



# Enteral Glutamine Supplementation is Associated with Lowering Wound Infection Morbidity and Length of Hospital Stay among Burn Patients: A Meta-analysis and Systematic Review

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## Abstract

**BACKGROUND:** Significant nutritional support to meet increased energy expenditure is vital for burn patient's survival. Burn injury may lead to a significant decrease in glutamine levels, which inspired the hypothesis that glutamine supplementation following burn injury would improve outcomes.

**AIM:** Hence, the purpose of this meta-analysis study was to provide the rationale for determining the efficacy and safety of enteral glutamine in burn patients.

**METHODS:** We conducted a meta-analysis based on PRISMA design to assess the potency of enteral glutamine supplementation as adjuvant treatment in patients with burn trauma. PubMed, ScienceDirect, and Google Scholar were searched systematically using the following keywords: "Enteral glutamine," "burn patients," "critical ill," "infection," and "length of stay". Newcastle-Ottawa Scale (NOS) was used to assess the quality of papers included in our meta-analysis. A Z test was used to determine the significance of pooled effect estimates. Publication bias was assessed using Egger's. We used comprehensive meta-analysis (CMA) version 2.1 to analyze the data.

**RESULTS:** A total of 12 studies recording 344 cases and 335 controls were enrolled for our analysis. Data on hospital length of stay (LOS) were found that enteral glutamine supplementation provided a significant result in reducing the LOS (Std mean diff: 0.70, 95% CI: 0.16–1.24;  $P = 0.0100$ ). We also found that a higher risk of positive wound culture was significantly observed in patients without the supplementation of enteral glutamine (OR 2.15, 95% CI: 1.41–3.27;  $P = 0.0003$ ) compared to patients receiving enteral glutamine supplementation among burn patients.

**CONCLUSION:** In our meta-analysis study, enteral glutamine in burn patients confers significantly shorter LOS and lower risk of wound infection among burn patients. We suggest that enteral glutamine supplementation may be a beneficial intervention for the management of burn patients.

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## Introduction

Burn injury is the most devastating injury worldwide, affecting nearly 11 million people worldwide, with approximately 300,000 deaths annually [1]. Morbidity and mortality of burn injury vary with age and region of the world. The pathological mechanisms of burn injury are complex. Briefly, burns result in an inflammatory response and catabolism, resulting in substantial nutrient loss and deficiency [2]. Burns of high severity result in significant metabolism disturbances, a prolonged and persistent hypermetabolic state, and increased catabolism [2], [3]. If not treated properly, this can lead to muscle loss and cachexia. The metabolic rate in patients with burns can be twice that of normal conditions. If this large energy requirement is not compensated, it can disrupt the wound healing process, organ dysfunction, and susceptibility to infection. In the past 20 years, many studies have reported the importance of assessing nutritional needs and providing proper nutrition in burn patients [2].

Nutritional support is an important aspect in managing patients with burns to meet the increased energy expenditure [2], [3]. Enteral nutrition plays an important role in critically ill patients, especially patients with burns. Burn patients are often in a persistent catabolic state, which can lead to malnutrition [2]. Malnutrition in critically ill patients is a predictor of poor outcomes [2]. Although nutritional interventions did not result in a significant reduction in early mortality, adequate nutritional therapy can speed healing and thus reduce the length of stay. The presence of nutrients in the intestinal lumen results in increased gastrointestinal function maintains the anatomic structure and function of the mucosal epithelium, reduces the occurrence of bacterial translocation, and increases gut-associated immune function [4], [5].

Glutamine is a pharmacconutrient that has a major role in burn patients. Burns result in a significant decrease in glutamine levels, so it is thought that glutamine supplementation in burns will improve outcomes [6]. Low blood glutamine levels

have been associated with poor clinical outcomes in critically ill patients [7]. Several previous studies on enteral glutamine supplementation found that it reduced infection, wound infection, and increased surrogate markers of intestinal mucosal barrier function [7], [8], [9]. Six more randomized trials of glutamine supplementation in burns patients had been completed, and the results suggested a significant reduction in mortality and hospital length of stay [10].

## Methods

### Study design

During August–October 2020, we conducted a meta-analysis to assess the potency of enteral glutamine supplementation as adjuvant treatment in patients with burn trauma. In effort to reach this goal, we collected several papers from PubMed, ScienceDirect, and Google Scholar concerning this association to calculate the combination of pooled effect estimates and 95% confidence interval (CI) using a Z test. This design of the study was adapted from Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).

### Search strategy

PubMed, ScienceDirect, and Google Scholar were searched systematically up to August 25, 2020 with no language restrictions, using specified search terms to identify potential relevant papers. The search strategy involved the combination of following keywords adapted from Medical Subject Heading (MeSH): ["enteral glutamine,"] ["burn patients,"] ["critical ill,"] ["infection,"] and ["length of stay"]. The reference lists of related articles were handsearched manually to gain additional papers. If more than one article was published using the same study data, only the study with largest sample size was included in the study.

### Eligibility criteria

The selection criteria for inclusion in this study were as follows: (1) Study design: Retrospective, prospective, cross-sectional, and randomized-controlled trials (RCT); (2) age of sample more than 18 years old; (3) given intervention with enteral glutamine versus control; (4) evaluating one of the following parameters as the outcome measures: APACHE II score, infection, length of hospital stays, and mortality; and (5) providing sufficient data for calculation of effect estimates. Articles were excluded because of: (1) Obviously irrelevant title and/or abstract; (2) review or commentary, (3) incomplete and/or ungeneralized data, and (4) low quality article (NOS score <5).

### Quality assessment

Newcastle-Ottawa Scale (NOS) was used to assess the quality of papers included in our meta-analysis. This assessment was conducted by three independent authors (Author 1, Author 2, and Author 3). The assessment consisted of three factors such as study selection (4 points), the comparability of the groups (2 points), and the ascertainment of exposure (3 points). In this evaluation, each paper had the score scaled from 0 (the worst) to 9 (the best). The quality was interpreted as good (score  $\geq 7$ ), moderate (score 5–6), and poor (score  $\leq 4$ ). If the discrepancy between three independent authors was found, we established a consensus.

### Data extraction

The following information was extracted from each study: (1) Name of first author, (2) year of publication, (3) study design, (4) sample size of enteral glutamine group and control group, (5) age (in years), (6) total burn surface area, (7) dose of enteral glutamine administration, (8) duration of administration, (9) APACHE II score, (10) morbidity of sepsis, (11) positive blood culture, (12) positive wound culture, (13) length of hospital stays, and (14) mortality.

To provide data with high validity and to prevent errors in data extraction, the extraction was conducted by three independent authors (Author 1, Author 2, and Author 3) using a pilot form.

### Outcome measures

The predictor covariate in our present study was enteral glutamine supplementation. While, the outcome measures were APACHE II score, morbidity of infection, length of hospital stays, and mortality. Data were presented in mean SD or frequencies and percents. Outcome measures were determined by initial searching. The covariates providing data for calculation of effect estimates were included in our analysis.

### Statistical analysis

We estimated the impact of outcome measures between enteral glutamine group and control group by calculating pooled effect estimates. A Z test was used to determine the significance of pooled effect estimates ( $p < 0.05$  was considered statistically significant). A Q test was performed to evaluate whether the heterogeneity existed. Random effect model was used to calculate effect estimates if heterogeneity existed ( $p < 0.10$ ). Otherwise, a fixed effect model was used. Publication bias was assessed using Egger's test ( $p < 0.05$  was considered having publication bias). We used comprehensive meta-analysis (CMA) version 2.1 to analyze the data.

## Results

### Characteristics of the studies

A total of 8227 potentially relevant papers were identified based on the literature search strategy. Of these, 8177 papers were excluded because of obvious irrelevance by reading their titles and abstracts. After the full texts were read, four papers were excluded because they were reviews; thirty-two papers were excluded because they did not provide sufficient data; and two papers were excluded because of low quality study. A flow chart demonstrating the inclusion or exclusion of studies is displayed as Figure 1. Finally, a total of 11 randomized controlled trials (RCT) studies and one case-control study were eligibly included in the meta-analysis, as described in Table 1.

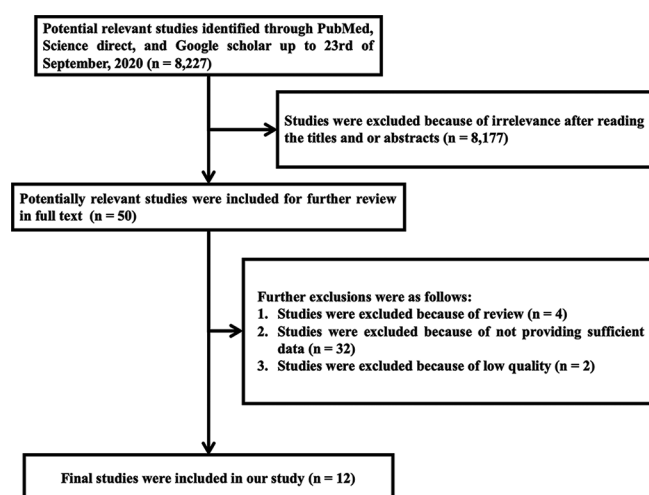


Figure 1: Selection of studies for inclusion in meta-analysis

### Quantitative data synthesis

A total of 12 studies recording 344 cases and 335 controls were enrolled for our analysis. Data on hospital LOS were found that enteral glutamine supplementation provided a significant result in reducing the LOS (Std mean diff: 0.70, 95% CI: 0.16–1.24;  $p = 0.0100$ ). We also found that higher

risk of positive wound culture was significantly observed in patients without the supplementation of enteral glutamine (OR 2.15, 95% CI: 1.41–3.27;  $p = 0.0003$ ) compared to patients receiving enteral glutamine supplementation among burn patients. On the contrary, enteral glutamine supplementation was not correlated with the risk of sepsis morbidity. Moreover, enteral glutamine supplementation was not correlated to positive blood culture, APACHE II score, and mortality among burn patients. The summary of the correlation between enteral glutamine supplementation and the outcomes among burn patients is presented in Table 2.

### Source of heterogeneity

Evidence of heterogeneity between studies was found in positive wound culture ( $p = 0.0003$ ) and length of hospital stays ( $p = 0.0100$ ). Therefore, these data were assessed using random effect model. While, other variables including APACHE II score ( $p = 0.1300$ ), sepsis morbidity ( $p = 0.6500$ ), positive blood culture ( $p = 0.4300$ ), and mortality ( $p = 0.5800$ ) were assessed using fixed effect model because we found no heterogeneity between studies. The summary of heterogeneity of the studies is described in Table 2.

### Potential publication bias

Egger's test was used to assess the potency of publication bias among all included studies. We found that publication bias was observed in APACHE II score ( $p < 0.0001$ ). In other variables, we found no publication bias (Figure 2). The summary of publication bias is described in Table 2.

## Discussion

Our study found that burn patients treated with glutamine had shorter LOS and a lower risk of wound infection compared to burn patients without glutamine. Our results were in line with the previous meta-analysis

Table 1: Baseline data of studies included in our study

Study, year	Study design	Sample size		Age (years)		Percentage TBSA (%)	Dose of EN GLN administration	Duration of administration (days)	NOS
		Control	GLN	Control	GLN				
Conejero <i>et al.</i> , 2002	RCT, SB	33	43	54.0 ± 21.0	57.0 ± 18.0	NA	30.5 g/day	≥10	7
Garrel <i>et al.</i> , 2003	RCT, DB	22	19	38.0 ± 8.0	39.0 ± 7.0	20–80	26 g/day	≥10	8
Hall <i>et al.</i> , 2003	RCT, TB	4	3	44.0 ± 28.0	47.0 ± 27.0	NA	19 g/day	>10	7
Heyland <i>et al.</i> , 2013	RCT, DB	10	9	62.8 ± 13.7	62.5 ± 15.0	<30	30 g/day	≤28	6
Houdjik <i>et al.</i> , 1998	RCT	37	35	34.5 ± 13.4	35.1 ± 11.8	≤15	3.5–30.5 g/day	≤5	6
Jones <i>et al.</i> , 1999	RCT	24	26	60.0 ± 21.0	56.5 ± 21.0	NA	20 g/day	8–14	6
Juang <i>et al.</i> , 2007	Case-control	15	17	45.5 ± 17.0	42.3 ± 20.0	<20–80	0.52 g/kg/day	>20	6
Kibor <i>et al.</i> , 2014	RCT and DB	120	120	29.5 ± 10.7	29.5 ± 10.7	NA	NA	4–14	6
Pattensheti <i>et al.</i> , 2009	RCT and SB	15	15	29.1 ± 9.2	33.9 ± 10.4	20–60	0.52 g/kg/day	>10	8
Peng <i>et al.</i> , 2004	RCT and DB	23	25	36.5 ± 13.9	39.5 ± 15.8	30–75	0.5 g/kg/day	14	7
Zhou <i>et al.</i> , 1999	RCT and DB	12	12	18–60	>20	>20	0.5 g/kg/day	12	6
Zhou <i>et al.</i> , 2003	RCT and DB	20	20	40.0 ± 4.3	43.7 ± 3.8	20–80	0.35 g/kg/day	12	8

RCT: Randomized controlled trial, SB: Single blinded, DB: Double blinded, TB: Triple blinded, SD: Standard deviation, GLN: Glutamine, TBSA: Total burn surface area, EN: Enteral nutrition, NA: Not available, NOS: Newcastle-Ottawa scale.

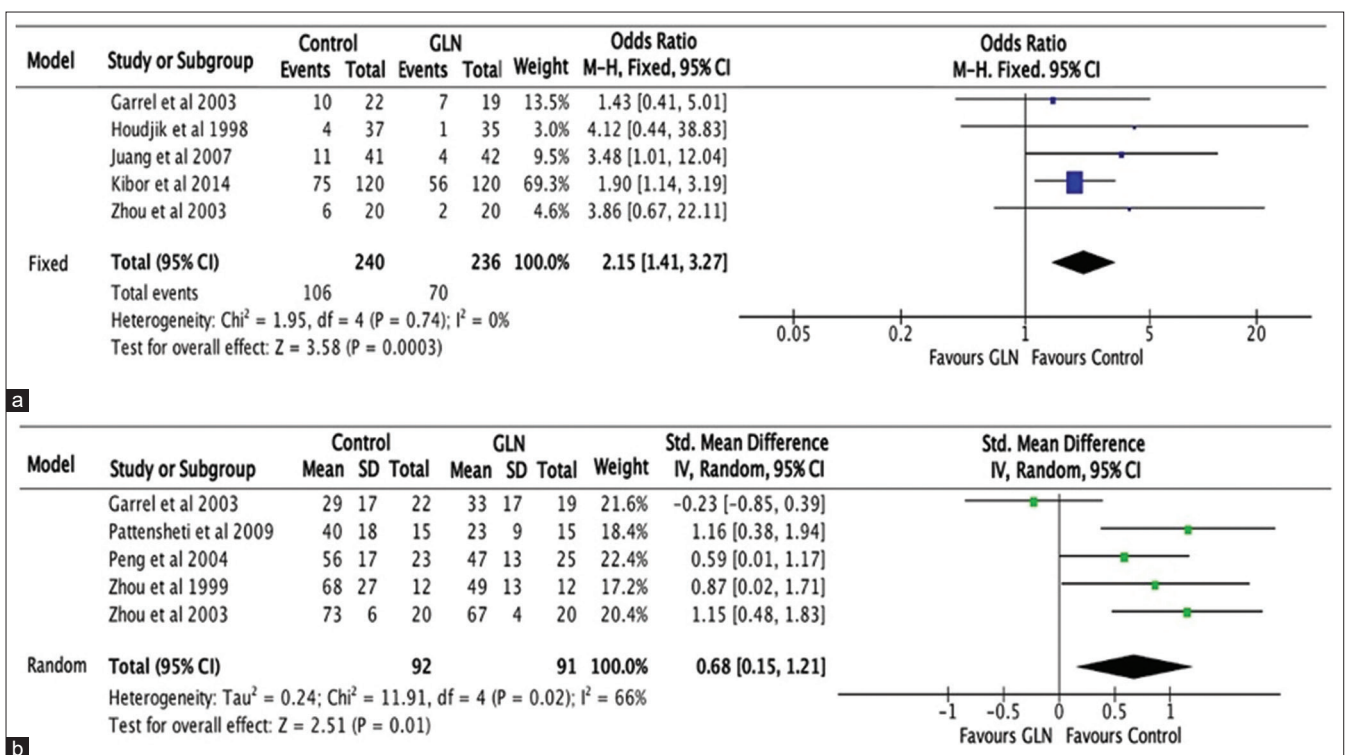


Figure 2: Forest plot regarding the effects of enteral glutamine supplementation on (a) incidence of positive wound culture and (b) length of hospital stay among burn patients in our study

studies. A previous meta-analysis reported shorter LOS in critically ill burn patients who received glutamine supplementations than patients without glutamine [11]. Another meta-analysis reported similar findings. They found that a lower risk of gram-negative bacteremia was associated with glutamine supplementation [12]. Another meta-analysis also reported a lower incidence of nosocomial infection in the glutamine supplementation group [13]. Furthermore, several meta-analyses also found lower mortality risk in patients with glutamine supplementation [11], [12]. However, one meta-analysis on critically ill patients found no important benefit of glutamine supplementation [14].

Glutamine supplementation has been a controversy in medical communities. Some studies supported the efficacy of glutamine, while some others failed to clarify the effectiveness of glutamine. The theory reveals that the depletion of glutamine levels in burns patients may be due to the catabolic pathway. This condition may have an adverse effect on the immune system as glutamine is one of the main energy sources for enterocytes, lymphocytes, and

macrophages. Therefore, glutamine supplementation may help resolve this pathological process [15]. On the other hand, several studies have revealed evidence on the impact of glutamine supplementation toward attenuation of inflammation and lung injury, cardiac protection, and preserving muscle metabolism. The evidence suggested that a broad mechanism might involve glutamine's function in maintaining cellular and tissue integrity in post-burn traumatic states [6].

The findings of our meta-analysis supported the beneficial effects of glutamine supplementation on burn patients. Our study is the first meta-analysis assessing the potential role of glutamine in treating burn patients. Several similar previous meta-analyses on this topic had been performed. The previous meta-analysis studies were performed on the general critically ill population, including a combination of medical, surgical, and trauma patients. Therefore, the findings might have the potency of bias due to the population effect. In our present study, we only included the population of burn patients. The benefits of glutamine in our meta-analysis were observed to reduce infection risk and LOS.

Table 2: Summary of the association between enteral glutamine supplementation and outcome measures among burn patients in our study

Parameters	NS	Model	Outcome measure		Effect estimate	95%CI	pE	pHet	p
			Control	GLN					
APACHE II score	7	Fixed	115 ± 51	117 ± 61	-0.04 <sup>a</sup>	-0.29-0.21	0.0000	0.7300	0.1300
Morbidity of sepsis	5	Fixed	22.32%	21.58%	1.07 <sup>b</sup>	0.79-1.46	0.3300	0.2000	0.6500
Positive blood culture	6	Random	29.27%	22.22%	1.56 <sup>b</sup>	0.52-4.68	1.1900	0.0000	0.4300
Positive wound culture	5	Fixed	44.17%	29.66%	2.15 <sup>b</sup>	1.41-3.27	0.0700	0.7400	0.0003
Hospital LoS	5	Random	266 ± 85	219 ± 56	0.70 <sup>a</sup>	0.16-1.24	0.2400	0.0100	0.0100
Mortality	7	Random	26.49%	29.27%	1.17 <sup>b</sup>	0.67-2.05	0.4600	0.0500	0.5800

<sup>a</sup>SDM, <sup>b</sup>OR. Data were presented as mean ± SD or percentage. APACHE: Acute physiology and chronic health evaluation, LoS: length of stay, GLN: Glutamine, CI: Confidence interval, pE: p Egger, pHet: p Heterogeneity, SDM: Standard difference in mean, OR: Odds ratio.

Infection risk reduction was especially important as it is one of the most frequently occurring complications on burn patients [16]. Infection in burn patients has been associated with morbidity and mortality risk [17]. Meanwhile, LOS indicated the resource-effectiveness in the care of burn patients. Shorter LOS was also associated with faster recovery and better quality of life in the post-hospitalization period [18].

However, we also had to discuss the limitation of our study. First, the potential factors that might affect the risk of bias were not analyzed, including A, B, and C. Second, the small sample size in our current analysis should be carefully interpreted. Third, the heterogeneity of included papers might also contribute to the risk of bias analysis. Therefore, the future studies with better design might be warranted.

## Conclusion

In our meta-analysis study, we demonstrate that enteral glutamine confers significant shorter LOS and lower risk of wound infection among burn patients. We suggest that enteral glutamine supplementation may be a beneficial intervention for the management of burn patients. However, larger studies are warranted, as our observations are based on a small number of patients.

## Author Contribution

All of authors are equally contributed to the study.

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