CROHN'S DISEASE: A REVIEW ON EPIDEMIOLOGY, DIAGNOSIS AND THERAPEUTIC MANAGEMENT

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ABSTRACT

Crohn's disease (CD) is a kind of inflammatory bowel disease (IBD) characterized by the chronic transmural inflammatory state of gastrointestinal tract that typically affects ileum, colon, and perineum. Although the precise etiology is unknown, the major risk aspects concerned with CD consist of several environmental factors, altered microbiota, unhealthy low fiber- high carbohydrate diet, and certain medicines like non-steroidal anti-inflammatory drugs. The disease has wide distribution and inflammation may affect the different areas of the alimentary tract in diverse people. In about 80 % of patients, only small bowel involvement is typically present, affecting distal ileum resulting in ileitis. In about 50 % patients, both ileum and colon are affected resulting in ileocolitis and in approximately 20 % patients, disease is limited to colonic portion. Perianal disease affects almost one-third of patients. As per the various genetic researches in the CD patients, various genetic mutations affect the body's immunological system that results in severe inflammatory state. The two major gene mutations which result in the pathological state of CD are autophagy-related 16-like 1 (ATG16L1) and nucleotide-binding oligomerization domain-containing protein 2 (NOD2/ Card15). The main techniques used for diagnosis of CD include the combination of pathological findings, endoscopic and radiographic findings demonstrating the disease features. The utmost preferred radiologic study for assessing the small bowel CD is abdominal computerized tomography (CT). The goal of current treatment strategies is to address symptomatic relief. Sequence of treatment includes induction therapy, followed by maintenance of remission. The currently used drugs that effectively can cause induction as well as maintain remission include 5-aminosalicylic acid, Tumor Necrosis Factor (TNF) inhibitors, immunomodulators and steroids. Treatment and management should be integrated with lifestyle and dietary amendments to prevent therapeutic failure and consideration of surgical intervention.

Keywords: Crohns's disease, Colitis, Inflammatory bowel disease, Inflammation, Pain

INTRODUCTION

Crohn's disease (CD) was originally investigated in research literature in 1932[1], where the disease was recognized by a chronic state of gastrointestinal inflammation. CD is a part of a broad group of provocative disorders known as inflammatory bowel disease (IBD)[2]. The ailment condition is primarily characterized by tissue lesions and transmural (full thickness) inflammation along with weight loss and bloody diarrhea[3]. The disease location is widespread over the entire alimentary tract affecting any location from oral cavity to perineum and as per the inflammatory state, the disease is further categorized as terminal ileitis, ileocolitis, regional ileitis and granulomatous enteritis[4]. Nearly 50 % of the patients complain chronic inflammation in terminal ileum and the colon, while 30 % complain of small-bowel provocative irritation, and approximately 20 % patients suffer from chronic colon inflammation. Additionally, 25 % patients grieve from the perianal difficulties together with fissures and fistula. Rarely (about <10%)[5], patients may suffer with

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Table I: Affected sites in Crohn's disease with associated symptoms and diagnosis[6,9,10]

Site	Frequency	Symptoms	Diagnosis
Small bowel	28 %	Abdominal cramps, diarrhea, gastric pain, weight loss	CT enterography, colonoscopy, capsule endoscopy, enteroscopy, MRI, biopsy, enterography
Gastro-duodenal	5 %	Nausea, loss of appetite and weight, vomiting	Enteroscopy, esophago-gastroduodenoscopy, small bowel follow-through
Ileum and colonic tissue	35 %	Abdominal pain, loss of weight, diarrhea, cramps	Ileoscopy, colonoscopy, biopsy
Colon	32 %	Anal bleeding, abscess, diarrhea, perirectal fistula and ulcer	Ileoscopy, colonoscopy, biopsy CT enterography

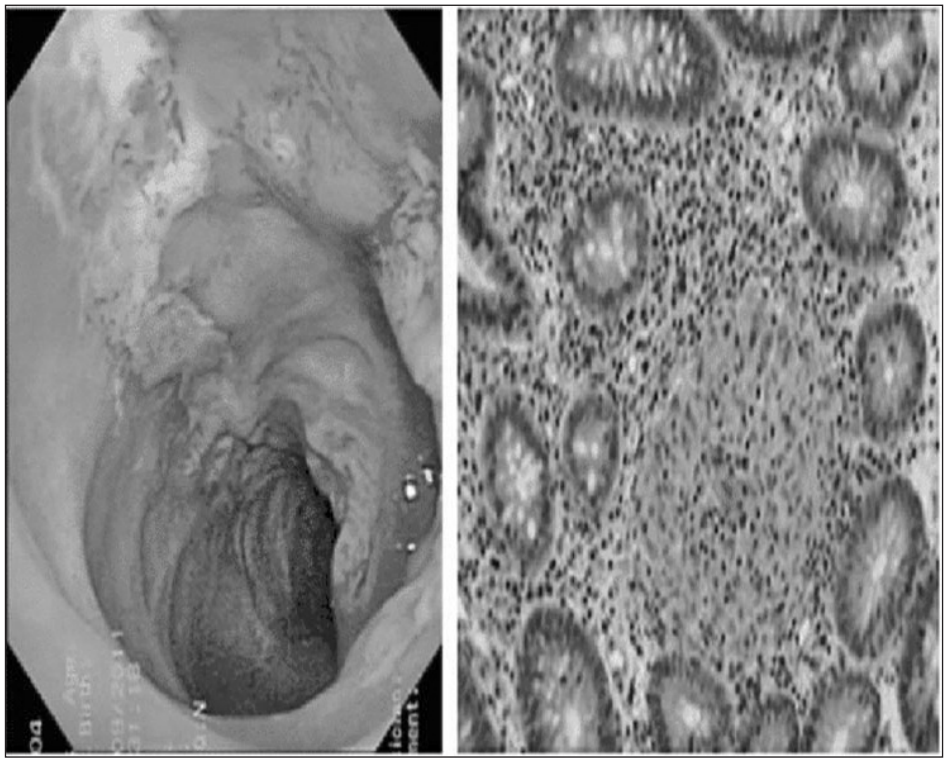

Fig. 1: Endoscopic and histological features of Crohn's disease and ulcerative colitis[7]

enduring symptoms such as upper gastrointestinal and isolated perianal inflammation, as well as extra intestinal manifestations (EIMs) of the disease[6]. Fig. 1 shows the endoscopic and histological features of Crohn's disease and ulcerative colitis and Table I shows the different sites, symptoms and diagnosis procedure of CD.

Unlike CD, ulcerative colitis (UC), another type of IBD, affects mainly the entire portion of colon and rectum and is restricted to the intestinal mucosal layer[7]. CD is primarily characterized by skip lesions that originate gradually and the patient experiences a range of symptomatic transformations and remissions and which eventually become worse over the time. The disease may develop at any age, but it most frequently affects the people within the age group of 20 to 29, having a previous family history[8]. The commencement of the disease has two age crests: the primary and main peak arises amidst the ages 15-30 years and the secondary peak is amidst 50-70 years. IBD can be diagnosed in only 10-15 % people having age of 60 or above[9]. CD has become more common among children, also due to excessive intake of junk food and unhealthy diet. Many a times, due to overlapping symptoms of CD and UC, they may not be accurately distinguished, and it became problematic to precisely diagnose CD and the disease

Table II: Classification of Crohn's disease[9,13]

Clinical factor	Vienna classification	Montreal classification
Age	**A1 -** less than forty years of age. **A2 -** Forty or more than forty years of age	**A1 -** 16 **A2 -** 17-40 **A3 -** Over 40
Location	**L1 -** Ileum along with cecum. **L2 -** Colonic tissue between cecum and rectum, upper GIT not involved **L3 -** Ileum and ascending colon as well as rectum **L4 -** Upper GIT primarily involved and disease progresses from proximal to terminal ileum,	**L1 -** Ileum **L2 -** Colon **L3 -** Ileum and colon **L4 -** Upper GIT
Behavior	**B1 -** Non-penetrating, non-stricturing **B2 -** Luminal narrowing, gut obstruction as examined by endoscopy, radiological methods, or surgical methods, **B3 -** Penetrating and presence of inflammatory masses, perianal fistulae, and abscesses	**B1 -** Non-stricturing as well as non-penetrating **B2 -** Stricturing **B3 -** Penetrating

can unknowingly be termed as colitis in about 2 %-16 % cases of inflammatory bowel disease[10].

Not only is CD substantially devastating but the sporadic relapses and degeneration of the disease may result in a substantial negative influence on the quality of life of the affected person[11]. The occurrence and incidence of CD is cumulative worldwide and will result in an upsurge in the therapeutic demand by the primary healthcare physicians. The prevalence of CD is more in developed countries, urban cities and southern climate as compared to the undeveloped countries, rural areas and northern climates. The risk is slightly higher among smokers[8]. The occurrence and frequency appear to be lesser in South America, Japan and Asia. An incessant escalation in the prevalence of CD has been constantly observed over the last 60 years, though it is presently reducing in Western countries[10,12].

The disease development is divided into phenotypic stages: inflammatory, stricturing, and fistulizing. CD initially is represented by a characteristic inflammation of the gut and alimentary tract with no probable indication of intestinal stricturing or fistulizing disease. This irritation can gradually progress to form luminal tapering and tissue fibrosis that eventually lead to structuring disease. Eventually the enduring transmural inflammation can lead to the consequence of sinus development or fistulous tract. Fistulae may also develop amid the bowel and any in line organ including bladder, vagina, and other bowel areas[10]. The scientists have further classified the disease on the basis of age, location and behavior for proper assessment of the disease. Table II explains the classification of Crohn's disease on the basis of age, location and behavior. Crohn's disease is further classified according to the Vienna classification and Montreal classification.

Sign and symptoms

The symptoms depend on the disease location and its severity. In certain patients, CD may only affect a last portion of ileum while in others the disease may be confined to the colon of the large intestine. The most common parts exacerbated by CD are the terminal portions of ileum and colon. The sign and symptoms of CD can vary from mild to moderate to severe in nature[10-12]. Usually, the symptoms develop gradually, but even so often they may appear suddenly. Some patients may experience unnoticed symptoms for years until the disease can be diagnosed or identified[13]. Some patients may actually have long enduring underlying disease without reflecting any potent signs or symptoms. Symptoms can include the ones described below.

Gastrointestinal

Few patients with CD may experience enduring recurrent phases of flare-ups while most of the patients experience abdominal pain, dysphagia, vomiting, cramps, aphthrous ulcers, fistulization, abscess around the anal

area, ulcerative colitis, sclerosing cholangitis, stenosis, nausea, intestinal stenosis, blotting, bleeding, flatulence, watery feces and systemic symptoms like fever, weight loss, mall absorption, fatigue, malaise and anorexia[14].

Extraintestinal

In adults: Pyoderma gangrenosum, uveitis, photophobia, inflammation of sclera, decrease in bile acid reabsorption, seronegative spondyloarthropathy, arthritis, enthesitis, renal stone, pulmonary embolism and epiglottis and deep venous thrombosis[15].

In children: Delayed sexual development in children, stunted growth, malnutrition and bone demineralization[16].

Etiology

Though the precise cause is unidentified, CD appears to evolve due to a combination of genetic predisposition and environmental triggers/factors. Earlier, stress as well as diet were not considered as a causative reason, however, now many researchers have reported these factors to initiate and aggravate the symptoms of CD[17].

Genetic factors

Genetic risk factors are being highlighted continuously as nearly more than 210 genes have been found to be linked with the disease expansion and progression. Gene NOD2 locus on chromosome 16 was the first gene that was identified as a main culprit of the disease origin[18]. The primary genetic mutation that was evident to be linked with CD pathophysiology was a frame shift in the NOD2 gene[19]. Researchers identified more than seventy one different gene loci with the robust associations with caspase recruitment domain family, member 15 (CARD15), that encodes the NOD2 pathogen recognition protein, and additional loci, like IBD5 locus, interleukin-23 receptor, and the autophagy gene ATG16L1 (ATG16 autophagy 16-like 1). Genotype may also influence the severity of CD[20-22]. The genetic variations of NOD2/CARD15 appear to be associated with small-bowel participation, whereas other major genes such as IL23R, ATG16L1, SLC11A1, and IRGM lead to the augmented risk of CD development and progression. Homozygotic variations at NOD2 result in nearly 30 to 40 times increased risk of evolving the disease, whereas heterozygous variation can augment the disease development risk by 2 to 4 times. Various other genetic foci involved in several vital pathways such as adaptive immunity, autophagy, and epithelial function have shown to be connected with CD pathophysiology[23].

Immune system

IBD is an autoimmune disorder arises due to abnormal immunological reactions inside the body, where defensive-immune system outbreaks the healthy cells. Various experts reported that microbiota present in the gastrointestinal tract may triggers immune system in an atypical manner, stimulating the release of various inflammatory cytokines and resulting in induction of various inflammatory pathways leading to development of various symptoms of CD. Originally, the theories stated that CD is mainly a T-cell autoimmune disorder, resulting from impaired innate immunity[24]. Later, various hypotheses stated that turbulent secretions of cytokine and their release by macrophages are also a major contributing factor for the development of impaired innate immunity[25,26]. The resulting cytokine storm leads to develop microbes-mediated inflammatory response in the colonic tissue. Another theory states that an overactivation of T-helper (Th) 1 and Th17 cytokine response also exaggerate the inflammatory state of CD. Another theory specifies that the presence of parasites and other microbiota inside the bodys help to conventionally evolved the human immunological system and that their deficiency due to ultra- modern lifestyle changes and hygiene standards lead to immune system deterioration[27,28]. The role of ATG16L1 gene in the induction of autophagy and hampering the body's immunity has also been implicated in CD[29].

Microbes

Dysregulation of commensal bacteria in gut can result in immunological disturbances. A particular species known as *Mycobacterium avium paratuberculosis* (MAP) is identified to perform a potential role in development of CD. NOD2 gene suppresses the phagocytic property of macrophage mediated MAP clearance, diminishes innate immune response and impairs body capability to counterattack MAP infection[30,31]. Another microbe that is commonly found in CD patients is a definite type of *Escherichia coli* known as adherent-invasive *E. coli* (AIEC)[32,33]. It has potential to block autophagy and triggers neutrophils infiltration, resulting in induction of inflammation. Both MAP and AIEC replicate expansively within the macrophages and thereby prompting the excessive secretion of TNF-α. Other bacteria such as *Listeria*, *Yersinia* and protozoa such as *Blastocystis* also play a crucial role in disease pathogenesis. An uncertain association also found between *Candida* colonization and CD[34,35].

Environmental factors

Environmental factors such as unhealthy diet, western lifestyle, smoking, high consumption of sugars, reactive oxygen species[36], pollution and other stressors to the immune system, use of medicines such as oral contraceptives and painkillers[37], nutritional insufficiencies particularly zinc, and certain infectious agents may provoke pathogenesis of CD. People living in northern climate possess a greater risk of developing CD[38,39]. These factors interact with a specific gene leading to dysregulated immune response and progression of disease pathophysiology[40,41]. The studies reported that cigarette smoking is allied with the double menace of ailment development as compared to non-smokers and this applies to both the current and former smokers[42]. It must be noted that exposure to a particular potential factor is associated with the disease progression and development, but that does not ensure that it is the main cause. The link between junk diet and development of CD too remains uncertain[43,44]. Certain studies reported that augmented intake of milk protein, animal protein, oil, fats, an amplified proportion of omega-6 to omega-3 polyunsaturated fatty acids and high sugary products intake is also associated with CD pathophysiology[45]. Dietary microparticles, hormonal contraception, consumption of fish protein also play a certain role[46]. Consumption of vegetable proteins, a diet rich in fibers and fruits is associated with the lower occurrence of CD[47]. All the environmental triggers may ignite the CD pathogenesis by either irreversibly triggering the defense system of the body or by directly deteriorating the intestinal mucosal lining and augmenting the disease manifestations[48].

Other factors

Disproportionate and unnecessary use of certain medications such as antibiotics, oral contraceptives and NSAIDs[49] may increase the chances of CD development to certain extent[50]. High-fat diet also plays a significant part in CD[51]. Hormone replacement therapy may also intensify the risk of IBD in women[52, 53].

Complications

Complications of CD affects people in different ways, and these may vary from local intestinal inflammation to systemic complications[54]. Intestinal problems that can be potentially life-threatening include rupture and obstruction of intestine, gigantic distention of the colon known as megacolon and tissue perforation[55]. Although these complications are rare, they may necessitate surgery rather than the treatment only. Research reports state that long-standing chronic CD has higher risk for the development of intestinal cancer[56]. CD can present two kinds of complications:

Local complications

Small intestinal bacterial overgrowth (SIBO)[42,57], fistulae, tissue fissures and perforations, toxic megacolon, intestinal abscess, bloody diarrhea, hemorrhage, malnutrition, malabsorption, strictures may cause acute and sub-acute intestinal obstruction, fistulae among bowel loops. Pregnant women with active CD can face serious complications such as unprompted miscarriage, still birth, abortion and disease exacerbation[58]. CD is accompanied by the higher risk of colon carcinoma[59].

Systemic complications

Systemic complications may include arthritis, inflammatory arthropathies, scleritis, nephrolithiasis, cholelithiasis, osteoporosis, erythema nodosum, skin problems, mouth ulcers, pyoderma gangrenosum, scleritis, uveitis, episcleritis, hydronephrosis, uric acid stones, kidney stones, fistulas, pancreatitis, fatty liver disease, jaundice, hepatic cirrhosis, hepatitis, gall bladder stones, primary sclerosing cholangitis, physical development problems, growth failure and delayed puberty[60].

Diagnosis

Part of the gastrointestinal tract involved, type of complications and degree of inflammation govern the clinical diagnosis and investigation of CD. There is no specific test for identifying CD, instead, it may become problematic to analyze due to the deceptive and overlapping characteristic with colitis. The diagnosis of CD can be established by clinical evaluation of manifestations by using the techniques of physical examination, endoscopy, biochemical investigations, histopathological examination and radiological investigations[61].

Patient's history

Patient must provide information that should include previous medical history, family history, medicine information as well as current disease type, onset, symptoms, duration and its severity. It should also address the pattern of clinical manifestations as well as their frequency[62]. Diagnosis can be scrutinized properly if the main target risk factors can be addressed and should also include food intolerance, recent antibiotic and other medication exposure, travel history, smoking habits and genetic history of IBD[63].

Physical examination

Change in body weight, basal metabolic index (BMI), examination of abdominal region, rectal and perineum area, along with investigation of extraintestinal manifestations are included in the physical examination. Tenderness of lower abdominal quadrant and palpable abdominal mass are also examined. Additionally, examination of perineal skin tags and rectum for abscesses, occult blood and mass exclusion, fistulae and inspection of oral ulcers, are performed. The skin can also be investigated for signs of erythema nodosum and pyoderma gangrenosum as extra intestinal manifestations of CD[64].

Laboratory tests

Laboratory tests are performed for checking the symptoms of infection, internal bleeding, monitoring the levels of essential substances such as protein, iron and minerals as well as detecting complications, and monitoring drug response[48,65].

The initial tests may generally include

- Blood cell count, especially WBS and platelets
- Hematocrit volume
- Hemoglobin determination
- Comprehensive metabolic panel (CMP)
- Erythrocyte sedimentation rate (ESR)
- Measurement of C-reactive protein
- Creatinine and blood urea nitrogen monitoring
- Estimation of liver enzymes

C-RP as well as ESR are inflammatory markers that can correlate accurately with the disease severity[66]. Autoantibody blood tests can help to determine the variations between inflammatory conditions induced by CD from other types of IBD. These antibody tests help to detect the various proteins triggered by immune system that help to indicate the presence of any ailment. Autoantibodies such as anti-*Saccharomyces cerevisiae* antibodies (ASCA) and perinuclear neutrophil cytoplasmic antibodies (p-ANCA) may help to distinguish CD from UC. A negative test report for p-ANCA and positive ASCA reports suggests CD, while the reverse suggests UC[67,68]. However, in clinical situations, their diagnostic role is limited, as sensitivity and specificity are low[69].

Bowel movement tests, also called as stool or feces tests, may help to perceive the presence of red blood cells in feces as a result of inflamed and perforated intestines, signifying potent ailment of digestive tract. Stool culture may also help to detect the presence of any disease-causing micro-organisms in the intestinal tract. Existence of antibodies to *Escherichia coli, Clostridium difficile* and *Saccharomyces cerevisiae* is indicative of CD[52,70]. Consequent tests to examine common complications can also consist of determination of serum ferritin, iron, folate, prealbumin, albumin, vitamin B12, vitamin D, calcium, and total iron-binding capacity. Initially, fecal granulocyte proteins were employed to differentiate between irritable bowel syndromes (IBS) and IBD[71]. Recently, fecal calprotectin and lactoferrin may be used as surrogate markers for distinguishing among IBD and IBS and to detect gut inflammation[53,72]. Calprotectin is a macromolecule that can be found in WBCs and during intestinal inflammatory conditions, these WBCs migrate to intestine and release their contents including this protein in massive amount. The augmented level of fecal calprotectin represents higher inflammatory state[73].

Imaging tests

These tests help to internal images of various body parts that represent the zones of disease activity and recognize probable complications and supplement to successful diagnosis. These tests include conventional X-rays, contrast X-rays, magnetic resonance imaging (MRI), colonoscopy and more.

Conventional X-rays: X-Ray of the abdominal area is a conventional method to observe the contraction and obstruction of the intestinal portion due to chronic inflammation.

Contrast X-rays: This test is performed using barium compound to evaluate the intestine. The barium dye covers the bowel lining, creating a shadow of intestine, colon and rectum, that can be easily observable in X-ray.

Computerized tomography (CT scan): A CT scans along with concurrent X-rays help to generate a cross-sectional bowel images along with pictures of surrounding tissues, that are not visible in other tests. CT scan aims to detect the site and degree of the inflammatory disease. They also help to determine latent complications, including intestinal and extra-intestinal symptoms and differentiate with similar conditions such as appendicitis.

Magnetic resonance imaging (MRI): It is the most employed diagnostic tools for CD. Huge, tubular magnets employed in a magnetic field and radio waves are used to generate the intestinal images. Pelvic MRI can be helpful in detecting fistulae near the anal region.

Magnetic resonance imaging (MRI) enterography: It is normally employed for observing bowel and lumen without using any ionizing radiations.

Leukocyte scintigraphy (White blood cell scan): This test is used to detect and trace the migration of WBCs to the inflammatory sites and detect the level and severity of inflammation in CD. Ultrasonography of the small bowel and pelvis is an alternative to CT and MRI[55,74]. It is particularly useful if pelvic pathology, such as abscess, is suspected. It also helps to determine the vascular flow rate, sinus tracts, abscess and lymphadenopathy.

Endoscopy: The technique employs a flexible and thin tubular part with camera at the tip to explore the various parts of GIT. Sigmoidoscopy helps to examine sigmoid colon and rectum while colonoscopy helps to examine the entire portion of colon and small intestine along with detection of fistula, irritation, as well as stricture of terminal ileum or colon for obtaining the biopsy samples[75].

Capsule endoscopy: The procedure uses a small wireless camera that is in form of a small capsule to be swallowed. The camera may click about 50,000 images, as the capsule moves along the entire alimentary canal. These pictures can be transferred to a computer to monitor the symptoms of CD. As the capsule has travelled along the digestive tract, the camera can be easily and painlessly passed through the stools. Capsule endoscopy should be considered when imaging and colonoscopy fail to establish a diagnosis[76]. It is also a safe and useful investigation tool in children[77].

Esophagogastroduodenoscopy (EGD): It is also called as upper gastrointestinal tract endoscopy that can help to diagnose the disease when CD affects the esophagus, stomach and the duodenum.

Endoscopic retrograde cholangiopancreatography (ERCP): The technique is a combination of upper GIT endoscopy and X-rays and it is quite helpful for examining the bile ducts in pancreas and liver, the areas that may also be affected with CD in certain people.

Double-balloon endoscopy: This technique uses two inflatable balloons to investigate the portion of gut where typical endoscopes are not able to penetrate.

Endoscopic ultrasound: The technique combines an ultrasound probe with an endoscope for examination of deep intestinal lining and fistulae in the rectum portion area[78].

Treatment and management of CD

Most of affected CD patients are administered with anti-inflammatory drugs, corticosteroids and immunosuppressant treatment and around 20 % may require biological treatment[81]. Healing and curative therapeutic are assigned on the basis of disease severity, activity, location in gut, as well as ailment-linked complications[82]. The aim of therapeutic management is to minimize the exacerbation of clinical signs, orientation of clinical remission, and preservation of remission with negligible side effects (Table III)[83].

Anti-inflammatory drugs

Medication such as or mesalamine (Asacol HD), sulfasalazine (Azuldifine) works in the large intestine

Table III: Differential diagnosis[79,80]

This is used to differentiate between CD and UC whose clinical manifestation is similar in nature.

Ulcerative colitis[79]	**Crohn's disease[80]**
Inflammation and irritation are restricted to mucosa and apparent sub-mucosa	Inflammation is transmural in nature
Contiguous ailment with absence of skip lesions	Sporadic, patchy ailment with the presence of skip lesions
Mainly confined to colon	Entire GIT can be involved
Absence of granulomas	Granulomas evident
Principally show the presence of neutrophilic infiltration along with crypt abscesses	Mainly lymphocytic infiltration
Perinuclear anti-neutrophilic cytoplasmic antibodies (pANCA) promote disease development	Anti-*Saccharomyces cerevisiae* antibody (ASCA) promote disease development

and may help keep flare-ups from being painful. 5-ASA or sulfasalazine is a modestly effective therapy but is poorly tolerated[84]. 5-ASA is often used for treating the mild to moderate form of CD and helps to reduce the disease inflammation and severity[85]. However, data are conflicting that 5-ASAs are not effective for inducing remission[86].

Corticosteroids

Corticosteroids such as budesonide can also help in inflammation, but should only be used short term in children because of side effects. Steroids are able to induce remission, although they may not be efficient in maintenance of immune system[87].

Table IV: List of therapeutics used in CD and their major adverse effects[98]

S. No.	Medication	Drug	Dose	Route of Administration	Adverse Effects
1	5-ASA[81,99,100]	Mesalamine Balsalazide Olsalazide Sulfasalazine Dipentum	1 g 4 times a day, 2250 mg three times daily, 500-1000 mg twice daily, 500-1000 mg twice 4 time daily	Orally Orally Orally Orally	Hepatitis, pancreatitis, Hemolytic anemia, Interstitial nephritis, Leukopenia
2	Corticosteroids[82,83]	Prednisone Budesonide	0.5-0.75 mg kg^{-1}, 9 mg once daily	Orally Orally	Insomnia, osteoporosis, osteopenia, delirium, weight gain, cataracts, serious infection, mood changes, avascular necrosis, glaucoma, adrenal insufficiency, skin changes, delayed wound healing
3	Immunomodulator [83,101, 102]	Azathioprine Mercaptopurine Methotrexate	1-0.25 mg kg^{-1} $dose^{-1}$ once daily, 0.75-1.5mg kg^{-1} $daily^{-1}$, 25 mg	Orally Orally Intramuscular	Pancreatitis, anemia, leukopenia, thrombocytopenia, Non-Hodgkin lymphoma, pulmonary toxicity, cirrhosis, flu-like symptoms, bone marrow suppression, cervical dysplasia, oral ulcers
4	TNF – Blocker [84]	Infliximab Adalimumab (Humira)	5 mg $kg^{-1}$$dose^{-1}$ in a week, 160 mg once a week 0, then 80 mg once a week 2, then 40 mg every two weeks	Intravenously subcutaneously	Non-Hodgkin lymphoma, lupus erythematosus, reactivation of latent TB, demyelinating disease, eczema
5	IL-12/IL-23 inhibitors[89]	Ustekinumab	one-time injections administered sub-cutaneously every 8 weeks.	Subcutaneous	Skin cancer Infusion reactions TB
6	Adhesion molecule Inhibitors[90]	Vedolizumab	300mg $kg^{-1}$$dose^{-1}$ at week 0,2,6 followed by 5mg kg^{-1} $dose^{-1}$ every 8 week	Intravenous	Infections, Nasopharyngeal polyps, Infusion reactions

Immunosuppressants

Drugs such as azathioprine or adalimumab may help reduce inflammation and prevent the immune system from producing chemicals that cause inflammation and are useful for maintenance of remission as compared to remission induction[88].

Anti-TNF therapy

This therapy is one of the most efficient for treating severe to moderate forms of chronic CD. They are being administered alone or as a synergistic combination with anti-inflammatory drugs and an immunomodulator[89]. They are employed to induce and maintain remission. The combination of infliximab and an immunomodulators proved to be most efficient in treating CD as compared to the individual infliximab or immunomodulators in patients who are never administered with any of these agents in the past[90]. Anti-integrin therapy in a combination with an immunomodulator is able to treat moderate and active CD in its chronic state[91].

Interleukin inhibitor

Ustekinumab is a humanized monoclonal antibody to the p-40 subunit of IL-12 and IL-23. The drug is usually instilled as a single dose infusion trailed by subcutaneous injections every eight weeks[89]. Like anti-TNF agents, before initiating the therapy, the patients must be examined for hepatitis B and latent tuberculosis. The efficiency increases with concurrent administration of anti-TNF therapy that eventually aid in remission induction and maintenance[85,92].

Selective adhesion molecule inhibitors

Vedolizumab and natalizumab are the primary gastrointestinal specific adhesion molecule inhibitors that are used for treating moderate to severe form of CD[85,93].

Other effective treatment options and their complications

Antidiarrheal medication, such as loperamide, can be administered with an initial dose of 4 mg, followed by administration of 2 mg of drug after every unformed stool, maximum up to 16 mg day^{-1}. It is contraindicated during episodes of active colitis, as they can result in toxic megacolon. However, it may be administered for controlling chronic diarrhea for the patients with active disease[86,94].

Pain relievers are used for pain associated with Crohn's disease. Vitamin B-12 shots to prevent vitamin deficiency. Iron, calcium, and vitamin D supplements following a special diet based on the nutritional needs (for example, eliminating dairy, eating small meals, and drinking plenty of liquids)[95]. Antibiotics such as metronidazole (500 mg TID), ciprofloxacin to treat bacterial infection and possible related fistulas and abscesses medications that suppress immune system and decrease inflammation, such as immune-modulators or biologic drugs. Antibiotics can be added if septic complications are suspected[87,96]. Abdominal cramps controlled by antispasmodics drugs of dicycloverine, hyoscyamine. Providing intestinal obstruction has been excluded. Primary or polymeric diets are less effective than corticosteroids but may be used for induction of remission in selected patients with active disease who are unable or unwilling to take corticosteroid therapy, or as an adjunctive therapy. Total parenteral nutritionally diet is appropriate adjunctive therapy in complex, fistulating disease. Nutrition approaches include a trial of exclusive enteral feeding with an elemental or polymeric diet. The aim of this is to suppress intestinal inflammation and promote mucosal healing. Trials of enteral feeding are often limited by poor patient tolerability[88,97]. Table IV shows few examples of drugs used in treatment of Crohn's disease.

CONCLUSION

IBD includes two chronic, idiopathic, inflammatory ailments known as CD and UC. CD is a provocative and critical disease that affects majority of gastrointestinal part. The disease can affect the mucosa severely in the inner part of digestive tract like ileum, colon and perineum. The common symptoms experienced by the patient include weight loss, loose stools and anal bleeding. The diagnosis may include a blend of entire patient history, radiographic test, MRI, CT-scans as well as endoscopic examination. These examinations may help to distinguish between UC and CD. The treatment options are selected on the basis of disease severity. Mild to moderate form of disease can be cured with the anti-inflammatory drugs that can be administered both orally as well as rectally. Severe stages can be managed and treated by effective drugs such as immune-modulators, while extreme cases often require corticosteroids to prevent disease flares up. Anti- TNF alpha drugs and immune-modulators are most frequently used to suppress the disease complications. The treatment objective aims on induction of remission and to prevent the further progression of CD flares.

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