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REVIEW

Gut Microecological Prescription: A Novel Approach to Regulating Intestinal Micro-Ecological Balance

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Abstract: The intestinal microecology is comprises intestinal microorganisms and other components constituting the entire ecosystem, presenting characteristics of stability and dynamic balance. Current research reveals intestinal microecological imbalances are related to various diseases. However, fundamental research and clinical applications have not been effectively integrated. Considering the importance and complexity of regulating the intestinal microecological balance, this study provides an overview of the high-risk factors affecting intestinal microecology and detection methods. Moreover, it proposes the definition of intestinal microecological imbalance and the definition, formulation, and outcomes of gut microecological prescription to facilitate its application in clinical practice, thus promoting clinical research on intestinal microecology and improving the quality of life of the population.

Keywords: intestinal microecology, risk, gut microecological prescription, definition, faecal microbiota transplantation

Introduction

Human gut microorganisms and their environment constitute the intestinal microecology, which includes various bacteria, fungi, archaea, viruses, and other intestinal microorganisms, host mucosa, nutrients, and metabolites. The gut microbiota occupies an important position in intestinal microecology, which is the largest and most complex ecosystem in the human body. The relationship between intestinal microecology and human health has been a popular research topic throughout history. Hippocrates, the founder of Western medicine, once proposed, "All diseases begin in the gut".[1] The characteristics of intestinal microecology include stability that gut microbiota oscillates around a stable ecological state without interference, resilience, and symbiosis with the host,[2] of which stability is the most important. Intestinal microecological balance refers to the state of dynamic equilibrium between intestinal microecology (including gut microbiota, nutrients, and metabolites) and the host mucosal barrier. Intestinal microecological imbalance has been associated with various diseases, including colorectal tumors,[3] diabetes,[4–6] respiratory diseases,[7] inflammatory bowel disease (IBD),[7] neurological diseases,[8] renal diseases,[9] and liver diseases.[10] As the intestinal microecological system is complex and constantly changing, regulating the intestinal microecological balance is a challenge we are striving to solve. In 300 A.D., Ge Hong proposed a prescription to use 'fermented faeces' to treat terminal patients, which is the earliest record of using gut microecological prescription (GMP) to restore intestinal balance.[11] Probiotics have also been used to treat various diseases.[12] With the increase in cases of intestinal microecological imbalances, systematisation and regulation of intestinal microecological balance have become the focus of our research. As the number of cases of intestinal microecological imbalance increases, the systematic and scientific identification and evaluation of intestinal microecological imbalance and the adoption of a rational approach to correct intestinal microecological imbalance has become an urgent challenge, and the use of gut microecological prescription (GMP) is an important method. This study describes the development and application of GMP considering previous research and current investigations.

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Methodology

This review aggregates and synthesises primary data generated and presented by various academic researchers investigating intestinal microecology, including the definitions, testing methods, processes, and interventions. The following search terms were employed in Google Scholar to identify pertinent studies for this analysis: the definition of dysbiosis, intestinal microbes, risk factors of intestinal microbes (genes, age, diet, region, pregnancy, delivery, feeding, stress, xenobiotics or drugs, infections, and diseases), small intestinal bacterial overgrowth (SIBO), assessment methods (intestinal gas testing, intestinal flora testing, intestinal barrier function assessment, and intestinal motility testing), gut microbes, and interventions (dietary prescription, antibiotics, probiotics/prebiotics/synbiotics/postbiotics, exercise prescription, faecal microbiota transplantation [FMT], prokinetic agents/digestive enzyme supplements/antidepressants, Traditional Chinese Medicine [TCM], and nutritional preparations). Only those studies that addressed issues related to intestinal microecology, whether beneficial or harmful, were included.

Development of GMP

Gut microbiota specialists should prescribe lifestyle interventions (such as exercise and diet), medications, nutrition, FMT, and other nutritional supplements to patients based on a comprehensive assessment of the intestinal microbiota. This assessment should include evaluating the risk factors and clinical symptoms and conducting intestinal microbiota function tests specific to the individual's condition to restore the intestinal microecological balance.

The development of a GMP is divided into five parts: identification of risk factors, clinical presentation, assessment methods, diagnostic criteria, diagnostic ideas, and intervention methods.

Identification of Risk Factors

The first step in assessing intestinal microecological imbalance is identifying individuals who are at a high risk. Several factors influence intestinal microecological imbalance, as listed in Figure 1.

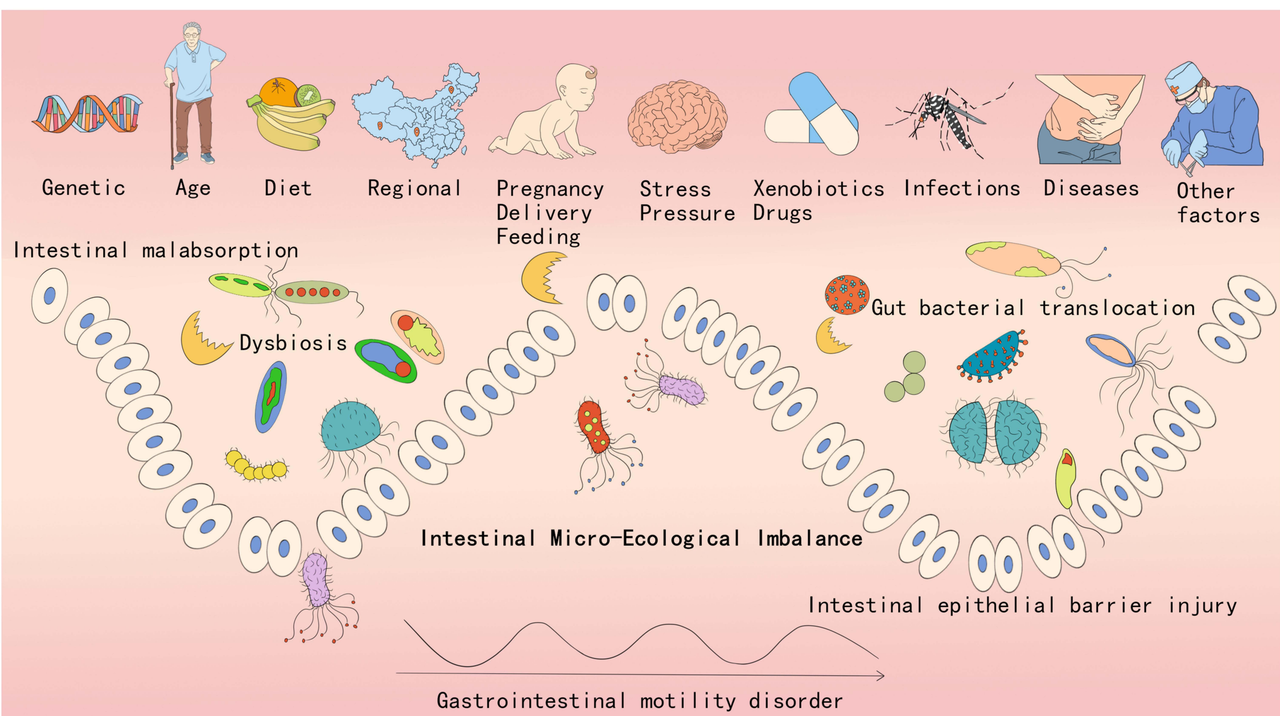

Figure 1 Factors affecting intestinal microecology and classification of intestinal micro-ecological imbalances.

(1) Genetic: Although family members may share similar gut microbiota, each individual's microbiota varies within specific bacterial lineages, with comparable levels of covariation between identical and fraternal adult twins. Nevertheless, a large amount of shared microbial genes exist among family members, including a broad, recognisable "core microbiome" at the gene level rather than at the level of the genealogy of the organisms.[13] The Christensen family of bacteria is significantly influenced by genetic factors and is primarily associated with weight gain.[14] This finding suggests that genetic factors selectively colonise certain flora, which play an important role in the intestinal microecological imbalance. Therefore, family history is a high-risk factor.

(2) Age: The gut microbiota varies with age. Generally, microbial diversity increases from childhood to adulthood and decreases with age (>70 years). Between the ages of 0 and 3 years, the microbiota in children is dominated by the mucinophilic *Ackermannia, Bacteroidetes*, and *Veillonella*.[15] After the age of 3 years, the gut microbiota of children becomes comparable to that of adults, with three major microbial phyla, Firmicutes, Bacteroidetes, and Actinomycetes, becoming predominant.[16] Changes in diet and the immune system also occur with advancing age. Older adults typically reveal a decrease in beneficial bacteria, such as *Bifidobacteria*, and an increase in harmful bacteria, such as *Clostridioides difficile* and *Proteobacterium*.[17] Therefore, ages 0–3 years and >70 years are considered high-risk factors.

(3) Diet: Diet shapes the intestinal microecology and is a major factor that alters the diversity of the intestinal microbiome in both the short and long term. The typical "Western diet" is associated with chronic low-grade inflammation, metabolic disease, and obesity. Diets rich in saturated fats can alter the gut microbiota by increasing lipopolysaccharide (LPS) and trimethylamine-N-oxide levels and decreasing short-chain fatty acids (SCFAs).[18] Thus, the consumption of high-fat, high-glycaemic, and low-fibre foods and excessive food additives and reduced intake of polyphenols, fermented foods, and probiotics are considered high-risk factors.

(4) Region: Studies have reported that differences in adult faecal microbiomes are related to geographical and cultural traditions. An analysis of populations in Venezuela, Malawi, and the United States revealed that the intestinal microbiome of populations in the United States differed significantly from that of the others.[16] A British study of South Asian immigrants revealed that second-generation immigrants had a prevalence rate as high as that of indigenous Whites and Asian Jews, which was comparable to that of European or North American Jews in Israel, suggesting the role of environmental factors.[19] Poor hygiene, environmental pollution, inadequate food intake, and unbalanced nutrition are considered high-risk factors.

(5) Pregnancy, delivery, and feeding: Early life may alter the intestinal microbes, and different microbial exposures and colonisations may affect allergies and atopic diseases.[20] Current research suggests that the colonisation and formation of neonatal intestinal microbes may begin during in utero development.[21] The overall profile of a child's gut microbiota may be related to microbial alterations occurring before and during gestation.[22] The type of delivery (vaginal or caesarean section) significantly affects the composition of the gut microbiota.[23] The composition and development of the infant's gut microbiota may be influenced by several prenatal factors, such as the mother's diet, obesity status, smoking status, and use of antibiotics during pregnancy, which are typically cited as the major determinants of initial colonisation. Breast milk stimulates the development of the most balanced microbiome in infants, largely because of its uniquely high oligosaccharide content.[24] Pre-pregnancy and gestational comorbidities, use of antibiotics or other medications during pregnancy, poor lifestyle, smoking or alcohol use during pregnancy, caesarean section, and lack of breastfeeding are considered high-risk factors.

(6) Stress or pressure: Stress has been revealed to affect the intestinal microbes. Moreover, in both animals and humans, stress causes a decrease in *Lactobacillus* and *Bifidobacterium* and an increase in *Clostridioides spp*. and *Escherichia coli* due to an increase in catecholamines.[25] Thus, stress is considered a high-risk factor.

(7) Xenobiotics or drugs: Xenobiotics (exogenous substances) are synthetic chemicals, including drugs, pesticides, natural food ingredients, food additives, and other contaminants, that can inhibit or promote bacterial growth, alter bacterial metabolism, and affect the enteroviralome and virulence of enteric bacteria, which in turn can metabolise and bioaccumulate xenobiotics, thereby altering their activity or toxicity.[26] Intestinal microbes are the first to interact with orally administered drugs. The intestine is the second largest metabolic organ in the body after the

liver. Drugs can alter the intestinal microenvironment, microbial metabolism or growth, and the composition and function of the microbial community.[27] Hence, antibiotics, pesticides, food additives, and other pollutants are considered high-risk factors.

(8) Infections: Infections by intestinal pathogens are among the most direct causes of acute imbalances in intestinal microecology. Common pathogens include *Clostridioides difficile*, enterohaemorrhagic *Escherichia coli, Salmonella spp*., and *Klebsiella pneumoniae*. Foodborne pathogens are extremely lethal and often break through the defence barrier of the host's gut microbiota.[28] Opportunistic enteric pathogens may migrate to other infection sites owing to decreased body resistance or immune function. A direct example is spontaneous peritonitis in patients with cirrhosis. Both foodborne pathogenic infections and opportunistic pathogens are considered high-risk factors for intestinal microecological imbalances.

(9) Diseases: Several diseases can cause intestinal microecological imbalances and vice versa. Conditions such as IBD, surgical infections, or tumours can directly impair the intestinal barrier or affect intestinal motility. On the other hand, psychosomatic disorders or endocrine and rheumatological-immunological disorders indirectly influence intestinal microecology through the cerebral-intestinal axis, affecting the localised physicochemical properties, hormone levels, or dietary factors.[29]

(10) Other factors: Other risk factors may include lack of exercise[30] and gastrointestinal surgery.[31] Traditional Roux-en-Y Gastric Bypass (RYGB) was approved to improve the disrupted gut microbiota linked with obesity,[32] There are also other relevant risk factors that this review has not yet addressed, which deserve more investigation in the future.

Clinical Manifestations

Intestinal microecology is characterised by stability, resistance, and resilience.[33] Healthy individuals experience intestinal microecological imbalances that return to normal after short-term fluctuations, and the imbalance arises only when they are unable to maintain stability or restore equilibrium. Intestinal microecological imbalances can be divided into acute, subacute, and chronic, depending on the time of onset. Acute imbalances generally occur within 4 weeks, and the aetiological factors include food, drugs, IBD, irritable bowel syndrome (IBS), infections, and certain surgical disorders. Acute imbalances are generally characterised by fever, nausea, and vomiting, based on gastrointestinal symptoms, and these can result in water and electrolyte imbalance, hypoalimentation, and shock in severe cases. Subacute imbalances typically last for 5–23 weeks, whereas chronic imbalances last for ≥24 weeks. Subacute and chronic imbalance manifestations include diarrhoea, bloating, abdominal pain, abdominal discomfort, allergies, and leaky gut syndrome.[34]

The pathogenesis can be categorised based on decreased gut microbiota diversity, imbalance (decreased beneficial bacteria and increased harmful bacteria), impaired intestinal barrier function (leaky gut syndrome), gut bacterial translocation,[35] gastrointestinal motility disorder, and absorption disorders (Figure 1).

Assessment Methods

The current methods for assessing intestinal microecological imbalances include intestinal gas testing, gut microbiota testing, intestinal barrier function assessment, and intestinal motility testing.

Intestinal Breath Test

The breath test is a safe, simple, and non-invasive method for detecting SIBO. It primarily measures the hydrogen concentration in the breath sample, and methane levels ≥10 parts per million (ppm) indicate methanogenic bacterial overgrowth. According to the 2017 North American expert consensus, an increase of 20 ppm at 90 min and 10 ppm at 2 h can confirm the diagnosis.[36] The traditional test substrates used are glucose and lactulose. Currently, its results are affected by proton pump inhibitors, and it has low sensitivity and specificity. However, it can be used to detect gut microbiota and intestinal motility disorders. Gas-sensing capsule technology has been developed to measure the concentrations of various gases accurately in real time; however, its diagnostic value has not been investigated.[37]

Detection of Gut Microbiota

Owing to the differences in the microbiota of different parts of the intestinal tract, testing different parts of the tract, including small intestinal and faecal testing, is important. Although macrogenetic testing of the small intestine can be performed, it is not possible to determine the normal value limits as there is no standardised index for the normal value of the small intestinal bacterial flora test. The most commonly used intestinal bacterial test is faecal testing, which includes the methods described below.

Direct Smear

Currently, this method is the most widely used and is easy to perform. It mainly uses a microscope to observe gram-stained faecal smears, including the total number of bacteria, proportion of cocci and bacilli, ratio of gram-positive bacteria to gram-negative bacteria, and presence or absence of special infections, including yeast hyphae and *Clostridioides difficile*.

Faecal Bacterial Culture

This method involves inoculating fresh faeces directly onto different culture media, conducting strain identification after incubation, and quantifying the gut microbiota using fixed faeces. However, the bacterial cultures used in clinics are mainly restricted to pathogenic bacteria, and most bacteria cannot be cultivated in ordinary culture media. Moreover, it takes a long time, and the commonly used index is the *Bifidobacteria/Enterobacteriaceae* (B/E) value,[38] where B/E >1 indicates normal composition of gut microbiota, and B/E <1 is considered abnormal. Furthermore, the sensitivity and specificity of this assessment index are poor, and this index provides a relatively approximate assessment. Novel methods, such as culturomics, can be used to identify and isolate most bacteria; however, they are still far from being clinically applicable.

16s Ribosomal RNA Gene Sequencing and Metabolite Testing of Gut Microbiota

Current clinically applicable metagenomic methods of assessing gut microbiota include 16s ribosomal RNA (rRNA), high-throughput sequencing, and other methods. Among these, 16s rRNA has been gradually introduced in clinical settings because of its advantages of measuring more bacterial species and high sensitivity and specificity; however, they still need to be optimised in terms of time efficiency, normal range for healthy individuals, and cost effectiveness. It can detect indicators such as gut microbiota diversity, pathogen species, intestinal barrier, harmful bacteria, beneficial bacteria, colonisation resistance, and antimicrobial resistance. Intestinal metabolite testing can also indirectly reflect overall intestinal microecology.

Assessment of Intestinal Permeability

Research shows that gut microbiota affects intestinal permeability through various mechanisms. For example, the byproducts of probiotics, such as short-chain fatty acids (SCFAs), can strengthen the tight junctions between intestinal epithelial cells, which helps lower intestinal permeability. However, when the microbiome is out of balance, the growth of bad bacteria can make intestinal inflammation worse, which can damage the intestinal barrier and lead to leaky gut syndrome.[39] Therefore, testing for intestinal permeability is key to understanding gut microbiome imbalance.

Lactulose/Mannitol Test

This is a simple, non-invasive test to assess intestinal permeability. In this test, the patient drinks a solution containing lactulose and mannitol, and urine samples are collected over a 6 h period. Lactulose and mannitol levels are measured to determine the presence and extent of intestinal leakage. The test investigates the lactulose concentration, mannitol concentration, total urine volume, and mannitol/lactulose ratio. Values <0.03% are considered normal, and elevated ratios indicate excessive intestinal permeability. Different periods, geographic locations, diets, renal injury, and allergies can affect the results. Nevertheless, this test remains a cost-effective screening test for intestinal permeability.[40] Different sugar solutions and collection times can be used to measure the intestinal permeability at different sites. Currently, 'polysaccharide tests', involving sucrose, lactulose, sucralose, erythritol, and rhamnose, can be used to assess the permeability of the human gastroduodenum, small intestine, and colon.[41] Moreover, the urinary fraction of saccharide excretion can be measured following oral administration of a molecular probe.[42] As it is not absorbed, it serves as an indirect measure of intestinal permeability.

Endoscopy

The leakage of fluorescein after intravenous injection was measured using a confocal microscope equipped with a 488 nm laser. The parameters observed included the percentage of gap enhancement between the epithelial cells, leakage of fluorescein into the intestinal lumen, and shedding of cells.[43] However, owing to its invasiveness and high cost, it is not available for wide-scale application in clinical practice. In contrast, the endoscopic mucosal impedance test measures the electrical resistance of the mucosal tissue directly through an endoscope, thus determining the permeability of the intestinal mucosa.[44]

Serum Markers

The search for suitable serum markers has become an important research topic owing to the complexity and cost-effectiveness of other assays. Currently, the two types of measured markers include molecular markers that enter the bloodstream from the intestinal lumen owing to damage to the intestinal barrier, such as endotoxins (LPS), and endotoxin-binding proteins (LPS-binding protein).[45] The first step is to screen for increased levels of proteins in the intestinal barrier, such as intestinal fatty acid-binding proteins[46] or tight junction molecules (zonulin). Currently, zonulin is the most widely used protein for determining intestinal barrier permeability. Zonulin proteins are used to treat celiac disease, Type 1 diabetes mellitus, IBD, obesity, and others diseases.[47]

Gastrointestinal Motility Test

The relationship between IMEI and gastrointestinal motility is getting increasing attention. Research shows that gut microbiota is really important in digestion and nutrient absorption, but also affects how the gut moves through its metabolic products and signaling. IMEI can cause a bunch of gastrointestinal diseases, including constipation, diarrhea, and irritable bowel syndrome (IBS), that are closely linked to motility issues.One study found that changes in the gut microbiome can impact how the intestines move and sense things, leading to functional dyspepsia and intestinal motility disorders.[48] Furthermore, short-chain fatty acids (SCFAs) made by gut microbes are seen as key players in controlling how the intestines move, since SCFAs help the intestinal smooth muscle contract and boost overall gut movement.[49] The gastrointestinal motility test mainly examines the motility of the stomach, intestine, and anus; oesophageal motility tests are not included here. The different test methods are described below.

Gastric Motility Test

Gastric scintigraphy is the gold standard method for examining gastric emptying rates. This method generally involves the ingestion of a test radioisotope-labelled meal, typically 99 mTc. At 0, 1, 2, and 4 h after ingestion, photographs are captured in the anterior and posterior positions using a gamma camera to visualise the distribution of the labelled food within the stomach. Normal rate of gastric emptying is characterised by <90% gastric retention at 1 h, <60% retention at 2 h, and <10% retention at 4 h. However, if the rate of gastric retention is >10% at 4 h, delayed solid emptying is diagnosed.[50,51] Other methods utilised include gastrointestinal manometry techniques,[36] C13 breath test,[52] wireless motion capsule,[53] and electrogastrography.[50]

Gastric Tolerance Test

Gastric tolerance tests include electron-constant pressure testing,[54] ultrasonography, magnetic resonance imaging, single-photon emission computed tomography,[55] and liquid nutrient-meal testing.[56] The electron constant pressure test is an invasive test with several drawbacks that limit its use in clinical settings. The liquid nutritional meal test is a relatively simple and non-invasive measure of gastric tolerance; however, its fit is relatively demanding. Currently, imaging tests, such as ultrasonography, are mainly used for scientific research but not used on a wide clinical scale yet.

Bowel Mobility Test

Currently, bowel mobility tests are performed using gastric sinus duodenal manometry,[57] flash shrinkage imaging,[51] wireless motion capsule,[53] hydrogen breath test,[36] and colonic transport test. The colon transport test is widely used and is mainly based on the use of impermeable radiographic markers for patients to swallow; the diagnostic criterion is the inability to expel 80% of the markers within 72 h. However, the test is easily affected by medication, food, and other factors and can be repeated if necessary.[58] Wireless motion capsules are more promising because they react to colonic transport and collect information on various parameters, including gastric, small intestinal, and colonic transport (function), intraluminal pressure (motility), and pH (metabolites of bacterial fermentation in the colon).[59,60]

Rectal/Anal Function Test

The main measurements include the function of the rectal and anal sphincters and the pelvic floor musculature. The test methods included anal ultrasonography, anal manometry, rectal function tests, balloon evacuation tests, and defecography test.[61] The defecography test simulates the structure and function of the pelvic floor during defecation.[62]

Absorption and Secretion Function Test

This test mainly focuses on the absorption and secretion functions of the pancreas, gallbladder, and intestines, which are components of the normal intestinal microecological environment. The pancreatic exocrine function tests include both direct and indirect tests that are sensitive but invasive, and their clinical application is limited. Indirect tests include the faecal elastase-1 test, C13-MTG-BT breath test,[63] and others. Trypticin-stimulated magnetic resonance cholangiopancreatic duct imaging involves a semi-quantitative test of pancreatic exocrine function.[64] Assessing haematological electrolytes, liver and renal function, blood counts, vitamins, folic acid, and iron can assist in diagnosing small intestinal malabsorption dysfunction. The faecal test, a 72-h faecal assessment of fat excretion, is the most sensitive for investigating fat malabsorption syndrome.[65]

Diagnostic Criteria

Currently, there are no clear diagnostic criteria for intestinal microecological imbalance. According to the definition of diarrhoea and the intestinal microbiota recovery rhythm after using antibiotics,[66–68] acute intestinal microecological imbalance lasts for ≤4 weeks, subacute intestinal microecological imbalance for 5–23 weeks, and chronic intestinal microecological imbalance for ≥24 weeks. The diagnostic criteria are mainly based on risk factors, gastrointestinal symptoms (diarrhoea, abdominal distension, pain, discomfort, Leaky Gut Syndrome), laboratory or examination evidence. So far, there's no objective testing method to diagnose imbalance in gut microbiota, We have just provided a framework for diagnosing gut microbial imbalance. The more positive the risk factors or test results, the more reliable the diagnosis. The difference between this definition and dysbiosis is that the intestinal microecological imbalance emphasises an imbalance of the overall intestinal ecosystem rather than a purely microbial imbalance.

Diagnostic Approach

Given the complexity of intestinal microecology, intestinal microecological imbalance diagnosis and GMP should follow the structure depicted in Figure 2.

Methods of Intervention

The main approaches currently used to treat intestinal microecological imbalance include dietary prescriptions, antibiotics, probiotics/prebiotics/synbiotics/postbiotics, exercise prescriptions, FMT, prokinetics/digestive enzyme supplements, herbal medicines (TCM), and nutritional agents (Figure 3).

Dietary Prescription

Dietary prescriptions should be individualised according to patient symptoms and intestinal microecological balance test results. A low-fat, high-fibre diet can positively alter the intestinal microbiota by reducing harmful bacteria, such as *Acanthamoeba*, and increasing the beneficial bacteria, such as *Prevotella* and *Bacteroides*.[69] The Mediterranean diet, which is predominantly plant-based, high in fibre and omega-3 fatty acids, and low in animal proteins and saturated fatty

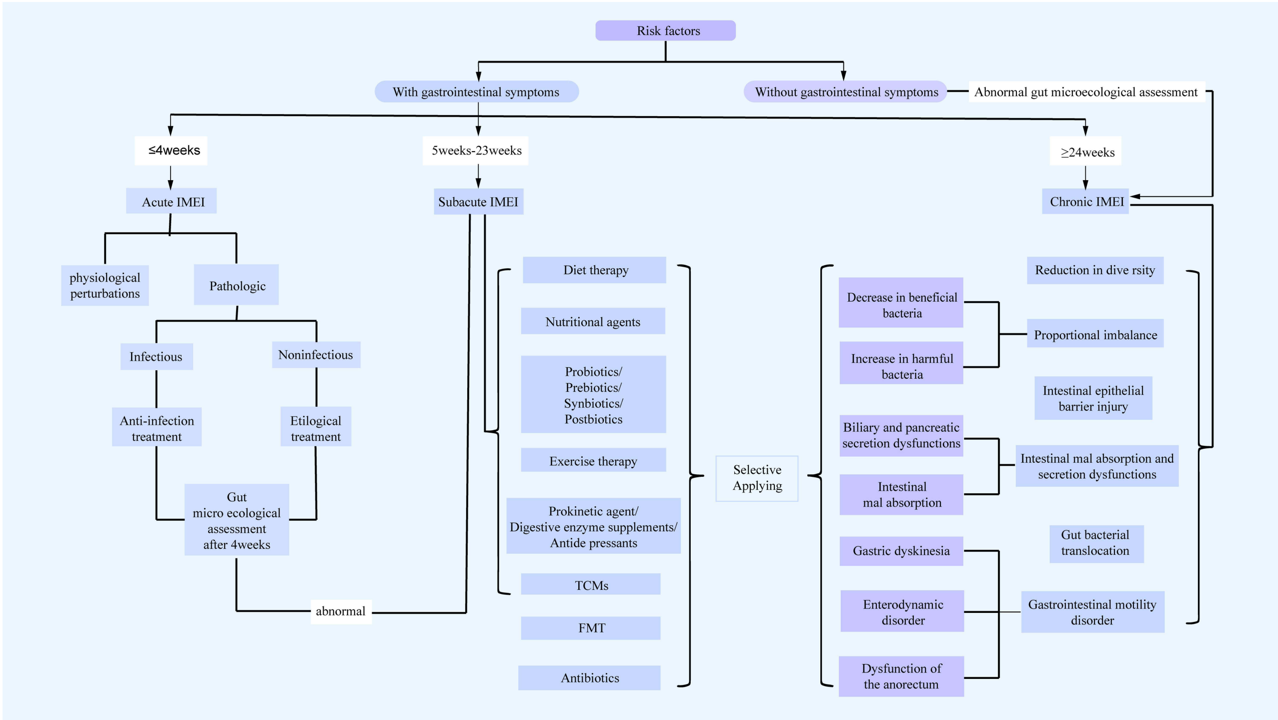

Figure 2 The diagnostic ideas and intervention process of GMP.
Abbreviations: IMEI, intestinal micro-ecological imbalance; FMT, Fecal Microbiota Transplantation; TCMs, Traditional Chinese Medicines.

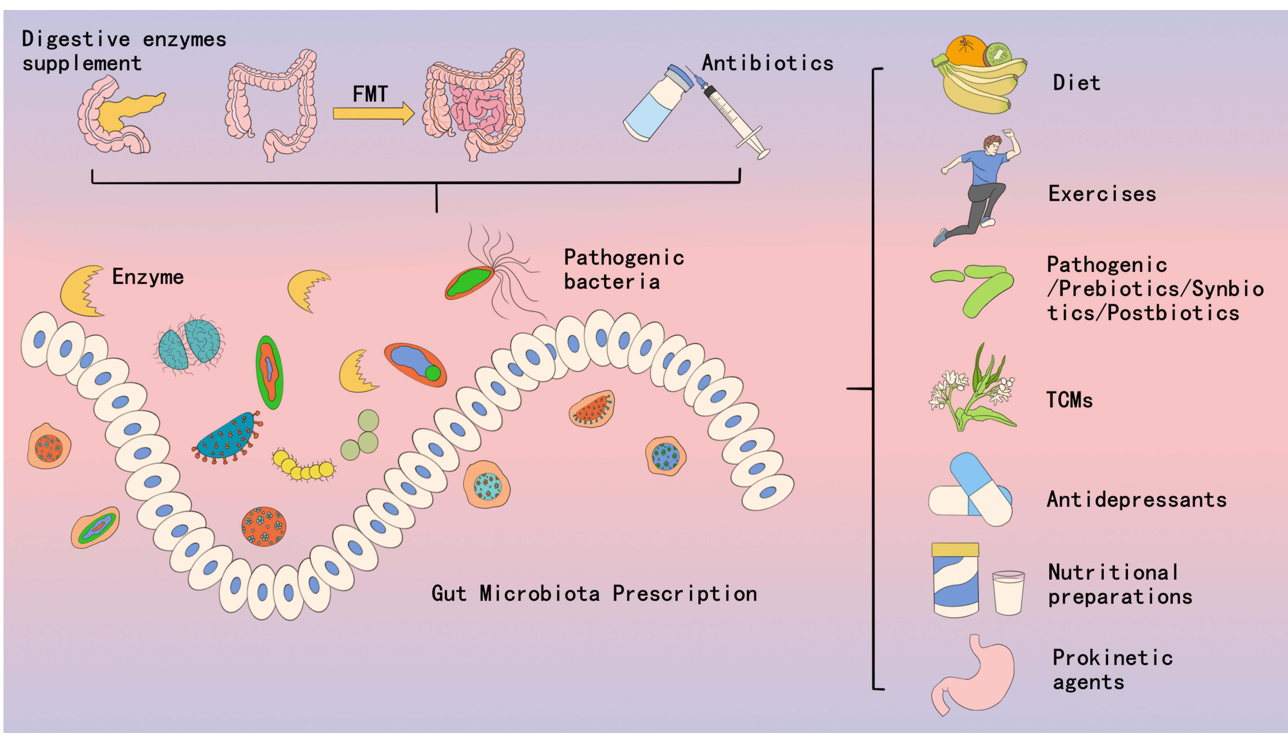

Figure 3 The intervention methods of GMP.
Abbreviations: FMT, Fecal Microbiota Transplantation; TCMs, Traditional Chinese Medicines.

acids, has been reported to increase the diversity of the gut microbiota compared to the Western diet.[70] The Mediterranean diet positively affects health by increasing the levels of SCFAs and anti-inflammatory components, thereby reducing the incidence of chronic diseases.[71,72] FODMAP diet is an acronym for Fermentable Oligosaccharides (fructans and oligogalactans or galacto-oligosaccharides), Disaccharides (lactulose), Monosaccharides (excess fructose), and Polyols (sorbitol, mannitol, xylitol, and maltitol). FODMAPs are common in our daily diets, which can increase intestinal water content,[73] produce large amounts of gas,[74] and produce excess SCFAs.[75] Reduced intake of FODMAP diets can provide some degree of symptomatic relief to patients with IBS.[76,77] Intermittent fasting regimens can directly influence the gut microbiome by amplifying diurnal fluctuations in bacterial abundance and metabolic activity. This process subsequently leads to fluctuations in the levels of microbial constituents (LPS) and SCFAs, which are metabolites that act as signalling molecules for the host's peripheral and central clocks. These metabolites are important for the treatment and prevention of disorders associated with circadian disruption (obesity and metabolic syndrome).[78] Similar dietary regimens include alternate-day fasting, time-restricted fasting, and intermittent energy restriction; all these approaches have a similar effect.[79] The ketogenic diet was initially used to treat refractory childhood epilepsy and is characterised by reduced intake of carbohydrates (5–10% of the total caloric intake), sufficient to increase ketone production. The gut microbiota's response to the ketogenic diet seemed to improve the efficacy of interventions in children with epilepsy.[80] Currently, microbe-targeted diets are gaining attention, and there is a consensus that foods containing probiotics or metabolites modulate the gut microbiota and provide health benefits.[81,82] Although higher-level clinical evidence is lacking, dietary regimens based on intestinal microbial targeting are gradually becoming mainstream.

Antibiotics

Antibiotics are a two-edged sword. They typically eradicate *Bacteroides, Firmicutes*, and *Actinobacteria*, which are responsible for important gut microbiota functions. Antibiotic therapy in adults typically causes an increase in the relative abundance of parthenogenetic anaerobes, such as *Enterobacteriaceae, Enterococcus*, and *Clostridioides*, as well as *Streptococcus*.[68,83–85] Different antibiotics are selected depending on the intestinal microbial pathogens. *Clostridioides difficile* infections (CDI) require discontinuation of antibiotics and treatment with vancomycin.[86] Both ciprofloxacin and azithromycin decrease the diversity of the gut microbiota.[87–89] Ciprofloxacin also decreases the abundance of *Bifidobacteria* and *Rumenococci*.[90] Antibiotics can have both favourable and unfavourable effects on intestinal micro-ecology, and selective antibiotics must be administered based on the outcome of the gut microbiota. The tendency of antibiotics to bioaccumulate in the gastrointestinal tract varies depending on their chemical composition, formulation, and administration route.[91] The use of oral β-lactamase,[92] DAV132,[93] prebiotics,[94,95] gut microbiota transplantation,[96,97] and probiotics[98] can minimise the effects of antibiotics on intestinal microecological imbalances, thereby restoring intestinal microecological balance as quickly as possible. Narrow-spectrum antibiotics can target the removal of certain pathogenic bacteria with less impact on the overall intestinal microbial balance. Future research should focus on the more targeted use of antibiotics and reducing their influence on intestinal microecology.

Probiotics/Prebiotics/Synbiotics/Postbiotics

Probiotics can contribute to the balance of the host's gut microbiota[99] or improve the properties of the commensal microbiota.[100] The most widely used probiotics include *Lactobacillus, Bifidobacterium*, and *Saccharomyces* spp. Some bacteria, such as *Roseburia, Akkermansia muciniphila, Propionibacterium*, and *Faecalibacterium prausnitzii*, reveal promise as probiotics. They have several mechanisms of action, including modulation of immune function, production of organic acids and antimicrobial compounds, interactions with the commensal microbiota, host interactions, improvement of intestinal barrier integrity, and enzyme formation.[101] Prebiotics are defined as "substrates that are selectively used by host microorganisms for beneficial health effects". Prebiotics cannot be simply considered as mere growth stimulators for *Lactobacillus* and *Bifidobacterium*; they can have positive effects on the physiological and metabolic systems throughout the body.[102] The elucidated actions of prebiotics include defence against colonisation by pathogens,[103] immunomodulation,[104] increased mineral absorption,[105] improved intestinal function,[106] regulation of metabolism,[107] and effects on appetite.[108] Synbiotics are a combination of prebiotics and probiotics. Postbiotics are preparations of inanimate microorganisms or other components that are beneficial to the health of the host and are not purified microbial metabolites or vaccines.[109] Postbiotics can enhance the function of the intestinal epithelial barrier,[110] regulate the immune response[111] and systemic metabolic capacity,[112] and transmit neural signals.[113] The use of probiotics or prebiotics for intestinal microecological imbalances is currently recognised; however, the specific types and dosages for different imbalances remain to be investigated.

Exercise Prescription

Recent studies have reported that exercise can alter the abundance and function of the intestinal bacteria.[114] An early study on gut microbiota revealed that professional rugby players have a significantly higher abundance and diversity of gut microbiota and metabolic function than the general population of the same age and body mass index.[115] Another study on people with Type 2 diabetes reported that exercise intensity plays a role in shaping the gut microbiota. Eight weeks of aerobic training resulted in a higher abundance of *Bifidobacterium, Akkermansia muciniphila*, butyric acid-producing *Lachnospira eligens, Enterococcus*, and *Clostridioides* than high-intensity interval training.[116] The ability of exercise to increase the intestinal microbiome diversity (Shannon index) suggests that regular exercise may modulate the microbial composition and ameliorate intestinal microecological imbalances.[117] Coordinated interventions with multiple types of exercise have a significant effect on the diversity of the gut microbiota.[118] Thus, multiple forms of exercise interventions possibly increase diversity than a single type of exercise. Exercise increases the number of beneficial bacteria and decreases the number of harmful bacteria in adults.[119] The relative abundances of *Roseburia hominis* and *Akkermansia muciniphila* were significantly higher in active adults than in sedentary individuals.[120] Moreover, both exert beneficial effects on host gastrointestinal health, lipid metabolism, and the immune system owing to their production of butyric acid.

FMT

FMT involves the transfer of minimally processed faeces from a healthy donor into the intestinal tract of a recipient to treat diseases associated with intestinal microbiota imbalance. FMT has been successfully used in severe and recurrent CDI with efficacy rates approaching 90%.[121] Owing to its excellent performance in the treatment of CDI, FMT has been used to treat various chronic disorders associated with intestinal microbiota imbalance, including IBD,[122] IBS,[123] metabolic syndrome,[124] and neurologic psychiatric disorders.[125] Although the use of FMT in treating diseases other than CDI is controversial, it remains an important approach for improving intestinal microecological imbalance in the future. The main challenges in applying FMT in other diseases include inconsistent transplantation results, donor characteristics,[126] recipient characteristics,[127] and transplantation specifications.[128] As several chronic diseases are treated over a long period, the use of novel flora transplantation methods, such as capsules, may be important for large-scale clinical applications in the future.[129] However, FMT may be a double-edged sword, as it can remove or colonise certain harmful microorganisms during transplantation.[130,131] Future studies should investigate the long-term efficacy and adverse effects of FMT.

Prokinetic Agents/Digestive Enzyme Supplements/Antidepressants

Gastrointestinal motility is essential for the smooth passage of food through the intestine.[132] In addition to host-specific genetic predispositions to normal peristalsis, diet and the microbiota are important regulators of gastrointestinal motility.[133–135] Dysregulation of these factors leads to impaired peristalsis, causing several disorders, such as IBS with hypoplasia of transmission.[136,137] The most notable intrinsic factors preventing SIBO[138] are gastric and bile acid secretion, peristalsis, normal intestinal defence mechanisms, mucin production, intestinal antimicrobial peptides, and the prevention of retrograde translocation of bacteria from the lower to the upper intestines via the ileocecal valve.[139,140] Extrinsic factors include nutrient intake and diet, bacterial and viral infections, medications (prokinetic drugs) that alter gastrointestinal motility, and agents that modulate gut microbiota, such as prebiotics, probiotics, proton pump inhibitors, H2 blockers, and antibiotics.[141,142] Prokinetic agents can improve dyskinesia in the gastrointestinal tract.[143] Patients with chronic pancreatitis suffer from digestive enzyme deficiency, which leads to an imbalance in the gut microbiota.[144] Pancreatic enzyme replacement therapy can improve digestive symptoms in chronic pancreatitis.[145] Selective serotonin reuptake inhibitors are particularly effective against gram-positive bacteria, such as *Staphylococc*i and *Enterococcus*, as well as against certain harmful bacteria, such as *Citrobacter, Klebsiella pneumoniae, Clostridioides perfringens*, and *Clostridioides difficile*.[146,147]

TCM

TCM formulations are generally processed by the gut microbiota. The interaction between the gut microbiota and TCM formulations mainly occurs through three different pathways. One pathway is where the gut microbiota "digests" the herbal medicines into absorbable active small molecules, which enter the body and induce physiological changes. Second, the TCM formulations regulate and change the composition of the gut microbiota and its secretion, thereby achieving the purpose of regulating the intestinal microecological balance.[148] Third, intestinal microbiota mediates the interactions (synergistic and antagonistic) between various chemicals in TCM formulations.[149] The isoquinoline alkaloid berberine extracted from the Chinese medicine Huanglian has been reported to have specific antimicrobial activity and can improve intestinal imbalance in mice with colon carcinoma, which can result in tumour suppression.[150] Carboxymethylated Poria polysaccharide is modified from the structure of polysaccharides isolated from *Poria cocos* and exhibits specific antimicrobial activity. Recent studies have shown that it can increase the proportion of anabolic, lactic acid-producing, butyric acid-producing, and acetic acid-producing bacteria, thus restoring the diversity of the gut microbiota in intestinal microecological imbalances.[151] *Ephedra sinica* and *Rehmannia glutinosa* modulate intestinal microecological imbalances in patients with obesity.[152] Bacillus Calmette-Guérin has been reported to modulate the species and composition of gut microbiota, increase the levels of beneficial bacteria, and elevate neurotransmitter levels in the brain and colonic faeces, thereby improving insomnia.[153] Thus, herbal medicines play an important role in correcting intestinal microecological imbalances.

Nutritional Preparations

Some nutritional agents can restore intestinal microecological balance. Malnutrition has a significant impact on the gut microbiota of older individuals, with changes occurring primarily in *Bacteroidetes, Firmicutes*, and *Proteobacteria*. Enteral nutritional suspensions (triple-protein formula [TPF] for diabetes management) prevent further decline in nutritional status and facilitate the restoration of the gut microbiota of older adults.[154] For some patients with malnutrition, the use of TPF may improve the intestinal barrier and restore the intestinal microecological balance. Glutamine may also improve the intestinal microecological imbalance in patients with obesity[155] and increase the ratio of *Bacteroidetes* to *Proteobacteria* in animal models of constipation.[156] Furthermore, it prevents bacterial translocation and increases the intestinal permeability.[157] When ingested in large quantities or delivered to the colon, some vitamins may increase microbial diversity by increasing the abundance of presumed commensal bacteria (vitamins A, B2, D, E, and β-carotene), increase or maintain microbial diversity (vitamins A, B2, B3, C, and K) and abundance (vitamin D), increase the production of SCFAs (vitamin C), or increase the abundance of SCFA-producing bacteria (vitamins B2 and E) to modulate the intestinal microbiota beneficially. Other vitamins, such as vitamins A and D, may modulate intestinal immune responses or barrier functions, thus indirectly affecting gastrointestinal health or microbiota.[158] Other nutrient agents that may have a modulatory effect on the intestinal microecological balance are still being discovered, and extensive clinical studies are needed to confirm this.

Potential GMP Suggestions

We have summarised various GMP interventions according to recent systematic reviews (Table 1). Despite the complexity of intestinal microecology and heterogeneity of randomised controlled studies, we can prescribe GMPs based on the currently available evidence that helps to improve intestinal microecological balance, as summarised below. (1) Different dietary approaches can have different effects on intestinal microecological imbalance. Among them, the Mediterranean diet can improve the diversity of gut microbiota in most of the population. (2) Engaging in moderate to high-intensity exercise for 30 to 90 minutes at least three times a week, or for a total of 150 to 270 minutes weekly over at least 8 weeks, can likely change the intestinal microbiota. (3) Probiotics are the most researched and play a role in several diseases; however, the species, dosage, duration, and effects remain to be investigated. (4) TCM formulations play a role in some of the intestinal microecological imbalances. (5) FMT may be an effective solution for intestinal microecological imbalance, particularly in recurrent CDI. However, there is a shortage of high-quality studies on its safety and long-term effectiveness in other conditions. (6) High-quality systematic reviews on the effects of prokinetic agents/digestive enzyme supplements on IMEI are lacking. However, the interaction between antidepressants and intestinal microecology has been recognised. (7) Vitamins and certain nutritional preparations could regulate intestinal microecology; however, high-quality clinical studies are warranted to prove it. (8) Certain narrow-spectrum antibiotics can eliminate bacteria

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Table 1 Summary of Various Intestinal Microecological Interventions in the Literature

Intervention	Publication Year	Specific Intervention Strategies	Type of Article	Author	Number of Studies	Diseases/ Outcome	Quality of Evidence	Intervention Groups	Main Conclusions
Diet	2024	Dietary intervention	Systematic review	Linli Cai[159]	36 meta-analyses	Diabetic nephropathy	Moderate to low	Adult	Probiotics, vitamin D, soy isoflavones, coenzyme Q10, polyphenols, antioxidant vitamins, or salt-restricted diets may improve outcomes in diabetic nephropathy patients.
	2023	Honey, glutamine, and propolis	Systematic review	Reza Amiri Khosroshahi[160]	26 meta-analyses	Cancer therapy-induced oral mucositis	Moderate	Adult	Honey, glutamine, and propolis can significantly reduce the incidence of severe oral mucositis.
	2024	Mediterranean diet	Network meta-analysis	Ioannis Doundoulakis[161]	17 RCTs	Cardiovascular disease	Unknown	Adult	Mediterranean diet may play a protective role against cardiovascular disease and death in primary and secondary prevention.
	2024	Mediterranean diet	Systematic review	Armin Khavandegar[162]	17 observational and 20 interventional studies	Gut microbiota composition	Unknown	Adult	Adherence to the Mediterranean diet improves gut microbiota diversity and composition, leading to significant clinical benefits.
	2024	Low FODMAP diet	Systematic review	Sandra Jent[163]	19 real-world studies	Irritable bowel syndrome	Unknown	Adult	Low FODMAP diet improves outcomes compared to a control diet (efficacy studies) or baseline data (real-world studies).
	2024	Intermittent fasting	Network meta-analysis	Mohamed T Abuelazm[164]	8 RCTs	Metabolic dysfunction-associated steatotic liver disease	Unknown	Adult	Alternate-day fasting improved anthropometric measures, including lean body mass, waist circumference, fat mass, and weight loss.
	2023	Intermittent Fasting	Systematic review	Theodoro Pérez-Gerdel[165]	9 studies (all with longitudinal design)	Gut microbiota	Unknown	Adult	Firmicutes and Bacteroidetes increased, with 16 genera varying due to intermittent fasting, linked to clinical predictors like weight change and metabolic variables, boosting gut microbiota diversity.
	2023	Ketogenic diet	Systematic review	Mahdi Mazandarani[166]	9 clinical trials and cohorts	Gut microbiota, metabolites	Unknown	Neurological patients	A ketogenic diet reduces disease severity and recurrence, alters gut bacteria by increasing Proteobacteria and decreasing Firmicutes, and changes metabolite levels.
Exercise	2024	Exercise	Systematic review	Leizi Min[119]	25 controlled trials	Gut microbiota	Unknown	Adult	Exercise can improve gut microbiota in adults, with a significant increase in the Shannon index; however, responses vary by sex and age, indicating a need for further research.
	2023	Exercise	Systematic review	ML Lavilla-Lerma[167]	13 RCTs	Gut microbiota	Unknown	Adult	Modulating gut microbiota depends on exercise type, intensity, and duration, affecting specific microbial populations more than richness and diversity.
	2023	Exercise	Systematic review	Alexander N Boytar[168]	28 trials (randomised controlled trials, cohort studies and case-control studies)	Gut microbiota	Unknown	Adult	Regular moderate to high-intensity exercise for 30–90 min at least 3 times a week can change gut microbiota in 8 weeks, benefiting both clinical and healthy individuals.

Probiotics/ prebiotics/ synbiotics/ postbiotics	2024	Probiotics supplementation	Systematic review	Zihan Yang[169]	534 RCTs	*Helicobacter pylori* infection	High	Adult	Probiotic supplementation improved eradication rates (risk ratio 1.10) and reduced side effects (risk ratio 0.54) compared to standard therapy.
	2024	Probiotics	Systematic review	Minjuan Han[170]	13 systematic reviews/meta-analyses	Ventilator-associated pneumonia	Low	Adult	Probiotics may be associated with a reduced incidence of ventilator-associated pneumonia.
	2024	Probiotics	Systematic review	Yunxin Zhang[171]	7 systematic reviews/meta-analyses	Functional constipation	Low	Children	Probiotics may be beneficial in improving functional constipation in children.
	2023	Probiotics	Systematic review	Reza Amiri Khosroshahi[172]	13 systematic reviews/meta-analyses	Chemotherapy- and radiotherapy-related diarrhoea	Low	Adult	Probiotics use can reduce the incidence of diarrhoea induced by chemotherapy and radiotherapy in cancer patients.
	2023	Probiotics	Systematic review	Qingrui Yang[173]	20 systematic reviews	Antibiotic-associated diarrhoea	Moderate to low	Children	Probiotics prevent and treat antibiotic-associated diarrhoea in children, possibly showing a dose-response effect.
	2023	Probiotics/ prebiotics/and synbiotics	Systematic review	Pooneh Angoorani[174]	8 systematic reviews/meta-analyses	Polycystic ovarian syndrome	High to low	Adult	Probiotic supplementation may benefit some polycystic ovarian syndrome parameters like BMI, glucose, and lipids, but synbiotics are less effective.
	2022	Probiotics	Systematic review	Haissan Iftikhar[175]	3 systematic reviews	Allergic rhinitis	Moderate to low	Adult	Probiotics are useful in treating allergic rhinitis.
	2022	Prebiotics/ probiotics/ synbiotics/FMT	Systematic review	Nathalie Michels[176]	57 meta-analyses	Metabolic disorders	Moderate to low	Adult	Meta-evidence was the highest for probiotics and lowest for FMT.
	2021	Probiotics	Systematic review	E Earp[177]	3 systematic reviews	Atopic eczema	Low	Pregnancy of infancy	Probiotics during pregnancy or infancy were analyzed, but low-quality evidence indicates limited benefits of combined probiotics.
	2019	Probiotics	Systematic review	Mikołaj Kamiński[178]	8 systematic reviews/meta-analyses	Chronic idiopathic constipation	Low	Adult	Probiotics are recommended, but their effectiveness for adult constipation is unclear.
	2020	Probiotics	Systematic review	Tao Xiong[179]	98 meta-analyses of RCTs	Necrotising enterocolitis	Very low to moderate	Preterm Infants	Decreased risk of necrotising enterocolitis is observed with probiotics.
	2019	Probiotics	Systematic review	Rachel Perry[180]	16 systematic reviews	Infantile colic	Low	Infant	A particular focus on probiotics in non-breastfed infants is pertinent.
	2019	Probiotics	Systematic review	Ibrahim Nadeem[181]	7 systematic reviews	Depression	Unknown	Adult	Probiotics seem to produce a significant therapeutic effect in individuals with pre-existing depressive symptoms.
	2018	Probiotics	Systematic review	Rebecca A Abbott[182]	55 RCTs	Recurrent abdominal pain	Unknown	Children	He evidence for treatment decisions is poor; probiotics, cognitive behavioural therapy, and hypnotherapy may aid in managing children's recurrent abdominal pain.
	2016	Probiotics	Systematic review	Jinpei Dong[183]	36 systematic reviews/meta-analyses	Inflammatory bowel disease and pouchitis	Moderate to low	Adult	Probiotics may help ulcerative colitis but not Crohn disease remission; VSL#3 may aid pouchitis.
	2016	Probiotics	Systematic review	YA McKenzie[184]	9 systematic reviews and 35 RCTs	Irritable bowel syndrome	Unknown	Adult	Symptom outcomes for dose-specific probiotics varied, making specific recommendations for irritable bowel syndrome management in adults impossible now.
	2024	Probiotics/ prebiotics	Systematic review	Md. Nannur Rahman[185]	29 RCTs	Colonisation resistance in the gut	Moderate	Human and animal	Probiotics and prebiotics may reduce pathogens by modulating gut diversity, but more clinical data on specific strains is needed to confirm this.

(*Continued*)

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Table 1 (Continued).

Intervention	Publication Year	Specific Intervention Strategies	Type of Article	Author	Number of Studies	Diseases/ Outcome	Quality of Evidence	Intervention Groups	Main Conclusions
TCM	2022	Herbal medicine	Systematic review	Hyejin Jun[186]	18 systematic reviews	Irritable bowel syndrome	Low	Adult	Herbal medicines can be considered as an effective and safe treatment for irritable bowel syndrome.
	2019	Fennel extract	Systematic review	Rachel Perry[180]	16 systematic reviews	Infantile colic	Low	Infant	Fennel extract shows potential in alleviating colic symptoms.
FMT	2024	Chemical drugs/ FMT/Probiotics/ Dietary fibre/ Acupuncture	Network meta-analysis	Shufa Tan[187]	45 RCTs	Chronic functional constipation	Unknown	Adult	FMT shows the best clinical efficacy and stool form scores, along with improved patient quality of life.
	2024	Probiotics/ Prebiotics/ Synbiotics/FMT	Systematic review	Mahmoud Yousef[188]	27 RCTs	COVID-19-induced gut dysbiosis	Unknown	Adult	The review enhances our understanding of biotics' therapeutic potential for COVID-19-related intestinal issues and multi-organ complications.
	2024	FMT	Systematic review	Yan Yang[189]	4 RCTs	Type 2 diabetes mellitus	Unknown	Adult	FMT treatment in Type 2 diabetes reduces postprandial glucose, triglycerides, insulin resistance, cholesterol, ALT, and diastolic blood pressure, particularly with combined therapy, while also reshaping gut microbiota.
	2023	FMT	Systematic review	Azin Pakmehr[190]	11 clinical trials	Cardiometabolic risk	Unknown	Adult	While some articles noted FMT's benefits on metabolic parameters, we found no significant changes.
	2024	FMT	Meta-analysis	Shafquat Zaman[191]	17 observational studies and 2 RCTs	Chronic refractory pouchitis	Low	Adult	Current evidence from low-quality studies suggests a variable clinical response and remission rate.
	2023	FMT	Systematic review and meta-analysis	Serena Porcari[192]	15 clinical trials	rCDI	Unknown	Adult	FMT showed high cure rates for rCDI in inflammatory bowel disease patients, with overall FMT outperforming single FMT, similar to non-inflammatory bowel disease data, supporting FMT's use for rCDI treatment in these patients.
	2023	FMT	Systematic review and meta-analysis	Parnian Jamshidi[193]	7 RCTs	Irritable bowel syndrome	Unknown	Adult	Lower gastrointestinal administration of multiple-donor FMT significantly improves patient complaints over autologous FMT as a placebo.
	2023	FMT	Systematic Review and meta-analysis	Jing Feng[194]	13 RCTs	Ulcerative colitis	Unknown	Adult	FMT shows potential for inducing remission in ulcerative colitis, but achieving and maintaining endoscopic remission is challenging.
	2023	FMT	Systematic review and meta-analysis	Li Zecheng[195]	10 RCTs	Obesity metabolism	Unknown	Adult	FMT benefits obese patients with high blood pressure, glucose issues, and elevated lipids; studying metabolic factors in these patients will be our future focus.
Prokinetic agents/ Digestive enzyme supplements/ Antidepressants	2023	Psychotropic medications	Systematic review and meta-analysis	Amedeo Minichino[196]	19 longitudinal and cross-sectional studies	Gut microbiota	Unknown	Adult	Psychotropic medications alter gut microbiota, which may affect their efficacy and tolerability.

Nutritional preparations	2022	Antioxidants, probiotics, prebiotics, camel milk, and vitamin D	Systematic review	Cecilia N Amadi[197]	21 clinical trails	Autism	Unknown	Children	Dietary supplements like antioxidants, probiotics, prebiotics, vitamin D, and camel milk may reduce inflammation and improve autism symptoms by targeting the cerebral-intestinal axis safely.
	2023	Vitamin B12	Systematic review	Heather M Guetterman[198]	22 studies (3 in vitro, 8 animal, 11 human observational studies)	Gut microbiota	Unknown	Vitro, animal, human	Few prospective observational studies but no RCTs have been conducted to examine the effects of vitamin B-12 on the human gut microbiota.
	2021	Vitamin D	Systematic review	Federica Bellerba[199]	14 interventional and 11 observational studies	Gut microbiota	Unknown	Adult	Vitamin D supplementation changed microbiome composition, notably Firmicutes, Actinobacteria, and Bacteroidetes, correlating with serum vitamin D levels, reducing Veillonellaceae and Oscillospiraceae families.
Antibiotics	2021	Oral fidaxomycin	Systematic review	Adelina Mihaescu[200]	2 RCTs/2 Non-RCTs	CDI	Unknown	Adult	Treatment with oral fidaxomycin is more effective than oral vancomycin for the initial episode of CDI in patients with chronic kidney disease.
	2021	Azithromycin + metronidazole	Systematic review	Charlotte M Verburgt[201]	2 RCTs	Crohn disease	Unknown	Children	In mild-to-moderate Crohn disease, azithromycin + metronidazole (n = 35) showed no significant response difference from metronidazole alone (n = 38) (p = 0.07), but was more effective for remission induction (p = 0.025).

Abbreviations: FODMAP, Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols; TCM, Traditional Chinese Medicine; FMT, Faecal microbiota transplantation; RCTs, Randomised controlled trials; COVID-19, Coronavirus disease 2019; rCDI, Recurrent *Clostridioides difficile* infection; PCDI, pediatric Crohn's disease activity index.

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from certain specific infections, for instance, vancomycin for CDI, and the correction of intestinal microecological imbalance using other antibiotics should be investigated.

Discussion

Although we have proposed the concept of GMP, it is still an evolving concept and its application in the future has certain challenges. These challenges include but are not limited to the issues described here. The first is cost-effectiveness. For instance, although FMT has been used in diseases such as recurrent CDI, it remains relatively expensive owing to the high standards set for qualified donors and faecal disposal. Although its cost-effectiveness compared to drug therapies is not high, other GMP interventions for regulating intestinal microecology are more affordable. It is necessary to strengthen the economic benefits and perform cost analysis for the GMP. Second, the acceptance of patients is a challenge, because currently, except for FMT, which is relatively difficult to accept, other GMP interventions have earlier existed, but they have not formed a systematic intervention system for intestinal microecological imbalance. Third, compared to traditional methods, the advantage of GMP is that the new systematic approach to intestinal microecology can be used for diseases that have not been adequately treated in the past; however, the disadvantage is that it requires more complex intestinal microecology theories and more research to approve it for future applications. Fourth is the individualised application of GMPs. As we continue to progress in our research, doctors can prescribe individualised GMPs, such as selecting antibiotics or other medications that have minimal impact on the intestinal microecology, specific exercise prescriptions to improve intestinal microecological imbalances, and specific foods to enhance the diversity of the intestinal microecology.

The difference between gut microbiota prescriptions and probiotics lies in that Gut Microbiota Prescriptions systematically and specifically intervenes through various methods, including diet, exercise, FMT, probiotics, prebiotics, Traditional Chinese Medicine, medications and other methods. Its intervention methods include not just probiotics, but also provide more personalized and precise treatments.

This paper summarises the causes of intestinal microecological imbalance, defines it, and refines the aetiology and classification of intestinal microecological imbalance, GMPs, and detection and intervention methods for intestinal microecological imbalance. Although similar articles or concepts have existed in the past, we are the first to integrate these concepts systematically and to propose the concept of GMP and a GMP intervention strategy that can be applied clinically. However, owing to the complexity and dynamic balance of the intestinal microecology, the following problems still exist and need resolution:

(1) Clear diagnostic criteria for intestinal microecological imbalance: Although this paper broadly defines the framework of intestinal microecological imbalance, it still needs more evidence to prove it.
(2) Although this paper classifies intestinal microecological imbalance, there may be other imbalance types that have not been included.
(3) Different intestinal microecological imbalance types require different interventions for comprehensive treatment but currently lack systematic, individualised, and comprehensive therapies.
(4) Intestinal microecological imbalance is observed in patients and in healthy individuals, such as healthy individuals with short-term disturbances. GMPs can also be used for short-term interventions in healthy individuals with intestinal microecological imbalance, such as dietary and exercise therapies.
(5) Current studies have shown that the intestinal microecological imbalance may not completely recover after 6 months of antibiotic intervention.[66–68] For subacute intestinal microecological imbalance, regulation of the imbalance may be possible without antibiotics and using FMT; however, whether 6 months of antibiotics will work for chronic intestinal microecological imbalance remains to be elucidated.
(6) We strongly recommend that all drug inserts be labelled for their effects on intestinal microecology for the rational use of GMPs.

Conclusions

In summary, this review provides an effective method for applying current research on gut microbiota to clinical practice, even though there are still many issues to tackle. It reviews the risk factors that contribute to gut microbiota imbalance, framework of definition, classifications, and detection methods of microbiota imbalance. Additionally, building on previous research, it introduces the idea of gut microbiota prescriptions and summarizes the current potential evidence surrounding these prescriptions, which could help patients with gut microbiota imbalance and promote clinical applications.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors report no conflicts of interest in this work.

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