RJNMSR
Review Journal of Neurological & Medical Sciences Review

Volume 4, Issue 6, 2026

ROLE OF THERAPEUTIC NUTRITION IN CRITICAL AND CLINICAL CARE: A DIETITIAN'S PERSPECTIVE ON ICU PROTEIN INTAKE, ENTERAL NUTRITION IN INFECTION RECOVERY, AND INFLAMMASOME MODULATION IN HEART FAILURE

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DOI: https://doi.org/10.5281/zenodo.20606980

Received	Accepted	Published
11 April 2026	22 May 2026	09 June 2026

ABSTRACT

Therapeutic nutrition plays a pivotal role in the management of critically ill and clinically complex patients, yet optimal implementation requires integration of evolving mechanistic insights with pragmatic clinical protocols. This review synthesizes current evidence across three domains of high clinical relevance to dietitians: protein delivery in intensive care unit (ICU) settings, enteral nutrition strategies for infection and sepsis recovery, and dietary modulation of inflammasome pathways in heart failure. In ICU protein management, contemporary guidelines recommend staged escalation from low early doses to 1.2–2.0 g/kg/day after stabilization, with individualized adjustments for obesity, continuous renal replacement therapy, burns, and sepsis; however, randomized controlled trials demonstrate muscle-sparing effects without consistent mortality benefit, and delivery barriers necessitate active dietitian oversight. Enteral nutrition in infection recovery preserves gut barrier integrity, modulates the microbiome, and supports immune homeostasis, with early initiation (within 72 hours) associated with shorter ICU stays and reduced acute kidney injury, though clinical trial outcomes remain heterogeneous and immunonutrient formulas show context-dependent benefits and risks. Emerging evidence implicates the NLRP3 inflammasome in cardiac inflammation and heart failure progression; preclinical studies identify omega-3 fatty acids, polyphenols, short-chain fatty acids, and ketone bodies as inflammasome inhibitors through mitochondrial protection, redox modulation, and epigenetic mechanisms, yet clinical translation remains limited. Across all three domains, dietitians serve as essential integrators–assessing individual needs, prescribing tailored interventions, troubleshooting delivery obstacles, and bridging mechanistic science with bedside care. This review

provides a structured framework for evidence-based nutrition practice in critical and clinical care, highlighting both established interventions and areas requiring further investigation.

Keywords: *therapeutic nutrition, ICU protein intake, enteral nutrition, sepsis recovery, gut microbiome, NLRP3 inflammasome, heart failure, clinical dietetics, critical care nutrition, immunonutrition*

1. INTRODUCTION

Nutrition therapy has evolved from supportive care to a cornerstone intervention in critical and clinical medicine, with mounting evidence that macronutrient composition, timing, route, and bioactive food components directly influence immune function, metabolic homeostasis, and clinical outcomes (Lambell et al.,2020; van Zanten et al.,2019). Dietitians occupy a unique position at the intersection of nutritional science and clinical practice, translating mechanistic insights into individualized care plans that address the complex, dynamic needs of acutely ill patients (Wischmeyer et al.,2023). This review examines three high-impact domains where therapeutic nutrition intersects with critical pathophysiology: protein delivery in the intensive care unit (ICU), enteral nutrition strategies for infection and sepsis recovery, and dietary modulation of inflammasome-mediated inflammation in heart failure (Lambell et al.,2020; Moon et al.,2023; Pellegrini et al.,2021).

In the ICU, protein-energy malnutrition and muscle wasting are near-universal consequences of critical illness, driven by inflammatory catabolism, immobility, and inadequate nutrient delivery (Lambell et al.,2020). Contemporary guidelines advocate for staged protein escalation, yet randomized trials reveal a disconnect between muscle preservation and hard clinical endpoints such as mortality (Nakanishi et al.,2022; Wischmeyer et al.,2023). Special populations—including patients with obesity, those receiving continuous renal replacement therapy (CRRT), burn victims, and septic patients—present unique dosing challenges that demand individualized assessment and monitoring (Hurt et al.,2017; Wischmeyer et al.,2023). Barriers to achieving prescribed protein targets are multifactorial, encompassing feed interruptions, gastrointestinal intolerance, non-nutritional caloric sources, and formula limitations, underscoring the indispensable role of the clinical dietitian in optimizing delivery (Mitchell et al.,2019; Allaparthi et al.,2025).

Enteral nutrition in the context of infection and sepsis recovery extends beyond caloric provision to encompass preservation of gut barrier function, modulation of the intestinal microbiome, and support of mucosal immunity (Moon et al.,2023; Xu et al.,2024). Early enteral feeding maintains enterocyte mass, reduces bacterial translocation, and promotes immune tolerance, yet clinical trial data remain heterogeneous, with benefits concentrated in specific subgroups and outcomes (Sun et al.,2021; Xu et al.,2024). The gut microbiome emerges as both a mediator of sepsis susceptibility and a therapeutic target, with dysbiosis correlating with organ dysfunction and mortality (D'Amico et al.,2019; Shimizu et al.,2018). Immunonutrient formulas containing arginine, omega-3 fatty acids, and glutamine have shown promise in selected populations but also signal potential harm in severe sepsis, necessitating careful patient selection and protocol design (Galban et al.,2000; Briassoulis et al.,2005).

Heart failure represents a chronic inflammatory state in which sterile immune activation contributes to adverse remodeling and progressive dysfunction (Pellegrini et al.,2021; Wang et al.,2024). The NLRP3 inflammasome, a multiprotein complex that generates interleukin-1β (IL-1β) and interleukin-18 (IL-18), has been implicated as a central mediator of cardiac inflammation (Pellegrini et al.,2021). Preclinical studies identify marine omega-3 fatty acids, polyphenols, short-chain fatty acids (SCFAs), and ketone bodies as dietary inhibitors of NLRP3 through diverse mechanisms including mitochondrial protection, redox modulation, and epigenetic regulation (Sun et al.,2022; Chu et al.,2021; Lin et al.,2025). However, clinical translation remains incomplete, with omega-3

supplementation showing modest outcome benefits in large trials but limited direct evidence for other dietary components (Wang et al.,2024). Across these three domains, dietitians serve as essential integrators, bridging bench science and bedside care through comprehensive assessment, evidence-based prescription, proactive troubleshooting, and interdisciplinary collaboration (van Zanten et al.,2019; Wischmeyer et al.,2023). This review provides a structured synthesis of current evidence, practical implementation strategies, and critical knowledge gaps, equipping dietitians and clinical teams with a framework for optimizing therapeutic nutrition in critical and clinical care (Lambell et al.,2020; Allaparthi et al.,2025).

2. Section 1: ICU Protein Intake

2.1 Optimal Protein Dose: Guideline Recommendations and Evidence

Critical care nutrition guidelines have converged on a staged approach to protein dosing, balancing the need to attenuate muscle catabolism with concerns about metabolic stress during the acute phase of illness. Most expert recommendations endorse a target range of **1.2–2.0 g/kg/day**, with some guidelines extending to **2.5 g/kg/day** for selected high-need patients. This range reflects a consensus that protein requirements in critical illness exceed those of healthy individuals due to inflammatory catabolism, immobility, and wound healing demands. Practical targets commonly promoted in the literature include escalation to at least **1.2–1.3 g/kg/day** after the initial acute phase (first 48–72 hours) once hemodynamic stability is achieved.

Randomized controlled trials (RCTs) comparing higher versus lower protein delivery have typically achieved mean intakes near **1.3 g/kg/day** in the higher-protein arm versus approximately **0.9–1.0 g/kg/day** in the lower-protein arm. Pooled analyses of these trials reveal a consistent signal for **attenuation of muscle mass loss** and small improvements in activities of daily living (ADL) measures, but **no clear mortality benefit** across heterogeneous ICU populations. This disconnect between surrogate endpoints (muscle preservation) and hard clinical outcomes (mortality, length of stay) underscores the complexity of critical illness, where protein delivery is one of many interacting factors influencing recovery.

The staged approach to protein dosing reflects emerging understanding of metabolic phases in critical illness. During the early acute phase (first 48–72 hours), characterized by hemodynamic instability, high inflammatory burden, and insulin resistance, low-dose protein (or permissive hypocaloric feeding with prioritized protein) is often advised to avoid exacerbating metabolic stress. After stabilization, progressive escalation to guideline targets aims to support anabolism and muscle preservation during the recovery phase. This phased strategy is supported by observational data suggesting that early aggressive protein delivery may not confer benefit and could potentially increase ureagenesis and metabolic load in unstable patients.

2.2 Timing of Initiation and Clinical Outcomes

Timing recommendations for protein initiation prioritize caution during the very early unstable phase, with progressive escalation as patients stabilize. Low-dose enteral or parenteral protein may be started within **24–48 hours** in many patients, but escalation to standard or higher targets is typically deferred until clinical stabilization, often after day 3–5. This conservative early approach reflects concerns about feeding intolerance, hemodynamic compromise, and the potential for metabolic complications during the acute inflammatory phase.

Meta-analyses of RCTs examining higher versus lower protein delivery have consistently found **no mortality benefit** from higher protein intake across diverse ICU populations. However, higher protein delivery typically defined as achieving ≥1.0 g/kg/day early within days 4–10—is associated with **attenuated muscle loss** and modest improvements in functional outcomes in some pooled analyses and small trials. These findings suggest that protein delivery may influence body composition and physical function without translating into survival advantages, at least in the heterogeneous populations studied to date.

Observational studies have generated signals that early protein delivery may associate with improved survival in certain cohorts, with benefits potentially concentrating in subgroups with low baseline muscle mass or specific disease states. However, these observational associations are subject to confounding by indication, reverse causation, and survivor bias, limiting causal inference. Large ongoing RCTs, such as the REPLENISH trial, are testing supplemental enteral protein strategies with 90-day mortality and functional outcomes as primary endpoints, aiming to clarify whether protein delivery can improve hard clinical outcomes when delivered systematically and at adequate doses.

The heterogeneity of ICU populations—spanning medical, surgical, trauma, and burn patients with varying degrees of organ dysfunction, inflammatory burden, and baseline nutritional status—complicates the interpretation of pooled trial data. Subgroup analyses suggest that benefits of higher protein delivery may be most apparent in patients with prolonged ICU stays, those with low muscle mass at baseline, and non-septic populations, though these findings require prospective validation.

2.3 Special Populations: Obesity, Renal Failure, Burns, and Sepsis

Protein targets and associated risks vary substantially across special populations, necessitating individualized dosing strategies that account for body composition, organ function, metabolic demands, and clinical context.

Obesity: Patients with obesity present unique challenges in protein dosing due to altered body composition, with excess adipose tissue but often normal or reduced lean body mass. Recommended practice is to use a weight basis that accounts for body composition, such as adjusted body weight or ideal body weight, rather than actual body weight. Many ICU protocols prescribe higher protein relative to ideal body weight (up to **1.5–2.0 g/kg ideal body weight**) to meet absolute protein needs while avoiding overfeeding energy. Practical difficulty in reaching these targets without protein supplementation is commonly reported, as standard enteral formulas may not provide sufficient protein per volume for obese patients.

Renal Failure and CRRT: Patients receiving continuous renal replacement therapy (CRRT) have increased amino acid losses through the dialysate, necessitating higher protein intake to maintain nitrogen balance. Guidelines commonly endorse higher protein targets for CRRT patients, though specific recommendations vary. Conversely, in acute kidney injury (AKI) not requiring renal replacement therapy, early high protein delivery may be avoided until metabolic stability is achieved, as excessive protein can increase ureagenesis and potentially exacerbate uremia. Monitoring of blood urea nitrogen (BUN), urea-to-creatinine ratio, and clinical tolerance is essential in this population.

Burns and Major Trauma: Burn patients and those with major trauma have markedly elevated protein requirements due to wound healing, inflammatory stress, and hypermetabolism. Expert consensus supports higher-range protein dosing, often toward the upper end of guideline recommendations (approaching 2.0–2.5 g/kg/day), to support anabolic demands and attenuate muscle catabolism. However, high-quality RCTs in these populations are limited, and recommendations are largely based on observational data and physiologic rationale.

Sepsis: Evidence for protein dosing in sepsis is mixed and context-dependent. Some observational data link early higher protein delivery with improved outcomes in non-septic ICU subgroups, and subgroup signals suggest that patients with low muscle mass may benefit from higher protein intake. However, RCT data do not uniformly demonstrate mortality benefit from high early protein delivery in unstable septic patients, and concerns exist about exacerbating metabolic stress during the acute inflammatory phase. Current evidence is insufficient to recommend universal very-high early protein delivery in unstable septic patients, and individualized prescribing based on clinical trajectory and tolerance is advised.

Across all special populations, individualized prescribing requires careful selection of weight basis, monitoring of metabolic markers (urea,

urea-to-creatinine ratio, acid-base status), and assessment of clinical tolerance. Higher protein delivery can increase ureagenesis, ammonia production, and metabolic load in vulnerable patients, necessitating a balance between meeting anabolic needs and avoiding metabolic complications.

2.4 Barriers to Adequate Protein Delivery

Despite guideline recommendations and prescribed targets, actual protein delivery in the ICU frequently falls short of goals. Audits and cohort reports consistently document substantial gaps between prescribed and delivered protein, with multiple interacting barriers contributing to this shortfall.

Feed Interruptions and Delivery Shortfall: Enteral nutrition delivery is frequently interrupted for procedures, diagnostic tests, hemodynamic instability, and perceived or actual feeding intolerance. Audits show that median delivered protein is substantially less than prescribed, with low proportions of patients meeting targets during the early ICU stay. These interruptions are often unavoidable but cumulatively result in significant underdelivery of prescribed nutrition.

Non-Nutritional Calories: Sedative lipid emulsions, particularly propofol, contribute substantial non-nutritional calories that must be accounted for in the nutrition prescription. Propofol can provide 1.1 kcal/mL, and high-dose infusions may contribute hundreds of kilocalories per day, reducing the permissible enteral caloric volume and displacing protein delivery unless explicitly accounted for in the nutrition plan. Failure to adjust enteral prescriptions for propofol and other non-nutritional caloric sources is a common cause of protein underdelivery.

Gastrointestinal Dysfunction and Clinical Instability: Feeding intolerance, high gastric residual volumes, diarrhea, abdominal distension, and concerns about bowel ischemia frequently limit feed advancement and protein attainment. Hemodynamic instability, vasopressor requirements, and evolving organ dysfunction further constrain the ability to advance enteral nutrition to goal rates. These clinical factors are often dynamic and require ongoing reassessment and adjustment of the nutrition plan.

Product Limitations: Standard enteral formulas typically provide a fixed protein-to-energy ratio (often 1 g protein per 25–30 kcal), which may be insufficient for patients requiring high protein relative to energy needs, such as obese patients or those on CRRT. Without the use of protein-enriched formulas, modular protein supplements, or concentrated feeds, achieving high protein targets while avoiding overfeeding energy can be challenging.

These barriers are not insurmountable but require proactive identification, systematic monitoring, and coordinated interventions by the clinical team, with the dietitian playing a central role in troubleshooting and optimizing delivery.

2.5 The Dietitian's Role in ICU Protein Management

The clinical dietitian is essential to translating protein guidelines into individualized, achievable nutrition care plans and ensuring that prescribed targets are met despite the numerous barriers inherent to critical care.

Assessment and Prescription: Dietitians conduct comprehensive nutrition assessments early in the ICU stay, typically within 24–72 hours of admission. This assessment includes identification of nutrition risk, evaluation of baseline nutritional status and body composition, selection of an appropriate weight basis (ideal, adjusted, or actual body weight), and prescription of tailored protein targets based on clinical context, disease state, and organ function. Documentation of the rationale for weight basis selection and protein targets facilitates communication with the interdisciplinary team and ensures continuity of care.

Optimization and Troubleshooting: Dietitians actively troubleshoot barriers to protein delivery by adjusting enteral formulas, adding modular protein supplements or protein-enriched formulas, managing non-nutritional caloric sources (e.g., accounting for propofol calories), and addressing gastrointestinal dysfunction through prokinetic agents, post-pyloric feeding, or alternative feeding routes. They collaborate with

physicians, nurses, and pharmacists to minimize feed interruptions, optimize feeding protocols, and balance nutrition goals with other clinical priorities.

Monitoring and Handover: Dietitians track delivered versus prescribed intake on a daily or near-daily basis, using bedside flow sheets, electronic health records, and indirect calorimetry (where available) to assess adequacy and adjust prescriptions dynamically. They monitor metabolic markers (BUN, creatinine, acid-base status) and clinical tolerance to ensure that protein delivery is safe and effective. At ICU-to-ward transfer, dietitians ensure continuity of nutrition care through structured handover, preventing the common phenomenon of nutrition de-escalation or neglect during transitions of care.

Impact Evidence: Dietetic-led interventions and protocol changes have been shown to increase prescription adherence and improve the proportion of patients meeting protein targets in audits and cohort studies. Systematic dietitian involvement is associated with higher delivered protein, better attainment of nutrition goals, and improved nutrition-related processes of care, though direct effects on mortality and length of stay remain difficult to isolate from other aspects of ICU care.

Practical implementation strategies for ICU teams include: (1) confirming weight basis and protein target early and documenting rationale; (2) accounting for non-nutritional calories and using protein supplements when formula volume limits attainment; (3) prioritizing protein advancement after initial stabilization while avoiding overfeeding energy in the acute phase; and (4) ensuring daily dietitian oversight for adjustment, monitoring, and ICU-to-ward handover to sustain gains.

3. Section 2: Enteral Nutrition in Infection Recovery

3.1 Mechanisms of Gut Mucosal Protection

Enteral nutrition exerts physiologic effects that extend beyond macronutrient provision, serving to preserve gut barrier integrity, support mucosal immunity, and maintain homeostatic interactions between the intestinal epithelium, immune system, and microbiota. These mechanisms provide the primary rationale for preferring enteral over parenteral nutrition when the gastrointestinal tract is functional.

Mucosal Integrity: Enteral feeding maintains enterocyte mass and gut barrier function, reducing intestinal permeability and the risk of bacterial translocation and gut-origin sepsis. The physical presence of nutrients in the intestinal lumen provides trophic stimulation to the epithelium, supporting tight junction integrity and preventing atrophy. In contrast, prolonged absence of enteral nutrition (as occurs with exclusive parenteral nutrition) is associated with villous atrophy, increased permeability, and loss of barrier function.

Immune Tolerance: Luminal nutrients and enteral stimulation promote appropriate mucosal immune responses, supporting immune tolerance to commensal organisms and dietary antigens while maintaining the capacity to respond to pathogens. Enteral nutrition helps preserve the balance between pro-inflammatory and regulatory immune pathways in the gut-associated lymphoid tissue (GALT), reducing maladaptive systemic inflammation that can exacerbate critical illness.

Substrate for the Mucosa: Specific enteral components, including fermentable fiber and other substrates, support colonic nutrition and the production of short-chain fatty acids (SCFAs)—acetate, propionate, and butyrate—through microbial fermentation. SCFAs, particularly butyrate, serve as the preferred energy source for colonocytes and exert anti-inflammatory and barrier-protective effects through multiple signaling pathways. Enteral nutrition that includes fermentable substrates thus supports both the epithelium and the beneficial microbial community.

Clinical Translational Examples: Enteral feeding approaches have been linked to more rapid restoration of a eubiotic (healthy) microbiome and favorable SCFA profiles after profound insults such as hematopoietic stem cell transplantation, consistent with preserved epithelial function and microbial-epithelial cross-talk. These observations support the mechanistic rationale for early enteral nutrition in infection and sepsis recovery.

3.2 Timing and Route: Early Enteral Nutrition versus Parenteral Approaches

The timing of nutrition initiation and the choice between enteral and parenteral routes have been subjects of extensive investigation, with implications for both physiologic endpoints and clinical outcomes. Early enteral feeding is commonly defined as initiation within approximately 72 hours of ICU admission in observational and database studies.

Early Initiation and Clinical Outcomes: A large propensity-matched analysis found that initiating enteral nutrition within 3 days was associated with **shorter ICU length of stay** and a **lower incidence of stage-3 acute kidney injury (AKI)**, though overall mortality was not reduced after adjustment for confounders. These findings suggest that early enteral nutrition may influence specific morbidity endpoints without conferring a survival advantage in unselected ICU populations. A recent systematic review examining early enteral nutrition in sepsis found inconsistent definitions of "early" across studies and heterogeneous methods, and did not demonstrate a clear short-term mortality benefit. The review noted variable reporting of intestinal complications, highlighting the need for standardized definitions and outcome measures in future trials.

Route Comparisons: Studies in burn patients and hematopoietic transplant recipients have shown **fewer infections** and **faster microbiome recovery** with enteral versus parenteral nutrition, supporting the preference for enteral feeding when the gut is usable. Parenteral nutrition is associated with gut atrophy, delayed microbiome recovery, and potentially higher infection risk, though it remains a necessary intervention when enteral feeding is contraindicated or insufficient.

Adequacy and Combination Feeding: In critically ill sepsis cohorts, meeting energy and protein targets in the first week was associated with lower short-term mortality in observational analyses. When more than 70% of nutritional requirements were achievable, combining enteral nutrition with supplemental parenteral nutrition outperformed enteral nutrition alone or parenteral nutrition alone for some longer-term outcomes, suggesting that adequacy of delivery may be more important than route in selected patients.

Heterogeneity and Safety Signals: Trials of enteral immune-enhancing formulas in severe sepsis have produced conflicting results. Some studies show reduced infections and bacteremia, whereas others have signaled higher mortality in severe sepsis subgroups, highlighting that formula composition, patient severity, and timing modulate both risk and benefit. These findings underscore the importance of patient selection and individualized nutrition strategies.

3.3 Impact on the Gut Microbiome

The gut microbiome is increasingly recognized as both a mediator of sepsis susceptibility and a therapeutic target. Feeding modality, nutrient composition, and adjunctive interventions such as probiotics and synbiotics alter microbial composition and metabolic output, with downstream effects on immune function and clinical outcomes.

Dysbiosis in Sepsis: Sepsis is accompanied by profound alterations in the gut microbiome, including loss of commensal diversity, expansion of opportunistic pathogens (e.g., *Enterococcus*, certain *Bacteroides* species), and altered metabolic pathways affecting amino acid and tryptophan metabolism. These dysbiotic changes correlate with worse organ dysfunction scores, longer ICU stays, and higher mortality, suggesting that microbiome disruption contributes to sepsis pathophysiology.

Feeding Modality and Microbiome Effects: Enteral nutrition preserves microbial diversity and supports recovery of commensal organisms and SCFA production, whereas parenteral nutrition is associated with gut atrophy and delayed microbiome recovery. In transplant and burn cohorts, enteral feeding has been linked to faster restoration of a eubiotic microbiome and potentially lower infectious complications compared with parenteral nutrition.

Synbiotics and Probiotics: Synbiotic supplementation (combined probiotics and prebiotics) has been shown to increase beneficial bacteria such as bifidobacteria and lactobacilli and to elevate organic acids including acetate. In a

randomized ICU sepsis trial, early synbiotic administration reduced enteritis and ventilator-associated pneumonia without a clear mortality effect, suggesting potential benefits for specific infectious complications. However, safety considerations remain, particularly in immunocompromised hosts, and strain selection, timing, and patient selection require further validation.

The gut microbiome represents a promising therapeutic target in sepsis and infection recovery, with enteral nutrition and microbiome-directed adjuncts offering potential to preserve epithelial health, modulate immunity, and reduce infectious complications. However, clinical translation requires careful attention to patient selection, intervention timing, and safety monitoring.

3.4 Specific Immunonutrients: Arginine, Omega-3 Fatty Acids, and Glutamine

Immunonutrient-enriched enteral formulas containing arginine, omega-3 fatty acids, and glutamine have been extensively studied in critical care populations, with heterogeneous results that reflect the complexity of immune modulation in sepsis and infection.

Arginine and Omega-3 Fatty Acids: Enteral formulas containing arginine and omega-3 fatty acids have reduced infection rates, bacteremia, and mortality in some ICU sepsis populations in randomized or controlled studies. These formulas have also improved organ dysfunction scores in certain trials, supporting the biologic plausibility of immune modulation through enhanced T-cell function (arginine) and production of less inflammatory eicosanoids and pro-resolving mediators (omega-3 fatty acids).

However, an international multicenter trial subgroup analysis suggested **increased ICU mortality** with enteral immunonutrition compared with parenteral nutrition in patients with **severe sepsis**, indicating potential harm in the sickest subgroups. This safety signal has led to caution in the use of immunonutrient formulas in severe sepsis, with recommendations to individualize use based on illness severity and to avoid routine, unselected use in the most critically ill patients.

Glutamine: Glutamine is commonly included in immunonutrition mixtures and is considered a conditionally essential amino acid in critical illness due to its role in enterocyte metabolism, immune cell function, and antioxidant defense. However, the evidence base for glutamine supplementation specifically in sepsis is inconsistent, and robust, sepsis-specific clinical benefit has not been definitively established in the available literature. Some studies suggest potential benefit in selected populations, whereas others show no effect or potential harm with high-dose supplementation, particularly in patients with multiorgan failure.

Immunomodulation Endpoints: Trials in children and adults demonstrate that immune-enhancing feeds can alter cytokine production and other immune markers, showing biologic plausibility for clinical effects. However, translation into consistent mortality benefit is inconsistent, likely reflecting the heterogeneity of critical illness, the complexity of immune dysregulation in sepsis, and the potential for both beneficial and harmful immune modulation depending on timing and patient characteristics.

The use of immunonutrient formulas in sepsis and infection recovery requires careful patient selection, with consideration of illness severity, timing of intervention, and potential risks. Routine use in severe sepsis is not supported by current evidence, and individualized decision-making in consultation with the interdisciplinary team is essential.

3.5 Dietitian Protocols for Enteral Nutrition in Sepsis and Infection

Clinical dietitian protocols for enteral nutrition in sepsis and infection recovery should integrate early, tolerable enteral stimulation with realistic energy and protein targets, systematic monitoring, and selective use of adjuncts based on patient severity and gut function. The following protocol elements synthesize current evidence into actionable steps.

Start Timing: Initiate trophic enteral feeding within approximately **72 hours** when the gut is functional and there are no absolute contraindications (e.g., bowel ischemia, obstruction, high-output fistula). Early initiation is

associated with shorter ICU stays and less severe AKI in large cohort analyses, supporting the physiologic rationale for early gut stimulation.

Advancement and Targets: Aim to achieve energy and protein goals during the **first week**, with particular emphasis on adequate protein delivery. Higher average protein intake in the first week has correlated with lower in-hospital mortality in large retrospective cohorts, though causality remains uncertain. Progressive advancement of enteral feeding should be guided by tolerance, with attention to gastric residual volumes, abdominal examination, and hemodynamic stability.

Caloric Strategy: Consider moderate early underfeeding (approximately **60% of goal**) during acute sepsis if intolerance is present. A pilot trial found that 60% of goal improved gut barrier biomarkers without increasing feeding intolerance compared with full feeding, suggesting that permissive underfeeding may be appropriate during the acute inflammatory phase while prioritizing protein delivery.

Route and Combinations: Prefer enteral nutrition when feasible, given its physiologic advantages for gut barrier function and microbiome preservation. Add supplemental parenteral nutrition if enteral nutrition cannot meet more than **70% of needs**, as combined enteral and parenteral nutrition was associated with better outcomes in patients who reached adequate energy delivery in observational analyses. However, the decision to initiate parenteral nutrition should balance the benefits of meeting nutrition targets against the risks of overfeeding, hyperglycemia, and infection.

Immunonutrition Use: Individualize the use of arginine- and omega-3-enriched formulas based on illness severity and patient characteristics. These formulas may reduce infections in some ICU sepsis patients but have signaled harm in severe sepsis subgroups. Avoid routine, unselected use in the sickest septic patients, and review unit-level trial data and institutional protocols before adoption. When used, immunonutrient formulas should be initiated early (within 48–72 hours) and continued for at least 5–7 days to allow for immune modulation.

Microbiome Adjuncts: Consider synbiotic or probiotic adjuncts selectively, particularly in patients at high risk for enteritis or ventilator-associated pneumonia. Early synbiotic administration decreased these complications in a randomized septic ICU cohort, but strain selection, timing, and safety for immunocompromised hosts require careful consideration. Probiotics should be avoided in patients with severe immunosuppression, central venous catheters, or high risk of bacterial translocation unless evidence supports safety in that specific population.

Monitoring and Escalation: Monitor gastrointestinal tolerance, gastric residual volumes per local policy, and biomarkers of nutritional status and enterocyte mass when available. Escalate or combine feeding routes if targets are unmet, and reassess the nutrition plan daily in collaboration with the interdisciplinary team. Preservation of epithelial function and microbiome resilience should be considered key monitoring goals, even when direct measurement is not feasible.

These protocol elements provide a structured framework for dietitian-led enteral nutrition management in sepsis and infection recovery, balancing evidence-based targets with individualized assessment and pragmatic troubleshooting.

4. Section 3: Inflammasome Modulation in Heart Failure

4.1 NLRP3 Inflammasome in Cardiac Pathophysiology

The NLRP3 (NOD-like receptor family pyrin domain containing 3) inflammasome is a multiprotein complex that serves as a key innate immune sensor, detecting cellular stress signals and initiating inflammatory responses. In the context of heart failure, NLRP3 activation drives sterile cardiac inflammation, contributing to adverse remodeling, fibrosis, and progressive ventricular dysfunction.

Core Function: NLRP3 activation leads to caspase-1–dependent maturation of the pro-inflammatory cytokines interleukin-1β (IL-1β) and interleukin-18 (IL-18), and induction of

pyroptosis, a form of inflammatory cell death. These processes are implicated in cardiovascular pathology, including atherosclerosis, myocardial infarction, and heart failure. IL-1β and IL-18 promote myocardial inflammation, recruit immune cells, and stimulate fibroblast activation and extracellular matrix deposition, contributing to adverse remodeling.

Pathophysiologic Evidence: Increased NLRP3 signaling is associated with adverse remodeling and cardiac dysfunction in experimental models of obesity-related cardiomyopathy and pressure-overload heart failure. Genetic or pharmacologic inhibition of NLRP3 improves functional and structural endpoints in preclinical heart failure models, including reduced left ventricular hypertrophy, decreased fibrosis, and improved ejection fraction. These findings support a causal role for NLRP3 in heart failure pathophysiology and identify the inflammasome as a plausible therapeutic target.

Clinical Implications: Reviews of cardiovascular disease identify NLRP3 as a central mediator linking metabolic and sterile inflammatory stimuli—such as oxidative stress, mitochondrial dysfunction, and damage-associated molecular patterns (DAMPs)—to myocardial damage. In heart failure, chronic activation of NLRP3 contributes to a pro-inflammatory milieu that perpetuates cardiomyocyte injury, fibrosis, and ventricular remodeling, suggesting that interventions to inhibit NLRP3 could slow disease progression and improve outcomes.

4.2 Dietary Inhibitors and Molecular Mechanisms

Emerging evidence identifies several dietary components as inhibitors of NLRP3 inflammasome activation, acting through diverse molecular mechanisms that converge on reducing inflammatory signaling and protecting cellular homeostasis. The major dietary inhibitors include omega-3 fatty acids, polyphenols, short-chain fatty acids, and ketone bodies.

Omega-3 Fatty Acids: Marine-derived omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been shown to attenuate NLRP3 activation and downstream cytokine production in animal and cellular studies. Krill oil, a rich source of omega-3 phospholipids, inhibited cardiac NLRP3 expression in diabetic cardiomyopathy models. Mechanistic pathways include **mitochondrial protection** (reducing mitochondrial reactive oxygen species [ROS] that trigger NLRP3 activation), **reduction of pro-inflammatory eicosanoids** (shifting from arachidonic acid–derived mediators to less inflammatory EPA- and DHA-derived mediators), **production of specialized pro-resolving mediators** (resolvins, protectins, maresins), and **upregulation of SIRT3 and PGC-1α**, which are negative regulators of NLRP3. These pleiotropic effects position omega-3 fatty acids as multi-target inhibitors of inflammasome-mediated cardiac inflammation.

Polyphenols: Polyphenolic compounds, particularly quercetin, have been shown to suppress NLRP3 activation via redox and transcriptional regulators. Quercetin inhibits NLRP3 through modulation of thioredoxin-interacting protein (TXNIP), sirtuin 1 (SIRT1), and nuclear factor erythroid 2–related factor 2 (NRF2), which collectively reduce oxidative stress and inhibit nuclear factor-κB (NF-κB) priming of NLRP3. Broader phytochemical literature reports NLRP3 inhibition by other polyphenols, including resveratrol and curcumin, though direct trial evidence for these compounds in heart failure is limited in the available literature. Polyphenols exert **antioxidant effects**, **inhibit NF-κB priming**, and modulate epigenetic regulators, providing multiple points of intervention in the inflammasome pathway.

Short-Chain Fatty Acids and Ketone Bodies: SCFAs (acetate, propionate, butyrate) and the ketone body β-hydroxybutyrate inhibit NLRP3 activation in mechanistic studies and are proposed as protective mediators in heart failure with preserved ejection fraction (HFpEF) models. Mechanistic pathways include **G-protein coupled receptor (GPR) signaling** (SCFAs activate GPR41, GPR43, and GPR109A, which modulate immune cell function and reduce inflammation), **AMP-activated protein kinase (AMPK) activation** (promoting metabolic homeostasis and inhibiting inflammatory

signaling), **histone deacetylase (HDAC) inhibition** (altering gene expression to favor anti-inflammatory programs), and **reduced NF-κB priming and mitochondrial ROS**. β-hydroxybutyrate functions as an endogenous NLRP3 inhibitor and HDAC modulator, with proposed cardioprotective signaling in metabolically stressed hearts.

Complex Botanical Preparations: Several traditional Chinese medicine (TCM) extracts and mixed phytochemical preparations reduce cardiac NLRP3 expression and improve remodeling in animal heart failure models. These preparations exert multi-target actions, including gut microbiota modulation (which may increase SCFA production), decreased NF-κB signaling, and direct inflammasome inhibition, though the active components and mechanisms are often incompletely characterized.

The molecular mechanisms by which dietary components inhibit NLRP3 converge on several key nodes: (1) **priming and activation steps**—nutrients may reduce NF-κB–dependent priming of NLRP3 gene expression or block the activation step driven by mitochondrial ROS and DAMPs; (2) **SIRT/PGC-1α axis**—omega-3 fatty acids upregulate SIRT3 and PGC-1α, which act as negative regulators of NLRP3; (3) **redox/TXNIP pathway**—polyphenols suppress TXNIP and engage SIRT1/NRF2 to blunt NLRP3 activation; (4) **microbiota-derived metabolites**—dietary fiber–driven SCFAs signal through GPRs, activate AMPK, inhibit HDACs, and reduce NF-κB/NLRP3 signaling; and (5) **ketone signaling**—β-hydroxybutyrate functions as an endogenous NLRP3 inhibitor and epigenetic modulator.

4.3 Clinical Trial Evidence and Limitations

Clinical data directly linking nutritional modulation of NLRP3 to improved heart failure outcomes are limited, and the strongest clinical signal in the available literature concerns omega-3 fatty acids and inflammatory or clinical endpoints rather than direct inflammasome readouts.

Omega-3 Clinical Outcomes: The GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca–Heart Failure) trial, a large randomized controlled trial in heart failure patients, reported modest reductions in mortality and heart failure–related events with omega-3 supplementation (1 g/day EPA+DHA). This trial provides the strongest clinical evidence for benefit of a dietary intervention in heart failure, though the mechanisms were not definitively established and likely include effects beyond NLRP3 inhibition, such as anti-arrhythmic effects, improved endothelial function, and modulation of lipid metabolism.

Inflammatory Biomarker Trials: A meta-analysis of RCTs in heart failure patients found that omega-3 supplementation lowered circulating tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) but did not change C-reactive protein (CRP). These findings indicate anti-inflammatory effects that could relate to inflammasome pathways, as IL-1β (a product of NLRP3 activation) drives downstream production of IL-6 and other inflammatory mediators. However, the meta-analysis did not measure IL-1β or direct markers of NLRP3 activity, limiting inference about inflammasome-specific effects.

Context Matters: A small randomized study after myocardial infarction found no benefit of 1 g/day EPA+DHA on inflammatory or lipid markers when background diet quality worsened during the trial, suggesting that supplementation without dietary modification may be ineffective. This finding underscores the importance of overall dietary pattern and the potential for poor diet quality to negate the benefits of isolated nutrient supplementation.

Other Nutrients: The available literature contains preclinical and mechanistic reports for polyphenols, SCFAs, and ketone bodies, but no robust heart failure RCTs directly testing resveratrol, curcumin, SCFA supplementation, or dietary interventions with measured NLRP3 outcomes. Therefore, clinical efficacy specifically via NLRP3 modulation is currently unproven in humans for these dietary components. The gap between mechanistic promise and clinical evidence highlights the need for well-designed trials that measure inflammasome biomarkers (e.g., circulating IL-1β, IL-18, or NLRP3 protein in

peripheral blood mononuclear cells) alongside clinical outcomes.

4.4 Dietitian Care Considerations for Inflammasome-Targeted Nutrition

Dietitians can operationalize current mechanistic and clinical insights into inflammasome-targeted nutrition while recognizing the limited direct clinical proof of NLRP3-specific therapy. Practical interventions should be integrated into comprehensive heart failure nutrition care, which prioritizes sodium restriction, fluid management, caloric balance, and management of comorbidities such as diabetes and chronic kidney disease.

Assessment and Goals: Baseline dietary assessment should evaluate fish and omega-3 intake, fiber intake, and overall dietary pattern to identify deficits linked to lower SCFA production or omega-3 status. Clinical priorities include addressing heart failure–specific dietary needs (sodium, fluid, weight management) while integrating anti-inflammatory targets when feasible. Assessment of polyphenol-rich food intake (fruits, vegetables, tea, berries) and fermentable fiber sources (whole grains, legumes, vegetables) provides a foundation for targeted dietary counseling.

Practical Interventions:

1. **Increase Marine Omega-3s:** Encourage consumption of oily fish (salmon, mackerel, sardines, herring) at least twice per week, or clinician-approved omega-3 supplementation (typically 1 g/day EPA+DHA) as an adjunct to medical therapy. Document dose, formulation, and potential drug-nutrient interactions (e.g., with anticoagulants). Given the GISSI-HF trial evidence for modest benefit, omega-3 supplementation represents a low-risk, evidence-based intervention in heart failure.
2. **Boost Fermentable Fiber:** Promote fiber sources to enhance SCFA production (acetate, propionate, butyrate) as a low-risk strategy that may reduce NLRP3-related signaling via GPR and AMPK pathways. Target fiber intake of 25–30 g/day from whole grains, legumes, vegetables, and fruits, with gradual increases to minimize gastrointestinal intolerance. Fiber intake also supports glycemic control, lipid management, and weight management, providing multiple benefits beyond inflammasome modulation.
3. **Encourage Polyphenol-Rich Foods:** Recommend fruits (berries, apples, grapes), vegetables (onions, leafy greens), tea (green and black), and other polyphenol sources to deliver compounds such as quercetin that have demonstrated NLRP3 suppression in mechanistic studies. Emphasize whole foods over isolated supplements, as whole foods provide synergistic phytochemicals, fiber, and micronutrients.
4. **Coordinate Supplementation:** If supplements (omega-3, targeted botanicals) are considered, align with the treating team to ensure appropriate dosing, monitor for interactions (particularly with anticoagulants, antiplatelet agents, and antiarrhythmic drugs), and pair supplementation with dietary counseling. Supplementation alone may be nullified by poor overall diet quality, as demonstrated in post-myocardial infarction trials.

Monitoring and Outcomes: Focus on clinical endpoints—symptoms (dyspnea, fatigue, exercise tolerance), functional status (6-minute walk distance, quality of life), hospitalization rates, weight, and standard biomarkers (BNP/NT-proBNP, renal function, electrolytes)—rather than NLRP3 assays, which are not routinely available clinically. Where possible, enroll patients in trials or registries measuring inflammasome biomarkers to help bridge mechanistic and clinical evidence.

Evidence Caveats: Clinical translation of inflammasome-targeted nutrition is promising but incomplete. Omega-3 fatty acids have the most robust human outcome data in heart failure, whereas evidence for resveratrol, curcumin, isolated polyphenol supplements, or SCFA supplements in heart failure patients via NLRP3 modulation is insufficient. Dietitians should communicate the current state of evidence to patients and clinicians, emphasizing that dietary interventions are adjunctive to guideline-directed medical therapy and not replacements for pharmacologic treatment.

5. Discussion

This review synthesizes evidence across three domains of therapeutic nutrition in critical and clinical care, revealing both established interventions and persistent knowledge gaps. Across ICU protein management, enteral nutrition in infection recovery, and inflammasome modulation in heart failure, several overarching themes emerge.

Individualization and Context-Dependence: Optimal nutrition therapy is highly individualized, with benefits and risks varying by patient characteristics, disease severity, timing of intervention, and clinical context. In ICU protein management, special populations (obesity, CRRT, burns, sepsis) require tailored dosing strategies that account for body composition, organ function, and metabolic demands. In enteral nutrition for sepsis, immunonutrient formulas show context-dependent benefits and risks, with potential harm in severe sepsis subgroups. In heart failure, the efficacy of dietary interventions may depend on background diet quality, comorbidities, and heart failure phenotype (HFrEF versus HFpEF). This context-dependence underscores the essential role of the clinical dietitian in comprehensive assessment, individualized prescription, and ongoing monitoring.

Disconnect Between Surrogate and Clinical Endpoints: A recurring theme is the disconnect between surrogate endpoints (muscle mass, gut barrier biomarkers, inflammatory cytokines) and hard clinical outcomes (mortality, length of stay, hospitalizations). In ICU protein trials, higher protein delivery attenuates muscle loss but does not consistently reduce mortality. In enteral nutrition trials, early feeding improves some morbidity endpoints (ICU length of stay, AKI) without clear mortality benefit. In heart failure, omega-3 supplementation reduces inflammatory biomarkers and shows modest clinical benefit, but direct evidence for NLRP3 inhibition translating to improved outcomes is lacking. This disconnect may reflect the multifactorial nature of critical illness and chronic disease, where nutrition is one of many interacting determinants of outcome, or it may indicate that current interventions are suboptimal in dose, timing, or composition. It also highlights the need for trials powered for clinical endpoints and designed to identify subgroups most likely to benefit.

Barriers to Implementation: Even when evidence supports specific nutrition interventions, implementation is frequently impeded by practical barriers. In the ICU, feed interruptions, non-nutritional calories, gastrointestinal intolerance, and product limitations result in substantial underdelivery of prescribed protein. In enteral nutrition for sepsis, hemodynamic instability, perceived contraindications, and lack of standardized protocols limit early feeding. In heart failure, patient adherence to dietary recommendations, cost of supplements, and competing dietary restrictions (sodium, fluid, potassium) complicate implementation of anti-inflammatory dietary strategies. Overcoming these barriers requires systematic approaches, including protocol development, interdisciplinary collaboration, patient and family education, and active dietitian involvement in troubleshooting and optimization.

The Gut as a Central Mediator: The gut emerges as a central mediator of both pathophysiology and therapeutic response across multiple domains. In sepsis, gut barrier dysfunction and dysbiosis contribute to systemic inflammation, organ dysfunction, and mortality, while enteral nutrition preserves barrier integrity and supports microbiome resilience. In heart failure, gut-derived SCFAs modulate inflammasome activation and cardiac inflammation, linking dietary fiber intake to cardiac outcomes. This recognition of the gut as a key interface between nutrition, immunity, and systemic health supports the mechanistic rationale for enteral nutrition and microbiome-targeted interventions, and highlights the need for further research on gut-directed therapies.

Mechanistic Insights Outpacing Clinical Translation: In inflammasome modulation, mechanistic insights from preclinical studies have identified multiple dietary inhibitors of NLRP3 and elucidated molecular pathways, yet clinical translation remains limited. This gap reflects the challenges of translating mechanistic findings to

human disease, including differences between animal models and human pathophysiology, the complexity of dietary interventions (whole foods versus isolated nutrients), the influence of background diet and lifestyle, and the difficulty of measuring inflammasome activity in clinical settings. Bridging this gap will require well-designed clinical trials that incorporate mechanistic endpoints (inflammasome biomarkers, immune cell phenotyping) alongside clinical outcomes, and that test dietary interventions in the context of comprehensive dietary patterns rather than isolated nutrients.

The Dietitian as Integrator: Across all three domains, the clinical dietitian serves as an essential integrator, translating complex and evolving evidence into individualized care plans, troubleshooting barriers to implementation, and collaborating with the interdisciplinary team to optimize nutrition therapy. Dietitians bring expertise in assessment, prescription, monitoring, and patient education that is distinct from and complementary to the roles of physicians, nurses, and pharmacists. Evidence from audits and cohort studies demonstrates that dietitian-led interventions improve nutrition-related processes of care and attainment of nutrition goals, though direct effects on mortality and length of stay remain difficult to isolate. Recognizing and supporting the dietitian's role is essential to realizing the potential of therapeutic nutrition in critical and clinical care.

Future Directions: Key areas for future research include: (1) large, adequately powered RCTs of protein delivery in ICU subgroups (low muscle mass, prolonged critical illness, specific disease states) with functional outcomes and long-term follow-up; (2) trials of enteral nutrition strategies in sepsis that incorporate microbiome and immune profiling to identify responders and optimize timing and composition; (3) clinical trials of dietary interventions targeting NLRP3 in heart failure that measure inflammasome biomarkers and test comprehensive dietary patterns rather than isolated nutrients; (4) implementation science studies to identify effective strategies for overcoming barriers to nutrition delivery in real-world settings; and (5) development of point-of-care biomarkers (muscle mass, gut barrier function, inflammasome activity) to guide individualized nutrition therapy and monitor response.

6. Conclusion

Therapeutic nutrition is a cornerstone of critical and clinical care, with the potential to influence immune function, metabolic homeostasis, body composition, and clinical outcomes. This review has synthesized current evidence across three high-impact domains: ICU protein intake, enteral nutrition in infection recovery, and inflammasome modulation in heart failure, providing a structured framework for evidence-based practice from a dietitian's perspective.

In ICU protein management, contemporary guidelines recommend staged escalation to 1.2–2.0 g/kg/day after stabilization, with individualized adjustments for special populations. While higher protein delivery attenuates muscle loss, consistent mortality benefit has not been demonstrated, and delivery barriers necessitate active dietitian oversight. In enteral nutrition for infection recovery, early feeding preserves gut barrier function, modulates the microbiome, and is associated with reduced morbidity, though clinical trial outcomes remain heterogeneous and immunonutrient formulas require careful patient selection. In heart failure, the NLRP3 inflammasome represents a promising therapeutic target, with preclinical evidence supporting omega-3 fatty acids, polyphenols, SCFAs, and ketone bodies as dietary inhibitors, yet clinical translation remains incomplete and omega-3 supplementation has the strongest outcome data.

Across all three domains, optimal nutrition therapy is individualized, context-dependent, and requires integration of mechanistic insights with pragmatic clinical protocols. Barriers to implementation are substantial but surmountable through systematic approaches, interdisciplinary collaboration, and active dietitian involvement. The clinical dietitian serves as an essential integrator, bridging bench science and bedside care through comprehensive assessment, evidence-

based prescription, proactive troubleshooting, and patient-centered education.

As the field advances, future research must address persistent knowledge gaps, including the disconnect between surrogate and clinical endpoints, the identification of subgroups most likely to benefit from specific interventions, and the development of practical biomarkers to guide individualized therapy. By continuing to integrate evolving evidence with clinical expertise and patient values, dietitians and interdisciplinary teams can optimize therapeutic nutrition to improve outcomes for critically ill and clinically complex patients.

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