



WJG 20th Anniversary Special Issues (3): Inflammatory bowel disease

Role of the gut microbiota in inflammatory bowel disease pathogenesis: What have we learnt in the past 10 years?

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Author contributions: Hold GL and Mukhopadhyia I designed the outline for the review; Hold GL, Smith M, Grange C, Watt ER and Mukhopadhyia I wrote the review; El-Omar EM, Hold GL and Mukhopadhyia I revised and edited the final version.

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Received: September 28, 2013 Revised: November 19, 2013

Accepted: January 6, 2014

Published online: February 7, 2014

Abstract

Our understanding of the microbial involvement in inflammatory bowel disease (IBD) pathogenesis has increased exponentially over the past decade. The development of newer molecular tools for the global assessment of the gut microbiome and the identification of nucleotide-binding oligomerization domain-containing protein 2 in 2001 and other susceptibility genes for Crohn's disease in particular has led to better understanding of the aetiopathogenesis of IBD. The microbial studies have elaborated the normal composition of the gut microbiome and its perturbations in the setting of IBD. This altered microbiome or "dysbiosis" is a key player in the protracted course of inflammation in IBD. Numerous genome-wide association studies have identified further genes involved in gastrointestinal innate immunity (including polymorphisms in genes involved in autophagy: *ATG16L1* and *IGRM*), which have helped elucidate the relationship of the local innate immunity with the adjacent luminal bacteria. These developments have also spurred the search for specific pathogens which may have a role in the metamorphosis of the gut

microbiome from a symbiotic entity to a putative pathogenic one. Here we review advances in our understanding of microbial involvement in IBD pathogenesis over the past 10 years and offer insight into how this will shape our therapeutic management of the disease in the coming years.

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Key words: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Gut microbiota; Innate immune response; Probiotics; Prebiotics; Faecal transplant

Core tip: In the last decade there have been enormous strides in our understanding of the role of gut microbiota in the aetiopathogenesis of inflammatory bowel disease (IBD). Newer molecular and genetic diagnostic tools have elucidated distinct changes in the gut microbiota in IBD patients and clarified the deficiencies of innate immunity. A link between environmental factors like diet, host immunity and the gut microbiota has been established. This review aims to enumerate these diverse strands of converging research in the last decade to outline the exciting prospects of possible personalized therapeutic interventions for patients with IBD in the coming years.

Hold GL, Smith M, Grange C, Watt ER, El-Omar EM, Mukhopadhyia I. Role of the gut microbiota in inflammatory bowel disease pathogenesis: What have we learnt in the past 10 years? *World J Gastroenterol* 2014; 20(5): 1192-1210 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v20/i5/1192.htm> DOI: <http://dx.doi.org/10.3748/wjg.v20.i5.1192>

INTRODUCTION

Inflammatory bowel disease (IBD) comprises two distinct

conditions, ulcerative colitis (UC) and Crohn's disease (CD) that are characterized by chronic relapsing inflammation of the gut in genetically susceptible individuals exposed to defined environmental risk factors^[1,2]. IBD was historically considered to be a "Western" disease but in the last decade there has been a definite increase in its incidence and prevalence suggesting that it is progressively emerging as a global epidemic^[3]. In the high prevalence regions the incidence of IBD has continued to rise in the past decade^[4,5].

There has been a parallel rise in our understanding of the critical role of the gut microbiota in the aetiopathogenesis of IBD. This is aptly exemplified by entering the key words, "microbiota" or "microflora" and "inflammatory bowel disease" into the PubMed database. On restricting the search to the last 10 years, over 800 articles published on this subject can be retrieved as opposed to 100 articles in the decade preceding it. This radical explosion of interest has been primarily due to the advent of culture-independent techniques like next generation sequencing and metagenomics which has enabled the global assessment of the gut microbiota much more accurately and in a vastly more sophisticated manner^[6,7]. The largest and perhaps the most ambitious initiative that has emerged in the last decade is the NIH sponsored Human Microbiome Project with a total budget of \$115 million to study the changes of the human microbiome in health and disease^[8]. It has recently led to the publication of 5177 microbial taxonomic profiles from a population of 242 healthy adults sampled at 15 or 18 body sites up to three times, with over 3.5 terabases of metagenomic sequence so far, which will serve as a comprehensive framework for future research in this field^[9].

This expansion of knowledge in the last decade has also shifted the search from external environmental triggers to a trigger within the complex luminal microbiome or the so called "in-vironment" that we harvest within ourselves^[10-12]. Prior to these radical developments research had focussed on unearthing a pathogen amidst the vast plethora of microbes in the gut lumen, which could be held responsible for initiating the inflammatory cascade that is typical of IBD^[13]. This endeavour was akin to searching for the veritable "needle in the haystack". The findings in the last decade has turned this whole concept on its head by revealing that the gut microbiome as a whole is altered in IBD, suggesting that perhaps the entire "haystack" is faulty. This concept of an altered gut microbiome or dysbiosis is possibly the most significant development in the field of IBD research in the past decade.

The other major shift in our knowledge of the aetiopathogenesis of inflammatory bowel disease has been from the host perspective. The dogma that CD and UC are typical autoimmune disorders was based on the characteristic histological appearance of these conditions and the response to immune-modulator drugs but the veil has lifted from this deep-embedded misconception^[14,15]. Over the past decade, genome wide association studies and newer genetic technologies have elucidated distinct genet-

ic defects in IBD patients. This has particular relevance with respect to host-microbial interaction at the luminal surface in the gut. A similar analysis on the PubMed database with the search items "genetics" and "inflammatory bowel disease" leads to a staggering yield of more than 5600 publications in the last decade as opposed to 2000 articles in the decade prior. It must be said that the avenue of research in this field was first opened up in 2001 when the first association of the nucleotide-binding oligomerization domain-containing protein 2 (NOD-2) gene mutation and susceptibility to Crohn's disease was documented^[16,17]. This has resulted in a drastic paradigm shift wherein IBD is no longer considered an autoimmune disease but may be an immunodeficient condition instead^[15]. This putative genetic susceptibility leads to a complex interaction between the diverse gut microbiome and the local innate immune system and forms the current basis for the aetiopathogenesis of IBD (Figure 1).

DYSBIOSIS

The normal gut microbiome comprises 100 trillion diverse microbes, mostly bacteria, encompassing over 1100 prevalent species, with at least 160 species in each individual^[18]. An exhaustive analysis of normal global gut bacterial communities suggests the possible existence of distinct enterotypes (*Bacteroides*, *Prevotella* or *Ruminococcus*) which are predominantly driven by dietary intake but independent of age or BMI^[19,20]. Further analysis suggests that the *Bacteroides* enterotype is associated with a "western" protein rich diet as opposed to the *Prevotella* enterotype which was associated with a carbohydrate rich diet^[21]. It remains to be seen whether this western enterotype turns out to be a distinct risk factor for developing IBD.

Dysbiosis or a definitive change of the normal gut microbiome with a breakdown of host-microbial mutualism is probably the defining event in the development of IBD. The shift from predominant "symbiont" microbes to potential harmful "pathobiont" microbes has now been well documented^[22]. Some of these changes in the gut microbiome have been detected in the common subset of IBD patients but some have been clearly delineated either in CD or in UC patients. The most well defined change that has been noted in patients with IBD is the reduced abundance of the phyla *Firmicutes*^[23-25]. Amongst the *Firmicutes*, the reduced presence of *Faecalibacterium prausnitzii* has been well documented in patients with CD as opposed to controls^[23,26-30]. This has been countered in a paediatric cohort of patients with CD where there were increased levels of *Faecalibacterium prausnitzii* suggesting a more dynamic role for this bacterium with a putative protective effect at the point of onset of IBD^[31]. In addition, there was a definite decrease in diversity of *Firmicutes*, with fewer of its constituent species detected in patients with IBD^[23,32,33]. Unlike *Firmicutes*, there have been reports of increased number of bacteria from the phylum *Bacteroidetes* in patients with IBD^[34-36]. Paradoxically, there

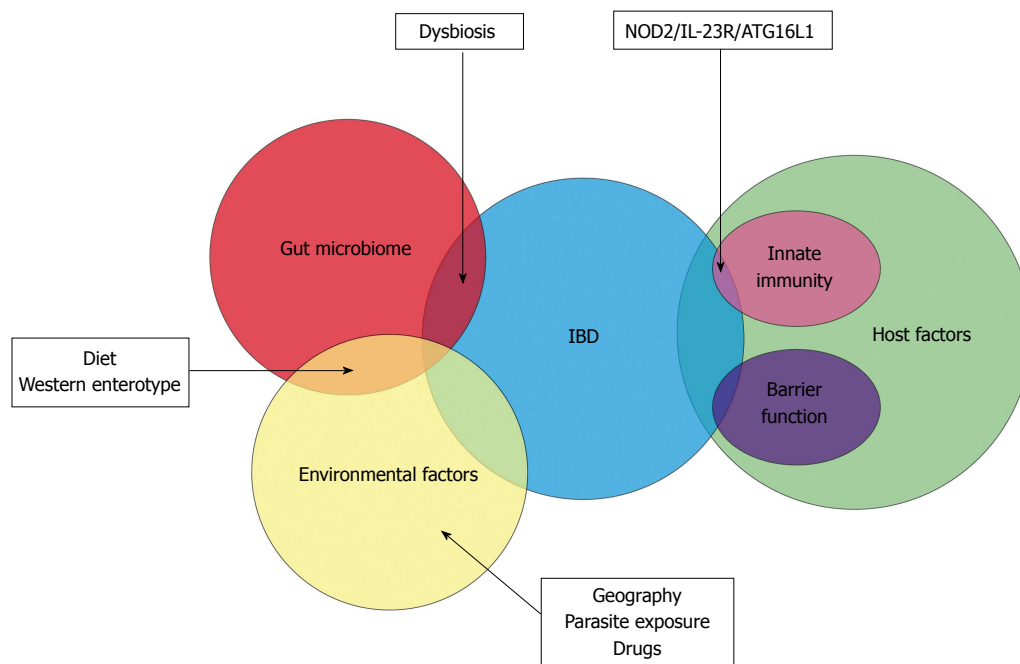


Figure 1 The Venn diagram depicts the overlapping role of the gut microbiome, host and environmental factors in the aetiopathogenesis of inflammatory bowel disease. Dysbiotic changes in the gut microbiome may be influenced by diet and other environmental factors and predispose to inflammatory bowel disease (IBD). A small proportion of IBD patients have demonstrable genetic susceptibility factors. NOD2: Nucleotide-binding oligomerization domain-containing protein 2; ATG16L1: Autophagy related protein 16-like 1; IL-23R: Interleukin 23 receptor.

have been some studies which have shown reduction in these bacterial species as well^[23]. There is a suggestion that there may be spatial reorganization of the *Bacteroides* species in patients with IBD, with *Bacteroides fragilis* being responsible for a greater proportion of the biofilm mass in patients with IBD compared to controls, suggesting increased adherence^[37]. Bacteria belonging to these two phyla make up for 90% of the phylogenetic categories in the normal microbiome and it is interesting to see the disparate ways in which they are altered in IBD.

Most of the known pathogenic bacteria in humans belong to the phylum *Proteobacteria*, which have been increasingly found to have a key role in IBD^[38]. Microbial diversity analysis has shown a shift towards an increase in bacterial species belonging to this phylum, suggesting an aggressor role in the initiation of chronic inflammation in patients with IBD^[39-42]. More specifically, increased concentrations of *Escherichia coli* including pathogenic variants have been documented in ileal CD^[28,45].

This interesting shift within the gut microbiome with a decrease in obligate anaerobes of the phylum *Firmicutes* and an increase in facultative anaerobes of *Proteobacteria* has given rise to a putative “oxygen” hypothesis wherein disruption in anaerobiosis points to a role for oxygen in intestinal dysbiosis^[44]. Similar functional disruptions associated with changes of the gut microbiome in patients with IBD may have more long reaching effects. Metagenomic analysis has revealed that the altered microbiome in IBD has 25% fewer genes and metaproteomic studies have shown a depletion of proteins and functional pathways^[18,45]. The ileal CD patients were found to have alterations in bacterial carbohydrate metabolism, bacterial-host

interactions, as well as human host-secreted enzymes^[45]. Elucidation of the functional impact of the changes seen as a result of dysbiosis will help design remedial measures that will help in the treatment of IBD patients.

The immediate question which follows is how the host responds to dysbiosis. Host genetics factors, specifically those pertaining to the innate immunity arm, is expected to play a role in the aetiopathogenesis of IBD. The “chicken and the egg” question is what comes first. Are the changes in the gut microbiome a result of an aberrant immune response in a genetically susceptible individual or does the abnormality in the gut microbiota lead to an aberrant immune response in such an individual? Twin studies have shown that disease phenotype rather than host genotype plays a greater role in determining changes in gut microbiota^[46]. However, studying the microbiota in subsets of patients with and without NOD2 and autophagy related protein 16-like 1 (ATG16L1) risk alleles showed that the affected genotypes were significantly associated with microbial compositional change but disease phenotype played a role as well^[47]. The confounding factor is that these two alleles are associated with ileal CD and not colonic CD. It makes it difficult to attribute these genetic defects as a cause of dysbiosis but highlights the intricate role of innate immunity in IBD.

INNATE IMMUNITY AND IBD

The gastrointestinal microbiota is a major source of immune stimulation. The colonic epithelium lies in close proximity to a high density of diverse microbes leading to a continuous network of communication between

host cells and microbes. This continual communication is essential for the maintenance of normal homeostasis though contribution to processes including supply of nutrients, xenobiotic metabolism and protection from pathogenic microorganisms, can have deleterious effects and contribute to intestinal inflammation^[48,49]. In patients with IBD this delicate balance is disturbed as a result of host immune defects in microbial recognition or handling/clearance strategies^[50]. Pattern recognition receptors (PRRs) are essential in distinguishing “friend from foe” in this very complex interaction and hold the key to understanding how genetic factors lead to an abnormal immune environment wherein normal commensal organisms can lead to pathological chronic inflammation. Ten years ago toll-like receptors (TLRs) and NOD2 were known to be involved in IBD pathogenesis although our understanding of their location, function and involvement was still very rudimentary. Evidence from IBD genetic studies had demonstrated that several innate immune genes had functionally relevant polymorphisms. Of those studied NOD2 genetic variants confer the greatest risk.

A decade ago the novel association between the recently characterised TLR4 Asp299Gly was described for both CD and UC^[51]. This finding supported previous evidence of PRR genetic influence in IBD susceptibility which had shown that polymorphisms in NOD2 (Arg-702Trp, Gly908Arg, and leu1007fsinsC) and the CD14-159C/T promoter polymorphism were associated with CD^[16,17]. Since then, additional polymorphisms in TLRs have been identified including TLR1 R80T and TLR2 R753G which have been associated with pancolitis in UC patients^[52]. The TLR9-1237T/C promoter polymorphism (TLR9-1237), which is associated with increased nuclear factor kappa B (NF- κ B) binding affinity, has also been associated with CD^[53,54].

The normal colonic epithelium constitutively expresses a variety of PRRs although expression levels are generally low with many receptors located basolaterally thus preventing interaction with luminal antigens^[55]. Nevertheless, intestinal epithelial cells are responsive to TLR ligands and recognise/respond to commensal bacteria secreting antimicrobial proteins and cytokines which facilitate intercellular interactions^[48]. Primary human intestinal epithelial cells express constitutive TLR3 and TLR5 and low levels of TLR2 and TLR4^[56]. TLR2, 4 and 5 are expressed on the cell surface and recognise extracellular microbes. TLR3 detects viral particles and is located intracellularly on early endosomal vesicles. The critical role of TLR4 as a first line of defence against potential bacterial pathogens is now beyond doubt. Impairment of TLR4 function permits bacterial invasion and persistence, and leads to the characteristic inflammation of IBD. The importance of TLR5 in intestinal homeostasis has also been effectively demonstrated using microbiota transfer from knockout mice^[57,58].

Distinct changes in TLR expression have been documented in IBD. TLR4 is found to be up regulated in

both UC and CD, whereas the levels of TLR2 and TLR5 remain unchanged^[56,59]. Altered TLR2 and TLR4 expression has been documented in the intestinal macrophages compared to peripheral monocytes, and a higher percentage of intestinal dendritic cells (DCs) have been shown to express TLR2 and TLR4 in IBD compared to control subjects^[59]. Intestinal macrophage signalling through PRRs has also been shown to be affected by increased expression of suppressor of cytokine signalling 1 and sterile and Armadillo motif-containing protein^[60,61]. Dysregulation of β -catenin and phosphatidylinositol-3-kinase pathways are also involved with alterations in these pathways involved in colitis susceptibility^[62,63]. In IBD patients increased cytokine production is seen by lamina propria DCs and macrophages, consistent with dysregulated tolerance^[64-66]. These changes can explain some of the abnormal response to the resident gut microbiota. However, it is difficult to elucidate whether the change in TLR expression initiates disease or is an epiphenomenon resulting from pro-inflammatory cytokine release. In many cases absence of epithelial cell-derived antimicrobial pathways increases susceptibility to intestinal inflammation, with IBD patients expressing lower levels of α -defensin compared to healthy individuals^[67,68].

Animal models had played a significant role in driving forward our understanding of IBD pathogenesis, especially murine colitis models. TLR4 and MyD88 knockout mice have been shown to demonstrate distinctly less pathology following chemical induction of colitis with dextran-sodium sulphate although bacterial translocation to mesenteric lymph nodes was more commonly detected^[69]. Impairment of TLR4 and TLR5 function has been shown to facilitate bacterial invasion and persistence (TLR4) and impact on intestinal homeostasis; development of metabolic syndrome (TLR5)^[57,58].

Alterations in NOD2 function due to genetic polymorphisms have demonstrated an inability to respond to bacterial muramyl dipeptide (MDP) leading to ineffective downstream signalling of NF- κ B^[70]. NOD2, is expressed on several different cell types including myeloid-derived, epithelial and endothelial cells. As with impairment of TLR function, NOD2 deficiency increases translocation of enteric bacteria to the lamina propria, with alterations in cytokine expression following exposure of peripheral blood mononuclear cells to MDP also reported potentially explaining the alterations in cytokine profiles typically seen in CD^[71,72]. Interestingly, NOD2 has more recently been shown to respond to viruses^[73]. With increasing interest in non-bacterial microbes in IBD pathogenesis, namely viruses and fungi, this may prove to be an increasing area of consideration. A decrease in the protective, anti-inflammatory Th-2 cytokine IL-10 has been documented in NOD2 mutants further adding to our understanding of the functional abnormalities characteristic of CD^[74].

Counter-intuitively, NOD2 can also contribute to down-regulation of inflammatory responses with chronic stimulation of NOD2 acting to tolerise cells against bac-

terial stimulation and ultimately down regulating other PRRs^[75-77]. Hence, in CD patients with dysfunctional NOD2 this restraint is removed and the inflammatory response from other PRRs increases.

NOD2 is also implicated in mechanisms of microbial killing. Autophagy, an important mechanism of microbial cell clearance, is regulated through PRRs^[78]. NOD2 interacts with ATG16L1^[78,79]. Therefore dysregulation of NOD2 impacts not only on microbial recognition but also handling. Genetic variants in ATG16L1 and also a second autophagy gene, immunity-related GTPase family M have been associated with CD^[80,81].

ROLE OF INDIVIDUAL PATHOGENS IN IBD

The rapid development of molecular techniques has also kindled hopes in the search for specific pathogenic agents initiating the inflammatory process of IBD. The pathophysiology of IBD does suggest that either primary or secondary pathogens play an important role in the cycle of inflammation. Many organisms have been proposed but those deemed to have been of the most interest over the last ten years are discussed below (Table 1).

Mycobacterium avium subspecies *paratuberculosis*

Mycobacterial infection has been postulated in the aetiology of Crohn's disease since its first description in 1913. The association stems from the observed similarity between Crohn's disease and the bovine condition Johne's disease, a condition caused by *Mycobacterium avium paratuberculosis* (MAP) infection leading to granulomatous enterocolitis. There have been vast numbers of studies in this area but the role of MAP remains uncertain^[50,82,83].

MAP can be widely isolated from meat, dairy products and water, indicating sources of infection and supporting its role^[82,83]. However, a large study found a lack of epidemiological support for environmental exposure^[84]. Over the last decade research into the prevalence of MAP in IBD patients has been inconclusive. A large number of researchers have successfully shown a higher prevalence of MAP in Crohn's patients compared to controls but, it seems for each of these there has been an equivalent study yielding no association^[85-97].

In support of its role the ability of MAP to invade gut epithelial cells, inducing tissue damage and inflammation, has been shown^[98]. A dominant T-cell response to MAP has also been seen in CD patients and macrophages infected with viable MAP are associated with high production of tumour necrosis factor-alpha (TNF- α), a marker for CD^[95,99,100]. Using mouse models, MAP has been found to induce full-thickness necrotizing colitis after subcutaneous and transmucosal injection^[101].

The discovered association between CD and the autophagy gene *ATG16L1* lends further credence to the theory as it is known that autophagy is essential for inhibition of mycobacterium tuberculosis in infected macrophages^[102,103]. Defective innate immune killing mecha-

nisms in patients with *NOD2* polymorphisms at first also seem to support the idea, and indeed it has been found that monocytes heterozygous for a *NOD2* polymorphism are more permissive to the growth of MAP^[104]. Beyond contemplation, however, evidence for this hypothesis is limited. MAP has been detected most commonly in colonic disease; this is in direct contrast with the prevalence of *NOD2* mutation in ileal disease^[105,106]. In fact a study directly looking at the relationship between *NOD2* and MAP serology found no association^[107]. Combining this with the response of CD to immunosuppressant and anti-TNF therapy, known to cause MAP proliferation and a lack of success of anti-mycobacterial therapy, the role of MAP is clearly still in doubt^[108].

Helicobacter

Helicobacters, as human gastrointestinal pathogens, have assumed great research interest since the discovery by Robin Warren and Barry Marshall of *Helicobacter pylori* as the infectious agent in gastric and duodenal ulceration. Also, similar to MAP, one of the main prompts of research into the role of *Helicobacter* in IBD has been their propensity to cause colitis in animal models like Cotton-top tamarin monkeys (*Saguinus oedipus*). Despite this, there has been a lack of success in the last decade establishing presence of *Helicobacter* in IBD patients. The findings of studies looking into the molecular evidence of *Helicobacter* presence are varied and studies aimed at culturing viable *Helicobacter* from IBD tissue have failed^[109-121]. Interestingly the only seemingly universally accepted action of *Helicobacter* in IBD is the apparent protective effect of *Helicobacter pylori* which has convincingly been found to be negatively correlated with IBD^[113,118-122]. This may conform to the "hygiene hypothesis" for the development of IBD^[123].

The evidence for an association is much stronger with enterohepatic *Helicobacter* species. Non-*pylori Helicobacter* organisms have been shown to induce colitis in a number of rodent models; *Helicobacter hepaticus* and *Helicobacter bilis* (*H. bilis*) most prominently but, also *Helicobacter troglontum*, *Helicobacter rodentium* and *Helicobacter typhlonius* with cytokine patterns which were very similar to that of human IBD^[124-128]. When studying the response to *H. bilis*, Jergens *et al*^[126] showed that there was an IgG mediated response to the microbiota prior to the development of colitis, suggesting the ability of *H. bilis* to induce the hosts immune response to commensal bacteria, leading to the observed immune-mediated intestinal inflammation of IBD. In human subjects, enterohepatic *Helicobacter* species prevalence was significantly higher in colonic biopsy samples from patients with UC group compared to control subjects^[118].

Campylobacter

Campylobacter is a relatively new and important player in IBD. Unlike the other IBD suspects, *Campylobacter* does not have a suitable animal disease model; instead interest stems from the recognition of *Campylobacter jejuni* (*C. je-*

Table 1 Evidence for the role of specific major pathogens in the aetiopathogenesis of inflammatory bowel disease in the last decade *n* (%)

Year	Pathogen	Disease	Sample type	Detection rate			Reference
				CD	UC	Control	
2003	MAP	CD	Tissue	34/37 (92)		9/34 (26)	[85]
2003	MAP	CD and UC	Tissue	0/24 (0)	1/28 (4)	6/19 (32)	[94]
2003	<i>Helicobacter</i>	CD and UC	Tissue	0/9 (0)	0/11 (0)	0/10 (0)	[109]
2004	MAP	CD and UC	Blood	107/283 (37.8)	50/144 (34.7)	135/402 (33.6)	[92]
2004	MAP	CD and UC	Blood	13/28 (46)	4/9 (45)	3/15 (20)	[86]
2004	<i>H. pylori</i>	UC	Tissue	8/42 (19)		7/74 (9.5)	[110]
2004	<i>Helicobacter</i>	CD and UC	Tissue	1/25 (4)	5/33 (15.2)	0/29 (0)	[111]
2004	<i>Helicobacter</i>	CD and UC	Tissue	0/30 (0)	0/26 (0)	0/25 (0)	[112]
2004	EHH	CD and UC	Tissue	3/25 (12)	3/18 (17)	1/23 (4)	[113]
	<i>H. pullorum</i>			2/25 (8)	0/18 (0)	1/23 (4)	
	<i>H. fennelliae</i>			1/25 (4)	3/18 (17)	0/23 (0)	
	<i>H. pylori</i>			8/25 (32)	5/18 (28)	14/23 (61)	
2004	<i>Helicobacter</i>	CD, UC and IC	Tissue	0/11 (0)	1/20 (5)	0/37 (0)	[114]
2004	<i>E. coli</i>	CD and UC	Tissue	11/14 (79)	8/21 (38)	10/24 (42)	[157]
	AIEC			10/14 (71)	10/21 (48)	7/24 (29)	
2004	AIEC	CD	Tissue	7/63 (11.1)		1/16 (6.3)	[155]
2004	<i>E. coli</i>	CD	Tissue	12/15 (80)		1/10 (10)	[159]
2006	<i>E. coli</i>	CD and UC	Tissue	9/12 (75)	7/7 (100)	2/8 (25)	[160]
2007	AIEC	CD and UC	Tissue	8/13 (61.5)	11/19 (57.9)	4/15 (26.7)	[161]
2008	<i>Helicobacter</i>	CD	Faeces	17/29 (59)		1/11 (9)	[115]
	EHH			11/29 (38)		1/11 (9)	
	<i>H. pylori</i>			6/29 (21)		0/11 (0)	
	<i>H. trogontum</i>			4/29 (14)		1/11 (9)	
	<i>H. canis</i>			5/29 (17)		0/11 (0)	
	<i>H. bilis</i>			4/29 (14)		0/11 (0)	
	<i>H. cinaedi</i>			1/29 (3)		0/11 (0)	
2009	AIEC	CD	Tissue	14/27 (51.9)		4/24 (16.7)	[156]
2009	<i>Helicobacter</i>	CD	Tissue	32/73 (43.8)		43/92 (46.7)	[116]
	EHH			18/73 (24.7)		16/92 (17.4)	
	<i>H. pylori</i>			29/73 (39.7)		39/92 (42.4)	
	<i>H. pullorum</i>			8/73 (11)		6/92 (6.5)	
	<i>H. canndensis</i>			10/73 (13.7)		10/92 (10.9)	
2009	<i>Campylobacter</i>	CD	Tissue	27/33 (82)		12/52 (23)	[131]
	<i>C. concisus</i>			17/33 (51)		1/52 (2)	
	<i>C. showae</i>			3/33 (9)		0/52 (0)	
	<i>C. hominis</i>			2/33 (6)		2/52 (4)	
	<i>C. gracilis</i>			2/33 (6)		0/52 (0)	
	<i>C. rectus</i>			1/33 (3)		2/52 (4)	
	<i>C. jejuni</i>			1/33 (3)		3/52 (6)	
	<i>C. ureolyticus</i>			1/33 (3)		2/52 (4)	
2010	<i>Helicobacter</i>	CD	Tissue	32/77 (41.6)		23/102 (22.5)	[117]
	EHH			18/77 (23.4)		12/102 (11.8)	
	<i>H. pylori</i>			14/77 (18.2)		11/102 (10.8)	
	<i>H. bilis</i>			1/77 (1.3)		1/102 (1.0)	
	<i>H. canis</i>			2/77 (2.6)		0/102 (0.0)	
	<i>H. hepaticus</i>			2/77 (2.6)		2/102 (2.0)	
	<i>H. trogontum</i>			5/77 (6.5)		4/102 (3.9)	
2010	<i>Campylobacter</i>	CD	Faeces	39/54 (72)		10/33 (10)	[132]
	<i>C. concisus</i>			35/54 (65)		11/33 (33)	
2010	<i>C. concisus</i>	CD and UC	Saliva	13/13 (100)	5/5 (100)	57/59 (97)	[136]
2011	<i>Helicobacter</i>	UC	Tissue		32/77 (42)	11/59 (19)	[118]
	EHH				30/77 (39)	2/59 (3)	
	<i>H. pylori</i>				2/77 (3)	9/59 (15)	
2011	<i>C. concisus</i>	CD, UC and IC	Tissue	8/12 (66.7)	3/8 (37.5)	11/26 (42.3)	[133]
2011	<i>Campylobacter</i>	UC	Tissue		51/69 (73.9)	15/65 (23.1)	[135]
	<i>C. concisus</i>				23/69 (33.3)	7/65 (10.8)	
	<i>C. ureolyticus</i>				15/69 (21.7)	2/65 (10.8)	
	<i>C. hominis</i>				14/69 (20.3)	5/65 (7.7)	
	<i>C. curvus</i>				3/69 (4.3)	4/65 (6.2)	
	<i>C. showae</i>				4/69 (5.8)	0/65 (0)	
	<i>C. jejuni</i>				2/69 (2.9)	0/65 (0)	
	<i>C. gracilis</i>				1/69 (1.4)	0/65 (0)	

2011	<i>Campylobacter</i>	CD and UC	Tissue	12/15 (80)	11/13 (85)	18/33 (48)	[134]
	<i>C. concisus</i>			10/15 (67)	9/13 (69)	12/33 (36)	
	<i>C. showae</i>			1/15 (7)	2/13 (15)	2/33 (6)	
	<i>C. hominis</i>			1/15 (7)	1/13 (8)	3/33 (9)	
	<i>C. ureolyticus</i>			2/15 (13)	1/13 (8)	2/33 (6)	
	<i>C. gracilis</i>			1/15 (7)	1/13 (8)	0/33 (0)	
	<i>C. rectus</i>			0/15 (0)	1/13 (8)	0/33 (0)	
	<i>C. jejuni</i>			1/15 (7)	0/13 (0)	0/33 (0)	
2012	AIEC	CD and UC	Tissue	1/17 (5.9)	1/10 (10)	0/23 (0)	[167]
2013	<i>Helicobacter</i>	CD and UC	Tissue	4/29 (13.8)	1/13 (7.7)	5/42 (11.9)	[119]
	<i>H. brantae</i>			1/59 (3.4)	0/13 (0)	0/42 (0)	
	<i>H. hepaticus</i>			1/59 (3.4)	0/13 (0)	0/42 (0)	
2013	<i>Campylobacter</i>	CD and UC	Tissue	22/29 (75.9)	9/13 (69)	32/42 (76.2)	[119]
	<i>C. concisus</i>			13/29 (44.8)	4/13 (30.8)	16/42 (38.1)	
	<i>C. curvus</i>			2/29 (6.9)	0/13 (0)	3/42 (7.1)	
	<i>C. gracilis</i>			1/29 (3.4)	0/13 (0)	2/42 (4.8)	
	<i>C. hominis</i>			9/29 (31.0)	5/13 (38.5)	14/42 (33.3)	
	<i>C. rectus</i>			0/29 (0)	0/13 (0)	4/42 (9.5)	
	<i>C. showae</i>			9/29 (31.0)	5/13 (38.5)	9/42 (21.4)	
	<i>C. ureolyticus</i>			0/29 (0)	0/13 (0)	2/42 (4.8)	

CD: Crohn's disease; UC: Ulcerative colitis; IC: Indeterminate colitis; IBD: Inflammatory bowel disease; MAP: *Mycobacterium avium subspecies paratuberculosis*; EHH: Enterohepatic *Helicobacter*; *E. coli*: *Escherichia coli*; AIEC: Adherent-invasive *E. coli*.

jejuni) as the leading cause of gastroenteritis worldwide^[129].

The role of *C. jejuni* in human disease has been long recognised and its prevalence in IBD investigated^[130]. The main advance in the last decade has been the recognition of the importance of non-*jejuni* *Campylobacter* as human pathogens. Zhang *et al.*^[131] found a higher prevalence of *Campylobacter concisus* (*C. concisus*) DNA and IgG levels in newly diagnosed paediatric patients with Crohn's disease, even managing to culture *C. concisus* from a biopsy sample, indicating viability. Another study using faecal samples from newly diagnosed CD patients also found a significant association with *C. concisus*, 35 of 54 CD patients testing positive and only 11 of 33 healthy controls. This study also found that *C. hominis* was present in 13% of Crohn's samples, *Campylobacter ureolyticus* in 9%, *Campylobacter showae* (*C. showae*) in 4%, *Campylobacter gracilis* (*C. gracilis*) in 2% and *C. rectus* in 2%. Interestingly *C. gracilis*, *Campylobacter rectus* and *C. showae* were only detected in patient samples^[132]. Similar results have been obtained in a number of studies in adult patients^[119,133-136]. Mahendran *et al.*^[134] also showed an increased prevalence in UC, a finding supported by Mukhopadhyaya *et al.*^[135] who found *C. concisus* DNA in biopsy samples in 23/69 (33.3%) of UC patients compared to 7/65 (10.8%) of controls. This study also found *C. ureolyticus* to be in higher prevalence in UC patients. The most recent study found that although *Campylobacter* appear to be surprisingly common, with positive PCR in 33/44 IBD patients and 32/42 controls, there was no association with IBD^[119]. A dominant serological antibody response to *C. concisus* has been documented in IBD patients indicating the prevalence of infection^[137,138]. Specifically CD patients have been shown to recognise flagellin B, ATP synthase F α subunit and outer membrane protein 18 of *C. concisus*^[137].

The origins of *Campylobacter* have led to a few researchers looking into the risks of developing IBD after acute gastroenteritis. A long term study published in 2009 documents the risk of developing IBD after acute

infection with *Campylobacter* (*C. jejuni*) or *Salmonella*^[139]. The findings indicated a significant increased risk in the exposed group for subsequently developing IBD, which has been supported by similar studies^[140-142].

The pathogenesis of *C. jejuni* had been fairly well established prior to the last decade. *C. jejuni* has been used to induce colitis in rodent models and previous exposure correlated with disease severity^[143]. The ability of *C. jejuni* to attach and invade the gut epithelium is well documented^[144]. The newest discovery has been that *C. jejuni* can promote translocation of commensal luminal bacteria. This is a natural process thought to be essential for immunological tolerance and mucosal surveillance in the GI tract. Up regulation could affect the normal mucosal response to the intestinal microbiota leading to the chronic immune-mediated intestinal inflammation of IBD^[145].

A number of studies have demonstrated the ability of *C. concisus* to colonise and adhere to intestinal epithelial cells, causing cell damage and microvillus degradation^[146]. Man *et al.*^[146] comprehensively described the method of *C. concisus* attachment and invasion. They showed *C. concisus* to attach to the intracellular junction, disrupting barrier function - increasing permeability by causing a loss of tight junction proteins and decreasing transepithelial electrical resistance and to invade by a process mediated by polar flagellum^[147]. Other non-*jejuni* *Campylobacters* have also been shown to be invasive and induce pro-inflammatory cytokines as well as producing a number of virulence factors such as haemolysins, cytolethal distending toxin and zonula occludens toxin^[129,147-151]. These mechanisms could have an important bearing when one considers a causative role for this group of pathogens in IBD.

Adherent and invasive *Escherichia coli*

A specific pathogenetic group of *Escherichia coli* (*E. coli*), adherent-invasive *E. coli* (AIEC) have recently been extensively implicated in human IBD and are currently one of the most exciting players in the pathogen story. This

group are characterised by their ability to adhere and invade epithelial cells using actin microfilaments and microtubule recruitment. AIEC strains have been shown to be the cause of granulomatous colitis in boxer dogs and to induce granulomas, similar to early epithelioid granulomas, *in vitro*^[152-154]. Similarly to the previously discussed bacteria, they have been documented to induce colitis in infected animals.

There is a growing body of evidence supporting the prevalence of AIEC in human disease. A number of studies initially showed a disproportionate increase in *Enterobacteria* as a whole^[36,47]. When looking at AIEC organisms specifically, Darfeuille-Michaud *et al.*^[154] found them to be more prevalent in ileal Crohn's lesion tissue (36.4%) than controls (6.2%)^[155]. This study also found that AIEC seemed to be rarely found in colonic tissue with 3.7% detected from Crohn's patients and 1.9% from controls, and none in UC specimens. This suggests a specific association of AIEC with ileal Crohn's. The findings of this initial study have been backed up by many researchers obtaining similar results^[28,156-162]. Additionally, antibodies to the *E. coli* membrane protein C and the CD associated bacterial sequence I2 have been shown to not only be more prevalent in CD but also to be associated with more severe disease, with small bowel involvement, faster disease progression and increased need for surgical intervention^[158,163].

The mechanism by which AIEC might induce colitis has been fairly well established towards the end of the decade. AIEC have type one pili and flagella that can bind to host adhesion receptor carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6)^[164,165]. CEACAM6 has been shown to be more highly expressed in ileal CD tissue, to be increased after- γ or TNF- α stimulation and to be upregulated by AIEC itself^[164,165]. AIEC have also been shown to possess long polar fimbriae and so can cross the mucosal barrier to access lymphoid cells^[166]. They can then invade macrophages without inducing cell death, allowing them to replicate and continuously activate immune cells, triggering TNF-alpha release and granuloma formation, which are hallmarks of Crohn's disease. In fact the use of TNF-alpha antibodies has been shown to decrease the number of intramacrophagic bacteria, relating this to the success of anti-TNF therapy and further supporting the role of AIEC^[167].

Other putative bacterial pathogens

In the last decade, there has been renewed focus in studying the role of various other bacterial strains in the aetio-pathogenesis of IBD as well. The role of *Fusobacterium* was studied in mucosal biopsies of patients with IBD and was found to be significant compared to controls in a number of studies prior to this review period. More recently seropositivity to *Fusobacterium varium* (*F. varium*) infection was found to be higher in UC patients as opposed to controls with increased severity of disease in seropositive UC patients^[168]. Further study has revealed the ability of *F. varium* to adhere to and invade colonic

epithelial cells, increasing IL-8 and TNF- α secretion, providing a mechanism whereby *F. varium* infection may induce inflammation similar to that seen in IBD^[169].

A similar association has also been found with *Klebsiella* infection, with Anti-*Klebsiella* antibodies found more commonly in IBD patients than in controls with the bacteria being implicated in disease relapses^[170]. *Klebsiella pneumoniae* has recently been shown to increase the severity of colitis in mouse models, increasing COX-2, IL-1 β , IL-6 and TNF- α expression and reducing tight junction associated proteins^[171]. Colitis has been shown to be induced even in wild type mice highlighting the high pathogenic potential of this bacteria^[172].

The role of *Salmonella* infection has been postulated from numerous studies that have documented the risk of developing IBD after acute *Salmonella* gastroenteritis^[130,140-142]. When searching for a mechanism it has been found that a *Salmonella* virulence factor, the invasion-associated type Darfeuille-Michaud secretion system induces inflammation by activation of the NOD1/NOD2 signalling pathways^[173]. This ties *Salmonella* nicely to the growing body of research into the genetics of IBD, supporting the role of the pathogen.

The potential role of *Yersinia* was proposed at the beginning of the last decade based upon the observed parallel increase in IBD and refrigeration, "the cold chain hypothesis"^[174]. Similarly to *Salmonella* and *Campylobacter* there has been evidence that acute *Y. enterocolitica* infection increases the short and long term risk of developing IBD^[175]. Despite some later successes in isolation *Yersinia* from IBD patients there has yet to be a compelling body of evidence coupling the prevalence of *Yersinia* with established IBD^[176-178].

MODULATION OF THE GUT MICROBIOTA AS A TREATMENT OPTION IN IBD PATIENTS

The past decade has seen rapid and definitive strides in determining distinct changes in the gut microbiota in patients with IBD. The effects seem to be global, involving not only the physical composition of the principal components but also significantly altering their function. The role of individual pathogens in this complex milieu still needs to be elucidated. The proof of concept of "dysbiosis" as an important step towards developing IBD needs to be proven with therapeutic trials attempting to reverse the process.

Role of probiotics and prebiotics

Probiotics are beneficial microorganisms that, when ingested, may influence the gut microbiota composition, metabolic activity and immunomodulation to confer benefit to the host^[179]. They can alter microbial diversity through competitive inhibition of other microbes, increase mucosal barrier function through the production of short chain fatty acids (SCFA) and interact with

intestinal DC to stimulate an anti-inflammatory response^[180-183]. These probiotic strains must be of human origin, be non-pathogenic and have the intrinsic ability to survive the gastrointestinal transit in order to confer maximal benefit^[184]. The most common probiotics used in the treatment of IBD have been *Lactobacillus* sp, *Bifidobacterium* sp, *Saccharomyces bouladrii*, *E. coli* Nissle 1917 and the probiotic combination VSL#3^[185-192]. The strongest indication for the use of probiotics in IBD has been in the treatment of pouchitis in the post-operative setting in UC patients^[193]. *E. coli* Nissle 1917 and VSL#3 have been found to be effective in preventing relapse and inducing remission in this setting^[194-197]. The data is not very robust with respect to the role of probiotics maintaining remission in UC and a recent Cochrane Database System Review has not recommended its use^[198]. The current body of evidence does not show any demonstrable benefit in patients with CD^[199,200].

Prebiotics are non-digestible oligosaccharides that are selectively fermented in the colon into SCFAs and can alter microbial composition and activity and confer benefit to the host^[201]. Examples include inulin, fructooligosaccharide (FOS), galactooligosaccharides and lactulose^[202-207]. Prebiotics can selectively stimulate the growth of certain probiotics such as *Lactobacillus* and *Bifidobacterium*, decrease intraluminal pH and increase the production of SCFA, such as acetate and butyrate, which play an important role in epithelial and DC function^[208,209]. SCFAs have also been found to have an anti-inflammatory effect^[210]. In an open labelled trial FOS use decreased the disease activity index in patients with active CD and resulted in increased faecal *Bifidobacterium*, but this benefit was not demonstrated in a subsequent randomized placebo controlled trial^[206,207]. Another prebiotic inulin showed some promise in a randomized controlled trial in patients with UC and was also found to decrease inflammation in patients with pouchitis^[203,204]. A couple of studies have also found a potential role of germinated barley foodstuff in maintaining remission in patients with active UC^[211,212]. Lastly, some benefit was also accrued with the use of Ispaghula husk in patients with UC^[213]. The important studies and their brief outcomes are summarized in Table 2.

Antibiotics

A couple of recent meta-analyses on antibiotics in IBD found that the use of antibiotics improved clinical outcomes of patients with IBD^[214,215]. There is evidence that metronidazole and ciprofloxacin are useful in the treatment of CD and pouchitis^[216,217]. Support for the use of antibiotics as the primary treatment in UC is less convincing, however, there are some studies which suggest that rifaximin and ciprofloxacin could be useful as an adjunctive treatment for UC^[214]. The mechanisms through which antibiotics are thought to benefit patients with CD are through the inhibition of pathogenic bacteria or through reducing overall bacterial numbers. The main issues with antibiotic treatment include lack of understand-

ing of which bacteria may be involved in the initiation of inflammation, lack of specificity and the potential for antibiotic resistance. There have been several trials in the past studying the specific role of anti-mycobacterials in the treatment of CD and this has been summarized in a European consensus document which has deemed the futility of such treatment^[218].

Faecal transplantation

Faecal transplantation or faecal microbial therapy (FMT) as it is more commonly known is a technique in which stool is taken from a healthy surrogate and inserted into an unhealthy person, with curative intent^[219]. The origins of faecal transplantation as a method of treating enteric pathology can be traced back for more than two millennia, when it was used as a traditional Chinese medicine to treat diarrhoea^[220].

In recent times, FMT is perhaps best known for its potential role in treating *Clostridium difficile* (*C. difficile*) infectious diarrhoea^[221]. After donor-faeces infusion in a group of patients infected with *C. difficile*, there was an alteration in the gut microflora with an increased faecal bacterial diversity, similar to that in healthy donors, with an increase in *Bacteroidetes* species and *Clostridium* clusters and a decrease in *Proteobacteria* species. This therapeutic benefit by FMT as documented in this trial, would theoretically have a beneficial effect in patients with IBD as well. The use of this form of intervention is still restricted to few exploratory trials. Donor faecal enemas were given to a group of ten children over five days with moderate to severe UC and resulted in 78% clinical response after a week and 67% with sustained response after a month in the nine children who could tolerate the treatment^[222]. This was similarly documented in a subset of six adult UC patients who were treated over a period of 5 d. Complete reversal of symptoms was achieved in all patients by 4 mo, by which time all other UC medications had been ceased and at 1 to 13 years post FMT and without any UC medication, there was no clinical, colonoscopic, or histologic evidence of UC in any patient^[223]. However, a single infusion in six adult patients with severe UC did not have a similar beneficial effect and the faecal microbiota changed to the donor phenotype in only 50% of those treated, suggesting that as opposed to treatment of *C. difficile* a prolonged treatment is indicated in IBD^[224]. Although the data described above is certainly promising, there is clearly a need to move on from individual case reports and conduct more large scale randomised control trials before any benefit of FMT can be claimed with any certainty. Some concerns have also been raised regarding safety and side effects, with some IBD patients suffering mild side effects following FMT, and the obvious issues surrounding potential transmission of host infectious disease^[225]. The efficacies of different administration techniques and dosing regimens for FMT also need to be refined and investigated. Literature to date describes a range of methods including colonoscopy, duodenal or gastric tubes and self-administered

Table 2 Probiotics and prebiotics in inflammatory bowel disease

Active component	Study	Design	n	Duration	Intervention	Result	Reference
<i>Lactobacillus</i>	CD remission	RCT	98	6 mo	<i>Lactobacillus johnsonii</i> LA1 4×10^9 cfu/d	No difference	[185]
	IBD		40	1 mo	<i>Lactobacillus rhamnosus</i> GR-1 and <i>L. reuteri</i> RC-14 supplemented yogurt	Anti-inflammatory effects	[186]
<i>Bifidobacterium</i>	Active UC	RCT	20	12 wk	Bifido-fermented milk [<i>B. breve</i> , <i>B. bifidum</i> and <i>acidophilus</i>] (1×10^{10}) or placebo	Decreased clinical activity ($P < 0.05$) decreased endoscopic/histological scores ($P < 0.01$)	[187]
	Active UC	Open label	12	4 wk	BGS 4.5 g/d	Decrease in clinical activity index ($P < 0.01$) and endoscopic scores ($P < 0.05$)	[188]
	C57BL/6 mice	Experimental	16	3 d	<i>B. bifidum</i> S17	Decrease in microscopic inflammation and reduction in inflammatory cytokines	[189]
<i>E. coli</i> Nissle 1917	UC remission		327	12 mo	200 mg <i>E. coli</i> Nissle 1917 or 1500 mg mesalazine/d	<i>E. coli</i> Nissle 1917 was equivalent to mesalazine in maintaining remission	[190]
VSL#3	UC remission	Open label	34	6 wk	VSL#3, 3.6×10^{12} , bacteria/d	ITT analysis demonstrated remission in 18/34 and response in 8/34	[191]
	Active UC	RCT	29	12 mo	VSL#3 450-1800 billion bacteria/d	Remission was achieved in 13/14 VSL#3 and 4/15 placebo ($P < 0.001$) Relapses within 1 yr of followup occurred in 3/14 VSL#3 and 11/15 placebo Endoscopic and histological score were significantly lower in VSL#3 vs placebo ($P < 0.05$)	[192]
Inulin	Active UC	RCT	19	2 wk	3 g/d mesalazine and either 12 g/d oligofructose-enriched inulin or placebo	Dyspeptic symptoms scale decreased significantly and an early reduction of calprotectin was observed in oligofructose-enriched inulin group	[203]
	Pouchitis	RCT	20	3 wk	24 g/d inulin or placebo	Reduction in inflammation, increase butyrate conc and decreased inflammation associated factors	[204]
Inulin and FOS	HLA-B27 rat model IBD			12 wk	8 g/kg body weight inulin or FOS	FOS increased <i>Bifidobacterium</i> spp. FOS and inulin reduced Clostridium cluster XI and <i>C. difficile</i> toxin gene expression correlating with a reduction of chronic intestinal inflammation	[205]
FOS	Active CD	RCT	103	4 wk	15 g/d FOS or placebo	No clinical benefit, despite impacting on DC function	[206]
	Active CD	Open label	10	3 wk	15 g/d	Significant reduction in Harvey Bradshaw index ($P < 0.01$) significant increase in faecal bifidobacteria conc. ($P < 0.001$) and modifies DC function	[207]

CD: Crohn's disease; UC: Ulcerative colitis; IBD: Inflammatory bowel disease; RCT: Randomized control trial; FOS: Fructooligosaccharides; *E. coli*: *Escherichia coli*.

enema yet to date there is no clear evidence to support one method over any other. There is no doubt that manipulation of the gut microbiota could have enormous therapeutic potential and FMT will play an important role in its future.

CONCLUSION

The understanding of the aetiopathogenesis of IBD has undergone radical shifts in the past decade with the advent of modern molecular techniques that can character-

ize the gut microbiome more accurately and host genomic analysis that can explore the vast genetic universe of IBD. At the heart of the inflammatory process in IBD is "dysbiosis" of the gut microbiome, which may be driven by host genetics and environmental factors like diet. The next decade will help unravel the intricacies of the host immune defences that determine this intriguing host-microbiome ecology. The relationship of the genotype of the host and the extent to which it determines the composition of the microbiome needs to be elucidated. It will open the doors to more "personalized" therapeutic

interventions, which would encompass the host genotype and serotype, the disease phenotype, the gene expression profiles of the immune cells and the microbiome composition to decide the best strategy for treating patients with IBD. This will usher in a paradigm shift in patient management with a move away from standard generic therapy to a scientific, tailored approach based on the needs of individual patients.

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ISSN 1007-9327



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