Fifth yearTherapeutics

Inflammatory Bowel Disease

IBD involvestwo **idiopathic** diseases of the gastrointestinal tract with closely related clinicalpresentations [**ulcerative colitis (UC) and Crohn's disease (CD)]**[(1)].
Ulcerative colitis is characterized by inflammatory changes affecting the **colon and rectum only** in a **continuous** pattern[(2)].
Crohn's diseasecan involve **any part** of the G.I. tract, often in **a discontinuous pattern**[(2)] (**CD**often involves **segments** of the bowelseparated by **normal** appearing segmentswhich arecalled**"skip lesions")** [(3)].

Pathophysiology

1- Etiology of IBDinvolves a **combination of *infectious, genetic,* and *immunologicfactors***[(4)] (The incidence of IBD is 10to 40 times greater in patients with a first-degree relative whohas IBD compared to the general population) [(5)].

2-IBD is currently considered **an *inappropriate immune response*** to the ***endogenousmicroflora of the GIT***.
This ***inappropriate immune response***causes inflammationofGIT part(s) and subsequent release of inflammatorymediators, such as **interleukin-12 (IL-12) and tumor necrosis factor (TNF)**[(7)]leading to edema, ulceration,and destruction of the tissue[(8)].

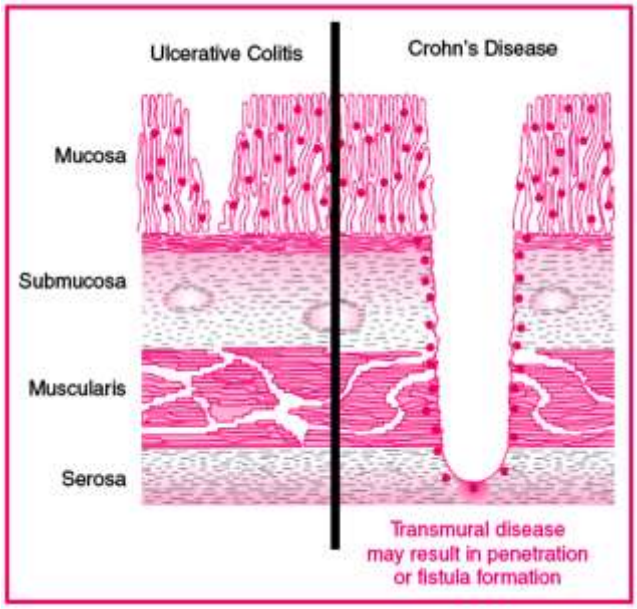


Figure 1-Depth of disease in UC and CD [(5)]

3-Ulcerative colitis and Crohn's disease differ in two general aspects:**anatomic sites involved and depthof bowel wall affected.**

A-UC is **confined to the colon and rectum and affectsthe mucosa and the submucosa**[(4)] (theinflammation is superficial and does not typically extendbelow the submucosal layer of the GIT (Fig. 1)) [(5)].

B-In CD, **any part of the entire GIT may be involved**. The small intestine is the most common site[(5)].Furthermore, the inflammation may be **transmural**, penetratingto the muscularisor serosa layers of the GI tract(Fig. 1).

4-Smoking appears to be **protective for UC,** but associated **with increased frequency of CD**[(4)].

5-The differences between UC and CD are summarized in the following table

Table -1-Differences Between Ulcerative Colitis and Crohn's Disease[8-10]		
Characteristic	**Ulcerative Colitis**	**Crohn's Disease**
Anatomical location	Colon and rectum	Mouth to anus
Tissue	Superficial (mucosa and submucosa)	Deeper within the lining of the bowel
Distribution	**Ulcers** with uniform inflammation throughout the affected area	**Ulcers** separated by areas of normal bowel lining (patchy appearance).
Development of toxic megacolon	Possible, but occasional	Rare
Possibility of developing colorectal cancer	Greatly increased	Slightly increased
Fistula/perforation/ Strictures	Not possible	Possible

Note:**Fistula**:is an **abnormal connection** between **two internal organs** or between an internal organ and the exterior or skin (e.g. fistula which connects between the intestine and the skin).
Stricture: An area of narrowing (stenosis) of **a tubular structure**

Signs and Symptoms

1-**Chronic, loose, bloody stools are the most common symptoms of UC**.
Othercommoncomplaints include **tenesmus** (urge to defecate) and **abdominalpain**[8].
Signs of a **worsening** clinical course include the development of severe abdominal pain, dehydration, fever, and tachycardia [2].

2-Patients with **CD usually present with abdominal pain especially in association with food and chronic, often nocturnal, diarrhea** (often non bloody). **Weightloss**& low-grade fever are also common[8].

3-Most patients with IBD follow afluctuating chronic course *of* ***intermittent acute attacks of active disease (exacerbations) with periods of quiescence (remission).*** A small number of patients suffer from a continuous course of persistent symptoms and no remission[3].

Extra intestinal features[4, 6, 11]

Both UC & CD are associated with manifestations in other organ systems.
1-Arthritis: The most common extra intestinal manifestation of IBDand is typically **asymmetric** (unlike rheumatoid arthritis)

2-Dermal & Mucosal manifestations:

A-Pyodermagangrenosum (skin ulcerations with a necrotic center).They can be seen on any part of the body but are more commonly found on the lower extremities.

B- ***Erythemanodosum*** (raised, red &tender nodules). They are typically found on the tibial surfaces of the legs and arms.

Oral ulceration (aphthous ulcers) may be present in **some patients** with IBD**.**

3-Eye complications:The incidence of ocular complications in IBD patients is 1–10%. The most common are **conjunctivitis**, **uveitis**/**iritis**, and **episcleritis**.

يرجى الاطلاع على تشريح العين لرؤية هذه الأجزاء

[Uveitis symptoms include ocular pain, photophobia, and blurred vision (prompt intervention, sometimes with systemicglucocorticoids, is required to prevent scarring and visual impairment). **Episcleritis** is **a benign** disorder presenting with mildocular **burning**, and is treated with topical glucocorticoids].

4-Hepatobiliary complications: The hepatic complications of IBD include fatty liver, **cholangitis** (inflammation of the bile ducts), **pericholangitis** (ie, inflammation of the tissues surrounding the bile ducts), chronic active **hepatitis**, **gallstone** and **cirrhosis**.

5-Thromboembolic complications: with arterial, as well as venous events (e.g. **deep venous thrombosis (DVT) and pulmonary emolism**), occur in about 1 to 2 per cent of patients with IBD.

6-Anaemia: Anaemia is **a frequent**extraintestinal manifestation in IBD. Multiple mechanisms may contribute (Chronic intestinal bleeding, inadequate diet & (iron and folate) malabsorption)

Complications

1-Toxic megacolon (Life-threatening distention of the colon that may lead to perforation of the colon, septicemia and peritonitis) occurs mainly in patient **with UC**. It may require urgent surgical intervention) [2, 11].

2-Patients with UC and Crohn's colitis carry an increased risk for developing **colorectal cancer**[11].**The risk of cancer greatly increased in case of UC**, but in CD the risk is slightly increased [8].

3-**Small-bowel stricture** (and subsequent bowel obstruction that may require surgery), and formation offistulas are common in CD and occur more frequently than with UC[4].

4-**Urinary complications**occur to more extent in association with CD. **Calcium oxalate stones** are the most common type of renal calculi associated with CD[13].

Diagnosis

1-Diagnosis of IBD depends on thecombination of **clinicalfeatures**, **laboratoryabnormalities**, **imagingstudies**and **endoscopic** findings which includeexamination of mucosal biopsies[14].

A-Endoscopic examination(**colonoscopy** or **sigmoidoscopy**) with **biopsy** confirms the diagnosis of IBD, differentiates UC from CD, and establishes the extent and severity of disease[3].

B-**Bariumcontrast** studies are used in CD when involvement of the small bowel or fistula is suspected[3].

C-**Laboratorytests** are usually nonspecific and do not establish the diagnosis.
Leukocytosis [3](elevated WBC count in peripheral blood)[14]and an elevated erythrocyte sedimentation rate (**ESR**) may reflect the inflammatory process.
Hypoalbuminemia may reflect the patient's poor nutritional status and overall clinical condition.
The blood count may reveal **anemia** from blood loss, or nutritional deficiencies[3].

2-After the diagnosis is made, the information derived fromdiagnostic testing and the patient's medical history and symptomsare used to stage disease severity.
The severity of active IBD is generally classified as mild, moderate, severe, or fulminant[5].

Treatment

Desired outcome

Goals of treatment include resolution of acute inflammatory processes, resolution of accompanied complications (e.g., fistulas, abscesses), alleviation of systemic manifestations (e.g., arthritis), and maintenance of remission from acute inflammation [4].

Nonpharmacologic Treatment

A-Nutritional Support

Moderate to severe IBDis often associated with malnourishment. The nutritional needs of the majority ofpatients can be adequately addressedwith enteral supplementation. Some patientswho have severe disease may require acourse of **parenteralnutrition**[4].

B-Surgery

1-For **UC**, **colectomy** may be performedwhen the patient has diseaseuncontrolled by maximum medicaltherapy or when there are complicationsof the disease, such as colonicperforation, toxic dilation (megacolon), or uncontrolled colonic hemorrhage[4].

2-The indications for surgery with Crohn's disease are not as well established asthey are for UC, and surgery is usuallyreserved for the complications of thedisease. **There is a high recurrence rateof Crohn's disease after surgery**[4].

Pharmacologic Therapy

The major types of drug therapy are:**Aminosalicylates**, **Corticosteroids**, **Immunosuppressants**, **Biologic agents** and **Antibiotics (for CD).**

Important: Traditional management of IBD involves **step-up therapy**, a method in which ***less-aggressive agents (e.g., 5-ASA compounds) are used prior to the use of agents that are more aggressive (e.g, immunosuppressants, biologicals)***[19].

A-Aminosalicylates (5-Aminosalicylic Acid (5-ASA))

The 5-ASA is **a topically** active agent that has a variety of anti-inflammatory effects. It is used in the **active** treatment ofUC and CD as well as during disease**inactivity** to maintain remission[15].A number of oral and topical compounds havebeen designed to target delivery of 5-ASA to the colon orsmall intestine while minimizing absorption. Commonlyused formulations of 5-ASA are mesalamine,and azo-compounds[15].

1-Oral mesalamine agents

Which involve 5-ASA agentscoated in various **pH-sensitive** resins (Asacol®, Apriso®, andLialda®) or packaged in **timed-release** capsules (Pentasa®)[15]..
Pentasa releases 5-ASA slowly throughout the small intestineand colon. Asacol, Apriso, and Lialda tablets dissolve atpH 6.0–7.0, releasing 5-ASA in the terminal small intestineandproximal colon. Lialda has a system thatgradually releases 5-ASA throughout the colon[15].
(**see figure 2 below**).

2-Azo-compounds

Sulfasalazine, balsalazide and olsalazinecontain 5-ASA linked by an azo bond that requires cleavage by colonic bacterial azoreductases to release5-ASA. After release within the colon, the 5-ASAacts topically and is largely unabsorbed[15].

A-**Olsalazine** containstwo 5-ASA molecules connected by the azo bond.
B-**Balsalazide** contains 5-ASA linked to an inert carrier.
C-**Sulfasalazine** contains 5-ASA linked to a sulfapyridinemoiety[15].

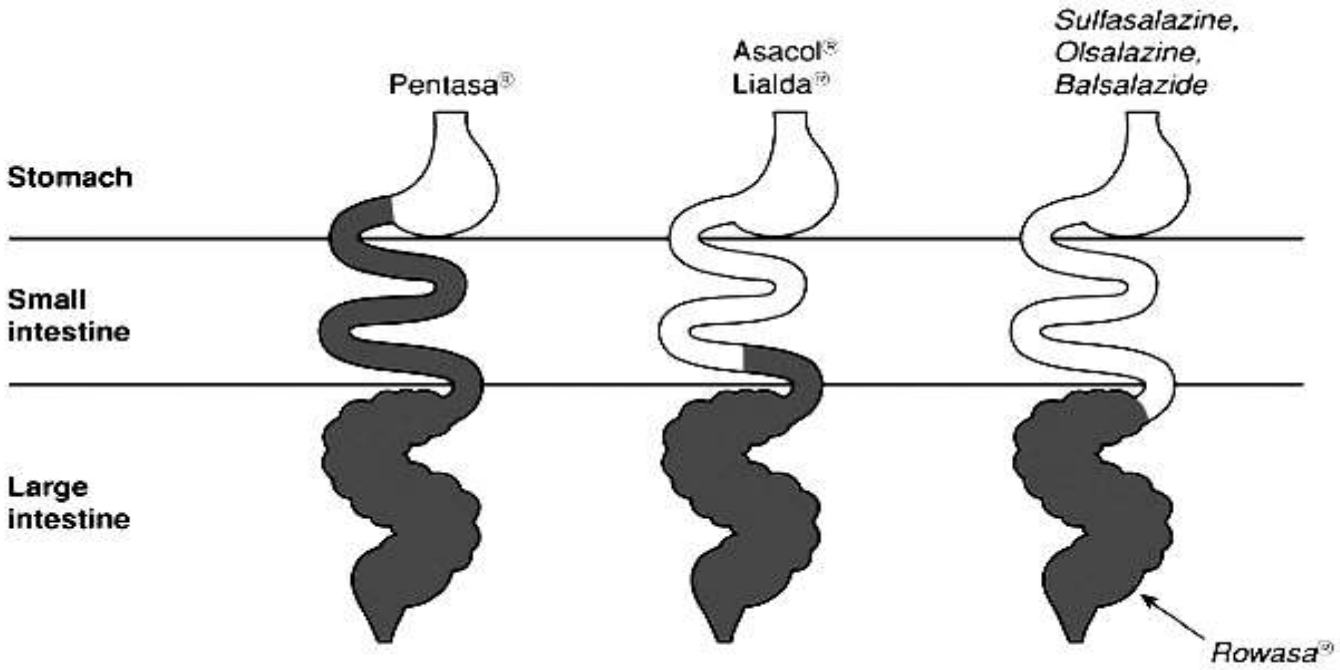
Systemic absorption of the sulfapyridine isresponsible for most of the drug's adverse effects, but contributesnothing to the therapeutic benefit[8]. The 5-ASA agents should always be administered in conjunctionwith folate[15].

3-Topical mesalamine

5-ASA is provided in the formof **suppositories and enemas**. These formulations can deliver much higherconcentrations of 5-ASA to the distal colon than oral compounds.Side effects are uncommon[15].

5-ASA suppositories are indicated for **proctitis**,whereas enema formulations can be useful in IBD confined tothe distal colon.Enemas or suppositories should be administered in the**evening**[8].

Table 2 : Mesalamine Derivatives for Treatment of Inflammatory Bowel Disease[4]		
Product	**Formulation**	**Site of action**
Sulfasalazine	**Tablet**	**Colon**
Olsalazine	**Oral capsule**	**Colon**
Balsalazide	**Oral capsule**	**Colon**
Mesalamine	**Pentasa ® (Mesalamine capsules encapsulated in ethylcellulosemicrogranules)**	**Small boweland colon**
	Asacol®(Mesalamine tablet coatedwith Eudragit-S)	**Distal ileumand colon**
	Enema (e.g.Rowasa ®, Pentasa ®)	**Rectum,terminalcolon**
	Suppository	**Rectum**
	Lialda ®(Mesalamine tab. formulated with Multi Matrix delayed-release system, allows foronce-daily dosing)	**Colon**



(Figure 2 Sites of action of the 5-ASA compounds[16].)

B-Corticosteroids

Corticosteroids have potent anti-inflammatory properties andare used in active IBD to rapidly suppress inflammation[5].**Steroids are efficacious in *inducing* remission but ineffective in *maintaining* remission**[14].

A variety of intravenous, oral, and topical corticosteroidformulations have been used in IBD. They have utility in the short-term treatment ofmoderate to severe disease. **However, long-term use is associated with serious, potentially irreversible side effects andis to be avoided**[15].

The most commonly used I.V formulationshave been hydrocortisone ormethylprednisolone. Oral formulations are prednisone or methylprednisolone.
Topical preparations areprovided as hydrocortisone suppositories,foam, and enemas [15].

Budesonide is an oral glucocorticoid with high topical anti-inflammatory activity***but low systemic activity due to high first-pass hepaticmetabolism***. A controlled-release formulation is available(Entocort®) that targets delivery to ***the terminal ileum andproximal colon***. It produces less suppression of the hypothalamic-pituitary-adrenal axis and fewer steroid-relatedside effects than hydrocortisone or prednisone[15].

C. Immunosuppressantsdrugs: Mercaptopurine, Azathioprine, cyclosporine or Methotrexate.

1-**Azathioprine and 6-mercaptopurine** (ametabolite of azathioprine) aresometimes used for the treatment ofIBD[4] as maintenancetherapy for bothUCandCDandmay be used as "steroid-sparing"agents in patients unable discontinue corticosteroids[8].
[***They are indicated only for maintenance because of its long onset of action***[10] (The onset of action of these agents isslow, up to 3 to 4 months)] [14].

2-**Methotrexate**can be used to induce remissioninpatientswithCD[14] (but not UC)[17]thathasnot respondedtoconventionalagents.Once remissionhas been achieved, methotrexate can be used to maintain remission[14].

3-Cyclosporine has beenof short-term benefit in acute, severeUC when used in a continuous infusion[4].

D-Biologicagents

1-Biologic agents highly effective for patients with corticosteroiddependentor refractory disease. The potential benefitsof these agents, however, must be carefully weighedwith their **high cost and risk of serious and potentially lifethreateningside effects**[15].

1-Anti-TNF therapies:

Three monoclonal antibodies to TNF currently areavailable for the treatment of inflammatory bowel disease (**Infliximab**, **Adalimumab**, and **Certolizumab**) [15]:

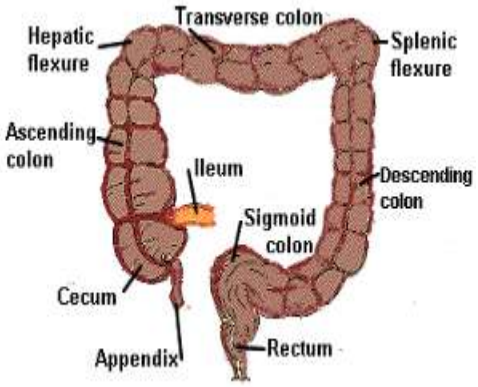
Infliximab: Indicated for both CD and UC[10].
Adalimumab and **Certolizumab**:Indicated for both induction and maintenance therapy for CD in patientsunresponsive to other therapy[10].

2-**Natalizumab** is a leukocyte adhesionand migration inhibitor that is used forpatients with CD who areunresponsive to other therapies[4].

E-Antibiotics

Antimicrobial agents, particularly**metronidazole**, are frequently used inattempts to control **Crohn's disease**,particularly when it involves ***the perineal area or fistulas***. **Ciprofloxacin**has also been used for treatment of**Crohn's disease**[4].

Treatment of Ulcerative Colitis



Classifying UC based on anatomic disease extent is useful for determiningmedical therapy. **Distal disease (below the splenic flexure) can be treated effectively with topical therapy. Extensive disease (above the splenic flexure) normally requires systemic therapy**. Severity of acute UC is alsouseful in determining medical therapy. Severity is generally defined as mild,moderate, severe, or fulminate[1] (Table below يفهم ولا يحفظ)[18].

Step-up therapy وإنما معرفة الخطة العلاجية العامة وهي توضح لما

Assessing the severity of ulcerative colitis

Feature	Mild	Moderate	Severe
Motions/day	< 4	4–6	> 6
Rectal bleeding	Small	Moderate	Large amounts
Temperature	Apyrexial	Intermediate	> 37.8°C on 2 days out of 4
Pulse rate	Normal	Intermediate	> 90 b.p.m.
Haemoglobin	> 11 g/dL	Intermediate	< 10.5 g/dL
ESR	< 20 mm/h	Intermediate	> 30 mm/h

Stepwise therapy of IBD:

Topical , oral aminosalicylates, and topical corticosteroids ⟹ oral corticosteroids

⟹ immunosuppressants⟹ biologic agents~~parenteral steroids.~~

Inflammatory bowel disease and pregnancy

1-**Drug therapy for IBD is not a contraindication for pregnancy**, andmost pregnancies are well managed inpatients with these diseases(4).

2-**Sulfasalazine, mesalamine, and balsalazide are safe for use in pregnancy and nursing**, but folate supplementation must be given concurrently. **Topical 5-ASA agents are also safe during pregnancy and nursing**(6).

3-**Glucocorticoids are generally safe for use during pregnancy** and are indicated for patients with moderate to severe disease activity(6).

4-**Metronidazole can be used in the second or third trimester**. Ciprofloxacin causes cartilage lesions in immature animals andshould be avoided because of the absence of data on its effects on growth and development in humans(6).

5- The **6-MP and azathioprine pose minimal or no risk during pregnancy**, but experience is limited.If the patient cannot be weaned from the drug orhas an exacerbation that requires 6-MP/azathioprine during pregnancy, she should continue the drug. Methotrexate is**contraindicated** in pregnancy and nursing(6).

6-Infliximab,adalimumab, and **certolizumab**areclassified as pregnancy category B andappear to be relatively safe for pregnantpatients(4).

References

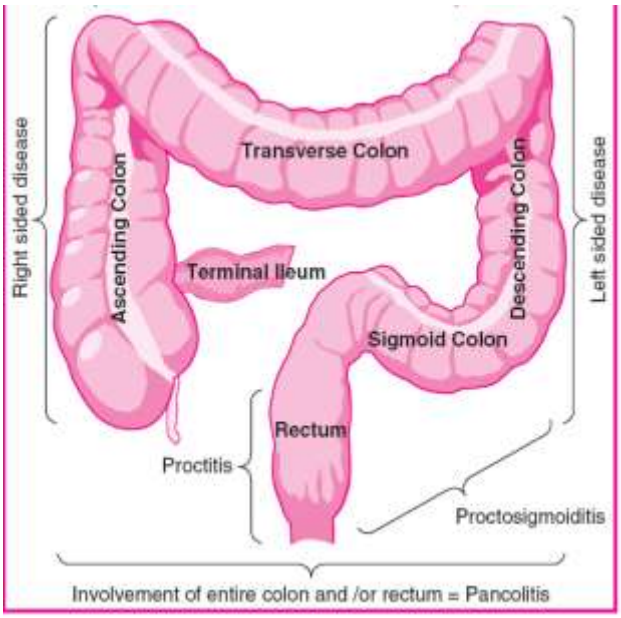
1- Leon Shargel , Alan H. Mutnick . ***Comprehensive pharmacy review***. Fifth edition 2007.
2-Anderioli **. Cecil essential of medicine .** 6thedition
3- David J Quan, Richard A Helms. ***Textbook of Therapeutics***: Drug and Disease Management. 8th edition.
4- Joseph T. DiPiro, Robert L. ***Pharmacotherapy: A Pathophysiologic Approach***, 8th Edition. Copyright 2011.
5- Marie A. Chisholm-Burns **.Pharmacotherapy Principles & Practice** Copyright © 2008 by The McGraw-Hill Companies.
6- Dan L. Longo, et al, eds. ***Harrison's Principles of Internal Medicine***, 18th Edition. Copyright © 2012 by the McGraw-Hill Companies, Inc.
7-davidson
8-Koda-Kimble and Young's. ***Applied Therapeutics***: ***The clinical use of drugs***, 10th ed., 2013 by Lippincott Williams & Wilkins.
9-Edward **M**.DeSimone **.** ManagementandTreatmentofCrohn'sDisease **.US pharmacist may 2006**.
10- ACCP Updates in Therapeutics® 2012: ***The Pharmacotherapy Preparatory Review and Recertification Course*.**

11-ChiedzoMpofu, and Alan Ireland . Inflammatory bowel disease the disease and its diagnosis **. *Hospital pharmacist* .** MAY 2006 -VOL. 13 pages : 153-158
12-Zdanowicz**,** Martin M. **Essentials of pathophysiology for pharmacy .** © 2003 by CRC Press LLC .
13-WilliamA Rowe, Inflammatory Bowel Disease **. e-medicine . Updated Apr 28, 2008 .**
14- Edward T. Bope, et al, eds. **Conn's Current Therapy.** . Copyright 2013.
15- Maxine A. Papadakis**,** et al, eds.***Current Medical Diagnosis & Treatment***, 52nd Edition 2013 .
16-Mary Anne koda-kimble (ed.), **Applied Therapeutics: The clinical use of drugs, 9th ed., Copyright ©2009 Lippincott Williams & Wilkins**
17- Cooper, Daniel H.; Krainik, Andrew J.; Lubner, Sam J.; Reno, Hilary E. L. ***Washington Manual of Medical Therapeutics***, The, 33nd Edition. Copyright 2010 . Published by Lippincott Williams & Wilkins
18-pocket consultant gastroenterology. 3rd edition.
19-*Lori F. Fede.* Crohn's Disease: Current Management and Prospective Therapies.
US Pharm. 2010;35(1):HS-10-HS-19.

Further reading

1-Management of mild to moderate active UC

1- First-line therapy of mild to moderate disease involves oral or topical aminosalicylatederivatives.
Topical suppositories and enemas are preferred foractive distal UC (left-sided disease and proctitis), as they delivermesalamine directly to the site of inflammation.
Enemas are appropriate for patients withleft-sided disease[(5)].
Oral and topical mesalamine preparations may be used togetherto provide maximal effect[(5)].



2-**Topical corticosteroids** are typically reserved for patients whodo not respond to topical mesalamine[(5)].

3-For patients with more extensive disease, **oral sulfasalazine or any of the newer oral mesalamine** products is considered first-line therapy[(5)].

2-Management of moderate to severe disease

For patients with moderate disease unresponsiveness to mesalamine or severe disease**, *oral corticosteroid*** may be necessary, but it should be used for as short a period as possible, and, **if it is not possible to taper and discontinue the steroid within 6 weeks, an *immunosuppressant* should be added**[(14)].

Infliximab is another option for patients with moderate to severe active UC who are unresponsive to steroids or other immunosuppressive agents [(4)].

3-Management of severe or intractable disease

1-Patients with uncontrolled severe colitisrequire**hospitalization**. Most medication is givenby the parenteral route.

2-With severe **colitis**, there is a muchgreater **reliance *on parenteral steroids* andsurgicalprocedures**.

3-Sulfasalazineor mesalamine derivatives have not been proven beneficial for the treatment of severe colitis[4].

4-Maintenance of remission in UC

Once remission from active disease hasbeen achieved, the goal of therapy is tomaintain the remission[4].

A-**Aminosalicylates** are the preferred agents for maintenance of remission[10].
B-Steroids do not have a role in themaintenance of remission with UC[4].
C-**Azathioprine** or **6-MP** is an effective agent for maintenance of remission;can be used in combination with aminosalicylates[10].

Treatment of Crohn's Disease

1- Management of mild to moderate CD

1-**Induction of remission of mild to moderate active CD is accomplished with oral aminosalicylates**[5].**Budesonide**(Entocort EC®) 9 mg orally once daily maybe used for mild to moderate active CD in patients withinvolvement of the **terminalileum** or **ascendingcolon**[5].

2-**Conventional oral corticosteroids such as prednisone and methylprednisolone may be used for patients who are unresponsive to aminosalicylates or budesonide**[5].

3-If it is not possible to wean the patientoff steroids within 6 weeks, an immunodulatory agent shouldbe started, typically 6-mercatopurine, azathioprineormethotrexate in those unable to tolerate these agents[14].

2-Management of moderate to severe CD

1-Patientswith moderate to severe active CD may be treated with oral corticosteroids, such as prednisone 40 to 60 mg daily[5].
Budesonide 9 mg orally once daily may be used for moderateactive CD involving the terminal ileum or ascending colon[5].

2-**The immunomodulators (azathioprine and mercaptopurine) are generally limited to use for patients not achieving adequate response to standard medical therapy** or to reduce steroid doses when highsteroid doses are required.Although mostly used in the setting of maintenance therapy, methotrexate is anotheroption for use as induction therapy for patients with moderate to severe CD[4].

3-Infliximab, Adalimumamb, Natalizumab and Certulizumabare treatment option for moderate to severe active CD **in patients failing immunosuppressive therapy**, or in those who are corticosteroid dependent[4].

3- Management of severe-fulminant CD

1-Patients often require **hospitalization** because of the severity of the disease and riskof complications[1].

2-Typical therapy may include

A-**Intravenousfluids**[1].**Parenteralnutrition** may be needed[10].

B-**Intravenouscorticosteroids**[1].

C-**Anti -TNF** therapy may be useful for patients who do not respond to intravenous Corticosteroids [1].

D-**Surgicalintervention** may be required in patients who do not respond tointravenous corticosteroids and infliximab[1].

4-Maintenance of Remission in CD

1-The most effective step, and one greater than any pharmacological intervention, is **smokingcessation**[7].

2-**Prevention of recurrence of disease is clearly more difficult with Crohn's disease than with ulcerative colitis**[4].

3-In contrast to their use in UC, **sulfasalazine and the newer aminosalicylates are less effective in preventing CD relapse**[5]. Despite these findings, an attempt to maintain remission with sulfasalazine and oral mesalamine is reasonable option (less side-effect and cost compared with the immunosuppressive and biologic agents) [4].

4-**Systemic steroids have no place in the prevention of recurrence of Crohn's disease**[4].

5-**Azathioprine**, **mercaptopurine**, **methotrexate**, **infliximab**, **certulizumab**, **natalizumab** and **adalimumab** are **effective** in maintaining remission in Crohn's disease [4, 10].