THE ROLE OF GUT MICROBIOTA DYSBIOSIS IN THE PATHOGENESIS AND PROGRESSION OF CHRONIC INFLAMMATORY BOWEL DISEASE IN CHILDREN (LITERATURE REVIEW)

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Abstract

Chronic inflammatory bowel disease (IBD), encompassing Crohn’s disease (CD) and ulcerative colitis (UC), represents a growing burden in the pediatric population, with gut microbiota dysbiosis increasingly recognized as a central pathogenic driver. This review synthesizes current evidence linking gut microbial imbalance—characterized by reduced diversity, depletion of short-chain fatty acid (SCFA)-producing commensals, and expansion of pro-inflammatory species—to mucosal barrier dysfunction, immune dysregulation, and chronic intestinal inflammation in children. Persistent dysbiosis activates innate immune pathways including Toll-like receptors (TLRs) and the NLRP3 inflammasome, perpetuating a cycle of epithelial injury, cytokine release, and fibrotic remodeling. Early-life disruptions to microbial colonization, including antibiotic exposure, cesarean delivery, and formula feeding, further predispose children to IBD onset. Despite growing mechanistic understanding, pediatric-specific longitudinal microbiome data remain scarce, highlighting the urgent need for validated biomarkers and microbiota-targeted therapeutic strategies. Interventions such as dietary modulation, fecal microbiota transplantation (FMT), and probiotic supplementation offer promising avenues to restore microbial homeostasis and preserve intestinal integrity in affected children.

Keywords: Inflammatory bowel disease; children; gut microbiota; dysbiosis; mucosal immunity; NLRP3 inflammasome; intestinal fibrosis; fecal microbiota transplantation.

Introduction

Chronic inflammatory bowel disease (IBD) constitutes a significant and escalating contributor to pediatric morbidity worldwide, with incidence rates in children rising markedly over recent decades (Benchimol et al., 2017; Ng et al., 2018). IBD encompasses two principal phenotypes—Crohn's disease (CD) and ulcerative colitis (UC)—both characterized by relapsing and remitting intestinal inflammation, mucosal injury, and progressive structural damage. Pediatric-onset IBD is frequently associated with more extensive disease involvement and a more aggressive clinical course compared to adult-onset disease, underscoring the necessity of early identification and targeted intervention (Rosen et al., 2015).

The gut microbiota—a complex ecosystem of trillions of microorganisms inhabiting the intestinal tract—plays an indispensable role in immune education, epithelial barrier maintenance, and metabolic homeostasis. Disruption of this delicate microbial balance, termed dysbiosis, has emerged as a pivotal pathogenic mechanism in IBD (Lloyd-Price et al., 2019). Timely recognition of dysbiotic signatures is critical, as uncorrected microbial imbalance perpetuates mucosal inflammation and accelerates disease progression, potentially culminating in intestinal strictures, fistulae, and the need for surgical resection.

Pathophysiological links between gut microbiota dysbiosis and IBD

The progression of IBD, irrespective of phenotypic subtype, converges on a final common pathway of sustained mucosal inflammation and tissue remodeling, driven by disordered interactions between the host immune system and the resident intestinal microbiome (Sartor & Wu, 2017; Vangay et al., 2018). Dysbiosis initiates and propagates intestinal pathology through several interwoven mechanisms:

Microbial Imbalance and Innate Immune Activation:

Dysbiosis in IBD is typically characterized by reduced microbial diversity, depletion of obligate anaerobes such as Faecalibacterium prausnitzii and Roseburia species, and a relative expansion of potentially pathobiontic organisms including adherent-invasive Escherichia coli (AIEC). These microbial-associated molecular patterns (MAMPs) are recognized by pattern recognition receptors including Toll-like receptors (TLRs) on intestinal epithelial and immune cells, triggering NF-κB-dependent pro-inflammatory cytokine release and inflammasome activation (Sokol et al., 2009). Activation of the NLRP3 inflammasome results in caspase-1-mediated processing and secretion of IL-1β and IL-18, amplifying the mucosal inflammatory cascade characteristic of IBD (Zaki et al., 2010).

Barrier Dysfunction and Oxidative Stress:

Compositional and functional microbiota alterations impair the production of SCFAs—principally butyrate, propionate, and acetate—which are essential fuels for colonocytes and critical regulators of intestinal barrier integrity. SCFA deficiency leads to decreased tight junction protein expression, increased epithelial permeability, and translocation of luminal antigens into the lamina propria (Maslowski & Mackay, 2011). Concurrently, microbial dysbiosis promotes oxidative stress through enhanced reactive oxygen and nitrogen species (ROS/RNS) generation, overwhelming mucosal antioxidant defenses and inducing mitochondrial dysfunction in epithelial cells (Almenier et al., 2012).

Hypoxia and Fibrotic Remodeling:

Severe mucosal inflammation and sustained immune cell infiltration create a state of local hypoxia within the intestinal wall. Hypoxia-inducible factor (HIF) pathway activation triggers pro-fibrotic programs, including transforming growth factor-β (TGF-β)-mediated myofibroblast differentiation and excessive extracellular matrix (ECM) deposition (Glover et al., 2020). This progressive fibrotic remodeling creates a detrimental feedback loop: ECM accumulation compromises mucosal perfusion, intensifying hypoxia and further stimulating fibrogenesis, ultimately leading to stricture formation and irreversible bowel damage.

Adaptive Immune Dysregulation:

Children with IBD demonstrate characteristic defects in T-regulatory cell function and an imbalance between Th1/Th17 effector responses and tolerogenic pathways. The gut microbiome normally instructs immune tolerance by promoting the differentiation of $Foxp3^+$ regulatory T cells and IL-10 production; dysbiotic communities fail to provide these homeostatic signals, permitting unchecked effector T cell activation and perpetuating intestinal inflammation (Atarashi et al., 2011).

Impact of specific microbiota-related factors

Dysbiosis, SCFA Depletion, and Mucosal Immunity

Reduced abundance of butyrate-producing organisms constitutes one of the most reproducible microbiome signatures in pediatric IBD. Butyrate exerts pleiotropic anti-inflammatory effects, including histone deacetylase inhibition, NF-κB suppression, and induction of regulatory T cell differentiation. Its deficiency in IBD is associated with accelerated disease activity, impaired mucosal healing, and increased risk of relapse. In the context of pediatric CD, depletion of F. prausnitzii correlates inversely with post-operative recurrence risk, establishing this organism as both a potential biomarker and therapeutic target (Sokol et al., 2009). Microbial metabolites also influence systemic immune tone; reductions in secondary bile acid production by the dysbiotic microbiome further impair intestinal Th17/Treg balance.

Early-Life Microbiome Disruption and IBD Susceptibility

The developmental trajectory of the gut microbiome during the first years of life is a critical determinant of long-term mucosal immune programming. Several early-life exposures that disrupt normal microbial colonization have been identified as significant risk factors for subsequent IBD development in children:

• Antibiotic Exposure: Repeated antibiotic courses during infancy and early childhood disrupt microbial diversity, deplete commensals, and select for dysbiotic communities, increasing IBD risk in a dose-dependent fashion (Ungaro et al., 2014).
• Mode of Delivery: Cesarean section-born children acquire an altered initial microbiome, lacking maternal vaginal and fecal inoculation, which is associated with increased IBD susceptibility (Biasucci et al., 2010).
• Diet and Feeding Practices: Breastfeeding confers protective bifidobacterial colonization and immunological factors; formula-fed infants exhibit less diverse microbiomes with higher proportions of proteobacteria, augmenting intestinal immune dysregulation risk (Penders et al., 2006).

Biomarkers of Progression

Given the frequently insidious onset and diagnostic delay in pediatric IBD, validated non-invasive biomarkers of intestinal inflammation and microbiome disruption are critically needed:

• **Fecal Calprotectin and Lactoferrin:** These neutrophil-derived proteins are elevated in active intestinal inflammation and serve as accessible, non-invasive surrogates of mucosal disease activity in children. Fecal calprotectin correlates with endoscopic severity and predicts relapse risk (Bremner et al., 2015).

• **Microbiome-Derived Metabolites:** Fecal SCFA concentrations, particularly butyrate, provide insight into functional microbiome integrity. Reduced SCFA profiles combined with elevated inflammatory markers may constitute composite biomarkers for early IBD detection and monitoring (Lepage et al., 2011).

• **Serum Markers of Barrier Dysfunction:** Elevated serum intestinal fatty acid-binding protein (I-FABP) and zonulin reflect increased intestinal permeability and may identify children at risk of disease exacerbation prior to overt symptomatic relapse.

Prevention and Management

The overarching goal of management is mucosal healing and microbiome restoration, ideally commencing at the preclinical or early symptomatic stage.

• **Dietary Modulation:** Exclusive enteral nutrition (EEN) is established as a first-line induction therapy for pediatric CD, achieving mucosal healing while simultaneously modulating the gut microbiome toward a less dysbiotic composition. Mediterranean and plant-rich dietary patterns that promote microbial diversity

represent promising adjunctive strategies in maintenance phases (Ruemmele et al., 2014).

• **Fecal Microbiota Transplantation (FMT):** FMT constitutes an emerging therapeutic approach aimed at restoring eubiotic microbial communities in IBD. Pediatric clinical trials have demonstrated preliminary efficacy of FMT in inducing and maintaining remission in UC, though optimal donor selection, delivery route, and dosing schedules require further refinement (Paramsothy et al., 2017).

• **Probiotic and Prebiotic Interventions:** Specific probiotic formulations, including VSL#3 and Lactobacillus rhamnosus GG, have demonstrated efficacy in maintaining remission in pediatric UC, though evidence in CD remains limited. Prebiotic fibers that selectively promote SCFA-producing commensals represent a complementary strategy to reinforce mucosal barrier function (Jonkers et al., 2012).

• **Targeted Biological Therapy:** Anti-TNF agents (infliximab, adalimumab) and newer biologics targeting IL-12/23 and integrin pathways achieve mucosal healing and secondarily promote microbiome normalization in pediatric IBD. Combination strategies integrating microbiome-directed therapy with immunomodulation may synergistically improve outcomes.

• **Minimizing Antibiotic Overuse:** Antimicrobial stewardship in pediatric practice represents a critical preventive strategy, limiting unnecessary dysbiosis-inducing antibiotic exposure in children with IBD risk factors.

Conclusion

Gut microbiota dysbiosis constitutes a major, modifiable pathogenic driver in the onset and progression of chronic IBD in children. Core mechanisms encompass SCFA depletion with consequent barrier dysfunction, MAMP-mediated innate immune activation and NLRP3 inflammasome engagement, oxidative stress, adaptive immune dysregulation, and hypoxia-driven intestinal fibrosis. Early-life microbiome disruptions further predispose the developing immune system to aberrant inflammatory responses.

While mechanistic understanding has advanced considerably, pediatric-specific longitudinal microbiome datasets and validated composite biomarkers remain insufficiently developed. Future research must prioritize prospective cohort studies capturing microbiome trajectories from early life through IBD onset, enabling precision identification of at-risk children. Crucially, evidence-based preventive programs targeting dysbiosis correction—through antibiotic stewardship, dietary optimization, and early microbiome-directed interventions—must be developed and implemented at the population level. The integration of microbiome science into pediatric IBD care holds transformative potential for altering the natural history of this debilitating group of diseases.

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