Journal of Biomedical and Pharmaceutical Research
Available Online at www.jbpr.in
CODEN: - JBPRAU (Source: - American Chemical Society)
NLM (National Library of Medicine): ID: (101671502)
Index Copernicus Value 2018: 88.52
Review Article
Volume 10, Issue 1: January-February : 2021, 99-113
ISSN (Online): 2279-0594
ISSN (Print): 2589-8752

AN ADVANCED REVIEW ON DIAGNOSIS AND TREATMENT AND EXTRA-INTESTINAL MANIFESTATIONS ASSOCIATED WITH INFLAMMATORY BOWEL DISEASE

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Article Info: Received 23 January 2021; Accepted 26 February 2021
DOI: https://doi.org/10.32553/jbpr.v10i1.848
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Conflict of interest statement: No conflict of interest

Abstract
Inflammatory Bowel Diseases are mainly a group of bowel disorders which are generally associated with chronic inflammation of the intestinal tract due to the reason of an imbalance in the presence of the intestinal microbiota. Inflammatory bowel disease can have two different types based on their clinical pathology which are mainly Crohn's Disease and Ulcerative Colitis. Both of these clinical sub-types are most likely to be focussed among all of the inflammatory bowel diseases due to their increasing risk of incidence as well as associated difficulties in their treatment. However, the main cause of inflammatory bowel disease has not been cleared till the date but from last three decades, there is a hub of researchnes being going on to get a clear idea about the cause of disease. Among these studies most of researchers have found the role of Nucleotide Oligomerization Domain 2 genes in the pathophysiology of disease. For the treatment of ulcerative colitis, there are severalapproaches available, based on the severity of the disease. Aminosalicylates are used to treat mild disease, use of corticosteroids is the effective treatment in the moderate case whereas use of cyclosporine in severe disease. In Crohn's disease, drug choices are dependent on both location and behavior ofthe disease. Nowadays, the advanced treatments have been included such as use of monoclonal antibodiesor fusion proteins including anti-TNF drugs as biological therapy of disease. Also the post treatment remission of this disease makes it more complicated to be cured.

Keywords: Inflammatory bowel diseases, Crohn's disease, ulcerative colitis, nucleotide oligomerization domain, monoclonal antibodies, treatment.

Introduction

Inflammatory bowel diseases (IBD) are associated to an immunological variance of the intestinal mucosa, mostly related with cells of the adaptive immune system, which counter against self-antigens generating chronic inflammatory disorder in the patients. IBD is the term used for a set of diseases with still unspecified aetiology, generality of which is expanding virtually every-where in the world. Inflammatory bowel disease (IBD) include two distinnct entities i.e., ulcerative colitis (UC) and Crohn's disease (CD) each having its own spectrum of presentations and clinical course [1]. However these two disorders are clearly distinct by different clinicopathological characteristics, including different locations within the gastrointestinal tract, sundry histological patterns of inflammation, and the diverse disease-specific complications. In 5% of patients the disease is designated indeterminate colitis as characteristic of both UC and CD are present. The incidence of UC is stable at around 10–20 per 100,000 per year, with a prevalence of 100–200 per 100,000. The incidence of CD is round about 5–10 per 100,000 per year [2].

It is broadly studied that the number of bacteria in the gastrointestinal tract is about 10 times higher when compared to eukaryotic cells in the body. Also, the normal enteric bacterial flora is a complex biosphere of around 300–500 bacterial species [3]. Also the balance of the innate and adaptive immunity is critical for this micro-environmental homeostasis. In this sense, the immune system has the principal role of promoting immune tolerance, thereby circumvent the specific immune response

against the large mass of commensal bacteria. The local immunity in intestinal mucosa is basically guaranteed by gut connected lymphoid tissue (GALT), constituted by Peyer's patches, lymphoid follicles, and mesenteric lymph nodes [4].

Along with cellular, environmental, and genetic factors, deregulation of immune responses in the intestinal mucosa has been linked with the etiology of IBD. Modification in the autophagy- a cellular process associated to the degradation of intracellular pathogens, antigen processing, regulation of cell signaling and T cell homeostasis, usually results in decreased clearance of pathogens, thus contributing to the onset of inflammatory disorders in susceptible subjects. In this sense, mutations on ATG16L1 gene, a member of a family of genes involved in autophagy were finding out in patients with CD [5].The breakage of self-antigens tolerance in the intestinal mucosa, by injury or genetic predisposition, may give on to CD or UC [6]. Cells of the inborn immunity, such as macrophages and dendritic cells are peculiar in identifying microorganism's molecular patterns by means Pattern Recognition Receptors(PRR), as for example Toll-Like Receptors (TLR) and Nucleotide-Binding Oligomerization Domains (NOD). In this aspect, mutations in the caspase recruitment domain-containing protein 15 (CARD-15) genes encoding the NOD_2 proteins were linked with the occurrence of IBD, particularly CD [6]. NOD_2 is an intracellular microbial sensor which behaves like a powerful activator and also the inflammation regulator. Therefore, deficiency in this protein promotes major changes on the immune response in the lamina propria, leading to a chronic inflammation in the tissue. Clinically, it is of interest to discover the relationship between NOD_2 gene status and the effectiveness of antibiotic treatment in CD [7].

In addition, the variance between T_h1 and T_h2 cytokines released by the intestinal mucosa govern the intensity and duration of the inflammatory response in experimental colitis [8]. The secretion of certain cytokines such as tumour necrosis factor-alpha (TNF-α), Transforming Growth Factor-**β** (TGF-**β**), and interferon-gamma (IFN-ϒ) also the response to self-antigens are factors that seem to be associated to the onset and initiation of IBD. Although UC is often report as T_h2-mediated diseases while CD is called T_h1 condition, the classic paradigm has recently been changed, since cytokines can have different and antagonistic actions [9].

Latest data revealed that T_h17 cells and other cells generating interleukin IL-17 shows a crucial role in the intestinal inflammatory manifestations. IL-17 and IL-22 are associated with the colitis induction, since these cytokines start and amplify the signs of local inflammation and encourage the activation of counter-regulatory mechanisms targeting intestinal epithelium cells. In addition IL-23 also released by macrophages and dendritic cells which are located in the intestinal mucosa, activates signal transducer and activator of transcription (STAT-4) in memory T lymphocytes, stimulating the IFN production. In turn, IFN-α is responsible for triggering the inflammatory cytokines production in cells of the innate immune system that contributes to the increase of the inflammation present in colitis [10].

Recent results from Neurath group identified a pathogenic role of IL-9 in experimental and human ulcerative colitis by regulating intestinal epithelial cells. It is also important to report that environmental factors can play a major role in the development of IBD, but this relationship is poorly understood. Specifically, there are lot of evidences that shows tobacco can play significant role in triggering this type of intestinal inflammation [11].

- **Crohn's Disease:**

CD is most chronicform of inflammatory disease whichisdistinguishby the development of fistulas, ulcers, and granulomas in the mucosa. Even though the CD's gastrointestinal manifestation may principally influence the terminal ileum region, furthermore compromise any region from the mouth to the rectum of affected patient. The clinical manifestations of CD include diarrhoea or bloody diarrhoea, malnutrition, abdominal pain and weight loss. Extra intestinal findings, such as arthropathy or skin disorders occur rarely. Although, manifestations on skin, muscle, or bone of metastatic CD may lead to identification of occult intestinal disease. Generally CD has an inherent background and the first-degree relatives of affected individuals have a five time greater risk of disease development [12].

The localized release of some cytokines i.e., IL-12, IL-17, TNF and IFN has been implicated in the chronic intestinal inflammation noticed in CD patients. The generation of IL-12 and IL-18 by antigen-presenting cells (APC) and macrophages produce a polarized differentiation towards T_h1 lymphocyte which leads to an increased release of proinflammatory cytokines, including TNF-α and IFN-α . In addition, T_h1 cytokines stimulate the antigen-presenting cells to secrete a wider spectrum

of inflammatory cytokines like IL-1, IL-6, IL-8, IL-12, and IL-18 which result in a self-sustained cycle [13].

- **Ulcerative Colitis***:*

UC is another form of IBD identified 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. Additionally in Montreal classification system the classification of IBD phenotypes include UC which is most widely used, data on its authenticity are very limited because of its significant variety of clinical presentations of UC. Generally, the clinical manifestation of UC may include release of blood and mucus, petechial haemorrhage and granulation [14].

1. Pathogenesis of IBD:

Data that diverge from the traditionally accepted view of the pathogenesis of IBDs have recently been published [15]. This new information has substantially challenged our conception on the pathophysiology of IBD and has complicated what was originally believed to be a simple dichotomy between CD and UC. According to the latest adopted hypothesis, UC and CD result from a deregulated response of the mucosal immune system toward intraluminal antigens of bacterial origin in genetically predisposed persons [16].

Furthermore, this hypothesis has been confronted by unanticipated outcomes from animal models of intestinal inflammation, which have led investigators to reject traditional pathogenetic concepts of these diseases. Such animal models permit investigational manipulations that cannot be done in humans and are frequently used to test the efficacy of candidate therapies. In this study, we present emerging pathophysiologic concepts and confer about their outcome on the classical paradigms for IBD [17].

a. The role of the Innate Immune System in IBD:

The innate immune system is the body's unidentified protection against pathogens; it acknowledge instantly or within the first few hours after a challenge. It is commonly considered the first line of defence and includes some physical barriers such as the skin, the intestinal mucosa and immune cells that identify and remove foreign agents. The innate immune system reacts to the chemical properties of the antigen rather than to the specific antigen itself. The acquired immune system, though responds especially to antigens [18]. Pathogenesis of IBD (Figure 1) includes intestinal inflammation which is mediated by cells of the acquired immune system. It was found that over aggressive activity of effector lymphocytes and proinflammatory cytokines could leads to chronic inflammation, which overcome the control mechanisms. On the other hand, IBD can result due to primary failure of regulatory lymphocytes and cytokines, like interleukin-10 and transforming growth factor to control inflammation and effector pathways [19].

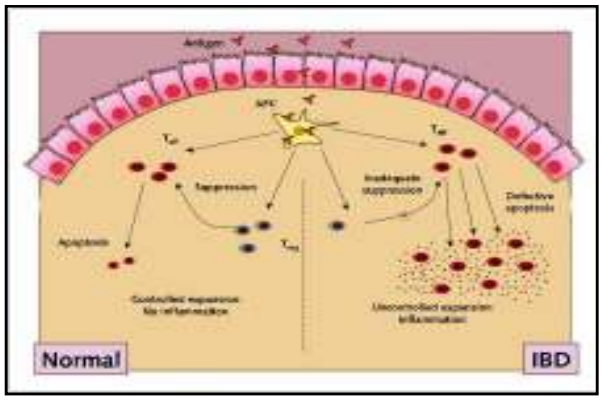

Figure 1: The traditional diagram for the pathogenesis of inflammatory bowel disease (*IBD*).

In addition, in CD the resistance of T cells to undergoing apoptosis after activation is central pathogenic mechanism. The exact cause of this phenomenon still has not been fully known, the ability of antitumor necrosis factor and anti–interleukin-12 antibodies to efficiently stop or reverse clinical and experimental IBD is generally mediated by their potential to restore mucosal homeostasis and redirect mucosal effector T cells into apoptotic pathways. The lymphocytes are considered to be the major culprits in both scenarios. Although, there is emerging proof that defects in the innate immune system may play an equal or even more important role in IBD [20].

Evidence of the role of the innate immune system comes from the recently discovered association between CD and loss-of-function mutations in the caspase activating and recruitment domain 15 gene (card15) so named because the protein it encodes contains a CARD protein–protein interaction domain), which is also known as NOD_2. The NOD_2 protein is an intracellular receptor for a component of the bacterial cell wall and plays an important role in triggering cells of the innate immune system [21].

b. The NOD_2 Gene:

Inherent factors play a major role in the IBD pathogenesis with approximately 10% of patients reporting a positive family history. However, the both family and twin concordance studies showed that stronger genetic influence in CD than in UC, both diseases shows complex polygenic traits. Genome-wide searches have revealed that at least 7 loci that confer lack of resistance to CD or UC or both [22]. IBD1 is the first best identified and characterized locus, which is situated at chromosome position 16q12. Due to several genes are included within this locus, converging techniques have been used to identify predisposing genes. These techniques have singled out NOD_2 as playing a significant role in the predisposition to IBDs related with this locus [23]. Mutations in the NOD_2 gene are present in as many as one third of individuals with CD. Three common single nucleotide polymorphisms that independently related with CD have been known in the NOD_2 gene. Carriage of 1 pathologic allele enhances the risk for CD by 2 to 4 times which is compared with 15 to 40 times increased risk by 2 risk alleles when they are present. In spite this gene effect of dose, lesser than 2% of individuals with 2 risk alleles eventually show CD. Indeed, 20% of healthy white controls carry 1 risk allele and 1% carries2 risk alleles. Study of genotype–phenotype relationships in CD showed an connection of mutations in NOD_2 with ileal disease rather than colonic disease, an earlier age of disease onset, and possibly fibro-stenosis [24].

In contrary to CD, mutations in NOD_2 do not lead to an important risk factor in ulcerative colitis.NOD_2 is an intracellular protein that senses bacterial products and activates components of the innate immune system. The functional importance of CD is linked to mutations in NOD_2 is presently being studied, with several controversies remaining to be resolved. Although, the current observations reveals that an impaired inflammatory response rather than an over aggressive inflammatory response by a defective intestinal innate immune system may underlie the initial phase of IBD. In this context, the lack of appropriate secretion of defensins (peptides that are produced by enterocytes to control the levels of commensal microbes) may be relevant to the pathogenesis of IBD [25].

c. The role of the epithelium:

In maintenance of mucosal homeostasis the intestinal epithelium, which is considered to be part of the innate immune system, plays an important and active role. Consequently, dysfunction of epithelial cells may lead to the primary defect in IBD. However, between body and the intraluminal microenvironment epithelial cells form a tight, highly selective barrier.

Failure of this barrier can cause intestinal inflammation, most likely via exposure to fecal antigens which lead to inappropriate activation of the mucosal immune system. Indeed, mice with inherent defects in intestinal permeability generate intestinal inflammation. Within the intestinal mucosa, there is constant cross-talk between the epithelium and cells of the immune system [26]. Epithelial cells may act like antigen-presenting cells because they are able to take up and process antigens and present them to cells of the immune system, along with appropriate activating stimuli. Aberrant communication, therefore, has the ability to produce inappropriate signals that activate effector cells and cause inflammation. Epithelial cells produce chemokines, which regulate recruitment of acute and chronic inflammatory cells within the intestinal mucosa.

Additionally, several cytokines which are considered as central to the pathogenesis of IBD, like tumor necrosis factor, interleukin-1, and interleukin-6, are expressed in the intestinal epithelium. Aberrant secretion of these pro-inflammatory chemokines and cytokines by epithelial cells is an integral part of the dysregulated immune response that initiates or perpetuates intestinal inflammation [27].

2. Treatment of IBD:

In order to better illustrate the relevance of each of the different IBD treatments, Table 1 compares different forms of treatment, mechanisms of action, patterns, and adverse effects of each form of therapy.

a. Classical Treatments for IBD:

In ulcerative colitis, treatment decision is dependent upon the stage of the disease: patients with mild manifestations are usually treated with amino salicylates, whereas for patients with moderate disease corticosteroids are prescribed and to the patients with severe disease cyclosporine is given. In CD, drug therapy is depends upon both location and behaviour of the disease [28]. In spite of that, aminosalicylates and antibiotics are generally used as medication in CD for the treatment of mild mucosal disease, in moderate disease corticosteroid are used and to treat fistulising disease biological molecules are used. Additionally, some of other drugs like azathioprine, amino salicylates,

methotrexate, mercaptopurine metronidazole, and related drugs may be used as maintenance therapies. Regardless of their lessen cost, these drugs can produce so many adverse effects. In addition, these therapies do not attain clinical remission and they can lead to the onset of other conditions such as renal failure [29].

At the same time the classical treatments are widely used, new therapies are under development in the attempt of improving the patient's life quality. The new therapies aim to reduce the adverse effects and to treat patients who do not respond satisfactorily to conventional therapies [30]. Other therapeutic strategies, not covered in this review, are in very early evaluation. These involve the manipulation of the microbiome using antibiotics, probiotics, prebiotics, diet, and fecalmicrobiota transplantation [31].

b. Biological Therapies:

The application of biological therapy for the management of inflammatory diseases can be related with some studies that identified the pro-inflammatoryCytokines located in the gut lamina prairie of the patients suffering from IBD. These cytokines, particularly, TNF-α, play a significant role in the management of chronic inflammation of the intestinal mucosa. Among the biological molecules, the use of monoclonal antibodies specific against TNF- , cytokine related with the initiation of IBD, seems to be a relevant alternative. These antibodies can activate several mechanisms involved in the immune response, like induction of apoptosis as well as the growth factors blockage for the T_h cells, production of antibody, and complement activation [32]. However, IBD management with biological molecules, particularly with monoclonal antibodies, possess greater specificity and direct mechanism of action, the greater cost of this therapy is still a barrier to be overcome. For this reason, together with this being a therapy in early stages of development, these drugs are generally used as an alternative for patients that are refractory to corticosteroid and amino salicylates treatment [33].

Table 1: IBD Treatments :- Drugs in use, mode of action, and side effects.

Treatment type	Associated drugs	Mode of action	Characteristics	Potentials side effects
Aminosalicylates	Mesalamine Olsalazine Balsalazide Sulfasalazine	Inhibition of IL-1, TNF and PAF, decreased antibody secretion.	Locally immune-suppressive, nonspecific inhibitionof cytokines.	Headache, dyspepsia, epigastric pain, abdominal pain, nausea, vomiting, and diarrhea.
Immunomodulators	Azathioprine 6-mercaptopurine Methotrexate	Blockage of *de novo*pathway of purine synthesis.	Anti-proliferative effects, reduction of inflammation.	Black, tarry stools, bleedinggums, chest pain, fever, chills, swollen glands, pain, cough, and weakness.
Corticosteroids	Prednisone Methylprednisolone Hydrocortisone Budesonide	Blockage of phospholipase A2 in the arachidonic acid cascade altering the balance between prostaglandins and leukotrienes; stimulation of apoptosis of lymphocytes.	High immuno-suppression, risk of potential infections, adverse effects with long periods of use, low cost.	Full moon face, difficulty of healing, sleep and glucose into lerance, osteoporosis, subcapsularcataracts, myalgia, orintracranial hyper-tension, and pseudo-reumatism syndrome.
Biologicals: anticytokine drugs	Infliximab Adalimumab Certolizumab Golimumab	Induction of apoptosis in pro-inflammatory cells; binding specifically to TNF, blockage of the interaction receptor.	Specific inhibition of cytokine,Immunosuppressio n, high cost, advanced technology required.	Abdominal or stomachpain, chest pain, chills, cough, dizziness, fainting ,headache, itching, nasal congestion, bloody urine,diarrhea, pain, fever, abscess, back orside pain.

Biologicals: Anti cell adhesion molecules	Vedolizumab Natalizumab	Inhibition ofmigration.	Specific inhibition of cell adhesionmolecules high cost, advanced technology required.	Nasopharyngitis, headache and abdominal pain, increased risk of infections, serious infections, and progressive multifocal leuko-encephalopathy (natalizumab).

Alongwith, long-term therapy with biological molecules may lead to immunogenicity by producing anti-drug antibodies. These antibodies can promote acute and delayed infusion reactions and may decrease the duration of patient's response to each infusion or injection. In this regard, there is a significant role of complement system and the formation of immune complexes in the augmentation of immunogenicity as well. [34].

Among few of the patients, immunogenicity is limited to transient low level of antibodies that show no clinical effects. Although the patients with high levels of anti-drug antibodies are more suitably to show a loss of response by decreasing the drug levels that compromise the long-term therapy. Alternatively, concomitant immune-suppression appears to diminish immunogenicity and enhance therapeutic control, although it may increase risk of infection and malignancy [35].

Immunogenicity mainly depends upon the structure and origin of the biological agents. Biological agents may be fusion protein or a chimeric, and fully human antibody. In addition, the intake route, schedule of dose, and individual characteristics may have a larger effect on immunogenicity. It is necessary to measure the optimal treatment regimen in order to decrease the chances of anti-drug antibody formation [36].

c. Anticytokine Agents:

Currently, some anticytokine agents have been showing relevant results for the treatment of IBD. It is already known that antibodies specific for TNF play a significant role in maintaining the remission of CD, in both severe and moderate forms of the disease. These molecules were effective in inducing mucosal healing and clinical remission, decreasing the cases of hospitalization and surgical procedures in affected individuals [37]. The first commercially available anti-TNF molecule was infliximab (IFX), a chimeric monoclonal IgG1 antibody formed by a segment of the native mouse protein containing the binding site for the TNF- and a portion of human immunoglobulin responsible for the effector function of the antibody molecule [38].

3. Management Of IBD:

Management of IBD comprise of bringing active disease into remission followed by prevention of relapse (Figure 2). The type of disease is influenced by choice of treatment, distribution and related presenting characteristics like loss of weight, shortage of stature and pubertal status. Latest data advised that, in CD, the GI tract involvement is much more widespread, with only 7% of children having isolated colonic disease and 9% isolated small bowel disease [39]. The most of patient have both colonic and small bowel involvement, approximately 20% have jejunal disease and 50% have gastro duodenal disease. Also the majority of children show fast development of disease along with paediatric-onset IBD characterised by extensive intestinal involvement during diagnosis. Analysis of therapy effectiveness includes evaluation of symptomatic improvement, weight gain, and improved height velocity, biochemical remission, and in some cases, re-evaluation of disease activity to confirm mucosal healing by endoscopy.

There are several medications that are unlicensed for use in children and are not available in child-friendly formats such as large tablets rather than liquid form. The choice of medicine dependent on the child's cooperation of child as well as the readiness of the parents to administer treatment like, a child with distal colitis may not accept treatment with enemas. Therapy for IBD is a fast evolving field along with several new biological agents under examination that are probably to change therapeutic strategies in the coming decade [40].

The main agents used in IBD treatment are 5-aminosalicylates, corticosteroids, immunomodulators and anti-TNF agents. The aim of treatment is to eliminate symptoms such as induction of clinical remission, maintain long-term clinical remission, and restore patient's quality of

life in the reduction of surgeries and hospitalizations as well as mucosal healing [41].

a. 5-Aminosalicylate Drugs

In Mexico and Central America sulfasalazine and mesalazine are available for the induction and maintenance of remission in UC. Concomitant treatment with oral and topical 5-aminosalicylates is superior to oral 5-aminosalicylate alone, as first-line treatment for inducing remission in patients with mild to moderately active UC, with any extension beyond the rectum. The use of 5-aminosalicylate drugs is limited to a small proportion of patients with CD focused in those with colonic involvement and is not used for maintenance of remission [42].

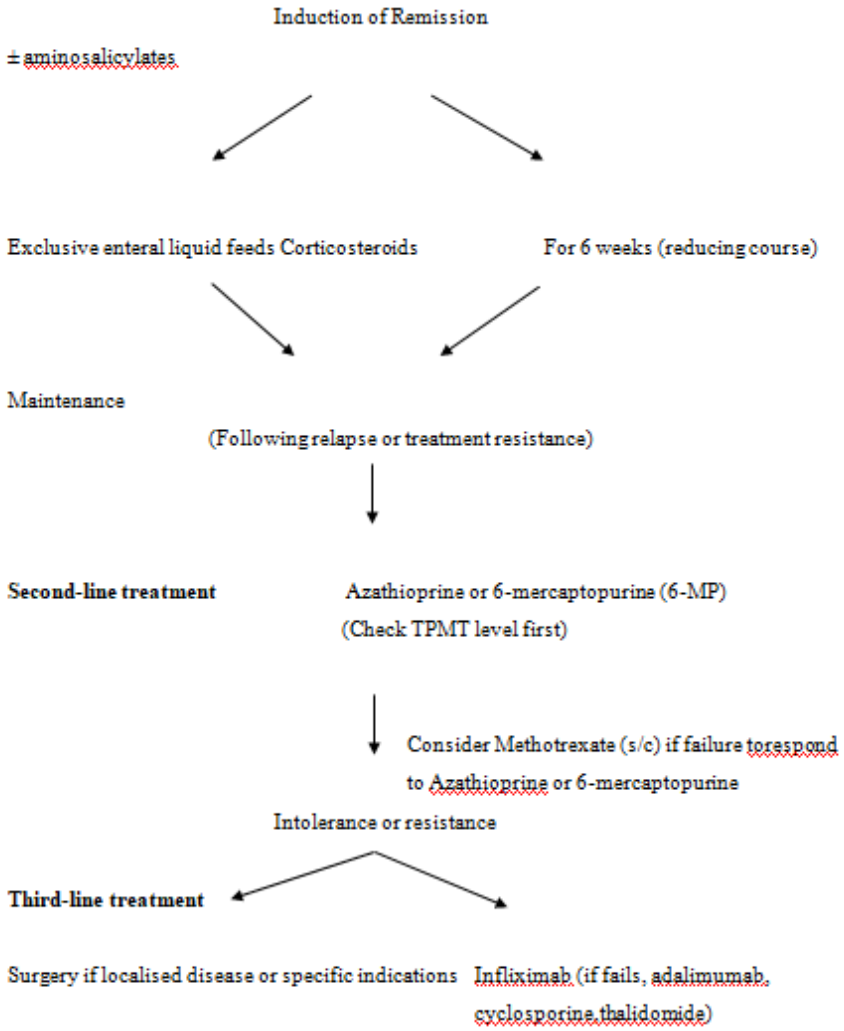

Figure 2: Flow chart for the conventional management of IBD

b. Corticosteroids

Corticosteroids are the major agents which are used to induce remission in moderate to severely active UC and ileocolonic CD and 80% response rates is expected. They are generally not effective for maintenance of disease remission. Budesonide at a dose of 9 mg/day is the therapy of choice for inducing remission in patients with CD with mild activity and ileal and right colonic disease. For inducing remission in patients with extensive small bowel CD, use of oral systemic corticosteroids is recommended. In patients with moderate to severe UC of any extent, the use of oral systemic steroids as first-line treatment is indicated for inducing clinical remission. The use of oral systemic steroids as second-line therapy in the induction of remission of patients with mild-to-moderately active UC that are resistant to 5-aminosalicylates is recommended [43].

c. Immunomodulating agents

Azathioprine, 6-mercaptopurine, methotrexate and cyclosporine are immunomodulating agents used in the management of IBD in selected patients. The use of thiopurine immunosuppressant is recommended for maintaining remission in patients

with corticosteroid-dependent IBD. In patients with CD that achieve remission with systemic corticosteroids, thiopurines or methotrexate is used in these patients. Methotrexate may be used in chronically active CD that is corticosteroid resistant or dependent. Remission rates after 16 weeks treatment may be achieved up to 40% and also than azathioprine and 6-MP, methotrexate have a faster onset of action. The drug may be continued as maintenance therapy, with 65% of patients remaining in remission at 40 weeks. Methotrexate has been less commonly used than azathioprine and 6-MP. Methotrexate is used in selected patients where other agents have failed or have not been tolerated due to adverse effects. Methotrexate is not effective in UC [43].

d. Biologic therapy

Antibodies against tumoral necrosis factor alpha (anti-TNF-alpha), such as infliximab, adalimumab, and certolizumabpegol, are indicated in patients with moderate-to-severe CD that have been refractory or intolerant to treatment with corticosteroids and immunomodulators. Further, infliximab and adalimumab are effective in closing fistulas and maintaining that closure in patients with CD. In moderate to severe UC, anti-TNF therapy (infliximab, adalimumab and golimumab) is indicated in patients with a lack of response or intolerance to treatment with 5-aminosalicylates, corticosteroids, or immunomodulators.

In severe UC refractory to IV steroids in hospital infliximab is an option, as an alternative to ciclosporin to avoid colectomy. Vedolizumab is a specific humanized monoclonal antibody that targets integrin α4ß7 (a variable surface glycoprotein expressed on the surface of circulating T and B cells), which interacts with the gut specific MAdCAM-1 adhesion molecule [44].

4. Management of extra-intestinal manifest-tations

In both CD and UC, EIMs (extra-intestinal manifestations) are found, though they are common in CD (especially colitis and ileocolitis). The musculoskeletal and mucocutaneous are most common EMIs forms including axial and peripheral arthritis, acute ocular inflammation, P*yodermag angrenosum* and E*rythema nodosum*. The ankylosing spondylitis is very important musculoskeletal manifestation, which occurs in 1-5% of patients. It must be treated with a rheumatologist along with biological therapy which is required for the axial disease. In this case gastroenterologist and rheumatologist must discuss choice of biological agent. Treatment for other EIMs consists of treating the underlying bowel disease, symptomatic relief and sometimes specific treatment of the EIM [45].

However, newer 5-ASA drugs has lower side effects than sulfasalzine, selected patients (such as those with a reactive arthropathy) may benefit. NSAIDs use should be avoided for symptom relief, especially in the patients suffering from active gut disease. Peripheral arthritis is usually related with active disease, and normally responds to management of the bowel disease. For more persistent symptoms in the absence of active gut disease specific therapy may be required, including immune suppression and rarely biological therapy. Erythema nodosum is the most common cutaneous manifestation, is generally related with active disease, and responds to management of the gut disease [46].

a. Primary sclerosing cholangitis

Liver biochemistry may be abnormal in every third patient suffering with IBD. Out of this about 6% have liver disease with primary sclerosing cholangitis (PSC) which is most common about 4.6%. Conversely, 70% of PSC patients have associated IBD. PSC is a rare but serious liver disease (incidence approximately 1:100000 population/ year). The average survival period ranges from 12 to 17 years from the day of diagnosis. High proportions of patients develop cirrhosis and need liver transplantation. There is a 15% lifetime risk of cholangiocarcinoma, which carries a poor prognosis. Several studies have indicated those patients with concomitant PSC are at a higher risk of colorectalneoplasia [47].

Patients with PSC often have quiescent colitis and so it is difficult estimating the exact onset of ulcerative colitis in this group. For the above reasons it is recommended such patients should have annual surveillance colonoscopy. The diagnosis of PSC is suggested by raised liver alkaline phosphatase, pANCA+, or changes of periductular fibrosis on liver biopsy. The diagnosis requires stricturing and dilatation of the intra- and/or extra hepatic bile ducts on imaging. Liver biopsy is necessary for diagnosis of small duct disease. Ursodeoxycholic acid improves liver biochemistry and at high dose may improve survival probability [48].

However, a recent large RCT was stopped early due to excess adverse events in the group receiving high dose Ursodeoxycholic acid. Therefore high dose Ursodeoxycholic acid may be harmful.

Ursodeoxycholic acid appears to reduce the risk of bowel cancer. Treatment of dominant strictures by ERCP and dilatation may be indicated and liver transplant is indicated for end stage liver disease [49].

b. Osteoporosis and osteomalacia

Both osteoporosis and vitamin D deficiency (including compensated deficiency states with normal calcium and high parathyroid hormone) are common in IBD. However, age, use of steroids and disease activity are the major risk factors for osteoporosis complicating IBD.

Recommendations for osteoporosis and osteomalacia:

- Supplementation of calcium and vitamin D is recommended when systemic steroid use is necessary.
- Co-administration of bisphosphonates with steroids is recommended for patients aged over 65 years or with known osteoporosis/ osteopenia. Unless advised on other grounds, the bisphosphonate should only be given while the patient is on steroids.

c. Anaemia:

IBD is most commonly associated with anaemia. Recently guidelines have been published by expert working group. The most common causes of anaemia in IBD are iron deficiency and anaemia of chronic disease. Drug-induced anaemia secondary to MP or sulfasalazine also occurs. Although, other causes of anaemia like coeliac disease and menorrhagia must be sought by proper history study and by use of coeliac serological testing. In older patients and those with a family history of cancer, investigation should exclude bowel cancer as a cause [50].

i. Screening for anaemia

IBD patients must have at least one annual haemoglobin check for screening of anaemia, alongwith ferritin, transferrin saturation and CRP must be tested in such type of patients. In an acute phase reaction CRP is significant to check the ferritin level as ferritin can be elevated. In iron deficiency state the level of ferritin less than 100 mg/L is advised. Those patients with small bowel disease at risk of folate or B_{12} malabsorption or with a macrocytosis should have levels of B_{12} and folate checked [51].

ii. Treatment of iron deficiency

Long-term prevention of anaemia by treatment of underlying IBD is primary alongwith this management iron replacement is also required to enhance the quality of life. Treatment may be with oral iron, such as ferrous sulphate 200 mg bis a day or another preparation with equal amounts of elemental iron, concentration 130 mg/day), but this may not be tolerated well and may exacerbate IBD symptoms measured by activity scores. The intravenous replacement is preferred in patients with poor tolerance to oral iron. Ferric carboxy-maltose (Ferinject), Iron sucrose (Venofer) does not have the magnitude of risk of anaphylaxis of iron dextran and are usually well tolerated and usually effective [52].

iii. Other anaemias

In CD, Vitamin B_{12} and folate deficiency may takes placeand replacement with IM B_{12} and oral folate is advised. Patients having ileal resections need for B_{12} replacement therapy should be anticipated. Monitoring or early replacement should be instituted. Thiopurines also leads to anaemia and macrocytosis and if vitamin levels and iron are normal then drug-induced anaemia must be recommended. Referral for bone marrow investigation and haematology opinion is needed along with the considered withdrawal of any implicated drug treatment [53].

iv. Non-responsive anaemia

In patients with IBD and severe anaemia that is non-responsive to iron therapy there is good evidence to show that erythropoietin analogue therapies will produce a response in 70-100%.of patients [54].

d. Vaccinations:

Patients with IBD may be at risk for infections due to underlying disease, malnutrition, surgery, or immunosuppressive therapy.

i. Infection and immunisation history

A vaccine and infection history is best taken at baseline when a patient is diagnosed with IBD, including TB exposure, chickenpox history and risk of hepatitis B. Varicella zoster serology is best checked if there is no history of infection. We recommend checking hepatitis B serology in high-risk patients and prior to anti-TNF therapy. If patients are sero-positive for hepatitis B [55].

ii. Recommended vaccinations

- Influenza, pneumococcal and HPV (females) vaccination is generally recommended for immunosuppressed adults and is best considered for all patients with IBD, given the frequent need for steroid

and immunosuppressive therapy. Booster vaccinations are appropriate for influenza (annually) and pneumococcus.

- Hep B vaccinations should be considered prior to immunosuppressive or anti-TNF monoclonal antibody therapy in the non-immune high-risk patient.
- Live vaccines should be avoided in patients on immunosuppression or steroids (MMR, oral polio, yellow fever, live typhoid, varicella).
- Varicella vaccination before treatment with steroids or immunosuppressants is now a possibility and has been recommended in Europe and the America in the non-immune.

iii. Post-exposure prophylaxis

Post-exposure prophylaxis of varicella and measles exposed non-immune individuals on high-dose steroid or immunosuppression is appropriate with immune globulin (varicella zoster immunoglobulin or human normal immunoglobulin). Acyclovir prophylaxis may also be used for varicella.

Recommendations for vaccinations

- In all patients with IBD vaccination and infection history must be recorded.
- To immunosuppressed patients with IBD, primary and booster vaccination for influenza and pneumococcus must be carried out [56].

e. Psychological Aspects:

i. Incidence and prevalence of mood disorders in IBD

In patients with IBD, anxiety is also most common mood disorders occurs in IBD patients is due to IBD itself and its medical treatment which include corticosteroid therapy, surgery, specifically colectomy and stoma formation also has psychosocial implications as do awareness of the risk of cancer and cancer surveillance [57].

ii. Psychological stress as a trigger for disease or relapse

Human and animal studies have revealed psycho-neuroimmunological mechanisms whereby stress could influence the course of IBD. Stress and adverse life events do not appear to trigger the onset of CD or UC, but most reports indicate that they may be involved in triggering relapse of IBD [58].

iii. Effectiveness of psychological support in IBD

There is no definitive evidence that psychological interventions improve the course of IBD itself but they do usually improve patient's quality of life and wellbeing. Generally, psychiatric and psychological support must be made available where psychological concerns are present [59].

5. Literature Survey:

Abraham C and Judy H. Cho *(2009),* published a review on various mechanisms associated with Inflammatory Bowel Disease, in which they effectively elaborated the various pathophysiological causes of IBD and CD. They concluded that interleukin-12–interleukin-23 blockade and anti–TNF-α monoclonal antibody techniques play a potent role in the treatment of IBD and CD [60].

Thia KT *et al.(2010),* did a research project on the risk factors associated with progression to intestinal complications of Crohn's disease in a population-based cohort, by using the various Medical records of all Olmsted County, Minnesota residents who were diagnosed with Crohn's disease from 1970 to 2004, and Kaplan-Meier method as a basic cumulative probability method. They concluded that, about 18.6% of patients with Crohn's disease experienced penetrating or stricturing complications within 90 days after diagnosis; 50% experienced intestinal complications 20 years after diagnosis [61].

Burger D and Travis S *(2011),* published a review paper on conventional medical management of Inflammatory Bowel Disease in which they focussed in detail on various conventional treatment measures and also the effective management of various treatment options against IBD and CD [62].

Nicholas JT *et al. (2011),* publicized a review article on the topic i.e. An Evidence-Based Systematic Review on Medical Therapies for Inflammatory Bowel Disease in which they provided the knowledge about the comparative data regarding Incidence of CD and UC invariouscountres. From those values they tried to aware the public about the extent of spread of UC and CD among the different countries [63].

Roblin X *et al. (2013),* communicated a review paper on the new strategies for the treatment of inflammatory bowel diseases, through which the provided the explained knowledge to people regarding the use of various novel management technologies for the potential treatment of IBD such as corticosteroid free treatment and treatment using biomarkers [64].

Ryan EC *et al. (2014),* published a research article on the role of family history of inflammatory bowel disease among patients with ulcerative colitis. They prepared a statistical Meta-analysis report regarding the family history of patients suffering from Ulcerative Colitis and successfully calculated the percent chances of acquiring IBD from those patients [65].

Bruno RRM *et al. (2015),*publicized a review on overview of immune mechanisms and biological treatments for IBD in which they theoretically explained the various immune responses associated with IBD as well as the use of biological agents such as Infliximab and Adalimumab for the treatment of IBD [66].

Geoffrey CN *et al. (2016),* communicated a review paper based on the Toronto consensus statements for the management of Inflammatory Bowel Disease in pregnancy which was specifically contained with the extracted data regarding the treatment of the pregnancy associated population suffering from IBD Toronto, Canada. They concluded that, because of adverse pregnancy outcomes such as preterm delivery, can lead to higher rates of infant mortality, appropriate and timely diagnostic and treatment interventions during the critical antenatal period can be considered lifesaving measures [67].

Forbes A*et al. (2017),* imparted a publication including the ESPEN guideline regarding the clinical nutrition in inflammatory bowel disease. The guideline generated ware based on extensive systematic review of the literature, but relies on expert opinion when objective data were lacking or inconclusive. They concluded that the available objective data to guide nutritional support and primary nutritional therapy in IBD were presented as 64 recommendations, of which 9 were very strong recommendations (grade A), 22 were strong recommendations (grade B) and 12 were based only on sparse evidence (grade 0); 21 recommendations were good practice points [68].

Seyedian SS *et al. (2019),* communicated a review publication base on thethe diagnosis, prevention, and treatment methods of inflammatory bowel disease, in which they effectively workforced on the number of factors can be attributed to the prevalence of CD and UC, some of which include geographical location, inappropriate diet, genetics, and inappropriate immune response. They concluded thatamongstall,only some of the most common foods that worsen the symptoms such alcohol, coffee, soft drinks, spicy foods, beans, fatty foods, nuts, seeds, and dairy products. On the other hand, learning stress management techniques can help improve IBD [69].

6. Summary and Conclusion:

IBD occurs due to activation of immune system triggered by exposure of certain genetic as well as environmental factors to a person results in production of various inflammatory mediators such as cytokines, chemokines, and certain growth factors which increase the process of inflammation itself and cause the tissue destruction at that local site, which are the resulting pathophysiological characterstics of the disease. The NOD_2 autophagy gene is the genetic cause of the disease occurance. However there are many available therapies for the initial management of the disease from mild to moderate level of spread like 5- ASA and corticosteroids. But these treatment approaches have been failed to treat severe cases and also result the chances of remission in more than 30% of cases. In severe cases, the frequently approved biological agents act as specifically acting local inhibitors of inflammatory mediators related to inflammatory bowel disease. Also the various approved TNF blockers, IFX and ADA are the choice of biological drugs for the treatment of severe IBD. Despite the fact that one third of the patients treated with these biological agents have shown remission of disease after treatment, there clinical benefits and safety analysis reports seemed to outweigh the risk of remission involved. The use of these advanced biological therapy including Monoclonal antibodies as well as anti-TNFα (IFX) has been recommended for treatment of IBD, but its excessive cost has limited its use.

In the conclusion, after doing the huge research, approximately from last three decades, the scientists have found a clear idea about the various causes related to IBD as well as their respective treatment. Among these management approaches, the use of biological therapy has been concluded as the best treatment approach due to its high safety margin amongst the other conventional treatments such as 5- ASA and corticosteroids. Also, the studies regarding the etiology and treatment of IBD are still going on. Hence in future there may be the possibility of amending the data regarding to causeas well as management of Inflammatory Bowel Disease based on future studies related to this.

List of abbreviations:

Abbrevations/ acronyms	Explanation
ADA	Adalizumab
APC	Antigen-presenting cells
ASA	Aminosalicylic acid
CARD	Caspase recruitment domain-containing protein
CD	Crohn's disease
CRP	C-reactive protein
CT	Computed tomography
EIMs	Extra-intestinal manifestations
ERCP	Endoscopic retrograde cholangio-pancreatography
ESR	Erythrocyte sedimentation rate
FBC	Full blood count
IBD	Inflammatory bowel diseases
IFN	Interferon
IFX	Infliximab
IgG	Immunoglobulin
IL	Interleukin
MAdCAM	Mucosal addressin cell adhesion molecule
mg/L	Milligram/ litre
MP	Mercaptopurine
MRI	Magnetic resonance imaging
NOD	Nucleotide-Binding Oligomerization Domains
PAF	Platelet activating factor
PRR	Pattern Recognition Receptors
PSC	Primary sclerosing cholangitis
S/C	Subcutaneous
STAT	Signal transducer and activator of transcription
TB	Tuberculosis
TGF	Transforming Growth Factor
T_h	T helper cell
TLR	Toll-Like Receptors
TMPT	Thiopurinemethyltransferase
TNF	Tumor necrosis factor
UC	Ulcerative colitis

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