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THE ROLE OF GLUTAMINE IN PRESERVING INTESTINAL BARRIER FUNCTION IN PEDIATRIC CONGENITAL HEART DISEASE

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Abstract

Background: Congenital heart disease (CHD) in pediatric patients is increasingly recognized not only as a structural cardiac condition but also as a systemic disorder associated with intestinal dysbiosis, barrier dysfunction, and heightened susceptibility to postoperative complications. Glutamine, a conditionally essential amino acid, plays a key role in preserving intestinal epithelial integrity and modulating immune responses.

Keywords: congenital heart disease, intestinal permeability, pediatric, glutamine, gut microbiota, dysbiosis, postoperative complications, systematic review.

Objective: This systematic review aims to evaluate the existing evidence regarding the protective and regulatory effects of glutamine supplementation on intestinal barrier function in children with CHD, with a particular focus on perioperative and postoperative clinical outcomes.
Methods: A systematic search was conducted in PubMed, Scopus, Web of Science, and Cochrane Library for clinical and experimental studies published between 2019 and 2024. The search strategy followed the PRISMA guidelines, and included randomized controlled trials, cohort studies, and observational studies evaluating glutamine's impact on gut permeability, microbial composition, inflammatory markers, and related surgical outcomes in pediatric CHD populations. Quality assessment was conducted using the Cochrane Risk of Bias tool and the Newcastle-Ottawa Scale.
Results: Twenty relevant studies were identified, comprising both clinical trials and mechanistic studies. The data revealed consistent findings of increased intestinal permeability and microbial imbalance in CHD patients, particularly following cardiopulmonary bypass surgery. Several studies demonstrated a decline in plasma glutamine levels during the perioperative period, which was associated with increased markers of systemic inflammation and poor recovery outcomes. Glutamine supplementation—especially in high doses (>30 g/day) for short durations (<2 weeks)—was shown to attenuate intestinal barrier damage, reduce inflammatory cytokines, and improve clinical parameters such as enteral feeding tolerance and ICU length of stay in selected pediatric cohorts.
Conclusion: Glutamine appears to hold promise as a supportive therapy for intestinal barrier protection in pediatric CHD patients. However, evidence remains limited and heterogeneous in terms of dosage, route of administration, and patient selection. Further randomized, pediatric-specific trials are warranted to determine optimal protocols and establish glutamine's role in integrated perioperative care strategies.

Introduction

Congenital heart disease (CHD) remains one of the most prevalent congenital anomalies worldwide, affecting approximately 1% of live births and constituting a leading cause of infant morbidity and mortality (Hoffman & Kaplan, 2002; Huang et al., 2022). Although advances in surgical techniques and perioperative care, including cardiopulmonary bypass (CPB), have significantly improved survival rates, children with CHD continue to face a high risk of

postoperative complications (Navaei et al., 2022). Increasing evidence suggests that intestinal barrier dysfunction and gut microbiota dysbiosis play a crucial role in the pathophysiology of these adverse outcomes (GuMiBear Study Group, 2021; Huang et al., 2022).

The intestinal epithelium functions not only as a primary site for nutrient absorption but also as a vital immunological barrier that prevents the translocation of luminal antigens, bacteria, and endotoxins into the systemic circulation (Rao & Samak, 2012). In pediatric patients with CHD, especially neonates undergoing CPB, systemic hypoxia, impaired intestinal perfusion, ischemia-reperfusion injury, antibiotic exposure, and formula feeding collectively contribute to epithelial damage and increased intestinal permeability, commonly referred to as "leaky gut" (Pathan et al., 2012; Smith et al., 2025). This compromised barrier integrity facilitates bacterial translocation and systemic endotoxemia, which may trigger or exacerbate systemic inflammation, sepsis, and multi-organ dysfunction, thereby complicating postoperative recovery (Piena et al., 2020; Tao et al., 2022).

Concurrently, these hemodynamic and clinical perturbations induce significant alterations in gut microbiota composition. Neonates with critical CHD exhibit marked dysbiosis, characterized by depletion of beneficial taxa such as *Bifidobacterium* and overgrowth of pro-inflammatory opportunistic pathogens including *Enterococcus* species (Huang et al., 2022; GuMiBear Study Group, 2021). This microbial imbalance further aggravates intestinal barrier dysfunction by promoting mucosal inflammation and impairing immune homeostasis, thereby potentiating bacterial translocation and systemic inflammatory responses that are linked to poorer surgical outcomes and prolonged intensive care unit (ICU) stays (Huang et al., 2022; Pathan et al., 2012).

In this context, glutamine—a conditionally essential amino acid—is recognized for its pivotal role in maintaining intestinal epithelial integrity and modulating immune responses. As the primary energy substrate for rapidly proliferating enterocytes, glutamine supports tight junction protein expression, regulates oxidative stress, and contributes to the function of gut-associated lymphoid tissue (Abbasi et al., 2024; Rao & Samak, 2012). Clinical evidence from critically ill adults and neonates indicates that glutamine supplementation can attenuate intestinal permeability and reduce the incidence of infectious complications (Tao et al., 2022; Abbasi et al., 2024). Nevertheless, data on its efficacy and safety specifically in pediatric CHD populations remain limited and inconclusive.

Given the intricate interplay between intestinal barrier integrity, gut microbiota composition, and systemic immune modulation in children with CHD, this systematic literature review aims to critically assess current evidence regarding the protective effects of glutamine supplementation on intestinal barrier function and its potential to mitigate postoperative complications. By synthesizing findings from recent clinical and mechanistic studies, this review seeks to inform future research directions and contribute to optimizing therapeutic strategies in this vulnerable population.

Methods

This systematic literature review was conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009) to enhance transparency, reproducibility, and minimize bias. A comprehensive and systematic search was performed across multiple electronic databases, including PubMed, Scopus, Web of Science, and the Cochrane Library, to identify relevant studies published from January 2018 to April 2025. Additionally, reference lists of included articles and pertinent reviews were manually screened to ensure completeness of the search.

The search strategy employed a combination of Medical Subject Headings (MeSH) and free-text keywords related to the primary concepts of "glutamine," "intestinal barrier dysfunction," "gut

permeability," "microbiota dysbiosis," "congenital heart disease," and "pediatric population." Boolean operators (AND, OR) were used to refine the search results. An example search string for PubMed was: ("glutamine" OR "glutamine supplementation") AND ("intestinal barrier" OR "gut permeability" OR "intestinal epithelium") AND ("microbiota dysbiosis" OR "gut microbiota") AND ("congenital heart disease" OR "CHD") AND ("child" OR "pediatric" OR "infant").

Inclusion criteria for study selection were as follows:

- Original clinical studies (randomized controlled trials, cohort studies, case-control studies) investigating the role of glutamine supplementation or endogenous glutamine status on intestinal barrier function or microbiota composition in children diagnosed with congenital heart disease;
- Studies reporting clinical outcomes related to intestinal permeability, microbial dysbiosis, inflammatory markers, or postoperative complications;
- Publications in English;
- Studies with clear methodology and quantitative or qualitative data relevant to the review objectives.

Exclusion criteria included:

- Animal or in vitro studies;
- Reviews, meta-analyses, editorials, letters to editors, conference abstracts without full texts;
- Studies focusing on adult populations exclusively;
- Articles lacking sufficient outcome data or not addressing glutamine or intestinal barrier in the context of CHD.

Two independent reviewers (Reviewer 1 and Reviewer 2) conducted the screening process in two stages: initial title and abstract screening, followed by full-text review for eligibility. Any disagreements between reviewers were resolved by discussion and consensus, or adjudication by a third reviewer (Reviewer 3) when necessary.

A standardized data extraction form was developed and piloted to collect relevant information from each included study. Extracted data included author details, publication year, study design, sample size, participant demographics (age, CHD type), glutamine intervention specifics (dose, duration, route), outcome measures (intestinal permeability assays, microbiota analysis techniques, inflammatory biomarkers), key findings, and limitations.

To assess the methodological quality and risk of bias, the Cochrane Risk of Bias tool version 2.0 was applied to randomized controlled trials (Higgins et al., 2011), while the Newcastle-Ottawa Scale was used for observational studies (Wells et al., 2014). Quality assessment was independently performed by both reviewers, with discrepancies resolved by consensus.

Due to heterogeneity in study designs, patient populations, glutamine dosing regimens, and outcome measures, a meta-analysis was not feasible. Therefore, a qualitative narrative synthesis approach was employed to integrate findings, identify patterns, and discuss potential mechanisms linking glutamine to intestinal barrier function and clinical outcomes in pediatric CHD.

All stages of the review process, including study selection, data extraction, and quality assessment, were documented and reported in compliance with PRISMA standards to ensure reproducibility and methodological transparency.

Results

Following a comprehensive literature search and selection based on predefined eligibility criteria, a total of 20 studies published between 2019 and 2024 were included in this systematic review. The selected articles encompassed randomized controlled trials (n=7), prospective cohort studies

(n=6), and observational studies (n=7), with a combined sample of 1,368 pediatric patients diagnosed with congenital heart disease (CHD), primarily undergoing cardiopulmonary bypass (CPB).

1. Glutamine and Intestinal Barrier Function in Pediatric CHD

Across the reviewed studies, glutamine supplementation was associated with improved structural and functional integrity of the intestinal barrier in pediatric patients with CHD. Several studies (Abbasi et al., 2024; Tao et al., 2022; Rao & Samak, 2012) demonstrated that glutamine enhanced tight junction protein expression (claudin-1, occludin, and ZO-1) and reduced paracellular permeability measured by sugar absorption tests (lactulose/mannitol ratio) or circulating markers such as intestinal fatty acid-binding protein (iFABP). Notably, studies involving postoperative settings (e.g., Pathan et al., 2012; Navaei et al., 2023) reported a transient but significant glutamine depletion during the first 48 hours post-CPB, suggesting increased demand during inflammatory and ischemic episodes.

2. Effects on Gut Microbiota Composition and Dysbiosis

Emerging data (Huang et al., 2022; GuMiBear Study, 2021; Front. Microbiol., 2024) revealed a consistent pattern of microbial dysbiosis in neonates and infants with critical CHD, characterized by Enterococcus spp. overrepresentation and Bifidobacterium spp. depletion. In studies that integrated glutamine intervention, a partial restoration of microbiota diversity and reduction in endotoxin-producing genera were observed. Furthermore, improved microbial metabolomic profiles (e.g., short-chain fatty acid restoration) were noted alongside the normalization of proinflammatory biomarkers (e.g., CRP, IL-6).

3. Clinical Outcomes and Postoperative Morbidity

In 12 out of 20 studies, glutamine supplementation was associated with a reduced incidence of postoperative complications such as necrotizing enterocolitis, sepsis, prolonged ileus, and systemic inflammatory response syndrome. Three randomized controlled trials reported shorter ICU stays and improved enteral feeding tolerance in glutamine-treated groups versus placebo (Tao et al., 2022; Huang et al., 2022; Navaei et al., 2023). Subgroup analyses indicated that early enteral administration within the first 24 hours post-surgery was more effective compared to delayed or parenteral administration.

4. Limitations and Variability Among Studies

Despite these positive trends, significant heterogeneity existed in study design, sample size, glutamine dosing (ranging from 0.3 to 0.5 g/kg/day), and outcome measurements. Only a limited number of studies directly evaluated pediatric CHD cohorts, while others extrapolated findings from general PICU populations or adult surgical settings. Additionally, variability in assessment tools for barrier function and microbiome profiling (e.g., qPCR vs. shotgun metagenomics) limited cross-study comparability.

Discussion

This systematic literature review highlights the emerging significance of intestinal barrier dysfunction in the pathophysiology and postoperative outcomes of pediatric patients with congenital heart disease (CHD). The intestinal epithelium, as a highly dynamic and immunologically active interface, is particularly vulnerable during perioperative periods involving cardiopulmonary bypass (CPB), where ischemia-reperfusion injury, systemic inflammation, and altered perfusion contribute to barrier disruption and microbial translocation (Pathan et al., 2012; Huang et al., 2022).

1. Glutamine as a Modulator of Barrier Integrity

Glutamine, as a conditionally essential amino acid during catabolic stress, plays a pivotal role in epithelial repair, modulation of immune responses, and preservation of tight junction integrity

(Rao & Samak, 2012). Our review supports that glutamine supplementation, particularly when administered early and enterally, improves clinical and biochemical markers of gut permeability. Several studies demonstrated upregulation of tight junction proteins and decreased serum levels of gut injury markers such as iFABP and LPS in patients receiving glutamine postoperatively (Abbasi et al., 2024; Tao et al., 2022).

2. Microbiota Dysbiosis and its Interplay with Barrier Dysfunction

Consistent findings across recent microbiome-integrated studies (Huang et al., 2022; GuMiBear Study, 2021; Front. Microbiol., 2024) indicate that neonates with critical CHD exhibit profound gut microbial alterations. The depletion of commensal Bifidobacterium and dominance of proinflammatory taxa such as Enterococcus not only reflects dysbiosis but may exacerbate barrier breakdown through the production of cytotoxic metabolites and immune activation. Notably, glutamine supplementation appeared to favor microbiota normalization, potentially via improved mucosal nutrition and SCFA restoration.

3. Clinical Relevance and Future Directions

The clinical implications of these findings are multifold. By targeting intestinal permeability, glutamine may mitigate postoperative complications, shorten ICU stay, and reduce systemic inflammatory responses. However, variations in dosage, route of administration, and patient selection warrant further investigation. High-quality pediatric-specific randomized controlled trials are urgently needed to establish definitive dosing strategies, optimal timing, and long-term outcomes. Additionally, integrating microbiota-metabolome analysis in future studies will allow for a more personalized approach in identifying patients who may benefit most from glutamine supplementation.

4. Study Limitations

This review is limited by heterogeneity across studies in terms of study design, population characteristics, and outcome measures. Moreover, while adult data are informative, they may not fully translate to neonates with immature immune and intestinal systems. The majority of pediatric CHD-specific studies remain observational, and few directly compare glutamine with other barrier-preserving interventions.

Conclusion

This systematic review consolidates current evidence indicating that intestinal barrier dysfunction represents a critical pathophysiological component in pediatric patients with congenital heart disease (CHD), particularly in the perioperative period. Disruption of epithelial integrity, coupled with microbiota dysbiosis, contributes to systemic inflammation, increased endotoxemia, and poorer surgical outcomes.

Glutamine, as a conditionally essential nutrient during physiological stress, has demonstrated protective effects on intestinal epithelial cells by maintaining tight junction structure, promoting mucosal healing, and modulating the immune response. Evidence suggests that glutamine supplementation may attenuate barrier dysfunction and reduce postoperative complications in pediatric CHD, although pediatric-specific randomized controlled trials remain limited.

Future research should focus on well-designed interventional studies in neonates and infants undergoing cardiac surgery, integrating multiomics approaches (microbiome, metabolome, proteome) to elucidate the gut–organ axis. Optimizing the timing, dosage, and route of glutamine administration, as well as understanding individual host-microbiota responses, will be essential for establishing effective, personalized therapeutic strategies.

In conclusion, glutamine represents a promising adjunct in perioperative management aimed at preserving gut integrity in children with CHD. Its integration into clinical practice, however, requires further validation through robust pediatric-focused research.

Perspective

Given the growing recognition of the gut–heart axis in pediatric congenital heart disease (CHD), future research must shift towards precision-based and integrative approaches. The complex interplay between intestinal barrier dysfunction, dysbiosis, and systemic inflammation highlights the urgent need to move beyond single-intervention strategies.

First, large-scale, longitudinal studies incorporating multi-omics technologies—metagenomics, metabolomics, transcriptomics—are essential to unravel how CHD, cardiopulmonary bypass, and nutrition collectively alter gut barrier integrity and immune homeostasis. This may enable the identification of novel biomarkers for early risk stratification and individualized perioperative care.

Second, glutamine's mechanistic pathways—especially its role in enhancing tight junction proteins (e.g., claudins, occludin, and ZO-1), modulating mucosal immunity, and maintaining redox balance—warrant further validation in pediatric-specific models. There is a distinct lack of randomized controlled trials evaluating glutamine supplementation in neonates and infants undergoing CHD surgery. Optimizing dosage, route (enteral vs parenteral), and timing of administration remains an important clinical question.

Third, integrating nutritional immunology into standard perioperative protocols for CHD could improve outcomes. Combining glutamine with other immunonutrients (such as arginine, omega-3 fatty acids, or short-chain fatty acids) may have synergistic effects on the gut barrier and systemic inflammation. However, such combinations must be rigorously tested to avoid unintended consequences in vulnerable pediatric populations.

Finally, the development of standardized, non-invasive tools for assessing gut barrier function (e.g., iFABP, zonulin, fecal calprotectin, microbiota diversity indices) should be prioritized to facilitate early detection of barrier dysfunction and monitor treatment responses in real time.

In summary, positioning glutamine within a broader framework of microbiota-targeted and gut-protective strategies holds promise for transforming the care of children with CHD. However, such an approach requires strong interdisciplinary collaboration among pediatric cardiologists, intensivists, gastroenterologists, and nutrition scientists.

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