Review Article

Inflammatory Bowel Disease, its Etiopathogenesis and Treatment Approaches: A Review

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ABSTRACT

Inflammatory bowel disease is a chronic disease of the gastrointestinal tract, which is characterized by serious events of inflammation in either specifically colon (ulcerative colitis) or the whole length of the gut (Crohn's disease). IBD affects people greatly all over the globe. It is observed that it is more prevalent in the urbanized countries. Both the etiology and pathogenesis of IBD are complex to understand. Yet many researchers have taken great efforts to figure out the etiopathogenesis. Diagnosis of IBD is also difficult thus it is required to differentiate between UC and CD. Thus, we have shed some light on the diagnostic tools too. Since the cure for IBD is difficult, treatment is the only option, hence various recent treatments are also explained with the help of this review. This review gives a brief overview of the disease also highlights the various etiopathogenesis involved.

Keywords: Inflammatory bowel disease, ulcerative colitis, Crohn's disease, toll-like receptor, TNF-α.

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INTRODUCTION

Inflammatory Bowel Disease (IBD) is a term used to collectively describe a group of two chronic diseases of the Gastrointestinal tract (GIT). This encompasses Crohn's disease (CD) and Ulcerative colitis (UC). There exists severe inflammation in IBD which is manifested with episodes of pain in the abdomen region, severe diarrhea along with bloody stools, and weight loss. UC generally affects the large intestine (more specifically colon and rectum) whereas CD affects the entire GIT (mouth to anus). Inflammation along with ulceration of the intestinal mucosa occurs in IBD, this inflammation and ulceration are a result of the production of free radical species, proteolytic enzymes certain cytokines.[1]

UC and CD both are chronic relapsing as well as remains incurable to date. Ulcerative colitis and Crohn's disease, both are similar yet there are certain marked differences between the two. Ulcerative colitis can be defined as a disease condition in which inflammation and morphological modifications are restricted to the colon. Inflammation is primarily confined to the mucosa layer of the large intestine, which involves severe hemorrhage, edema along with ulcerations. Depletion of goblet cells, disruption of the mucosal gland, abscesses of the crypt, and chronic and acute inflammation of the mucosal layer by mononuclear cells and neutrophils are all common histological findings. [2]

Crohn's disease (CD) - Unlike UC, CD affects any part of the alimentary canal, from the oropharynx to the perianal region. Inflammation may be transmural, spreading through the serosa and leading to the development of sinus tracts or fistulas. Tiny surface ulcers on the Peyer's patch (aphthoid ulcer) and localized chronic inflammation spreading to the submucosa, often with granuloma formation, are histologic findings. [2]

Some other marked differences between UC and CD are summed up in table 1.

Table 1: Differentiation between Ulcerative colitis and Crohn's disease

Clinical manifestations		
	CD	**UC**
Weight loss	Often	More seldom
Fistulae	Common	Seldom
Fever	Common	Indicates severe disease
Tenesmus	Less common	More common
Defecation	Often porridge like	Often bloody with mucus
Diagnostic Findings		
Endoscopy	Deep snake like ulcers (serpiginous)	Continuous ulcers
Rectum involvement	Seldom	About 95%
Terminal ileum involvement	Common	Seldom

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Depth of inflammation	Transmural, deep into tissues	Continuous area of inflammation
Colon involvement	Usually	Always
Pathophysiology		
Cytokine response	Associated with Th17	Vague association with Th2

Ulcerative colitis can be further subdivided into different types (figure 1) depending on location and severity, this includes distal colitis (inflammation reaches from rectum and up to the left colon), proctosigmoiditis (inflammation confined to the rectum and lower end of the colon), severe acute ulcerative colitis (a rare type, causes inflammation across the full length of the colon which leads to severe pain), universal colitis or pancolitis (inflammation spreads along the entire length of the colon), ulcerative proctitis (inflammation stays within the rectum, mildest form of ulcerative colitis).

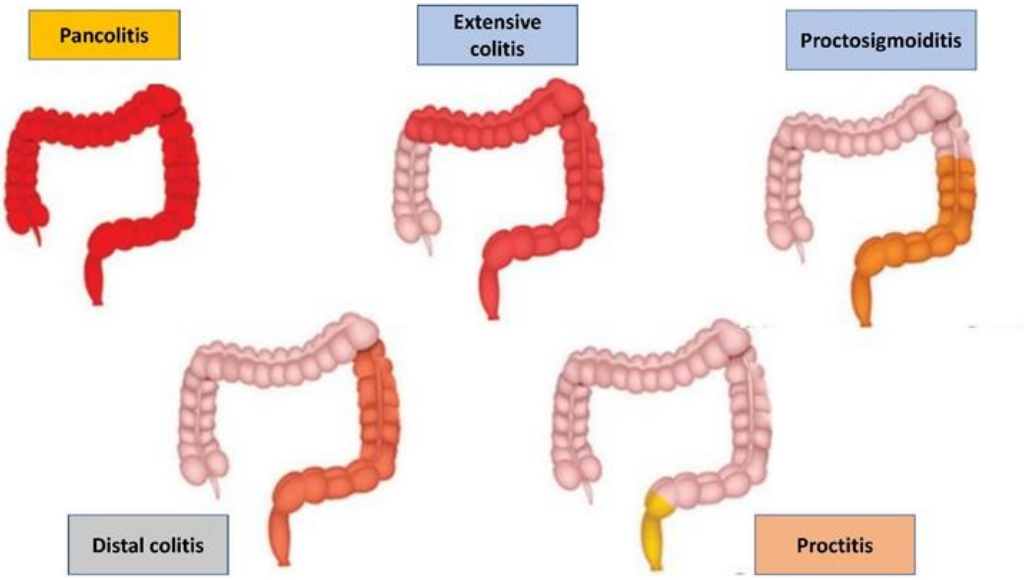

Figure 1: Different types of ulcerative colitis

While the cause of IBD is unclear, substantial progress has been made in recent years to understand the disease pathogenesis.[1] After a lack of immune reaction to the intestinal flora, IBD develops in genetically susceptible people. Many causes have been suggested, but none of them are seen in all patients. Crohn's disease has a clear correlation to tobacco use, which is one constant aspect. Smoking, on the other hand, tends to be protective against ulcerative colitis. Diet's role is also disputable. The caspase recruitment domain-containing protein 15 (CARD15) gene has been believed to be linked with IBD, thus it is impossible to predict which part of the alimentary canal would be influenced due to its polymorphic nature. In ulcerative colitis, genes play a smaller role than in Crohn's disease.[3]

In North America and Europe, IBD is much more widespread than in Asia and Africa. The prevalence of IBD in North America varies between two to nineteen occurrences per one lakh patient-years as far as UC is concerned and three to twenty occurrences per two lakh patient-years in case of CD. While most IBD patients are between the ages of 15 and 30, about 25% of patients are believed to acquire IBD by adolescence. There exists a bimodal spread, with 10% to 15% of people developing IBD over 60 years of age. While females are significantly more likely than males to develop Crohn's disease, ulcerative colitis tends to affect both genders equally. IBD is a condition that is more often found in developing countries with colder climates.[3]

The immune system of the intestine is responsible for the pathogenesis of IBD. By sealing intercellular junctions, the intestinal epithelium helps prevents bacteria or antigens from entering the bloodstream. These junctions are dysfunctional in IBD due to either a barrier function defect or extreme inflammation. Two defensive mechanisms are involved, goblet cells aid in mucus formation as well as α-defensins, both of which possess antimicrobial activity. Excessive inflammatory reactions cause the epithelium to degrade and increased exposure to intestinal bacteria, exacerbating the inflammation. Excessive inflammatory responses cause further degradation of the epithelium and increased exposure to intestinal bacteria, exacerbating the inflammation.[3]

Microscopic examination of active IBD patients shows a significant invasion of the lamina propria by natural killer (NK) cells, accessory cells, phagocytes, and polymorphonuclear leukocytes (PMN). Increasing the amount and stimulation of the above-mentioned cells raises levels of interleukin-23-TH17 cytokines, interferon-g, interleukin-1b, and TNF-α. In ulcerative colitis, the mucosa and submucosa are only involved, resulting in the development of abscesses in the crypt and mucosa layer ulcers. Biopsy samples reveal a PMN infiltration, as well as crypt damage and abscesses. Ulcerative colitis may not

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show the presence of granulomas. The appearance of pseudo polyps is another characteristic of ulcerative colitis.[3]

A collection of endoscopic biopsies, imaging findings, laboratory markers, and clinical findings are needed to diagnose IBD. Microcytic anemia, leukocytosis, and thrombocytosis are all hematologic findings. Inflammatory markers including Westergren ESR and high-sensitivity C-reactive protein (hsCRP) are often found to be elevated. A complete blood count (CBC) can detect albumin level, leukocytosis, and anemia. To rule out ova and parasitic infections, stool tests must be performed. MRI, CT scan, and ultrasound have also been used to diagnose IBD or check for complications. To obtain biopsies and confirm a diagnosis of IBD, endoscopic evaluation can be done with either colonoscopy or esophagogastroduodenoscopy, or both.[3]

Treating IBD involves managing mild to severe disease. Drugs that were previously reserved for severe disease are now being used earlier. Treatment for UC is highly dependent on the severity of the disease and the occurrence of extraintestinal symptoms. Aminosalicylate agents like mesalamine are common treatments for rectum disease that is mild to moderate. Mesalamine is given rectally, but it can be used in conjunction with oral therapy to help cause or sustain remission. A stepwise therapeutic approach is used in the treatment of IBD. Amino salicylates are the first-line treatment for IBD. If the Aminosalicylate dose is insufficient to relieve the patient, corticosteroids are added, which usually result in a substantial reduction in inflammation. Stage III drugs are immune-modifiers (e.g., anti-TNF agents). If the patient is unresponsive to the corticosteroids, these can be used. Step IV contains disease-specific clinical trial agents, such as those that function only for ulcerative colitis and those that function only for Crohn's disease. Interleukin (IL)-11 and thalidomide are employed for CD, whereas heparin, a patch of nicotine, and butyrate enema for UC are examples of these experimental agents. These experimental drugs are associated with several contraindications and severe side effects.[3] Many proven non-drug therapy is also employed along with various drugs that have helped overcome remission. They are discussed in the latter part of the review.

The review will give a brief insight into the disease, IBD. Through this review, we have tried to explain the various etiologies, the underlying pathogenesis, and the prevalence of the disease. The diagnosis and various treatment approaches are also described in the further sections of the review.

Epidemiology

IBD is most commonly seen in those whose age ranges from 55 to 65 years and 15 to 30 years. This may be possible because of closed working environments, a complete stationary lifestyle and well socioeconomic status.[4,5] The prevalence of IBD was seen highest till the mid-20th century particularly in North America and the Western part of Europe. IBD incidence has also greatly extended to the Asian continent too.[4,6] Due to various factors such as habits of South Asian foreigners, environmental and racial differences along with food lifestyles, there is a higher incidence of IBD in Asian populations than that of European populations.[4,7] Speaking about the Western countries, every year 10 to 20 out of 105 people suffer from IBD. In the Northern part of America, the incidence of IBD seen is two to fifteen cases per 100,000 patients per year and the prevalence rate being thirty-seven to two hundred and forty-six cases per 100,000 patients per year.[4,8] Apart from these studies, throughout the globe, hundreds of population-based studies of IBD have been done and reported for the prevalence and incidence.[9] According to the burden of the evidence of IBD is highest in India as compared to different countries of the world. According to a study conducted in the year 2012, the epidemiological data are very limited. Thus, it is not clear how many Indians are suffering from IBD, but from a study conducted in the year 2017, it was estimated that more than 1.1 million people were suffering from UC. In India CD is often misdiagnosed with intestinal tuberculosis, thus delaying its diagnosis leading to delay of the treatment and further worsening of the disease. Physicians have reported that the patients who show a severe form of the disease are more of the younger age.[10] Thus we can conclude that those societies are affected with IBD which adopt the Western habits, increasing urbanization and industrialisation, improvement of the economic status of the country and changes in the agricultural practices.[9]

Etio-Pathogenesis

Various etiologies are thought to be associated with the IBD, yet a clear understanding of the etiology associated with the IBD is still questionable and not yet fully understood. Figure 2 gives a complete overview of various etiologies involved in IBD.

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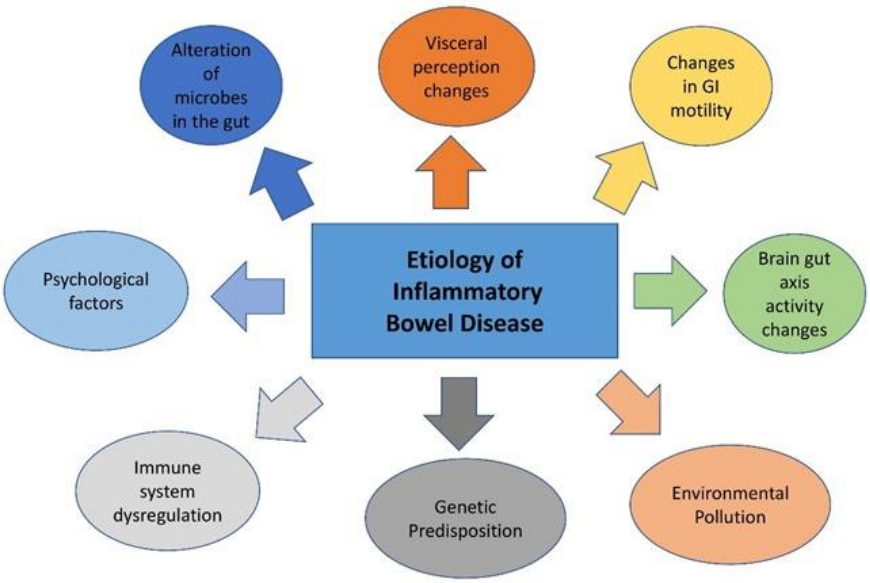

Figure 2: Etiologies involved in inflammatory bowel disease

Diet

Dietary agents that are associated with the etiology of IBD are yet to have proper shreds of evidence. Though certain dietary factors are associated with IBD, this includes protein and energy intake, intake of fast food and fat along with milk and fiber consumption. There have been several studies performed that showed that there is a link between ingestion of refined carbohydrate-rich foods and CD.[11] But the mechanism of diet or food intake as a trigger is yet to the date not fully understood. It has been observed in many patients suffering from IBD that they can identify those foods which can exacerbate their symptoms example milk and spicy foods. It has been also observed that 5 percent of patients suffering from UC improved by cutting their intake of cow's milk. Whereas patients with CD showed improvement in their condition when they started taking elemental amino acids, oligomeric peptides, and whole proteins. Breastfed infants were shown to have a reduced risk of developing IBD.

Smoking

It is estimated that about 40% of patients suffering from CD are smokers. Smoking worsens the condition to such an extent that surgery is then mandatory. About 10% of patients with UC smokes. Former patients are at a very high risk of developing UC while later have a lower risk. Cessation of smoking can give rise to UC. This is indicative that smoking helps prevent the onset of disease. The explanation for this is not clear. Yet it is believed that chemicals that are absorbed from cigarette smoke affect smooth muscles of the colon, this alters gut motility and GI transit. Some studies suggest the use of nicotine in the treatment of UC.[12]

Infection

Mycobacterium paratuberculosis has been considered as the causative agent for the CD. Though current evidence suggests it is not an etiological factor. UC may precipitate after an episode of infectious diarrhea, but there is a lack of evidence to support the role of one single infective agent.

Enteric microflora

The microbiome of the intestines is significantly involved in the pathogenesis of IBD since the systemic immune responses are governed by the gut. There is a significant loss of immunological tolerance to the microflora of the intestine in the case of patients suffering from IBD, thus antibiotics frequently play a good part in treating IBD. Effective strategies recently employed include the use of probiotics, prebiotics, and symbiotics. *Bifidobacteria* and *Lactobacillus* which are considered probiotics maintain the intestinal balance favorably. Prebiotics are employed for the growth and maintenance of probiotics in the colon.

Drugs

NSAIDs (diclofenac) have been shown to precipitate IBD.[13] This may be because of inhibition of cytoprotective prostaglandins. There occurs a relapse of the disease with the use of antibiotics, this is due to the destruction of enteric microflora. Those women who are on contraceptives are thought to have the risk of developing CD, this may be due to vascular changes.

Stress

Animal models have suggested that stress causes or triggers a recurrence of IBD. Various inflammatory mediators at the enteric nerves of the gut are thought to be initiated by stress. Moreover, living with IBD is also stressful.

Genetic

Mutations of certain genes such as CARD15/NOD2 which are present on chromosome no. 16 are associated with the CD. OCTN 1 (chromosome 5) and DLG 5 (chromosome 10) have recently studied genes that have a link with CD. HLA

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(human lymphocyte antibody) is strongly linked with UC, genetics studies revealed.

Xiaofa Qin has made certain findings and concluded that saccharine can be an etiologic factor responsible for IBD. Saccharine consumption is varied among the different countries. In the developed countries the saccharine consumption is more than that in developing countries as suggested by Xiaofa Qin. Thus, in the case of developed countries due to high socio-economic factors, and due to increased consumption of saccharine, the incidence of IBD is also high.[14]

Several pathogeneses are involved in the IBD. A summary of various contributing factors responsible for the pathogenesis of IBD is given in figure 3.

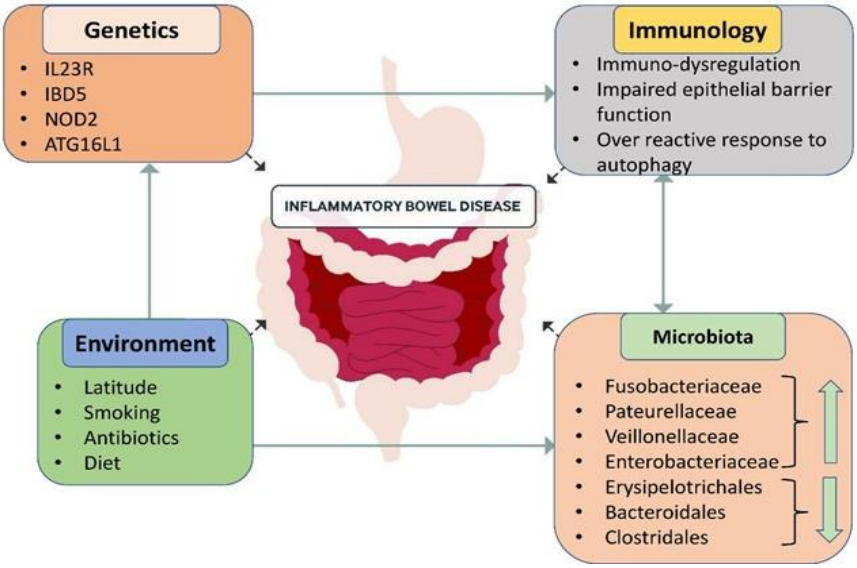

Figure 3: Summary of factors associated with the pathogenesis of IBD

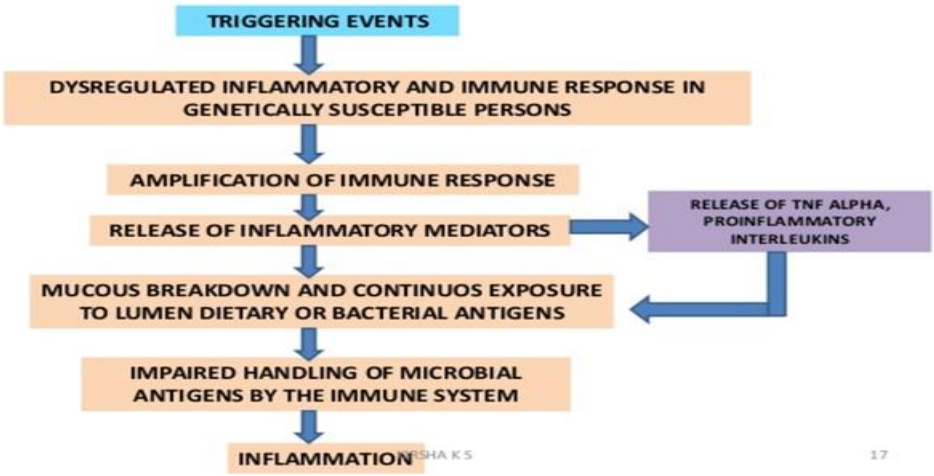

Figure 4(a): The cascade of triggering events leading to inflammation

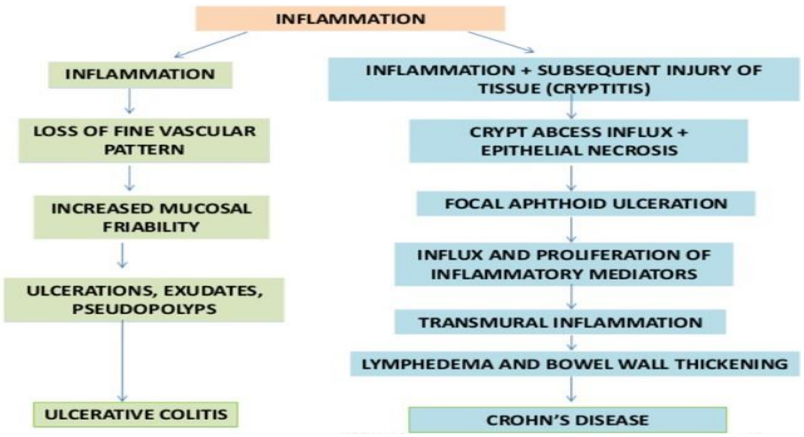

Figure 4(b): Series of events occurring after inflammation leading to UC and CD

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Figure 4 (a) gives an idea about how exactly inflammation occurs, and what causes inflammation. Figure 4 (b) depicts the cascade of events occurring after inflammation and the individual pathway of how UC and CD are precipitated.

Overall, the pathogenesis of IBD can be divided into 4 categories: Genetics, Environmental, Microbial, and Immunological.

Genetics

A genetic locus is a particular distinct position of a chromosome on which a specific gene or a marker of the gene is situated. More than 200 genetic loci are identified, of which 30 are proving to be responsible in the case of UC and CD. These were identified using GWAS (genome-wide association studies), next-generation studies on sequencing, and various analyses. These different analyses of genetic loci lead to the identification of the various pathways that play a crucial role in the maintenance of homeostasis in the intestine. These homeostasis mechanisms involve functions of the epithelial barrier, the defense system of the mucosal lining, regulation of the immune system along with adaptive immunity. In about one-third of patients suffering from CD, NOD 2 (nucleotide-binding oligomerization domain 2) was the first gene found to have its association with the disease. Increased responses of cytokines are associated with mutations R702W and G908R. Those patients in which there occurred mutations of 1007fs on the NOD2 gene are likely to show critical symptoms of CD. [1] The role of autophagy is also indispensable in generating immune responses in the case of IBD, as revealed by genetic analyses. ATG16L1 and IRGM are two genes associated with autophagy. Autophagy contributes to intracellular homeostasis by regenerating and recycling the contents of cytosol as well as provide resistance to the infection and aids in the elimination of micro-organisms present intracellularly. ATG16L1 is important for almost all types of autophagy. It was found out that there was an elevated risk of CD in the case of T300A mutation. Polymorphisms associated with CD in the IRGM gene are found out to decrease protein expression. Studies have shown that IBD has a link to the IL23R gene also. IL23R gene is responsible for the interleukin IL23 which is a pro-inflammatory cytokine. Some defects in the functioning of the IL-10 gene have also shown a link with UC and CD. Some other genes that aid in the regulation of immune functions are PRDM1, SMAD3, CARD9, REL, IL1R2. A “genetic vacuum” also known as the “mystery of missing heritability of common traits” is also observed in the case of IBD since many susceptible gene loci have been extensively studied to understand the pathogenesis of IBD yet these loci account for only twenty to twenty-five percent of the heritability. This is termed a “genetic vacuum”.[15]

Environmental

Pieces of evidence suggest that environmental factors are very significantly responsible for pathogenesis. Psychological elements, diet, drugs, social stress, geography, drugs, and smoking are some of the environmental factors that are involved in the pathogenesis of IBD. (15) (8) Among the above-mentioned factors, smoking is most popular and also broadly examined. This is because smoking has a miraculous effect on UC. According to the first study explained in 1982, heavy smoking has a protective effect on UC, also decreases the susceptibility of remission of development of UC.[15-18] On the contrary, smoking worsens the condition, or the risk of development of CD increases.[15,19]

Another important environmental factor is diet, which is believed to affect the condition of IBD. Recent studies have highlighted the fact that many dietary components play a crucial in the IBD, and their mechanisms are also proposed recently. Dietary fibers an important dietary component gets fermented to short-chain fatty acids (SCFA) with the help of colonic bacteria. This results in strengthening of the mucosal barrier and stimulates the production of IgA antibodies, another effect includes a reduction in cytokine production and also suppression of functions of inflammatory cells. Thus these lead to improvement of the condition of disease. A diet that is low in Fermentable Oligosaccharides Disaccharides, Monosaccharides, and Polyols (FODMAP) have been used in IBD patients to improve the symptoms of IBD. FODMAP diet gets fermented by the commensal bacteria present in the gut, producing gas and thus distension. Thus, excluding FODMAP from the diet improves the symptoms of IBD. Recent animal studies have shown that mice that were on a 50% sucrose diet had a marked increase in the permeability of the gut (prove by an increase in serum lipopolysaccharide), reduced microbial flora. Thus, susceptible to develop IBD. Yet human studies are lacking. Intestinal inflammation due to gluten was seen in the TNF-α knockout mice. Gluten in the diet is responsible for the release of cytokines, which are regulated by amylase trypsin inhibitors (ATIs). ATIs are found in gluten. Toll-like receptors are also found to be activated by ATIs. Studies have shown that 28% of IBD patients showed improvement in their condition after gluten avoidance.[20]

The immunological role of vitamin D has been identified nowadays. Works of the literature suggest the diverse functions of vitamin D in various ailments along with its role in IBD. Deficiency of vitamin D was commonly diagnosed in cases of IBD suffering patients, and it was concluded that low vitamin D levels had imparted a higher risk of IBD.[15,21,22]

NSAIDs such as aspirin have serious adverse effects on the GIT, but very little proof is available that NSAIDS have a provoking effect on IBD. Ananthakrishnan et al had found no such evidence about the dose, duration, and frequency of aspirin that develop the risk of IBD but found out that a very high dose of aspirin and its prolonged use can increase the risk of IBD.

Stress, depression, and anxiety contribute greatly to the pathogenesis of IBD. Those individuals with a decreased level of stress had a lower risk of development of IBD, a

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study performed by Bitton et al had suggested. Antidepressants are effective in the treatment of IBD.[15,23]

Air pollution augments the circulation of neutrophils and cytokines in the plasma, thus contributes to increased risk of UC and CD.[15]

Microbial

The gut of the human body is a hub for micro-organisms. Near about 1150 bacterial species lodges in the gut of a human. Many studies have shown that in the case of UC and CD, with and without inflammation segments showed that there was a decreased number of microbiomes in IBD compared to healthy people.[15,24,25] Studies have shown that in the case of intestines of healthy individuals, there was a preponderance of *Bacteroidetes and firmicutes*, whereas on the contrary there was a lack of these phyla of bacteria in the case of CD patients. It also has been reported that there was a significant decrease in the *Clostridium* species along with an increased number of *E. coli* in the case of UC.[15,26] A mucus lining is present on a healthy colon, it comprises of two layers, the inner layer is a tight adherent layer and usually sterile. The outer layer is loosely adherent and it is good for the bacteria to grow. In IBD more specifically CD there occurs a significant increase in the number of bacteria that are related to the adherent mucus layer of the colon.[15] Thus the homeostasis in the gut is maintained with the help of balanced microbial flora along with the "good bacteria". These include members of the *clostridia* family too. But whether IBD-associated dysbiosis is responsible for causing inflammation in the intestine remains controversial to date.[27]

Immunological

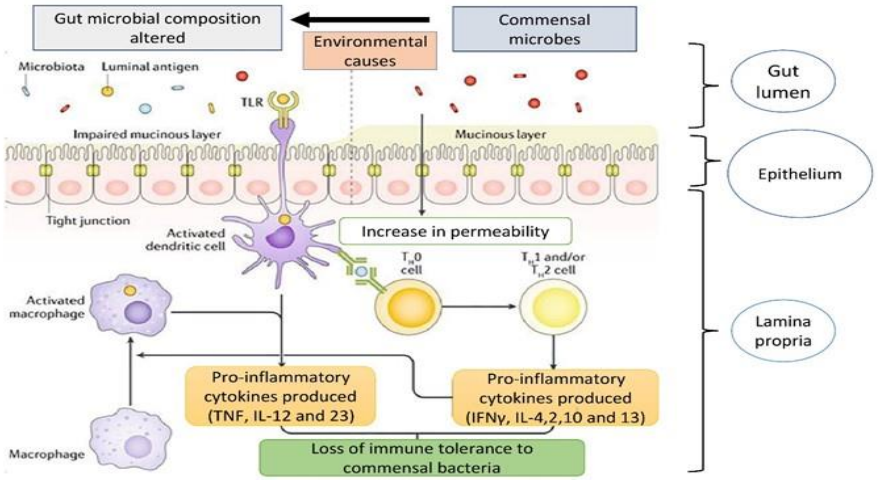

Figure 5: The immune responses involved in IBD.

Figure 5 depicts the various immunological responses that are involved in the development of IBD.

Examination of mucosal immunity, more specifically the responses of T cells are studied for a long-time to understand and investigate the pathogenesis of IBD. Immunity is broadly divided into two types- Innate and Acquired. Evidence suggests that the downregulation of these innate and acquired immunity pathways play also plays a significant role to produce inflammation and thus produce aberrations in the intestine ultimately precipitating IBD. Two decades of extensive studies and research had concluded that CD is primarily linked to the Th1 inflammatory response, whereas Th2 has been associated with UC.[15,28,29] Th17 cells are newly found cells also thought to be involved in the inflammation occurring in IBD.[15,30] In the case of innate immunity, responses such as autophagy and epithelial barrier integrity are the mucosal responses thought to be involved in IBD.[15]

Protection against pathogens is governed by the first-line defence, which is innate immunity. The innate immunity responses are governed by different cellular structures such as monocyte, large granular lymphocytes, accessory cells. This type of immunity is recognized by the protease-activated receptors (PARs) such as TLR (toll-like receptors) situated on the cell surface and NOD-like receptors situated in the cytoplasm.[15]

TLRs (toll-like receptors) contribute to giving the shape to intestinal microbiota, in controlling the different immune responses, along with maintaining homeostasis of the gut. A total of 9 TLR receptors is identified, each of their roles is given the table no. 2.

Table 2: Various Toll-like Receptors and their role.[31]

TLRs	Function in IBD
1 and 2	Prevention of chronic inflammation
2 and 6	Promotes colitis, suppress immune response
3	Promote protective immunity within inflammation conditions
4	Intestine tissue destruction, ulceration
5	Prevention of disease related to intestinal inflammation
7	Promote protective immunity within inflammation conditions
8	Induction of mucosa inflammation
9	Protection

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In a finding, it was found out that after giving an oral treatment of antibiotics, there was an upregulation of TLRs 4, 5, and 9 in the ileum while in the colon there was an upregulation of TLRs 3, 4, 6, 7, and 8. But there was a diminished response of TLRs 2, 3, 6 in the ileum and TLRs 2 and 9 in the colon.[31-33]

Diagnosis

Proper diagnosis is mandatory for distinguishing UC and CD. Yet there is no such gold standard that is used to properly diagnose UC and CD. Several diagnostic methods are available, all of them can be grouped into three major types. Table 3 gives a brief idea about the classification of various diagnostic methods.

Table 3: Diagnostic methods used to diagnose IBD

Lab Tests	Endoscopic Procedures	Imaging Procedures
Tests for anemia or infection Stool Examinations	Colonoscopy Flexible sigmoidoscopy Upper endoscopy Capsule endoscopy Balloon assisted enteroscopy	X-ray Computerized tomography (CT) scan Magnetic resonance imaging (MRI)

As summarized above, there are various methods and medical tests that aid the clinician to diagnose IBD.

One such technique is capsule endoscopy is effective in the diagnosis of CD. Before taking this test, the colon of the patient should be clean enough, hence before undergoing the test patient is assisted to drink a formulation to clean the colon. After oral ingestion of the capsule, which is pill-sized, takes the pictures of the inner linings of GIT. The pictures captured gives an idea to the physician about the location of the inflammation, ulceration, and erosion.[34,35]

Radiology tests, which are an alternative to endoscopy can also be used to diagnose IBD. This technique is useful in the diagnosis of CD where the small intestine is involved. In this procedure, the patient is given a barium sulfate-containing drink, which develops white on X-ray, and thus internal layers of the bowel are observed.[35]

Laboratory blood testing is yet useful and commonly used examination procedure. Blood testing results show an increased rate of sedimentation along with WBC counts. Both of these are results of inflammation in the intestine. A CBC (complete blood count) of IBD patients shows anemia, this is due to deficiency of Vit B12 and hemolysis due to autoimmunity.[35,36]

Other commonly used techniques include X-ray computer tomography and MRI (magnetic resonance imaging) for examination of complications (fistulae, small bowel obstruction, abscesses) in the abdomen region.[35] Computed tomography uses a multidetector scanning device with excellent resolution to visualize the mucous layer and the lumen.[35,37] It helps in the detection of fat deposition, an indication of chronic inflammation. MRI has also undergone many advances as that of computed tomography. Its high-resolution imaging allows examination of the bowel wall, thickening of the wall along with any edema, etc. These examinations are important for the diagnosis of IBD activity.[35]

Colon biopsies are required for confirmation of the diagnosis. The method is effectively used to differentiate types of inflammation. Few marked characteristic features of inflammation are seen in the case of the pathology of CD. These include transmural inflammation i.e., inflammation along with the depth of the intestine wall. Under a microscope, the biopsy of the colon shows the damage of mucosa and white blood corpuscle in the epithelium.[35,38] Specifically in the case of CD, aggregation of immune cells i.e., granulomas are also observed.[35,39]

Deformation of crypt structure and hemorrhage of lamina propria cells are marked pathological findings of UC. Some marked differences between UC and CD are there. Considerable thickening of the mucosa and less thickening of submucosa was observed in the case of UC but these structures seem normal in the case of CD.[35,40]

Treatment and Management Approach

A complete cure for IBD is not available to date. Treatment is the only option to control or manage IBD. Treatment may include either a pharmacological or non-drug approach.

Pharmacological Approach

As of UC is concerned, the treatment approach is generally stage-wise. For mild symptoms generally, amino salicylates are prescribed, for moderate symptoms generally corticosteroids are used, whereas cyclosporine is generally prescribed for the more severe symptoms.

In the case of CD, a location-based treatment approach is generally utilized. Almost the same drugs are used in the case of both CD as well as UC. For the maintenance therapy Aminosalicylate, azathioprine, metronidazole, methotrexate, and mercaptopurine are utilized.[41]

Detailed information of various treatments used in IBD is summarized in table no. 4. It also gives an idea about the various mechanism of action along with the side effects and characteristic features of several drugs.

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Table 4: Treatment types, examples of drugs, characteristic features, mechanism of action, and adverse effects of drugs used in IBD [41]

Type of Treatment	Drugs	Characteristic features	Mechanism of action	Adverse effects
Amino salicylates	Balsalazide Mesalamine (mesalazine) Sulfasalazine Olsalazine	Local immunosuppressive, non-specifically inhibits cytokines, average cost	Inhibit IL-1, Platelet activation factor and TNF-α, antibody secretion decreased.	Epigastric pain, dizziness, abdominal pain, dyspepsia and headache
Immunomodulators	Methotrexate 6-mercaptopurine Azathioprine	Anti-proliferation effect, decrease in the inflammation.	Blockade of de novo pathway of synthesis of purine	Black, tarred stools, chills, swollen glands, cough, fever
Corticosteroids	Budesonide Hydrocortisone Methyl-prednisolone Prednisone	Highly immune suppressive, increased risk of infection, cost is low	Blockade of phospholipase A2 of arachidonic cascade thus producing imbalance between PG and leukotrienes, Stimulate apoptosis in lamina propria, suppress cytokine transcription.	Intracranial hypertension, myalgia, subcapsular cataracts, glucose intolerance, malaise, acne, mood disturbance, full moon face
Biologicals: Cytokine Antagonists	Ustekinumab Golimumab Adalimumab Infliximab Certolizumab-pegol	Cytokine specific inhibition, immunosuppressive, cost is high, requires advanced technology	Induces apoptosis in cells which are proinflammatory, TNF-α specific binding, blockade of interaction receptor.	Tuberculosis, constipation, hernia, facial oedema, abdominal or stomach pain, itching, joint pain.
Biologicals: Anti- cell adhesion molecule	Natalizumab Vedolizumab	Cell adhesion specific inhibition, cost is high, requires advanced technology	Inhibition of migration	Leukoencephalopathy in case of natalizumab, increased risk of infections, nasopharyngitis.

Amino salicylates

Amino salicylates are used combinedly with corticosteroids for control of remission of patients suffering from IBD. For mild to moderate symptoms generally, mesalamine(5-ASA) is used. Sulfasalazine (mesalamine linked with sulphapyridine joined through azo linkage) was found to be effective in the maintenance of remission as of UC is concerned. After reaching the colon cleavage of the diazo bond occur due to enzyme bacterial azo reductase, thus liberating sulphapyridine along with mesalamine. Absorption and metabolism of sulphapyridine occur with the help of hepatic acetylation and then glucuronidation. If 5-ASA or sulphapyridine is given orally, its absorption occurs in the upper GIT. Sulfasalazine is an advantageous molecule since the azo linkage present in it prevents its absorption in the stomach and small intestine until the bacteria of the colon does not cleave the bond. The different sites of action of sulfasalazine and mesalamine include inhibition of NF-kB (nuclear factor kappa B), free radical and oxidants scavenging, inhibition of interleukin 1, TNF-α, lipoxygenase pathway inhibition. Due to several side effects of 5-ASAand sulphapyridine, second-generation 5-ASA compounds are developed. These can be divided into two categories: prodrugs (olsalazine, balsalazide) & coated drugs (delayed-release pH-sensitive coating on mesalamine) Oral sulfasalazine showed 60 to 80% efficacy in mild to moderate UC.[42,43]

Corticosteroids

Corticosteroids are used either alone or in combination with mesalamine. Azathioprine is combined with other lower doses of steroids, because of its steroid-sparing property. Steroid responses in each patient can be divided into three classes. Steroid responsive (patients improve within 1 to 2 weeks, discontinuation of dose causes remission), steroid-dependent (relapse of symptoms occur as the dose is tapered), steroid unresponsive (unimprovement of the condition even at high dose). Steroids are utilized for a long period to control the symptoms, but alternative therapies (immunosuppressives) are taken into consideration in those patients who suffer from a relapse. In both UC and CD, there is the ineffectiveness of maintaining relapse

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through steroids. Budesonide is used in the case of ileocecal CD; it is an enteric-release formulation.[42]

Immunosuppressants

Drugs that are developed for cancer chemotherapy and organ transplants are being utilized for the treatment of IBD. Though immunosuppressants have several side effects, they are well tolerated than steroids. But these agents are not to be used in young patients. Those patients who are steroid-resistant or dependent, are administered with mercaptopurine and azathioprine. These are antimetabolites that disrupt the biosynthesis of purine. Methotrexate is another such immunosuppressant. It inhibits the dihydrofolate reductase enzyme, thus blocking DNA synthesis and finally the death of the cell. This mechanism of inhibition of the dihydrofolate reductase enzyme is believed to be responsible for its anti-inflammatory action. Side effects with methotrexate are rare.[42]

Some of the very recent treatment approaches are summarized in table 5.

Table 5: Recently used treatment approaches.[44]

Treatment class	Examples of drugs
New anti-TNFs	AVX-470
Anti-Adhesion biologics	Vedolizumab Etrolizumab Abrilumab PF-00547659
IL-12/IL-23 inhibitors	Ustekinumab Risankizumab
Small molecule drugs	JAK inhibitors (Tofacitinib) Sphingosine-1- phosphate receptor modulators (Ozanimod and Fingolimod) Phosphodiesterase 4 inhibitors (Apremilast)
Stem cell transplant	
Faecal microbiota transplant	

AVX-470 a recently available new anti-TNF is a polyclonal oral immunoglobulin obtained after purification of cow colostrum (recombinant human TNF immunized cows). Poor absorption of this drug occurs from the GIT into the systemic circulation and hence these are suitable for oral administration. The risk of immunosuppression by this drug is quite low. With its decreased immunogenicity and systemic side effects, AVX-470 has the potential to be used as an alternative to traditionally available anti-TNF for IBD. Yet further trials are needed.[44]

Natalizumab, the first anti- adhesion biologic had gained an evidence base in IBD. It is a non-specific inhibitor of α4β7 and α4β1 integrins. It was used as rescue therapy for the treatment of IBD (second-line treatment). But natalizumab develops a condition known as PML (progressive multifocal leukoencephalopathy) which is a destructive neurological disorder. Vedolizumab targets the α4β7 integrin adhesion molecule which is situated on the surface of gut-specific lymphocytes. It binds to mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1) which is located on intestinal vasculature. Similar to vedolizumab, certolizumab binds selectively to the β7 subunit of α4β7 and αεβ. This approach is therefore called the double-headed treatment approach. Vedolizumab showed the presence of very minor adverse events (less than 6%) such as headache, nasopharyngitis, upper respiratory tract infection, arthralgia, nausea, and fatigue. Various clinical trials have shown no cases of PML with the use of vedolizumab. Abrilumab, a selective inhibitor of α4β7 can be given subcutaneously has a long half-life and higher bioavailability. A recent randomized phase 2 b study has shown that there was a significant improvement in the patients. Mucosal healing was also seen in about one-third of patients. Incidence of PML was not observed in patients treated with Abrilumab.[44]

Interleukin 12 (Il-12) activates macrophages and natural killer cells (NK). It is also an inducer of Th 1 cells (T helper 1). Il- 23 is responsible for Th 17 differentiation, which is responsible for the production of various inflammatory cytokines. Thus, by inhibition of IL-12 and 23, the production of cytokines Il-17 and Il-22 is prevented. This can be inhibited by Ustekinumab and Risankizumab. Ustekinumab is an approved treatment for mild to severe CD, it is a monoclonal antibody. Risankizumab, a humanized monoclonal antibody is more selective than that of Ustekinumab. Risankizumab, unlike Ustekinumab, does not inhibit or affect the Il-12 pathway which is responsible for immunity against cancer and infection. Worsening of the condition of CD was observed with Risankizumab. Therefore, many further investigations are required as far as Risankizumab is concerned.[44]

Small-molecule drugs (SMDs) are low molecular weight compounds (less than one-kilo dalton) that can diffuse easily across cell membranes unlike macromolecules such as anti- TNF which are unable to diffuse easily. As compared to other biologics, SMDs have much more advantages, the patient does not require hospital attendance or any kind of injections, since these SMDs are administered orally. Thus, these are patient compliant. Another advantage is their lack of immunogenicity. Tofacitinib is an oral JAK inhibitor (JAK 1,2,3). The JAK-STAT pathway has been responsible for the pathogenesis of IBD. Studies have shown that the patients showed significant mucosal healing after oral administration of tofacitinib. But the risk of herpes zoster infection, cellulitis, pneumonia, thromboembolism, and the anal abscess was also observed. Ozanimod is a sphingosine-1-phosphate receptor modulator (S1P). S1P binds to five different types of GPCR S1P $_{1\text{-}5}$ These receptors are responsible to mediate lymphocyte trafficking, tone, and permeability of blood vessels and angiogenesis. S1P modulators get bind to S1P receptors and cause a decrease in the level of T cells, thus leading to immunosuppressive action. Ozanimod

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selectively binds to $S1P_1$ and $S1P_5$. Currently, it is under phase 2 clinical trial. Fingolimod, a similar drug to ozanimod has been developed which is used in the case of multiple sclerosis. But it has shown serious adverse events such as oedema of the macula, blockade of atria, and ventricle along with bradycardia. Studies have shown that those on S1P receptor modulators treatment are at major risk of developing PML. Phosphodiesterase 4 (PDE 4) inhibitors such as Apremilast inhibits enzyme phosphodiesterase 4 which is responsible for regulating the concentration of cyclic adenosine monophosphate (cAMP). cAMP is responsible for the regulation of NF-κ-B. Inhibition of PDE4 causes reduction of TNF-α along with an increase in the synthesis of Il-10 which is an anti-inflammatory cytokine. Apremilast is an approved oral drug against psoriatic arthritis. Since IBD and psoriatic arthritis shares many pathogenic pathways, Apremilast is a potent agent used against IBD. Recent studies have shown that there was a marked reduction in the C-reactive protein (CRP) levels and healing of mucosa.[44]

Stem-cell transplant is currently an emerging new method to the inflammation caused by IBD. This therapy aims to use multipotent cells i.e., hematopoietic stem cells (HSCs) and mesenchymal cells (MSCs). HSCs are isolated from either the umbilical cord or bone marrow, they can differentiate into the immune cells and the blood, thus they migrate to the damaged tissue and help in restoring the mucosa. MSCs can inhibit the function of Th1 and Th17 cells and thus promote the healing of tissues. Recent studies have focused on hematopoietic stem cell transplant (HSCT). Faecal microbiota transplant (FMT) is also gaining much attention to be used in the treatment of IBD. It gained much attention after *C. difficile* was treated successfully using FMT.[44]

Non-drug approach

There are some ways by which one can treat IBD along with the drugs which are also found efficacious. These approaches are termed non-pharmacological treatments. Following are some of them, which are found effective to treat IBD.

Practicing mindfulness

Mindfulness includes focusing on the present moments, as per the American Psychological Association. Mindfulness helps to improve the state of mental health-related to IBD. Improvement in the quality of life, reduction of symptoms of depression, and better coping strategies are observed after the patient practices mindfulness.

A low-FODMAP diet

FODMAP is an acronym for Fermentable Oligosaccharides Disaccharides, Monosaccharides, and Polyols. These are short-chain carbohydrates and sugar alcohols that are not completely absorbed by the body. This leads to abdominal pain and bloating. The Low FODMAP diet involves withdrawing such foods containing high carbohydrates for 8 weeks. Once the 8 weeks are complete, gradual introduction of these is done in the diet.

Incorporation of Cardiovascular exercise in routine

Regular physical exercise is good and beneficial for IBD patients. Both walking and running are found excellent for IBD patients as reported by researchers.

Cognitive Behavioural Therapy (CBT)

Mental health issues run along with IBD. The risk of depression and anxiety increases with IBD. CBT is a type of problem-solving approach between the patient and the therapist. It challenges some of the patients' thought processes. A study conducted in 2018 saw improvement in the condition of IBD with the help of CBT.

Stress management

Management of stress is of utmost importance in such chronic diseases. Thus, it has been found out that stress management can do wonders in improving the patient's condition of IBD.

Regular intake of vitamins and minerals

Risk of deficiencies of calcium, vitamin D, B6, iron, magnesium is much more in IBD. This may lead to anaemia. Thus, a regular intake of vitamins and minerals is necessary.

Cessation of smoking

Since the relationship between smoking and IBD is still a big question but negative impact of smoking outweighs its benefits. Smoking has a very negative impact on fertility. Thus, it is best to stop smoking.

CONCLUSION

It is clear from the review that inflammatory bowel disease is an incurable, chronic disease that is manifested by serious episodes of inflammation. The disease is incurable to date and it is only that treatment options are the only resort clinicians are dependent on. There are several treatment options available but they come with serious side effects. Yet it is only the lifestyle changes that will help battle this disease since it is being observed that the prevalence of the disease is much more in the urbanized nations. Hence, only lifestyle changes can help battle this serious disease.

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