Evaluating the Impact of Enteral Glutamine Supplementation on Preventing Ventilator-Associated Pneumonia: A Pilot Randomized Clinical Trial in Critically Ill Patients

Zahra Soleymani Dashtaki[1], Saeed Abbasi[2], Shadi Farsaei[1,3*]

[1]Department of Clinical Pharmacy, School of Pharmacy, Isfahan University of Medical Sciences, Isfahan, Iran.

[2]Anesthesiology and Critical Care Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.

[3] Isfahan Pharmaceutical Sciences Research Center, School of Pharmacy, Isfahan University of Medical Sciences, Isfahan, Iran.

Received: 2025-07-08, Revised:2025-08-27, Accepted: 2025-09-02, Published:2025-09-30

Abstract

Background: Ventilator-associated pneumonia (VAP) is a common and serious complication of mechanical ventilation in intensive care units (ICUs). The current study evaluates the effectiveness of enteral glutamine (GLN) supplementation in preventing VAP in ICU patients.

Methods: This controlled, randomized clinical trial was performed on mechanically ventilated ICU patients who had a Clinical Pulmonary Infection Score (CPIS) of ≤ 6 within 48 hours of starting ventilation. Patients in the intervention group received 40 g of GLN during the first 48 hours after intubation, and this was continued for seven days. Both the intervention and control groups received standard preventive care. Outcomes were evaluated by comparing the incidence of VAP, the number of pneumonia-free days, and the duration of ventilation and ICU length of stay in each group.

Results: We analyzed the medical records of 613 patients to identify those who met the eligibility criteria for our study, resulting in a final cohort of 35 participants (16 in the intervention group and 19 in the control group). The present clinical trial did not reach its target sample size of 23 patients per group, primarily because of participant attrition and loss to follow-up. Our findings revealed no significant differences in the incidence of early, late, or overall VAP between the two groups. However, the number of pneumonia-free days was significantly higher in the intervention group compared to the control group (log-rank test: P-value= 0.05). Other secondary outcomes, such as mortality rate, and the duration of ICU stay, hospital stay, and mechanical ventilation, also showed no significant differences between the two groups.

Conclusion: The administration of oral GLN supplements has been associated with an increase in the number of pneumonia-free days among ICU patients; however, this benefit does not appear to reduce the incidence of VAP. Further high-quality studies are warranted to validate these observations and to investigate the potential efficacy of GLN supplementation within specific patient cohorts.

J Pharm Care 2025; 13(3): 188-196.

Keywords: Pneumonia; Ventilated-Associated; Intensive Care Unit; Glutamine

Introduction

Mechanical ventilation is a crucial intervention in the intensive care unit (ICU) for maintaining lung function and preserving life in many patients. Despite its necessity, it poses a considerable risk for the development of ventilator-associated pneumonia (VAP) (1). VAP is the second most common nosocomial infection, largely because mechanical ventilation compromises the body's innate immune defenses (2-4).

Managing VAP requires extensive antibiotic use, which contributes to the global healthcare crisis of multidrug-resistant

*** Corresponding Author:** Shadi Farsaei
Address: Department of Clinical Pharmacy, School of Pharmacy, Isfahan University of Medical Sciences, Hezar jarib Ave., Isfahan, Iran.
E-mail: sh.farsaei@gmail.com, Farsaei@pharm.mui.ac.ir

pathogen development (5, 6). Due to the high associated mortality rate of approximately 10% and the growing threat of antimicrobial resistance, VAP prevention remains an urgent and vital priority within the healthcare system (5, 7, 8).

To effectively prevent VAP, a coordinated, multidisciplinary approach is essential for ensuring patient safety. Comprehensive preventive measures, including strategies to prevent aspiration, reduce equipment contamination, and minimize aerodigestive tract colonization, along with the implementation of VAP care bundles, have been shown to significantly decrease the occurrence of VAP in developed countries (9).

Based on new insights into VAP, there is a clear need for alternative therapeutic strategies, including immunomodulatory agents (10).

Immune modulation is a promising strategy for restoring microbiome diversity and improving mucosal immunity, which may help prevent hospital-acquired pneumonia (11). Glutamine (GLN), a non-essential amino acid, plays a crucial role in sustaining homeostasis and physiological function during periods of stress. It has shown immunomodulatory properties that may be beneficial for ICU patients, making GLN a potential therapeutic target for modulating both suboptimal and hyperactive immune responses (12-14).

In preclinical and clinical research, GLN supplementation has been shown to support intestinal immune function and may reduce the risk of infection. However, there is no conclusive evidence that it prevents VAP (15). While multiple studies have theorized that GLN supplementation could lower the incidence of VAP, the existing evidence is not definitive (16-21). For instance, one study found a lower frequency of VAP in patients who received GLN supplements, but this difference was not statistically significant when compared to other nutritional treatments (16).

While meta-analyses suggest a potential trend toward a reduction in infectious complications, such as pneumonia, with GLN supplementation in specific patient groups, the results are not consistent (22-28). To definitively determine its efficacy in preventing VAP, well-designed clinical trials with adequate statistical power are necessary. Therefore, this study was undertaken to assess how enteral GLN supplementation affects VAP prevention in ICU patients.

Methods

This study was a controlled, randomized clinical trial that took place from September 2019 to August 2020 in the general ICU of a university hospital in Iran. The trial focused on mechanically ventilated patients admitted to the ICU. The research protocol received approval from the Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.RESEARCH.REC.1398.215). Before participating, the legal guardians of the patients provided written informed consent. The trial was officially registered with the Iranian Registry of Clinical Trials (IRCT) (IRCT20150221021159N5).

All adult ICU patients who met the inclusion criteria were enrolled within 24 hours of receiving mechanical ventilation, with a Clinical Pulmonary Infection Score (CPIS) of ≤ 6, and no clinical suspicion of pneumonia, coronavirus disease 2019 (COVID-19) infection, or hemodynamic instability (e.g., hypotension). Exclusion criteria included patients with a diagnosis of acute respiratory distress syndrome (ARDS), a recent history of aspiration, cancer, kidney or liver failure, or a history of ventilation during the past three months. Moreover, participants were required to tolerate enteral administration of tablets and were anticipated to remain in the ICU for a minimum of seven days.

Participants were subsequently allocated to either the intervention or control group through block randomization with a block size of four. A computer-generated sequence ensured a 1:1 allocation ratio, evenly distributing subjects between the two groups.

We established a significance level (α) of 0.05 and a statistical power of 80% ($\beta = 0.8$). The expected incidence rates were 40% in the control group and 5% in the intervention group (5). After adjusting for a 10% dropout rate, we calculated a required sample size of 23 patients per study group.

The intervention group was administered 40 g of enteral GLN dissolved in water daily for a period of seven days, with the regimen commencing within 24 hours of intubation. In contrast, the control group did not receive any GLN supplementation. Given that no placebo was utilized, the study precluded the blinding of both the ICU staff and the outcome assessors. Intensivists undertook continuous monitoring of patients for the incidence of VAP over a 14-day observation period. VAP was operationally defined as pneumonia that developed in a patient who had been intubated and mechanically ventilated for a minimum of 48 hours prior to the onset of the condition.

The CPIS, with a value of > 6 in conjunction with a high degree of clinical suspicion, serves as a diagnostic tool for VAP. The CPIS is a scoring system that uses signs and symptoms characteristic of pneumonia, such as fever and the extent of oxygenation impairment (29).

In the current research, we assessed the occurrence of early-onset VAP (defined as developing within < 5 days of intubation) and late-onset VAP (defined as developing after ≥ 5 days), which was the primary outcome (30). We measured and daily re-evaluated the baseline fever and complete blood count of patients and performed chest X-rays and obtained quantitative cultures from either tracheal aspiration or bronchoalveolar lavage when clinically indicated. We also measured the levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) at baseline and again on day 14.

The Acute Physiology and Chronic Health Evaluation II (APACHE II) score was determined on the initial day of the study, and the Sequential Organ Failure Assessment (SOFA) score was documented on a daily basis for the entire duration of the follow-up. Additionally, demographic information such as age and gender, the primary cause for ICU admission, any underlying medical conditions, antibiotics prescribed during the study, and a history of smoking were also systematically recorded.

The normality of quantitative data was evaluated using the Kolmogorov-Smirnov test. Based on the results of the normality test, either an independent Student's t-test or a Mann-Whitney test was applied to compare the data between the groups. Qualitative data differences were analyzed with the Chi-square test. To examine the impact of GLN supplementation on the development of VAP, a binary logistic regression analysis was conducted. This analysis controlled for potential confounding variables, including the baseline CRP levels and the administration of anti-methicillin-resistant Staphylococcus aureus (MRSA) antibiotics. Additionally, a Kaplan-Meier survival analysis along with a log-rank test was performed to compare the number of pneumonia-free days between the groups over the 14-day follow-up period. All statistical computations were carried out using SPSS software, version 20 (SPSS Inc., Chicago, IL, USA), and a P-value less than 0.05 was considered statistically significant.

Results

We screened 613 medical records of mechanically ventilated patients to assess their eligibility for inclusion in the study. Ultimately, 51 patients met the criteria and were enrolled. However, 16 of these patients were lost to follow-up, resulting in a final sample size of 35 patients for analysis (16 in the intervention group and 19 in the control group). As a result, this clinical trial failed to meet the original target sample size of 23 patients per group. The primary reason for this attrition was the COVID-19 pandemic (Figure 1).

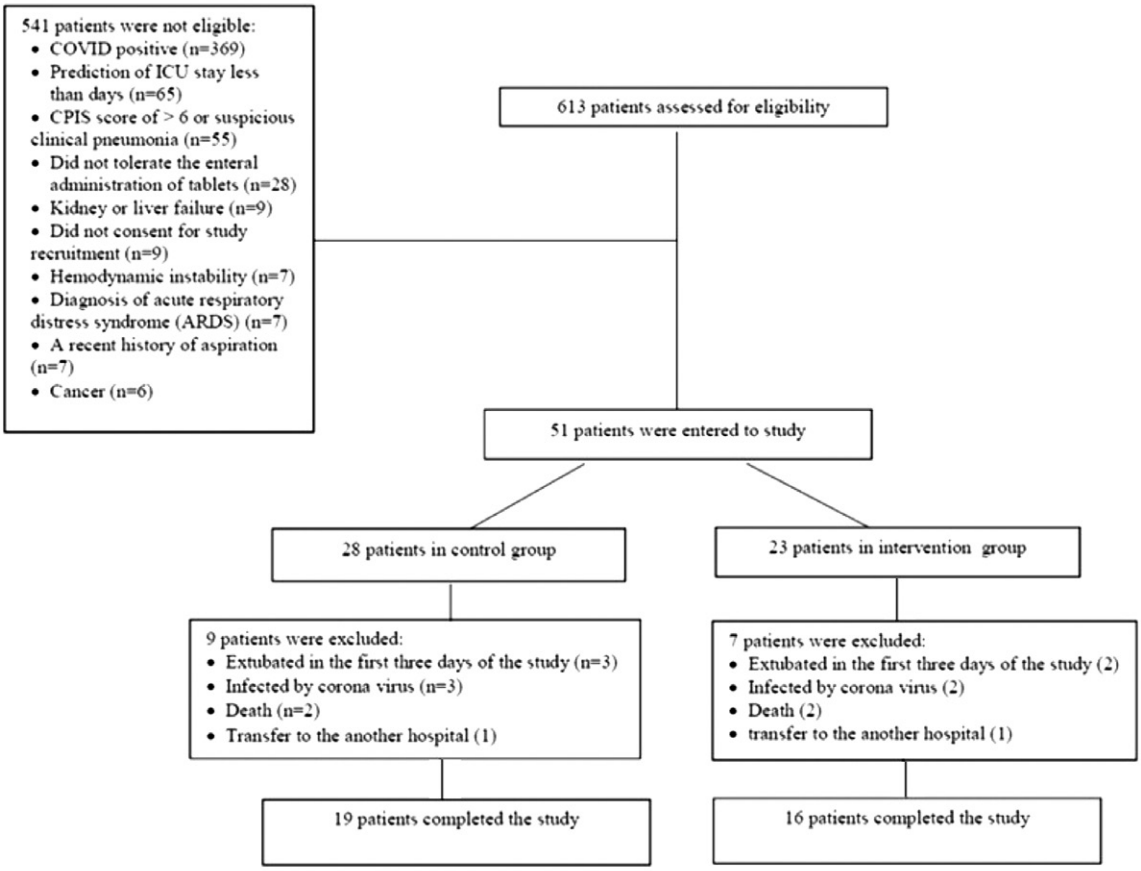

Figure1. Flow diagram of participant throughout the study

The groups showed no statistically significant differences in baseline demographic and clinical data, with the exception of CRP and albumin levels, which were significantly different between the groups (P-value < 0.05). Regarding antibiotics administered during the first two days of the study, no significant differences were observed, except for anti-MRSA antibiotics, which were prescribed more frequently in the control group than in the intervention group (P-value = 0.013). It is worth noting that these antibiotics were administered for post-surgical prophylaxis. Furthermore, the total CPIS score and related parameters were not significantly different between the groups at the study's initiation (Table 1).

Table 1. Demographic and clinical parameters of patients upon enrollment in the study

Variables	Control group (n=19)	Intervention group (n=16)	P-value
Age (years), mean ± SD	43.5 ± 16.3	49.8 ± 14.9	0.24‡
Gender (men), n (%)	14 (73.7)	12 (75.0)	0.92†
APACHE II (on admission), mean ± SD	26.3 ± 3.5	24.7 ± 4.9	0.24‡
SOFA (mean during ICU stay), mean ± SD	7.53 ± 1.611	12.19 ± 20.269	0.32‡
ESR (mm/hr), median (IQR)	8 (6 - 21.5)	15 (9.5 - 31.75)	0.33*
CRP (mg/L), median (IQR)	1 (1 - 4)	24.5 (9.25 - 67.25)	0.009*
Albumin (g/dl), median (IQR)	4.2 (3.6 - 4.3)	3 (2.5 - 3.5)	0.002*
History of smoking, n (%)	6 (31.6)	7 (43.8)	0.45†
Having chest tube, n (%)	0.0 (0.0)	1 (6/3)	0.26†
CPIS score, mean ± SD	4.60 ± 1.142	4.44 ± 1.294	0.880‡
Comorbidities[†], n (%)			
Diabetes	3 (15.8)	1(5.6)	0.33†
Hypertension	4 (21.1)	3 (18.8)	0.86†
Respiratory diseases	1 (5.3)	2 (12.5)	0.44†
Cardiac diseases	2 (10.5)	4 (25/0)	0.25†
Reason of admission[ᵃ], n (%)			
Surgery	4 (21.1)	7 (43.8)	0.332†
Trauma	11 (57.9)	5 (31.3)	
Medical (internal medicine)	4 (21.1)	4 (25.0)	
Antibiotics[§], n (%)			
Anti-MRSA	15 (78.9)	6 (37.5)	0.013†
Cephalosporin	16 (84.2)	12 (75.0)	0.50†
Carbapenem	2 (10.5)	1 (6.3)	0.65†
Fluoroquinolon	1 (5.3)	2 (12.5)	0.45†
Aminoglycoside	-	1 (6.3)	0.27†
Chest X-ray infiltrate, n (%)			
No infiltrate	9(47.4)	6(37.5)	0.691†
Diffuse infiltrate	8(42.1)	9(56.3)	
Localized infiltrate	2(10.5)	1(6.3)	
Temperature (°C), n (%)			
36.5-38.4	11(57.9)	12(75.0)	0.419†
38.5-38.9	4(21.1)	3(18.8)	
≤36.0 or ≥39.0	4(21.1)	1(6.3)	

Table 1. Continued

Pulmonary secretion, n (%)			
Absent	4(21.1)	0(0.0)	0.146†
Non-purulent	9(47.4)	9(56.3)	
purulent	6(31.6)	7(43.8)	
Oxygenation: Po2/FiO2 (mmHg), n (%)			
>240 or ARDS	4(21.1)	5(31.3)	0.492†
≤240 and no ARDS	15(78.9)	11(68.8)	
Blood leukocytes (cells/L), n (%)			
4000-11000	9(47.4)	9(56.3)	0.600†
<4000 OR >11000	10(52.6)	7(43.8)	

‡P-values are based on an Independent T-Test; † P-values are based on a Chi-square test or Exact-Fisher Test; * P-values are based on Mann-Whitney Test; § Antibiotic administration during the first two days of study for any reason except pneumonia. APACHE: Acute Physiology and Chronic Health Evaluation, CPIS: Clinical Pulmonary Infection Score, CRP: C-Reactive Protein, ESR: Erythrocyte Sedimentation Rate, IQR: Interquartile Range, SD:Standard Deviation, SOFA: Sequential Organ Function Assessment

The findings of this study are outlined in Table 2. Our analysis demonstrated that the overall incidence of VAP was 56.77 episodes per 1000 mechanical ventilation days in the control group, compared to 50.00 episodes per 1000 mechanical ventilation days in the intervention group (odds ratio [OR]: 0.462; 95% confidence interval [CI]: 0.116–1.829; P-value = 0.271). The incidence of early VAP was found to be 26.20 episodes per 1000 mechanical ventilation days in the control group and 25.00 episodes per 1000 mechanical ventilation days in the intervention group (OR: 0.722; 95% CI: 0.163–3.200; P-value = 0.668). Furthermore, the incidence of late VAP was 30.57 episodes per 1000 mechanical ventilation days in the control group, while the intervention group showed an incidence of 25.00 episodes per 1000 mechanical ventilation days (OR: 0.429; 95% CI: 0.085–2.17; P-value = 0.306).

A significantly higher number of pneumonia-free days was observed in the intervention group compared to the control group (log-rank test: P = 0.05). However, no statistically significant differences were found between the two groups for other outcomes, including mortality rate (P- value = 0.66), and the duration of ICU stay (P = 0.19), hospital stay (P = 0.25), and mechanical ventilation (P- value = 0.26).

Table 2. Primary and secondary outcomes of the study between study groups

Outcomes	Control group (n=19)	Intervention group (n=16)	P-value
Overall VAP incidence, n (%)	13(68.4)	8(50.0)	0.271†
Early VAP incidence, n (%)	6(31.6)	4(25.0)	0.668†
Late VAP incidence, n (%)	7(53.8)	4(33.3)	0.306†
Number of pneumonia free days	9.26 ± 4.99	13.25 ± 2.32	0.006‡
Duration of ICU stay (days), mean ± SD	29.11 ± 17.40	22.00± 12.62	0.19‡
Duration of hospitalization (days), mean ± SD	34.82 ± 18.34	27.92 ± 11.87	0.25‡
Duration of ventilation (days), median (IQR)	10.5 (6.0-21.5)	18 (12-30)	0.26*
Mortality rate, n (%)	4(23.5)	2(14.3)	0.664†

‡P-values are based on Independent t-Test; † P-values are based on Chi-square test or Exact-Fisher Test; * P-values are based on Mann-Whitney Test. IQR: Interquartile Range, SD: Standard Deviation, VAP: Ventilation-Associated Pneumonia

In a comparative analysis of bacterial culture samples, no significant difference was found between the control and intervention groups (Table 3). Causative pathogens were successfully isolated from the tracheal specimens of 13 patients in the control group and 8 patients in the intervention group. Acinetobacter baumannii was the most prevalent microorganism, identified in 7 patients (53.8%) in the control group and 3 patients (37.5%) in the intervention group. Concurrent growth of two pathogens was observed in 38.4% of patients in the control group and 25.00% of those in the intervention group. Additionally, multidrug-resistant pathogens were prevalent in 50% of the patients.

Table 3. The causative microorganisms of VAP isolated in both groups

Microorganisms n (%)	Control group (n=19)	Intervention group (n=16)	P-value†
Acinetobacter baumannii	7(53.8)	3(37.5)	0.46
Klebsiella pneumoniae	4(30.8)	2(25.0)	0.77
Enterobacter aerogenes	0(0.0)	2(25.0)	0.06
Staphylococcus aureus	2(15.4)	0(0.0)	0.24
Acinetobacter	2(15.4)	0(0.0)	0.24
Pseudomonas aeruginosa	1(7.7)	0(0.0)	0.24
Fungi	1(7.7)	2(25.0)	0.27
Simultaneous growth of two pathogens	5(38.4)	2(25.0)	0.63
Prevalence of MDR bacteria	6(50.0)	3(50.0)	1.00

† P-values are based on Chi-square test or Exact-Fisher Test. MDR: Multidrug-Resistant

Discussion

Despite the implementation of various preventive strategies, the prevalence of VAP remains a significant concern. This has led to the investigation of novel prophylactic approaches, including the use of antibiotics and probiotics. Nevertheless, the widespread adoption of these methods for VAP prevention has been restricted due to concerns about antibiotic resistance and a lack of conclusive evidence regarding their efficacy (31-35).

The biological properties of GLN, including its crucial role in bolstering immune function and preserving the integrity of the intestinal barrier, provide a strong basis for exploring GLN supplementation. These functions are particularly important for preventing infections, such as VAP, in critically ill individuals (36).

In this randomized trial involving mechanically ventilated ICU patients with an initial CPIS of ≤ 6, administration of GLN supplementation (40 g within 48 hours, with a total duration of seven days) did not lead to a significant reduction in the incidence of VAP. However, it is noteworthy that the number of pneumonia-free days was slightly greater in the intervention group (log-rank P-value = 0.05). No statistically significant differences were observed between the two groups in secondary outcomes, such as mortality rate and the duration of mechanical ventilation or ICU stay.

Several large clinical trials offer critical insights into the role of GLN supplementation in preventing VAP, which provides important context for our own findings (19-21). Our results are consistent with those of larger studies, including the oxygen-reduction (REDOX) trial (19), the special interest group network (SIGNET) trial (20), and the multicenter surgical ICU (SICU) trial (21). These studies also found that GLN did not reduce infections in critically ill or SICU patients who were receiving parenteral nutrition. However, our findings are in contrast with the REDOXS trial, where high doses of both intravenous and enteral GLN in patients with multi-organ failure did not provide an infection benefit and actually led to an increase in mortality. The REDOX and SIGNET trials employed fixed-dosing strategies, whereas the SICU trial, which used a weight-based approach, also failed to show a significant decrease in the incidence of VAP.

The present trial was a small, single-center, unblinded study on fixed-dose enteral GLN supplementation, with a final analysis that included 35 patients. As a result, the trial was markedly underpowered to detect differences in the incidence of VAP or mortality. In contrast, the larger, aforementioned multicenter trials enrolled substantially larger and more diverse patient populations, employed rigorous double-blind, placebo-controlled designs, used standardized dosing protocols, and had adjudicated endpoints. The strong research methods used in these studies were crucial for identifying not only the lack of a positive effect but also a possible indicator of harm in particular groups of critically ill patients with multi-organ failure, as seen in the REDOXS trial. The discrepancies observed between our results and those from larger randomized controlled trials can be attributed to differences in patient demographics (e.g., medical versus surgical patients), timing and method of GLN administration (e.g., early intravenous and enteral versus enteral only), dosage

(fixed versus weight-based), blinding techniques, and the definitions of outcomes (19-21).

A study by Aydogmus et al. (2012) in Turkey also investigated parenteral GLN supplementation. This research involved 60 patients, who were divided into three groups: Those receiving enteral nutrition, those receiving total parenteral nutrition (TPN), and an intervention group receiving 40 g of parenteral GLN daily for seven days. Consistent with our findings, the results showed no significant link between GLN supplementation and the prevention of VAP. Similar to our study, this research did not measure blood GLN levels (16).

While, according to our study, the intervention group exhibited a greater number of pneumonia-free days (P-value = 0.05), this outcome indicates a potential benefit of GLN supplementation. This finding supports existing literature, which acknowledges the complexities and challenges of VAP prevention and suggests that while GLN may positively affect patient outcomes, its role remains inconclusive.

In a study, GLN supplementation was shown to reduce late-onset VAP more than early-onset VAP, although this difference wasn't statistically significant. The incidence of early-onset VAP decreased slightly from 26.2 to 25.0 cases per 1000 ventilator days in the control and intervention groups, respectively. In contrast, late-onset VAP showed a more notable reduction from 30.57 to 25.0 episodes per 1000 ventilator days. It is suggested that the time needed for GLN to boost the immune system and prevent VAP may be why it is more effective against late-onset VAP.

The small sample size and incomplete follow-up in this study compromised its statistical power and the generalizability of the findings. These limitations primarily stemmed from logistical difficulties arising from the coronavirus pandemic. Additionally, our results were constrained by confounding variables, including the uneven allocation of anti-MRSA antibiotics between the study groups. To draw more conclusive inferences, these limitations highlight the need for further investigation. Finally, given that GLN supplementation may be unnecessary for patients with sufficient baseline GLN levels, we recommend measuring blood GLN levels prior to implementing any intervention.

Conclusion

While GLN may offer some clinical benefits, its effectiveness in preventing VAP has not been proven. The existing evidence does not support its routine use for this specific purpose (28, 37). However, the observed increase in pneumonia-free days hints at a potential early protective effect, which warrants further research. To clarify the role of GLN in VAP prevention, larger and sufficiently powered studies are needed, particularly in mechanically ventilated patients with early or moderate illness.

Conflicts of Interest

The authors declare that they have no competing interests

Acknowledgments

This study was financially supported by the Isfahan University of Medical Sciences, Isfahan, I.R. Iran (Grant No. 398291).

References

1. Silva PL, Rocco PRM. The basics of respiratory mechanics: ventilator-derived parameters. Ann Transl Med. 2018;6(19):1-11.
2. Atashi V, Yousefi H, Mahjobipoor H, Bekhradi R, Yazdannik A. Effect of oral care program on prevention of ventilator-associated pneumonia in intensive care unit patients. Iran J Nurs Midwifery Res. 2018;23(6):486-90.
3. Aykac K, Ozsurekci Y, Basaranoglu ST. Future directions and molecular basis of ventilator associated pneumonia. Can Respir J. 2017;2017:2614602.
4. Rouzé A, Jaillette E, Poissy J, Préau S, Nseir S. Tracheal tube design and ventilator-associated. Pneumonia Respir Care. 2017;62(10):1316-23.
5. Papazian L, Klompas M, Luy C. Ventilator-associated pneumonia in adults: a narrative review. Intensive Care Med. 2020;46(5):888-906.
6. Weiss E, Essaied W, Adrie C, Zahar JR, Timsit JF. Treatment of severe hospital-acquired and ventilator-associated neumonia: a systematic review of inclusion and judgment criterial used in randomized controlled trials. Crit Care. 2017; 21(1):162.
7. Cotoia A, Spadaro S, Gambetti G, Koulenti D, Cinnella G. Pathogenesis-targeted preventive strategies for multidrug resistant ventilator-associated pneumonia. Microorganisms. 2020;8(6):1-18.
8. Feng DY, Zhou YQ, Zhou M, Zou XL, Wang YH, Zhang TT. Risk factors for mortality due to ventilator-associated pneumonia in a chinese

hospital: a retrospective study. Med Sci Monit. 2019;25:7660-5.

9. Labeau SO, Van de Vyver K, Brusselaers N, Vogelaers D, Blot SI. Prevention of ventilator-associated pneumonia with oral antiseptics: a systematic review and meta-analysis. Lancet Infect Dis. 2011;11(11):845-54.
10. Fernández-Barat L, López-Aladid R, Torres A. Reconsidering ventilator-associated pneumonia from a new dimension of the lung microbiome. EBioMedicine. 2020;60:102995.
11. Roquilly A, Torres A, Villadangos JA, Netea MG, Dickson R, Becher B, et al. Pathophysiological role of respiratory dysbiosis in hospital-acquired pneumonia. The Lancet Respiratory Medicine. 2019;7(8):710-20.
12. McRae MP. Therapeutic benefits of glutamine:An umbrella review of meta-analyses. Biomed Rep. 2017;6(5):576-84.
13. Stehle P, Kuhn KS. Glutamine: An obligatory parenteral nutrition substrate in critical care therapy. Biomed Res Int. 2015;2015:545467.
14. Wernerman J. Glutamine supplementation. Ann Intensive Care. 2011;1(1):25.
15. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Crit Care Med. 2013;41(2):580-637.
16. Aydoğmuş MT, Tomak Y, Tekin M, Katı İ, Hüseyinoğlu Ü. Glutamine supplemented parenteral nutrition to preventventilator-associated pneumonia in the intensive care unit. Balkan Med J. 2012;29(4):414-8.
17. Estívariz CF, Griffith DP, Luo M, Szeszycki EE, Bazargan N, Dave N, et al. Efficacy of parenteral nutrition supplemented with glutamine dipeptide to decrease hospital infections in critically ill surgical patients. JPEN J Parenter Enteral Nutr. 2008;32(4):389-402.
18. Aboelmagd R, Moez K, Salem W. Role of parenteral glutamine supplementation on patient outcome in the surgical ICU. Crit Care. 2009;13(1):P136.
19. Heyland D, Muscedere J, Wischmeyer PE, Cook D, Jones G, Albert M, et al. A randomized trial of glutamine and antioxidants in critically ill patients. N Engl J Med. 2013;368(16):1489-97.
20. Andrews PJD, Avenell A, Noble DW, Campbell MK, Croal BL, Simpson WG, et al. Randomised trial of glutamine, selenium, or both, to supplement parenteral nutrition for critically ill patients. BMJ. 2011;342:d1542.
21. Ziegler TR, May AK, Hebbar G, Easley KA, Griffith DP, Dave N, et al. Efficacy and Safety of Glutamine-supplemented Parenteral Nutrition in Surgical ICU Patients: An American Multicenter Randomized Controlled Trial. Ann Surg. 2016;263(4):646-55.
22. Wischmeyer PE, Dhaliwal R, McCall M, Ziegler TR, Heyland DK. Parenteral glutamine supplementation in critical illness: a systematic review. Crit Care. 2014;18(2):R76.
23. Pimentel RFW, Fernandes SL. Effects of parenteral glutamine in critically ill surgical patients: a systematic review and meta-analysis. Nutr Hosp. 2020;34(3):616-21.
24. Apostolopoulou A, Haidich AB, Kofina K, Manzanares W, Bouras E, Tsaousi G, et al. Effects of glutamine supplementation on critically ill patients: Focus on efficacy and safety. An overview of systematic reviews. Nutrition. 2020;78:110960.
25. van Zanten AR, Dhaliwal R, Garrel D, Heyland DK. Enteral glutamine supplementation in critically ill patients: a systematic review and meta-analysis. Crit Care. 2015;19(1):294.
26. Yeh CL, Su LH, Wu JM, Yang PJ, Lee PC, Chen PD, et al. Effects of the Glutamine Administration on T Helper Cell Regulation and Inflammatory Response in Obese Mice Complicated with Polymicrobial Sepsis. Mediators Inflamm. 2020;10;2020:8869017.
27. Stehle P, Ellger B, Kojic D, Feuersenger A, Schneid C, Stover J, et al. Glutamine dipeptide-supplemented parenteral nutrition improves the clinical outcomes of critically ill patients: A systematic evaluation of randomised controlled trials. Clinical Nutrition ESPEN. 2017;17:75-85.
28. Liang B, Su J, Chen J, Shao H, Shen L, Xie B. Glutamine enteral therapy for critically ill adult

patients: An updated meta-analysis of randomized controlled trials and trial sequential analysis. Clin Nutr. 2024;43(1):124-33.

29. Frondelius T, Atkova I, Miettunen J, Rello J, Jansson MM. Diagnostic and prognostic prediction models in ventilator-associated pneumonia: Systematic review and meta-analysis of prediction modelling studies. J Crit Care. 2022;67:44-56.
30. Ben Lakhal H, M'Rad A, Naas T, Brahmi N. Antimicrobial susceptibility among pathogens isolated in early- versus late-onset ventilator-associated pneumonia. Infect Dis Rep. 2021;13(2):401-10.
31. Batra P, Soni KD, Mathur P. Efficacy of probiotics in the prevention of VAP in critically ill ICU patients: an updated systematic review and meta-analysis of randomized control trials. J Intensive Care. 2020;8(81).
32. Gu WJ, Wei CY, Yin RX. Lack of Efficacy of Probiotics in Preventing Ventilator-Associated Pneumonia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. CHEST. 2012;142(4):859-68.
33. Weng H, Li J-G, Mao Z, Feng Y, Wang C-Y, Ren X-Q, et al. Probiotics for preventing ventilator-associated pneumonia in mechanically ventilated patients: a meta-analysis with trial sequential analysis. Front Pharmacol. 2017;8(717).
34. Póvoa FCC, Cardinal-Fernandez P, Maia IS, Reboredo MM, Pinheiro BV. Effect of antibiotics administered via the respiratory tract in the prevention of ventilator-associated pneumonia: A systematic review and meta-analysis. J Crit Care. 2018;43:240-5.
35. Zha S, Niu J, He Z, Fu W, Huang Q, Guan L, et al. Prophylactic antibiotics for preventing ventilator-associated pneumonia: a pairwise and Bayesian network meta-analysis. Eur J Med Res. 2023;28(1):348.
36. Shah AM, Wang Z, Ma J. Glutamine metabolism and its role in immunity, a comprehensive review. Animals (Basel). 2020; 10(2):326..
37. Sun Y, Zhu S, Li S, Liu H. Glutamine on critical-ill patients: a systematic review and meta-analysis. Ann Palliat Med. 2021;10(2):1503-20.

PLEASE CITE THIS PAPER AS:

Soleymani Dashtaki Z, Abbasi S, Farsaei Sh. Evaluating the Impact of Enteral Glutamine Supplementation on Preventing Ventilator-Associated Pneumonia: A Pilot Randomized Clinical Trial in Critically Ill Patients. J Pharm Care. 2025;13(3):188-196.
DOI:10.18502/jpc.v13i3.20322