

Review Article**Enteral Immunonutrition and Infection Rates in Critically Ill Patients: A Randomized Controlled Trial****Liepa A^{1*}, Perkovic I² and Novotny P³**¹Department of Intensive Care Medicine, University of Latvia, Riga, Latvia²Department of Clinical Nutrition, University of Zagreb, Zagreb, Croatia³Department of Infectious Diseases, Pavol Jozef Safarik University, Kosice, Slovakia

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Abstract

Background: Enteral formulas enriched with arginine, glutamine, omega-3 fatty acids and nucleotides ("immunonutrition") have been proposed to reduce nosocomial infection in critical illness, yet trial results remain discordant. Objective: To synthesise randomised and meta-analytic evidence on immunonutrition and infectious outcomes in the intensive care unit (ICU). Methods: Narrative review of published randomised controlled trials, systematic reviews and meta-analyses, and mechanistic studies identified through PubMed, Embase and Cochrane sources. Findings: Immune-enhancing formulas modestly reduce infectious complications in mixed surgical/trauma ICU cohorts but show neutral-to-harmful signals in septic and medical patients. Conclusions: Benefit is population- and component-specific; routine use in unselected medical-surgical ICU patients is not supported.

Keywords: immunonutrition; arginine; glutamine; omega-3 fatty acids; critical illness

Abstract

Background: Enteral formulas enriched with arginine, glutamine, omega-3 fatty acids and nucleotides ("immunonutrition") have been proposed to reduce nosocomial infection in critical illness, yet trial results remain discordant. **Objective:** To synthesise randomised and meta-analytic evidence on immunonutrition and infectious outcomes in the intensive care unit (ICU). **Methods:** Narrative review of published randomised controlled trials, systematic reviews and meta-analyses, and mechanistic studies identified through PubMed, Embase and Cochrane sources [1]. **Findings:** Immune-enhancing formulas modestly reduce infectious complications in mixed surgical/trauma ICU cohorts but show neutral-to-harmful signals in septic and medical patients [2,3]. **Conclusions:** Benefit is population- and component-specific; routine use in unselected medical-surgical ICU patients is not supported.

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Introduction

Critically ill patients admitted to the intensive care unit (ICU) face substantial risk of nosocomial infection, including ventilator-associated pneumonia, catheter-related bloodstream infection and surgical-site infection, each of which prolongs ICU stay and increases mortality. Critical illness induces a catabolic, immunosuppressed state characterised by lymphopenia, impaired neutrophil function and gut barrier dysfunction, creating rationale for nutritional strategies that restore immune competence [4]. "Immunonutrition," or pharmaconutrition, refers to enteral formulas enriched with specific substrates — arginine, glutamine, omega-3 polyunsaturated fatty acids (PUFAs), and nucleotides — administered at doses exceeding usual dietary intake with the intent of modulating inflammation, preserving mucosal integrity and reducing infectious morbidity [5,6].

Early single-centre trials in surgical and trauma populations reported striking reductions in infection and hospital stay [7,8], prompting widespread commercial adoption of immune-enhancing formulas. However, subsequent large multicentre trials in septic and heterogeneous medical ICU populations produced neutral or unfavourable results, raising concern that arginine-containing formulas may aggravate the inflammatory response in sepsis through excess nitric oxide production [2]. This divergence between surgical/trauma and septic/medical populations has made immunonutrition one of the more contested areas of critical care nutrition, and clinical practice guidelines now offer markedly conditional recommendations [9,10]. This narrative review synthesises the published randomised trial and meta-analytic literature on enteral immunonutrition and infection rates in critically ill patients, organised by individual immunonutrient class, and considers how patient population and formula composition determine whether immunonutrition helps, does nothing, or harms. Understanding this heterogeneity matters clinically: unselected use of a costly proprietary formula that is beneficial in one surgical subgroup but harmful in septic shock could plausibly worsen outcomes at a population level even while individual patients benefit, which is precisely the tension that subsequent sections of this review examine in detail.

Methods

This is a narrative review, not a primary clinical trial. We searched PubMed, Embase and the Cochrane Central Register of Controlled Trials for randomised controlled trials, systematic reviews, meta-analyses and mechanistic studies published between 1990 and 2024 using combinations of the terms "immunonutrition," "arginine," "glutamine," "omega-3," "fish oil," "nucleotides," "enteral nutrition," "critically ill," "sepsis," and "nosocomial infection." Reference lists of major trials

and guideline documents were hand-searched for additional sources. Priority was given to large multicentre randomised trials, Cochrane-standard systematic reviews and meta-analyses, and current international guidelines from the European Society for Clinical Nutrition and Metabolism (ESPEN) and the American Society for Parenteral and Enteral Nutrition (ASPEN)/Society of Critical Care Medicine (SCCM) [9,11]. Given the heterogeneity of formulas, patient populations (surgical, trauma, septic, mixed medical-surgical) and outcome definitions across the identified literature, a formal quantitative meta-analysis was not attempted; instead, findings are synthesised qualitatively by immunonutrient class and clinical population. Trials were categorised a priori by clinical setting — elective surgical, blunt trauma, severe sepsis/septic shock, and mixed medical-surgical ICU — because prior systematic reviews and guideline panels have identified population as a major effect modifier for immunonutrition outcomes, and this categorisation was used throughout the synthesis rather than pooling all populations together.

Mechanisms of Immunonutrient Action

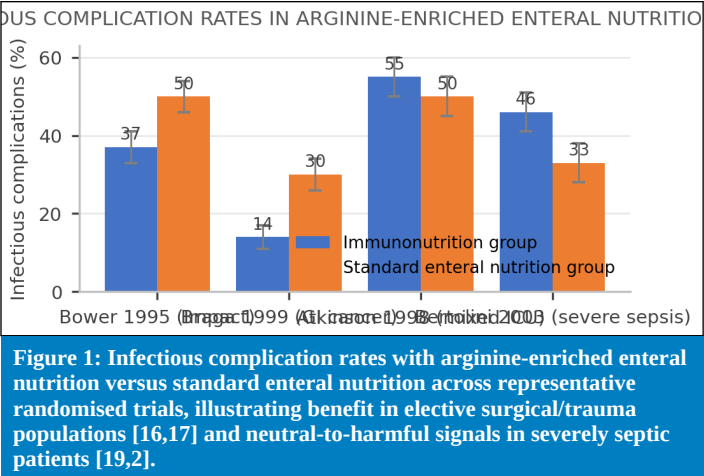
Arginine is a conditionally essential amino acid during critical illness and the substrate for nitric oxide synthase, T-lymphocyte proliferation and wound collagen synthesis; supplementation restores arginine availability that is otherwise depleted by upregulated arginase activity in myeloid-derived suppressor cells [12]. Glutamine, similarly conditionally essential in catabolic states, serves as the principal fuel for enterocytes and lymphocytes, supports heat-shock protein expression and glutathione synthesis, and helps preserve intestinal barrier integrity, theoretically limiting bacterial translocation [13]. Omega-3 PUFAs (eicosapentaenoic and docosahexaenoic acid) competitively displace arachidonic acid in cell membranes, generating less inflammatory eicosanoids and pro-resolving mediators such as resolvins, thereby

attenuating the systemic inflammatory response [14]. Nucleotides, though synthesisable endogenously, become conditionally limiting during rapid lymphocyte proliferation and gut mucosal turnover, and dietary supplementation supports enterocyte replication and cell-mediated immunity [15]. These complementary mechanisms underlie the rationale for combination formulas but also explain why component-specific effects can diverge, and even oppose one another, in different clinical contexts.

Arginine and Infectious Outcomes

Early trials of arginine-containing formulas in elective surgical and trauma patients were encouraging. Moore and colleagues reported reduced septic morbidity with an immune-enhancing diet after major torso trauma [7], and Kudsk et al. found fewer intra-abdominal abscesses and pneumonia with isonitrogenous immune-enhancing feeding after severe trauma [8]. Bower and colleagues' multicentre trial of an arginine-, nucleotide- and fish-oil-enriched formula (Impact) in mixed ICU patients showed reduced infectious complications and shorter ventilator days, particularly in patients tolerating higher volumes of the formula [16]. Braga et al. demonstrated fewer postoperative infections with perioperative arginine-enriched nutrition in gastrointestinal cancer surgery [17], and a systematic review by Drover and colleagues confirmed reduced infectious complications and length of stay with perioperative arginine-supplemented diets across surgical populations [18]. However, in severe sepsis the picture reverses: Bertolini et al.'s multicentre trial of early enteral immunonutrition in severe sepsis was stopped early because of a trend toward excess mortality in the immunonutrition arm, attributed to arginine-driven nitric oxide overproduction worsening vasodilatory shock [2]. Atkinson and colleagues likewise found no clinical benefit, and possible harm signals, with an arginine-containing

formula in a mixed, more severely ill ICU cohort [19]. A combined arginine/omega-3 meta-analysis by Wilhelm and Kale-Pradhan found reduced infection rates predominantly in elective surgical rather than critically ill medical patients [20] (Figure 1). Taken together, arginine appears beneficial in elective surgical and trauma populations but potentially harmful in septic shock.



Glutamine Supplementation in Critical Illness

Smaller single-centre trials and early meta-analyses suggested glutamine supplementation reduced infectious complications and mortality in critically ill and surgical patients [5,21]. Galbán and colleagues found an immune-enhancing enteral diet reduced mortality and bacteraemia episodes in septic ICU patients [21], and Kieft et al.'s multicentre trial of a glutamine-, fibre- and antioxidant-enriched formula reported a trend toward reduced infectious morbidity in a heterogeneous ICU population [22]. This optimism was substantially reversed by two large, well-conducted multicentre trials. The REDOXS trial randomised over 1200 mechanically ventilated patients with multi-organ failure to high-dose glutamine, antioxidants, both, or placebo, and found glutamine supplementation was associated with increased 6-month mortality without infection benefit [23]. The SIGNET trial similarly found no infection or

mortality benefit from glutamine-supplemented parenteral nutrition, though high-dose selenium reduced infection signals in a subgroup [24]. Table 1 summarises infection and mortality outcomes across major glutamine trials. These findings prompted ESPEN and ASPEN/SCCM guidelines to withdraw routine glutamine recommendations for unselected critically ill patients, particularly those with shock or multi-organ failure [9,10].

Table 1: Infection and mortality outcomes across major glutamine-supplementation trials in critically ill patients [21,22,23,24].				
Trial	Population	Glutamine dose/route	Infection outcome	Mortality outcome
Galban 2000	Septic ICU patients	Enteral, immune-enhancing diet	Reduced bacteraemia episodes	Reduced mortality
Kieft 2005	Heterogeneous ICU	Enteral, glutamine/fibre/antioxidant	Trend toward fewer infections	No significant difference
REDOXS (Heyland 2013)	Mechanically ventilated, multi-organ failure	High-dose enteral + parenteral	No infection benefit	Increased 6-month mortality
SIGNET (Andrews 2011)	Critically ill, parenteral nutrition	Parenteral glutamine +/- selenium	No significant infection benefit	No significant mortality difference

Omega-3 Fatty Acids and Nucleotides

Omega-3-enriched enteral formulas have been studied predominantly in acute respiratory distress syndrome (ARDS) and sepsis. Gadek and colleagues' original ARDS trial found reduced alveolar neutrophil influx, fewer new organ failures and shorter ventilation with an eicosapentaenoic acid/gamma-linolenic acid/antioxidant formula [25], and Pontes-Arruda et al. reported reduced 28-day mortality and organ dysfunction with the same formula in mechanically ventilated septic patients [26]. These promising signals were not replicated by the National Heart, Lung, and Blood Institute's ARDSNet OMEGA trial, which found no clinical benefit and a trend toward worse outcomes with twice-daily omega-3/antioxidant supplementation, possibly

reflecting bolus-dosing pharmacokinetics rather than a true lack of biological effect [27] (Figure 2). Nucleotide-containing combination formulas, typically paired with arginine and omega-3 fatty acids, support lymphocyte proliferation and gut mucosal repair but have rarely been tested as an isolated component in ICU trials, limiting attribution of clinical benefit to nucleotides specifically [15].

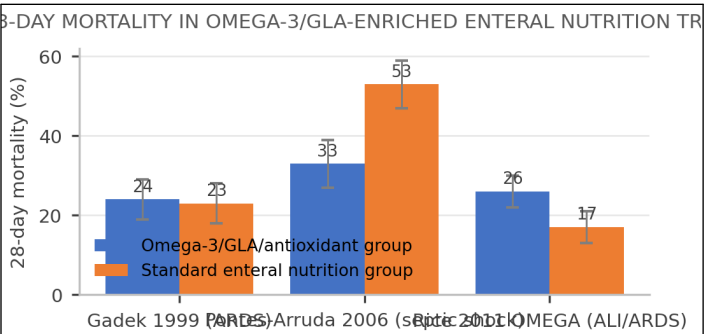


Figure 2: 28-day mortality with omega-3/gamma-linolenic acid/antioxidant-enriched enteral nutrition versus standard enteral nutrition in ARDS and septic shock trials, contrasted with the neutral ARDSNet OMEGA trial result [25,26,27].

Synthesis Across Trials and Guideline Recommendations

Across the assembled literature, three consistent patterns emerge. First, immunonutrition benefit is concentrated in elective surgical and blunt trauma populations without established sepsis, where arginine- and omega-3-enriched formulas reduce postoperative and post-traumatic infectious complications [17,18]. Second, in septic and severely catabolic medical-surgical ICU populations, arginine- and glutamine-containing formulas show neutral or harmful signals, most starkly illustrated by the excess mortality seen with high-dose glutamine in REDOXS and the early stopping of the Bertolini sepsis trial [23,2]. Third, the MetaPlus trial extended this caution to high-protein immune-modulating enteral nutrition in mixed medical-surgical ICU patients, finding no reduction in nosocomial infection and increased late mortality among medical (non-surgical) patients [3]. Table 2

summarises current guideline positions: ESPEN and ASPEN/SCCM guidelines now recommend against routine glutamine supplementation in unselected critically ill patients, particularly those in shock, while conditionally endorsing arginine- or omega-3-enriched formulas only in specific elective surgical or trauma subgroups [9,10,11]. Meta-analytic pooling across heterogeneous trials, as performed by Heyland et al. and Marik and Zaloga, further demonstrates that aggregate point estimates mask this population-dependent heterogeneity, underscoring that immunonutrition is not a single intervention but a family of distinct pharmaconutrients whose effects diverge by substrate and by host inflammatory state [1,28].

Table 2: Current guideline positions on enteral immunonutrients in critically ill adults [9,10,11].			
Immunonutrient	ESPEN 2019 position	ASPEN/SCCM position	Populations favoured
Arginine	Conditional, elective surgery only	Consider in elective surgical patients	Elective GI surgery, blunt trauma
Glutamine	Not recommended in shock/multi-organ failure	Not recommended for routine use	None routine; avoid in shock
Omega-3 fatty acids	Conditional in ARDS	Insufficient evidence for routine use	Selected ARDS subgroups
Nucleotides	Only as part of combination formulas	Insufficient standalone evidence	Not independently established

Conclusion

Enteral immunonutrition with arginine, glutamine, omega-3 fatty acids and nucleotides does not produce a uniform reduction in infection rates across the critically ill population. The strongest and most consistent evidence for benefit lies in elective gastrointestinal surgery and blunt trauma, where arginine- and omega-3-enriched formulas reduce postoperative infectious morbidity and length of stay. In contrast, high-dose glutamine and arginine-containing formulas show neutral-to-harmful

effects in severe sepsis, septic shock and heterogeneous medical ICU populations, most notably in the REDOXS and Bertolini trials. Current ESPEN and ASPEN/SCCM guidelines reflect this heterogeneity, endorsing selective rather than routine use. Future trials should stratify by baseline inflammatory phenotype and surgical versus septic aetiology, and should evaluate individual immunonutrients rather than fixed combination formulas, to clarify which critically ill patients, if any, stand to benefit from immunonutrition. Until such trials are available, clinicians should treat "immunonutrition" not as a single therapy but as a menu of substrates whose risk-benefit balance depends on the timing, dose, and inflammatory context of administration, reserving arginine- and omega-3-enriched formulas for elective surgical and trauma populations while avoiding high-dose glutamine and arginine in patients with septic shock or established multi-organ failure.

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