Inflammatory Bowel Diseases

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Dr. Swaroop's interests include epidemiology and new/emergent treatments for inflammatory bowel diseases, and colorectal cancer in inflammatory bowel disease.

EPIDEMIOLOGY

Inflammatory bowel diseases, namely Crohn's disease (CD) and ulcerative colitis (UC), have different incidence based upon the population studied, geographical region, ages and races. It was recently reported that there has been a rising trend in the incidence and prevalence of inflammatory bowel disease (IBD) in Asia. It has also been noticed that African-American children commonly present with Crohn's disease and at an older age.
Other studies have reported African American CD patients were more likely to develop esophagogastroduodenal CD, colorectal disease, perianal disease but were less likely to have ileal involvement. Hispanics on the other hand had a higher prevalence of perianal CD and Erythema Nodosum. Geographically, northern areas have a higher incidence of IBD as compared to southern, yet this difference, although noticeable, is not as prominent between west and east. Women tend to have a higher prevalence of Crohn's disease and men have slightly higher prevalence of ulcerative colitis.
In the US, the prevalence of CD and UC in children younger that 20 was found to be 43 and 23, respectively, and in the adults, the prevalence of CD and UC was 201 and 238 per 100,000, respectively.
Familial aggregation is seen in both UC and CD, suggesting heritability. Up to 20% of patients with IBD may have a family history. Genome-wide association (GWA) studies have shown up to 80% of family members with affected members are concordant. Other findings suggest that there may be a subset of genes that may be common in both CD and UC. Age-correlated risk among all first degree relatives of an affected individual is 3.9%.

Genetic susceptibility

- Role of Medications e.g NSAIDs, Isotretinoin, Oral contraception
- Infectious agents: mycobacterium avium subsp paratuberculosis
- Appendectomy

DIFFERENTIAL DIAGNOSIS:

Infectious colitis (Salmonella, shigella, E. Coli, Clostridium difficile, Amebiasis)
Microscopic colitis (Lymphocytic colitis, collagenous colitis, eosinophilic gastroenteritis)
Small bowel lymphoma
Diverticulitis
Diverticular bleeding
Colorectal cancer
IBS
Radiation colitis
Ischemic colitis

PATHOPHYSIOLOGY

The manifestions of IBD are varied, but two entities are widely recognized, e.g ulcerative colitis and Crohn's disease. Both of these diseases have common pathophysiology, but there are enough differences in their manifestations so as have different treatment options based upon these differences.

Alterations in the barrier function of the epithelium are seen as in important initial event. It appears that bacteria in association with perturbations of epithelial-cell barrier function activate dendritic cells. This in turn causes the dendritic cells to move to the mesenteric lymph nodes and results in promotion of differentiation of naïve T cells into effector and regulatory T cells. It is not clear why this inflammatory response becomes self perpetuating. In Crohn's disease, a novel set of IL-17 producing cells (T_H17) have been identified as having a key role in intestinal inflammation. In a study by Wehkamp et al, patients with Crohn's disease were shown to have reduced expression of human defensin 5 (HD 5) and HD 6 in their ileums where as expression of other paneth cell products remains unchanged or elevated as compared to controls suggesting that patients with ileal CD may have compromised innate immune defenses of the ileal mucosa.

Recently, defects in autophagy has been described in Crohn's disease. A SNP (Ala281Thr) in the autophagy gene ATG16L1 has been reported to be highly associated with Crohn's disease. Autophagy is an important mechanism in restricting growth of certain microorganisms. Variations within the IRGM gene has also been reported to be associated with Crohn's disease.

Genome wide association studies have revealed IL-23R polymorphisms to be associated with Crohn's Disease, Ulcerative colitis as well as ankylosing spondylitis (4).

In a meta-analyis of three studies which included 3230 cases and 4829 controls, Genome-wide association study identified 30 distinct susceptibility loci. 11 of them were previously reported and significant evidence of 21 additional loci was reported. It appears that IL-23 signaling contributes to the inflammatory cascade and new therapies are being developed targeting the p40 and p19 subunits of IL23.

CLINICAL MANIFESTATIONS

Most common clinic symptom of Ulcerative colitis is that of bloody diarrhea associated with cramping abdominal pain. Several patients who have limited disease to the rectum may have symptoms of tenesmus and sensation of incomplete evacation. Several of these patients will complain of clustering of bowel movements in mornings and possibly before bedtime. Abdominal pain can be present in patients of ulcerative colitis, but it is more prominent in Crohn's disease especially in patients with stricturing disease.

Once the patient has clinical signs of rebound tenderness, distension or guarding, close clinical watch must be maintained as they may have toxic megacolon. Physical examination of Ulcerative colitis patients may detect a left lower and left upper quadrant tenderness and occasionally extent of colonic involvement may be deduced by careful physical examination.

Patients with Crohn's disease may have varied symptoms which depend upon the behavior of their disease. Perianal fistulae can be distressing manifestation and may parallel clinical flares. Patients with inflammation in the terminal ileum may have diarrhea as a predominant symptom but bloody diarrhea is not uncommon. Stricturing behavior may cause signs of intestinal obstruction as well as abdominal pain. Intestinal narrowing may be due to either edema due to inflammation or fibrosis due to chronic inflammation or combination of these two factors. Presence of a mass in the right lower quadrant may be due to ileal disease associated with stricturing disease as well as involvement of the mesentery. Patient with upper gastrointestinal Crohn's disease may present with dysphagia, early satiety, fear of food leading to weight loss. Pneumaturia is manifestation of internally perforating Crohn's disease where there may be a fistula connecting the gastrointestinal tract to either the ureters or urinary bladder. Recto-vaginal fistulae may lead to passage of air from vagina and possibly repeated urinary tract infections.

In clinical trials several tools are used to measure the degree of clinic severity of disease. For Crohn's disease CDAI and Harvey Bradshaw index are commonly used. IBDQ has been validated in several Ulcerative colitis studies.

Diarrhea though common is not universal in Crohn's disease. Inflammation of the ileum as well as inflammation of the colon can cause diarrhea. Occasionally, diarrhea may be due to small intestinal bacterial overgrowth, especially in patients with fistulizing disease. In ulcerative colitis, tenesmus is associated with proctitis. Bloody diarrhea is common.

DIAGNOSIS

Diagnosis of Inflammatory bowel disease is based upon the combination of clinical feature, laboratory abnormalities, imaging studies and radiological investigations. None of these tests by themselves are diagnostic of IBD. In a patient with new symptoms, infectious agents should be ruled out. Common pathogens that may mimic IBD are *Salmonella, Shigella, Aeromonas, Campylobacter, Yersinia, Clostridium difficile, Plesiomonas* and parasites like *Giardia lamblia, Entamoeba* should be ruled out. Uncommonly *histoplasma, mycobacterium tuberculosis* may also result in similar symptoms. In immunocompromised host, viral infections like CMV and HSV may cause ulcers suggestive of IBD. Once infection is ruled out, further diagnostic testing like imaging and endoscopy can be carried out.

Hematologic abnormalities include evidence of microcytic anemia, elevated WBC in peripheral blood and thrombocytosis. Markers of inflammation e.g ESR and hsCRP may be also elevated. hsCRP is elevated more commonly in patients with Crohn's disease that in Ulcerative colitis. Very high hsCRP may be associated with infections like CMV or clostridium difficile.

Serologies measuring pANCA (peri-nuclear anti-neutrophilic cytoplasmic antibody), ASCA IgG and IgA (anti-Saccharomyces cerevisiae antibodies), OmpC (antiporin antibody), CBir 1 (antiflagellin antibody) may be helpful as a corroborative evidence and also help in identifying patients who are at higher risk of complicating events. It may also be helpful in differentiating between Crohn's disease and Ulcerative colitis in patients where colectomy is being considered.

Hypoalbuminemia can be a sign of poor nutritional status and these patients should be considered for TPN for surgery in being planned.
Stool lactoferrin is commonly elevated in these patients and can be used as a marker of response to therapy or an exacerbation.
Among the imaging modality commonly used in diagnosis and management of IBD, CT of the abdomen and pelvis can alert physicians to perforation, bowel obstruction and extent of inflammation. CT enterography can be used to evaluate the degree and extent of inflammation in the small bowel. In stenotic lesions of the small bowel, it can be especially helpful in identifying the inflammatory component as evidence by mural stratification. Lack of mural stratification in stenotic portions of small bowel suggest fibrosis and if there is evidence of proximal dilation in a symptomatic patient, surgical approach should be considered.
MRI can be a helpful adjunct along with examination under anesthesia and rectal EUS (endoscopic ultrasound) for perianal fistulizing disease.
Endoscopic examination is helpful to establishing the extent of disease as well as obtaining tissue samples. EGD (esophagogastroduodenoscopy) should be done when upper gastrointestinal Crohn's is suspected. Occasionally, patchy gastritis can be seen in Ulcerative colitis. Single balloon and double balloon enteroscopies have allowed gastroenterologists to obtain tissue sample from jejunum and proximal ileum. Colonoscopy is helpful both in diagnosis and follow up to assess response to various therapeutic modalities. It can also obtain biopsies from terminal ileum as well as colon helping in the diagnosis of opportunistic infections. Newer imaging modalities like NBI (narrow band imaging) may be helpful is identifying dysplasia with greater accuracy in patients who are going colonoscopy for surveillance.
Wireless capsule endoscopy is used to establish the extent in small bowel disease in patients who do not have significant small bowel stenosis. This is a small capsule with embedded power source, LED, camera which is swallowed by the patient. Once ingested, it transmits pictures over several hours to an external wearable recording device.

MANAGEMENT OPTIONS

Traditionally, the treatment algorithm for IBD has been divided into management of mild, moderate and severe disease. The roles of various agents have evolved and as more data is being accumulated patients are being treated earlier with agents that had been in the past reserved for more severe disease. Treatment goals of these patients are:

1. Improvement in quality of life to as close to normal as possible
2. Maintenance of remission
3. Avoidance of surgery
4. Minimize the risk of steroid dependence
5. Minimize the risk of treatment associated complications

Steroids

The National Co-operative Crohn's Disease Study and the European Co-operative Crohn's Disease Study have demonstrated the efficacy of steroids in inducing remission, but it is ineffective in maintaining remission. In patients who have been started on steroids about 26% will have partial response and 16% will have no response, among patients who have had either complete response or partial response about 28% will become steroid dependent at the end of one year . Requirement for surgery is exceptionally high in this group of patients, about 38% of these patients would require surgery at the end of a year

Adverse effects of steroids can be classified into early adverse effects and delayed adverse effects associated with prolonged use (more than 12 weeks). Acne, moon facies, mood changes, sleep disturbances, gastro-intestinal intolerance, hyperglycemia, weight gain and ulcers of the gastrointestinal tract can be seen early. Formation of cataracts, loss of bone mineral density, asceptic necrosis, suppression of hypothalamic-pituitary axis, myopathy are associated with prolonged used.

Budesonide which is used for ileal inflammatory and colonic Crohn's disease has been reported to have less incidence of acne, moon facies, adrenal suppression and loss of bone mineral density. Alternative therapies either Immunomodulators or biological agents should be discussed with the patient if they have not responded to steroid in a few weeks.

Aminosalicylate preparations

Aminosalicylate preparations have been used for the treatment of Ulcerative colitis and Crohn's disease. Current data suggests that the role of Mesalamine products in treatment for Crohn's disease may be very limited.

In patients with limited distal Ulcerative colitis e.g. proctitis, treatment may be begun with either a Mesalamine enema or suppository. For more extensive disease, oral therapy should be considered. 5-ASA compounds in appropriate dosages are effective in inducing and maintaining remission in Ulcerative colitis. It has also been demonstrated to reduce the rates of dysplasia and colorectal cancer due to ulcerative colitis.

AMINOSALICYLATE PRODUCTS

Aminosalicylate Product	Indication	Dosage per day	Frequency
Sulfasalazine	Ulcerative colitis	500 mg to 2 gm	Every 6 to 8 hours
Asacol (Mesalamine)	Ulcerative colitis	1.6 gm to 2.4 gm	Every 8 hours
Pentasa (Mesalamine)	Ulcerative colitis	2gm to 4 gm	Four times a day
Colazal (Balsalazide)	Ulcerative colitis	6.75 gm	Three times a day
Dipentum (Olsalazine)	Ulcerative colitis	1gm	Twice a day
Lialda (Mesalamine)	Ulcerative colitis	2.4 gm to 4.8 gm	Once a day
Canasa (Mesalamine)	Ulcerative proctitis	1 gm	Once a day
Rowasa (Mesalamine)	Distal Ulcerative colitis	4 gm	Once a day

Antibiotics

Antibiotics are commonly used in the treatment of fistulizing Crohn's disease. Active antibiotics are metronidazole, ciprofloxacin, clarithromycin and rifaximin. These agents have been shown in several case series to be effective in treating perianal Crohn's disease. The role of antibiotics in the treatment of Ulcerative colitis is very limited except in the setting of infectious complication. Patients with proctitis and pouchitis may also derive benefit with the use of these antibiotics. In some studies, metronidazole has been shown to have modest effect in reducing post surgical recurrence of Crohn's disease at one year, but the difference was not statistically significant at the end of two and three years.

Immunomodulator therapy

Azathioprine (AZA) and 6-mercaptopurine (6-MP) are common Immunomodulators used in the therapy for both Crohn's disease and Ulcerative colitis. It is used as a steroid sparing agent. Immunomodulators have been shown to modestly reduce the incidence of post-surgical recurrence in Crohn's disease. The onset of these agents is slow and sometimes may take up to 8 weeks. Ultimate metabolites of these two agents are 6TGN, 6MMP and 6TU. 6TGN is the active metabolite responsible for inducing remission as well as neutopenia. Elevated levels of 6MMP have been associated with hepatotoxicity. Enzymes responsible for catabolism of AZA and 6MP are TPMT (thiopurine methyl transferase), Xanthine oxidase and HGPRT (hypoxanthine guanine phophoribosyl transferase). A large proportion (89%) of humans wild type TPMT (full TPMT enzyme activity), 11% have intermediate enzyme activity and 0.3% have none. In patients with full TPMT enzyme activity, therapy should be started with 1.5mg/kg of 6MP per day or 2.5mg/kg/day of AZA, those who have intermediate activity should have dosage reduced by half. Those who do not have any TPMT expression should not be started on these agents due to very high risk of bone marrow toxicity.
Monitoring of thiopurine metabolites may be helpful is establishing inadequate dosing either due to non adherence or for monitoring toxicity
Pancreatitis, serum sickness like syndrome cannot be predicted by measuring metabolites. It is recommended that patients starting these medications have complete blood counts and liver function tests every other week while their medications are being adjusted. Once on a stable dosage, these tests should be done every 2-3 months.

Parenteral Methotrexate (MTX) 15-25 mg per week can be used to induce remission in Crohn's disease in patients who have not responded to conventional agents. Recently, there has been an increase in its use. Once remission has been achieved in up to 16 weeks, oral MTX (15 mg) can used to maintain remission. It is absolutely contraindicated in pregnancy. Leukopenia, hepatic fibrosis, nausea and vomiting and hypersensitivity reactions are potential side effects. Risk of hepatic fibrosis is associated with cumulative

dose of more than 1.5 gm, diabetes and concomitant use of alcohol. At this time, MTX is not indicated in the treatment of Ulcerative colitis

Cyclosporine

In patients with severe UC, IV cyclosporine at the dose of 2-4mg/kg/day has been shown to be effective in inducing remission. A significant proportion of these patients may ultimately require colectomy within a year. Those patients who have achieved response and remission on IV cyclosporine should be started on oral cyclosporine for a few months as well as prophylaxis against *pneumocystis carinii* while steroid is being tapered down. 6MP or AZA can be used as a maintenance agent.
Side effects commonly seen with cyclosporine include renal dysfunction, seizures, hypertension, gingival hyperplasia, electrolyte abnormalities and hirsutism.
Thalidomide
In 1999 a case report was published describing efficacy of thalidomide in Crohn's disease, subsequently several case series have been published showing thalidomide to be effective in some refractory Crohn's disease patients (5).

Biologic agents

Infliximab
Infliximab (Remicade) is a chimeric monoclonal antibody to human tumor necrosis factor which has been approved to induction and maintenance of remission for both Crohn's disease and Ulcerative colitis. At the time of this writing, it is the only biological agent approved by F.D.A for Ulcerative colitis. It was initially approved for the treatment of fistulizing Crohn's disease, subsequent studies have shown it to be effective in maintenance therapy as well . In several other studies, it has been demonstrated to be efficacious in reducing steroid use, hospital stays, surgical intervention as well as achieving mucosal healing. Infliximab is administered intravenously with or without premedication to avoid allergic reactions. For induction, 5mg/kg is administered at week 0, 2 and 6 and maintenance begun at 5mg/kg every 8 weeks. Some of the patients will require dose escalation due to diminution of response or failure to maintain remission. In these cases, depending upon the clinical scenario, the dose should be increased to 10 mg/kg or interval reduced to every 6 weeks. In the past, infliximab had been used with concomitant immunomodulator therapy to reduce the possibility of infliximab antibodies, but concomitant use of immomodulators with biological agents has been demonstrated to be associated with higher risk of Hepato-splenic T cell lymphoma, a rare post thymic T cell lymphoma. It has occurred predominantly in the pediatric population. Although rare (8/10000 or 8 cases in about 7 years), but if it occurs it is likely to be fatal (7). Since reactivation of latent TB has been reported, patients should be undergo a purified protein derivative (PPD) test and a chest X-ray before commencement of therapy. Hepatitis B immune status should also be ascertained as there have been reports of reactivation of latent hepatitis B in patients receiving infliximab.
Results from recently released SONIC trial has demonstrated superiority of combination therapy (immunomodulator and infliximab) over either alone, especially in patients who had elevated C-reactive protein and ulcers in their baseline colonoscopy.

Adalimumab
Due to fear of immunogenicity of chimeric proteins, a recombinant fully human immunoglobulin targeting TNF was devised. In CLASSIC and CHARM trials, Adalimumab has been demonstrated to be an effective agent in inducing and maintaining remission. It has also been shown to be effective in patients who have lost response to Infliximab or are intolerant to it. Serious reactions, reactivation of TB, allergic reactions, lupus like reaction, demylenating diseases are some of the concerns.
For induction, Adalimumab 160 mg is given subcutaneously at week 0, 80 mg at week 2 and then for maintenance of remission 40 mg every other week.

Certolizumab
Certolizumab is a polyethylene glycolated Fab fragment of humanized anti-TNF monoclonal antibody. In PRECISE 1 and 2 studies, it was shown to result in modest improvement in response but no clinically significant improvement in remission

Natalizumab
Natalizumab is a humanized monoclonal antibody against adhesion molecule α 4 integrin. In several studies it has been shown to be efficacious in inducing remission and maintaining response in Crohn's disease patients .

MANAGEMENT OPTIONS

ULCERATIVE COLITIS:
The cornerstone of treatment of ulcerative colitis remains mesalamine and mesalamine like products. In the initial evaluation of treatment of ulcerative colitis patients, it is important to establish the extent and degree of inflammation as well as any other extraintestinal manifestation if present.
Since no diagnostic test is conclusive, combination of clinical, laboratory, endoscopic as well as histopathological studies are used. In the absence of concominant infections like Clostridium difficile, CMV and other infections, treatment should be started with mesalamine with or without steroids.

EXTENT OF COLITIS

- Proctitis
- Left sided colitis
- Pancolitis
- Pouchitis

TREATMENT OPTIONS FOR ULCERATIVE COLITIS

- Mesalamine
- Steroids
- Role of Immunomodulator therapy
- Role of Biological agents
- Indications for surgery
- Complications of surgery

CROHN'S DISEASE

Treatment of Crohn's disease is based upon its manifestations, prior history of the patient e.g duration between diagnosis and surgical intervention, fistulizing disease, history of fibro-stenotic behavior, history of steroid dependence, history of failure with another agents and contraindications (e.g malignancy, opportunistic infections, TB, intolerance to medications). Before deciding on treatment options for Crohn's disease, one must know

1. Behavior: Fistulizing, stricturing or inflammatory
2. Location: Ileal, colonic or ileo-colonic
3. Severity: Presence of elevated inflammatory markers, extraintestinal complications, clinical symptoms, eg nutritional deficiencies, anemia

TREATMENT OPTIONS FOR CROHN'S DISEASE

- 5-ASA
- Budesonide
- Steroids
- Antibiotics
- Immunomodulators
- Biologic agents

SUMMARY OF TREATMENT REGIMEN

Ulcerative Colitis

- Proctitis:
  - Initial treatment choices are:
    - Mesalamine suppositories/enema to induce remission.
    - Steroid foam enema to induce remission
    - Mesalamine suppositories/enema to maintain remission
  - 2nd Line treatment choices are:
    - Oral Mesalamine in combination with local therapy.
    - Adjunctive treatment with antibiotics (Ciprofloxacin, metronidazole or rifaximin)
    - Probiotics

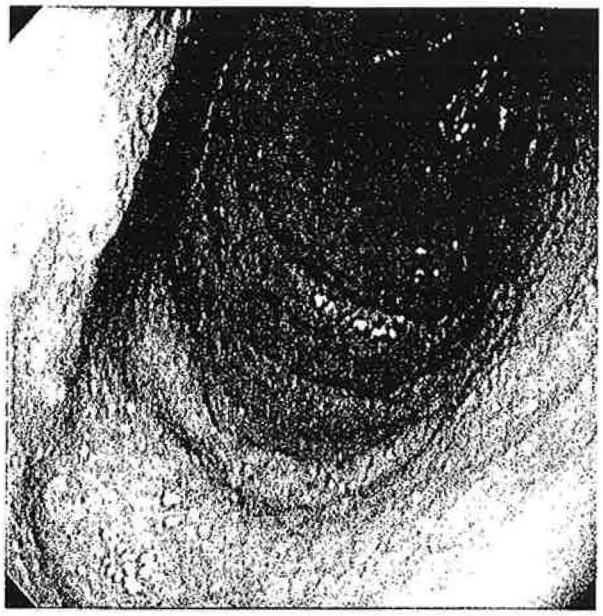
- Left sided Colitis:
  - Initial treatment choices are:
    - Oral Mesalamine product with or without local therapy
  - 2nd Line treatment choices are:
    - Oral or IV Steroids
    - Immunomodulator therapy, or
    - Infliximab
    - Cyclosporine as inpatient (avoid cyclosporine after IFX therapy due to risk of severe immunosuppresion)
- Pancolitis:
  - Initial treatment choices are:
    - Oral Mesalamine with short course of oral or IV steroids
  - 2nd line treatment choices are:
    - Immunomodulator therapy
    - Infliximab
    - Cyclosporine as inpatient. (Avoid cyclosporine after IFX therapy due to risk of severe immunosuppresion)

Crohn's Disease

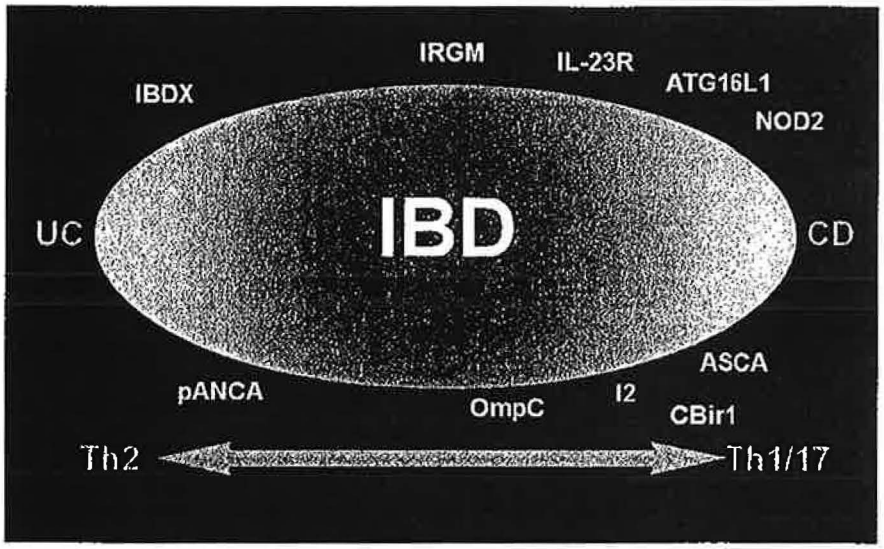
- Ileo-cecal inflammatory Crohn's disease:
  - First line treatment:
    - Oral mesalamine (asacol for ileal disease; pentasa for more proximal small bowel disease)
    - Budesonide 9 mg orally once a day
    - Immunomodulator therapy
    - Biological agents with or without concomitant immunomodulators
- Ileal Stricturing Disease:
  - No proximal dilation:
    - Trial with Budesonide or Biological agents (patients with elevated hsCRP are more likely to respond)
  - Proximal small bowel dilation:
    - Consider surgical approach
- Internally fistulizing disease without intra abdominal abscess:
  - Stricture immediately distal to fistula
    - Surgical approach
  - No stricture
    - Biological agents with or without concomitant immunomodulators
- Externally fistulizing disease without intra abdominal abscess
  - Biological agent with or without concomitant immunomodulators
- Fistulizing disease with intra abdominal abscess
  - IV antibiotics as appropriate
  - Percutaneous drainage if appropriate
  - Surgical drainage if indicated
  - Biological agents with or without concomitant immunomodulators once infectious process has been treated.

- Perianal Crohn's disease without abscess formation
    - Antibiotics (Ciprofloxacin, metronidazole, rifaximin)
    - Immunomodulators
    - Biological agent with or without concomitant immunomodulators
    - Seton placement
    - Diverting Ostomy
- Colonic Crohn's disease
    - Oral Steroids to induce remission
    - Immunomodulator therapy
    - Biological agent with or without concomitant Immunomodulator therapy

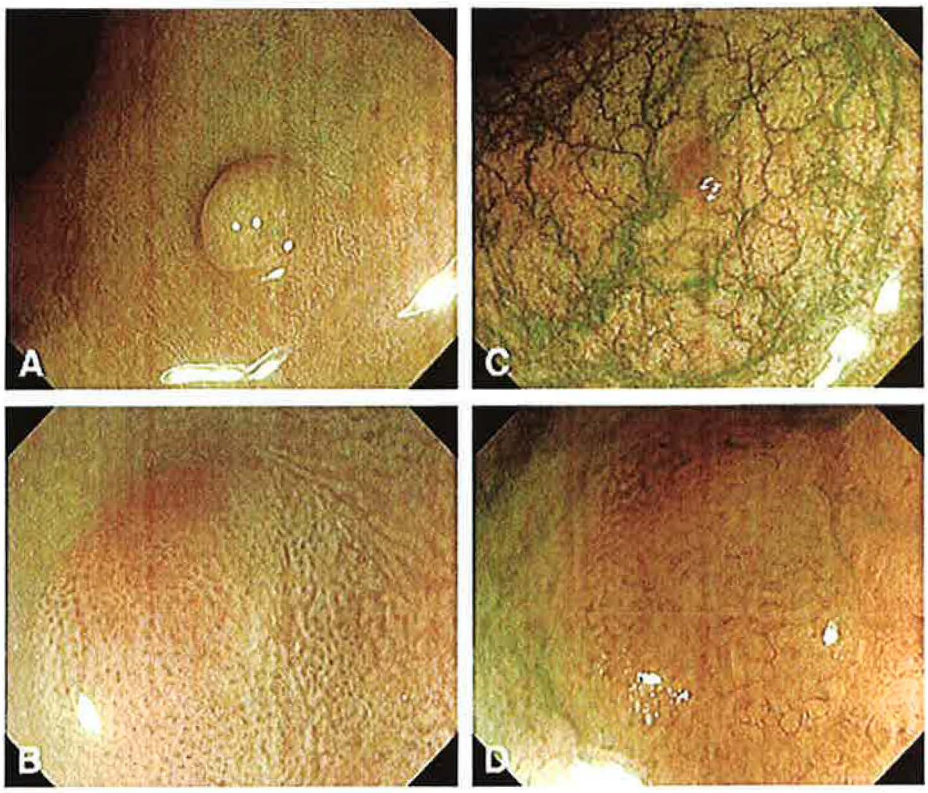
IMAGES



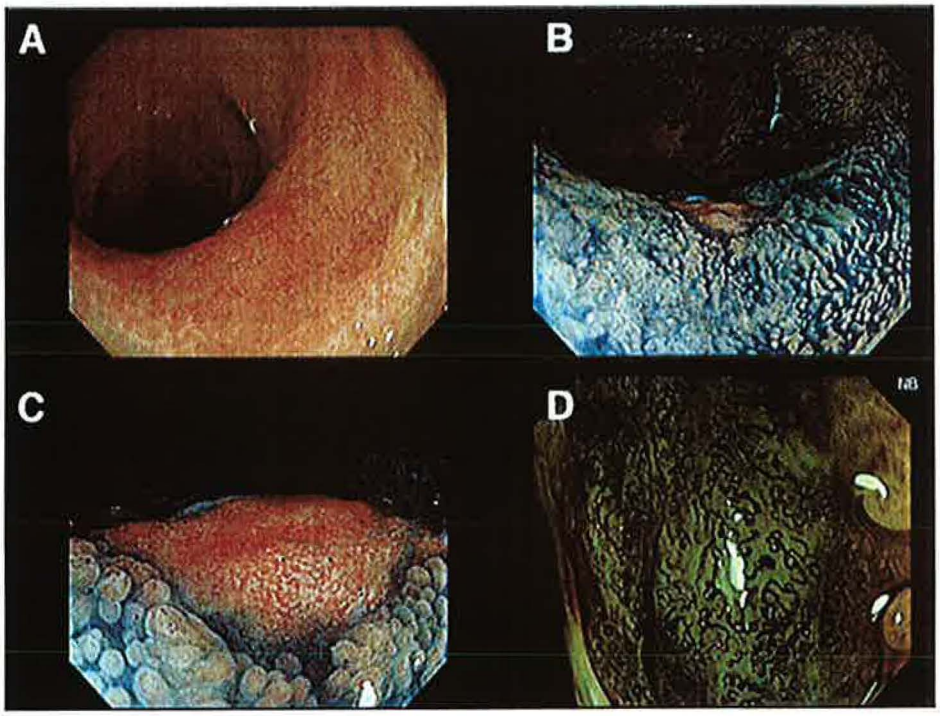
Duodenitis in Ulcerative Colitis



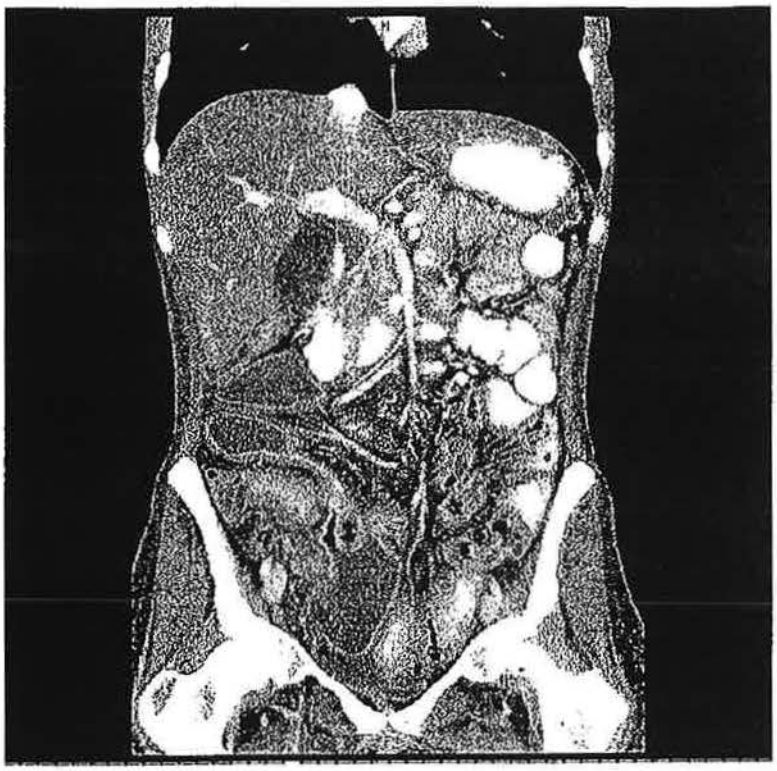
Current Classification of IBD



Narrow Band Imaging



Chromoendoscopy



CT Enterography

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