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Inflammatory Bowel Disease

By

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Crohn's Disease

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Definition

- Crohn's disease is a chronic inflammatory disease of the GIT which has the potential to involve the entire GIT.
- The inflammation is localized to the ileocecal region in approximately 50% of cases, the small bowel in approximately 25% of cases, the colon in 20% of cases and the upper gastrointestinal tract or perirectum in 5%.

Clinical picture

Symptoms of Crohn's disease are determined by the site and type of involvement, that is, inflammatory, stenotic, or fistulizing:

- The most common site of involvement is ileocolitis. These patients present with diarrhea; abdominal pain that is usually insidious in the right lower quadrant, triggered or aggravated frequently after meals; weight loss; and an association with a tender, inflammatory mass in the right lower quadrant.

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- The diarrhea is usually nonbloody, and this may be one of the clues in clinical history that helps differentiate Crohn's disease from ulcerative colitis, where bloody diarrhea is almost universal. Patients frequently have fever, weight loss, perianal fistulas and/or fissures, and extra-intestinal manifestations, such as aphthous stomatitis, arthritis, and erythema nodosum.

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Cont.

- Patients with isolated colonic disease present usually with diarrhea, abdominal pain, and weight loss.
- Perianal skin tags are very common and, at times, mistaken for external hemorrhoids.
- At times the main symptoms are related to perianal fistulas and/or abscess, even though most of these patients have other areas of involvement by Crohn's disease.

Cont.

- Gastroduodenal Crohn's disease is less common and can mimic complicated peptic ulcer disease with abdominal pain, early gastric satiety, or symptoms of duodenal obstruction.
- Patients can present with mild, moderate, or severe disease. The clinical judgment is based on factors such as the severity of diarrhea, abdominal pain, the presence or absence of dehydration, anemia, malnutrition, and tachycardia.

Diagnosis

The diagnosis of Crohn's disease is established by:

- ❑ History.
- ❑ Physical examination.
- ❑ Endoscopy.
- ❑ Biopsies.
- ❑ X-rays, air contrast barium enema, small bowel series with or without a per-oral pneumocolon
- ❑ Laboratory tests.

Serologic tests:

- 1- Anti -*Saccharomyces cerevisiae* antibody (ASCA) is seen in over 60% of patients with Crohn's disease (sensitivity) and in less than 10% of patients with other gastrointestinal diseases, such as ulcerative colitis and irritable bowel syndrome.

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2- Perinuclear antineutrophil cytoplasmic antibody (pANCA), a test with a 70% sensitivity for ulcerative colitis and a 10% sensitivity for Crohn's disease, ASCA and pANCA, testing together, have a sensitivity and specificity of over 90%.

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Differential Diagnosis

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The differential diagnosis of Crohn's disease is long. The most common mimics of Crohn's colitis are:

- ❑ Ulcerative colitis
- ❑ Ischemic colitis.
- ❑ Diverticulitis
- ❑ Colorectal cancer.
- ❑ Infection with *Yersinia enterocolitica*
- ❑ Intestinal tuberculosis.

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- ❑ In immunosuppressed patients, viral infections such as cytomegalovirus (CMV)
- ❑ Irritable bowel syndrome
- ❑ Intestinal lymphoma
- ❑ Celiac sprue
- ❑ Radiation enteropathy
- ❑ Nonsteroidal anti-inflammatory drug-induced enteropathy.

Some distinguishing characteristics of ulcerative colitis and Crohn's disease:

Characteristics	Ulcerative Colitis	Crohn's Disease
Rectal bleeding	Usual	Sometimes
Abdominal mass	Rare	Often
Abdominal pain	Sometimes	Often
Perianal disease	Extremely rare	5-10%
Upper GI symptoms	Never	Occasional
Cigarette smoking	Very rare	Common
Malnutrition	Sometimes	Common
Low-grade fever	Sometimes	Often
Rectal disease	Usual	Sometimes
Continuous disease	Usual	Rare

Cont.

Characteristics	Ulcerative Colitis	Crohn's Disease
Granulomas	Never	10-30%
Crypt abscesses	Common	Rare
Discrete ulcers	Rare	Common
Aphthoid ulcers	Rare	Common
Cobblestone lesions	Never	Common
Skip lesions	No, except rarely in treated patients	Common
Ileal involvement	Rare, backwash ileitis	Usual
Fistulas	Never	Common
Cancer	Rare	Very rare
Microscopic skip lesions	No, except rarely in treated patients	Common
Transmural inflammation	Only in fulminant disease	Common

Aetiology

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1- Cigarette smoking

2- Infection

- **Mycobacterium paratuberculosis**
- **Measles virus or the measles vaccine**

3- Genetic predisposition

Extraintestinal manifestations of Crohn's disease:

The extraintestinal manifestations of Crohn's disease are similar to those seen in ulcerative colitis:

- Polyarticular nondeforming arthritis; is the most common extraintestinal manifestation
- Primary sclerosing cholangitis.
- Erythema nodosum
- Pyoderma gangrenosum
- Iritis, uveitis
- Pancreatitis
- Cholelithiasis
- Amyloidosis
- Osteoporosis
- Ankylosing spondylitis
- Nephrolithiasis most often by oxalate stones.

Treatment

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I- Therapeutic options:

a) 5-Aminosalicylic acid (5-ASA):

5-ASA	Carrier Molecule	Release	Site of Activity
Asacol (mesalamine)	Eudragit-S	pH >7.0	Terminal ileum and colon
Pentasa (mesalamine)	Ethylcellulose beads, time release	pH >6.0	Small bowel and colon
Dipentum (olsalazine)	Azo bond	Bacteria	Colon (ileum with bacterial overgrowth)
Salazopyrine (sulfasalazine)	Sulfapyridine	Bacteria	Colon (ileum with bacterial overgrowth)
Colazal (balsalazide)	dimer	Colon	Colon

b) Corticosteroids:

Steroids are effective in treating inflammatory-type Crohn's disease. Long-term use is not recommended, however, due to the many serious adverse effects. Steroids are not effective in stricturing Crohn's disease and may actually worsen patients with fistulas

Budesonide is a very potent steroid with a very high rate first-pass metabolism, 85-90%. Given this, the systemic side effects are diminished greatly but not entirely eliminated. Budesonide is available as an enema. It has been effective for induction of remission in patients with moderately active Crohn's disease and has some effect in maintenance of remission.

c) Immunosuppressive therapy:

Both azathioprine and 6-mercaptopurine are used commonly in Crohn's disease patients. Both are purine analogs that interfere with DNA synthesis of rapidly dividing cells, such as lymphocytes and macrophages.

Because these drugs do not have a clinical effect for 2-3 months or longer, they are used primarily in maintaining remission in inflammatory-type and fistulizing-type Crohn's disease.

d) Biologic therapies:

- TNF α antibodies in Crohn's disease:
 - Infliximab
 - Etanercept
 - CDP571
- Alternative Approaches in Crohn's Disease:
 - Antisense Oligonucleotides
 - Intercellular adhesion molecule-1
 - Nuclear factor Kappa B.
 - IL-10
 - IL-11
 - G-CSF
 - Anti-integrins Antibodies (Natalizumab)

Infliximab:

It is an IgG, chimeric mouse-human antibody to tumor necrosis factor (TNF) that, when infused intravenously, binds to soluble TNF and to the TNF on surface membranes of inflammatory cells causing cell lysis. It has been approved for use in inflammatory-type Crohn's disease and fistulizing Crohn's disease. Forty eight percent of patients with inflammatory-type disease and 55% of patients with fistulizing disease achieved complete remission.

Side effects:

- ❑ During the infusion; such as nausea, headache, and pharyngitis, can be attenuated with slowing the infusion.
- ❑ Tuberculosis and opportunistic infections have been the main complications of its use.
- ❑ With chronic use, patients form anti-infliximab antibodies that may decrease its effectiveness, in which case higher doses or more frequent infusions are required.
- ❑ When a long period of time elapses between infusions, there is a higher risk of immediate or delayed infusion reactions that precludes its subsequent use.

e) Maintenance of remission:

- ❑ Long-term therapy with azathioprine or 6-mercaptopurine has the best maintenance effects.
- ❑ Methotrexate is effective in some patients and can be used in patients who fail treatment with either azathioprine or 6-mercaptopurine, or in those who have side effects precluding the use of these agents.
- ❑ 5-ASA agents are rarely effective for maintenance.
- ❑ Infliximab infusions every 8 weeks have been approved for maintenance therapy of inflammatory-type Crohn's disease.

f) Indications for surgery in CD:

- Active inflammatory-type disease refractory to medical therapy
- Prednisone dependence
- Intestinal strictures, fistulas and abscesses
- Growth retardation
- Bleeding
- Perforation
- Severe anorectal disease
- Dysplasia, and cancer.
- Strictureplasty (opening a stricture without removing bowel).
- Advancement flap surgery (removing a perirectal fistula by advancing normal mucosa over the internal os).

II- Type-oriented therapeutic regimens:

a) Inflammatory-type Crohn's disease:

- Inflammatory-type Crohn's disease should respond to anti-inflammatory agents. In mild disease, 5-ASA agents are usually tried first due to the limited toxicity; however, their efficacy is limited.
- Antibiotics such as ciprofloxacin or metronidazole are effective, particularly in patients with colonic and perianal disease.
- Steroids or infliximab are tried next due to the relatively rapid onset of action.
- Azathioprine/6-mercaptopurine and methotrexate are reserved usually for steroid-dependent inflammatory disease and for maintenance of remission.

b) Stricturing-type Crohn's disease:

□ Usually, stricturing-type Crohn's disease will require surgery. Anti-inflammatory therapy is not likely to relieve symptoms. The goals of surgery are to relieve symptoms and preserve bowel length. Strictureplasties of strictured segments of small bowel or anastomosis can provide long-term relief of obstructive symptoms.

□ In some patients, endoscopic balloon-dilatation at the site of an ileocolic anastomosis relieves symptoms, delaying the need for surgery.

c) Fistulizing Crohn's disease:

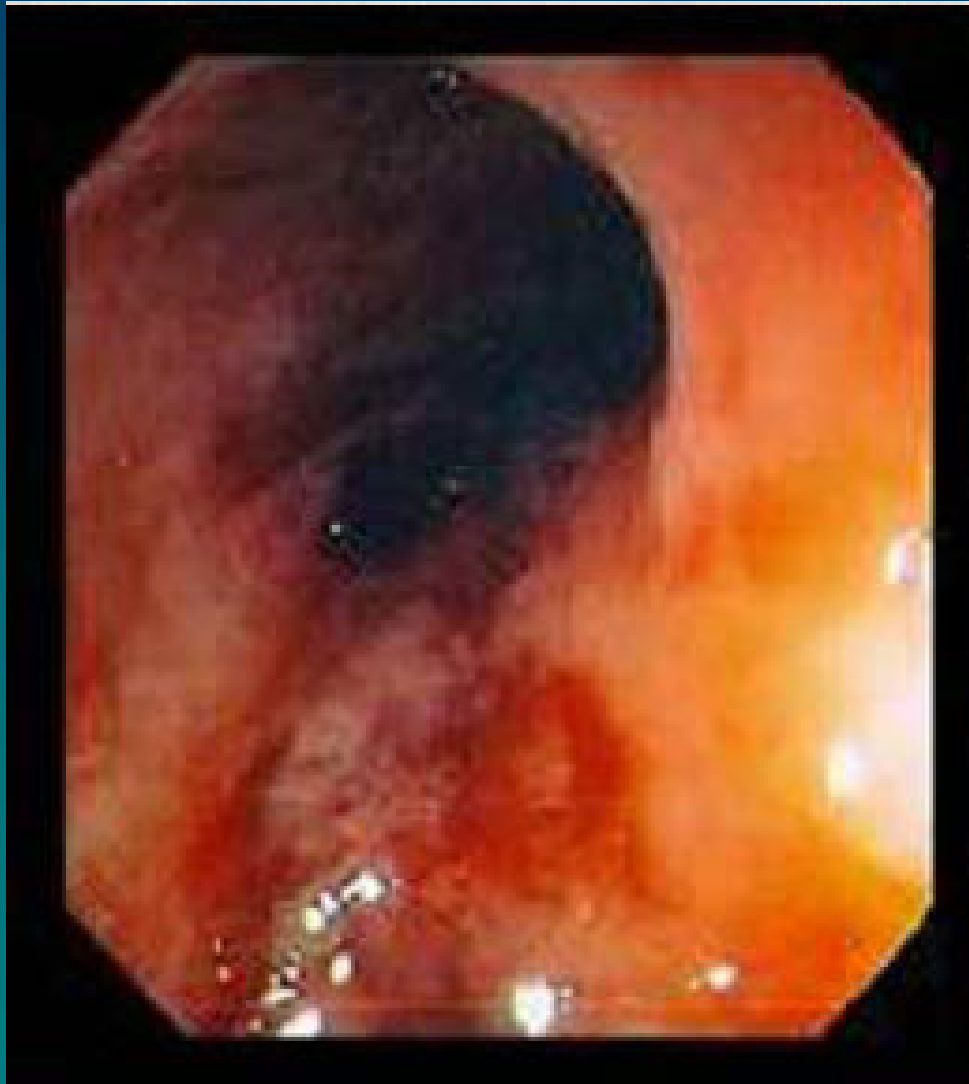
An assessment of the degree of mucosal activity is an important determinant of therapy for fistulizing Crohn's disease:

- When active disease is present, anti-inflammatory therapy with azathioprine, 6-mercaptopurine, or infliximab can be extremely helpful.
- In perianal fistulas, combined medical and surgical treatment is usually required.
- Sepsis should be adequately drained, and placement of noncutting Seton sutures can facilitate continued drainage and promote healing.
- Antibiotics, azathioprine, 6-mercaptopurine, or infliximab are usually beneficial.
- If the mucosal disease is quiescent, then surgical therapy with an advancement flap procedure may be appropriate.

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Crohn's ileitis



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Crohn's ulcer

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Pseudopolyps



Pseudopolyps

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Crohn's colitis

Ulcerative colitis

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Definitions

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Ulcerative colitis (UC) is a chronic inflammatory disease of the colon. It is distinct from Crohn's disease (CD) of the colon in that the inflammation is restricted mostly to the mucosa and involves only the colon. The rectal segment is almost always involved, whereas in CD of the colon the rectum is usually spared.

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Backwash ileitis refers to unusual cases of ulcerative colitis that involve the terminal ileum. The endoscopic, histologic, and radiologic appearances of backwash ileitis is the same as those of ulcerative colitis. When deep linear ulcers and strictures are seen in the ileum, Crohn's ileitis is the more likely diagnosis.

Indeterminate colitis In about **7% of patients**, when the inflammatory process is limited to the colon (no ileal involvement), the endoscopic, histologic, or radiologic findings are insufficiently distinct to separate the two diseases. The colitis is then referred to as "indeterminate."

Other patients carry the diagnosis of UC for many years until a change in signs and symptoms, consistent with CD, influences a change in diagnosis.

In some patients, the diagnosis of CD of the colon is recognized only after colectomy and the development of recurrent ileitis in the ileostomy or ileoanal pouch performed for what was thought to be UC.

Aetiology

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- ❑ The cause remains technically unknown, although research has clarified that there are genetic, environmental, and immunologic contributions.
- ❑ The exact genetic link for UC has not been identified.
- ❑ Dietary antigens and bacteria have been proposed as possible triggers, but no evidence supports these theories.
- ❑ The incidence of UC is significantly higher in nonsmokers than in smokers and higher still in ex-smokers than in nonsmokers, supporting a protective effect of smoking.

Clinical picture

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The predominant symptom at onset of UC is diarrhea, with or without blood in the stool. If inflammation is confined to the rectum (proctitis), blood may be seen on the surface of the stool; other symptoms include tenesmus, urgency, rectal pain, and passage of mucus, without diarrhea.

Other distributions of UC are proctosigmoiditis; left-sided disease, and universal colitis, which involves any length proximal to the mid-transverse colon and often the entire colon. The inflammation is almost always confluent in distribution and almost always involves the rectum, when it is untreated with medication by enema.

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More extensive colitis may be accompanied by systemic symptoms, such as weight loss and malaise, in addition to bloody diarrhea.

Although pain is not a dominant feature, patients may complain of crampy abdominal discomfort relieved by a bowel movement and may have abdominal tenderness, localized usually to the left lower quadrant.

Occasionally, patients may present with "constipation" secondary to rectal spasm.

Patients may present with extraintestinal manifestations before bowel symptoms, more often they parallel the severity of the primary bowel disease.

The clinical guide for severity of UC is as follows:

- ***Mild.:*** fewer than four stools daily, with or without blood, with no systemic disturbance and a normal erythrocyte sedimentation rate (ESR).
- ***Moderate:*** more than four stools daily but with minimal systemic disturbance.
- ***Severe:*** more than six stools daily with blood and systemic disturbance as shown by fever, tachycardia, anemia, or ESR >30.

Extraintestinal manifestations of ulcerative colitis are similar to Crohn's disease

Hepatic complications of ulcerative colitis:

- Fatty liver
- Pericholangitis
- Chronic active hepatitis
- Cirrhosis
- Primary sclerosing cholangitis.
- Patients with sclerosing cholangitis and ulcerative colitis have a higher risk of developing cancer colon and cholangiocarcinoma.

Serologic tests and differential diagnosis: as in Crohn's disease

So evaluation of a patient with ulcerative colitis depends on the severity and location of disease activity, which are best assessed by a careful clinical history with emphasis on the duration and severity of symptoms and physical examination, followed by endoscopic evaluation to determine the extent and severity of mucosal involvement.

Although flexible sigmoidoscopy may indicate the severity of the disease, full colonoscopy is essential to determine the extent as well as the full severity.

A plain radiograph of the abdomen should also be performed in flat and upright positions to recognize depth of ulceration and early or advanced toxic megacolon, which may be suspected by the presence of tympany in any of the segments of the abdomen.

Treatment

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a) Proctitis and proctosigmoiditis:

For mild-to-moderate ulcerative *proctitis*, topical therapy may suffice. If disease is limited to the anorectal region. A Pentasa suppository can be used once or twice daily. Hydrocortisone foam (cortifoam) or hydrocortisone enemas (Cortenema) may also be used either alone or in alternation with the 5-ASA product.

For *proctosigmoiditis*, the Pentasa enema, used alone or in alternation with a hydrocortisone enema, is effective.

Only the Pentasa enema-not the Cortenema- has maintenance value. The patient must lie on the left side for at least 20 minutes after introducing the enema to ensure adequate delivery to the affected area. In some instances when tenesmus is severe, the enema is better introduced in the knee-chest position, taking advantage of the downhill gravity. Occasionally, oral therapy may work better than enemas or suppositories; in other cases, a combination is required.

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b) Treatment of an exacerbation of ulcerative colitis:

- When the disease extends more proximally, oral therapies are required in addition to, or instead of, topical therapy. Choice of oral 5-ASA product is determined by the extent of involvement.

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Dipentum (1 gm) for left-sided colitis and

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Pentasa (4 gm) can be used for universal colitis.

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- If the disease fails to resolve with 5-ASA therapy or is moderately severe at presentation, a short course of oral corticosteroids should be prescribed to bring the disease under control. The maximal effective oral dose of prednisone is 60 mg daily. The dose may be tapered to 40 mg/day after 2-7 days, if the disease is brought under control.

c) Management of severe disease:

- Severe disease requires admission to hospital for intravenous corticosteroids and fluids. Patients should be monitored carefully by serial physical examination, lab tests, and plain radiographs of the abdomen.
- Severe UC may progress to toxic megacolon and/or perforation. It is treated with intravenous corticosteroids, antibiotics, a small bowel tube attached to suction, "log rolling" from side to side and to the supine and prone positions, and sometimes by rectal tube. If these maneuvers are not successful, subtotal colectomy should be considered, preferably before a perforation occurs.

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- If there is no response to intravenous corticosteroids, intravenous *cyclosporine* should be considered. Rapid deterioration in clinical condition warrants early surgical intervention with ileostomy and subtotal colectomy. If there is time for a trial of *cyclosporine*, it should be administered only by physicians with extensive experience in its use.

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- **Cyclosporine** is administered at a dose of 4 mg/kg/day intravenously by continuous infusion, with close monitoring of blood pressure, renal function, electrolytes, and drug blood levels. **Cyclosporine** should not be initiated if the serum cholesterol is low because it increases the risk of seizures. Bactrim is administered concurrently to prevent *Pneumocystis carinii* pneumonia. Failure to respond within 3 days portends a poor prognosis for medical therapy.
- Severe UC sometimes responds to intravenous infliximab, even though more frequent success has been confirmed by trials in CD.

d) Toxic megacolon:

- Toxic megacolon is defined as a severe attack of colitis with total or segmental dilation of the colon (diameter of transverse colon usually >5-6 cm). Megacolon is considered toxic if two or more of the following criteria are positive, in addition to the colon persistently outlined by air:
 - Tachycardia with a pulse rate >100 beats/min
 - Temperature >101.5°F
 - Leukocytosis >10,000 cells/mm³
 - Hypoalbuminemia <3.0 gm/dL

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e) Prevention of a relapse:

- Maintenance therapy should be initiated at the same time or soon after acute-phase therapy.
- For mild-to-moderate disease, a 5-ASA product may be all that is necessary.
- For more severe or recurrent disease, an immunosuppressive medication such as 6-mercaptopurine (6-MP) or azathioprine is more effective.
- Anti-tumor necrosis factor; there is evidence that it might be effective in the treatment of UC.

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f) Surveillance colonoscopy:

The current recommendations are as follows:

- For patients with left-sided colitis, surveillance should begin after 15 years of colitis.
- For patients with universal colitis, surveillance should begin after 8 years of colitis.

Three biopsy specimens should be obtained every 10 cm through-out the colon.

In addition, any strictured, raised, polypoid areas, or those with unusual shapes or textures, should be biopsied. Surveillance colonoscopy should be repeated annually.

g) New treatments for UC:

- **Probiotics** are indigenous nonpathogenic microorganisms that are being used in mainstream medical therapy. Currently proposed mechanisms of **action in IBD include:**

- Competition with microbial pathogens for cell surface receptors.
- Immunomodulation.
- Suppression of pathogens via release of antimicrobial factors.
- Induction of T cell apoptosis in the lamina propria.

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- ***Infliximab*** (anti-tumor necrosis factor) is well established as an effective therapy for Crohn's disease.

Several open label studies have demonstrated an approximately 50% clinical response rate in UC.

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- ***Natalizumab*** is a monoclonal anti-alpha4 integrin antibody that has emerged from recent trials as a promising new agent for the treatment of UC. Further trials are underway.

h) Role of surgery:

- ❑ Ulcerative colitis is “curable” by total colectomy whereas Crohn’s disease can never be considered cured by resection.
- ❑ When medical management fails, or complications such as perforation or dysplasia occur, subtotal colectomy with ileostomy or ileoanal pouch is the procedure of choice. Many patients are frightened by the prospect of having an ileostomy, but education can do much to alleviate their fears. Fortunately, a large number of patients with ileostomies become accustomed to them and continue to lead normal lives.

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- The ileoanal pouch is a possible alternative; preserving the anal sphincter. *Disadvantages* of the pouch include recurrent inflammation or "pouchitis," frequent bowel movements, nocturnal incontinence, and the continued need for surveillance endoscopy. Pouchitis responds well to metronidazole and/or ciprofloxacin.

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Normal colon



Mild UC



Severe UC

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Severe UC

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**Thank
you**