



## Effects of enteral glutamine supplementation on intestinal permeability in acute pancreatitis: A literature review

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Received 7 January 2021  
Accepted 15 July 2021

Link to DOI:  
10.25220/WNJ.V04.i2.0007

Journal Website:  
[www.worldnutrijournal.org](http://www.worldnutrijournal.org)

### Abstract

**Background.** Glutamine has been shown to improve the gut mucosal barrier. However, the evidence for benefit of enteral glutamine on intestinal permeability in acute pancreatitis (AP) is limited.

**Objective.** To identify the effect of enteral glutamine supplementation on intestinal permeability in patients with AP.

**Method.** A systematic search was conducted by extracting evidence from published studies on enteral glutamine supplementation in three databases (PubMed, Cochrane Central Register of Controlled Trials, and SciElo) relevant to AP from 1 January 2010 till 31 December 2020. Outcomes assessed were intestinal permeability, infectious complication, hospital length of stay, and mortality rate.

**Results.** A total of 6 studies found by search, in which 2 human RCTs with 7 days duration of intervention with 1b-1c quality based on Criteria by Center of Evidence-Based Medicine, University of Oxford. Both studies showed the benefit of early enteral glutamine supplementation on intestinal permeability in patients with AP.

**Conclusions.** Enteral glutamine supplementation has been shown to improve the gut mucosal barrier in AP. Despite its significant improvement in intestinal permeability, glutamine supplementation did not display a consistently positive effect on clinical outcomes.

**Keywords** glutamine, enteral, acute pancreatitis, intestinal permeability

### Abbreviations

AP: acute pancreatitis

EN: enteral nutrition

LMR: lactulose mannitol ratio

LOS: length of stay

SAP: severe acute pancreatitis

TPN: total parenteral nutrition

### Introduction

Acute pancreatitis (AP) is one of the most common causes of hospitalization for a gastrointestinal condition in the United States, with a global incidence ranging from 5–30 cases per 100,000 population per year.<sup>1</sup> In the Eastern countries, especially Asia, the most common cause of AP is biliary disease (49–54%) followed by alcohol abuse (20%).<sup>2</sup> AP is an acute, non-bacterial inflammation of the pancreas, in which auto digestion of activated pancreatic enzymes occurs and results in edema, vascular damage, bleeding, and necrosis of the pancreas.<sup>3</sup> Approximately 20% of patients develop severe acute pancreatitis (SAP) with a substantial mortality rate of 20–40% in the presence of

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pancreatic necrosis.<sup>4</sup> In SAP, inflammatory response causes disruption of the intestinal barrier and translocation of gram-negative bacteria which can be responsible for infection of the necrotic pancreas, systemic inflammatory response (SIRS), sepsis, and multi organ dysfunction syndrome (MODS). Hence, the main goals of treatment in SAP is to maintain the integrity of the gut barrier since the early phase focusing attention on the role of gut as the first course for SAP systemic complications.<sup>3,5</sup>

Originally, patients with SAP were made nil per os (NPO) to minimize stimulation of the pancreas and to reduce pain. Despite the NPO state, patients were given total parenteral nutrition (TPN).<sup>6</sup> Lack of enteral feeding in TPN results in gastrointestinal mucosal atrophy, bacterial overgrowth, increased intestinal permeability and translocation of bacteria, which contribute to poorer prognosis.<sup>7</sup> In contrary, meta-analysis by Petrov, et al.<sup>8</sup> showed that enteral nutrition (EN) results in significant risk reduction for morbidity and mortality in patients with predicted SAP. Moreover, systematic review by McClave, et al.<sup>9</sup> also suggested that patients with SAP should begin EN early as it allows a trophic action on the intestinal wall, which maintain the intestinal barrier and prevent the bacterial translocation and results in better outcome.<sup>6</sup> Recent meta-analysis by Zhou, et al.<sup>10</sup> showed beneficial effect of adding immune-enhanced formulas to the standard nutrition therapy in patients with AP either via the enteral or parenteral route. Glutamine, as one of the immunonutrition, which is also the major substrate for intestinal cells, have been investigated for its protective effects on intestinal mucosal integrity and modulation of inflammatory response.<sup>11,12</sup> Several meta-analysis have been performed assessing the effects of parenteral and enteral administration of glutamine compared with conventional methods.<sup>10,13,14</sup> Studies confirm the improvements in serum albumin, C-reactive protein (CRP),<sup>13,14</sup> incidence of infection and mortality rate.<sup>10,13,14</sup> To our knowledge, there are no review yet discussing the effects of enteral administration of glutamine on intestinal integrity. This review will investigate the role of enteral glutamine supplementation on intestinal integrity in acute pancreatitis, along with mortality and morbidity in terms of infectious complication and hospital length of stay (LOS).

### *Clinical question*

A 30-year-old woman was admitted to the hospital with 24h severe epigastric pain and intractable vomiting. Two days before admission, the patient began to have fever, headache, and nausea. The pain was worsened with eating. Her past medical history was otherwise negative, and she had no allergies. She denied alcohol intake or tobacco use. She has a two-time history of cesarean section, which was last two years ago. Examination revealed a woman with 38.5°C fever and epigastric abdominal pain during superficial palpation, with no peritonitis signs. There were non-palpable masses and bowel sounds were normal. Abdominal ultrasonography showed a contracted gallbladder without lithiasis with normal biliary tree, hypoechoic extrapancreatic inflammation and pancreatic parenchymal inhomogeneity, with small amount of fluid localized peri-hepatic and in rectouterine pouch. Laboratory investigations showed leucocytosis, elevated serum lipase (3212 U/L) and amylase (278 U/L), and elevated IgM/IgG EndoCab. The patient was diagnosed with acute pancreatitis and immediately placed on a nasogastric tube and started to be given EN within 24 hours. The physician in charge would provide early enteral nutrition and investigate whether enteral glutamine has a role to improve intestinal permeability and subsequently reduce morbidity and mortality rate in patients with AP.

### **Methods**

Three electronic bibliographic databases (Pubmed, Cochrane Central Register of Controlled Trials, and SciElo) were systematically searched by author E.A.S. All randomized controlled trials (RCTs) of enteral glutamine supplementation in acute pancreatitis between January 1, 2010 and December 31, 2020 were included in this review. Any included study had to assess intestinal integrity as an outcome and had to be a human trial in adults. We used the search terms 'glutamine' AND ('enteral' OR 'oral') AND ('pancreatitis' OR 'acute pancreatitis') AND ('intestinal permeability' OR 'gut permeability') to identify relevant studies (**Table 1**). Publications in non-English languages, unpublished studies, online proceeding, and non-full text paper were not included.

Titles and abstracts were screened by author E.A.S to identify relevant studies. Full-text articles of potentially eligible studies that met the selection criteria were obtained. The inclusion criteria for this review were RCT, participants aged at least 18 years old, single glutamine intervention, enteral administered intervention, and intestinal permeability as main outcome. Non-RCT, participants aged under 18 years old, and review articles were excluded. Any discrepancy was discussed with the senior author D.S.

All data from the eligible studies were extracted into tabular form. Extracted data included information on the first author, the country where the trial was held, the study population and sample size, intervention and comparison groups, the duration of intervention, the outcomes measured and their time of assessment, and the results of the clinical and/or laboratory parameter outcomes. The quality of the studies was assessed by two authors (E.A.S., D.S.) using guideline for RCT based on Criteria by Center of Evidence-Based Medicine, University of Oxford and the summary is provided in Table 2. Outcome measurements included intestinal integrity, incidence of infectious complication, hospital LOS, and mortality rate.

## Results

The study selection process is summarized in Figure 1. The initial systematic search identified 6 citations of which 2 potentially eligible articles<sup>15,16</sup> was critically appraised. We excluded 4 study for duplications and non-human study. One record from PubMed excluded was a non-human study and three records from Cochrane were excluded for duplication. Details of the included studies are presented in Table 3 and Table 4. Two studies included in this review were RCTs of enteral glutamine supplementation in acute pancreatitis for 7 days which investigated intestinal permeability as an outcome.<sup>15,16</sup> Biomarkers used to assess intestinal permeability were different in both studies. Other outcomes included in this review were incidence of infectious complication, hospital LOS, and mortality rate.

## Discussion

Study by Arutla M, et al.<sup>15</sup> showed significant reduction of polyethylene-glycol (PEG) in the intervention group after 7 days of supplementation. PEG, as well as sugars, or 51chromium-labelled ethylenediamine tetra-acetic acid (51CrEDTA) are probes used for examining intestinal permeability. Intestinal permeability analysis is based on the appearance of orally administered probes in the circulation and/or urine after permeation of the intestinal epithelium. Each probe has its specific advantages and disadvantages and requires a specific method of detection. PEG is one of the commonly used option for permeability analysis which is based on the use of PEG probes. PEG has few advantages over the use of 51CrEDTA and sugars for permeability analysis, such as it does not require radioactivity, it is not metabolized by enzymes or degraded by bacteria within the human gastrointestinal tract, and it is analyzed using less expensive and time-consuming method than other probes.<sup>17</sup> High levels of PEG found in the circulation indicates increased intestinal permeability. Significant reduction of PEG after enteral glutamine supplementation in AP demonstrate the beneficial effect of glutamine on intestinal permeability.

Glutamine is essential for the growth, survival, and physiological health of actively dividing cells such as enterocytes, fibroblasts, and lymphocytes. Gastrointestinal mucosal integrity is quickly restored and maintained by cell proliferation, migration, and differentiation. Enteral feeding appears to be the primary stimulus for the regulation of proliferative response in the intestinal tract, which is accomplished mainly by the glutamine. Gut mucosa is the major site of glutamine metabolism in which glutamine is a major source of energy for proliferation and differentiation of intestinal epithelial cells. Under conditions of severe inflammation, the physiological level of glutamine is inadequate to balance the damage and needs to be replaced.<sup>18</sup> Not only act as fuel for enterocyte, glutamine also modulates the inflammatory response and oxidative reactions, in which ultimately maintain the tight junction of intestinal cells.<sup>19</sup>

It has been identified that glutamine administration influences intestinal permeability.

However, which route is the most appropriate in providing glutamine supplementation to benefit gut integrity is still debatable. Enteral and parenteral glutamine supplementations have different metabolic pathways. A pilot study by Uranjek, et al.<sup>20</sup> investigating the effect of the route of glutamine supplementation on intestinal permeability in 81 intensive care unit (ICU) patients. The study showed no significant difference in lactulose mannitol ratio (LMR) between enteral glutamine compared with parenteral route.

Ligthart-Melis, et al.<sup>21</sup> demonstrated their study in 16 patients undergoing upper gastrointestinal surgery to receive an IV or EN infusion of L-[2-(15)N]glutamine. The study revealed that arterial [(15)N] glutamine was significantly lower during EN reflecting intestinal metabolism preferably takes up enterally administered glutamine compared with intravenously provided glutamine. This suggests that the route of administration of glutamine supplementation is influenced by the underlying condition.

The second study included in this review was study by Singh, et al.<sup>16</sup> which evaluating the effect of oral glutamine supplementation on gut permeability and endotoxemia (surrogate end point) in patients with SAP. The study discovered there was no significant difference in LMR between intervention and control group after intervention. However, there was significant increase in IgM antiendotoxin antibodies in intervention group.

Similar to study by Sharma, et al.<sup>22</sup> investigating the intestinal permeability and anti-endotoxin antibodies immunoglobulin in SAP compared to healthy controls. The study showed that the intestinal permeability (LMR) at day 1 and day 7 of admission was no different when compared with controls. In the natural course of AP, intestinal permeability has been found to increase gradually within the first 72 hours and normalize slowly from the second week to one and a half months.<sup>23-25</sup>

Singh, et al.<sup>16</sup> also demonstrated insignificant changes in LMR after glutamine supplementation in the intervention group as well as control group, possibly because of the maintained gut mucosal barrier of patients that were fed enterally. The IgM endotoxin antibody titer is an indirect marker for endotoxemia. The study found a significant increase in IgM endotoxin antibody in the group receiving

glutamine after 7 days of intervention suggesting the decreased of endotoxemia. Compared to other studies with non-conclusive results, Pearce, et al.<sup>26</sup> conducted a study on 31 AP patients given enteral feed containing glutamine, arginine, and omega-3 fatty acid compared to isonitrogenous & isocaloric enteral feed for 3 days. There was significant difference in increment of IgG antiendotoxin antibody in control group compared to intervention group, however this effect was not seen in the IgM antiendotoxin antibodies and the explanation for this effect is not entirely clear.

Even though there was significant increase in intestinal permeability with enteral glutamine administration, both studies did not show a consistent clinical improvement as evidenced by equal infectious complications, hospital stay, or mortality in both groups. In line with meta-analysis investigating clinical benefit of immunonutrition over standard enteral formulas in patients with acute pancreatitis. There is no evidence that enteral nutrition supplemented with glutamine, arginine and/or omega-3 fatty acids has beneficial effect on infectious complications, hospital LOS, and mortality rate in acute pancreatitis compared to standard EN.<sup>8</sup>

Both included studies reported significant improvement in intestinal permeability. These studies were conducted in the same country. India, like any other developing countries, is concerned with spectrum of enteropathies, characterized by small intestinal inflammation, reduced absorptive capacity, and increased intestinal permeability.<sup>27</sup> This condition commonly affect people in developing countries as Menzies, et al.<sup>28</sup> speculated that in many tropical countries, especially where there is widespread poverty and poor sanitation, may be exposed to repeated gastrointestinal infection leading to a chronic reversible impairment of intestinal function.

Studies included in this review demonstrated beneficial effects of enteral glutamine supplementation on intestinal permeability in acute pancreatitis. However, this beneficial effect did not in accordance with any clinical improvements, for instance incidence of infectious complications, hospital LOS, and mortality rate. Despite significant improvement in intestinal permeability, both studies were underpowered consequently the results

obtained with enteral glutamine cannot be advocated for routine administration in patients with AP. An adequately powered larger study with longer duration of supplementation is required to substantiate the evidence.

## **Conclusion**

The goal of nutritional support in AP is to reduce inflammation and maintain intestinal permeability. Enteral glutamine supplementation has been shown to improve gut mucosal barrier in AP. Despite its significant improvement in intestinal permeability, glutamine supplementation did not display a consistent positive effect on clinical outcome.

### *What is Already Known*

Acute pancreatitis (AP) is associated with altered gut mucosal barrier.

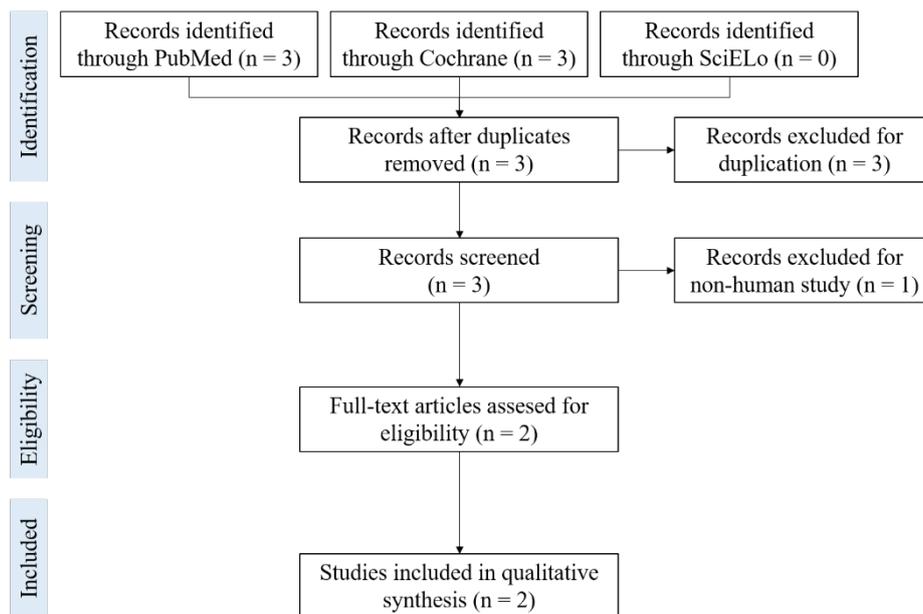
Glutamine supplementation have been shown to improve gut mucosal barrier in AP.

### *What This Study Adds*

Enteral glutamine supplementation improves intestinal permeability in AP patients

### *What are the future clinical and research implications of the study findings?*

Investigators need to evaluate the effects of long-term enteral glutamine supplementation in a large multicenter RCTs of patients with AP.



**Figure 1.** PRISMA flow chart depicting the article selection process for the review

**Table 1.** Terminology used in three databases

Database	Terminology	Hits	Result
PubMed	(((glutamine[Title/Abstract] OR (glutamine[MeSH Terms])) AND (((enteral[Title/Abstract] OR (enteral[MeSH Terms]) OR (oral[Title/Abstract] OR (oral[MeSH Terms])))) AND (((pancreatitis[Title/Abstract] OR (pancreatitis[MeSH Terms]) OR (acute pancreatitis[Title/Abstract] OR (acute pancreatitis[MeSH Terms])))) AND (((intestinal permeability[Title/Abstract] OR (intestinal permeability[MeSH Terms]) OR (gut permeability[Title/Abstract] OR (gut permeability[MeSH Terms]))))	3	2
Cochrane Central Register of Controlled Trials	Filter: published in January 1 <sup>st</sup> , 2010 – December 31 <sup>st</sup> , 2020 (glutamine):ti,ab,kw AND ("Enteral"):ti,ab,kw AND (pancreatitis):ti,ab,kw AND ("intestinal permeability"):ti,ab,kw Filter: published in the last 10 years	3	0
SciElo	(glutamine) AND (enteral) AND (pancreatitis) AND (intestinal permeability) Filter: published in the last 10 years	0	0

**Table 2.** Critical appraisal of the RCT study based on criteria by Center of Evidence-Based Medicine, University of Oxford

Parameters	Questions	Arutla M, et al. <sup>15</sup>	Singh N, et al. <sup>16</sup>
<b>Validity</b>	Was the assignment of patient to treatments randomized?	Yes	Yes
	Was the randomization list concealed?	No	Yes
	Were the groups similar at the start of the trial?	Yes	Yes
	Aside from the allocated treatment, were groups treated equally?	No	Yes
	Were all patients who entered the trial accounted for?	Yes	Yes
	Were they analyzed in the group to which they were randomized?	Yes	Yes
	Were measures objective or were the patients and clinicians kept “blind” to which treatment was being received?	No	Yes
<b>Importance</b>	How large was the treatment effect?	Polyethylene glycol reduction in intervention group (7.61 ± 4.5), $P = 0.02$	IgM antiendotoxin Ab increment in intervention group ( $P = 0.0164$ )
	How precise was the estimate of the treatment effect?	Precise, the 95% CI of the results are narrow. Poly-ethylene glycol reduction in intervention group (7.61 ± 4.5), $P = 0.02$	Precise, the 95% CI of the results are narrow.
<b>Applicability</b>	Is my patient so different to those in the study that the results cannot apply?	Precise, the 95% CI of the results are narrow. The study has the same characteristic as case scenario	The study has the same characteristic as case scenario
	Is the treatment feasible in my setting?	No	No
	Will the potential benefit of treatment outweigh the potential harms of treatment for my patient?	Yes	Yes
<b>Level of evidence of this study based on Oxford CEBM</b>		1c	1b

**Table 3.** Characteristic of the included studies assessing the effect of enteral glutamine supplementation on intestinal permeability in acute pancreatitis

Included studies	Participants (age at enrollment)	Sample size	Intervention	Control	Feeding start	Duration of intervention	Glutamine dosage
<b>Arutla M, et al.<sup>15</sup> 2019 (India)</b>	Patients aged 18-60 years old with AP with $\leq$ 72 hours of the onset of abdominal pain + APACHE II score $\geq$ 8 or SOFA score $\geq$ 2 or SIRS $>$ 2 for 48 h or BUN rise $>$ 5 mg/dL over 48 h from admission	n: 31 I: 18 C: 22	Standard nutrition + enteral glutamine	Standard nutrition	$\leq$ 48 hours of admission	7 days	0.57 g/kg body weight per day
<b>Singh N, et al.<sup>16</sup> 2014 (India)</b>	Consecutive patients aged 18-80 years old with acute pancreatitis admitted to the ward	n: 80 I: 41 C: 39	10 g glutamine (KABIMMUNE) twice a day	10 g whey protein twice a day	$\leq$ 7 days of the onset of symptom	7 days	20 g/day

AP, acute pancreatitis; APACHE, acute physiology and chronic health evaluation; BUN, blood urea nitrogen; C, control group; I, intervention group; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment

**Table 4.** Summary of clinical outcomes of included studies

Included studies	Number of patients	Intestinal permeability	Complication of infection	Length of stay	Mortality
<b>Arutla M, et al.<sup>15</sup> 2019 (India)</b>	I: 18 C: 22	There was significant PEG reduction in I group.  Group I Day 1 (n 18/18): 39.91 ± 11.9 Day 7 (n 18/18): 32.30 ± 7.4 <b>P = 0.02</b>  Group C Day 1 (n 22/22): 48.73 ± 12.6 Day 7 (n 22/22): 45.25 ± 7.9 <i>P</i> = 0.32	There was no difference in complication of infection (development of infected necrosis) between I and C group.  I: 5/18 C: 6/22 <i>P</i> = 0.53	There was no difference in duration of hospital stay between I and C group.  I: 15.58 ± 10.3 days C: 15.63 ± 18.8 days <i>P</i> = 0.99	There was no difference in in-hospital mortality between I and C group.  I: 1/18 C: 1/22 <i>P</i> = 0.43
<b>Singh N, et al.<sup>16</sup> 2014 (India)</b>	I: 41 C: 39	There was no significant difference in LMR between I and C group after intervention.  Group I Day 7 (n 29/41): 0.15 (0.02-2) Group C Day 7 (n 28/39): 0.14 (0.01-5) <i>P</i> = 0.8732  There was no significant increase in IgG antiendotoxin antibody in both I and C group. Group I Day 0 (n 39/41): 72 (4-1600) Day 7 (n 36/41): 86 (4-1600) <i>P</i> = 0.1667  Group C Day 0 (n 35/39): 74 (4-1760) Day 7 (n 29/39): 100 (2-1640) <i>P</i> = 0.7293  There was significant increase in IgM antiendotoxin antibody in I group. Group I Day 0 (n 41/41): 33 (4-175) Day 7 (n 37/41): 40 (8-350) <b>P = 0.0164</b> Group C Day 0 (n 38/39): 45 (2-180) Day 7 (n 32/39): 56 (7-350) <i>P</i> = 0.1552	There was no difference in complication of infection between I and C group.  I: 21/41 C: 19/39 <i>P</i> = 1.000	There was no difference in duration of hospital stay between I and C group.  I: 12 (1-101) days C: 11 (2-36) days <i>P</i> = 0.236	There was no difference in in-hospital mortality between I and C group.  I: 5/41 C: 6/39 <i>P</i> = 0.753

AP, acute pancreatitis; C, control group; I, intervention group; LMR, lactulose mannitol ratio; PEG, polyethylene glycol

## Conflict of Interest

Authors declared no conflict of interest regarding this article.

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