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- 26 Bacterial biofilms in human gastrointestinal tract: An intricate balance between health and inflammatory bowel diseases

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## Bacterial biofilms in human gastrointestinal tract: An intricate balance between health and inflammatory bowel diseases

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### Abstract

Inflammatory bowel disease (IBD) has been a worldwide health problem. It is characterized by severe intestinal inflammation due to immune responses against the gut microbes in genetically susceptible individuals. The understanding of gut microbiota for its composition and complex interaction in normal and diseased conditions has been assisted by the use of molecular, metagenomics and meta transcriptomics studies. The alteration of intestinal microbiota is the key determinant in the degree of inflammation caused and the prolonged course of disease. The relationship between luminal gut bacteria and innate immunity is also of prime significance. Such developments have further led to the search of specific (including bacteria and fungi) as a causative agent of IBD. Although detailed research has been done for the role of gut microbiota in IBD, molecular mechanisms and related gene expression are still not well understood in this disease, which hampers the generation of effective therapeutic agents for IBD. This paper assessed various factors contributing to IBD, genetic dysbiosis and pathogenic influence in the gut microbiota, interactions such as microbiome-host immune system interaction and microbe-microbe interactions involved in IBD, currently available IBD therapies, followed by a detailed review on bacterial infections that might be involved in IBD, globally and specifically in India.

**Key words:** Ulcerative colitis; Crohn's disease; Inflammatory bowel disease; Gut microbiota; Lactic acid bacteria

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**Core tip:** Ulcerative colitis and Crohn's disease are two clinical forms of inflammatory bowel disease (IBD) causing recurring diarrhea, abdominal bleeding, pain and inflammation. Scientific evidence clearly indicated the role of heredity in IBD, but an

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accurate cause of IBD is still unclear. However, complex interactions between genes, environmental factors and the immune system could be one of the leading causes in IBD. Gut microbiome is a key link between these factors and progression of IBD. This article reviews all contributing factors and pathogenic association in IBD. Identifying such microbial causes of the onset of IBD can help researchers to develop effective treatment strategies.

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## INTRODUCTION

Inflammatory bowel disease (IBD) is a common gastrointestinal disorder whose pathophysiology is still not completely understood due to its complex and multifactorial nature. It is generally characterized by abdominal pain and recurring diarrhea. It occurs in genetically vulnerable populations or individuals due to inappropriate and intensified immune response to commensal bacteria, which leads to intestinal inflammation<sup>[1,2]</sup>. The two main clinical forms of IBD according to their location and nature of histological modifications/damage caused in the gastrointestinal wall are ulcerative colitis (UC) and Crohn's disease (CD). UC is limited to mucosal surfaces of the colon, cecum and rectum. Several microbes such as *Salmonella spp.*, *Shigella spp.*, *Fusobacterium spp.*, and adhesive *E. coli* have been found in the inflamed colon, but no causative microbial species has yet been made responsible for UC<sup>[1-4]</sup>. CD exhibits transmural inflammation and the mucosal bacteria concentration in CD patients has been found to be twice as high as that of a healthy individual<sup>[5,6]</sup>. The most predominant bacterial species found in CD was *Bacteroides spp.*, which composed 80% of the total mucosal bacteria as compared to 15% in UC. Also, the role of *Listeria monocytogenes* and adherent-invasive *E. coli* (AIEC) has been determined in CD<sup>[5,6]</sup>. Both UC and CD cause diarrhea with or without bleeding and patients display a weakened tolerance to antigens present in the intestines<sup>[1]</sup>. Its occurrence is similar in both sexes (men and women), and most cases are recorded in young adults<sup>[6,7]</sup>.

Depending upon the type of microbes, several unfriendly and mutuality interactions occur between the residing gut microbes. The three main mechanisms by which the bacteria communicate with fellow bacteria around them are: combatting, competing and cooperating. Also, formation of biofilms protects the bacterial population from host immune responses and antimicrobials/antibiotics by secretion of extracellular matrix and binding bacteria together in layers. Thick, dense and resistant biofilm formation is very common in IBD patients and is the prime cause of dysbiosis and resistance to treatments/therapies including antibiotics<sup>[5,8]</sup>. The residing microbes also regulate their gene expression in response to changing microbial cell population and its concentration through a cell-cell communication known as quorum sensing<sup>[9]</sup>.

## UC

UC is the chronic and recurring IBD in which severe inflammation and immune responses (T helper cell and production of cytokines) are generated in the intestinal mucosa. The initiation site for ulcers is distal large intestine, and eventually the inflammation moves towards the proximal bowel. UC can severely disturb the quality of life, and if oral medicines are not effective, surgical removal of parts of ulcer affected intestines is obligatory. Several microbes such as *Shigella spp.*, *Fusobacterium spp.* and adhesive *E. coli* have been found in the inflamed colon, but no causative microbial species has yet been made responsible for UC<sup>[2-4]</sup>.

## CD

CD exhibits transmural inflammation and epithelioid granulomas in the gut tissues with T-helper cell (Th1) responses and elevated levels of interferon gamma. The mucosal bacteria concentration in CD patients has been found to be twice as high as that of a healthy individual<sup>[5,6]</sup>. Higher levels of antibody IgG is a characteristic of CD patients. The most predominant bacterial species found was *Bacteroides spp.*, which composed 80% of the total mucosal bacteria as compared to 15% in UC. Also, the role of AIEC has been determined in CD<sup>[5,6]</sup>.

Rural populations are less susceptible to IBD. Environmental factors such as poor sanitation, decreased use of antibiotics, rural environment, consumption of whole unrefined food, *etc* decrease the risk of IBD. That is increased exposure to microbes or infection will lead to low susceptibility for IBD infection. Also, the mucosal immunity in intestines is changed during IBD. UC and CD patients tend to secrete more antibodies (IgG and IgA) against the commensal intestinal microflora and damage their intestinal mucosa<sup>[10,11]</sup>. Thus, the pathogenesis of IBD is partly understood, and it has also been discovered that multiple factors are associated with IBD such as genetic vulnerability, environmental factors, host-commensal/pathogenic microbe interaction and disturbed mucosal immune responses<sup>[12-14]</sup>.

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## ENVIRONMENTAL FACTORS CONTRIBUTING TO IBD

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The maximum occurrence of IBD has been reported in Northern Europe and North America, whereas it is rare amongst Asians and Africans. Incidences of IBD vary depending on race, and its prevalence increases in regions with industrialization. According to the hygiene hypothesis, the autoimmune and inflammatory responses in the body occur due to the absence or low exposure to pathogens in childhood/infancy due to rigorous sanitation practices.

The effect of smoking was guarding against UC and aggravating for CD. That is smoking may improve one's condition during UC, but CD patients may suffer with a declined quality of life. Other factors, such as domestic hygiene, prenatal events, oral contraceptives, microbial agents and refined sugar consumption require further evaluation to confirm their involvement in IBD and to describe their strength<sup>[15-17]</sup>. Another accepted factor to increase IBD inflammation and cause relapse of the disease is psychological stress. Any sort of depression, adverse life situations or chronic stress can deteriorate the course of disease<sup>[18,19]</sup>. Several clinical studies suggest that IBD is not a psychosomatic disease, but stressful life events and depression are associated with high risk of relapse and increased pathogenesis of IBD<sup>[20,21]</sup>.

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## GENETIC SUSCEPTIBILITY IN IBD

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Heterogeneous geographical distribution and occurrence of ancestral forms of IBD as well as monozygotic twin studies strongly support the genetic component of IBD. High risk in patients having family members with IBD, relatively high risk of siblings acquiring the disease and high concordance rate of monozygotic twins than dizygotic twins of being affected by IBD further strengthen the hypothesis. Therefore, genetic makeup plays an important role in both forms of IBD. Also, several susceptibility genes have been reported. Autophagy genes such as ATG16L1, IRGM and Card15/NOD-2 have been reported to be associated with CD for innate immunity responses. Other candidate genes involved in UC are HERC2, STAT3 and PTPN2<sup>[22,23]</sup>. Several other susceptible genes such as IL23R, IBD5, NKX2-3, BSN, IL12B and CCNY have been found to be associated with both UC and CD. **Table 1** lists some of the genes and their respective roles in IBD. Mutations in these particular genes can lead to abnormal immune response generation in the gut mucosa and adversely affect healthy microbial population in terms of composition and concentration.

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## COMPLEXITY OF GUT MICROBIOTA

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The complex anaerobic environment of the gut is home to several microbial communities including bacteria, archaea and fungi. This microbial diversity in the gut has been studied by the culture independent 16S rRNA studies. These studies indicate that the gut is mainly inhabited by Gram-positive *Firmicutes* and Gram-negative *Bacteroidetes*, while *Actinomycetes*, methanogens and fungi are present in lower quantities<sup>[24]</sup>. Most *Firmicutes* were identified as clostridia and are butyrate-producing bacteria. Several *Proteobacteria* and *Actinomycetes* were also identified out of which *Bifidobacteria* (subgroup of *Actinomycetes*), which has health promoting utilities was

Table 1 Susceptible chromosomal loci for inflammatory bowel disease

No.	Related disease	Gene(s)	Role(s) in inflammation	Ref.
1	UC + CD	NOD2/CARD15, CD19, CD11, IL4R	Detection of cytosolic bacterial components	[105]
2	UC + CD	IL23R, PTGER4	Generation and maintenance of Th17 cells; prostaglandins signaling	[23,106]
3	CD	IRGM, IL12B	Autophagy	[22,23]
4	CD	STAT3, ORMDL3	Development of T cell response	[22,23]
5	CD	IL3, IL4, IL5 and IL13, OCTN1, OCTN2, CSF2, SLC22A5	Mucosal barrier function, cytokines production, Regulation of inflammation	[106]
6	UC + CD	MST1, BSN, GNAI2	Regulation of expression of proinflammatory mediators	[105]

CD: Crohn's disease; UC: Ulcerative colitis; NOD2: Nucleotide-binding oligomerization domain-containing protein 2; CARD15: Caspase recruitment domain-containing protein 15; CD19: Cluster of differentiation 19; IL4R: Interleukin 4 receptor; IL23R: Interleukin 23 receptor; PTGER4: Prostaglandin E receptor 4; IRGM: Immunity related GTPase M; IL12B: Interleukin 12B; STAT3: Signal transducer and activator of transcription 3; ORMDL3: Orosomucoid like 3; OCTN1: Organic cation transporter, novel, type 1; CSF2: Colony stimulating factor 2; SLC22A5: Solute carrier family 22 member 5; MST1: Macrophage stimulating 1; BSN: Bassoon (presynaptic cytomatrix protein); GNAI2: G protein subunit alpha I2.

found to be 5% of the microbiota. Archaeal diversity consists of *Methanobrevibacter smithii* and *Methanosphaera stadtmanae*. Eukaryotic microbes in the human gut consist of *Blastocystis* sp., (uni- and multicellular protists) and several fungi belonging to *Ascomycetes* (53.5%) or *Basidiomycetes* (46.5%) with the majority belonging to the genera *Candida albicans*, *C. glabrata* (6%), *Penicillium italicum*, *P. glabrum*, *P. sacculum*, *P. verruculosum* (61.5%), *Saccharomyces cerevisiae*, *S. cariocanus* and *S. bayanus* (24.1%)<sup>[24-26]</sup>.

## PATHOGENIC INFLUENCE OF GUT MICROBIOTA IN IBD

Several studies aiming to distinguish residing microbes in a healthy gut and an IBD gut revealed an overall decline in bacterial diversity in IBD patients. Further, a decrease in methanogen diversity and an increase in fungal diversity were noted in the guts of IBD patients<sup>[25,26]</sup>. Clustering of microbial communities was found over inflamed gut surfaces, but the microbial communities did not vary over the healthy gut tissues.

Different studies have also reported the presence of pathogenic microbes in the gastrointestinal tract of IBD patients. *Saccharomyces cerevisiae*, *Candida albicans*, *Listeria monocytogenes*, *Mycobacterium avium* subsp. paratuberculosis, *Chlamydia pneumonia* and AIEC have been reported as the potentially infectious microbes in the spread of CD. In CD, *Bacteroides*, *Peptostreptococcus* and *Eubacteria* are increased, whereas *Bifidobacteria* numbers are considerably reduced. Moreover, in UC the presence of facultative anaerobic bacteria is amplified. Table 2 lists the infectious agents (viral, bacterial, fungal and parasitic agents) that have been suspected in IBD etiology. *E. coli* has been reported to induce the release of cytokines in the inflamed IBD gut. AIEC, which is a facultative pathogen, has been reported to cause CD in genetically susceptible hosts<sup>[27-29]</sup>. Even though these studies have shown relation between pathogens and IBD, specific pathogenic microbes responsible for CD or UC is still contentious.

## GENETIC DYSBIOSIS IN IBD

IBD may not be caused by any specific microbial infection; instead it occurs due to a change in the overall residing microbes in the gut (intestinal microbe biofilms). It may also be caused by misrecognition of normal, commensal microbes as foreign leading to immune responses and inflammation. This change in intestinal microbiota (in terms of species and their concentration) or misrecognition by the body is termed genetic dysbiosis<sup>[30,31]</sup>. This ever-changing gut microbiota can modify the expression of certain genes that are involved in various activities in the intestines. Further, it can cause inflammation and disease in genetically susceptible individuals who have mutations or polymorphism in genes involved in immune responses (as described in previous

**Table 2 Suspected pathogenic microorganism in tissue of patients with inflammatory bowel disease**

Bacteria	Virus	Fungi
<i>Campylobacter</i> spp.	Adenovirus	<i>Saccharomyces cerevisiae</i>
<i>Escherichia coli</i>	Cytomegalovirus	<i>Candida albicans</i>
<i>Helicobacter</i> spp.	Coronavirus	
<i>Legionella</i> spp.	Rotavirus	
<i>Mycobacterium</i> spp.	Measles virus	
<i>Pseudomonas</i> spp.	Paramyxovirus	
<i>Shigella</i> spp.	Epstein-Barr virus	
<i>Yersinia</i> spp.		Parasite
<i>Bacteroides vulgatus</i>		<i>Borrelia</i> spp.
<i>Listeria monocytogenes</i>		<i>Treponema</i> spp.
<i>Staphylococcus</i> spp.		
<i>Streptococcus</i> spp.		
<i>Enterococcus</i>		
Adherent-Invasive <i>E. coli</i>		
<i>Chlamydia</i> spp. ( <i>Chlamydia trachomatis</i> )		

spp.: Species.

sections)<sup>[30,31]</sup>. **Figure 1** represents how genetic dysbiosis can lead to diseases.

## INTESTINAL MUCOSAL BARRIER FUNCTION IN IBD

The intestinal mucosal barrier consists of two layers of mucus (inner and outer), which are associated with antimicrobial factors. Under this mucus layer are the gut epithelial cells that are joined together by a network of connecting proteins called tight junctions. Hence, this intestinal mucosal barrier splits the luminal components (food particles, microbes, *etc.*) from the immune system components (innate and adaptive immunity) (**Figure 2**)<sup>[32]</sup>.

## MICROBIOME–HOST IMMUNE SYSTEM INTERACTION IN IBD

Under normal conditions the microbiota does not interact with the epithelial cells, other than the controlled interaction in the Peyer's patches. Under the condition of disturbed microbiota composition or genetic dysbiosis, as is the case with IBD, this mucosal barrier is interrupted, and the interaction between the microbiota and immune system components occurs, which leads to generation of a heightened immune response and inflammation as shown in **Figure 2**.

In IBD, the mucus layer is permeable and defective due to improper secretion of mucus components by goblet cells (decreased mucin, antimicrobial factors, glycosylation products, *etc.*). In the case of UC, the goblet cells are depleted in the epithelium, and the mucus layer formed is very thin. Also, the tight junction protein network becomes increasingly penetrable in IBD, which further increases the interaction between immune and luminal components. Such changes are a result of environmental factors and genetic dysbiosis as discussed earlier<sup>[33,34]</sup>.

Various studies have shown that microorganisms that pass the mucus layer and invade the epithelial cells, activate various components of the immune system comprising innate immune responses, adaptive immune responses and autophagy<sup>[35,36]</sup>. According to Parkes, CD is linked to mutations in autophagy genes such as nucleotide oligomerization domain 2 and ATG16L1. Intracellular pathogens have also been observed to form autophagic vacuoles to prevent interaction with immune components and remain protected<sup>[37]</sup>.

Microorganisms that pass through the damaged tight junctions mesh and reach the lower surface of epithelial cells are recognized by the pattern recognition molecules similar to toll-like receptors present there. This interaction then activates the innate

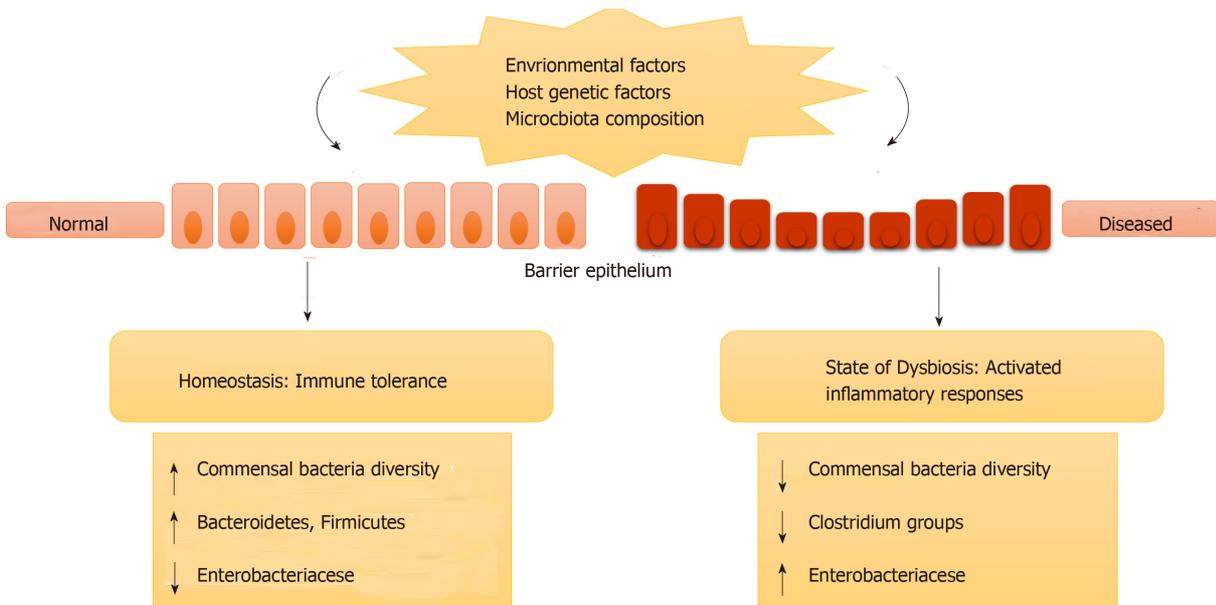


Figure 1 Pathway for genetic dysbiosis.

immune responses (including phagocytic cells, natural killer cells, dendritic cells, inflammation-related proteins, cytokines and antimicrobial peptides such as defensins and cathelicidins) and adaptive immune response including several cytokine profiles<sup>[38,39]</sup>. Fernandes *et al*<sup>[40]</sup> reported that in IBD, the expression of regulatory molecules of immune system and toll-like receptors is different from that in a healthy tissue.

## MICROBE–MICROBE INTERACTIONS IN IBD

Other than interaction with the host cells, the survival and activity of gut microbiota also depends upon their interaction with the other surrounding microbes. These interactions can be unfriendly or mutualistic, which primarily depends upon the type of microbes. The three main mechanisms by which the bacteria communicate with fellow bacteria around them are: combatting, competing and cooperating (Figure 3).

### Combatting

Gut bacteria combat other microbes by production of antimicrobial peptides (AMP) and specialized secretions. Bacteriocins, colicins and microcins are some AMP that inhibits other microbial invading species without harming the eukaryotic gut cells. Bacteriocins are produced by Gram-positive bacteria, and they fight against other microbes by pore formation in their cell wall. Gram-negative bacteria produce colicins and microcins, which kill other microbes by a variety of strategies such as nuclease activity, inhibition of RNA polymerase, intervention cell wall synthesis and pore formation<sup>[41,42]</sup>. These bacterial AMPs under the effect of environmental factors control surrounding microbiota composition and concentration.

Other mechanisms of combatting surrounding microbes are contact dependent growth inhibition systems and type VI secretion systems. In contact dependent growth inhibition system, the C terminal end of CdiA protein move in on the target cell and kill it by nuclease activity. Type VI secretion system cells inject toxins in Gram-negative bacteria and eukaryotic cells to combat bacterial competition and cause pathogenesis, respectively<sup>[41,42]</sup>.

### Competing

One of the essential parameters that governs colonization of microbes and dysbiosis in gut is the competition for carbohydrates. Other than carbohydrates, bacteria also compete for phosphorus, nitrogen, vitamins, trace elements and other vital cofactors. Bacteria encode a variety of transporters for smooth uptake of vitamins and essential cofactors<sup>[43,44]</sup>. Some bacteria interfere with the uptake of trace elements by other bacteria by secretion of some inhibitors or AMP. For instance, a study by Raffatellu *et al*<sup>[45]</sup> showed that *Salmonella typhimurium* produced lipocalin-2 to inhibit iron uptake by surrounding microbes.

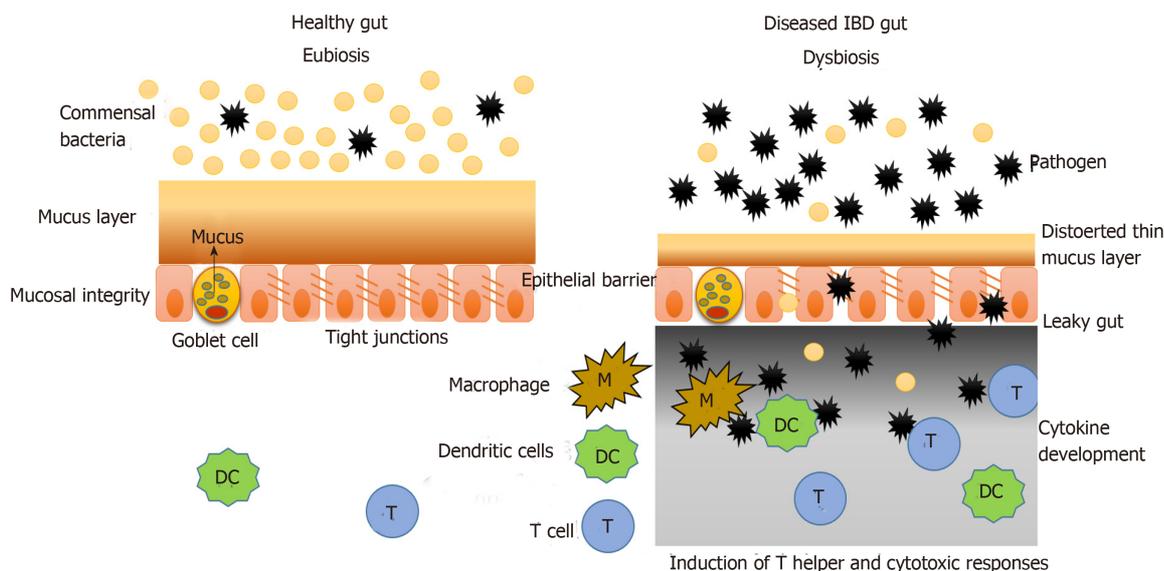


Figure 2 Mechanism of inflammatory bowel disease.

### Cooperating and communicating

Even after such limiting conditions and competition for food, gut bacteria also communicate and live in cooperation and share by-products. One of the methods of such cooperation is horizontal gene transfer. Horizontal gene transfer is responsible for secretome molecules, which is the most common method to help in production of certain molecules for communal use. For instance, chelators of iron (siderophores), which help in absorption of iron from the surrounding, can be used by any bacteria in the surrounding. In this way, horizontal gene transfer of such genes and public use of these secretions helps the bacterial population to live in cooperation in the gut<sup>[46,47]</sup>.

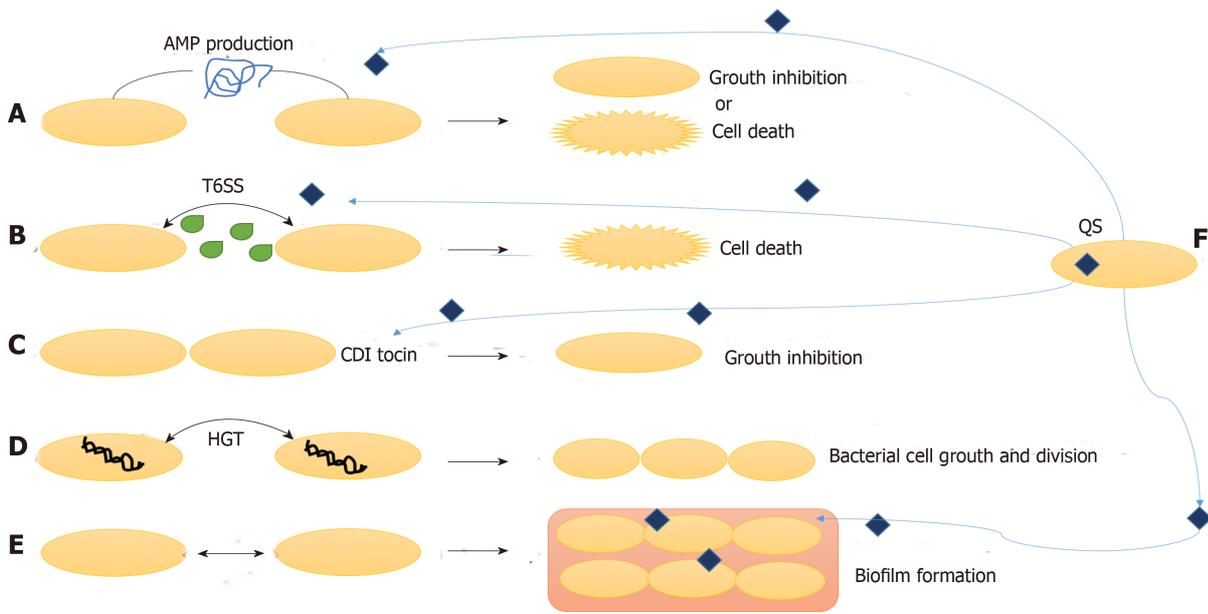
Formation of biofilms also protects the bacterial population from host immune responses and antimicrobials/antibiotics by secretion of extracellular matrix and binding bacteria together in layers. It prevents the loss of useful secretions and nutrients from a population of microbes living in cooperation with other surrounding microbes. Thick, dense and resistant biofilm formation is very common in IBD patients and is the prime cause of dysbiosis and resistance to treatments/therapies including antibiotics<sup>[5,8]</sup>.

Many cooperative/group behaviors in the gut are governed by the cell-to-cell communication called quorum sensing (QS). The signaling molecules are released in the environment and regulate gene expression in the surrounding communities. QS governs several mechanisms important to survival such as biofilm formation, antibiotic production and expression and release of secretions like type VI secretion systems. Although QS has been known in *Lactobacillus* species and probiotics, its role in human gut commensal bacteria and pathogens is still not understood well. Further studies are necessary for understanding the microbial communication in both homeostasis and IBD conditions<sup>[48-50]</sup>.

### Quorum sensing

QS occurs by the production and release of extracellular chemical signal molecules called autoinducers by bacteria that are subsequently detected by other bacteria. When a particular threshold concentration of autoinducers is reached, the gene expression is altered in all the bacterial cells residing there. This alteration in gene expression is associated with the variations in cell population density<sup>[9]</sup>. Several physiological activities such as biofilm formation, virulence, competence, symbiosis, conjugation, antibiotic production, sporulation and motility are controlled by QS communications in bacteria. This communication through autoinducers can take place both within and amongst the bacterial species. Acylated homoserine lactones are produced as autoinducers in Gram-negative bacteria, while Gram-positive bacteria release oligopeptides for communication<sup>[9,51]</sup>.

Gram-negative bacteria *V. fischeri* demonstrated LuxI/LuxR-type QS. LuxI-like proteins synthesized a particular acylated homoserine lactone signaling molecule, which is an autoinducer. When these homoserine lactone signaling molecules reach a threshold concentration, LuxR-like proteins bind to them and stimulate particular gene transcription<sup>[52]</sup>. Several other Gram-negative bacteria, including those involved



**Figure 3** Various communication mechanisms used by bacteria (combatting: A-C; cooperating: D-F). A: Antimicrobial peptides; B: Type 6 secretion system; C: Contact-dependent growth inhibition systems; D: Horizontal gene transfer; E: Formation of a protective biofilm; F: Quorum sensing<sup>[39]</sup>.

in pathogenesis of IBD regulate gene expression through homologous LuxI/LuxR-type circuit. For instance, in *P. aeruginosa*, LasI/LasR-RhII/RhIR virulence system circuit regulates QS. Homoserine lactone signaling autoinducers N-(3-oxododecanoyl)-homoserine lactone and N-(butyryl)-homoserine lactone are produced by the action of LasI and RhII autoinducers. Expression on several virulence factors (lasB, lecA and aprA) in *P. aeruginosa* is controlled by this circuit<sup>[53,54]</sup>.

Gram-positive bacteria also show QS mediated regulation by secreting peptides as autoinducers. An example of this is *Staphylococcus aureus* AgrC/AgrA virulence system. An RNA molecule named RNAIII regulates biofilm formation and pathogenicity in *S. aureus*. The agrBDCA operon regulates the levels of RNAIII. Function of RNAIII is to express several virulence factors in *S. aureus*<sup>[55,56]</sup>.

In a recent study by Goliska et al<sup>[57]</sup>, pathogenicity of enterococci (*Enterococcus faecalis*) in IBD was studied. The expression of several genes encoding the virulence factors (gelatinase, extracellular surface protein, cytolysin and hyaluronidase) was studied in IBD patients and control groups. The strains with these virulence genes were also found to have QS genes *fsrA-C* that regulates the expression of these virulence factors.

## IBD THERAPIES

Any effective therapeutic strategy to treat IBD should be able to treat all its pathophysiological constituents including inflammation, dysbiosis and leaky gut. The currently available medical treatments of IBD involve three approaches: immune-based therapies, microbiota-based therapies and barrier function-based therapies. Even after these advanced approaches, some patients still require surgical removal of severely affected portions of GI tract<sup>[58]</sup>.

### Immune-based therapies

Immune-based therapies directly modulate the immune system to avoid further destruction of commensal microbiota and the gut tissues to relieve inflammation. Furthermore, these therapies also indirectly modulate the mucosal barrier function and the microbiota<sup>[58,59]</sup>. Immune-based therapy medication includes immunomodulators (e.g., methotrexate, azathioprine), aminosalicylates, corticosteroids, integrin inhibitors and antitumor necrosis factor agents. Several other biologics are being developed to downregulate inflammatory cytokines and their receptors along with rebuilding healthy barrier function<sup>[59]</sup>. Mesalamine and other salicylates are known to modulate the intestinal microbial composition and decrease microbial adherence and biofilm formation in the gut<sup>[39,58]</sup>.

### Microbiota-based therapies

Microbiota-based therapies are based upon use of antibiotics, probiotics, fecal microbiota transplantation and alteration in diet.

**Antibiotics:** Antibiotics have been found most effective in CD and only of little use in UC, where it is sometimes used to treat children. Antibiotics such as rifaximin, metronidazole, ciprofloxacin and antimycobacterial agents are being used. These antibiotics decrease the concentration of some pathogens and increase the content of healthy microbiota including *Bifidobacteria* and *F. prausnitzii*. Indiscriminate use of antibiotics can lead to severe side effects such as reduction in microbial biodiversity in gut and developing resistance in microbes<sup>[60,61]</sup>.

**Probiotics:** Probiotics can be defined as the living organism (specific bacterial strains together) that when ingested provides health benefits and protective regulatory activities in the body. Commonly the content of yogurts such as *Lactobacilli*, *Bifidobacteria* and *Streptococci* play the role of probiotics. Probiotics have more efficiently been used in UC and are less effective for CD patients. The most extensively used probiotics for IBD are VSL#3 and *E. Coli* Nissle 1917. VSL#3 are a combination of eight diverse bacterial strains (four strains of *Lactobacilli*, three strains of *Bifidobacteria* and one strain of *Streptococcus*). These bacteria stimulate the growth of anti-inflammatory bacteria and prevent the growth of pathogenic microbes<sup>[62,63]</sup>.

The use of lactic acid bacteria, which includes *Lactobacillus*, as probiotics for treatment and prevention of IBD has been proposed in several studies. They are Gram-positive bacteria that normally reside in anaerobic conditions but are facultative aerobes<sup>[64,65]</sup>. They provide probiotic action by production of bacteriocins, hydrogen peroxide, lactic acid and by forming dense biofilms on gut epithelium, which block all the adhesion sites for attachment of pathogens<sup>[65]</sup>. *Lactobacillus* species such as *L. casei*, *L. acidophilus*, *L. plantarum*, *L. rhamnosus*, *L. fermentum*, *L. amylovorus* and *L. delbrueckii*, etc have been extensively studied for probiotic action against *H. pylori*, *Salmonella*, *E. coli*, *Clostridium difficile*, *Yersinia enterocolitica* and *Listeria monocytogenes*, etc<sup>[65,66]</sup>. The microbial interactions amongst themselves and with other commensal/pathogenic microbes in the biofilms formed in the gut are regulated by the *luxS* gene QS mechanisms. Several other proteins that are involved in biofilm formation in different *Lactobacillus* strains consist of collagen-binding protein, biofilm associated proteins, glycosyl-transferases and mucus-binding protein<sup>[66,67]</sup>. Most of the *Lactobacillus* species are bacteriocin producing. A specific class of bacteriocin, called plantaricins are produced by some species such as *L. plantarum* and *L. fermentum*. The plantaricin genes which can be identified in *Lactobacillus* are *plnA*, *plnB*, *plnC*, *plnD*, *plnEF*, *plnI*, *plnJ*, *plnK*, *plnG*, *plnN* and plantaricin structural genes<sup>[68,69]</sup>.

**Fecal microbiota transplantation:** This strategy of re-establishing healthy microbiota and treating IBD involves ingestion of healthy donor stool by an ill individual. This has been extensively used with mixed and moderate results in IBD patients. Repetitive infusions are required for sustained results. Keeping in view the chance of transmitting infectious microbes, recent studies suggest the use of artificial stool with limited risk of such infections<sup>[70,71]</sup>.

**Alteration in diet:** A balanced, high fiber, healthy diet with vegetables, fruits and grains is recommended for IBD patients. Diets with high protein content, excessive red meat and alcohol abuse are discouraged in IBD as it may aggravate or relapse the inflammation. Specific carbohydrate diets that eliminates milk, grains and sugar from the diet has been found effective in some cases of IBD showing an improvement in microbiota diversity<sup>[72,73]</sup>.

### Barrier function-based therapies

This therapy is evolving as the most effective and future approach for treating IBD. If the mucus layer in the gut epithelia is restored, then eventually the immune responses and inflammation can be controlled as well as microbiota diversity can flourish.

Establishing healthy microbiota and inhibition of TNF $\alpha$  and other inflammatory cytokines have recorded an enhanced barrier function in case of IBD. Amino acid, L-glutamine supplements and natural ingredients such as curcumin have been shown to restore tight junctions and hence can be used in treating IBD. Delayed released drugs such as phosphatidylcholine are also being examined extensively as a cure for IBD<sup>[69,74-76]</sup>.

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## BACTERIAL INFECTION IN IBD

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### Prominence worldwide

A number of studies with the aim to distinguish between residing microbes in a healthy patient and an IBD patient revealed an overall decline in bacterial diversity in the gut of patients with IBD<sup>[25,26]</sup>. Clustering of microbial communities was found over inflamed gut surfaces, but the microbial communities may not vary over the healthy gut tissues. Different studies have also reported the presence of pathogenic microbes in gastrointestinal tracts of IBD patients.

Ma *et al*<sup>[77]</sup> studied the occurrence of *Campylobacter concisus* in CD patients colonic biopsy samples and concluded there may be potential involvement of *C. concisus* in IBD. In another study by Arora *et al*<sup>[78]</sup> the risk of *C. jejuni* infection in UC was established.

Similarly, the presence of several virulence factors such as hyaluronidase, cytolysin and extracellular surface protein in *Enterococcus* strains isolated from colon tissue samples of children with IBD was observed<sup>[57]</sup>.

There are several studies that link *Helicobacter pylori* biofilms with gastrointestinal diseases, but it still remains debatable. Mice have developed IBD symptoms in the presence of abnormal immune response and *H. pylori* infection. No symptoms appeared in germfree conditions that establish single pathogen infection<sup>[79]</sup>. Halme *et al*<sup>[80]</sup> and Luther *et al*<sup>[81]</sup> observed contradictory results and demonstrated a protective or inverse relation of *Helicobacter* towards IBD.

Furthermore, a study by Saebo *et al*<sup>[82]</sup> concluded that infection of *Yersinia enterocolitica* was an activator for IBD. Similarly, Ruckdeschel *et al*<sup>[83]</sup> analyzed the impact of virulence factors (such as cytotoxin, invasin and adhesin) of *Y. enterocolitica* against the action of polymorphonuclear leukocytes.

As far as the role of *Listeria monocytogenes* in IBD is concerned, studies revealed uncertain outcomes. *L. monocytogenes* was found proliferating at a higher rate in the colon of patients with IBD than in healthy controls<sup>[84]</sup>. *Listeria* forms resistant biofilms on several surfaces including synthetic as well as gut epithelium. The biofilm formation is regulated by QS autoinducer 2 genes *luxS* and *pfs*. Chen *et al*<sup>[85]</sup> studied the presence of *L. monocytogenes* in gut biopsies of IBD patients and controls in New Zealand and reported no direct role of *L. monocytogenes* in causing IBD. Another study by Huijsdens *et al*<sup>[86]</sup> also reported a similar result. However, Ooi *et al*<sup>[87]</sup> found *L. monocytogenes* responsible for causing mucosal inflammation in healthy individuals. Another recent study by Miranda-Bautista *et al*<sup>[88]</sup> confirmed the presence of *L. monocytogenes* in patients of CD and concluded that IBD patients are at a serious risk of *L. monocytogenes* infection.

Numerous studies also demonstrate a relation between *Salmonella enterica* infection and IBD. It has been reported that IBD and *Salmonella* infection with coinciding medical and histological symptoms in an elderly woman. This case study reports that colitis may be associated with *Salmonella* infection<sup>[89]</sup>. There are various other studies which elucidate the high risk of *S. enterica* infection in IBD<sup>[90-92]</sup>.

Even though these studies have shown a relationship between pathogens and IBD, a specific pathogenic microbe being responsible for CD or UC is still debatable.

### Prominence in India

The majority of IBD has been reported in northern Europe and North America, whereas it has been considered rare among Asians and Africans. But, in the past two decades cases of such western diseases have been witnessed in India, including UC and CD, and the number of affected individuals is rising alarmingly<sup>[93]</sup>. Detailed studies regarding epidemiology and pathogenesis of IBD are lacking in developing countries like India due to neglected health care services, lack of reliable data collection and patient based studies<sup>[93,94]</sup>.

Several studies have reported the possible involvement of specific pathogens in IBD. Verma *et al*<sup>[95]</sup> described that different sets of bacteria are responsible for pathogenesis of UC and CD. An increase in Gram-positive *Eubacterium* and *Peptostreptococcus* was reported in CD patients but not in UC patients, whereas *Campylobacter spp.* significantly increased in both CD and UC patients. A study by Patra *et al*<sup>[96]</sup> reported the presence of various serogroups of adherent *Escherichia coli* in rectal biopsies of individuals and associated it with epithelial damage and CD. Banerjee *et al*<sup>[97]</sup> reported occurrence of parasitic and viral infections (such as *Ankylostoma duodenale*, *Strongyloides stercoralis*, *Entamoeba histolytica*, etc) in UC patients by analysis of stool samples and rectal biopsies. Iyer *et al*<sup>[98]</sup> investigated the relationship between intestinal infections (with *Clostridium difficile* and other parasites) and UC. They reported that the presence of such infections in UC patients deteriorated the condition and is associated with disease severity. Tripathi *et al*<sup>[99]</sup> detected the presence of *Salmonella enterica* in the stool of 80% of UC patients and concluded an active infection of *Salmonella sp.* in IBD.

Another recent study examined the gut microbiota profile of vegetarian and non-

vegetarian healthy individuals and IBD individuals and colon carcinoma and reported that IBD and colon cancer patients had higher proportions of *Bacteroidetes* than *Firmicutes*<sup>[100]</sup>. Several studies discuss the food-borne infection of *Listeria monocytogenes* in India. In another study<sup>[101]</sup> established the expression of virulence gene regulator *prfA* in *L. monocytogenes* infecting mammalian host, which helps in formation of resistant biofilms and virulence. Expression of *prfA* was also studied in co-cultured biofilms with *B. subtilis*, which made *L. monocytogenes* less virulent in such biofilms.

Several studies have also been conducted regarding the anti-biofilm nature and probiotic properties of lactic acid bacteria against pathogenic bacteria. Kaur *et al*<sup>[102]</sup> reported the action of *Lactobacillus spp.* against diarrhea causing *Vibrio cholerae*, which causes high mortality in developing countries like India. Another study examined the antimicrobial action of *Lactobacillus spp.* from curd and milk against several human infecting pathogens such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumonia*, *Salmonella enterica serovar Typhi*, *Bacillus cereus*, *Listeria monocytogenes* and *Shigella flexneri*[103]. Furthermore, in some studies it has been demonstrated the antimicrobial action of thirteen *Lactobacillus* isolates from the gastrointestinal track of broiler chicken against *Escherichia coli* and pathogenic fungi such as *Aspergillus niger*, *Aspergillus flavus*, *Penicillium expansum*, *Penicillium roqueforti* and *Candida albicans*, *etc*<sup>[104-106]</sup>. The lactic acid bacteria showed effective inhibition against these pathogens.

## CONCLUSION

The understanding of gut microbiota in terms of composition and its complex interaction in both normal and diseased conditions has been assisted by the use of molecular, metagenomics and meta transcriptomics techniques. Even though several studies (as mentioned above) have shown relationships between pathogens and IBD, a specific pathogenic microbe being responsible for CD or UC is still debatable. Also, detailed research has been done for gut microbiota and IBD, but the molecular basis of their virulence and biofilm formation still remains to be discovered. This has hampered the generation of effective therapeutic agents for IBD that would benefit a high percentage of the world population affected by the disease. Therefore, we need to understand the pathogenesis of IBD and develop strong treatment strategies against it.

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