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Crohn's disease: Current approaches in the management and remission

P Sailaja Rao and Pingili Divya

Abstract
Crohn's disease (CD), characterized as inflammatory bowel disease (IBD), is a chronic disease that affects the lining of digestive tract and includes lifelong therapy. High incidence of this disease is witnessed in western countries like USA, Canada, UK and is slightly apprehending in Asian countries. Medical treatments for IBD are restricted and were aimed at bestowing symptomatic amelioration. When conventional treatments are not responding in patients suffering from Crohn's disease, chemotherapy with drugs like infliximab, adalimumab, methotrexate, and cyclophosphamide may aid in treating the symptoms and inclines the disease into remission. Though medication is helping out in the maintenance of Crohn's, the lifestyle improvement can support in the better management of the disease. An improved perceptive of pathological mechanisms endeavors new castles in air for tailored therapies. In the present review, emphasis was laid on portrayal of pathological mechanisms, newer diagnostic techniques, chemotherapy and the prominence of diet, exercise, yoga and pranayama in the remission of Crohn's disease.

Keywords: Crohn's disease, pathophysiology, management & remission

1. Introduction
Crohn's disease (CD) is a debilitating chronic ileitis disease characterized by repeated episodes of inflammation in any part of the gastrointestinal tract from mouth to anus. This is one of the types of IBD (Inflammatory Bowel Disease) with annual incidence of 1-10 cases in one lakh people. However, the prevalence varies from region to region [1]. CD is a systemic granulomatous disease with strictures, micro perforations and fistulae. The clinical manifestations of CD include abdominal pain, weakness, fecal incontinence, weight loss, diarrhea and hemorrhage in the rectum. Other complications like, anemia, arthritis, skin rashes, and erythema nodosum are also associated with CD. CD is an immunodeficiency state which occurs in genetically susceptible individuals due to environmental, bacterial and immune factors [2].
NOD2 gene (Nucleotide binding oligomerization domain containing protein 2) was the first gene identified in CD. Interestingly Chinese and Japanese are devoid of NOD2 gene mutation. Smoking plays a critical role in the progression of disease and cessation of smoking ameliorates the severity of disease. Inadequate immune system may provoke the alteration in dendritic cell distribution, expression of TLR (Toll like receptors), co-stimulatory markers, cytokines and imbalance between Th1 and Th17 (Pro-inflammatory effectors) and TNF-α (Tumor necrosis factor) [3]. Reduced concentration of micro-organisms like firmicute (especially Faecalibacterium prausnitzii) and bacteroides spp. organism lying in the intestinal mucosa constitutes one of the etiological factors in CD [4].

2. Prevalence of CD
An epidemiological trend of CD during the last 25 years was quite fascinating. A race or population with low menace of CD in their terrain may be provoked in an industrialized country or vice-versa, because of environmental changes which results in genetic changes. High ubiquity of CD is perceived in western countries like USA, Canada, UK and New Zealand. The denouement of antecedent compendium in the western countries witness high rate of CD among females than in males [5]. A statistical analysis for preponderance of CD around the world indicates that the western and northern European countries (Switzerland, Scotland and Sweden) evidenced high incidence and prevalence of CD. However, Eastern European countries experienced fewer incidences. North America also manifested high proportion of CD cases of which Canada ranks first.

In the oceanic continent, Australia and New Zealand ranked first and second respectively in the prevalence of CD [6]. Asian and African countries evince low incidence of CD and insufficient data was found with Persian Gulf region countries. Recent data suggest that all the countries are working actively in diagnosing and stabilizing its incidence and prevalence [7].

3. Pathophysiology

Crohn's disease is immune mediated condition that affects distal ileum, the colon, duodenum, stomach, esophagus and the perineum. The presence of skip lesions is one of the characteristic features of CD. The triggering factors like perturbation of mucosal barrier; alter the balance of gut microorganisms and provides abnormal stimulus of gut immune responses. The intestinal wall becomes rubbery and thick, as a consequence of edema, inflammation, fibrosis and hypertrophy of the muscularis propria [Figure 1]. The size of the lumen is narrowed with appearance of strictures in the colon. A characteristic sign of early disease is focal mucosal ulcers resembling canker sores, edema and loss of the normal mucosal texture. Narrow fissures are developed between the folds of the mucosa.

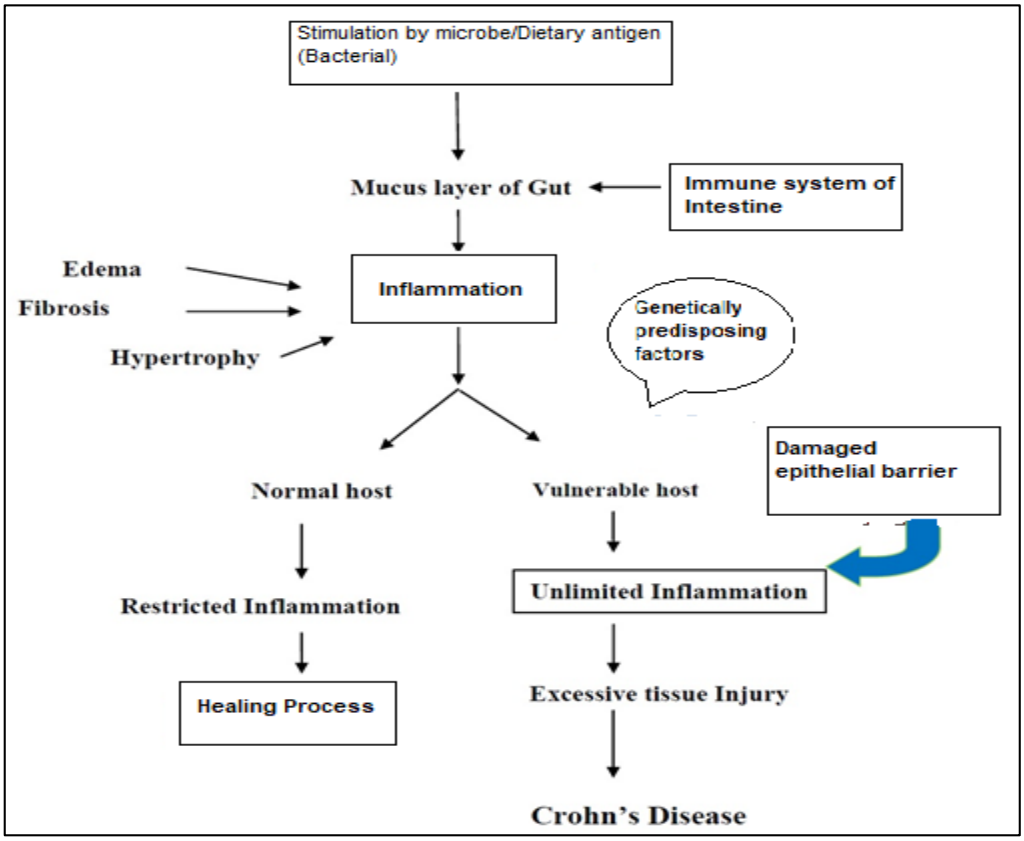

Fig 1: Pathophysiology of Crohn's disease [20, 21]

Immune system of intestine gets stimulated by microorganism or any dietary antigen. This inclines to inflammatory process, characterized by edema, fibrosis and hypertrophy. As the impact of genes is higher, it leads to everlasting inflammation causing tissue injury and finally CD.

3.1 Role of NOD2 (CARD 15)

Nucleotide-binding oligomerization domain-containing protein 2 (NOD2) also known as caspase recruitment domain-containing protein 15 (*CARD15*) or inflammatory bowel disease protein 1 (IBD1) is a protein that in humans is encoded by the NOD2 gene located on chromosome 16. NOD2 is a cytosolic pattern recognition receptor (PRR) that controls immunity against intracellular bacteria [8].

NOD2 is expressed in limited number of tissues that include intestinal epithelial cells (mainly paneth cells) and monocyte-derived immune cells residing in the lamina propria. In both the human and murine studies, defects in NOD2 function can affect microbial sensing, Paneth cell function, anti-microbial peptide (AMP) production, antigen presentation, intracellular bacterial killing, and innate immune signaling, such as Toll-like receptor (TLR) function [9]. NOD2 provides critical host anti-bacterial defense and pro-inflammatory responses, and NOD2 acts to regulate innate immune responses. NOD2 activation after recognition of MDP (Muramyl dipeptide, a component of bacterial cell walls with inflammatory properties) triggers nuclear factor kappa-B (NF-kB)-dependent signaling but is relatively weak in this respect compared with other PRRs (Pattern recognition receptor), such as the TLRs. NOD2 plays a key role in amplifying the release of certain pro-inflammatory cytokines particularly IL-1b, IL-6, and IL-23, from macrophages. In addition to the direct role in innate immunity, several studies show that NOD2 indirectly modulates the gut microorganisms, perhaps linked to defective AMP production by Paneth cells [10].

3.2 Autophagy

Autophagy is a lysosomal degradation pathway that is essential for cellular survival, differentiation, development, and homeostasis. Principally this process protects the body against infections, cancer, neurodegeneration, and aging [11]. The autophagy genes exhibit polymorphism (ATG16L1, IRGM, and LRRK2), which had triggered significant research in CD [12].

3.3 CD4 T cells as a part of CD

There are several lines of evidence which elaborate a major contribution of CD4 T cells in the pathogenesis of CD. Receptor for interleukin (IL-23), a cytokine essential for the survival of the T-helper cells (Th) 17, subset of $CD4^+$ T cells, is implicated in the pathogenesis of several animal models [13]. Similarly, large clinical trials of drugs targeting proteins have been identified for $CD4^+$ T cells. Reports have been recognized that $CD4^+$ T cells are present in the intestinal mucosa. IBD patients had an increased percentage of $FoxP3^+$ T bet^+ cells in the lamina propria (LP), representing T-regulatory (Treg)/ Th 1 crossover T cells. CD patients have an increased number of $FoxP3^+$ Treg's with features of Th2 cells such as IL-13 production or transcription factor GATA-3 expression. Chronic intestinal inflammation may be because of either impaired regulatory T cell activity or excessive effector T cell function. A critical role for $CD4^+$ T cells was shown in different animal models of experimental colitis [14, 15].

MICA, (*MHC class I* polypeptide-related sequence A), an MHC related class Ib molecule was expressed on normal intestinal epithelial cells, which could be involved in the activation of mucosal lymphocytes. A study was conducted to examine the role of MICA – NKG2D (natural-killer group 2, member D) interactions in the activation of T lymphocytes in CD. It was also observed that there was a significant increase in CD4 NKG2D lymphocytes [16].

4. Crohn's disease and Cancer

It was recognized that there is an increased risk of colorectal cancer in patients with IBD (Inflammatory bowel disease), particularly in those patients with long established and substantial ulcerative colitis. Cancers like small bowel carcinoma, which is attributed to digestive tract tumors, are more noticed in CD patients. A report says that colorectal cancer was identified in 8 out of 449 CD patients [17]. Also a study says that there is 4 fold increased risk in patients with CD [18]. In Asia, CD has now become an eye catching, with a highest rate of colorectal cancer, especially in the lower rectum and anal area. A recent Meta-analysis has also confirmed that there is increased risk of colorectal and small bowel cancer in CD [19]. Moreover, other type of malignancies like myeloid and lymphoid were also been reported, and might be possibly related to the wider use of immunosuppresants or biological agents. Carcinoid tumors may be increased in CD patients with a 15 fold risk. Pre-cancerous cells only appear in areas of inflammation. Therefore, the risk of colon cancer is highest in people who have Crohn's colitis. Till date, there is a very limited data available in elderly patients who were recommended for screening and surveillance colonoscopy in chronic and extensive Crohn's colitis.

5. Diagnosis

The clinical diagnosis of Crohn's disease is based on the history, examination, laboratory, radiological and histological investigations. Different biological tests include full blood count, renal infection, liver function, albumin levels, blood sedimentation rates, body minerals levels, Red blood cell count and stool examination for blood or infectious microbes.

The radiological investigation includes endoscopy and imaging which help identify the severity and location of CD. Endoscopy is done by illeocolonoscopy with biopsy which assesses the disease activity. An imaging technique, fluoroscopy (Barium and gastrografin follow through) has long been backbone for abdominal imaging in Crohn's disease. This technique has displaced the MRE (Magnetic resonance elastography) and CTE (Chronic traumatic encephalopathy) which also provides good images in diagnosis. It is also critical to consider the differential diagnosis especially with the Tuberculosis infection. New techniques are being developed to diagnose CD in the early stages which could help in its remission. They include MSOT (Multi spectral optoacoustic tomography) and PET (Positron emission tomography) [22, 23].

5.1 MSOT (Multi spectral optoacoustic tomography)

MSOT, a neoteric, less invasive imaging technique is being employed recently to diagnose Crohn's disease. The technique of MSOT is based on assessment of haemoglobin levels in the intestinal wall which distinguishes active disease from that of remission in CD patients. MSOT induces photo acoustic effect in the target tissues by incitement of short pulsed laser with that of near IR wavelength. This results in generation of detectable sound waves by means of thermoplastic expansion. Further research is going on to contrive the technique [24].

5.2 PET (Positron emission tomography)

PET is yet another novel technique developed to diagnose CD. PET targets a specific subset of $CD4^+$ T cells which are characteristic of IBD. The principle of this technique involves the usage of the anti CD4 engineered antibody fragment labeled with Zirconium-89. It is a non-invasive imaging technique which measures the distribution of $CD4^+$ T cells. This technique successfully detected in $CD4^+$ T cells in colon and mesenteric cancers [25].

6. Management of disease

CD is considered as a chronic relapsing inflammatory condition which needs certain therapeutic goals towards the betterment in the treatment of disease. They include

- Nutritious diet
- Monitoring ADR
- Fast resolution of exacerbations
- Supervision of complications
- Improving the quality of life

CD has no cure, but medications can help to manage the symptoms and prevent the progression

6.1 Amino Salicylates

Amino Salicylates are the drugs which are preferred in treating mild to moderate CD, as they could easily relieve from inflammatory symptoms. Sulfasalazine and Mesalamine are the most commonly used medications of which sulfasalazine finds use in treating joint pains while mesalamine progresses the remission of the disease in post-operative condition [26].

6.2 Corticosteroids

Corticosteroids are the drugs which reduces inflammatory symptoms. Budesonide is the first line therapy for induction of remission in CD. However in severe cases, Prednisone or methyl prednisolone can be used for the treatment. The steroid therapy should be supplemented with calcium and vitamin-D to prevent long time side effects. Steroids are advisable only for shorter period of time, as they are associated with many side effects. Hence the preferred drug to

maintain the therapy is Methotrexate which helps in remission of CD [27].

6.3 Immunomodulators

In Crohn's disease, the normal cells which safeguard the body, attack the gastrointestinal tract, hence the medication which regulate the immune system can help in treating Crohn's disease. Immunosuppresants were recognized as remarkable drugs with overall good tolerance and were proposed. The various immunosuppressive medications include Azathioprine, Methotrexate, Cyclosporine, and 6-Mercaptopurine (6-MP). In chronic CD, the thiopurines (6-MP & Azathioprine) are preferred medication. The frequent side effects are headache, nausea, vomiting and diarrhea. The uncommon side effects include pancreatitis, liver problems, myelosuppresion, fibrosis of lungs and thyroid.

6.4 Monoclonal Antibody Therapy

Monoclonal antibody therapy, also called as Biologics or Anti-TNF therapy was found to be efficient in maintaining revocation of CD. Drugs like Infliximab, Adalimumab, Certolizumab, Nakalizumab, Vedolizumab and Ustekinumab are preferred upon steroid medications for moderate to severe symptoms of CD and are also considered as alternative treatment in case of resistance [28]. Some among these drugs are into various phases of clinical trials and are yet to prove their complete efficiency [Table 1].

Table 1: Clinical status of drugs for CD [29, 30, 31]

Drug	Type	Clinical Status for CD
Anti-adhesion molecule		
Vedolizumab	Monoclonal antibodies	Approved
Etrolizumab	Monoclonal antibodies	
Natalizumab	Monoclonal antibodies	
Blockade of downstream signaling Pathways		
Tofacitinib	Small molecule	Phase III Clinical Trial
Blockade of Pro-inflammatory Cytokines		
Ustekinumab	Monoclonal antibodies	Phase II Clinical Trial

6.5 Combination therapy for CD

Biologic therapies such as infliximab and adalimumab have become a cornerstone for the treatment of IBD. Few studies have emphasized that with the combination therapy (CT) the immunogenicity can be minimized with improvisation in the outcome. There are three strategies to treat CD in combination of drugs. The first one, which is the classical step-up approach, involves steroids, then switching to other if steroid therapy fails, and finally utilizing anti-TNF agent in case of immunosuppressant therapy failure. Second one is a rapid step-up approach in which an immunosuppressant is added to the steroid. The third strategy is a combination therapy, in which both an immunosuppressant and anti-TNF agents are given together. To induce a deep remission in patients with CD, a target of combination therapy is preferred. It includes both remission of clinical symptoms and also full healing of the transmural inflammatory process that occurs in CD, hence avoiding the complications, surgeries and disability linked to surgery. Gastroenterologists are keen to avoid bowel damage in patients with CD. The rationale supports the use of combination therapy, as it is the most effective treatment option available. When there is a severity of disease, the efficacy of combination offers a huge potential benefit [32].

6.6 Other Drugs

In CD, antibiotics, probiotics and prebiotics are not evidenced with proper benefits and patient compliance. A randomized placebo controlled trial revealed that probiotics could not prevent the occurrence if Crohn's disease [33].

6.7 New therapy for CD

Ingestion of Trichris Suis, a porcine whip worm offers a unique alternative for managing CD. T. Suis inhibits the intestinal inflammation by inducing production of interleukin (IL-4 & IL-13) which depresses the Th1 cytokines and hence reduces the colitis severity. Further a double blind controlled clinical trial hypothesized that exposure of helminthes also proffers protection against CD.

6.8 Indolines

The novel low molecular weight indolines were synthesized which showed potent activity against release of pro inflammatory cytokines and toxic effects of reactive oxygen species [34].

6.9 Chemotherapeutic agents

As CD is an autoimmune disease that causes inflammation, primarily in the digestive tract, there is no cure for Crohn's, however some types of chemotherapy could reduce the symptoms and cause the disease to go into remission. Taking chemotherapeutic drugs can help put troublesome symptoms of CD into remission

6.9.1 Infliximib: It is a type of tumor necrosis factor blocker. TNF is a specific protein that helps to regulate the immune system. It acts like an anti-inflammatory agent [35].

6.9.2 Methotrexate: It is a potential drug used to treat immune disorders, such as IBD and rheumatoid arthritis. It acts by lowering cell production to reduce the activity of the condition. Considering the adverse effects of methotrexate, it is important to administer the folate or folic acid supplements as it blocks the folate intake in the body [36].

6.9.3 Adalimumab: It is another TNF blocker that may be helpful in treating CD. It acts by binding to the TNF – alpha cells, preventing them from causing inflammation. This may reduce the defense mechanism of the body, so people taking the drug may be at higher risk of infection [37].

6.9.4 Mercaptopurine: 6-mercaptopurine, an immunosuppressive drug was thought to decrease the inflammation associated with CD by blocking the immune system. But in randomized trials conducted in a total of 1211 participants, it was found not to be effective in inducing remission of Crohn's disease. This antimetabolite therapy can only decrease the consumption of steroid medication [38].

6.9.5 Cyclophosphamide: It is another chemotherapeutic drug which may be helpful in CD. A retrospective study was conducted to review the efficacy and safety of CPT (Cyclophosphamide pulse therapy) in mainly tumor necrosis factor (TNF) – refractory complicated CD patients. In this study cyclophosphamide was given for 411 days, and was observed that 1/3rd of the patients went into clinical remission due to CPT. Keeping in view of this, CPT might be considered as a therapeutic alternative to minimize the side effects [39].

7. Diet and CD

There is no special diet proven effective for CD, however certain foods cause flare-ups in the symptoms of the disease. The foods like dairy, high-fiber grains, alcohol and hot spices which aggravate the symptoms need to be avoided. Deficiency of nutrients is another common worry since inflammation in the CD interferes with nutrient absorption. Hence, people with CD need a nutrient-rich diet with adequate calories, protein and healthy fats. The recommended foods include probiotics and prebiotics, with dietary supplements such as iron, calcium, vitamin D, folate, zinc and vitamin B 12 to prevent or treat deficiencies. However, further clinical investigation of the different diets should be valuable in the greatest unsolved challenge of CD [40].

8. Physical exercise in CD

Prescribing physical exercises in CD patients remained speculative because there were only three studies so far been carried out on these patients, which might not be enough to make detailed recommendations and to narrate how training sessions should be structured. However, according to the previous clinical findings/studies, two main types of physical interventions have been suggested: aerobic activity and muscular resistance trainings [41].

9. Aerobic activity:

Walking or aerobic exercise should be recommended for CD patients for beneficial effects on their quality of life. It has been shown that CD patients can walk 3.5 kms on an average without experiencing any sort of exacerbation in symptoms. In case of any fatigue or any aggravating sign, aerobic activity must be stopped [42]. Finally, it must be noted that although other aerobic activities such as swimming, pedaling on a recumbent bike or weight-bearing walking could be advisable, currently there is no available information regarding their effects on CD patients [43].

10. Muscular resistance training:

This is gold standard exercise treatment to prevent bone loss and to improve body composition in CD patients. The training sessions should start with a 5-minute warm-up, consisting of general whole body mobility and finish with a 5-minute cool-down period of muscular stretching. In order to avoid the intensification of symptoms, patients should rest for 15-30 s in between each exercise [44].

In regard to the physical exercise on CD patients, it is important to follow some practical advices from an exercise physiologist or sport physician. It also depends on age, fitness level, exercise goals and preferences. Finally, the status of the CD must be noted, whether remission or with mild activity or with high and then suitable exercises are recommended [45].

11. Yoga practices, Pranayama and CD

With origins in ancient India, the practices of yoga are being incorporated into treatment methodology for everything right from IBD [Both Crohn's disease and Ulcerative colitis (UC)] to arthritis. The researchers found that the meditation aspect of yoga that relieves stress also inhibits the inflammation and immune system in people with IBD. In people suffering from IBD over 1000 genes were altered by the yoga and meditation. Yoga is a great way to exercise and de-stress. It consists of a mixture of 5 main practices – asana, breathing practices, meditation techniques, relaxation and nutrition. These all techniques combine to become yoga. Yoga helps to detoxify body and removes toxins and bacteria in the body. Also it improves flexibility, tones and strengthens muscle. It revitalizes refreshes and energizes the body with ease and decrease the sense of pain and discomfort [46].

12. Maintenance of Remission:

The idea of deep remission is a very important evolving concept because clinicians are now treating patients with the goal of not only obtaining clinical remission but also achieving full bowel healing. Maintenance of remission is quite a difficult task in CD. Understanding the etiological factors and also using new medicinal agents aim at the subsequent maintenance of remission. The Immuno modulators have an established role in CD maintenance. Treatment of patients with the anti-tumor necrosis factor alpha antibody (TNF-α antibody), infliximab has been shown to be effective in the induction of remission. It was also observed that this drug delayed relapse and maintained remission. However, the results obtained were unsatisfactory. Hence, in order to maintain the remission of CD, an insight into current and emerging therapeutic agents are needed for potential therapy in future.

13. Conclusion

Crohn's disease is a perpetual disease with no known cure. However medications are serving as a prominent tool in diminishing its symptoms. Beyond anti-tumor necrosis factor agents, selective lymphocyte inhibitors are proposed as potent drugs for IBD. Novel biological agents like Tofacitinib and Utsekinumab which are in different phases of clinical trials are expanding the treatment options for CD. But with the usage of medications, increase in the side effects and progression of disease condition has been perceived. Hence the better way of attaining remission is to bring legitimate changes in the life style like adapting yoga, pranayama and physical exercises in the daily routine. Research is still in progress to hit an agent which succor in satisfactory remission of Crohn's disease.

14. References

1. Hendy P, Hart A. A Review of Crohn's Disease. EMJ Gastroenterol. 2013; 1:116-23.
2. Baumgart DC, Sandborn WJ. Crohn's disease. Lancet. 2012; 380:1590-1605.
3. Basu D, Lopez I, Kulakarni A, Sellin JH. Impact of race and ethnicity on inflammatory bowel disease. Am J Gastroenterol. 2005; 100:2254-61.
4. Yau Y, Leong RW, Zeng W. Wasinger VC. Proteomics and metabolomics in inflammatory bowel disease. J Gastroenterol Hepatol. 2013; 28:1076-86.
5. Behzadi P, Behzadi E, Ranjbar R. The incidence and prevalence of Crohn's Disease in global scale. SOJ

Immunology. 2015; 3(2):1-6.
6. Pinzon MCM, Hayden DM. Crohn's Disease. Common Surgical Diseases: Springer, 2015, 161-63.
7. Logan I, Bowlus CL. The geoepidemiology of autoimmune intestinal diseases. Autoimmun Rev. 2013; 9(5):A372-78.
8. Wehkamp J, Harder J, Weichenthal M, Schwab M, Schäffeler E, Schlee M. NOD2 (CARD 15) mutations in Crohn's Disease are associated with diminished mucosal α- defensin expression. Gut. 2004; 53:1658-64.
9. Hampe J, Cuthbert A, Croucher PJ, Mirza MM, Mascheretti S, Fisher S. Association between insertion mutation in NOD2 gene and Crohn's Disease in German and British populations. Lancet. 2001; 357:1925-28.
10. Rosenstiel P, Fantini M, Brautigam K, Kühbacher T, Waetzig GH, Seegert D. TNF – alpha and IFN gamma regulate the expression of the NOD2 (CARD15) gene in human intestinal epithelial cells. Gastroenterology. 2003; 124:1001-1009.
11. Boyapati R, Satsangi J, Gwo-Tzer H. Pathogenesis of Crohn's disease. F1000Prime Reports. 2015; 7:44.
12. Nguyen HT, Lapaquette P, Bringer MA, Arlette DM *et al.* Autophagy and Crohn's Disease. Journal of Innate Immunity. 2013; 5:434-43.
13. Franke A, McGovern DP, Barrett JC, Wang K, Radford-Smith GL, Ahmad T. Genome-wide metaanalysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. Nat genet. 2010; 42:1118-25.
14. Boden EK, Lord JD. CD4 T cells in IBD: Crossing the line? Dig Dis Sci. 2017; 62:2208-10.
15. Li J, Uneno A, Iacucci M, Fort GM, Jijon HB, Panaccione R. Cross-over subsets of CD4 + T lymphocytes are increased in the lamina propria of Crohn's disease and Ulcerative colitis patients. Dig Dis Sci, 2017, 4596-99.
16. Weedon DD, Shorter RG, Ilstrup DM, Martha SL, Susanne KK. Crohn's disease and cancer. N Engl J Med. 1973; 289:1099-1103.
17. Gyde SN, Prior P, Macartney JC, Thompson H, Waterhouse JAH, Allan *et al.* Malignancy in Crohn's disease. Gut. 1980; 21:1024-29.
18. Canavan C, Abrams KR, Mayberry J. Meta-analysis: colorectal and small bowel cancer risk in patients with Crohn's disease. Aliment Pharmacol Ther. 2006; 23:1097-1104
19. Loftus EV, Silverstein MD, Sandborn WJ, Tremaine WJ, Harmsen WS. Crohn's disease in Olmsted County, Minnesota, 1940-1993: Incidence, prevalence and survival. Gastroenterology. 1998; 114:1161-68.
20. Stephen RV, Rogler G. New insights into the pathogenesis of Crohn's disease: are they relevant for therapeutic options? Swiss Med Wkly. 2009; 139:527-34.
21. Duerr RH. Update on the genetics of inflammatory bowel disease. J Clin Gastroenterol. 2003; 37:358-67.
22. Firemen Z, Mahajna E, Broide E, Shapiro M, Fich L, Sternberg A *et al.* Diagnosing small bowel Crohn's Disease with wireless capsule endoscopy. Gut. 2003; 52:390-92.
23. Schulz C, Monkemuller K, Salheiser M, Bellutti M, Schutte K, Malfertheiner P. Double-balloon enteroscopy in the diagnosis of suspected isolated Crohn's disease of the small bowel. Dig Endosc. 2014; 26(2):236-42.
24. Knieling F, Neufert C, Hartmann A, Claussen J, Urich A, Egger C *et al.* Multispectral Optoacoustic Tomography for Assessment of Crohn's Disease Activity. N Engl J Med. 2017; 376(13):1292-94.
25. Dmochowska N, Tieu W, Keller M, Wardill HR, Mavrangelos C, Campaniello MA *et al.* Immuno-PET of innate immune markers CD11b and IL-1β detect inflammation in murine colitis. J Nucl Med. 2019; 60(6):858-63.
26. Spinelli A, Sacchi M, Fiorino G, Silvio D, Marco M *et al.* Risk of postoperative recurrence and postoperative management of Crohn's disease. World J Gastroenterol. 2011; 17:3213-19.
27. Dignass A, Panes J, Beaugerie L, Beaugerie L, Karagiannis J, Allez M *et al.* The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Definitions and diagnosis. J Crohns Colitis. 2010; 4(1):7-27.
28. Rutgeerts P, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF *et al.* Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. Gastroenterology. 2004; 126(2):402-13.
29. Lee HS, Park SK, Park D. Novel treatments for inflammatory bowel disease. Korean J Intern Med. 2018; 33:20-27.
30. Friedman S. Tofacitinib for ulcerative colitis-A promising step. N Engl J Med. 2017; 376:1792-93.
31. Narula N, Rubin DT, Sands BE. Novel therapies in inflammatory bowel disease: An evaluation of the evidence. Am J Gastroenterol Suppl. 2016; 3:38-44.
32. Sultan KS, Berkowitz JC, Khan S. Combination therapy for inflammatory bowel disease. World J Gastrointest Pharmacol Ther. 2017; 8(2):103-13.
33. Julia BE, Levinus AD. Probiotics and prebiotics in chronic inflammatory bowel diseases. World J of Gastroenterol. 2006; 12(37):5941-50.
34. Zeeli S, Weill T, Efrat FG, Corina B, Michal M, Svetlana F *et al.* Synthesis and Biological Evaluation of Derivatives of Indoline as Highly Potent Antioxidant and Anti-inflammatory Agents. Journal of Medicinal Chemistry. 2018; 61(9):4004-19.
35. Dignass A, Lindsay JO, Sturm A, Windsor A, Colombel JF, Allez M *et al.* Second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 2: Current management. J Crohns Colitis. 2012; 6:991-1030.
36. Rutgeerts P, Sandborn WJ, Feagan BG, Walter R, Allan O, Jewel J *et al.* Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005; 353:2462-76.
37. Sandborn WJ, Hanauer SB, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh DG *et al.* Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut. 2007; 56:1232-39.
38. Chande N, Townsend CM, Parker CE, MacDonald JK. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2013, Issue 4. Art. No.: CD000545. DOI: 10.1002/14651858.CD000545.pub4.
39. Amezaga AJ, Vermelre S, Prenen H. Use of Biologics and chemotherapy in patients with inflammatory bowel disease and cancer. Annals of gastroenterology. 2016; 29:127-36.
40. Levi AJ. Diet in the management of Crohn's disease.

Gut. 1985; 26:985-88.
41. Ng V, Millard W, Lebrun C, Howard J. Exercise and Crohn's disease: Speculations on potential benefits. Can J Gastroenterol. 2006; 20(10):657-60.
42. Ng V, Millard W, Lebrun C, Howard J. Low-intensity Exercise improves the quality in patients with Crohn's Disease. Clin J Sport Med. 2007; 17(5):384-88.
43. Perez CA. Prescription of physical exercise in Crohn's Disease. Journal of Crohn's and Colitis. 2009; 3:225-31.
44. Dlinca R, Varnier M, Mestriner C, Martines D, D'Odorico A, Sturniolo GC *et al*. Effects of moderate exercise on Crohn's disease patients in remission. Ital J Gastroenterol Hepatol. 1999; 31(3):205-10.
45. Loudon C, Coroll V, Butcher J, Rawsthorne P, Bernstein CN *et al*. The effects of physical exercise on patients with Crohn's disease. Am J Gastroenterol. 1999; 94:697-703.
46. Sharma P, Poojary G, Dwivedi SN, Deepak KK *et al.* Effect of Yoga-Based Intervention in Patients with Inflammatory Bowel Disease. Int J Yoga Therap. 2015; 25(1):101-12.