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20. INFLAMMATORY BOWEL DISEASE

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20. INFLAMMATORY BOWEL DISEASE

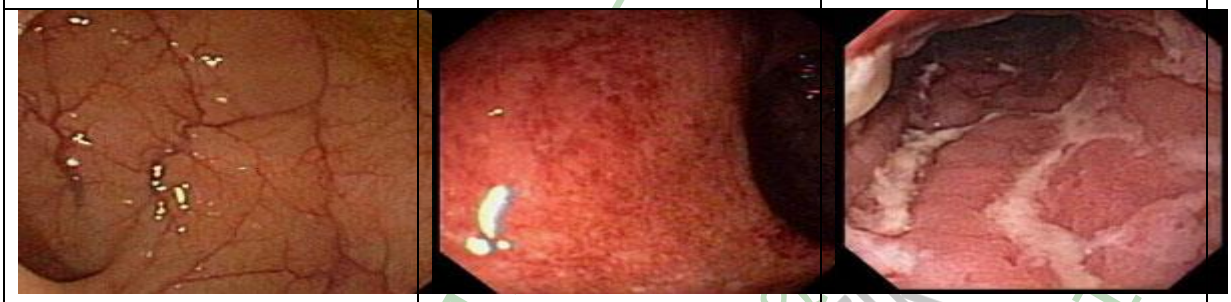
INTRODUCTION:

- Inflammatory bowel disease (IBD) refers to a group of poorly understood conditions of chronic inflammation in the digestive tract, most often the small or large bowel (although these diseases can sometimes manifest themselves anywhere along the digestive tract or even outside of it in other organ systems such as skin, joints or eyes). By far the two most common diseases in this category are **Crohn's disease (sometimes referred to as transmural colitis) and ulcerative colitis.**
- Crohn disease (CD) is also known as the regional enteritis, regional ileitis, granulomatous colitis, or transmural colitis, this disease is one of the inflammatory bowel diseases. It is different from ulcerative colitis, with which it can be confused, in several major respects. First is that crohn disease tends to extend completely through the intestinal wall, whereas ulcerative colitis is limited (expect in the case of toxic megacolon) to the surface mucous membrane of the bowel. Next is that crohn disease is segmental, often with areas of normal bowel interspersed with diseased bowel; ulcerative colitis begins in the rectum and extends up the colon in a solid wave of diseased bowel mucosa. Crohn disease can affect any segment of the git, from the mouth to the anus; ulcerative colitis affects only the colon.
- Ulcerative colitis (UD) is a chronic inflammatory disorder of unknown cause, which is localized to the colon and spares the upper gastrointestinal tract - in contrast to crohn's disease, with which it may be initially confused. Ulcerative colitis almost always begins in the rectum and extends up the colon for a variable distance.

Feature	**Crohn disease**	**Ulcerative colitis**
Rectal bleeding	Sometimes	Common
Abdominal mass	Common	Not present
Rectal disease	Occasionally	Nearly universal
Small bowel involvement	Common	None
Perianal disease	Common	Unusual
Strictures	Common	Unusual
Fistula	Common	Unusual
Discontinuous (skip) lesion	Common	Unusual

Transmural involvement	Common	Unusual
Granulomas	Common	Unusual
Risk for colonic cancer	Slightly increase	Greatly increase

Comparison chrat of CD & UD

Normal colon	Ulcerative colitis	Crohn's disease
		

Endoscopic examination of colon in different condition

Epidemiology

- An estimated 1 - 2 million Americans suffer from inflammatory bowel disease (IBD) and about 400,000 of these patients have Crohn's disease. (This wide statistical variation is due to the difficulty in diagnosing these disorders and because people in remission may not be identified.) The number of people with Crohn's disease may be increasing, and **Crohn's disease is now considered the second most common chronic inflammatory disorder (after rheumatoid arthritis).** IBD often runs in families. The incidence may vary depending on gender, age, and geography:
- Women may be slightly more at risk for Crohn's disease than men. Both genders are equally at risk for ulcerative colitis.
- IBDs in general are diagnosed most often in young people between the ages of 10 and 19, but they can occur at any age. Another lesser peak onset occurs between ages 50 and 80. About 2% of IBD cases appear in children below age 10. Between 10 - 15% of patients with Crohn's are children and the childhood prevalence appears to be increasing
- Both types of IBD may increase risk of cancer. The prevalence of IBD varies by study and by country. Typical frequencies range between 12 and 40 per 100,000. The risk of colorectal cancer in patients with IBD is increased 4 to 20-fold compared to the general population, and some malignancies can develop in apparently uninvolved sites**.** Patients with UC and CD have been reported to develop leukemia, suggesting a potential relationship between IBD and leukemia. IBD occurs four times more often in Americans of Northern European descent than in African Americans. Scandinavia has the highest rate

of Crohn's disease in the world. Studies in Britain suggest, however, that Asians may have a higher rate of IBD than people of European descent. Jewish people of European descent have an even higher risk: Five times that of the general population.

- IBD seems to be more common among city than country dwellers and occurs more frequently in developed than in less developed nations, indicating that both genetic factors and environmental conditions, such as diet, may be involved in its development.

FACTOR RESPONSIBLE FOR OCCURRENCE OF IBD

A) The Inflammatory Response

B) Genetic Factors

C) Infections

D) Dietary Factors

E) Smoking

A) The Inflammatory Response:

In IBD the role of T-cell is highly important. T-cells are divided in to **helper T-cell and killer T-cell. Killer T-cell directly kills the antigen** while **helper T-cell** also recognizes antigens, but their role is two fold. They **stimulate B cells and other white cells** to attack the antigen. TH cells also secrete or stimulate the production of powerful immune factors called cytokines. In small amounts, cytokines are indispensable for healing. If overproduced, however, they can cause serious damage, including inflammation and cellular injury. Cytokines, particularly specific ones known as tumor necrosis factor, interferon-gamma, and interleukins, cause intestinal inflammation and damage, which, in a vicious cycle, attract even more helper T cells. **Helper T cells are further categorized as TH1 and TH2. An imbalance in these two types appears to occur in IBD,** although each disorder has a different balance. **Ulcerative colitis patients favor a TH2 response**, which activates the interleukins IL-5, IL-6, and IL-10. These mostly affect mucosal areas in the intestine. Research indicates that patients with **Crohn's disease have increased activity in TH1 helper cells,** activating interleukin-2 (IL-2) and interferon-gamma, which affect intestinal cells. **Tumor necrosis factor (TNF)** may be a particularly **potent immune factor in Crohn's disease**. It is important in properties that regulate inflammation and cell proliferation. If genetic or other factors increase production of this immune compound, it can lead to great harm.

Increased levels of certain molecules called E-selectin and intercellular adhesion molecule-1 (ICAM-1) also appear to play a major role in the inflammatory process by causing damaging immune factors to accumulate on intestinal cells. E-selectin may be involved in the early stages of the disease (especially ulcerative colitis) and ICAM-1 in the persistence of either inflammatory bowel disease.

Greater activity of enzymes called matrix metalloproteinase has been detected in the colons of patients with IBD. Such increased levels tend to break down the extracellular matrix, a barrier composed of structural proteins and elastic fibers that surrounds and supports cells, in this case in the colon. Researchers suggest that this activity may cause persistent damage once the inflammatory process has triggered IBD.

B) Genetic Factors:

Although the causes of inflammatory bowel disease are not yet known, genetic factors certainly play some role. Between 10 - 20% of people with ulcerative colitis have family members with the disease. Several candidate genes and chromosome locations have been identified that might prove to play a role in the development of ulcerative colitis, Crohn's disease, or both. Genetic factors appear to be more important in Crohn's disease, although there is evidence that they may have genetic defects in common. In either case, multiple genetic factors are likely to be responsible for susceptibility to these disorders. Specific Genes Involved. One of the most important genetic discoveries to date was the identification of a genetic variant called NOD2, which appears to alter the immune system so that it launches an over-reaction in response to bacteria, causing inflammation. This genetic factor might be involved in 15% of Crohn's disease cases. Those with one copy of the mutated gene have twice the average risk of developing Crohn's, and those with two defective genes face 20 - 40 times the risk.

Research study shows that several genes on different chromosomes have been linked to the development of CD and UC. The IBD1 gene, which is located on chromosome 16, has been linked to CD. Early-onset CD has been associated with a specific locus on chromosome 5. In another study, the strongest association with the susceptibility locus on chromosome 5 was observed in patients with perianal CD.

The most promising candidate gene is CARD15 (also known as NOD2), which is expressed in macrophages and paneth cells. The variant form of CARD15 results in paradoxically reduced macrophage activation of the NF-Î°B pathway. One would expect this to result in a diminished inflammatory response. However, homozygotes for this variant gene have a 20-fold increased risk of developing CD. Analysis of a recent study

may explain this paradoxical response. This study showed that CARD15 recognizes muramyl dipeptide, the minimal bioactive peptidoglycan motif common to all bacteria. Therefore, in patients with variant CARD15, bacterial antigens may bypass the host's initial immune defenses (because of defects in peptidoglycan sensing) and result in increased stimulation of the mucosal immune system. Recently, it has been noted that paneth cells, which are most numerous in the terminal ileum and play an important role in antibacterial defense in the intestine, express the CARD15 gene. Consequently, another intriguing hypothesis is that disruption of this property of paneth cell function by CARD15 variants may predispose patients to the development of ileal CD.

On the basis of ehich type of gene involved in the genesis of IBD & chromosomes location IBD associated in to various types

Loci Designation	Chromosome Location	Disease Association	Candidate Genes	Phenotype Correlation
IBD1	16q12	CD	CARD15/NOD2	Earlier disease onset, small intestinal localization and strictures
IBD2	12q13	Indeterminate colitis and terminal ileal CD	VDR, NRAMP2, STAT6, and MMP-18	Not reported
IBD3	6p13	CD and UC	Major histocompatability complex and TNF	Not reported
IBD4	14q11	CD	TCRα/δ, leukotriene B4 receptor, and major histocompatability complex type I, antigen presentation–associated proteosome cluster	Not reported
IBD5	5q	Indeterminate colitis and colonic and ileal–colonic CD	Cytokine cluster (IL-3, IL-4, IL-5, and IL-13; IRF-1; and CSF-2)	Perianal disease and early onset
IBD6	19p	CD	ICAM-1 and DDXL	Not reported
IBD7	1p	CD and UC	Mucin 3, EGFR, and HGF	Not reported

* CARD = caspase-activating and recruitment domain; CD = Crohn disease; CSF-2 = colony-stimulating factor isoform-2; DDXL = DEAD/DEAH box helicase; EGFR = epidermal growth factor receptor; HGF = hepatocyte growth factor; IBD = inflammatory bowel disease; ICAM-1 = intercellular adhesion molecule-1; IL = interleukin; IRF-1 = interferon regulatory factor isoform-1; MMP = matrix metalloprotease; NRAMP2 = natural resistance-associated macrophage protein 2; STAT = signal transducer and activator of transcription; TCR = T-cell receptor; TNF = tumor necrosis factor; UC = ulcerative colitis; VDR = vitamin D receptor.

Genetic associations in inflammatory bowel diseases

C) Infections

Viruses or bacteria within the intestine may alter properties in the lining and intestinal tract. Over time, these changes may trigger the injurious processes that lead to inflammatory bowel disease.

Some research studies report that children with IBD may have had more and earlier childhood infections. The measles virus has been of particular interest. According to the U.S. Centers for Disease Control, and many studies, the measles virus does not cause Crohn's or IBD. Much publicity has centered on whether the vaccine for measles, mumps, and rubella (the MMR vaccine) causes conditions such as autism and Crohn's disease. This theory has been rigorously reviewed and refuted in many well-conducted

studies, including several published in 2006. The evidence clearly indicates that the MMR vaccine does not increase the risk of Crohn's disease, other inflammatory bowel disease, or autism. **Cytomegalovirus (CMV)** is a common virus that is also under suspicion as a contributor to severe cases of IBD

Mycobacteria, a type of bacterium associated with tuberculosis is another possible candidate for an infectious cause of Crohn's disease. **Escherichia coli** are the intestine normally harbors E. coli bacteria. In most cases, the bacteria are harmless and even protective. Some E. coli strains, however, can bind to the intestinal walls and penetrate the lining. These damaging strains may be associated with Crohn's disease.

D) Dietary Factors

Inflammatory bowel disease is much more prevalent in industrialized nations and in higher-income groups. Experts believe, then, that diet must play some role, although studies have been conflicting over its importance. In order for the body to use protein from the food we eat, it is broken down into smaller parts called amino acids. Special enzymes then make changes to the amino acids so the body can use them.

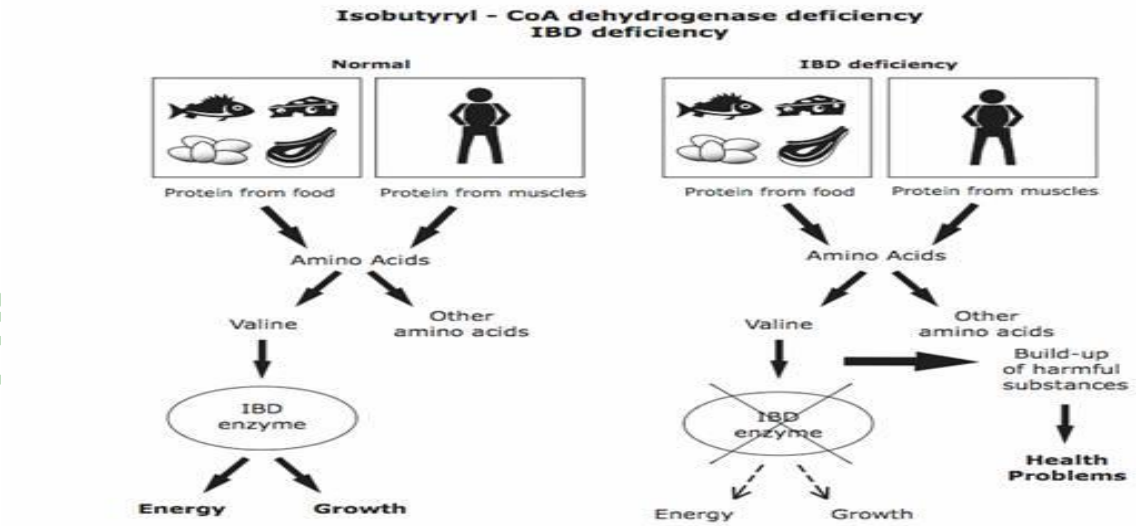


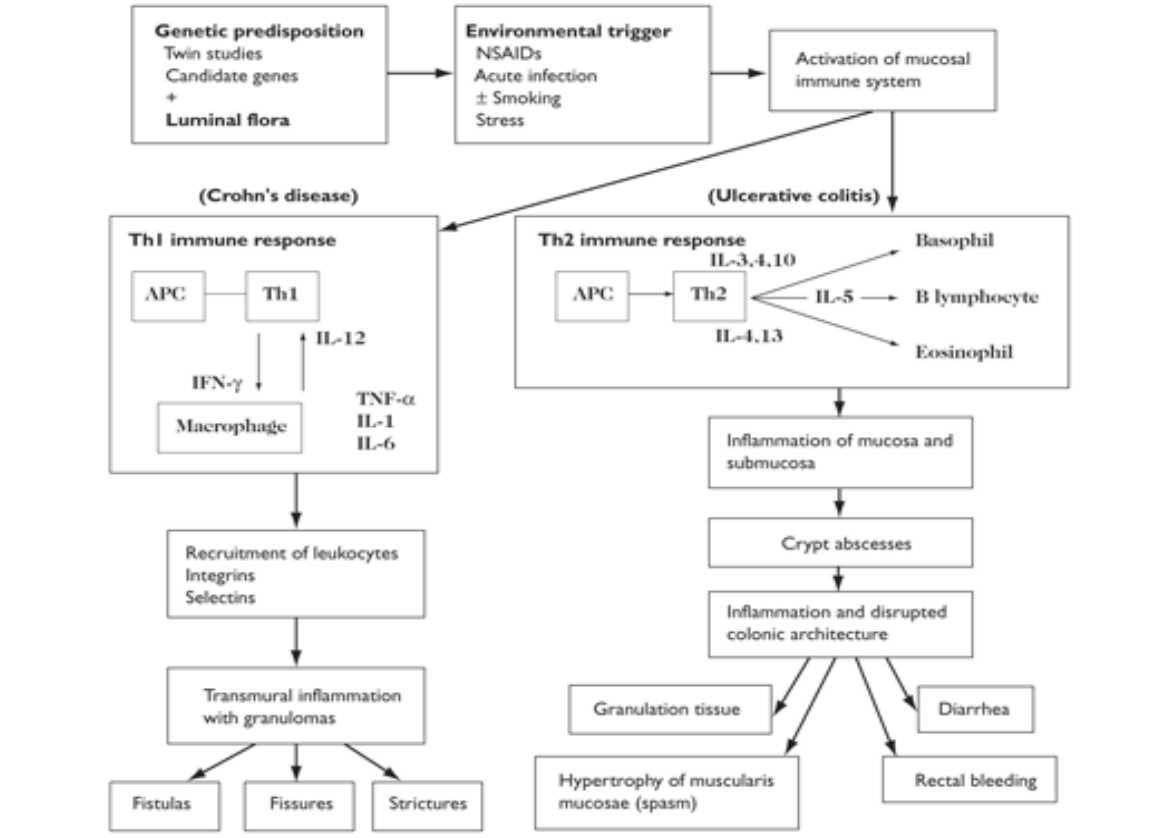
Figure 3.4: Enzyme deficiency

IBD deficiency occurs when an enzyme, called "isobutyryl-CoA dehydrogenase", is either missing or not working properly. This enzyme's job is to help break down valine. When a child with IBD deficiency eats food containing valine, harmful substances build up in the blood and cause problems. Valine is found in all foods that contain protein

E) Smoking

It is well established that smoking cigarettes is associated with Crohn's disease (CD) and that non-smoking is associated with ulcerative colitis (UC). Furthermore, there is convincing evidence that smoking cigarettes has a negative effect on the course of CD, and that smoking cigarettes may improve the disease severity or have a 'protective' effect in some patients with UC. Despite these well-described associations, the mechanism by which cigarette smoking affects CD and UC is not known. Researchers have studied the systemic effects, cellular and humoral immune effects, mucosal changes, and the intestinal permeability changes with inflammatory bowel disease (IBD) and smoking. To date, none of these studies adequately explains the observed clinical patterns. It has been assumed that nicotine is the active agent in these associations, but clinical trials of nicotine chewing gum and transdermal nicotine in UC have shown limited benefit, and have been complicated by significant side effects.

PATHOPHYSIOLOGY

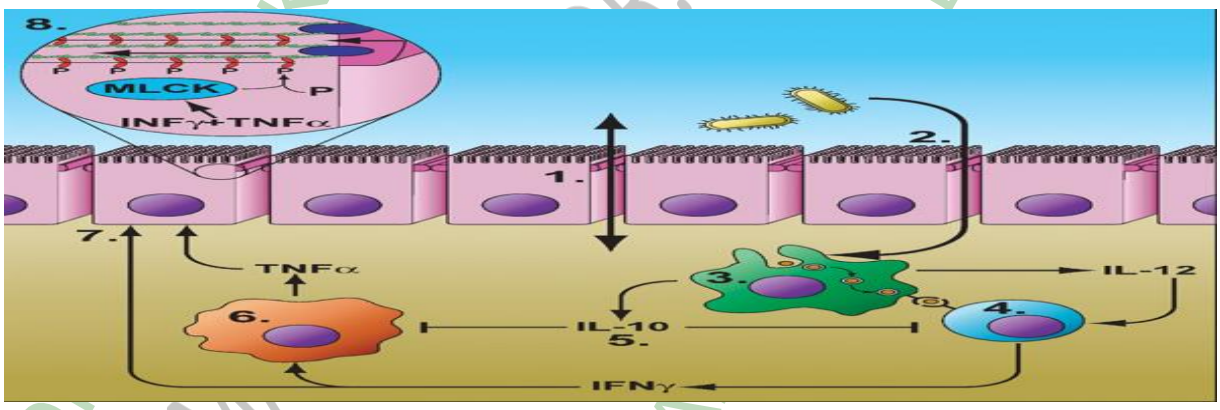


APC indicates antigen-presenting cell; IFN-γ, interferon γ; IL, interleukin; NSAIDs, nonsteroidal anti-inflammatory drugs; Th, T helper; and TNF-α, tumor necrosis factor α.

Role of various cells & mediators in the genesis of IBD

A) Role of the epithelial barrier:

Initial barrier disruption may be caused by injury (ischemia, infection), genetic predisposition, or by underlying inflammation. This leads to a mixing of luminal contents, including bacteria and other pathogens, with lamina propria contents, notably antigen presenting cells. These antigen presenting cells Process and present antigens in association with MHC class II molecules while simultaneously secreting cytokines such as IL-12 that promote a TH1 response. T cells Recognize the presented antigens and respond to the cytokine stimulus by secreting IFN to initiate the TH1 response. Simultaneously, loss or downregulation of anti-TH1 cytokines such as IL-10 allows the inflammatory reaction to grow large and persist longer than usual. The IFN secreted by T cells promotes macrophage activation these activated macrophages in turn secrete TNF to promote the inflammatory reaction. TNF and IFN also influence the epithelial barrier through unknown mechanisms, these cytokines activate MLCK, leading to MLC phosphorylation, actomyosin contraction, and opening of the tight junction. This leads to further loss of barrier function, continuing the cycle of disease progression.

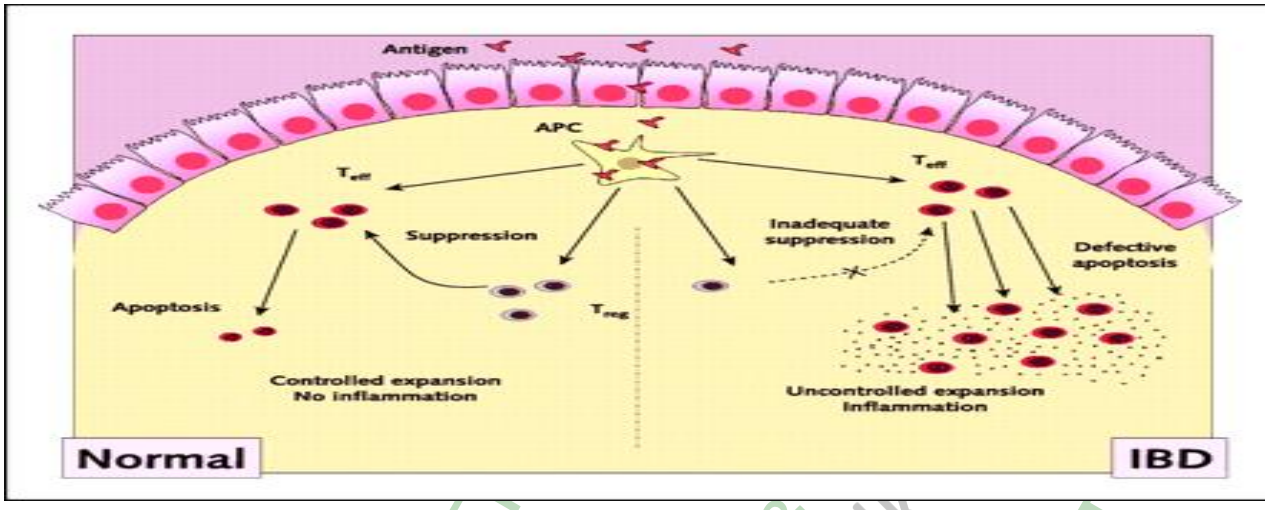


Role of epithelial barrier in IBD

B) The Role of the T-cell in IBD:

Presentation of intraluminal antigens to mucosal lymphocytes by antigen-presenting cells (*APCs*) leads to the generation of effector responses. In the normal gut, overt inflammation is prevented by controlling the activation of mucosal effector T cells (T_{eff}) through at least 2 distinct mechanisms. First, regulatory T-cell subpopulations (T_{reg}) in the mucosal immune system suppress effector T-cell activity in part through the production of interleukin-10 and transforming growth factor-ß. Second, control is also provided by eliminating T_{eff} by apoptosis, thereby preventing undesired overexpansion. In individuals with IBD, both of these regulatory mechanisms seem to be defective.

Aberrant signalling of regulatory cytokines such as transforming growth factor-ß has been well described in Crohn disease.



The traditional paradigm for the pathogenesis of inflammatory bowel disease (*IBD*).

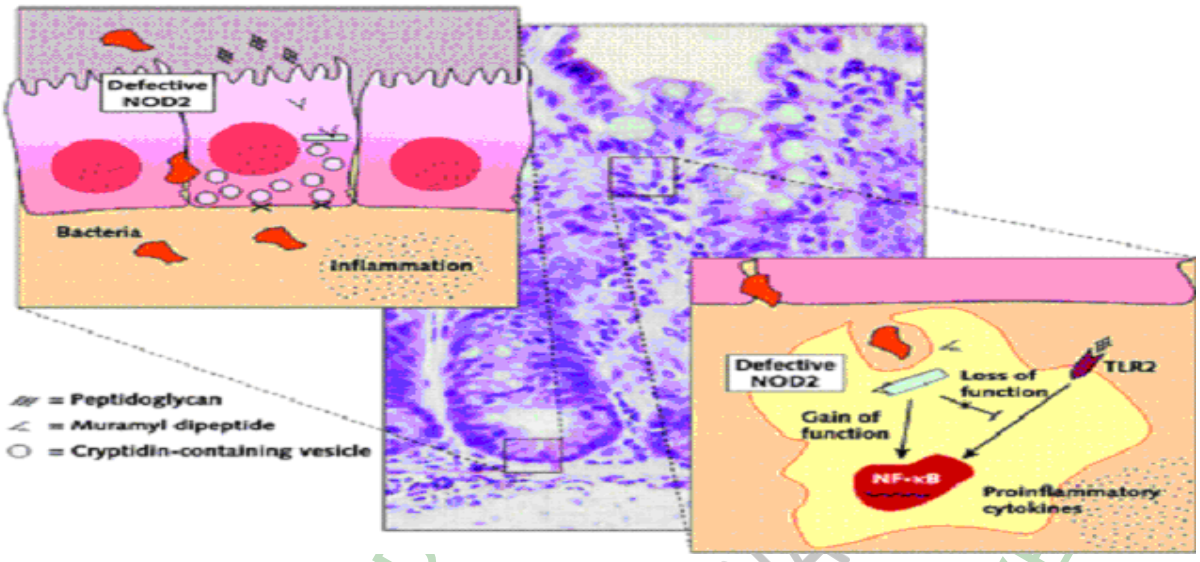
C) Role of hydrogen sulphide:

Medical therapy (unspecified) leading to High concentrations of sulfate-reducing bacteria with concomitant elevation of hydrogen sulfide have been noted in patients with UC. Hydrogen sulfide can potentially damage the gut mucosa by inhibiting butyrate oxidation in the mitochondria, essentially starving the colonocyte.

E) Role of the NOD receptors & Toll-like receptors (*TLRs*):

NOD2 is an intracellular protein that senses bacterial products and activates components of the innate immune system.Intracellular NOD receptors and transmembrane Toll-like receptors (*TLRs*) are important molecules for the recognition of pathogen-associated molecular patterns, activation of the innate immune system, and maintenance of mucosal homeostasis. Muramyl dipeptide, a component of the bacterial cell wall, binds to CARD15/NOD2, which then activates nuclear factor-B (*NF-B*). NOD2 is expressed in macrophages and in Paneth cells at the base of intestinal crypts. An epithelial-oriented "loss of function" pathway may be associated with inability to effectively clear intraluminal microorganisms, as a result of decreased antibacterial peptide (defensins) secretion by Paneth cells. Alternatively, the "loss of function" may also affect the ability of NOD2 to attenuate signaling through TLR-2 in macrophages, the net result being enhanced NF-B activation and proinflammatory cytokine production. An alternative hypothesis describes a "gain-of-function" phenotype, that is, direct MPD/NOD2-mediated increase in NF-B signaling, with a similar end result of increased secretion of

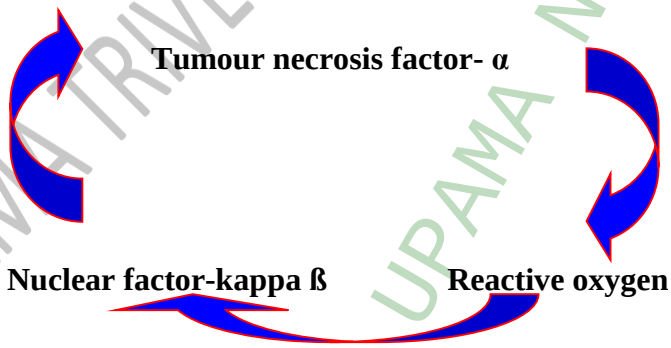
proinflammatory cytokines and chronic intestinal inflammation. More important, none of the NOD2 mutations results in spontaneous colitis in mice.



Proposed functional significance of NOD2 mutations in Crohn disease.

F) Role of the reactive oxygen species in inflammation:

Several research studies show that TNF-α production leads to generation of ROS which in turn active nuclear factor-kappa ß that then enhance further TNF-α production, sitting up a vehicle cycle.



Role of ROS in IBD

SYMPTOMS OF INFLAMMATORY BOWEL DISEASE

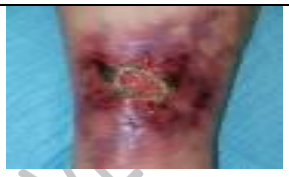
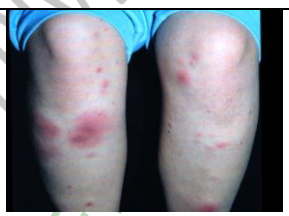
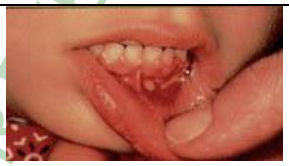
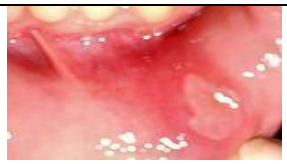
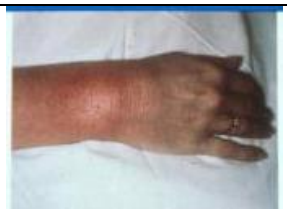
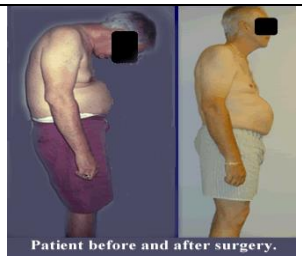
Various symptoms of UD & CD are summarized in the following table no 3.3:

Symptoms of Inflammatory Bowel Disease		
Symptoms	**Ulcerative Colitis**	**Crohn's Disease**
Diarrhea	Recurrent diarrhea is very common, but onset may be very gradual and mild or it may not be present. Feces may also contain mucus.	Recurrent diarrhea is fairly common.
Rectal Bleeding	Blood is almost always present in stools. It may be readily visible or visible only using a microscope (called occult blood).	Bleeding not as common as in UC, but can occur.
Constipation	Constipation can be a symptom of UC, but not as common as diarrhea. Can occur during flare-ups. May occur when the inflamed rectum triggers a reflex response in the colon that causes it to retain the stool.	Constipation in Crohn's disease is usually a symptom of obstruction in the small intestine.
Abdominal Symptoms	Pain is not prominent symptom, but can vary. May cause vague discomfort in the lower abdomen, an ache around the top of the hipbone, or cramps in the middle of the abdomen. Severe pain can occur during flare-ups. Vomiting and nausea.	Main symptom is recurrent episodes of pain in the lower right part of the abdomen or above the pubic bone. Often preceded by and relieved by defecation. Bloating, nausea, and vomiting may also occur. Intestinal pain may also be an indication of a serious condition, such as an abscess, or a perforation of the intestinal wall.

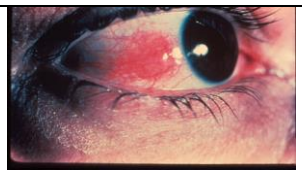
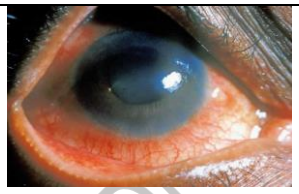
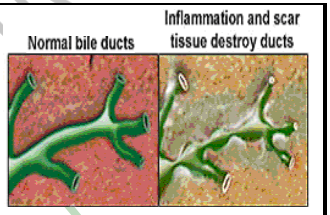
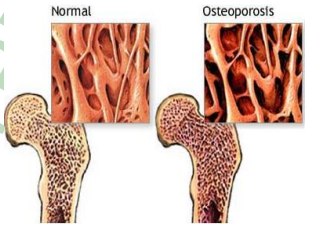
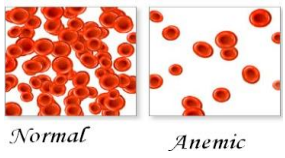
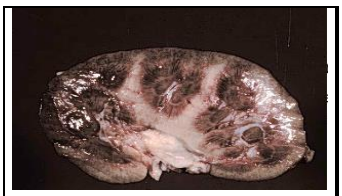
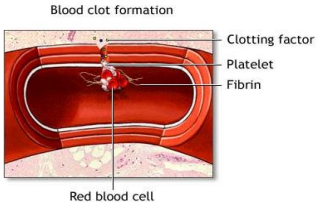
Fever	May occur with severe attacks.	Usually low-grade. Spiking fever and chills indicates complications.
Loss of appetite, weight loss, and impaired growth in children	Often not evident in mild or even moderately severe UC. Occasionally impairs growth in children and teenagers.	Common. Typical weight loss is 10 - 20% of normal. Commonly impairs growth in children and teenagers.
Abnormal defecation: Increased frequency, a feeling of incomplete evacuation, and tenesmus (a painful urge for a bowel movement even if the rectum is empty). Fecal incontinence.	Symptoms may be mild or severe.	Can occur in active stages.
Anal ulcers and fistulas: (channels that can burrow between organs, loops of the intestine, or between the intestines and skin).	Almost never a symptom.	Fistulas and ulcers around the anus may be early symptoms.
Neurologic or psychiatric symptoms	No.	May be early signs of Crohn's disease when accompanied by gastrointestinal problems.

EXTRA INTESTINAL COMPLICATIONS:

It occur in approximately 20% of patients with IBD. In some cases, they may be more problematic than the bowel disease itself

Site	Complication	Description	
Skin	Pyoderma gangrenosum	Rare, ulcerating sores most often on legs; usually with extensive and active colon disease	
	Erythema nodosum	Most common skin manifestation; more common with Crohn disease; may raise suspicion of IBD in previously healthy child	
Mouth	Recurrent aphthous ulcers	Most common skin manifestation; more common with Crohn disease	
	Other assorted mouth lesion	Lip swelling, fissures, gum inflammation (gingivitis)	
Joints	Migratory peripheral arthritis	Involves the large joints; redness, swelling and stiffness; generally non-destructive (as opposed to rheumatoid arthritis); parallels bowel disease	
	Ankylosing spondylitis	Inflammation of the vertebrae; usually begins in the early twenties, most commonly with ulcerative colitis who have a certain human leukocyte antigen (B27); low back pain and morning stiffness; back, hips, shoulders, and sacroiliac joints typically affected	

20. INFLAMMATORY BOWEL DISEASE

Eye	Episcleritis	Fiery red inflammation of the conjunctivae mimicing "pink eye" eyes red, burn; vision not affected	
	Anterior uveitis	Inflammation of the iris and accomodative muscle (ciliary body); eye pain, headache, blurred vision; possible glaucoma, cataracts, and permanent visual impairment; may initially be silent	
Liver	Primary sclerosing choloangitis	Chronic inflammation and obliteration of the bile ducts within and outside of the liver; cirrhosis; nonspecific fatigue, appetite loss, itching, and jaundice	
Bone	Osteoporosis	Mild bone loss affects 2/3 of IBD patients; increased risk of fractures, bone deformities, chronic pain	
Blood	Anemia	Nutritional: deficiencies of iron, B12 folate; the "anemia of chronic	
Kidney	Glomerulonephritis	It is rarely observed: deposition of immune antigen/antibody complexes in filtering tubules; amyloidosis; kidney stones	
Blood vessels	Blood clots	In extremities, or brain (stroke)	

	Arteritis	Inflammation of blood vessels in extremities, or brain (stroke)	

Extra intestinal complications

DIAGNOSIS

The diagnosis of IBD is based on a combination of examination like endoscopic, X-rays, and blood and tissue tests. Upon diagnosis, IBD patients may need additional tests to monitor the disease and diagnose possible complications or side effects of medications.

A) Laboratory Tests:

A CBC (complete blood count) test can detect infection and anemia, as well as monitor for side effects of certain IBD medications. Liver function tests help screen for liver and bile duct abnormalities seen in some IBD patients. Stool studies determine whether patients have treatable bacterial infections that can trigger a flare-up of IBD. Antibody tests can help clarify the situation for "indeterminate colitis" patients without a definite diagnosis.

B) Endoscopy:

Several types of endoscopy are used to determine if the patient has ulcerative colitis or Crohn's disease and how much bowel is affected. All use a thin, flexible tube with a lighted camera inside the tip, which allows doctors to look at the lining of the gastrointestinal (GI) tract. The image is magnified and appears on a television screen. Each procedure is named for the part of the GI tract examined:

- **Sigmoidoscopy** — Examines the lining of the lower third of the large intestine (the sigmoid colon).
- **Colonoscopy** — Examines the lining of the large intestine (colon), and sometimes can peek into the very end of the small intestine (or ileum).
- **EGD (Esophagogastroduodenoscopy)** — Examines the lining of the esophagus, stomach (gastro), and duodenum (first part of the small intestine).
- **ERCP (Endoscopic retrograde cholangiopancreatography)** — Examines the bile ducts in the liver and the pancreatic duct.

- **Endoscopic ultrasound**: Uses an ultrasound probe attached to an endoscope to obtain deep images of the gut. In IBD, this is most often used to look at fistulas in the rectal area.
- **Capsule endoscopy** — Patients swallow computerized cameras in vitamin-sized capsules to produce images of sections of the small intestine that are beyond the reach of an EGD. Read more on capsule endoscopy.

C) Radiology Tests:

Radiologic tests provide information that endoscopy cannot. EGD and colonoscopy can visualize only the stomach, the very upper small intestine (EGD) and the colon and very lower small intestine (colonoscopy). Most of the small intestine cannot be imaged by endoscopy, although capsule endoscopy can be useful. Radiographic tests can image the small intestine.

D) Plain X-rays examination:

Plain X-rays without contrast can be useful to detect blockage in the small or large intestine. While, Contrast X-rays are used with endoscopy in monitoring and treating IBD. These X-rays track special liquid contrast, usually barium, as it passes through the intestine, highlighting specific conditions.

E) CT Scan:

A CT scanner takes simultaneous X-rays from different angles to reconstruct images of the internal organs.

F) MRI:

Magnetic Resonance Imaging (MRI) is used to evaluate perianal fistulas and abscesses in patients with IBD. Other potential uses are being investigated.

G) White Blood Cell Scan:

Inflammation of the GI tract is characteristic of ulcerative colitis and Crohn's disease. Leukocyte scintigraphy (tagged white blood cell scan) detects white blood cell accumulation in inflamed tissue.

H) Ultrasound:

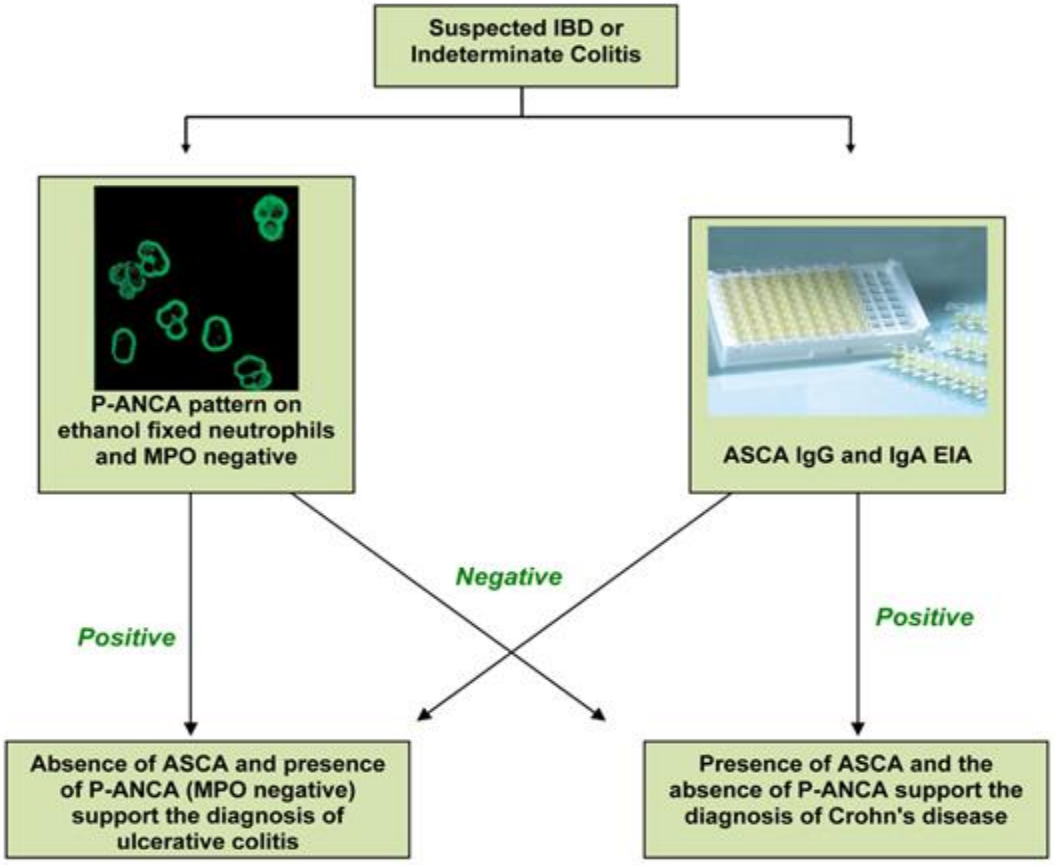
In general, ultrasound technology is not useful for examining the bowel, although sometimes it is used in combination with other radiological tests.

A definitive diagnosis of IBD is established by a combination of radiographic, endoscopic and histologic criteria with differentiation between ulcerative colitis and Crohn's disease being established in most cases. However, in 10-15% of patients, a distinction between UC and CD cannot be made with certainty even after a thorough pathological investigation. These patients are classified as having indeterminate colitis. Correct diagnosis of ulcerative colitis and Crohn's disease has major implications on the choice of treatment, surgical procedures and long-term prognosis. This is particularly important in paediatric patients with severe symptoms and prolonged history. In such cases an earlier diagnosis may decrease long-term morbidity of IBD e.g. delayed puberty, shorter ultimate height, nutritional deficiencies etc. Recent studies have indicated two serological markers, **anti-*saccharomyces cerevisiae* antibodies (ASCA)** and **perinuclear anti-neutrophil cytoplasmic antibodies (P-ANCA),** may assist in the differentiation of ulcerative colitis and Crohn's disease in patients with indeterminate colitis. ASCA occur more commonly in patients with CD (50-89%) but are less frequent in UC (<10%). It has been observed that a few patients have only IgG or IgA ASCA. However the levels tend to be lower than in patients who have both classes. Results are therefore more significant when both IgG and IgA ASCA are considered. P-ANCA (myeloperoxidase (MPO) negative) pattern is found predominantly in patients with ulcerative colitis. These P-ANCA reactions localise over the nuclear periphery and typically do not cross-react with MPO and other cytoplasmic antigens.

It is believed elevated serum levels of P-ANCA in ulcerative colitis are caused by P-ANCA production in the colonic mucosa. P-ANCAs are detected in 60-80% of adult and around 83% of paediatric patients with ulcerative colitis, but are less frequent in Crohn's disease (5-30%). Combined measurement of both ASCA and P-ANCA gives a better diagnostic differentiation between Crohn's disease and ulcerative colitis than measurement of the individual markers. Both the specificity and PPV are increased to clinically useful levels.

	Sensitivity (%)	Specificity (%)	PPV (%)
ASCA positive, P-ANCA negative for CD	56	92	95
ASCA negative, P-ANCA positive for UC	44	98	88

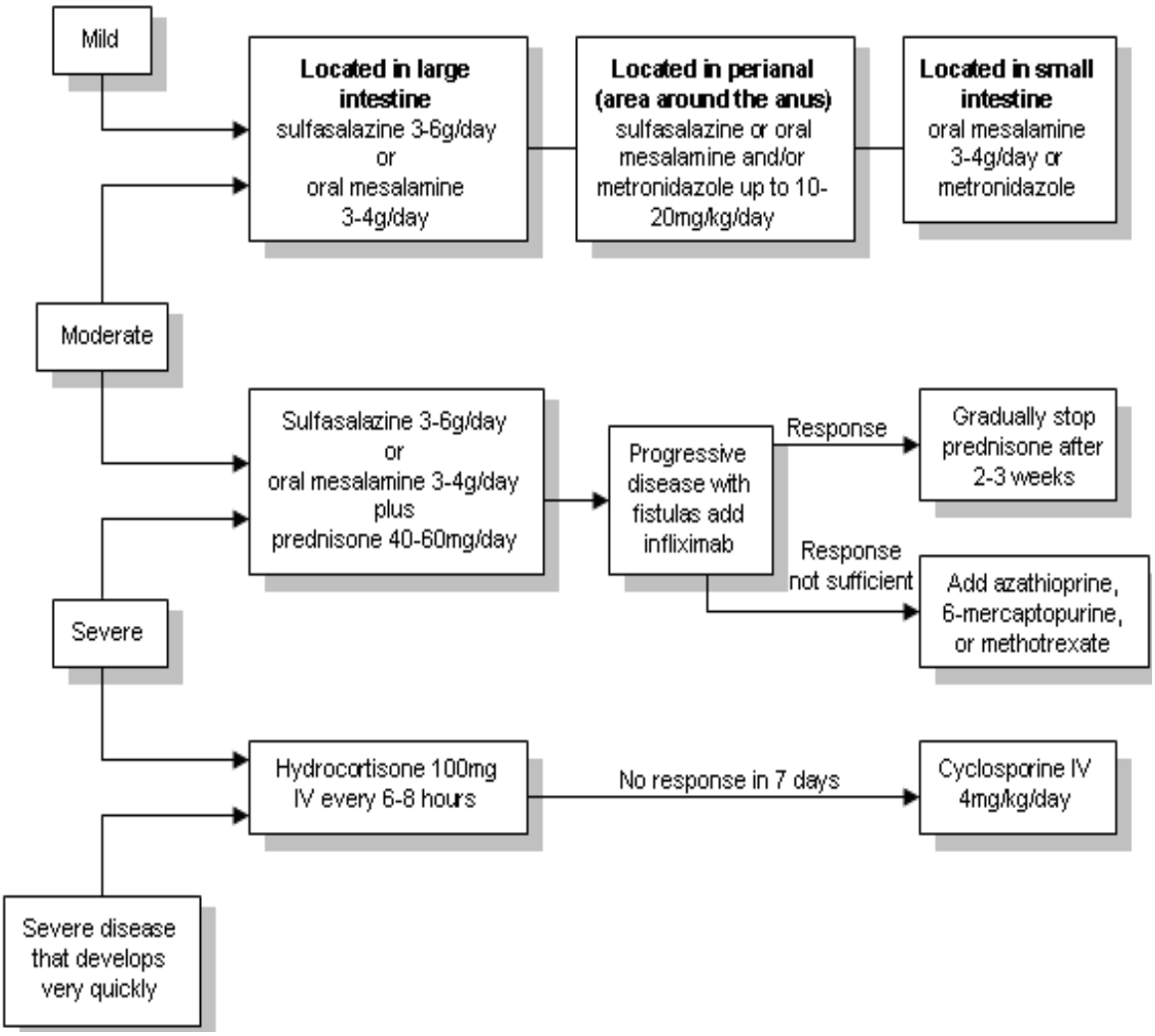
Proposed Testing Protocol



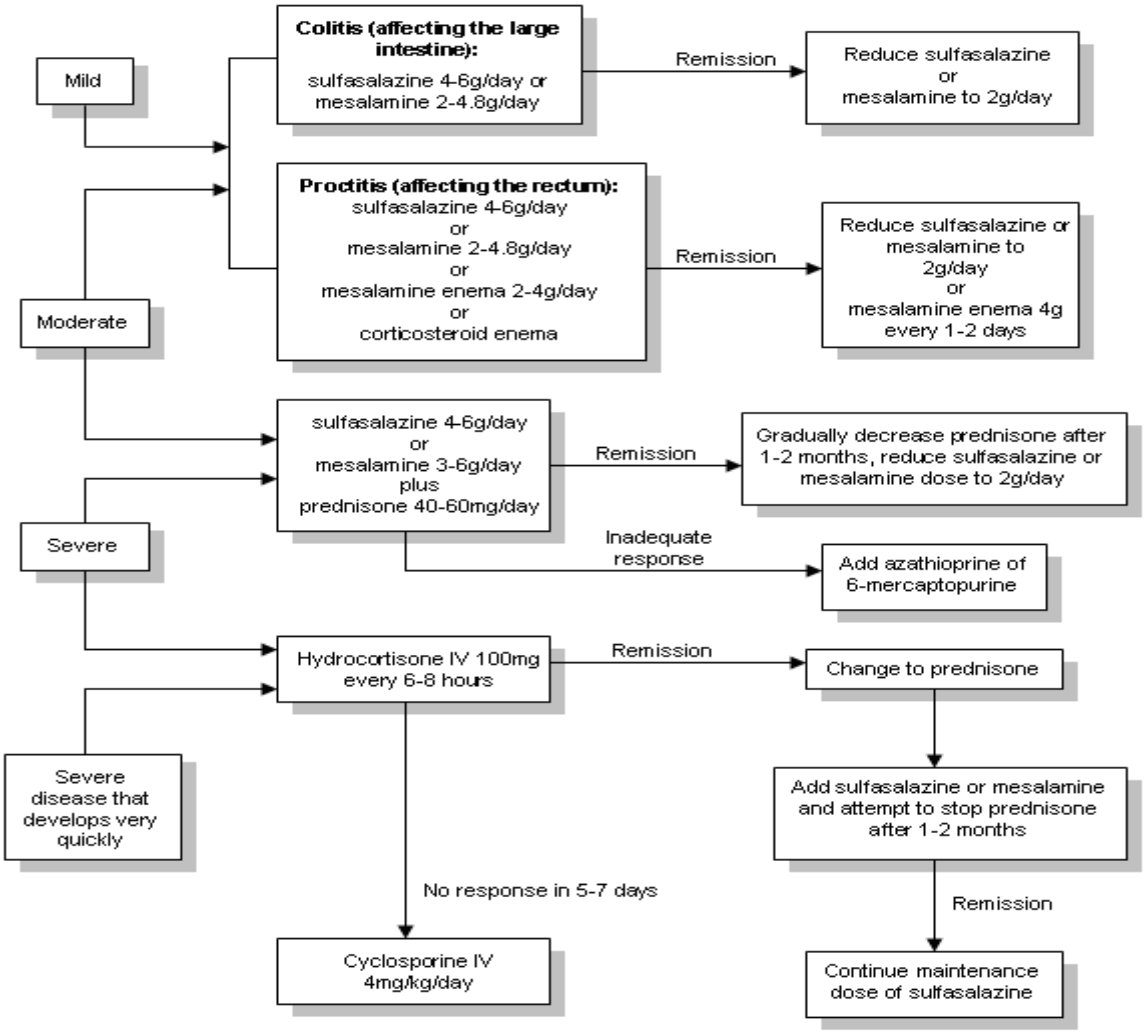
Identification technique for UC & CD

TREATMENT FOR INFLAMMATORY BOWEL DISEASE

Agents for symptomatic treatment include loperamide and the combination of diphenoxylate and atropine, which are useful in mild disease to reduce the number of bowel movements and to relieve rectal urgency. Cholestyramine, a resin that binds bile salts, is useful for reducing diarrhea in patients with CD who have had ileal resections. The anticholinergic agent dicyclomine may help relieve intestinal spasms. Antidiarrheal and anticholinergic medications must be avoided in acute severe disease because they may precipitate toxic megacolon. Avoid the long-term use of narcotics for pain. An iron supplement should be added when significant rectal bleeding is present.



Treatment approach for Crohn's disease



Treatment approach for ulcerative colitis