Gut microbiome dynamics in acute infectious diarrhea: A conceptual framework from acute dysbiosis toward precision restoration (Review)

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Abstract. Acute diarrhea affects >1 billion individuals annually, imposing a major health and economic burden worldwide. Although the involvement of the gut microbiota is increasingly acknowledged, the dynamics of microbiota disruption, recovery and related therapeutic opportunities remain poorly integrated. The present review proposed a conceptual framework that synthesizes current understanding of pathogen-driven structural and functional alterations of the microbiota, the staged ecological succession during convalescence (including risks of incomplete restitution) and emerging microbiota-based interventions, ranging from probiotics to phage therapy. The present review further highlighted the potential of artificial-intelligence-driven multi-omics integration, while mapping the distance between current evidence and future precision-medicine goals. Evidence-based interventions were explicitly distinguished from investigational strategies, and microbiota-derived diagnostic biomarkers were discussed as a promising research direction rather than ready-to-deploy clinical tools. Finally, the present review provided evidence-based recommendations to bridge ecological principles with bedside practice, framing acute infectious diarrhea as a severe but often reversible ecological perturbation (an acute dysbiosis) that reveals individual ecological vulnerability and offers a diagnostic window for risk stratification. The present review is intended as a conceptual and evidence-synthesis framework rather than a clinical practice guideline.

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1. Introduction

Acute diarrhea, clinically defined as the passage of three or more loose or watery stools per day for a duration not exceeding 14 days, represents a notable global public health burden (1-3). According to World Health Organization (WHO) estimates, diarrheal diseases are responsible for ~525,000 deaths annually in children <5 years of age, ranking among the top five causes of child mortality (4,5). Diarrheal diseases also result in substantial productivity losses and healthcare resource consumption, especially in low- and middle-income countries (6). The etiology is complex and diverse, mainly involving pathogenic microorganisms such as viruses, bacteria and parasites. At the microscopic level, the human gut harbors a vast and intricate microbial community of microorganisms, collectively termed the gut microbiota (7,8). The combined genetic pool of these bacteria, archaea, fungi and viruses exceeds that of the human genome, earning it the designation 'second genome' (9,10). This ecosystem plays a pivotal role in maintaining host health: It ferments indigestible dietary fibers to produce short-chain fatty acids (SCFAs; such as butyrate) that serve as an energy source for intestinal epithelial cells, synthesizes essential vitamins (such as vitamin K and some B vitamins), and is crucial in shaping and modulating the host immune system (including promoting immune tolerance and defending against pathogens). This reinforces intestinal epithelial barrier integrity, and directly inhibits the colonization of foreign pathogens through mechanisms such as niche occupation and nutrient competition, a concept known as 'colonization resistance' (11-14).

Traditionally, previous studies on acute infectious diarrhea primarily focused on the virulence factors of pathogens (for example toxins and adhesins) and their direct interaction with host cells (15). However, over the years there has been a profound shift in research paradigms. Scientists increasingly recognize that the onset and progression of diarrhea is far from a simple 'pathogen-host' binary confrontation model (16). Instead, it constitutes a complex dynamic interaction involving pathogen, host immune response and commensal gut microbiota (17). Pathogen invasion markedly disrupts the stability of the gut microenvironment, thereby leading to notable disturbances in the species composition, abundance distribution and functional metabolic activity of the microbiota, a state known as dysbiosis (18,19). This dysbiosis is often characterized by a reduction in beneficial commensal bacteria (such as specific butyrate-producing members of the *Bacteroidetes* and *Firmicutes phyla*) and a relative increase in potentially pathogenic or opportunistic bacteria (20). This disruption is not merely a passive side effect but a key driver of the disease process. Dysbiotic microbial communities may lose their protective functions; for example, reduced butyrate production weakens the intestinal barrier, while the release of pro-inflammatory molecules may exacerbate local inflammatory responses (21,22). These effects synergistically amplify the tissue damage caused by the pathogen and potentially prolong the illness. Furthermore, it has been reported that the recovery profile of the gut microbiota following acute diarrhea may be linked to long-term health outcomes, such as the potential development of post-infectious sequelae (such as irritable bowel syndrome or growth faltering) (23-25). Therefore, systematically elucidating the specific response patterns of the gut microbiota during acute diarrhea, its mechanistic role in disease outcomes and how therapeutic strategies can be improved by targeting the microbiota is key.

The present review provides a comprehensive, clinically oriented analysis of the gut microbiota in acute infectious diarrhea, structured in four principal sections: i) Pathogen-specific dysbiosis patterns and underlying functional mechanisms; ii) post-diarrheal microbial recovery trajectories, determinants of incomplete restoration and long-term sequelae; iii) clinical implications spanning microbiota-based diagnostic biomarkers, risk stratification and evidence-based bedside management strategies; and iv) current and emerging microbiota-targeted therapeutic strategies, from traditional probiotics to next-generation precision interventions including engineered probiotics, postbiotics and phage therapy. By integrating mechanistic insights with translational and precision-medicine perspectives, the present review aimed to move beyond the traditional pathogen-centric paradigm and frame acute diarrhea as an ecosystem disorder amenable to diagnosis, stratification and targeted rehabilitation. The core argument of the present review is presented in Fig. 1 as an integrative conceptual model, not a clinical decision algorithm.

Emerging frontiers in microbiome science are reshaping how acute diarrheal disease is approached by researchers. Artificial intelligence and machine-learning classifiers trained on fecal metagenomic datasets provide proof-of-concept for predicting diarrhea etiology, severity and risk of post-infectious sequelae in retrospective cohorts, although small training datasets, lack of external validation, unclear generalizability and absence of prospective trials limit current clinical applicability. Multi-omics integration, combining metagenomics, metatranscriptomics, metaproteomics and metabolomics, offers unprecedented resolution of host-microbe dynamics during infection. Furthermore, pharmacomicrobiomics reveals that inter-individual variation in gut microbiota composition modulates drug metabolism and therapeutic response, opening avenues for personalized treatment selection. These advances collectively support a precision-medicine paradigm in which baseline microbiota profiling, pathogen typing and host genetic background inform individualized diagnostic and therapeutic strategies, an approach the present review critically examines and advocates. These technologies are framed as promising research directions that are exploratory rather than imminent.

For the present review the databases PubMed/MEDLINE (pubmed.ncbi.nlm.nih.gov/), Web of Science(webofscience.com/) and Embase (embase.com/) were searched from inception to June 2025 using combinations of the following keywords: 'Gut microbiota' OR 'gut microbiome' AND 'acute diarrhea' OR 'infectious diarrhea' OR 'gastroenteritis'; 'dysbiosis' AND 'diarrhea'; 'probiotics' OR 'fecal microbiota transplantation' OR 'phage therapy' AND 'acute diarrhea'. Inclusion criteria were English-language articles focusing on human studies, with selected animal and *in vitro* studies included where human data were insufficient. Exclusion criteria were case reports with fewer than three patients, non-peer-reviewed sources and studies exclusively on chronic diarrhea without acute infection context. Formal quality scoring and meta-analysis were not performed, consistent with narrative review methodology.

2. Gut microbiota dysbiosis in acute infectious diarrhea

The clinical symptoms of acute infectious diarrhea (diarrhea, abdominal pain, fever and others) represent the direct response of the host to invading pathogens and their toxins (26). However, the underlying pathophysiological drivers are far more complex than the direct damage caused by the pathogens (27). Modern microbiome research has unequivocally demonstrated that one of the core pathological features of acute infectious diarrhea is the rapid disruption and dysfunction of gut microbiota homeostasis (eubiosis) within a short period (28). This dysbiosis is not a random or chaotic state but follows certain patterns, exhibiting both common features across different pathogens and distinct patterns determined by specific pathogens and their interactions with the host and resident microbiota. Understanding these patterns and their underlying mechanisms is required for developing novel diagnostic, preventive and therapeutic strategies.

Much of the current evidence on microbiota alterations in acute diarrhea is derived from cross-sectional studies or small longitudinal cohorts. Causal relationships between microbiota alterations and clinical outcomes remain incompletely established. It is unclear whether dysbiosis is a driver of disease progression, a consequence of infection and inflammation or both.

Common features of acute dysbiosis. Regardless of whether the pathogen causing diarrhea is a bacterium, virus or parasite, the intestinal microecosystem exhibits some consistent signs of acute dysbiosis during acute infection (29,30).

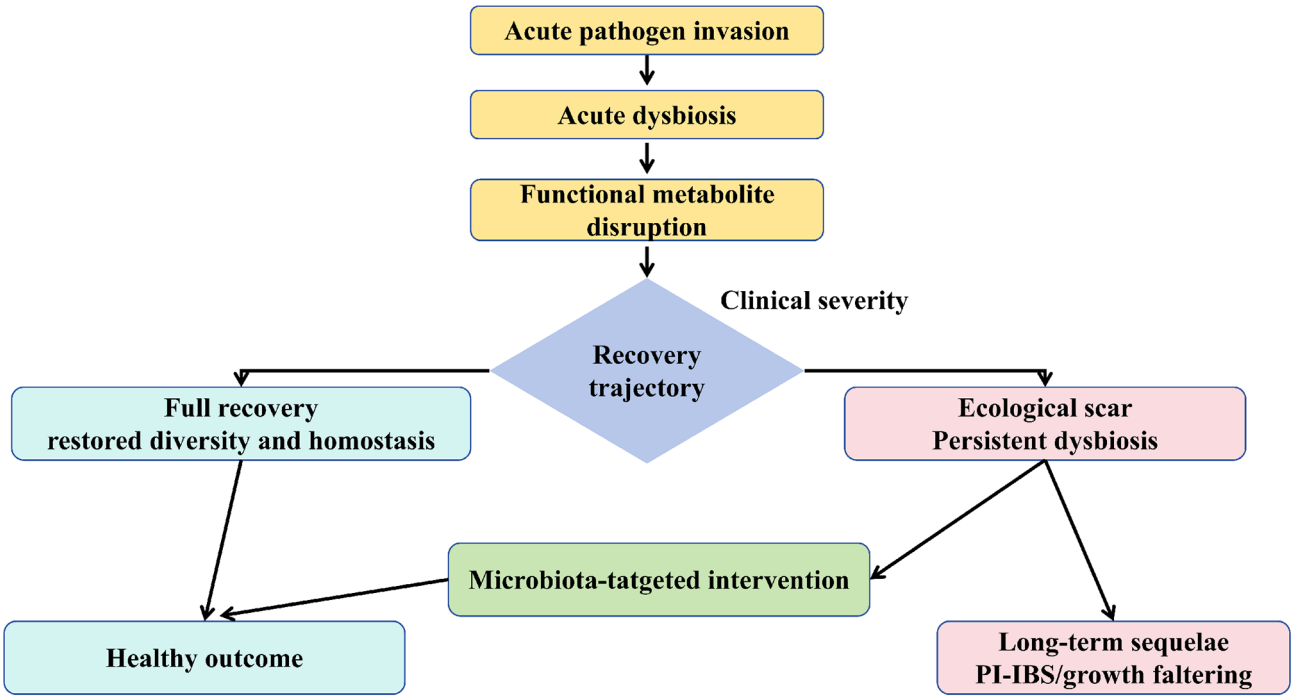

Figure 1. Gut microbiota dynamics in acute diarrhea: From dysbiosis to recovery and intervention. This schematic illustrates the sequential pathophysiological process following acute diarrheal infection. Pathogen invasion triggers core dysbiosis events, including reduced α-diversity, Proteobacteria expansion and impaired microbial metabolism. The recovery trajectory bifurcates into either complete restoration of microbial homeostasis or incomplete recovery leading to an ecological scar, which predisposes to long-term sequelae such as PI-IBS and childhood growth faltering. Corresponding therapeutic strategies are categorized into traditional microbial interventions, ecosystem-reshaping approaches, and next-generation precision therapies, targeting different stages and outcomes of dysbiosis. PI-IBS, post-infection irritable bowel syndrome.

Decline in α-diversity. α-Diversity (human-obs) measures ecosystem complexity and declines sharply during acute diarrhea. The α-diversity indices (Shannon index, Simpson index, Chao1 index) of the gut microbiota in the fecal samples of patients are often notably lower than those in healthy control groups, particularly in severe bacterial and some viral infections, while the magnitude of this decline is closely related to the pathogen type, antibiotic use and disease severity (31). This loss of diversity decreases functional redundancy and ecosystem resilience, rendering the gut more susceptible to pathogen colonization and secondary infections (32,33). The clinical significance lies in the association between diversity loss and disease severity, rather than in the ecological theory itself.

Shifts in β-diversity and remodeling of ecosystem structure. If α-diversity describes the 'internal' complexity of a single sample, then β-diversity measures the 'degree of difference' in microbial community composition between different sample groups (such as patients with diarrhea group vs. healthy control group) (34). In acute diarrhea, patient samples consistently cluster separately from healthy controls in ordination analyses (principal coordinates analysis and non-metric multidimensional scaling), indicating fundamental and consistent structural alterations (35,36).

The most prominent feature of this structural remodeling is the marked change at the phylum level. The gut microbiota of healthy adults is typically dominated by two major phyla: *Firmicutes* and *Bacteroidetes*, which together account for >90% of bacterial abundance (37). Most members of these phyla are strict anaerobes, adept at fermenting polysaccharides such as dietary fiber to provide energy and beneficial metabolites for the host (38,39). However, during acute diarrhea, the relative abundance of these dominant phyla typically decreases. Their decline creates vacant ecological niche for the abnormal proliferation of other bacteria (40).

Disruption of ecological stability and loss of colonization resistance. The gut microbiota collectively forms the first biological defense against invasive pathogens, a capability termed 'colonization resistance' (41-43). This resistance is achieved through multiple mechanisms: Commensal bacteria resist pathogen colonization through spatial occupation, nutrient competition, antimicrobial substance production and immune modulation. During acute diarrhea, these defense networks collapse.

During acute diarrhea, reduced α-diversity and the disruption of dominant phyla directly leads to ecological instability (44,45). The original commensal bacterial network is disrupted, causing the aforementioned microbiota-mediated defense mechanisms to fail comprehensively. This not only facilitates uncontrolled proliferation of the primary pathogen but also enables secondary overgrowth of resident opportunistic pathogens, amplifying tissue damage and disease severity. Therefore, acute infectious diarrhea represents not only the dominance of the pathogen but also a severe but often reversible disruption of the intestinal ecosystem defense system (46,47). These common features of acute dysbiosis are summarized in Table I.

Pathogen-specific alterations in the gut microbiota. Despite these common features, the dysbiosis patterns driven by different pathogens exhibit distinct specificity at the level

Table I. Common features of gut microbiota dysbiosis during acute diarrhea.

Feature	Description	Key manifestations/mechanisms	(Refs.)
Decline in α-diversity	An indicator measuring within-ecosystem complexity, including species richness and evenness.	α-diversity indices (Shannon, Simpson, Chao1) in patient fecal samples are markedly lower than in healthy controls. Total species number decreases, while a few species (often pathogens) proliferate abnormally.	(31-33)
Shift in β-diversity and remodeling of ecosystem structure	A measure of dissimilarity in microbial community composition between different sample groups.	Principal component analysis/non-metric multidimensional scaling analyses show separation between diarrhea patient samples and healthy controls, indicating a fundamental, directional shift in overall community structure.	(39,40)
Collapse of ecological stability and loss of colonization resistance	The collective defensive capability of the gut microbiota against invading pathogens.	Reduced diversity and collapse of dominant phyla disrupt the commensal network. Defense mechanisms, spatial occupation, nutrient competition, antimicrobial production and immune modulation, fail comprehensively.	(41-43, 57,58)
Notable change in dominant phylum abundance	Healthy adult gut microbiota is dominated by *Firmicutes* and *Bacteroidetes*.	During acute diarrhea, the relative abundance of these two phyla typically plummets, creating an ecological niche for the abnormal expansion of other bacteria (Proteobacteria).	(37-40)

of genera or even species (48). These differences reflect the unique survival strategies and virulence mechanisms of each pathogen, and their complex interaction networks with the host immune system and the resident microbiota. Over the years, metagenomic studies based on high-throughput sequencing have deepened our understanding of these specific patterns (49,50).

Bacterial diarrhea: Characteristic dysbiosis patterns. Diarrhea caused by pathogenic bacteria, such as diarrheagenic *Escherichia coli* (DEC), non-typhoidal *Salmonella spp.*, *Campylobacter spp.* or *Shigella spp.*, is typically accompanied by the most notable and characteristic changes in the gut microbiota (51-54). The increase in proteobacteria represents the most consistent finding in bacterial diarrhea and has become a hallmark feature of this disease category (48). Proteobacteria is a vast and diverse phylum containing numerous well-known Gram-negative pathogens and opportunistic pathogens, such as *E. coli*, *Salmonella*, *Shigella* and *Klebsiella* (55). In healthy individuals, the abundance of Proteobacteria in the gut is usually low (<1-2%) (56); however, during acute bacterial diarrhea, its relative abundance can markedly increase, sometimes >50% (29,57). Previous metagenomic studies on bacterial diarrhea in both children and adults have repeatedly confirmed this phenomenon (28,48).

The core mechanism underlying this process is linked to the formation of an inflammatory intestinal environment. When pathogenic bacteria invade the intestinal epithelium, they trigger a host innate immune response, leading to the infiltration of immune cells such as neutrophils and the release of large amounts of reactive oxygen species and reactive nitrogen species, such as superoxide and nitrate (58). These substances are toxic to most obligate anaerobic members of *Firmicutes* and *Bacteroidetes* (59). By contrast, numerous members of Proteobacteria (such as *E. coli* and *Salmonella*) are facultative anaerobes, can tolerate this oxidative stress environment and even utilize inflammatory byproducts such as nitrate as terminal electron acceptors for their respiratory chain ('nitrate respiration') (17,60,61). In animal models has demonstrated that inflammation-derived nitrate respiration can confer a potential growth advantage to facultative anaerobic Proteobacteria in the anaerobic gut environment, enabling rapid expansion (62-64). A metagenomic study on childhood diarrhea caused by DEC provides evidence for this phenomenon. In the gut of children with DEC infection, the abundance of the *Escherichia-Shigella* genus was markedly enriched, whereas the abundance of numerous key beneficial butyrate-producing bacteria, such as the renowned well-characterized anti-inflammatory commensal *Faecalibacterium prausnitzii*, was notably decreased (Human-obs) (65). In another metagenomic analysis of patients with acute secretory diarrhea, there was a similar pattern of changes, further confirming the universality of Proteobacteria expansion as a core event in bacterial diarrhea (Human-obs) (66). The competitive advantage of Proteobacteria in the inflamed gut is a well-supported mechanistic hypothesis derived from animal models and observational human studies, but direct *in vivo* human evidence remains limited. Its relative magnitude compared with other selective pressures, such as bile acid shifts, mucin degradation and host-derived antimicrobial peptides, requires further validation.

Changes in the *Firmicutes*/*Bacteroidetes* (F/B) ratio serve as another classical metric for assessing the macro-structure of the gut microbiota, often exhibiting notable changes in bacterial diarrhea (37,67). However, the direction of change is not consistent and may depend on the specific pathogen species, host age, dietary background and inflammation severity (68-70). For example, the aforementioned study on

DEC infection in children revealed a markedly higher F/B ratio in the DEC group compared with healthy controls. This reflects the relative preservation or proliferation of specific *Firmicutes* members (certain resilient *Clostridium* species) alongside a marked decrease in *Bacteroidetes* members (54). Conversely, decreased F/B ratios or no significant changes may be observed in other bacterial infections (71). Therefore, a more universal and functionally relevant finding than the F/B ratio itself is the widespread damage to functional genera within these two dominant phyla that are essential for maintaining gut homeostasis (54,65). Particularly, there is a persistent decline in the abundance of the 'workhorse' genera responsible for fermenting dietary fiber and producing SCFAs. These genera include, but are not limited to, *Roseburia*, *Blautia*, *Eubacterium* and *F. prausnitzii* from *Firmicutes* and specific members of *Bacteroides* and *Prevotella* from *Bacteroidetes* (72,73). The depletion of these functionally critical bacteria directly results in impaired SCFA production, which is a central component of the pathophysiology of diarrhea (74).

Functional metagenomic deterioration reveals another layer of this disruption, as metagenomics not only identifies species composition) but also reveals 'what they are doing' (functional potential). By annotating sequenced gene fragments against functional databases such as the Kyoto Encyclopedia of Genes and Genomes, researchers can reconstruct the functional profile of the entire microbial community (75). Functional metagenomic analysis of bacterial diarrhea reveals a substantial functional disruption of ecosystem deterioration. In the gut microbiome of patients with diarrhea, functional pathways related to pathogenicity are notably enriched, including virulence factor genes encoding toxins, adhesins and secretion systems that reflect enhanced attack capabilities; bacterial motility genes related to flagellar assembly that indicate increased movement and invasive capacity (57,76-79). Metagenomic analysis has revealed enrichment of bacterial two-component systems, including PhoQ/PhoP (magnesium sensing and virulence regulation in Salmonella), EnvZ/OmpR (osmotic stress response in *E. coli*) and QseC/QseB (quorum sensing and host adaptation) (76,80-82). Two-component systems that serve as key signaling mechanisms for environmental sensing and response, signifying improved bacterial adaptation and pathogenic regulation. Notably, antibiotic resistance genes, whose enrichment reveals selective pressure favoring resistant bacteria (especially *Proteobacteria*) under infection and inflammation stress, alongside potentially increased horizontal gene transfer that could increase the risk of future treatment failure (57,67,83,84). By contrast, core metabolic pathways essential for maintaining basic intestinal physiology are generally suppressed, including carbohydrate metabolism (especially complex cellulose and hemicellulose degradation), amino acid synthesis, vitamin synthesis and core energy metabolism (85). This functional 'malignant transformation' collectively points to a more aggressive, less stable and metabolically more simplistic and inefficient microbial ecosystem (86). A metagenomic study in diarrheic yak calves revealed analogous structural and functional alterations, suggesting cross-species conservation of dysbiosis patterns. However, extrapolation from animal models to human disease requires caution due to differences in diet, anatomy, and immune architecture (57).

Viral diarrhea. Unlike bacterial pathogens that reshape the microbiota by directly competing for nutrients and niches, viral enteric pathogens such as rotavirus and norovirus primarily infect intestinal epithelial cells. By disrupting the gut barrier and triggering host immune responses, they indirectly reshape the gut microbiota. Metagenomic studies have confirmed that rotavirus infection in children is associated with a reduced abundance of the phylum *Firmicutes*, specifically a marked decrease in butyrate-producing bacteria such as *F. prausnitzii* and *Roseburia spp.*, concomitant with an expansion of Proteobacteria (87,88). Notably, the severity of viral diarrhea associates positively with the magnitude of microbial perturbation. This suggests that the primary driver of dysbiosis is not direct competition between the pathogen and the microbiota, but rather the inflammatory response of the host to the infection.

This host-mediated mechanism of dysbiosis manifests uniquely at the functional level. Compared with bacterial diarrhea, viral infections may lead to specific alterations in gut metabolic pathways, particularly disruptions in carbohydrate metabolism, such as galactose and mannose metabolism, providing new clues for future etiological diagnosis (89,90). Although both types of infection result in decreased microbial diversity and an increase in opportunistic pathogens, the virus-induced environment, which is characterized by type I and type III IFN responses (IFN-α/β and IFN-λ), JAK-STAT pathway activation, and antiviral cytokine profiles enriched in IL-15 and IL-18, likely shapes a distinct micro-ecological landscape different from that of bacterial infections (91).

Norovirus deserves particular attention because it can establish persistent infections in immunocompromised hosts, potentially sustaining chronic dysbiosis for months or years. Host secretor status (*FUT2* genotype) modulates both norovirus susceptibility and baseline microbiota composition, creating a host-microbe-pathogen triad that shapes the dysbiosis landscape. The current core challenge lies in elucidating the impact of these differences on long-term recovery. Future research requires longitudinal comparisons to analyze recovery trajectories following viral vs. bacterial diarrhea, facilitating the development of etiology-specific micro-ecological intervention strategies (92-94).

Parasitic diarrhea. Parasitic infections such as giardiasis and cryptosporidiosis induce unique microbial signatures distinct from bacterial and viral etiologies (95). *Giardia lamblia*, an extracellular parasite that attaches to the intestinal brush border, does not invade tissue but disrupts epithelial barrier integrity and nutrient absorption (96). Clinical studies indicate that giardiasis is associated with reduced bacterial diversity and depletion of *Bacteroidetes*, with some evidence of enrichment in *Streptococcus* and *Veillonella* (97). *Cryptosporidium parvum*, an intracellular apicomplexan parasite, causes particularly severe dysbiosis in immunocompromised hosts, with marked depletion of butyrate-producing taxa (98). The unique pathophysiology of parasitic infection, including chronicity, malabsorption and modulation of host adaptive immunity, suggests that recovery trajectories and therapeutic approaches may differ fundamentally from acute bacterial diarrhea. Unlike bacterial dysbiosis, which is characterized by Proteobacterial

expansion, parasite-induced dysbiosis features *Bacteroidetes* depletion and a distinct metabolic signature involving tryptophan and lipid pathway alterations (decreased microbial conversion to aryl hydrocarbon receptor ligands such as indole-3-lactic acid and indole-3-propionic acid) and impaired bile acid biotransformation (decreased secondary bile acid production due to Bacteroidetes loss), compounded by parasite-driven lipid malabsorption. These differences underscore the need for etiology-specific restoration strategies. These pathogen-specific dysbiosis patterns are summarized in Table II.

Mechanisms revealed by functional metagenomics and metabolomics. Dysbiosis of the gut microbiota ultimately exerts notable effects on host physiology through alterations in its collective functions and metabolites (99-101). The two major 'functional' omics technologies (functional metagenomics and metabolomics) have unveiled the bridges linking structural changes in the microbiota to host pathophysiological changes (102,103).

Key SCFA-producing bacteria (butyrate, propionate, acetate) are depleted during acute diarrhea, compromising epithelial energy supply, tight-junction integrity and anti-inflammatory regulation (104-108). Bile acid-metabolizing bacteria are depleted during dysbiosis, reducing antimicrobial secondary bile acids and accumulating pro-inflammatory primary bile acids, which further weakens colonization resistance (109-116). Tryptophan, amino acid and lipid metabolic pathways are also disrupted, reflecting broad biochemical homeostasis impairment (57,117-119).

Iatrogenic dysbiosis: Antibiotic-associated diarrhea (AAD) as a special case. AAD represents a distinct clinical entity where the therapeutic intervention itself drives dysbiosis, fundamentally differing from infectious diarrhea in etiopathogenesis (120). Unlike infectious diarrhea, in which pathogens initiate the perturbation, AAD results from antibiotic-induced depletion of colonization resistance, enabling *Clostridioides difficile* overgrowth (in 10-25% of cases) or altering bile acid metabolism and carbohydrate fermentation by commensals (121,122). The microbiota signature of AAD is characterized by a near-total depletion of diversity, extinction of keystone taxa (particularly *Bacteroidetes* and *Clostridium* clusters XIVa and IV) and enrichment of *Enterococcus* and *Klebsiella* (123). This distinct etiopathogenesis necessitates different therapeutic considerations; while fecal microbiota transplantation (FMT) has emerged as an effective for recurrent *C. difficile* infection, prevention strategies (including narrow-spectrum antibiotics, shorter courses, and prophylactic probiotics) remain critical unmet needs (124-126). AAD is included as a comparative model of treatment-induced dysbiosis to provide mechanistic insights into colonization resistance and recovery dynamics, not as an infectious etiology or an expansion of the review scope. Examining AAD alongside pathogen-induced dysbiosis helps distinguish pathogen-specific microbial signatures from generic perturbation responses. The discussion is intentionally focused on these comparative insights rather than a comprehensive review of all acute diarrhea-related dysbiosis.

3. Gut microbiota recovery trajectories following acute diarrhea

An episode of acute diarrhea constitutes a marked ecological 'perturbation'. The ability of the gut microbiome to recover to a healthy state after such disturbance, and the trajectory of this recovery, are critical determinants of both short-term patient recovery and long-term health (27,32,127). This process is not a disordered event but rather demonstrates a staged, dynamic process following the principles of ecological succession.

Dynamic recovery process: Insights from a longitudinal study. Longitudinal cohort studies provide a dynamic perspective on microbial recovery trajectories (128,129). A landmark time-series analysis in children with acute rotavirus diarrhea tracked fecal samples at baseline and days 3, 5, 10 and 30, using 16S ribosomal RNA (rRNA) and shotgun metagenomic sequencing (130). This study revealed a three-stage ecological succession model: i) Acute phase (days 1-3), sharp diversity decline, Proteobacterial surge and loss of core commensals; ii) recovery phase (days 5-10), high instability with pioneer species colonization (such as *Lactobacillus*); and iii) stabilization phase (~day 14 onwards, with near-complete recovery by day 30), gradual diversity and F/B recovery, functional shift to metabolic homeostasis and new equilibrium establishment (27,45,131,132). The staged recovery trajectory of the gut microbiota after acute diarrhea is summarized in Table III.

Incomplete recovery and the risk of long-term sequelae. Although the gut microbiota exhibits considerable 'resilience' in the face of perturbation, recovery from severe disturbances such as acute diarrhea is often protracted, variable and frequently incomplete (27,133). Multiple long-term follow-up studies spanning months or even years warn that even after clinical symptoms such as diarrhea and abdominal pain fully resolve, the gut microbiota of numerous patients may fail to fully restore to its pre-illness baseline state (130,134-138). This failure to fully reconstitute, aptly termed an 'ecological scar', may serve as a potential long-term risk factor for various chronic diseases in the future. This 'incomplete recovery' or 'ecological scarring' can manifest in several forms. First is the persistent loss of diversity. This is one of the most common 'sequelae'. Despite a rebound in α-diversity during the stabilization phase, a notable proportion of patients (particularly those with severe or recurrent infections) exhibit diversity levels that remain markedly lower than those of healthy, age-matched controls, and potentially lower than their own pre-illness baseline for 6 months, a year or even longer post-diarrhea (139-141). Ecosystems with low diversity exhibit poorer functional redundancy and decreased stability. This prolonged diversity deficit renders individuals more vulnerable to new disturbances (such as dietary changes, stress, medication) and recurrent dysbiosis (32,142).

Second is the permanent loss of keystone species. In an ecosystem, certain species hold disproportionately greater importance for structure and function than others; these are 'keystone species' (143). In the gut microbiota, several important commensals play such a role; *F. prausnitzii* is a prime example. As one of the most abundant bacteria in the human gut, it is a primary producer of butyrate, and its

Table II. Pathogen-specific alterations in the gut microbiota.

Pathogen type	Core alteration features	Specific manifestations/mechanisms	(Refs.)
Bacterial diarrhea	1. Expansion of Proteobacteria	An inflammatory gut environment generates reactive oxygen species/reactive nitrogen species. Facultative anaerobic Proteobacteria (*E. coli*, *Salmonella*) tolerate and utilize these compounds (nitrate respiration), leading to explosive proliferation.	(29,65,72,74,78)
	2. Altered *Firmicutes*/*Bacteroidetes* ratio	The direction of change is inconsistent and may depend on pathogen and host factors. A more universal finding is the depletion of key functional genera (butyrate producers) within these phyla.	(71,79,82,85)
	3. Functional metagenomic deterioration	Enrichment of pathways for virulence factors, motility, two-component systems, and antibiotic resistance genes. Suppression of core metabolic pathways (carbohydrate metabolism, vitamin synthesis).	(70,74,77, 81,85-89)
Viral diarrhea	1. *Firmicutes* depletion and Proteobacteria expansion	Rotavirus infection is associated with reduced *Firmicutes* abundance, specifically a notable decrease in butyrate-producing bacteria (*Faecalibacterium prausnitzii*, *Roseburia* spp.), concomitant with an expansion of Proteobacteria. The severity of viral diarrhea positively associates with the magnitude of microbial perturbation.	(90,91)
	2. Distinct metabolic disruptions and host-factor modulation	Viral infections lead to specific alterations in gut metabolic pathways, particularly disruptions in carbohydrate metabolism (galactose and mannose metabolism). Norovirus can establish persistent infections in immunocompromised hosts, potentially sustaining chronic dysbiosis for months or years. Host secretor status (*FUT2* genotype) modulates both norovirus susceptibility and baseline microbiota composition, creating a host-microbe-pathogen triad.	(92-97)
Parasitic diarrhea	1. *Bacteroidetes* depletion and barrier disruption	*Giardia lamblia* is associated with reduced bacterial diversity and depletion of Bacteroidetes, a pattern distinct from bacterial dysbiosis (which is characterized by Proteobacterial expansion), with some evidence of enrichment in *Streptococcus* and *Veillonella*. *Cryptosporidium parvum* causes particularly severe dysbiosis in immunocompromised hosts, with marked depletion of butyrate-producing taxa.	(98-101)
	2. Specific metabolic pathway alterations and chronicity	Parasite-induced dysbiosis involves distinct metabolic signatures, including tryptophan metabolism (kynurenine pathway) and lipid pathway alterations. The unique pathophysiology of parasitic infections, including chronicity, malabsorption and modulation of host adaptive immunity, suggests that recovery trajectories and therapeutic approaches may differ fundamentally from acute bacterial diarrhea.	(95-98,101)

secreted metabolites possess potent direct anti-inflammatory properties (144,145). During acute diarrhea, the abrupt influx of oxygen and massive fluid loss render strictly anaerobic, environmentally sensitive bacteria such as *F. prausnitzii* the most susceptible to depletion (146). Once such a species is locally extirpated, the ecological niche they vacate may be rapidly occupied by other, more adaptable bacteria. Even if the intestinal environment later normalizes, these 'lost keystones' may struggle to return due to competition from established 'later arrivals' (147). The permanent loss or persistent low

Table III. Staged recovery trajectory of the gut microbiota after acute diarrhea.

Recovery phase	Main characteristics	Microbial and functional changes	(Refs.)
Acute phase	Peak ecological 'perturbation'	Sharp decline in α-diversity; surge of opportunistic pathogens (Proteobacteria); near-disappearance of core commensals.	(27,62,137)
Recovery phase	High community instability, colonization by pioneer species	Community instability is high; 'pioneer species' such as *Lactobacillus* colonize; overall structure remains far from normal.	(27,137,138)
Stable phase	Establishment of a new equilibrium	Gradual return of α-diversity and dominant phyla (*Firmicutes* and *Bacteroidete*s); microbial function shifts from inflammatory stress responses back to metabolic homeostasis.	(27,139)
Incomplete recovery ('ecological scarring')	Risk of long-term sequelae	1. Persistent low diversity; 2. Permanent loss of keystone species (e.g., *Faecalibacterium prausnitzii*); 3. Altered community composition or 'alternative stable states'. Associated with long-term sequelae such as post infection irritable bowel syndrome and childhood growth faltering.	(137,141,142, 146,149,156)

abundance of these functionally critical bacteria creates irreparable functional deficits, directly impacting intestinal barrier health and immune system balance (148).

The final form consists of the altered community composition and alternative stable states'. Ecological theory posits that complex systems can exist in multiple distinct stable states. When a system undergoes sufficiently strong disturbance, it may not revert to its original state but instead 'cross a threshold' into an entirely new yet equally stable configuration, an 'alternate steady state' (149,150). This scenario can occur in post-diarrheal microbial recovery. The recovered microbiota, while achieving a certain balance, may exhibit species composition and interspecies interaction networks entirely distinct from its pre-disease state (27,151). This 'new steady-state' may appear macroscopically normal (for example *Firmicutes* and *Bacteroidetes* remain dominant) but harbor subtle yet functionally notable differences (45,134). For instance, the new community may exhibit reduced efficiency in metabolizing specific dietary components, or its profile of produced neurotransmitters and immunomodulatory molecules may be altered, exerting long-term, subtle influences on host physiology (152,153).

This incomplete, 'scarred' recovery is considered the potential pathophysiological basis for several long-term post-diarrheal sequelae. The most extensively researched and clearly associated condition is post-infectious irritable bowel syndrome (PI-IBS) (154,155). Acute enteric infection is one of the most well-established risk factors for developing IBS (156). Epidemiological data indicate that ~10% (ranging from 7 to 30% depending on pathogen and study population) of individuals recovering from acute intestinal infections subsequently develop PI-IBS (138,154). These individuals had no prior bowel issues but begin to experience persistent or recurrent symptoms typical of IBS, including abdominal pain, bloating and altered bowel habits (diarrhea-predominant, constipation-predominant or mixed), consequently impacting quality of life after the initial infection resolves (154,157,158). Growing evidence indicates that persistent gut microbiota dysbiosis is a primary etiology of PI-IBS (24,159,160). Multiple case-control studies systematically comparing the gut microbiomes of patients with PI-IBS with those of individuals who fully recovered post-infection and healthy controls have revealed a series of microbial signatures associated with PI-IBS. Persistent structural abnormalities: Compared with full recovered individuals, patients with PI-IBS typically exhibit lower gut microbiota α-diversity and their microbiota structure (β-diversity) notably differs from that of healthy individuals (161). Specifically, their microbiota often shows reductions in beneficial bacteria such as *Bifidobacterium*, *Lactobacillus* and key butyrate producers such as *Faecalibacterium* and *Roseburia* (162-164). Concurrently, the abundance of potentially pathogenic or pro-inflammatory bacteria may be relatively increased, including certain *Bacteroides* species or *Enterobacteriaceae* members (18,58,165). Microbiota-driven pathophysiological mechanisms: This persistent dysbiosis is considered to be the key upstream driver of the core pathophysiological changes in PI-IBS, including low-grade chronic inflammation, visceral hypersensitivity and increased intestinal permeability (166-168). Persistent dysbiosis drives PI-IBS through low-grade inflammation (leaky gut, immune activation), visceral hypersensitivity (sensory nerve hyper-excitability) and altered gut motility (disrupted neurotransmitter signaling).

Long-term implications for early childhood. For infants and young children whose gut microbiomes remain in a dynamic developmental and maturation phase, the 'ecological scars' left by severe or recurrent acute diarrhea may yield more

profound long-term consequences (29,169,170). Early life is a key window for the 'dialogue' and 'co-development' of the microbiota with the host's immune, nervous, and metabolic systems (171-173).

Malnutrition and growth stunting. In developing countries, recurrent diarrhea is a primary cause of childhood malnutrition and growth stunting. This is partly attributable to a pathological condition known as environmental enteric dysfunction (EED), characterized by chronic intestinal inflammation, villous atrophy and malabsorption (174,175). Persistent microbiota dysbiosis is considered a central driver of EED. Incomplete recovery post-diarrhea prevents the gut from effectively absorbing nutrients from food, creating a vicious cycle (176-178).

Increased risk of allergic and autoimmune diseases. According to the 'hygiene hypothesis' and its modern extensions, sufficient and diverse microbial exposure in early life is crucial for 'educating' and 'training' the host immune system to establish immune tolerance. Severe diarrheal perturbations, especially when combined with antibiotic use, can disrupt this normal immunologic education, potentially predisposing to immune dysregulation. This can lead to excessive Th2-type immune responses to harmless environmental antigens (such as pollen and food) later in life, increasing the risk of allergic diseases such as asthma, eczema and allergic rhinitis (179,180).

Long-term metabolic disease risk. Early-life gut microbiota composition can 'program' the long-term metabolic phenotype of the host (181-183). Certain key bacteria that colonize during infancy, such as *Bifidobacterium infantis*, *Akkermansia muciniphila* and Bacteroides species, are involved in regulating fat storage, insulin sensitivity and energy expenditure (184-186). Deviations in microbiota developmental trajectory caused by diarrhea may increase the individual's risk of developing obesity, type 2 diabetes, and other metabolic syndromes in later childhood and even adulthood (122,187).

Factors influencing recovery. The speed, trajectory and ultimate degree of microbial recovery from acute diarrhea are not uniform but determined by complex interplay of multiple factors, resulting in markedly individualized outcomes. These factors collectively form a 'regulatory network' that determines the recovery endpoint.

Age as the determinative role of host developmental stage

Infants and young children. The gut microbiota of infants and toddlers undergoing notable succession and assembly, characterized by low diversity, poor stability and marked compositional fluctuation (188-191). Consequently, their normal developmental trajectory is susceptible to disruption or deviation when confronted with intense external disturbances such as acute diarrhea. Severe infections may result in the permanent loss of certain key early colonizers, triggering cascading effects on subsequent microbial maturation (170,192). This impact may be enduring and potentially linked to future immune and metabolic health outcomes.

Adults. The adult gut microbiota has formed a relatively mature, diverse and stable community with greater resilience and functional redundancy. When confronted with equivalent disturbances, it typically exhibits stronger and faster recovery capabilities (33,193). However, 'mature' does not equate to 'invincible'; severe infections or inappropriate treatment can still lead to long-term dysbiosis (127,194).

Elderly. With advancing age, the gut microbiota undergoes 'ecological aging', manifesting as decreased diversity, reduction of core probiotics (such as *Bifidobacterium*), and an increase in potential pathogens. This aged microbiota is inherently more fragile, and its recovery capacity is correspondingly diminished. This renders the elderly more susceptible to complications such as secondary infections following chronic diseases or diarrhea (195-198).

Pathogen type and infection severity: The nature of the perturbation source

Non-invasive pathogens. Examples include rotavirus, norovirus and enterotoxigenic *Escherichia coli*. These primarily infect intestinal epithelial cells, producing toxins that disrupt ion channels, leading to massive secretion of water and electrolytes into the lumen (osmotic diarrhea). They cause relatively 'superficial' ecological disruption with minimal physical damage to intestinal structures. Hence, microbiota recovery from diarrhea caused by such pathogens is generally quicker and more complete (199-201).

Invasive pathogens include *Shigella*, *Salmonella*, enteroinvasive *E. coli* and *Campylobacter*. These organisms invade the deeper intestinal mucosa, causing cell death, tissue necrosis, ulcer formation and notable inflammation (often presenting as mucoid or bloody stools). This 'deep destruction' not only directly kills large numbers of mucosal-layer commensals but radically alters the physicochemical environment of the gut (202-204). For instance, inflammation generates alternative electron acceptors such as nitrates, conferring a distinct competitive advantage to facultative anaerobic Proteobacteria. Recovery from such profound ecological damage is naturally slower, more arduous and carries a higher risk of leaving an 'ecological scar' (24,61,205,206).

Infection severity. This represents a dose-response relationship. The pathogen load, duration of illness and severity of symptoms (degree of dehydration, fever, inflammatory marker levels) directly reflect the intensity of the perturbation. Stronger perturbation delivers a greater initial influence to the microbiota, pushes the ecosystem further from its stable point, requires more 'energy' and time for recovery and increases the probability of incomplete restoration (127,207-210).

Host factors: Differences in the internal milieu of an individual

Genetic background. Host genetics, particularly genes encoding immune recognition and response molecules (such as Toll-like receptors, NOD-like receptors and cytokines), determine susceptibility to specific pathogens and the intensity and nature of the inflammatory response (211-214). Different immune response patterns shape distinct gut microenvironments, thereby influencing the clearance and reconstitution processes of the microbiota (215-217).

Baseline health status and microbiota. The overall health and gut microbiota state of an individual prior to infection constitute the 'initial conditions'. Individuals with markedly diverse, stable and functionally robust baseline microbiota inherently possess stronger ecosystems capable of resisting

disruption and recovering from it (98). Conversely, if an individual already harbors some degree of dysbiosis before infection (for example due to long-term unhealthy diet, chronic stress or other underlying diseases), the attack of acute diarrhea may be the precipitating factor, making recovery notably difficult (130,218).

Immune status. Competent immune function is a prerequisite for effectively clearing pathogens, controlling inflammation and creating a favorable environment for microbiota recovery (219). Individuals with compromised or deficient immune systems, such as those with acquired immunodeficiency syndrome, organ transplant recipients or patients undergoing chemotherapy, not only face heightened susceptibility to infection but also encounter greater challenges in restoring microbial balance post-infection. This often leads to prolonged illness and severe complications (220-222).

Therapeutic interventions, particularly antibiotic use. Antibiotics are necessary and can be life-saving when treating specific types of bacterial diarrhea, such as cholera and shigellosis (223,224). However, from a microbiological perspective, the administration of antibiotics constitutes a 'secondary assault' on an already markedly compromised intestinal ecosystem (225,226). Broad-spectrum antibiotics cause collateral damage to commensal communities, delay and distort natural recovery trajectories for months and increase susceptibility to secondary infections such as *C. difficile* by collapsing colonization resistance. Therefore, the importance of precision and prudence in antibiotic use cannot be overstated. For acute diarrhea, rational antibiotic use is paramount. Clinical decisions must be grounded in accurate pathogen identification: i) Most acute watery diarrhea is self-limiting and does not require antibiotics; ii) indications for empiric therapy include severe disease, dysentery, immunocompromise and systemic toxicity; iii) watchful waiting with supportive care and diagnostic testing is preferred when etiology is uncertain and the patient is stable; and iv) antibiotic choice should be narrowed once diagnostic results are available (227,228).

4. Clinical implications: From biomarkers to bedside

While mechanistic and ecological insights into microbiota dysbiosis have advanced considerably, their translation into actionable clinical practice remains limited.

Microbiota-based diagnostic and prognostic biomarkers. The gut microbiota and its metabolites offer a rich reservoir of potential biomarkers for acute diarrheal disease. Emerging evidence supports the clinical utility of several microbiota-derived indicators: i) Fecal calprotectin, a surrogate marker of neutrophilic intestinal inflammation, is elevated in acute bacterial and some viral infections and is associated with disease severity (Human-obs), although it lacks specificity for etiology (229); ii) SCFAs, particularly butyrate, are depleted in acute dysbiosis (Human-obs), and low fecal butyrate levels show promise for predicting prolonged recovery and higher risk of post-infectious sequelae in research cohorts, but prospective validation is still lacking (230); and iii) the proteobacteria/*F. prausnitzii* ratio captures the dual perturbation of pathogen expansion and commensal loss (Human-obs; Animal), and may serve as a composite dysbiosis index in research settings (231,232). Metagenomic signatures can differentiate bacterial from viral etiologies with moderate accuracy in retrospective studies, but these remain investigational biomarkers without established clinically actionable thresholds, standardized protocols or cost-effectiveness data. They should be considered only in research settings or specialized centers, not as part of routine clinical pathways (experimental stage, lacks prospective validation, clinically actionable thresholds and standardized protocols).

Risk stratification and clinical decision framework. Drawing on the factors influencing microbiota recovery, the present study propose a conceptual framework for risk stratification to guide future research and precision-medicine development, not as a current clinical practice guideline. This framework is intended to guide future research and requires prospective validation before any clinical implementation. Patients can be conceptually categorized as high or low risk. High risk for incomplete recovery/PI-IBS: elderly patients (>65 years), infants and young children (<2 years), those with invasive pathogens (such as Shigella, Campylobacter), severe dehydration, prolonged disease duration (>7 days), broad-spectrum antibiotic exposure or immunosuppression. The type of evidence supporting each risk factor is detailed in Table IV. Low risk: Older children and adults with non-invasive, self-limiting infections, no antibiotic use and intact immune function. Microbiota profiling at 1 and 3 months may be explored in research protocols but is not recommended in routine clinical practice (experimental stage, conceptual research framework requiring prospective validation; the 1/3-month microbiome follow-up is strictly limited to the research protocol). High-risk patients are candidates for biomarker-guided, stepwise escalation from probiotics and dietary rehabilitation to fecal microbiota transplantation and precision therapy, whereas low-risk individuals receive supportive care only (Fig. 2). This conceptual model requires prospective validation and is not intended as a current clinical practice guideline.

Practical clinical management recommendations

Diagnostic approach. Advances in metagenomics and 16S rRNA profiling hold considerable promise for future point-of-care diagnostics, potentially enabling rapid pathogen identification, resistance profiling and dysbiosis quantification. However, current evidence does not yet support their routine clinical use for acute diarrhea in standard practice, owing to substantial cost, turnaround time, interpretive complexity and lack of prospective validation in large clinical cohorts. Current evidence does not yet support their routine clinical use for acute diarrhea. Their application should be strictly reserved for research protocols, severe or refractory cases, and specialized referral centers, rather than routine clinical practice (experimental stage, metagenomic/16S rRNA testing is currently restricted to research and specialized centers; it is not supported in routine clinical practice).

Antibiotic stewardship. Adopt a microbiota-conscious antibiotic strategy. For viral diarrhea and most self-limiting bacterial gastroenteritis, avoid antibiotics. When antibiotics are indicated (dysentery, cholera, severe traveler's diarrhea), select the narrowest effective spectrum and shortest effective duration (typically 3-5 days for shigellosis;

Table IV. Evidence supporting proposed risk factors for incomplete recovery after acute diarrhea.

Risk factor	Type of evidence	Clinical readiness	Current limitations	(Refs.)
Age >65 years or <2 years	Epidemiological (cohort studies); Longitudinal microbiome (limited)	Expert inference; requires prospective validation	Age cut-offs arbitrary; microbiome data in elderly and infants predominantlyfrom high-income countries; limited pathogen-specific stratification	(201-205, 220-224)
Invasive pathogens (*Shigella, Campylobacter, Salmonella*, enteroinvasive *Escherichia coli*)	Epidemiological; animal models (inflammation-driven dysbiosis); Human-observation (metagenomic case series)	Promising but inconsistent; no validated point-of-care test	Invasiveness classification not always clinically apparent at presentation; metagenomic studies small and heterogeneous	(24,78, 228-232)
Disease duration >7 days	Epidemiological; expert inference	Expert inference; requires prospective validation	Duration threshold arbitrary (7 days not universally validated); confounded by treatment delay and pathogen type	(149, 233-236)
Severe dehydration	Epidemiological; physiological (dehydration severity associates with illness intensity)	Expert inference; widely accepted as severity marker but microbiome link indirect	Dehydration scoring varies across settings; microbiome-specific studies with dehydration stratification are sparse	(137,149, 220-223)
Broad-spectrum antibiotic exposure	Longitudinal microbiome (randomized controlled trial and cohorts); epidemiological (antibiotic-associated diarrhea risk)	Strongest evidence base among all factors; supports antibiotic stewardship recommendation	Specific antibiotic classes vary in dysbiosis impact; duration and timing not standardized in studies; pediatric vs. adult data inconsistent	(142-148, 250-263)
Immuno-suppression (HIV, transplant, chemotherapy, biologics)	Epidemiological; human-observation (immuno-compromised cohorts); preclinical	Expert inference; mechanistically plausible but microbiome-specific data limited	Heterogeneous immunosuppression types; microbiome studies in immunocompromised predominantly focus on *C. difficile*, not general acute diarrhea	(233-235, 244-247)

single-dose azithromycin for traveler's diarrhea). *C. difficile* risk should be assessed in patients with recent antibiotic exposure (clinically supported, antimicrobial stewardship strategies based on etiological diagnosis are well-supported by evidence) (233,234).

Probiotic therapy. When clinically indicated, specific probiotic strains with the strongest evidence base (such as *Lactobacillus rhamnosus GG*, *Saccharomyces boulardii*) can be considered early in the disease course (126,235,236). The optimal dose, duration and patient population remain areas of active investigation; the North American probiotic RCTs have highlighted marked heterogeneity in outcomes (237), underscoring the need for individualized rather than standardized prescribing. Clinicians should select strain-specific products with documented efficacy for the target condition and avoid generic 'multistrain' formulations lacking trial evidence (clinically supported, multiple RCTs and meta-analyses support the use of *L. rhamnosus GG* and *Saccharomyces boulardii* (236,238-240); however, the optimal dosage and duration remain to be determined).

Nutritional rehabilitation. Reject prolonged BRAT-type low-fiber diets. Instead, reintroduce diverse dietary fibers (fruits, vegetables, whole grains) within 24-48 h of symptom improvement to fuel SCFAs-producing commensals.

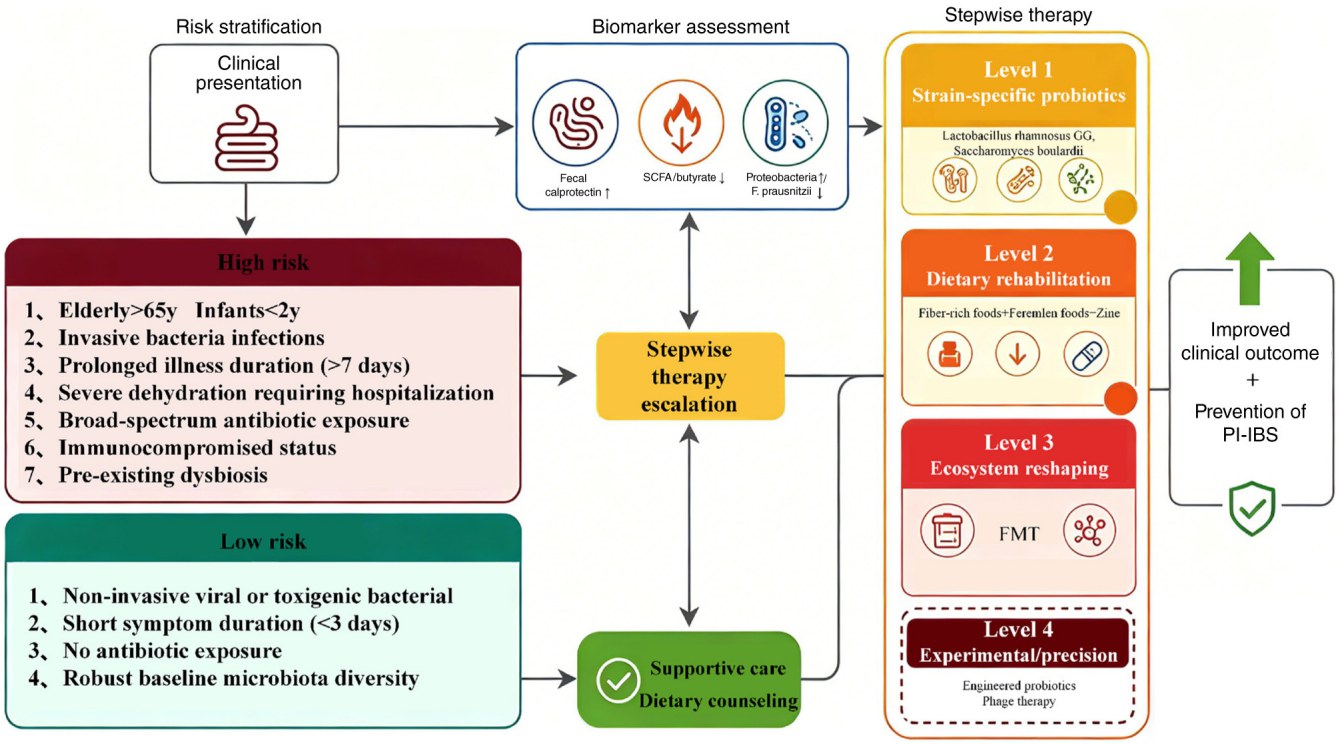

Figure 2. Proposed conceptual framework for risk stratification and recovery monitoring after acute infectious diarrhea. Patients are stratified into high-risk (such as elderly, infants, invasive pathogens, antibiotic exposure, immunocompromise) or low-risk (healthy adults with self-limiting disease). High-risk patients are assessed by microbiota biomarkers (calprotectin, butyrate, *Proteobacteria*/*F. prausnitzii*) to guide stepwise escalation: i) Probiotics (*L. rhamnosus* GG, *S. boulardii*); ii) dietary rehabilitation (fibers, fermented foods, zinc); iii) fecal microbiota transplantation for severe/refractory cases; and iv) experimental precision therapies. Low-risk patients receive supportive care only. This framework is a proposed conceptual model for future research and precision-medicine development, not a current clinical practice guideline. It requires prospective validation before any clinical implementation. Current routine practice (standard supportive care, oral rehydration, dietary rehabilitation) Specialized center/research settings only (metagenomic profiling, specific probiotic strains in high-risk patients). Investigational/future (microbiota follow-up at 1 and 3 months, AI/ML risk prediction, FMT for non-CDI). FMT, fecal microbiota transplantation; PI-IBS, post-infectious irritable bowel syndrome; SCFA, short-chain fatty acid.

Fermented foods (yogurt, kefir) provide live cultures and bioactive metabolites. Zinc supplementation (10-20 mg/day for children; per WHO guidelines) supports epithelial repair and exerts prebiotic-like effects on beneficial taxa (241-243) [clinically supported, early reintroduction of dietary fiber and zinc supplementation (per WHO guidelines) are evidence-based].

FMT and advanced therapies. For non-CDI acute infectious diarrhea, FMT is strictly experimental and not recommended for routine clinical use. FMT is established only for recurrent *C. difficile* infection (rCDI); for non-CDI acute infectious diarrhea, it is strictly investigational and should not be used outside clinical trials (244-247) (rCDI: clinically supported as standard therapy; non-CDI acute diarrhea, experimental stage, strictly limited to clinical trials).

Follow-up and surveillance. Patients who are high-risk should undergo clinical reassessment at 4-6 weeks post-infection. Microbiota reassessment may be explored in research protocols but is not recommended in routine clinical practice. Persistent dysbiosis patterns (decreased diversity, loss of *F. prausnitzii*, elevated Proteobacteria) may be associated with PI-IBS or environmental enteric dysfunction risk, but these associations require prospective validation (24,134,134,178) (experimental stage, microbiome reassessment is strictly limited to the research protocol; however, clinical reassessment for high-risk patients at 4-6 weeks is a routine recommendation).

5. Microbiota-targeted therapeutic strategies

Given the key pathological role of the gut microbiota in acute diarrhea, developing treatment strategies aimed at modulating and restoring this microbial community has become a major research focus. These strategies range from traditional approaches supplementing beneficial bacteria to interventions reshaping entire ecosystems, as well as next-generation precision targeted therapies, demonstrating broad potential applications (248-250). Microbiota-targeted therapeutic strategies are summarized in Table V and corresponding therapeutic interventions are shown in Fig. 3. Notably, Fig. 3 is structured as a continuum: The left-to-right progression from traditional microbial supplementation through ecosystem reshaping to next-generation precision interventions visually encapsulates the central thesis of the present review, of a trajectory from acute dysbiosis toward precision restoration. This design intentionally positions precision strategies not as isolated novelties, but as the logical evolution of microbiota-directed care, building upon the ecological understanding established in earlier sections. According to the clinical risk stratification and management framework presented in Section 4, the following sections critically evaluate the evidence base for each therapeutic modality, distinguishing established interventions from experimental approaches. The selection and sequencing of these interventions should be guided by the

Table V. Microbiota-targeted therapeutic strategies.

Strategy category	Definition/principle	Representative agents/methods	Clinical evidence and challenges	(Refs.)
Traditional microbial interventions	Live beneficial microorganisms, their selective substrates, or combinations.	Probiotics (*L. rhamnosus GG, S. boulardii*), prebiotics (FOS, inulin), synbiotics.	RCTs and meta-analyses support efficacy in shortening diarrhea duration, although effects are strain-specific. Some large RCTs show inconsistent results. Generally safe; caution in high-risk populations.	(261-264, 274-276,280)
Ecosystem reshaping	Transfer of complete fecal microbiota from a healthy donor.	Fecal microbiota transplantation via enema, colonoscopy, or oral capsules.	Standard therapy for recurrent *C. difficile* infection. Limited evidence for other acute infectious diarrhea. Challenges: donor screening, standardization, regulation.	(286-294)
Next-generation precision interventions	Targeted modulation using synthetic biology and gene editing.	Engineered probiotics, postbiotics, phage therapy.	Mostly preclinical/early clinical. Engineered probiotics show promise in animal models. Postbiotics offer safety and standardization. Phage therapy enables precise pathogen targeting (SNIPR001 Phase I). Challenges: resistance, cocktail formulation, regulation.	(298-301,303, 305,308,309, 314,322,323, 326,327)

RCTs, randomized controlled trails.

risk-stratification framework and clinical decision algorithm presented in Section 4, ensuring that therapeutic intensity is matched to individual patient risk profiles rather than applied uniformly.

Traditional microbial interventions: Probiotics, prebiotics and synbiotics

Probiotics: Evidence stratified by clinical population. Probiotics exert anti-diarrheal effects through pathogen competition, barrier enhancement, bacteriocin production and immune modulation (251-253). However, their efficacy in acute diarrheal disease is notably strain-specific, population-dependent and modest. The following sections critically evaluate the evidence by clinical population, emphasizing that benefits are not universal and should not be overstated.

Acute infectious diarrhea in children. Clinical evidence for probiotics stems from numerous RCTs, systematic reviews and meta-analyses evaluating their efficacy in treating acute diarrhea, particularly in children; overall evidence is positive but varies (235,236,237,254). Several meta-analyses indicate that the use of specific probiotic strains can notably shorten the duration of diarrhea, reduce stool frequency and shorten hospital stays (237,255). Notably, probiotic efficacy exhibits high strain specificity. For acute diarrhea treatment, the two strains with the strongest evidence are *L. rhamnosus GG* and *Saccharomyces boulardii* CNCM I-745 (236,256,257). Other strains, such as *Lactobacillus reuteri DSM 17938* and some *Bifidobacterium* strains, also show promise (258,259). However, large, high-quality RCTs, particularly those conducted in North America, have failed to replicate the positive outcomes of earlier studies. This suggests that probiotic efficacy may be influenced by various factors including geographic region, prevalent pathogen types, dietary habits and study design (235,259). Therefore, future research requires more precise identification of the target populations and contexts for probiotic use.

AAD. Meta-analyses of probiotic prophylaxis for AAD show moderate preventive efficacy in adults and children receiving antibiotics, but inter-study heterogeneity is substantial (260,261). Benefits are primarily observed with specific strains (such as S *L. rhamnosus GG* and *Saccharomyces boulardii*) and may not generalize to all antibiotic regimens. Probiotics should be considered as an adjunct, not a substitute for antibiotic stewardship.

Traveler's diarrhea. Evidence for probiotic prevention or treatment of traveler's diarrhea remains weak and inconsistent. Randomized trials have shown marginal or non-significant protective effects, and no specific strain has demonstrated reliable efficacy in this setting (262,263). Routine probiotic use for traveler's diarrhea is not recommended.

CDI. Probiotics are not primary therapy for CDI. Some evidence suggests adjunctive preventive efficacy in patients receiving antibiotics who are at high risk for CDI, but effect sizes are small and strain-dependent (264-266). For recurrent CDI, standard-of-care remains antimicrobial therapy followed by FMT; probiotics play no established role in treatment.

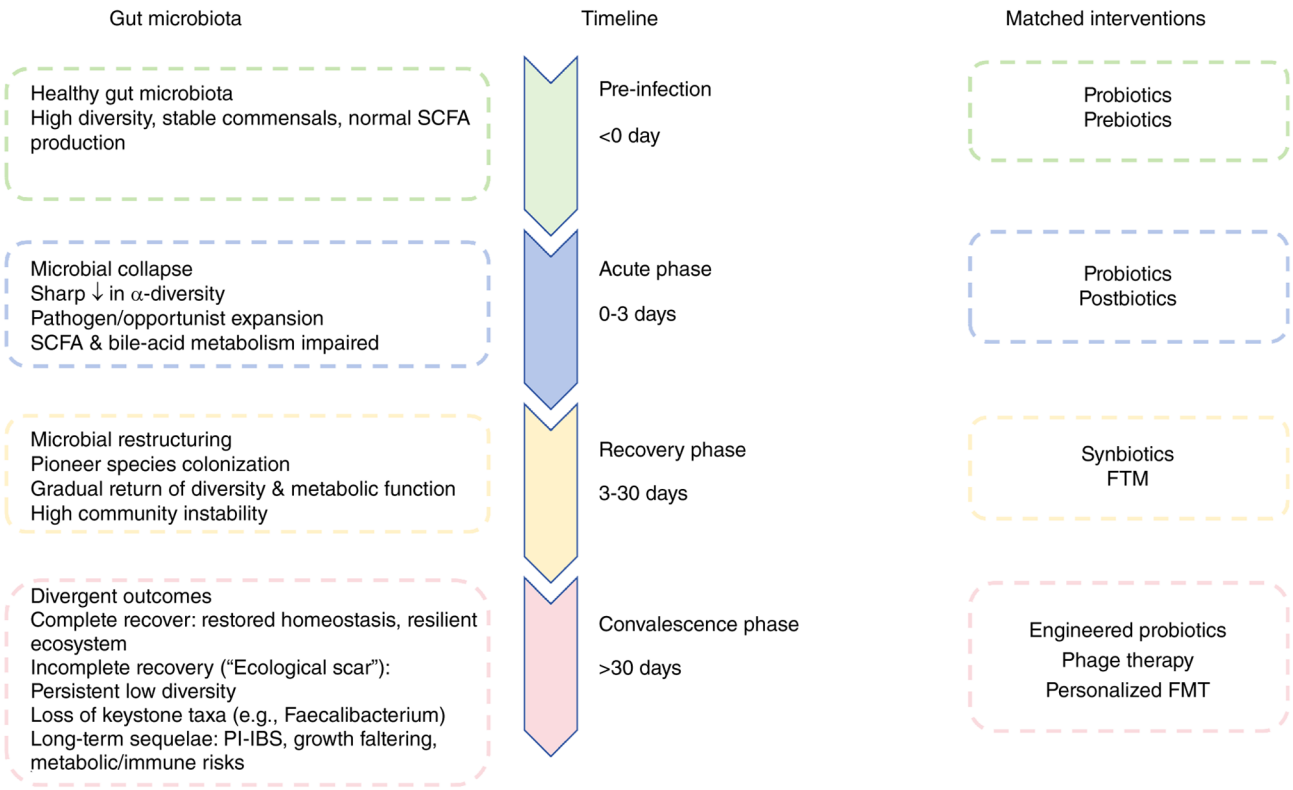

Figure 3. Stage-specific dynamics of the gut microbiota following acute diarrhea and corresponding therapeutic interventions. The left timeline illustrates the sequential phases of microbial disruption and recovery after infection. The acute phase is characterized by rapid collapse of diversity and pathogen expansion. During recovery, the microbiota undergoes restructuring, leading to either complete restoration or an incomplete recovery state ('ecological scar'), which predisposes to long-term sequelae. The right column outlines microbiota-targeted interventions recommended for each phase, ranging from preventive probiotics and acute-phase postbiotics to ecosystem-reshaping (FMT) and precision therapies (engineered probiotics, phage therapy) for chronic sequelae. FMT is standard-of-care only for recurrent C. difficile infection; its placement for non-CDI acute diarrhea reflects investigational status only. FMT, fecal microbiota transplantation; SCFA, short-chain fatty acid.

Immunocompromised and patients who are critically ill. Safety concerns are paramount in this population. Although probiotics are generally regarded as safe for healthy individuals, rare but serious adverse events-including bacteremia and fungemia-have been reported in preterm infants, patients in the intensive care unit and severely immunocompromised individuals (267-269). Current guidelines (IDSA/SHEA) do not recommend routine probiotic use in immunocompromised or patients who are critically ill (124,270). Caution is warranted, and the risk-benefit profile must be assessed individually (271).

Overall, probiotic benefits in acute diarrheal disease are modest, strain-specific and population-dependent. They should not be promoted as a universal solution. Clinicians should select strain-specific products with documented efficacy for the target condition and patient population and avoid generic 'multistrain' formulations lacking trial evidence (clinically supported, *L. rhamnosus GG* and *Saccharomyces boulardii* CNCM I-745 are the strains with the strongest human-derived RCT evidence; clinical readiness: established, *L. rhamnosus GG* and *Saccharomyces boulardii* CNCM I-745 are supported by multiple RCTs and meta-analyses for pediatric acute diarrhea; may be considered early in appropriately selected patients (235,236).

Prebiotics and synbiotics. Prebiotics are defined as 'a substrate selectively utilized by host microorganisms with health benefits' (272,273). Common examples include fructooligosaccharides and inulin. They serve as fermentable substrates for beneficial bacteria such as *bifidobacteria* and *lactobacilli*, promoting their proliferation and increasing the production of SCFAs (274-277). A study suggested that using prebiotics or prebiotic-containing infant formula during acute diarrhea may help shorten recovery time (278) (Preliminary and inconsistent evidence: Human-derived RCT results are mixed; routine recommendation is currently not supported. Clinical readiness, promising but inconsistent, human RCTs yield mixed outcomes for prebiotics; evidence is positive but heterogenous across populations and settings, precluding routine recommendation).

Synbiotics are combination products containing both probiotics and prebiotics. Their theoretical advantage lies in the prebiotic component providing a growth advantage to the co-administered probiotic, aiming for a synergistic effect (279). Several systematic reviews analyzing the use of synbiotics in treating pediatric acute diarrhea indicate positive effects in reducing diarrhea duration and hospital stay, potentially outperforming probiotics alone. Synbiotics are considered a promising strategy for restoring gut dysbiosis (280-283) (Preliminary and inconsistent evidence: Systematic reviews indicate positive effects, but RCTs show marked heterogeneity. Clinical readiness, promising but inconsistent, systematic reviews indicate positive effects in reducing diarrhea duration, but effect sizes vary substantially

by population, geography and pathogen; not yet ready for standardized prescribing).

Safety and practical considerations: General population. As aforementioned, safety concerns differ markedly by population. Probiotics, prebiotics, and synbiotics are generally regarded as safe for healthy individuals and most patients. However, in rare instances, particularly in vulnerable populations such as preterm infants, patients in the intensive care unit or markedly immunocompromised individuals, cases of bacteremia or fungemia linked to probiotic use have been reported (284,285). Therefore, caution is warranted when considering their use in these high-risk groups (clinical readiness: Established, generally regarded as safe for healthy individuals and most patients; caution warranted in preterm infants, patients in the intensive care unit or markedly immunocompromised hosts).

Ecosystem reshaping: FMT. FMT involves transferring a complete, healthy donor microbiota suspension into the recipient gastrointestinal tract via enema, colonoscopy or oral capsules (286-288). Unlike probiotics, which introduce only a few strains, FMT aims to restore a full, diverse ecosystem capable of displacing pathogens through colonization resistance and rapidly re-establishing key functions (such as SCFA production, secondary bile acid metabolism) (289-291).

FMT is established as standard therapy only rCDI (292-294). For non-CDI acute infectious diarrhea, evidence is limited to case reports and small studies (295,296); FMT is strictly investigational and should not be used outside clinical trials. Broader application faces challenges including donor screening, standardization and regulatory ambiguity (297-299) (rCDI: Clinically supported as standard therapy. Non-CDI acute diarrhea: Experimental stage, limited to case reports and small-scale studies).

Next-generation precision intervention strategies. While probiotics and FMT represent the current evidence-based armamentarium, they remain fundamentally non-specific. They introduce beneficial microbes or entire ecosystems without targeting the specific pathogen or host-microbiota deficit driving an individual's disease. As depicted in the right-hand panel of Fig. 3, the field is now advancing toward next-generation precision interventions, therapies engineered to sense, respond and eliminate with molecular specificity. Advancements in synthetic biology, gene editing and phage biology are fostering the development of next-generation precision microbial therapies that go beyond traditional probiotics and FMT. These approaches aim to intervene in the gut microbiota in a more controlled and targeted manner (300-303).

Engineered probiotics: Engineered microbial sentinels. Engineered probiotics are modified through genetic engineering to perform specific diagnostic or therapeutic functions (304). An illustrative example involves the successful modification of *L. rhamnosus* GG to display single-chain antibodies or immunoglobulin G-binding domains on its cell surface that bind to rotavirus (305,306). In mouse models, this engineered probiotic functioned as a 'biological trap', capturing and neutralizing rotavirus within the gut and notably alleviating diarrhea symptoms (307). This opens a new avenue for developing non-antiviral drug therapies against specific viruses (preclinical stage, currently limited to animal models and *in vitro* studies; not yet tested in human diarrheal disease).

Another frontier utilizes safe probiotic chassis, such as *E. coli Nissle 1917*, engineered as therapeutic production platforms (308). By incorporating clustered regularly interspaced short palindromic repeats (CRISPR) systems and specific genetic circuits, these engineered bacteria can be programmed to sense intestinal inflammation signals and, in response, produce and release anti-inflammatory molecules or antimicrobial peptides *in situ* (309). For instance, engineered bacteria producing the antimicrobial peptide microcin Mcc47 were designed to combat resistant *Klebsiella* (310). Such programmable probiotics hold promise for achieving precise, on-demand therapy with minimal off-target effects. Although most research remains in the preclinical stage, demonstrated potential signals the arrival of a new design phase for microbial therapeutics (311).

Postbiotics: Direct application of microbial metabolites. Postbiotics are defined as preparation of inanimate microorganisms and/or their components that confers a health benefit on the host'. They represent a potentially safer and more controllable form of microbial intervention (312,313). Compared with live probiotics, postbiotics contain no viable microorganisms, thereby eliminating the risk of causing infection and making them safer for use in patients who are immunocompromised (314). Furthermore, their chemical composition is defined, facilitating standardized manufacturing, quantification, storage and longer shelf-life (315). Active components of postbiotics are diverse, including SCFAs, cell wall components, exopolysaccharides and bacterial lysates (316). For instance, butyrate itself can serve as a postbiotic agent, directly providing energy and repairing the barrier for colonocytes (317,318). Metabolomic analysis of probiotic-supplemented infants revealed notably elevated concentrations of acetate and lactate in their intestines, key mediators of probiotic action that may indicate postbiotic effects (319). In the future, directly administering purified or synthetic 'cocktails' of these metabolites may bypass the uncertainties associated with live bacterial colonization, offering a more direct and stable therapeutic effect (320) (preclinical stage, the clinical application of defining metabolites is still in the conceptual stage and human pharmacokinetic data are limited; not yet tested in human diarrhea).

Phage therapy: Precision strike with bacterial 'predators'. In the face of rising antibiotic resistance, phage therapy, the use of viruses that specifically lyse bacteria to treat bacterial infections, is experiencing a renaissance as an ancient therapy with renewed relevance (321-323). The advantage of phages lies in their high specificity; a phage typically infects only one or a few closely related bacterial strains. This allows phage therapy to function similarly to targeted antimicrobial agents, precisely eliminating enteric pathogens without harming beneficial commensals, thereby avoiding the broad ecological disruption caused by antibiotics (324,325).

Encouraging progress has been made in applying phage therapy to bacterial diarrhea. A landmark development is the Phase I clinical trial of SNIPR001, a CRISPR-enhanced phage cocktail specifically targeting *E. coli* (326). Results demonstrated that oral administration of SNIPR001 was well-tolerated in healthy volunteers and led to a notable, durable reduction in

intestinal *E. coli* levels, including resistant strains. This marks a preliminary validation of the feasibility and safety of using engineered phages for precise modulation of the human gut microbiota (327,328). Although large-scale RCTs for acute diarrhea remain scarce, existing case reports and early trials show promise (329) (early clinical trial stage: SNIPR001 has only completed a Phase I safety trial, and large-scale confirmatory RCTs for acute diarrhea are still lacking. Represents a promising but not yet clinically validated direction).

Challenges in phage therapy include the potential for bacterial resistance to phages, the necessity for tailored formulations for different strains and complex pharmacokinetics and regulatory pathways. Nevertheless, it undoubtedly represents a promising new direction for combating bacterial diarrhea and antibiotic resistance (330-333).

Clinical readiness assessment of microbiota-targeted interventions for acute infectious diarrhea. The translational landscape of microbiota-targeted interventions for acute infectious diarrhea spans a broad spectrum of evidence maturity. To clarify the current basis and practical applicability of each approach, we stratify available strategies into four tiers, established, promising but inconsistent, investigational and preclinical, followed by a critical appraisal of evidence quality and generalizability.

Established: Routine clinical use supported by evidence. Only a limited number of specific probiotic strains are supported by RCTs and can be considered early in the disease course for appropriately selected patients. Representative examples include: i) *L. rhamnosus GG* (human RCTs); and ii) *Saccharomyces boulardii CNCM I-745* (human RCTs). These strains demonstrate consistent benefits across multiple studies, although effect sizes remain influenced by host baseline status, offending pathogens, and chosen endpoints (235-237,334).

Promising but inconsistent: Positive data but heterogeneity precludes routine recommendation. Several interventions have shown favorable results in human RCTs, yet considerable inter-study variability limits the formulation of general recommendations: i) Prebiotics/synbiotics (fructo-oligosaccharides, inulin), human RCTs yield mixed outcomes; and ii) strain-specific probiotic combinations for pediatric acute diarrhea, human RCTs indicate effect sizes that vary substantially by population, geographical setting and etiological agent.

Investigational: preliminary human data or strong mechanistic rationale, but not ready for routine use. The following strategies have entered human observational or early-phase trials but lack validated thresholds or large-scale confirmatory evidence: i) FMT for non-CDI diarrhea, only small case series (human observational); ii) phage therapy for bacterial diarrhea (SNIPR001 targeting *E. coli*), early-phase human RCT (Phase I); and iii) microbiota-based diagnostic biomarkers (fecal calprotectin, SCFA/butyrate, Proteobacteria/*F. prausnitzii* ratio), human observational studies only, with no clinically validated cut-offs.

Preclinical: Animal or in vitro evidence only, not yet tested in human diarrhea. The following innovative directions have theoretical or technological appeal but have not entered human validation: i) Engineered probiotics (*L. rhamnosus GG* displaying antibodies, *E. coli Nissle 1917* as therapeutic production platforms), animal and *in vitro* studies; ii) most postbiotics (defined microbial metabolites), *in vitro* data with very limited human pharmacokinetic information; and iii) artificial intelligence and machine learning (AI/ML) classifiers for etiological prediction and risk stratification, *in silico* studies based on retrospective cohorts.

Critical appraisal of evidence quality and generalizability. The aforementioned evidence hierarchy is markedly heterogeneous. Human RCTs supporting specific probiotic strains represent the strongest evidence base, yet even these must be interpreted with caution, as effect sizes depend on population, pathogen and clinical endpoint. Observational human studies (both cross-sectional and longitudinal) offer valuable mechanistic insights but cannot establish causality. Animal models have been instrumental in elucidating mechanisms such as nitrate respiration and colonization resistance; however, direct extrapolation to human disease requires circumspection owing to differences in diet, anatomy, immune architecture and gut microbiota composition. *In vitro* studies provide proof-of-concept for engineered probiotics and phage specificity but lack the complexity of *in vivo* host-microbe interactions. Hypothesis-driven proposals, including AI/ML classifiers, precision stratification based on baseline microbiota and microbiota-derived risk algorithms, are conceptually attractive but remain untested in prospective clinical trials.

6. Conclusion

The present review framed acute infectious diarrhea as a profound ecological perturbation within the intestinal ecosystem, integrating pathogen-specific dysbiosis patterns, staged recovery trajectories and microbiota-targeted interventions into a unified conceptual model. By embedding artificial intelligence-driven multi-omics integration and pharmacomicrobiomics, it charts a research pathway toward precision medicine, while critically appraising the distance between current evidence and clinical implementation. The present review is intended as a conceptual and evidence-synthesis framework rather than a clinical practice guideline. The aim was to map the trajectory from current clinical evidence toward future precision strategies, highlighting both the promise and the gaps that must be addressed before these approaches can enter routine practice. Fig. 3 aligns stage-specific microbiota dynamics with a staged escalation of interventions, from established probiotics to investigational precision therapies, thereby grounding the abstract concept of 'precision restoration' in concrete ecological and clinical context.

Clinically, microbiota-conscious management, including antibiotic stewardship, strain-specific probiotics, early dietary rehabilitation and risk-based follow-up, offers a tangible pathway to improve short-term outcomes and prevent long-term sequelae such as PI-IBS, malnutrition and immune dysregulation. Realizing this vision requires standardized multi-omics cohorts, head-to-head randomized trials of next-generation probiotics, FMT and phage cocktails, and the development of clinically validated point-of-care diagnostics. Until such evidence is available, clinicians are encouraged to adopt microbiota-conscious stewardship, minimizing unnecessary antibiotics, selecting strain-specific probiotics where supported and reintroducing diverse fibers early, while recognizing that most precision strategies remain investigational.

Limitations include notable inter-study heterogeneity and the preclinical status of most precision therapies. Future priorities are: i) Standardized multi-omics cohort studies to identify universal vs. context-specific recovery biomarkers; ii) head-to-head RCTs of FMT, next-generation probiotics and phage therapy in non-CDI acute diarrhea; iii) AI-powered predictive models integrating microbiota, host and pathogen data for personalized intervention selection; and iv) implementation science research to translate biomarkers and stratified therapies into routine clinical workflows. By shifting from pathogen eradication to ecosystem rehabilitation, microbiota-directed strategies can transform acute diarrhea from a transient infectious episode into an opportunity for long-term gut health optimization.

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Authors' contributions

CY conceived the idea, developed the study protocol and coordinated the project from start to submission. JT designed the research strategy. WQ contributed to writing the discussion section. QH reviewed and edited the final manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Availability of data and materials

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Competing interests

The authors declare no competing interests.

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