A COMPREHENSIVE REVIEW OF INFLAMMATORY BOWEL DISEASE

S.Sivakrishnan M.Pharm.,Ph.D.,[1*] J.Kavitha MDS., [1]

Assistant Professor, Department of Pharmacy, FEAT, Annamalai University,

Assistant Professor, Division of Periodontia, RMDCH, Annamalai University,

Annamalai Nagar, Chidambaram-608002, Tamilnadu, India

ABSTRACT

Inflammatory bowel disease (IBD) is a group of idiopathic chronic inflammatory intestinal conditions. The two main disease categories are Crohn's disease (CD) and ulcerative colitis (UC), which have both overlapping and distinct clinical and pathological features. Ulcerative colitis and Crohn's disease which cause inflammation of the bowel. This inflammation is thought to be due to dysfunction of your immune system, and is not due to an infection. Ulcerative colitis causes inflammation of only the inner lining of the colon and rectum (large bowel). When only the rectum is involved it is sometimes called ulcerative proctitis or just proctitis. When the entire colon is involved it is sometimes called pan-colitis. Crohn's disease causes inflammation of the full thickness of the bowel wall and may involve any part of the digestive tract from the mouth to the anus (back passage). Most frequently the ileum, which is the last part of the small bowel, the colon or both are involved. These patterns of disease location are referred to as ileitis, colitis and ileo-colitis. This review reveals to understand the maximum knowledge about the inflammatory bowel disease such as epidemiology, causes, pathophysiology, clinical features, diagnosis and treatment will explore the innovative ideas about researchers.

Keywords: Crohn's disease, Ulcerative colitis, Inflammatory Bowel Disease, Inflammation

INTRODUCTION

Inflammatory bowel diseases are a group of inflammatory conditions in which the body's own immune system attacks parts of the digestive system. The two most common inflammatory bowel diseases are Crohn's disease (CD) and ulcerative colitis (UC). CD and UC cause chronic inflammation of the GI tract. CD can affect any part of the GI tract, but frequently affects the end of the small intestine and the beginning of the large intestine. The inflammation in CD can affect all layers of the intestinal lining. Ulcerative colitis (UC) is characterized by inflammation in the large intestine (colon) and the rectum. The inflammation in UC occurs only in the innermost layer of the intestinal lining.

Crohn's Disease

Crohn's disease, one of the most frequent forms of inflammatory disease worldwide, is characterized by the formation of strictures, fistulas, ulcers, and granulomas in the mucosa. Although the CD's gastrointestinal manifestation can primarily affect the terminal ileum region, it can also compromise any region from the mouth to the rectum of affected patient. The clinical manifestations of CD can include diarrhea or bloody diarrhea, malnutrition, abdominal pain, and weight loss. Extraintestinal findings, for instance, arthropathy or skin disorders, rarely occur. However, manifestations on skin, muscle, or bone of metastatic Crohn's disease can actually lead to recognition of occult intestinal disease [1–3]. In general, CD has a genetic background and the first-degree relatives of affected individuals have a fivefold greater risk of developing the disease [4, 5]. The localized release of certain cytokines, such as IL-12, IL-17, TNF-α (Tumor Necrosis Factor Alpha), and IFN-γ (Interferon gamma), has been implicated in the chronic intestinal inflammation observed in CD patients [6, 7]. The production of IL-12 (IL-Interleukin) and IL-18 by antigen-presenting cells (APC) and macrophages generates a polarized differentiation towards Th1 lymphocyte, leading to an increased release of proinflammatory cytokines, including TNF-α and IFN-γ. Additionally, Th1(T helper (Th)) cytokines stimulate the antigen-presenting cells to secrete a wider spectrum of inflammatory cytokines such as IL-1, IL-6, IL-8, IL-12, and IL-18, resulting in a self-sustained cycle [8].

Ulcerative Colitis

Ulcerative colitis is another form of IBD characterized by superficial ulcerations, granularity, and a vascular pattern. In contrast with the inflammation found in CD transmural and being able to occur throughout the entire gastrointestinal tract inflammation in UC is limited to the mucosal layer of the colon[9,10]. Although Montreal classification—a system to classify IBD phenotypes including UC—is widely used, data on its reliability are very limited due to the great variety of clinical presentations of UC. In general, the clinical manifestation of UC can include release of blood and mucus, petechial hemorrhage, and granulation tissue, among others. However, in periods of remission, the mucosa may have normal appearance. In most severe forms of the disease, the intestine can get distended, presenting deep ulceration and possibly intestinal perforation [11]. In UC, there is a substantial increase in the secretion of IL-13, the main interleukin responsible for the inflammation and chronicity of this condition. Despite the Th1 involvement, UC patients also present a Th2 response with increased secretion of IL-4, IL-5, and IL-9 [12,13]. It has been suggested that the expression of the PU.1 transcription factor, a regulator of cellular communication, and the production of IL-9 by effectors' Th9 cells block the proliferation of intestinal epithelial cells and regulate the expression of several tight-junction proteins. Together, these aspects favor the translocation of specific bacterial species with subsequent activation of immune cells and mucosal inflammation in experimental and human UC. As in CD, Th17-related cytokines are also increased in UC [14, 15].

EPIDEMIOLOGY

Ulcerative colitis is slightly more common in males, while Crohn's disease is more frequent in women. The highest incidences of CD and UC have been reported in northern Europe [16], the United Kingdom [17, 18] and North America[19,20]. In those regions, such high incidences may indicate common etiologic factors. The incidence of UC is greater than that of CD, except in Canada [21-23] and several areas of Europe [24-27], although this has been changing over the past twenty years. Canterbury County, New Zealand, has among the highest incidence of CD (16.5/100,000 people)[28]; IBD has emerged in countries in which it had rarely been previously reported, including South Korea, China, India, Iran, Lebanon, Thailand, the French West Indies, and North Africa [29,30]. In these countries, the occurrence of UC preceded that of CD by about 10 years. In some countries, such as Japan, the incidence of IBD was initially low but has recently increased. The overall incidence of IBD can be broken down into several geographic zones: those with a high incidence, those with a moderate incidence, those with low incidence 15 years ago but where incidence has constantly increased, and those with unknown incidence. In Environmental factors, Ulcerative colitis is more common among ex-smokers and nonsmokers, while Crohn's disease is more common among smokers. IBD is more common in developed countries. There is north- to- south variation and is more common in urban communities compared with rural areas. These observations suggest that urbanization is a potential contributing factor. It is believed that this is the result of "westernization" of lifestyle, such as changes in diet, smoking, differences in exposure to sunlight, pollution, and industrial chemicals. United States have examined the relationship between socioeconomic factors and IBD. One study found both ulcerative colitis and Crohn's disease are more prevalent in white-collar occupations. Another study found Crohn's disease and ulcerative colitis were less common in groups with higher education and income. A third study found a minor association between specific occupations and IBD. Other factors such as, Diet, oral contraceptives, perinatal and childhood infections, or atypical mycobacterial infections have been suggested, but not proven, to play a role in developing IBD.

PATHOPHYSIOLOGY

Twin studies [31] have shown that a genetic predisposition [32], as opposed to environmental factors, plays a larger role in Crohn's disease than in ulcerative colitis. More than 160 risk genes are associated with Crohn's disease; most of them affect the interaction of microbes with the bowel [33] and are dependent on phenotype [34]. Important environmental factors include antibiotic consumption during childhood and adolescence and, for Crohn's disease, cigarette smoking [35]. The commensal microflora of the bowel are now thought to play a central role in the induction and maintenance of the chronic inflammatory process [36-40]. The normally peaceful coexistence of about 10 micro-organisms of at least 1000 bacterial species in the human gastrointestinal tract is an amazing phenomenon, particularly in the terminal ileum and colon, which is the site where the bacterial concentrations are highest and where the manifestations of Crohn's disease and ulcerative colitis are most commonly found. There is a "dysbiosis" of the microflora [41] of uncertain primary significance [42]; IBD patients, unlike normal individuals, have bacteria directly on and in their mucosal epithelium [43, 44]. The earlier interpretation of IBD as classic autoimmune diseases is obsolete [45]; instead, they are now thought of as complex barrier disorders. The mucosal barrier consists of the epithelial layer and the antibacterial mucus layer above it, which is made up of goblet cell mucins and epithelially secreted intrinsic peptide antibiotics (defensins) [46]. In ulcerative colitis, a defective, thinned mucus layer is seen [47]. In Crohn's disease of the small intestine, the Paneth cells at the base of the crypts and defective defensin formation seem to play a central role [48].Various defects of bacterial recognition (NOD2), autophagy,

endoplasmic reticulum stress, and monocyte function impair antimicrobial defenses and alter the microbiome [49-51]. Invading bacteria induce an inflammatory response involving both the innate immune cells (granulocytes, macrophages, dendritic cells) and the adaptive immune cells (T cells).

CAUSES

The exact cause of IBD remains unknown. Researchers believe that a folloeing factors lead to IBD: a genetic component, an environmental trigger, an imbalance of intestinal bacteria and an inappropriate reaction from the immune system. Immune cells normally protect the body from infection, but in people with IBD, the immune system mistakes harmless substances in the intestine for foreign substances and launches an attack, resulting in inflammation.

Age: IBD can occur at any age, but often people are diagnosed between the ages of 15 and 35.

Gender: In general, IBD affects men and women equally. Ulcerative colitis is slightly more common in males, while Crohn's disease is more frequent in women.

Ethnicity: IBD is more common among Caucasians, but it can affect people of any racial or ethnic group.

Family history: As many as one in five people with IBD have a first-degree relative (parent, child or sibling) with the disease.

Cigarette smoking: Smokers are more likely to develop CD. Ulcerative colitis is more common among ex-smokers and nonsmokers, while Crohn's disease is more common among smokers.

Other factors: Diet, oral contraceptives, perinatal and childhood infections, or atypical mycobacterial infections have been suggested, but not proven, to play a role in developing IBD.

CLINICAL FEATURES

Symptoms

IBD is a chronic, intermittent disease. The symptoms range from mild to severe during relapses, and they may disappear or decrease during remissions. In general, the symptoms depend on the segment of the intestinal tract involved.

Symptoms related to inflammatory damage in the digestive tract are diarrhea, nocturnal diarrhea, Incontinence, Constipation, Pain or rectal bleeding with bowel movement, bowel movement urgency, tenesmus, abdominal cramps and pain, nausea and vomiting may occur. General symptoms associated with UC and CD in some cases are fever, loss of appetite, Weight loss, Fatigue, Night sweats, Growth retardation and Primary amenorrhea.

Extraintestinal manifestations

Extraintestinal manifestations include musculoskeletal conditions (peripheral or axial arthropathy), cutaneous conditions (erythema nodosum, pyoderma gangrenosum), ocular conditions (scleritis and uveitis), and hepatobiliary conditions.

COMPLICATIONS

Intestinal complications

Proximal gastrointestinal involvement is a complication, or a different disease presentation. It may occur more often in children and in some adult ethnic groups (African-Americans, Ethiopians), but it is also sought more commonly in children, with whom gastroscopy is a routine early investigation, whereas in adults it is not.

Hemorrhage: profuse bleeding from ulcers occurs in UC. Bleeding is less common in CD. Massive bleeding in CD is more often seen due to ileal ulceration than in colitis. 5–10% of individuals with CD show ulceration in the stomach or duodenum.

Bowel perforation is a concern in CD, and in both CD (if the colon is involved) and UC if megacolon ensues, Intra-abdominal abscesses in CD, Strictures and obstruction, Scarring, Colonic strictures, Fistulas and perianal disease, pneumaturia or fecaluria, or passage of air from the vagina. This may result in urinary tract infection or gynecological inflammation and malignanacy.

Extraintestinal complications

Extraintestinal complications should be differentiated from extraintestinal manifestations, and they may be related to disease or to drugs used for IBD. e.g., drug-induced arthropathies (corticosteroids, biologicals), ocular complications, hepatobiliary complications, renal complications (drug-induced tubulointerstitial nephritis), anemia, bone complications, venous thromboembolic disease, arthralgias and mood and anxiety disorders

DIAGNOSIS

The diagnosis of IBD in adults requires a comprehensive physical examination and a review of the patient's history. Various tests, including blood tests, stool examination, endoscopy, biopsies, and imaging studies help exclude other causes and confirm the diagnosis.

Patient history

- ✓ Symptoms: Diarrhea, abdominal pain, vomiting, weight loss, extraintestinal manifestations, fistulas, perianal disease (in CD), fever.
- ✓ Duration of current complaints, nocturnal awakening, missing work or usual social activities.
- ✓ Extraintestinal manifestations: including, but not limited to, arthritis, inflammatory ocular disease, skin diseases, osteoporosis and fractures, venous thromboembolic disease.
- ✓ Mood disorders are present, or stressful situations known to precipitate IBD.
- ✓ Recent and past medical problems about intestinal infection.
- ✓ History of tuberculosis (TB) and known TB contacts.
- ✓ Travel history.
- ✓ Medications such as antibiotics, Non Steroidal Anti-Inflammatory Drugs (NSAIDs), and others like corticosteroids for acne.
- ✓ Family history (IBD, celiac disease, colorectal cancer, TB).
- ✓ Cigarette smoking.

Physical Examination

- ✓ **General:** General well-being, pallor, cachexia, clubbing, nutritional status ,pulse rate and blood pressure, body temperature and body weight and height
- ✓ **Abdominal region:** Mass, distension, tenderness, rebound, guarding ,altered bowel sounds, hepatomegaly and surgical scars
- ✓ **Perianal region:** Tags, fissures, fistulas, abscess and digital rectal examination (assess for anal strictures and rectal mass)
- ✓ **Extraintestinal inspection**: Mouth, eyes, skin, and joints: aphthous ulcers, arthropathy, uveitis, episcleritis, erythema nodosum, pyoderma gangrenosum, sweet's disease, primary sclerosing cholangitis and metabolic bone disease.

OTHER DIAGNOSTIC PROCEDURES

To help confirm a diagnosis of CD or UC, one or more of the following tests and diagnostic procedures may be performed.

Blood tests: The presence of inflammation in the body can be identified by examining the levels of several factors in the blood, including red and white blood cells, platelets and C-reactive protein (CRP). Tests may be performed to help health care providers differentiate IBD from non-IBD and CD from UC. In certain situations, blood tests may also be used to evaluate a patient's risk of developing disease complications, as well as to optimize treatment strategies (ex., Crohn's Prognostic test).

Stool tests: Stool tests look for signs of inflammation in the GI tract as well as infections.

Endoscopic procedures: This procedure utilizes a flexible tubular camera to look inside of the digestive tract by entering through the mouth or anus. The scope has other tools that may be used for additional purposes, including the collection of tissue samples or biopsies. A capsule endoscopy may also be performed. This involves swallowing a capsule equipped with a camera that takes pictures as it travels through the intestine. The images are wirelessly sent to a receiver worn by the patient. The capsule is expelled during a bowel movement, usually within a day.

External imaging procedures: These procedures utilize different technologies to generate images of the digestive organs and other soft tissue from outside the body, including computerized tomography (CT) scans and magnetic resonance imaging (MRI).

TREATMENT

The following medications were used to manage the disease and its symptoms:

Aminosalicylates, such as sulfasalazine, mesalamine, olsalazine and balsalazide, are medicines containing 5-aminosalycylic acid, an aspirin-like compound. They reduce inflammation in the lining of the intestine and are used in mild to moderate cases.

Monoclonal antibodies: Anti-TNF-α antibodies are frequently used to treat IBD because they are able to efficiently reduce the amount of TNF-α in the body. Recent studies suggest that infliximab, a monoclonal antibody, is a potential treatment for Crohn's disease because it neutralizes TNF-α by preventing it from interacting with its receptor. The complementarities between the TNF-α molecule and the variable region of infliximab make this antibody a promising treatment for Crohn's disease and other autoimmune disorders. Other antibodies, such as adalimumab and certolizumab, have also shown significant positive results in the treatment of IBD.

Thalidomide: Thalidomide is involved in the pathophysiology of Crohn's disease since it suppresses all the major cytokines that participate in intestinal inflammation. Likewise, thalidomide destabilizes TNF-α messenger RNA, leading to a significant decrease in the amount of TNF-α, a proinflammatory cytokine responsible for the inflammation of Crohn's disease. It also stimulates the production of cytotoxic T-cells, resulting in an increase in the number of T-lymphocytes. Although thalidomide is beneficial in dampening the production of proinflammatory cytokines.

Corticosteroids: including budesonide, prednisone and prednisolone, are steroids that are used as short term treatment during flares. They act on the immune system and suppress its ability to begin and maintain inflammation.

Immunomodulators: such as azathioprine, 6-MP (Mercaptopurine), cyclosporine and methotrexate, affect the body's immune system so that it is unable to maintain an inflammatory response. Unlike steroids, however, they are a long-term treatment.

Biologic therapies: including infliximab, adalimumab, certolizumab pegol, golimumab, lizumab and natalizumab, are antibodies grown in the laboratory that stop certain proteins in the body from causing inflammation.

Antibiotics: such as metronidazole and ciprofloxacin, are used when infection occurs, either from the disease itself or from post-surgical procedures.

DIET AND NUTRITION

It is also important for people with IBD to pay attention to fluid intake. When chronic diarrhea is present, it can lead to dehydration. Stay well hydrated to avoid complications. During periods of disease flare-ups, eating may cause abdominal discomfort and cramping. Here are some ways to reduce these symptoms:

Eat smaller meals at more frequent intervals. Eat five small meals a day, every three or four hours, rather than the traditional three large meals a day. Reduce the amount of greasy or fried foods. High-fat foods may cause diarrhea and gas if fat absorption is incomplete. Watch dairy intake. Persons who are lactose intolerant or who are experiencing IBD or IBS may need to limit the amount of milk or milk products they consume. Restrict the intake of certain high-fiber foods. If there is narrowing of the bowel, these foods may cause cramping. High-fiber foods also cause contractions once they enter the large intestine. Because they are not completely digested by the small intestine, these foods may also cause diarrhea. Avoid problem (trigger) foods. Eliminate any foods that make symptoms worse. These may include "gassy" food (such as beans, cabbage and broccoli), spicy food, popcorn and alcohol, as well as foods and drinks that contain caffeine, such as chocolate and soda.

CONCLUSION

Inflammatory bowel disease (IBD) is defined as a chronic intestinal inflammation that results from host-microbial interactions in a genetically susceptible individual. IBDs are a group of autoimmune diseases that are characterized by inflammation of both the small and large intestine, in which elements of the digestive system are attacked by the body's own immune system. This inflammatory condition encompasses two major forms, known as Crohn's disease and ulcerative colitis. In this article, we have

discussed on pathophysiology, epidemiology, causes, symptoms, clinical features, diagnosis and treatment of inflammatory bowel disease. The information obtained from various sources like journals, different literature reviews, medical and pharmacy textbooks, proceedings, and web sources will help us to better understand the inflammatory bowel disease and may have significant impact on treating patients with the disease.

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