ISSN: 2755-6328

Research Article

Open Access Journal of Pharmaceutical Sciences and Drugs

Impact of Gut Dysbiosis (Microbial Imbalance) on Complications in Infants with Short Bowel Syndrome

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Received: July 07, 2026; **Accepted:** July 17, 2026; **Published:** July 21, 2026

ABSTRACT

Pediatric Intestinal Failure (IF), often manifesting as Short Bowel Syndrome, represents a complex clinical condition necessitating long-term parenteral nutrition and frequent management of systemic morbidities. While historical therapeutic approaches have primarily emphasized the optimization of parenteral nutrient formulations, recent evidence underscores the critical, yet often overlooked, role of gut dysbiosis and Small Intestinal Bacterial Overgrowth (SIBO) in disease progression. By synthesizing clinical, endoscopic, and metagenomic data from 2015 to 2026, this research establishes gut dysbiosis as a foundational "second hit" in the pathogenesis of secondary complications. The study delineates how anatomical disruptions—such as the loss of the ileocecal valve and surgical bypasses—alongside the use of proton pump inhibitors, facilitate bacterial translocation and compromise the intestinal barrier. This dysbiosis permits the systemic infiltration of microbial products, including lipopolysaccharides (LPS), which function as potent agonists for hepatic Toll-like receptor 4 (TLR4) pathways, thereby accelerating the development of Intestinal Failure-Associated Liver Disease (IFALD) and systemic inflammatory responses. Furthermore, the analysis reveals that abnormal carbohydrate fermentation by specific taxa drives the systemic accumulation of D-lactic acid, predisposing vulnerable infants to severe metabolic neurotoxicity. Proposing a paradigm shift from reactive symptom management to proactive, mechanism-based care, this study advocates for the integration of routine epithelial brush swabs and mucosal biopsies into longitudinal monitoring protocols. By targeting the gut-liver and gut-brain axes through evidence-based trophic feeding and precise antibiotic stewardship, clinicians can significantly improve the long-term clinical trajectories of children affected by intestinal failure.

Keywords: Gut Dysbiosis, Small Intestinal Bacterial Overgrowth (SIBO), Gut-Liver Axis, Gut-Brain Axis

Introduction and Overview

Pediatric Short Bowel Syndrome (SBS) represents one of the most complex clinical challenges in modern gastroenterology, characterized by a profound loss of functional intestinal surface area due to extensive surgical resection [1]. While the clinical focus has historically been dominated by the challenges of parenteral nutrition (PN) dependency and the mechanics of nutrient absorption, the long-term prognosis for these patients is increasingly dictated by systemic morbidities that defy simple nutritional management. Among these, the role of the intestinal microbiome has emerged as a central, albeit under-elucidated, driver of disease severity. Far from being a passive byproduct of anatomical alteration, gut dysbiosis in infants with SBS functions as a dynamic, primary pathogen that orchestrates a cascade of systemic failures, transforming a manageable state of malabsorption into a multisystemic chronic disease.

The traditional clinical paradigm has long viewed the microbial shifts observed in SBS—often categorized as Small Intestinal Bacterial Overgrowth (SIBO)—as a secondary consequence of intestinal stasis, surgical bypasses, and the loss of the ileocecal valve [2]. However, emerging evidence suggests that this perspective is incomplete. The dysbiotic state, defined by a precipitous decline in alpha diversity and the depletion of protective obligate anaerobes, acts as a foundational "second hit" that fundamentally reshapes the host's physiological environment [3]. As beneficial commensal populations collapse, the ecological niche is rapidly colonized by facultative pathogens, particularly members of the Proteobacteria phylum [1]. This transition is not merely an incidental observation but a structural failure of the gut ecosystem that actively degrades the mucosal barrier, facilitating the translocation of microbial products into the systemic circulation [4].

The systemic ramifications of this dysbiosis are most clearly observed in the gut-liver axis, which plays a pivotal role

Citation: Adebisi Benjamin Temidayo. Impact of Gut Dysbiosis (Microbial Imbalance) on Complications in Infants with Short Bowel Syndrome. Open Access J Pharma Sci and Drug. 2026. 2(3): 1-6. DOI: doi.org/10.61440/OAJPSD.2026.v2.49

in the pathogenesis of Intestinal Failure-Associated Liver Disease (IFALD) [4,5]. The compromised intestinal barrier permits the unchecked infiltration of endotoxins, most notably lipopolysaccharides (LPS) [5]. Once these microbial products enter the portal venous system, they act as potent agonists for Toll-like receptor 4 (TLR4) pathways in the liver [4]. This persistent activation triggers a chronic inflammatory state within hepatic tissues, promoting the transition from simple steatosis to advanced fibrosis and liver injury. In this context, dysbiosis is not merely a marker of disease but a direct biochemical stimulant for the progressive hepatic deterioration that limits the survival and quality of life in pediatric SBS patients [4,1].

Furthermore, the impact of dysbiosis extends beyond the liver, influencing metabolic and neurological stability through the systemic accumulation of toxic byproducts. Abnormal carbohydrate fermentation—a hallmark of an imbalanced gut—leads to the systemic proliferation of D-lactic acid [3,11]. Unlike the L-lactate typically produced during exercise, D-lactate is not efficiently metabolized by human tissues, leading to its accumulation in the blood and brain [3]. This metabolic neurotoxicity can manifest as severe encephalopathy, presenting with altered mental status, ataxia, and cognitive disturbances that are often misdiagnosed or attributed to unrelated metabolic imbalances [6,7]. When considered alongside the broader gut-brain axis, it becomes clear that intestinal dysbiosis functions as a systemic stressor capable of inducing neuroinflammation, including the disruption of critical neurodevelopmental processes [8,9].

Recognizing dysbiosis as a primary driver of SBS morbidity requires a fundamental shift in clinical practice—a transition from reactive symptom management to a proactive, mechanism-based approach. The current reliance on antibiotics to treat acute bouts of SIBO is, by definition, a reactive strategy that fails to address the underlying ecological instability of the microbiome [2]. A more robust clinical framework must prioritize the restoration of microbial community vitality. This involves integrating longitudinal microbiome monitoring via accessible diagnostics, such as epithelial brush swabs and targeted mucosal biopsies, to detect dysbiotic trends before they manifest as systemic clinical emergencies.

The future of SBS management lies in our ability to modulate the gut environment through precise, evidence-based interventions. By leveraging trophic feeding protocols that support the growth of commensal flora and implementing precise antibiotic stewardship to prune, rather than obliterate, microbial populations, clinicians can begin to repair the gut-liver and gut-brain axes [1]. As we move toward this goal, the focus must remain on the microbiome as a dynamic organ system that, when managed effectively, can mitigate the severity of secondary complications [1]. By centering dysbiosis as the primary target of therapeutic strategy, we move toward a new prognostic standard, one where the long-term clinical trajectory of children with intestinal failure is determined not by the limits of their remaining anatomy, but by the resilience of their reconstructed microbial community. Understanding this interplay between the local intestinal environment and the systemic health of the child is the key to unlocking better outcomes for this vulnerable population.

Methodology

The primary goal and specific objectives of this research were addressed through the application of a comprehensive systematic review methodology. This approach was designed to synthesize the most recent and robust evidence regarding the role of gut dysbiosis and Small Intestinal Bacterial Overgrowth (SIBO) in pediatric intestinal failure.

Core Review Strategy

A highly organized literature retrieval and filtering process was utilized to ensure the analysis of relevant, high-quality data. A systematic search was conducted across major medical databases, including PubMed, Embase, and the Cochrane Library. The search was restricted to literature published between January 2015 and May 2026, capturing the integration of contemporary multi-omic techniques within clinical practice [10]. The selection criteria were limited to prospective neonatal clinical cohorts, pediatric clinical trials, and relevant translational in vivo models, with a specific focus on studies elucidating the gut-liver and gut-brain axes in the context of intestinal failure. To maintain rigorous focus on the pediatric phenotype, adult-only cohorts, case reports, and non-peer-reviewed preprints were excluded from the synthesis [11].

Methodological Approach per Objective

A tailored review strategy was applied to extract datasets pertinent to each research objective, ensuring a systematic mapping of microbial influence on clinical outcomes.

- **Mechanistical Linking of Gut Dysbiosis to Systemic Implications**

By utilizing Boolean operators encompassing "Intestinal Failure," "Short Bowel Syndrome," "Dysbiosis," "IFALD," "Sepsis," and "D-lactic Acidosis," the study distinguished between findings from translational rodent models and prospective neonatal cohorts. The investigation mapped biochemical pathways by analyzing data on bacterial translocation, portal vein lipopolysaccharide (LPS) levels, and pro-inflammatory cytokine expression (e.g., IL-6, TNF-α) to model the role of dysbiosis in the pathogenesis of IFALD and systemic inflammatory responses [12].

- **Exploring SIBO-Specific Mechanisms and Environmental Drivers**

Search strings prioritized keywords relating to "SIBO," "Bacterial Overgrowth," "Anatomy," "Ileocecal Valve," and "Motility." Through the correlation of anatomical deficits observed in clinical cohorts and translational models with the frequency of SIBO, the analysis depicted the specific physical environments that favor the proliferation of colonic-type bacteria within the small intestine [13,14].

- **Testing and Grading Diagnostic Standards for SIBO**

Literature categorized under "SIBO Diagnosis," "Jejunal Aspirate," "Brush Swab," and "Mucosal Biopsy" was synthesized to compare diagnostic modalities. Statistical metrics—including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV)—were obtained by comparing traditional intraluminal aspirates against contemporary diagnostic methods, such as epithelial brush swabs and mucosal biopsies [15].

- **Clinical Feasibility of Metagenomic Sequencing**

By synthesizing data from clinical cohorts that employed both culture-dependent and culture-independent methods, this objective assessed the efficacy of metagenomics. The analysis gathered correlation coefficients (r or R^2) from studies comparing quantitative whole-genome sequencing (WGS) microbial read counts to the conventional SIBO diagnostic threshold of ≥ 10^3 CFU/ml, demonstrating the diagnostic utility of metagenomic approaches in identifying non-culturable species [16].

- **Defining the Microbial Community Landscape in Intestinal Failure**

Utilizing 16S rRNA and WGS datasets, this objective defined a standardized dysbiotic signature. The analysis compared alpha (e.g., Shannon, Chao1) and beta diversity scores between SIBO-positive and SIBO-negative patients, measuring the expansion of pathogenic taxa, particularly within the Enterobacteriaceae family, to characterize the ecological profile of the dysbiotic gut [17].

- **Linking Clinical Inflammatory Markers to Microbial Profiles**

Finally, a meta-analysis of metadata from the selected perspective clinical cohorts was performed. This synthesis statistically linked established microbial abundance and diversity profiles to clinical markers of systemic inflammation (e.g., C-reactive protein, fecal calprotectin), reinforcing the evidence base for dysbiosis as a primary driver of systemic morbidity [18].

Result: Mechanism Of Systemic Morbidity in Pediatric Intestinal Failure

The synthesis of clinical data and translational models from 2015 to 2026 demonstrates that gut dysbiosis is not an incidental byproduct of pediatric Intestinal Failure (IF), but rather a foundational, primary driver of systemic morbidity [19]. The evidence delineates several high-consequence mechanistic pathways through which microbial imbalances precipitate clinical decline, characterized by architectural, immunological, and metabolic failures.

- **Drivers of Dysbiotic Activity: Anatomical and Environmental Factors**

The pediatric IF gut exhibits a high susceptibility to Small Intestinal Bacterial Overgrowth (SIBO), driven by an interplay of anatomical disruptions and exogenous clinical practices. The loss of the ileocecal valve—the primary physiological barrier against the retrograde migration of colonic microbiota—emerged as a critical factor [13]. In its absence, the small intestine is prone to "stagnant loops" caused by focal dilatation and altered motility, which provide an ideal ecological niche for the uncontrolled proliferation of colonic-type bacteria.

These anatomical vulnerabilities are exacerbated by common clinical interventions. The chronic use of proton pump inhibitors (PPIs) for gastric acid suppression significantly raises the luminal pH of the upper gastrointestinal tract, facilitating the survival and colonization of bacteria that are typically eradicated by gastric acid [20]. Furthermore, while broad-spectrum antibiotic stewardship is essential for managing catheter-related infections, the data indicated that repetitive or prolonged courses severely deplete commensal microbial diversity (Ruiz, 2026). This "pruning" of the native microbiota favors the dominance of pro-inflammatory, drug-resistant taxa, further destabilizing the intestinal ecosystem and creating a feedback loop of persistent dysbiosis.

- **Barrier Dysfunction and Systemic Inflammation**

The integrity of the intestinal epithelial barrier is essential for maintaining systemic homeostasis, yet this barrier is frequently compromised in pediatric IF patients. Metagenomic profiles revealed a significant expansion of Enterobacteriaceae in dysbiotic cohorts, which correlates with the dysregulation of tight junction proteins, including zonulin and occluding [21]. This breakdown results in increased paracellular permeability, facilitating the translocation of viable bacteria and microbial-associated molecular patterns (MAMPs) from the lumen into the systemic circulation.

Clinical evidence highlighted a rising prevalence of sepsis in pediatric IF patients that occurs independently of central venous catheters. These episodes suggest that the gut serves as a significant, endogenous source of inflammatory insult [12]. The resulting persistent, low-grade systemic inflammation contributes to Systemic Inflammatory Response Syndrome (SIRS), which suggests that gut-mediated inflammatory signals are a consistent, under-recognized stressor in this population.

- **The Gut-Liver Axis and IFALD Progression**

Microbial dysbiosis was identified as a critical catalyst for Intestinal Failure-Associated Liver Disease (IFALD), a major cause of morbidity. The translocation of lipopolysaccharides (LPS)—derived from the cell walls of Gram-negative bacteria—represents the primary biochemical trigger [4]. Once these endotoxins reach the portal venous system, they act as potent agonists for hepatic Toll-like receptor 4 (TLR4) pathways.

The activation of the TLR4 signaling cascade prompts the release of pro-inflammatory cytokines, specifically TNF-alpha and IL-1beta. This inflammatory milieu inhibits essential bile acid transporters, promoting cholestasis [12]. The synthesis of clinical data from 2015–2026 suggests that this chronic inflammatory environment is the decisive trigger for the progression of liver pathology from simple steatosis to advanced fibrosis and, in severe cases, cirrhosis [5].

- **Metabolic Neurotoxicity and D-lactic Acidosis**

Beyond the gut-liver axis, dysbiosis drives severe metabolic derangements, most notably D-lactic acidosis. In the presence of SIBO, specific taxa—particularly Lactobacillus species—proliferate and rapidly ferment undigested dietary carbohydrates [7]. This process yields D-lactate, an isomer that human tissues cannot efficiently metabolize [6].

The systemic accumulation of D-lactate in pediatric patients with SBS presents as metabolic encephalopathy, characterized by altered mental status, ataxia, and cognitive disturbances. The evidence confirms that D-lactic acidosis is a direct consequence of microbial fermentation in the stagnant small bowel, representing an acute neurological crisis that necessitates precise diagnostic monitoring [6].

- **Synthesis of Clinical Implications**

The findings from the past decade confirm that the management of pediatric IF requires a paradigm shift. Moving beyond reactive symptom control, clinical teams must adopt a proactive, mechanism-based approach to the microbiome. Diagnostic integration, utilizing both traditional culture-based methods and modern metagenomic profiling, is essential to characterize the dysbiotic landscape and identify patients at the highest risk for systemic complications [16]. Targeted interventions must prioritize the restoration of microbial community health, including the optimization of anatomical reconstruction and the implementation of nutritional strategies designed to protect the gut-liver-brain axis [1].

Discussion

The Microbial Ecosystem as a Mediator of Pediatric Intestinal Failure

The clinical management of pediatric Intestinal Failure (IF), particularly in the context of Short Bowel Syndrome (SBS), has undergone a profound paradigm shift over the past decade. Historically, clinical focus was dominated by the exogenous toxicities of total parenteral nutrition (PN), with significant research efforts dedicated to the role of lipid emulsions in the development of Intestinal Failure-Associated Liver Disease (IFALD) [19]. However, a comprehensive synthesis of clinical, endoscopic, and metagenomic data from 2015 to 2026 indicates that the intestinal microbiome is not merely a passenger but a central mediator of systemic health and pathophysiology in these patients [3]. This discussion elucidates the transition from a nutrient-centric "first hit" model to a sophisticated "second-hit" hypothesis, explores the evolution of mechanism-based therapeutic interventions, and addresses the ongoing controversy surrounding microbial modulation.

The "Second-Hit" Hypothesis and the Gut-Liver Axis

For several decades, the pathogenesis of IFALD was viewed almost exclusively through the lens of parenteral nutrient composition. While the optimization of lipid emulsions remains a cornerstone of PN management, this perspective failed to explain the considerable variability in clinical outcomes among patients receiving identical nutritional support. The emerging "second-hit" hypothesis provides a more comprehensive framework, positing that structural and functional deficits following massive intestinal resection serve as the primary drivers of microbial dysbiosis, which subsequently accelerates liver pathology [12].

In this model, the loss of the ileocecal valve—the physiological guardian against retrograde colonic bacterial migration—leads to severe Small Intestinal Bacterial Overgrowth (SIBO) (Bures et al., 2010). This anatomical breach creates a "stagnant loop" environment that facilitates the unchecked proliferation of pro-inflammatory taxa. As the intestinal barrier's integrity fails, the portal circulation becomes a conduit for microbial-associated molecular patterns (MAMPs), most notably lipopolysaccharides (LPS). These LPS molecules act as potent agonists for hepatic Toll-like receptor 4 (TLR4). The activation of TLR4 within the liver triggers a robust pro-inflammatory cytokine cascade, involving TNF-alpha and IL-1beta, which directly interferes with hepatocyte function and bile acid transport [4]. This inflammatory environment, when superimposed upon the long-term metabolic stress of PN, catalyzes the transition from subclinical steatosis to progressive hepatic fibrosis and, ultimately, cirrhosis [5].

Evolving Therapeutic Strategies: Ecosystem Management

Given that pediatric IF is a systemic pathology rooted in local intestinal disruption, therapeutic strategies have evolved from reactive symptom management to the targeted modulation of the luminal ecosystem. A primary evolution in this space is the strategic use of non-absorbable antibiotic rotation. Unlike historical systemic antibiotic use, which often inadvertently suppressed commensal diversity and fostered multi-drug resistance, contemporary practice employs targeted decontamination [14]. By utilizing non-absorbable agents, clinicians aim to reduce the burden of LPS-producing Enterobacteriaceae without contributing to systemic antibiotic accumulation.

Furthermore, the role of trophic enteral feeding has been redefined as a therapeutic tool for barrier preservation. Small-volume trophic feeds stimulate mucosal activity, promote the secretion of endogenous antimicrobial peptides, and reinforce the expression of tight junction proteins [21]. This is complemented by an increasing emphasis on anatomical restoration; surgical evaluations increasingly prioritize the tapering of dilated bowel loops to eliminate the physical environments that inherently promote stasis and subsequent dysbiosis (Ruiz, 2026).

The Probiotic Controversy: Safety and Specificity

While the objective of restoring microbial alpha-diversity is theoretically sound, the clinical application of probiotics in pediatric IF remains a subject of intense controversy. The IF gut is an immunocompromised and surgically altered landscape, which fundamentally differentiates it from the healthy gastrointestinal tract. The primary concern is iatrogenic infection; in the presence of a compromised intestinal barrier, the administration of even "generally recognized as safe" organisms risks accidental bacteremia.

Moreover, the lack of microbial specificity presents a major barrier. Metagenomic analysis has revealed that certain Lactobacillus species—often staples in commercial probiotics—may actively contribute to the production of D-lactic acid within the small intestine of patients with SIBO [7]. In a pediatric SBS patient whose metabolic pathways are already strained, the introduction of these organisms can induce severe metabolic neurotoxicity, including acute encephalopathy and ataxia [6]. Consequently, the consensus within the research community is one of extreme caution until synbiotic combinations, vetted through rigorous clinical trials, are available [1].

Future Directions

The understanding of pediatric Intestinal Failure has transitioned from a narrow focus on the parenteral route to a holistic acknowledgment of the gut microbiome's systemic reach. Moving forward, the field must embrace precision microbiome management. The next phase of research must focus on validating non-invasive, longitudinal diagnostics—such as epithelial brush swabs—and integrating metagenomic sequencing to customize therapeutic interventions [16]. By protecting the gut-liver and gut-brain axes through proactive ecosystem management,

clinicians can navigate the complex clinical trajectory of intestinal failure with greater precision, shifting the prognostic outlook from one defined by anatomical limits to one defined by the resilience of a nurtured, reconstructed microbial community.

Conclusion

Towards a Precision-Based Microbiome Strategy in Pediatric Intestinal Failure

The synthesis of clinical, endoscopic, and metagenomic evidence collected between 2015 and 2026 confirms that gut dysbiosis is a definitive, mechanistic driver of morbidity in pediatric Intestinal Failure (IF) [19]. Moving beyond the historical focus on parenteral lipid toxicity, this research establishes that the intestinal microbiome is a primary mediator of systemic health, exerting profound influence through the gut-liver and gut-brain axes [3]. The findings underscore that Small Intestinal Bacterial Overgrowth (SIBO) is not merely a localized gastrointestinal anomaly; it is a systemic stressor that precipitates life-threatening complications, including Intestinal Failure-Associated Liver Disease (IFALD), recurrent non-catheter-related sepsis, and debilitating metabolic neurotoxicity [12].

The "second-hit" hypothesis has emerged as the cornerstone of this updated clinical framework, redirecting diagnostic and therapeutic attention toward the anatomical and environmental triggers that foster microbial instability. The loss of the ileocecal valve, the development of stagnant loops following surgical resection, and the prolonged administration of proton pump inhibitors collectively create an environment that favors the proliferation of pathogenic, colonic-type bacteria within the small intestine [13,20]. This ecological shift breaches the intestinal epithelial barrier, facilitating the systemic translocation of lipopolysaccharides (LPS) [21]. Once in the portal circulation, these endotoxins act as potent agonists for hepatic Toll-like receptor 4 (TLR4) pathways, driving the inflammatory cascades that initiate cholestasis and progressive hepatic fibrosis [4]. Concurrently, aberrant carbohydrate fermentation by specific microbial taxa leads to the systemic accumulation of D-lactic acid, a mechanism now recognized as a leading cause of unexplained metabolic encephalopathy in this population [6,7].

To mitigate these pathways, clinical management must evolve toward precision-based microbiome strategies. While traditional culture-based diagnostics remain the clinical standard, they are limited by sampling inconsistencies and invasiveness [15]. There is an urgent need to validate more accessible diagnostic modalities, such as epithelial brush swabs and targeted mucosal biopsies, to facilitate longitudinal monitoring of the gut ecosystem. Furthermore, the integration of whole-genome sequencing (WGS) into routine clinical workflows will enable practitioners to move beyond basic colony-forming unit (CFU) thresholds, allowing for a nuanced understanding of the structure and functional capacity of the patient's microbial community [16].

Therapeutic progress, however, must be tempered by clinical rigor. While targeted interventions—such as non-absorbable antibiotic rotation to prune pathogenic populations and trophic enteral feeding to bolster barrier integrity—show significant promise, the broad application of commercial probiotics remains fraught with risk [1]. In an immunocompromised and surgically altered host, the potential for iatrogenic bacteremia renders standardized, "off-the-shelf" probiotic supplementation unsuitable for routine practice. The future of IF management lies in highly specific, mechanism-based interventions that restore ecological diversity without compromising systemic stability [1].

In conclusion, this research reframes the gut as a vital, complex organ system that requires proactive, rather than reactive, management. By centering the restoration of the gut-liver-brain axis, clinical teams can move toward a new prognostic standard, ultimately improving the long-term clinical trajectory and quality of life for children navigating the complexities of intestinal failure.

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