, and thus improving quality of life (QoL).[12]

Multiple studies over a twenty-year period have shown the benefits of using GLN when appropriately given to a specific patient that needs it, at the recommended approved dose for the specific clinical setting, and as part of nutritional therapy, thereby reducing mortality, infectious complications, and hospital LOS in critical illness.[15] However, GLN supplementation remains controversial in the clinical setting, even though there is a biological rationale for its use.[16]

Glutamine supplementation

General

Wischmeyer[15] compared the difference between 'traditional' IV-GLN supplementation trials and the 'reducing deaths due to oxidative stress' (REDOXS) trial. In 'traditional' trials, IV-GLN administration was only started later in the intensive care unit (ICU) when patients were stable, renal and liver failure patients were almost universally excluded, GLN was given at lower doses (0.3–0.5 g/kg body weight/day) and was given only as part of parenteral nutrition (not combined with enteral GLN). The REDOXS trial ignored previous inclusion and exclusion criteria of 'traditional' studies, thereby administering GLN independently from nutrition support to patients who were in shock or had multiple organ failure (MOF), at higher doses, and via multiple routes (enteral 30 g/d and intravenously 0.5 g/kg/d, totaling 0.6–0.8 g/kg/d). Interestingly, many of the 'traditional' trials' participants were surgical oncology patients, whereas the majority of patients in the REDOXS trial were not.[15] Wischmeyer, who was a co-author of the REDOXS trial, was of the opinion that GLN supplementation was still safe to administer to appropriate patient groups, either intravenously at 0.35 g/kg body weight/day or enterally at 0.5 g/kg bodyweight/day, and that the REDOXS trial showed where GLN can be given safely, via which route, at what time, and what dosages should be given to which patients.

Some of the same authors of the 2013 REDOXS study,[17] revisited the recommendations for IV-GLN in 2014 and stated that 'supplementation of parenteral glutamine, predominantly as a component of parenteral nutrition (PN), may improve clinical outcomes when given to *appropriate* patients as part of complete nutrition support'.[18] The authors also stated that 'parenteral supplementation with glutamine should continue to be considered safe and may potentially improve outcomes in ICU

patients without specific contraindications'.[18] In his 2015 commentary, Wischmeyer[15] reiterated that GLN still saved lives and that the right patients, including oncology patients, will continue to benefit from GLN-supplementation.

Supplementation on selected oncology settings

Administration route

Oral GLN is considered safe and effective in adults,[19] but it is unclear whether oral GLN is as effective as IV-GLN, although animal and human studies show similar benefits by either route.[20] Enteral GLN absorption occurs in the upper part of the jejunum, which leaves the rest of the gastrointestinal tract (GIT) unsupported. It is highly likely that parenteral GLN may become critical for the intestine when enteral nutrition (EN) is not feasible.[6] The meta-analysis by Kang *et al.*[21] found that GLN-supplemented EN was superior in improving immune function, reducing the incidence of infectious complications, and shortening the hospital LOS, thereby playing an important role in the rehabilitation of surgical gastrointestinal cancer patients.

Oral GLN may reduce the duration and severity of mucositis,[9,12,19,22,23] with fewer days on opiods.[22,23] The exact mechanism by which oral GLN prevents mucositis is not clear.[9] Van Zyl's systematic review[20] on oral GLN provided new evidence of a significant reduction ($p = 0.03$) in > grade 2 mucositis with a relative risk reduction of 24%. Trends for less days of opiate use with mucositis[22] were seen in autologous ($p < 0.01$), but not allogeneic, bone marrow transplant (BMT) patients.[19]

Oral GLN may reduce graft-versus-host disease (GVHD).[22,23] It may decrease the severity and duration of stomatitis in children and adults after chemotherapy, as well as in head and neck cancer patients.[12]

Oral GLN may also prevent or delay the occurrence of radiation-induced oesophagitis among cancer patients treated by radiotherapy to the thoracic area with or without chemotherapy.[11] The reduction in oesophagitis also led to less weight loss in lung cancer patients undergoing thoracic irradiation.[11] Optimal nitrogen retention was reached at a GLN dose of 0.57 g/kg/day in this group of patients.[11] Oral GLN alone appeared to have no effect on mortality, [20,22] infections, time to neutrophil recovery, or relapses.[22]

Oral GLN may reduce some chemotherapy-induced complications, such as mucositis and diarrhoea, among colon and colorectal cancer patients,[5] especially among those on 5-fluorouracil/folinic acid chemotherapy.[5,12] GLN supplementation maintains glutathione levels during the administration of doxorubicin, methotrexate, and cyclophosphamide.[3] High-dose doxorubicin causes cardiac toxicity,[3] but GLN up-regulates glutathione and induces heat shock proteins 72 and 27, which protect the myocardium.[3] There are some studies that found a reduced severity of peripheral neuropathy in breast cancer patients on paclitaxel,[24] when supplemented with 30 g oral GLN/day (10 g thrice daily).[12] However, there was no reduction in severity of paclitaxel-induced myalgias and arthralgias.[12] In metastatic colorectal cancer patients on oxaliplatin, oral GLN significantly reduced the incidence and severity of peripheral neuropathy, without affecting survival or response to chemotherapy.[25] GLN, when administered in conjunction with probiotics, reduces chemotherapy-induced diarrhea.[24] GLN also significantly reduces the duration of diarrhoea, but has no effect on prevention.[20]

The review by Sayles *et al.* found weight gain or less weight loss in patients receiving oral GLN, but only one study showed a significant difference. In both Van Zyl's review[20] and the Cochrane review,[26] mean body weight changes were inconclusive and not significant.

Azman *et al.*[27] states that their study is the first to show significant post-operative improvements in serum albumin ($p < 0.001$), fat free mass ($p < 0.001$), and patient QoL parameters ($p < 0.05$) after four weeks of enteral GLN supplementation at 0.3–0.4 g/kg/day. There was also a significant correlation ($p < 0.05$) between retention of lean body mass and improved QoL with GLN supplementation.[27]

Studies conducted in paediatric oncology are limited. In children with solid tumours on chemotherapy, GLN supplementation showed significant improvements in pre-albumin, transferrin, lymphocyte counts, complement 3 and 4,[19,28] antibiotic necessity,[19] as well as reduced stomatitis severity. Non-randomised preliminary clinical studies demonstrated safety. GLN supplementation may reduce hospital costs in children receiving chemotherapy or BMT.[19] Currently, the reported reduction of severe mucositis or infection rates in children is not statistically significant.[29] Sung *et al.*[30] found that GLN was not consistently effective in reducing mucositis in paediatric patients in more than one study.

In the study by Ward *et al.*,[31] GLN was safely given enterally or orally at 0.65 g/kg/day for five days alongside chemotherapy to patients aged > 1 to < 22 years old (mean = 8.8 years). GLN did not reduce the incidence or severity of oral mucositis, but significantly reduced both the number of patients requiring total parenteral nutrition (TPN) ($p = 0.049$) and the amount of days necessary for TPN administration ($p = 0.023$), thereby reflecting a possible improvement in 'lower gut' mucositis.[31] Most other trials tested oral GLN at a daily dose of 4 g/m^2 body surface area in various paediatric oncology patients receiving cancer treatment (Table 1).[19]

Table 1: Oral glutamine recommendations for the prevention of mucositis in children[31,44]

High risk patient groups	Dose and duration	Administration method
Intensive chemotherapy regimens, e.g.: • Burkitt's Lymphoma • Acute Myeloid Leukemia	• Give at 0.57 g/kg for duration of chemotherapy • Start administration after completion of leucovorin rescue as part of multi-agent regimens containing high dose methotrexate	• Mix into any beverage or soft moist food • Dissolve 10 g powder in at 100 ml of clear liquid–swish around in the mouth and swallow, or administer enterally • Use within 30 min
Radiotherapy to upper GIT, e.g.: • Head and neck cancers • Rhabdomyosarcoma	• Give at 0.57 g/kg for duration of radiotherapy	

Since GLN becomes unstable in solution, enteral supplements are not routinely supplemented with GLN. Powdered GLN is recommended for enteral administration.[20] A water-based solution of GLN should be prepared prior to GLN administration via a feeding tube to avoid clogging the tube, and should be used as soon as possible thereafter as the solution is not stable for long periods of time.[8]

The effectiveness of the IV dipeptide (L-alanyl-L-glutamine) in treating or preventing oral mucositis in head and neck cancer patients, as well as haematopoetic stem cell transplantation (HSCT) patients has not been established given the limited IV-GLN research.[32] Concerns also exist about the stimulation of tumour growth during GLN supplementation.[12]

The local effects of oral GLN differ from its systemic effects.[9] GLN's gut protective effect is obtained by administering supplements either:

(1) Intravenously (alone as a alanyl-glutamine dipeptide or with PN);[22] or

(2) Orally (alone as a reconstituted powder or as part of EN. It seems that oral GLN provides an enhanced gut protective effect,[14,20] possibly due to the induction of heat shock protein number 72.[14] However, IV-GLN has been shown to enhance the effect on chemotherapy more so than enteral GLN.[12] Adequate GLN availability can benefit outcomes for BMT patients by reducing the incidence of infection and shortening the hospital LOS.[12]

Tumour growth

Tumour cells use GLN in protein catabolism for tumour growth, depleting GLN in the skeletal muscles of cancer patients, leading to cachexia (Figure 1). It is believed that tumours become GLN traps and worsen GLN loss in cancer patients, but also that GLN has the potential to retard or halt tumour growth due to its immuno-modulatory action.[8] Various studies suggest that GLN supplementation suppresses tumour growth by restoring the function of natural 'killer' cells, improving protein metabolism,[3] and enhancing the effect of cancer therapy.[9,11,20,22] The review by Kuhn *et al.*[12] confirmed that GLN improves the clinical state of patients with a variety of malignancies without increasing tumour growth.

Mucositis

Mucositis is the mucosal damage occurring in the mouth, pharynx, larynx, oesophagus, and other areas of the GIT, due to damage caused by cancer therapies, including chemotherapy or radiation therapy (RT), or a combination of both.[33] It is present in twenty to forty percent of patients receiving conventional chemotherapy, eighty percent receiving high-dose chemotherapy, and it occurs in almost all head and neck RT patients.[33] Severe mucositis can lead to a temporary reduction in chemotherapy dose or delays in RT in 35% to 60% of patients, leading to a less favourable prognosis.[9,33] The pathogenesis of mucositis is complex, and is thought to be initiated by cell damage from chemotherapy and/or RT. Factors that are believed to contribute to the amplification of tissue injury include: reactive oxygen species (i.e. free radicals), pro-inflammatory cytokines and pathways, and metabolic by-products of colonising microorganisms.[33] There are a number of classification systems used for staging mucositis, including that of the World Health Organisation (WHO) shown in Table 2.

Table 2: WHO staging of mucositis[34]

WHO score	Classification
Grade 1	Soreness, with or without erythema, but no ulceration
Grade 2	Erythema, ulcers, pain. Patient can swallow solid food
Grade 3	Ulcers with extensive erythema. Significant pain. Inability to swallow solid food. Liquid diet only
Grade 4	Ulcers. Intolerable pain. Feeding by mouth impossible, enteral or parenteral nutrition obligatory. Cannot talk

Opioid analgesics are usually needed in more severe cases of mucositis, because the condition is typically very painful. GIT mucositis presents with pain, nausea, vomiting, and diarrhea, and impairs dietary intake and QoL.[33] Disruption of the GIT mucosal barrier can also cause translocation of microorganisms and/or endotoxins.[35] Poor nutritional status may interfere with healing and mucosal regeneration by decreasing cellular migration and renewal.[36]

Mucositis severely affects QoL and clinical outcomes in cancer patients. Oral GLN, but not IV-GLN, may decrease mucositis and GVHD in BMT patients.[23] A possible trend in the objective reduction of mucositis by glutamine supplementation in non-BMT patients receiving chemotherapy and/or radiotherapy has been reported.[37] Furthermore, a Japanese study[38] using a combination of GLN, fibre and oligosaccharides (GFO) was the first retrospective comparative clinical study of mucosal injury in allogeneic HSCT using GFO. Iyama *et al*. concluded that GFO supplementation was an effective supportive therapy to decrease the severity of mucosal injury in HSCT.[38]

In the systematic review by Van Zyl,[20] significant associations (RR 0.14, $p = 0.05$) were reported in two studies with adult patients ($n = 45$) in which fewer grade 3 or 4 mucositis cases were present when patients received IV-GLN vs placebo. Significant results for interventions >14 days (RR 0.19, $p = 0.0003$) were also obtained in four studies ($n = 410$) in which presence of grade 3 or 4 mucositis was significantly less in the IV-GLN group after 14 days of consecutive administration.[20] Thus, there was a trend towards reduced risk and a delay in the development of severe mucositis with IV-GLN. Nevertheless, too few studies exist to either support or refute that GLN supplementation either reduces the duration of mucositis or prevents its progression to severe mucositis.[20]

IV-GLN has been described as more effective than oral GLN in patients with haematological malignancies (both with and without BMT or HSCT), colorectal cancer, head and neck cancer, and solid tumours undergoing BMT or HSCT, as IV administration ensures full availability of the substrate.[12,20] IV-GLN supplementation was favoured in many studies in order to bypass erratic bioavailability and variable compliance with oral administration, especially in patients with feeding difficulties.[7]

In the United States of America (USA), IV-GLN must be compounded from non-sterile powder, and Sayles *et al.*[9] argue that oral GLN may be more appropriate for the prevention of mucositis under these circumstances.

IV-GLN protects the liver cells from oxidative injury by increasing intracellular glutathione during chemotherapy.[3] The Academy of

Nutrition and Dietetics (AND)[32] associates IV-GLN with improved nitrogen balance and decreased morbidity in HSCT patients. There was an increase in short-term survival in allogeneic-HSCT with GLN-containing PN (Alanyl-GLN; 0.3–0.4 g/kg/body weight).[12] Both the ESPEN guidelines on PN in non-surgical oncology,[39] and the 2009 ASPEN guidelines on nutrition support during adult anti-cancer treatment and haematopoietic cell transplantation,[40] state that HSCT patients may benefit from GLN-supplemented PN.[16,22,40,41] Both organisations gave this recommendation a mid-level grade of evidence.[41] IV-GLN should be initiated early in patients undergoing HSCT.[32,41,42]

A decreased hospital LOS was found when data from allogeneic and autologous BMT patients were combined.[32] A recommendation was made against the use of IV-GLN for the prevention of oral mucositis in patients receiving high-dose chemotherapy prior to HSCT.[43] It seems that IV-GLN supplementation does not benefit well-nourished haematological and solid tumour patients treated by high-dose chemotherapy and autologous BMT.[12]

Murray and Pindoria[44] recommend that PN with GLN can be considered in patients with severe gastrointestinal failure, which can possibly cause one to consider including haematology patients with typhlitis or ileus.

PN with GLN may also be associated with fewer infections,[16,26] but not with shorter hospital LOS.[16,20,26] There is insufficient data on whether GLN supplementation reduces the incidence of infection, but Van Zyl's systematic review did find a trend towards a reduction.[20] A significantly lower incidence of infection and hyperglycaemia was seen in GIT-malignancy surgery patients on GLN-supplemented PN (0.5 g/kg body weight/day).[15] There was a reduction in infections with IV-GLN in patients undergoing BMT. However, there was also an increase in relapse in autologous transplantation patients in two small studies.[12,20,23]

In paediatric HSCT patients, IV-GLN supplementation decreased drug-related toxicity,[45] reduced the duration of fever, [19,45] and decreased the incidence of sinusoidal obstruction syndrome (OR = 0.195, $p = 0.067$).[45] The evidence that IV-GLN reduces both the incidence and severity of mucositis was not statistically significant,[29] although Kuskonmaz *et al.*[45] did notice a trend ($p = 0.1118$) towards a reduced incidence of severe mucositis (grade 3 and 4). There is also no significant evidence that IV-GLN supplementation reduces infection rates,[19,29] hospital LOS,[19,29] GVHD, mortality, or the need for total PN use in children.[19]

Guidelines

Suitable candidates for IV-GLN include, in particular, critically ill patients with burns, trauma, or cancer.[15,46] Wischmeyer *et al.*[18] recommend that IV-GLN supplementation, as a component of nutrition support, be considered as an approach to improve outcomes of critical illness in selected patients. The ASPEN 2016 guidelines on nutrition support for adult critically-ill patients also recommend against routine IV-GLN supplementation in the critical care setting; but, when PN is used, consideration should be given to supplementing the PN with GLN.[47] It should be noted that cancer patients also do get admitted to ICU, especially surgical and haematological cancer patients; and, therefore, the critical care setting guidelines may sometimes be applicable to this patient group.

IV-GLN 'may or may not' be recommended to prevent or treat oral mucositis in oncology patients with solid tumours, since the effectiveness of L-alanyl-L-glutamine in treating or preventing oral mucositis has not been established given the limited research in head and neck and HSCT patients.[32] The guidelines also recommend caution when considering provision of IV-GLN to oncology patients who have hepatic insufficiency or failure. Liver and kidney functions should be monitored.[32]

Both the 2009 ESPEN guidelines on PN in non-surgical oncology[39] and the 2009 ASPEN guidelines on nutrition support during adult anti-cancer treatment in HSCT[40] state that HSCT patients may benefit from GLN-supplemented PN,[16,22,32,40,41] at a dose of 0.2 to 0.5 g/kg/day.[32,41] and should be initiated early in the treatment course.[32] The dosage recommendations for administration of intravenousl glutamine in adults are set out in Table 3.

The Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) has set out evidence-based clinical practice guidelines for mucositis.[33] The guidelines, published by the European Society for Medical Oncology, as well as the USA National Comprehensive Cancer Network, are both adaptations of the MASCC/ISOO guidelines. The latest updated guidelines, based on systematic reviews of evidence for various interventions, were published in May 2014. However, owing to inadequate or conflicting evidence, a guideline was not possible in relation to GLN for all cancers, except in HSCT, where the recommendation was against the IV-GLN for the prevention of mucositis, based on level 2 evidence from previously published criteria used by MASCC.[33,43] IV-GLN is not recommended to prevent or treat oral mucositis in patients receiving high-dose chemotherapy prior to HSCT.[43] The MASCC/ISOO panel was unable to form a guideline on the systemic use of GLN specifically for the prevention of gastrointestinal mucositis (excluding the oral cavity), since newer evidence has emerged which is in conflict with their previous guideline; and, hence, advised against the use of systemic GLN in patients on chemotherapy.[33]

The 2011 ASPEN position paper on GLN-supplemented PN[41] state that specific patient populations may benefit from the use of PN GLN when indicated.[41] However, they did state that the full benefit of PN GLN supplementation is still unclear since no effect was seen in post-autologous BMT patients, whereas reduced LOS was seen when data from allogeneic and autologous transplants was combined.[32,41] They recommend that initiation of PN GLN supplementation in suitable candidates should probably occur soon after admission, and in doses of 0.2 to 0.5 g/kg/day, to be effective.[41] The ASPEN 2011 guidelines state that due to limited available data, no recommendations regarding the use of GLN supplemented PN can be made in paediatric and neonatal patients.[41]

There is no evidence of any clinical toxicity or generation of toxic metabolites at doses up to 0.3 g/kg.[11] There is little evidence for short periods of GLN administration (<7 days). A greater benefit was seen after at least 14 days, when GLN levels appeared most affected.[20] The dosage recommendations for administration of oral glutamine in adults are set out in Table 4.

The 2016 ASPEN guidelines for critically ill patients[47] suggest that neither supplemental enteral nor parenteral GLN should be routinely used in critically care, but do not specifically address the use of GLN in an oncology setting. Kuhn *et al.*[12] made no oncology-specific recommendations on GLN supplementation's route, dose, timing or duration. As stated previously, since

Table 3: Dosage recommendations for intravenous glutamine administration in adults

Recommendation	Form	Timing/Duration	Patient population	References
0.1–0.42 g/kg/day (7.5–30 g/day)	Dipeptide*	8–21 days - during chemotherapy or BMT with or without chemo and/or RT	Head and neck GIT Breast Solid tumours Haematological cancers	20
> 0.2 g/kg/day			Critical illness	42, 48
>0.2–0.5 g/kg/day	GLN-supplemented PN	Soon after admission	Critical care	41
0.22–0.42 g/kg/day (16–30 g/day)	Dipeptide*	14–21 days - during chemotherapy or BMT with or without chemo and/or RT	Haematological cancers Solid tumours Colorectal cancer	20
0.3–0.6 g/kg/day	Dipeptide* (GLN=0.2–0.4 g/kg/d)		ICU	41, 49
0.35–0.5 g/kg/day	Dipeptide*		ICU	15
0.3–0.5 g/kg/day	As part of total PN		ICU	6
<0.5 g/kg/day	As part of total PN and/or EN	After resolution of shock/MOF	ICU	18
0.57 g/kg/day	L-glutamine, as part of dipeptide*	Up to 30 days	Oncology patients on treatment	20
0.025 g/kg/hour	L-glutamine, as part of dipeptide*		Critical illness	42
0.57 g/kg/day	Combined with PN		Critical illness	42
0.65 g/kg/day	Dipeptide* (GLN=0.5 g/kg/d)	As early as possible	Burns, trauma, critical illness	42
20–30 g/day	Exogenous		Critical illness	6
0.6 g/kg/day	GLN-supplemented PN		Non-surgical oncology/HSCT	39
1 g/kg/day (70 g/day)	Dipeptide*	Up to 10 days	Oncology patients on treatment	20
Up to 40 g/day	Enteral or IV		BMT and high-dose chemo	22

BMT: bone marrow transplant; chemo: chemotherapy; EN: enteral nutrition; GIT: gastrointestinal tract;HSCT: haematopoetic stem cell transplantation; ICU: intensive care unit; IV: intravenous; MOF: multiple organ failure; PN: parenteral nutrition; RT – radiotherapy.
* The alanyl-glutamine dipeptide contains 13,5 g L-glutamine per vial.

Table 4: Dosage recommendations for oral glutamine administration in adults

Recommendation	Application	Type of cancer treatment	Duration	Patient population	References
0.42 g/kg/day (30 g/day)	-	Unspecified	up to 10 weeks	Oncology patients	20x
30 g/day	Mucositis	Radio-chemotherapy		Oesophageal cancer	12
30 g/day	Oral mucositis	Anthracycline-based chemo-therapy		Breast cancer	9
30 g/day	RIO	Radiotherapy or ra-dio-chemotherapy		Nondio-chemotherapy chemoth	9
0.22–0.42 g/kg/day (16–30 g/day)	Diarrhoea duration	Chemotherapy or BMT with or without chemo and/or RT	14–21 days	Haematological cancersSolid tumoursColorectal cancer	20x
0.1–0.42 g/kg/day (7.5–30 g/day)	Oral mucositis	Chemotherapy or BMT with or without chemo and/or RT	8–21 days	Head and neck GITBreastSol-id tumoursHaematological cancers	20x
10 g three times a day	RIO	RT with or without chemo-therapy	one month before starting radiation until one month after completion of radiation	RT to thoracic area (e.g. breast, head and neck, lung, lymphoma)	11, 53
Up to 40 g/day	-	BMT and high-dose chemo-therapy		Haematological cancers	22x

Notes: RIO: radiation induced oesophagitis; chemo: chemotherapy; RT: radiotherapy; GIT: gastrointestinal.

oncology patients may be admitted to ICU, the guidelines for ICU should not be ignored. GLN 'may or may not' be recommended to prevent or improve chemotherapy-induced peripheral neuropathy, as only limited success in preventing or improving peripheral neuropathy in oncology patients receiving specific chemotherapies has been reported.[32] Wernerman[50] recommends that GLN supplementation be restricted to where a safety protocol is used or within clinical studies.

Table 5: Contraindications for the use of Glutamine by any route[18,43,51,54]

Condition	Value
Renal failure or insufficiency	Creatinine clearance <25 ml/min
Liver failure or insufficiency	INR>1.5; altered liver function tests
Metabolic acidosis	Altered arterial blood gas, serum electrolytes and urine pH
Short use	Less than 7 days
Use delay	More than 24 h
Inappropriate dose	More or less than recommended
Protein imbalance	>30% of total amino acids
HSCT	Do not give IV-GLN prior to HSCT
	Do not give enteral GLN during HSCT
Acute phase of critical illness	>0.5 g/kg/d of PN, alone or combined with EN

Notes: EN: enteral nutrition; HSCT: haematopoetic stem cell transplantation; INR: international normal ratio; IV: intravenous; PN: parenteral nutrition.

The ESPEN guidelines on EN for non-surgical oncology patients[51] state that enteral administration of GLN is not recommended during HSCT due to inconclusive data.

The 2009 ESPGHAN guidelines on paediatric EN state that it is currently unknown whether 'immune-modulating formulae' (like GLN) provide benefit in children.[52]

Side effects and contraindications

Adverse reactions (Table 5) of GLN, noted by Azman *et al.*[27] included: abdominal discomfort; abdominal bloating; and diarrhoea. Other side effects of GLN include: chills; nausea; and vomiting, if the infusion rate is exceeds >0.1 g amino acid/kg body weight/hr.[54] The risk for infection with IV-GLN supplementation is similar to that of PN.[32]

GLN supplementation can cause or aggravate azotaemia in acute or chronic renal failure (not clinically significant).[41]

GLN is antagonised physiologically by lactulose during the treatment of high ammonia levels during liver failure.[3] It could cause or aggravate hepatic encephalopathy.[41]

GLN is generally safe in patients with stabilised circulatory shock and resolved metabolic acidosis, i.e. brain damage; respiratory failure receiving adequate mechanical ventilation; or gastrointestinal failure.[46] Monitoring of liver functions is recommended.[32,43,54] The REDOXS study[17] showed that early administration of GLN was harmful in critically ill patients with MOF. Avoid IV-GLN in the acute phase of critical illness, with MOF or unresuscitated shock requiring significant vasopressor support.[18] Glutamate, a by-product of the GLN metabolism, may cause brain excitation in epileptic patients.[3]

Conclusion

GLN use is still a clinical and economically attractive management strategy.[55] Sufficient GLN administration, as part of nutrition therapy of cancer patients, is safe,[12] when administered to the correct patient for the correct reason.[55]

A cancer patient's QoL requires careful consideration by the health practitioner, especially when it relates to the alleviation of pain and discomfort.[20] GLN supplementation may improve QoL,[20] by decreasing the incidence and/or severity of: chemotherapy-associated mucositis; irinotecan-associated diarrhoea; paclitaxel-induced neuropathy; anthracycline-induced cardiotoxicity; and hepatic veno-occlusive disease during high-dose chemotherapy and HSCT.

No published clinical guidelines or recommendations exist regarding the use of PN GLN supplementation in neonatal or paediatric patients.[41] Insufficient evidence exists to either recommend regular use of GLN in adults,[3] or to provide guidance on GLN supplementation for prevention or reduction of severe mucositis.

Larger, multicentre, randomised placebo-controlled studies are needed in both adult and paediatric oncology populations[3,19,20] Since oncology is a diverse field, studies would have to be specific to the cancer-type, as well as the side effects experienced with the cancer-specific treatment. More clarity is needed on: oncology-specific GLN supplementation of PN alone, or in combination with enteral/oral GLN; infection reduction; the use of free L-glutamine vs the dipeptide; the administration timing and dose; as well as the cost benefit analysis.

At this stage, the way forward would be to follow the existing guidelines as far as possible. If uncertainty exists as to whether a patient would benefit from GLN use, the duty of the health care professional is to first do no harm, and therefore GLN administration should then be avoided.

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