

World Gastroenterology Organization Practice Guidelines for the Diagnosis and Management of IBD in 2010

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Abstract: Inflammatory bowel disease (IBD) represents a group of idiopathic, chronic, inflammatory intestinal conditions. Its two main disease categories are: Crohn's disease (CD) and ulcerative colitis (UC), which feature both overlapping and distinct clinical and pathological features. While these diseases have, in the past, been most evident in the developed world, their prevalence in the developing world has been gradually increasing in recent decades. This poses unique issues in diagnosis and management which have been scarcely addressed in the literature or in extant guidelines. Depending on the nature of the complaints, investigations to diagnose either form of IBD or to assess disease activity will vary and will also be influenced by geographic variations in other conditions that might mimic IBD. Similarly, therapy varies depending on the phenotype of the disease being treated and available resources. The World Gastroenterology Organization has, accordingly, developed guidelines for diagnosing and treating IBD using a cascade approach to account for variability in resources in countries around the world.

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Key Words: Inflammatory bowel disease, Crohn's disease, ulcerative colitis, practice guidelines, cascades

INTRODUCTION

Inflammatory bowel disease (IBD) represents a group of idiopathic, chronic, inflammatory intestinal conditions. Its 2 main disease categories are Crohn's disease (CD) and ulcerative colitis (UC), with both overlapping and distinct clinical and pathological features.

The pathogenesis of IBD is incompletely understood. Genetic and environmental factors such as altered luminal bacteria and enhanced intestinal permeability play a role in

the dysregulation of intestinal immunity, leading to gastrointestinal injury.

Global Incidence and East/West Differences

- UC incidence
 - Increased in Western countries since the Second World War—beginning to level off.
 - Increasing in (previously) low-incidence areas in Eastern Europe, Asia, and developing countries.
- CD incidence
 - <1 per 100,000 (but probably increasing) in Asia and South America.
 - 1–3 per 100,000 in southern Europe, South Africa.
 - 16/100,000 in New Zealand and Australia, 14/100,000 in Canada.
 - 7 per 100,000 in the US (based on data only from Olmsted County, Minnesota).
 - CD prevalence seems higher in urban areas than in rural areas and in higher socioeconomic classes. Most studies show that when incidence first starts to increase it is mostly in those of higher social class but that the disease becomes more ubiquitous with time.

If prior to adolescence migration occurs to developed countries, persons initially belonging to low-incidence populations show a higher incidence of IBD. This is particularly true for the first generation of these families born in the country of high incidence.

- One hypothesis for the difference in incidence between developed and developing nations is the “hygiene hypothesis,” which suggests that persons less exposed to childhood infections or unsanitary conditions lose potentially “friendly” organisms or organisms that promote regulatory T-cell development, or alternatively do not develop a sufficient immune repertoire by not experiencing noxious organisms—they are associated with a higher incidence of chronic immune diseases including IBD.

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- In developed countries UC emerged first and then CD followed. In the past 20 years CD has generally overtaken UC in incidence rates. Among developing nations where IBD is emerging, UC typically is more common than CD. In India, for example, there are reports of a UC/CD ratio of 8:1 (was 10:1).
- The peak age of incidence of CD is the third decade, with a decreasing incidence rate with age, while the incidence rate in UC is quite stable between the third and seventh decades.
- There is a continued trend of greater incidence and prevalence of IBD across Asia (in particular in East Asia). While this emergence is occurring among developing nations it is also occurring in Japan, an advanced country from a socioeconomic perspective.
- While there are more females than males with CD among young children, the incidence rates are greater among males than females in the past decade and over time we may see equalization of sex distribution. However, the sex ratio is already equal in UC.

Differences in IBD Presenting Features Between East and West

CD is distinguished from UC by disease proximal to the colon, perineal disease, fistulas, histologic granulomas, and full thickness as opposed to mucosa-limited disease. In CD granulomas are evident in up to 50% of patients and fistulas in 25%. It is noteworthy that the presentation of both CD and UC are quite similar in such disparate areas of the world as North America, South America, Europe, Australia, and New Zealand.

But there are also differences. In Pakistan, for example, there is much less extraintestinal disease for both UC and CD than reported from the West (where up to 25% have extraintestinal manifestations if arthralgias are included). In Pakistan few have perianal or fistulizing disease.

In India, for example, the age of presentation of CD is a decade later than in the West, colonic involvement is more common, and fistulization appears less common.

DIAGNOSIS OF IBD IN ADULT PATIENTS

The diagnosis of IBD requires a comprehensive physical exam and review of the patient's history. Various tests, including blood tests, stool examination, endoscopy, biopsies, and imaging studies help to exclude other causes and confirm the diagnosis.

Clinical History

- Ask about symptoms—diarrhea (blood, mucus), abdominal pain, vomiting, weight loss, extraintestinal manifestations, fistulas, perianal disease (in CD), fever.

- Inquire as to whether any of the presenting symptoms occurred at any time in the past (not uncommonly flares of disease went undiagnosed in the past).
- Duration of current complaints, nocturnal awakening, missing work or usual social activities.
- Inquire as to possible extraintestinal manifestations including but not limited to arthritis, inflammatory ocular disease, skin diseases, osteoporosis and fractures, venous thromboembolic disease.
- Identify if mood disorders are present.
- Recent and past medical problems—intestinal infection.
- Past history of TB and known TB contacts.
- Travel history.
- Medications—antibiotics and nonsteroidal antiinflammatory drugs (NSAIDs).
- Family history (IBD, celiac disease, colorectal cancer).
- Cigarette smoking.

Symptoms

IBD is a chronic, intermittent disease. Symptoms range from mild to severe during relapses and may disappear or decrease during remissions. In general, symptoms depend on the segment of the intestinal tract involved.

Symptoms related to inflammatory damage of the digestive tract

- Diarrhea
 - Stool may contain mucus or blood.
 - Nocturnal diarrhea.
 - Incontinence.
- Constipation
 - Can be primary symptom in UC limited to rectum (proctitis).
 - To the point of obstipation and with no passage of flatus seen in cases of bowel obstruction.
- Pain or rectal bleeding with bowel movement
- Severe bowel movement urgency
- Tenesmus
- Abdominal cramps and pain
 - In the right lower quadrant of the abdomen common in CD or around the umbilicus, in the lower left quadrant in moderate to severe UC.
- Nausea and vomiting may occur, but more so in CD than UC.

General symptoms associated with UC and CD in some cases

- Fever
- Loss of appetite
- Weight loss
- Fatigue

- Night sweats
- Growth retardation
- Primary amenorrhea

Complications

Intestinal complications

- Hemorrhage: profuse bleeding from ulcers in UC. Bleeding less common in CD. Massive bleeding in CD more often seen from ileal ulceration than colitis
 - 5%–10% of persons with CD show ulceration in stomach or duodenum.
 - Proximal small bowel involvement occurs more often in children.
- Bowel perforation
- Intraabdominal abscesses in CD
- Strictures and obstruction (narrowing of the bowel may be from acute inflammation and edema, or from chronic fibrosis)
 - Strictures in CD often are inflammatory
 - inflammatory strictures can resolve with medical treatment
 - scarring (fixed or fibrotic) strictures may require endoscopic or surgical intervention to relieve the obstruction.
 - Colonic strictures in UC are presumed to be malignant until proven otherwise.
- Fistulas and perianal disease
 - Hallmark of CD
 - surgical intervention is required in cases not responding to vigorous medical treatment or where abscesses have developed
 - high risk of recurrence
 - some simple fistulas can be treated surgically if medical therapy not available.
 - Fistulas to the urinary tract or vagina are not uncommon and can lead to pneumaturia or fecaluria or passage of air from the vagina. This may result in urinary tract infection or gynecological inflammation.
- Toxic megacolon
 - Relatively rare, life-threatening colitis complication (characterized by dilatation of the colon diagnosed by plain abdominal x-ray) requiring aggressive medical therapy and urgent surgical intervention if no response within 24 hours (more common in UC than CD).
- Malignancy
 - Significantly increased risk of colon cancer in UC after 8 years of diagnosis; there is a similar risk in CD if substantial area of colon is involved. The risk increases relative to disease duration, early age of disease onset, and if there is a family history of sporadic colorectal cancer.

- Primary sclerosing cholangitis (PSC) in UC is also associated with an increased risk of cholangiocarcinoma and colorectal cancer. PSC is also increased in CD, although it is more common in UC.
- There is an increased risk of small bowel adenocarcinoma in small bowel CD, but it is rare.

Extraintestinal complications

- Affect up to 25% of those with IBD, although 15%–20% have arthralgias while the remainder have frank inflammatory disease in other organ systems. Some may antedate the diagnosis of the IBD and some may run an independent course from the IBD (even colectomy in UC does not affect the course of ankylosing spondylitis or PSC; however, for many, arthralgia activity parallels the activity of the bowel disease).
- May include:
 - Arthritis is the most common complication.
 - Other extraintestinal complications include ankylosing spondylitis, pyoderma gangrenosum, erythema nodosum, iritis, uveitis, episcleritis, PSC.
 - Patients may have multiple extraintestinal complications.
 - Osteoporosis, venous thromboembolism, avascular necrosis, and ischemic arterial events are all more frequent in IBD than in the general population.
 - Mood disorders such as anxiety and depression are increased in IBD.
 - The most common liver disorder is likely nonalcoholic fatty liver disease (NAFLD).
 - Nephrolithiasis and gallstones in CD.

Physical examination.

- General
 - General well-being.
 - Pallor.
 - Cachexia.
 - Clubbing.
 - Nutritional status.
 - Pulse rate and blood pressure.
 - Body temperature.
 - Body weight and height.
- Abdominal region
 - Mass.
 - Distention.
 - Tenderness, rebound, guarding.
 - Altered bowel sounds (obstruction).
 - Hepatomegaly.
 - Surgical scars.
- Perianal region
 - Tags.
 - Fissures.

- Fistulas.
- Abscess.
- Digital rectal exam (assess for anal strictures, rectal mass).
- Extraintestinal inspection of mouth, eyes, skin, and joints
 - Aphthous ulcers.
 - Arthropathy.
 - Uveitis, episcleritis.
 - Erythema nodosum.
 - Pyoderma gangrenosum.
 - Sweet's syndrome (acute neutrophilic dermatosis).
 - Primary sclerosing cholangitis (manifestations of chronic liver disease).
 - Metabolic bone disease.
- Decreased serum cobalamine—may indicate malabsorption.
- Liver enzyme and function testing (INR, bilirubin, albumin).
- HIV.
- Perinuclear antineutrophil cytoplasmic antibody (p-ANCA) and anti-*Saccharomyces cerevisiae* antibodies (ASCA) for cases of IBD unclassified
 - Positive p-ANCA antigen and negative ASCA test suggests UC.
 - Negative p-ANCA antigen and positive ASCA test suggests CD.
 - These tests are unnecessary as screening tests particularly if endoscopy or imaging is going to be pursued for more definitive diagnoses. p-ANCA can be positive in Crohn's colitis and hence may not be able to distinguish CD from UC in otherwise unclassified colitis. ASCA is more specific for CD.

Laboratory Examinations

- Stool examination
 - Routine fecal examinations and cultures to eliminate bacterial, viral, or parasitic causes of diarrhea.
 - *Clostridium difficile* (should be considered even in absence of antecedent antibiotics).
 - Checking for occult blood or fecal leukocytes if a patient presents without a history of blood in stool can heighten indication for lower endoscopy. Where lower endoscopy is readily available these tests are rarely indicated.
 - Cytomegalovirus (CMV); in those on immunosuppressives or chronic steroids).
 - Calprotectin, lactoferrin, α 1-antitrypsin.*
- Blood examination
 - Complete blood count (CBC).
 - Erythrocyte sedimentation rate, C-reactive protein, and orosomucoid—levels imperfectly correlate with inflammation and disease activity.
 - Electrolytes and albumin, ferritin—may indicate absorption or loss problems—calcium, magnesium, vitamin B₁₂.
 - Serum ferritin can be elevated in active IBD and may be in the normal range even in the face of severe iron deficiency. Transferrin saturation can also be done to evaluate anemia. Best test if available is soluble transferrin receptor (sTfR), although it is expensive (and is also an acute phase protein).
- Celiac antibody testing should be pursued unless presentations include obviously nonceliac features such as fistulas, perineal disease, blood in the stool.
- To exclude intestinal TB (in area of high pretest probability)
 - Tuberculin purified protein derivative (PPD) skin test (the PPD in some countries like Brazil is considered positive when over 10 mm; in the USA it is positive when over 5 mm).
 - Serum PPD antibody test.
 - Interferon- γ assays (Quantiferon, T-SPOT.TB test).

Imaging and Endoscopy

- Plain abdominal radiography
 - Can delineate if colitis present and extent in some cases.
 - Used in case bowel obstruction or perforation expected.
 - Exclude toxic megacolon.
- Barium double contrast enema/barium small bowel x-ray
 - Not typically recommended in severe cases.
 - Barium small bowel x-ray still widely used to assess upper gastrointestinal (GI) tract to distal small bowel.
 - Barium enemas can be helpful in areas that do not have access to endoscopy or when colonoscopy is incomplete or to delineate length of stricture.
- Sigmoidoscopy, colonoscopy
 - Examine for ulcers, inflammation, bleeding, stenoses.
 - Multiple biopsies of colon and terminal ileum.
 - Colonoscopy in severe or fulminant cases might be limited in extent due to the increased risk of perforation.
 - Sigmoidoscopy or colonoscopy in setting of lack of response to usual therapy including to consider for CMV if chronically on immunosuppressives and for *C. difficile* if stool test equivocal.

*Note: These tests are unlikely to be used in developing countries but may be used in more developed countries with limited access to colonoscopy. These tests can be used effectively to triage those less likely to have intestinal inflammation. They can also be used to follow already diagnosed patients as a warning sign of recurrent disease. The key reason for listing them here is their ability to rule out intestinal inflammation rather than a possible use as a positive diagnostic test.

TABLE 1. Diagnosis of UC and CD

Diagnosis	UC	CD
1. Suspected	Presence of typical clinical manifestations, further investigation required	
2. Suggested	Presence of clinical features + either positive image or endoscopic findings	
3. Rule out	<ul style="list-style-type: none"> • Chronic schistosomiasis • Amoebiasis • Intestinal tuberculosis (TB) • Ischemic colitis • Radiation colitis • CD in the colon 	<ul style="list-style-type: none"> • Chronic intestinal infections (small intestinal TB, amoebiasis, Yersinia) • Lymphogranuloma venereum, • Actinomycosis • Intestinal lymphoma • Chronic diverticulitis • Ischemia colitis • Behcet's disease • UC • NSAID enteropathy
4. Definite	Suggested diagnosis + other causes ruled out + typical histopathology of resected specimen. In areas of high TB prevalence: a negative TB culture (biopsy or resected bowel)	

- Screening colonoscopy for dysplasia surveillance is indicated after 8 years of UC or Crohn's colitis.
- Upper GI endoscopy
 - In case of upper GI symptoms (nausea, vomiting, epigastric pain) (note that since upper GI disease is more common in pediatric CD it is more routine in children).
- Cross-sectional imaging: computed tomography (CT) scan, ultrasound (US), MRI (including CT and MRI enteroscopy)
 - Helpful to determine disease extent and severity and assess for perforating complications of CD. US and MRI preferred since patients are often young and will likely require repeat imaging over time.
- Capsule endoscopy may be of help in patients with suspected CD and negative work-up.
- Push enteroscopy, double balloon enteroscopy
 - To assess for small bowel disease if highly suspected when other modalities have been negative.
 - May be a useful means of reaching small bowel strictures for balloon dilatation.
- MRCP or ERCP if there is evidence of cholestasis.
- DEXA to assess BMD in selected cases.
- Chest x-ray to exclude pulmonary TB and also to look for free air under the diaphragm in case of perforation.

Note: it is important to minimize conventional radiology due to the potential risk of radiation-induced malignancy.

Cascade: IBD Diagnosis

Cascade 1: Choices for Diagnosis

Cascade 1: choices for diagnosis, depending on resources available. Limited resources available:

1. Physical examination.
2. Stool tests for infection, occult blood, fecal leukocytes.
3. CBC, serum albumin.
4. HIV and TB testing if high-risk populations.
5. Flexible sigmoidoscopy or colonoscopy if available.
6. If endoscopy is not available but barium studies are, then obtain both small bowel barium study and barium enema.

If resources available:

1. Physical examination.
2. Stool tests for infection.
3. Stool for occult blood, fecal leukocytes (not necessary if endoscopy available).
4. CBC, serum albumin, serum ferritin, CRP.
5. HIV and TB testing if high risk populations.
6. Flexible sigmoidoscopy or colonoscopy if available.
7. If endoscopy is not available but barium studies are, then obtain both small bowel barium study and barium enema.
8. Abdominal ultrasound scan.
9. CT scan abdomen.

If greater resources available:

1. Physical examination.
2. Stool tests for infection.
3. CBC, serum albumin, serum ferritin, CRP.
4. HIV and TB testing if high risk populations.
5. Colonoscopy.
6. Abdominal ultrasound scan.
7. MRI abdomen preferred to CT scan abdomen because of lack of radiation.
8. During lower endoscopy in areas of high TB prevalence TB culture is essential.
9. If uncertain about small bowel disease, then small bowel barium study.

TABLE 2. WHO Diagnostic Criteria for CD

Criteria	Clinical	Radiological	Endoscopy	Biopsy	Resected Specimen
1. Discontinuous or segmental lesions		+	+		+
2. Cobblestone appearance or longitudinal ulcer		+	+		+
3. Transmural inflammation	+	+		+	+
4. Non-caseating granulomas				+	+
5. Fissures and fistulas	+	+			+
6. Perianal disorders	+				

- 10. Barium enema if colonic fistula expected and not defined by cross-sectional imaging or if colonoscopy incomplete.
- 11. Capsule endoscopy if diagnosis of CD is still unclear.

- Differential diagnosis between TB and CD shows a continuous course in TB and history of remissions and relapses in CD.
- Possible presence of ascites and hepatosplenomegaly in TB, whereas either are uncommon in CD. See Table 8.

EVALUATION

Diagnostic Criteria

See Tables 1–5.

Differentiation Between UC and CD

See Table 6.

Diagnostic Considerations

- Follow up patients for 3–6 months after a first attack if characteristic clinical, radiological, endoscopic, or histopathological features are lacking.
- Treat for TB and observe therapeutic effects in patients with difficulties differentiating between CD and intestinal TB.
- Colonoscopy findings of diffuse inflammatory changes and negative stool cultures are not sufficient for a UC diagnosis. This requires chronic changes over time (i.e., 6 months, in the absence of other emerging diagnoses) and signs of chronic inflammation histologically.
- Surveillance for colorectal cancer in patients with long-standing UC and CD colitis.

Differential Diagnosis

See Table 7.

IBD and Intestinal Tuberculosis

- Intestinal TB must be excluded before a diagnosis of IBD is made.
- A causal association between Mycobacterium paratuberculosis and IBD remains unproven.
- In high-risk population or jurisdiction if TB cannot be excluded, trial of anti-TB therapy is justified, and steroids should be withheld.
- Sequence of symptoms occur such as TB: fever, abdominal pain, diarrhea; CD: abdominal pain, diarrhea and fever (which is often absent).

IBD MANAGEMENT

Introduction

It is important that an explanation about the disease and individual information should be provided. Active patient participation in decision-making is encouraged.

IBD management often requires long-term treatment based on a combination of drugs to control the disease. Doctors should be aware of possible drug interactions and side effects. Often patients will require surgery and a close collaboration is required between surgeons and physicians to optimize the patient’s therapy.

IBD management should be based on:

- UC versus CD (although less important for early aspects of treatment).
- Disease location and phenotype.
- Severity.
- Complications.
- Individual symptomatic response.
- Tolerance to medical intervention.
- Patient access to diagnostic and treatment options.

TABLE 3. Disease Activity in UC adapted from Truelove and Witts: Journal of Crohn’s and Colitis 2008;2:1–23

	Mild	Moderate	Severe
1. Bloody stools/day	<4	4 or more <i>if</i>	≥6 <i>and</i>
2. Pulse	<90 bpm	≤90 bpm	>90 bpm <i>or</i>
3. Temperature	<37.5°C	≤37.8°C	>37.8°C <i>or</i>
4. Hemoglobin	<11.5 g/dL	≥10.5 g/dL	<10.5 g/dL <i>or</i>
5. ESR	<20 mm/h	≤30 mm/h	>30 mm/h <i>or</i>
6. <i>Or</i> CRP	Normal	≤30 mg/L	>30 mg/L

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

TABLE 4. Sutherland Disease Activity Index for UC: Sutherland et al. Gastroenterology 1987;92:1894–1898 (Requires Sigmoidoscopy or Colonoscopy)

Score	0	1	2	3
1. Stool frequency	Normal	1–2x/day >Normal	3–4 x/day >Normal	5 x/day Normal
2. Rectal bleeding	None	Streaks	Obvious	Mostly blood
3. Mucosal appearance	Normal	Mild friability	Moderate friability	Exudation, spontaneous bleeding
5. Physician's rating	Normal	Mild	Moderate	Severe

Total disease activity score (=sum of the item scores): 2, remission; 3–5, mild; 6–10, moderately active; 11–12, severe.

TABLE 5. Harvey-Bradshaw. Simplified CD Activity Index

Score	0	1	2	3	4
1. General well-being	Well	Slightly poor	Poor	Very poor	Extremely poor
2. Abdominal pain	None	Mild	Moderate	Severe	
3. Diarrhea	1 for each liquid stool per day				
4. Abdominal mass	None	Dubious	Definite	Definite and with tenderness	
5. Complications	1 for each item: arthralgia, uveitis, erythema nodosum, pyoderma gangrenous, aphthous ulcer, anal fissure, new fistula or abscess				

Total disease activity score (=sum of the item scores): ≤4, remission; 5-8, moderately active; 9≤, markedly active.

TABLE 6. Features to Differentiate UC from CD

Features Typical for	UC	CD
1. Clinical	–Frequent, small volume diarrhea with urgency –Predominantly bloody diarrhea	–Diarrhea accompanied by abdominal pain and malnutrition –Stomatitis –Abdominal mass –Perianal lesions
2. Endoscopic and radiological	–Diffuse superficial colonic inflammation –Involvement of rectum but can be patchy –Shallow erosions and ulcers –Spontaneous bleeding	–Discontinuous transmural asymmetric lesions –Mainly involving ileum and right- side colon –Cobblestone appearance –Longitudinal ulcer –Deep fissures
Histopathological	–Diffuse inflammation in mucosa or submucosa –crypt architecture distortion	–Granulomatous inflammation –Fissures or aphthous ulcers can be seen; often transmural inflammation
Serological markers	Anti-neutrophil cytoplasmic antibodies	Anti-Saccharomyces cerevisiae antibodies

TABLE 7. Main Differential Diagnoses for UC and CD

	UC	CD
Main differential diagnosis	–Acute self-limiting colitis (ASLC) –Amebic colitis –Schistosomiasis –CD –Colon cancer –Irritable bowel syndrome (IBS) (if there are inflammatory changes, then you are not dealing with IBS) –Intestinal TB –NSAID enteropathy	–Intestinal TB –Behcet's disease –UC –NSAID enteropathy –IBS –celiac disease
Other DD's	Infectious colitis, ischemic colitis, radiation colitis, Henoch–Schonlein purpura, collagenous or lymphocytic colitis, Behcet's disease, colitis complicated by HIV	Ischemic colitis, microscopic colitis, radiation colitis, diversion colitis chronic diverticulitis, and drug-induced enteropathy (e.g., NSAID), eosinophilic enteritis, intestinal lymphoma and colon cancer

TABLE 8. Distinguishing TB and CD

Features	TB	CD
Clinical	<ul style="list-style-type: none"> -Past or present history of TB -Positive TB contact -Less frequent fistulas, abdominal abscesses or perianal involvement -Abnormal CXR (not universal) 	<ul style="list-style-type: none"> -Fistulas -Bowel wall abscess -Anal peri-rectal disorders -Bloody stools -Bowel perforation -Recurrence after intestinal resection
Endoscopic	<ul style="list-style-type: none"> -Superficial, irregular transverse ulcers without predominant segmental distribution -Pseudopolyps -Cecum > ileum -ICV involved (gaping) 	<p>May appear similarly to changes in TB</p> <p>Features less common in ITB (favoring CD):</p> <ul style="list-style-type: none"> -longitudinal ulceration -cobble-stoning -aphthous ulceration -ileum > cecum -ICV may be stenosed or ulcerated
Histopathological	<ul style="list-style-type: none"> -Large, dense, confluent granulomas -Sub-mucosal granulomas -Caseous necrosis and submucosal stenosis -Caseating changes in intestinal wall and mesenteric lymph nodes -Positive for acid-fast bacilli -Disproportionate submucosal inflammation -Bands of epithelioid histiocytes lining ulcers 	<ul style="list-style-type: none"> -Non-caseous granulomas/necrosis may be found in up to 50%
Specific tests	<ul style="list-style-type: none"> -TB DNA analysis with TB-specific primer -TB bacteria culture -Tuberculin purified protein derivative (PPD) skin test -Serum PPD antibody test -IFN-γ assays -Chest X-ray for pulmonary TB -ASCA and p-ANCA are of no value in differentiating the 2 	
Cross-sectional imaging	<ul style="list-style-type: none"> -cecum > ileum -asymmetric thickening -ascites -small pericecal nodes -mesenteric nodes >1cm with calcification and central attenuation -fat wrapping is common 	<ul style="list-style-type: none"> -ileum > cecum -symmetrical thickening -fat wrapping is unusual -mesenteric nodes 3-8 mm -enlarged mesenteric vascular bundles -'comb sign'

- Past disease course and duration with number of relapses in a calendar year.

Treatment goals are to:

- Improve and maintain the general “well-being” of patients (optimize the quality of life, as seen from the patients perspective).
- Treat acute disease
 - Eliminate symptoms, minimize side effects and long-term adverse effects.
 - Reduce intestinal inflammation and if possible heal the mucosa.
- Maintain steroid-free remissions (decrease the frequency and severity of recurrences and reliance on steroids).

- Prevent complications hospitalization and surgery.
- Maintain good nutritional status.

Diet and lifestyle considerations:

- The impact of diet on inflammatory activity in UC/CD is poorly understood but dietary changes may help reduce symptoms:
 - During increased disease activity it is appropriate to decrease the amount of fiber. Dairy products can be maintained unless not tolerated.
 - A low-residue diet may decrease the frequency of bowel movements.

- A high-residue diet may be indicated in cases of ulcerative proctitis (disease limited to the rectum where constipation can be more a problem than diarrhea).
- There are limited data that reduction of dietary fermentable oligo-, di-, and monosaccharides and polyols may reduce the symptoms of IBD.
- Dietary or lifestyle changes may reduce inflammation in CD:
 - A liquid diet, predigested formula, or nothing by mouth (NPO status) may reduce obstructive symptoms. Exclusive enteral nutrition can settle inflammatory disease, especially in children.
 - Smoking cessation benefits patients with CD regarding their disease course and benefits UC patients from a general health perspective (smoking cessation is associated with flaring of UC).
- Reduction of stress and better stress management may improve symptoms or patients' approach to their disease. The assistance of a mental health worker may be useful, and attention to comorbid psychiatric illness is imperative.
- Orally (prednisone, prednisolone, budesonide, dexamethasone).
- Rectally (enema, foam preparations, suppository).
- Immune modifiers
 - Includes
 - Thiopurines: 6-mercaptopurine (6-MP) and azathioprine (AZA) in UC or CD.
 - Calcineurin inhibitors: cyclosporin A (CsA) in UC or tacrolimus in CD.
 - Methotrexate (MTX) in CD and UC (while there is no evidence in UC, clinical experience suggests it is worth trying—it is a cheap drug and may be available in countries where anti-TNF is not).
 - Onset of action relatively slow—may take 2–3 months after initiation of treatment for thiopurines and MTX but rapid (<1 week) for CsA.
 - Not suitable for acute flare-ups (except for CsA in acute severe UC).
 - Used for or helpful in
 - Reducing or eliminating corticosteroid dependence in IBD.
 - Selected persons with IBD when aminosalicylates and corticosteroids are either ineffective or only partially effective.
 - Maintaining remission in CD and in UC when aminosalicylates fail.
 - Primary treatment of fistulas.
 - Alternative treatment for CD relapse after steroid therapy.
 - For steroid-dependence to maintain remission and withdraw steroids.
 - Before starting AZA or 6MP measuring thiopurine methyl transferase levels (TPMT) phenotype (enzyme levels) or genotype will help direct dosing and if enzyme levels very low then risk may be too high to use these drugs. Where this testing is not available CBC needs to be obtained at 2 weeks, 4 weeks, and every 4 weeks thereafter. Even where this testing is available monthly CBCs still indicated.

Drugs in IBD Management

- Aminosalicylates: antiinflammatory agents
 - Includes
 - 5-Aminosalicylic acid (5-ASA), mesalazine.
 - Preparations available in the US and western Europe for oral use: sulfasalazine, mesalamine, olsalazine, balsalazide, and for rectal use: mesalamine enemas (liquid or foam) and suppositories.
 - Useful both for treating colitis flare-ups and maintenance of remission.
 - Aminosalicylates for UC treatment during remissions
 - Oral or rectal 5-ASA.
 - Combination therapy of oral and topical 5-ASA.
 - Rectal 5-ASA is superior to rectal steroids.
 - In CD sulfasalazine is mainly effective in disease affecting the colon.
 - Patients on sulfasalazine should take folic acid.
 - Important to use adequate doses: 2–4.8 g/day for active disease, ≥ 2 g/day for maintenance.
- Corticosteroids (steroids)
 - Usually provide significant suppression of inflammation and rapid relief of symptoms.
 - Indicated in IBD for acute flare-ups not responding to adequate doses of 5-ASA.
 - No role in the maintenance of remission.
 - Side effects limit (long-term) use.
 - Route of administration depending upon the location and severity of disease
 - Intravenously (IV; methylprednisolone, hydrocortisone).
 - Calcineurin inhibitors: reserved for special circumstances.
 - Use of CsA limited almost exclusively to acute severe colitis.
 - Use of tacrolimus almost exclusively limited to CD that has failed other proven therapies.
 - Discontinue calcineurin inhibitors within 6 months to limit nephrotoxicity and so alternate immunosuppressive such as AZA, 6-MP or MTX will be required if considering CsA.
 - High colectomy rate 12 months following introduction of CsA.
 - After IV CsA, switch to oral therapy when clinical response is achieved, or add 6-MP, AZA, or MTX.

- Anti-TNF agent (but not for “first-line” therapy)
 - Infliximab, adalimumab, and certolizumab are US Food and Drug Administration (FDA)-approved for treatment of moderate-to-severe CD + inadequate response to standard medications.
 - Infliximab (IFX) is used as rescue therapy in steroid-refractory severe UC.
 - There is an increased risk of reactivation of latent TB and of hepatitis B, which is endemic in many parts of the developing world.
 - IV IFX treatment effects last for ≈ 8 weeks—regular scheduled dosing leads to better remission rates than episodic therapy. In suboptimal response dosing can be increased from 5 mg/kg to 10 mg/kg or the interval reduced. Adalimumab and certolizumab are administered subcutaneously every 2 and 4 weeks, respectively. In the case of adalimumab dosing can be increased to weekly if there is suboptimal response.
 - The value of concomitant immunosuppression is contentious, given the opposite results of the SONIC and COMMIT studies. In resource-poor units regular scheduled maintenance therapy often remains a distant dream and episodic therapy is currently the only option (with the inherent issue of immunogenicity). If possible, AZA should be administered concomitantly, which will reduce immunogenicity and enhance efficacy (as per the SONIC study).
 - Infliximab is the only proven therapy in the treatment of fistulas based on adequately powered randomized controlled trials.
 - The risk of lymphoma is very low but remains a concern. Other cancers may be increased.
 - The risk of both minor and serious infections are concerns.
 - If patients fail or become intolerant to an anti-TNF a second anti-TNF can be effective.
- Antibiotics
 - Metronidazole and ciprofloxacin are the most commonly used antibiotics in CD.
 - Used for the treatment of CD complications (perianal disease, fistulas, inflammatory mass, bacterial overgrowth in the setting of strictures).
 - There has never been a randomized controlled trial proving the efficacy of metronidazole and/or ciprofloxacin in perineal fistulas but these are typically first-line therapies.
 - There is an increased risk for *C. difficile*-associated disease (CDAD) and patients presenting with flare of diarrheal disease should be checked for *C. difficile* and other fecal pathogens.
 - There are no data that any antibiotics are effective in UC but are used in the setting of fulminant colitis.
- Probiotics
 - IBD may be caused or aggravated by alterations in the gut flora.
 - While many patients may use probiotics there is no evidence that they are effective in either UC or CD.
 - There are a few studies that suggest that *E. coli* Nissle 1917 is not inferior to 5-ASA but response rates were low in these studies. VSL#3, which is a combination of 8 probiotics, has been shown to reduce flares of pouchitis (post-ileoanal pouch procedure in UC) in 2 Italian studies and 1 Italian/British study.
- Experimental agents (for example)
 - UC: antiadhesion molecules, anticytokine therapies, antiinflammatory proteins.
 - CD: antiadhesion molecules, anticytokine, and T-cell marker therapies, mesenchymal stem cells.
- Symptomatic therapy and supplements—antidiarrheals such as immodium if colitis is not fulminant; cholestyramine if past ileal resections
 - Analgesics such as acetaminophen or even codeine if acetaminophen insufficient.
 - Nutritional supplementation for those with malnutrition or during periods of reduced oral intake.
 - Vitamin B₁₂ replenishment for those who are deficient.
 - Vitamin D supplementation if area does not allow sun exposure for much of the year.
 - Routine vitamin D and calcium supplementation for steroid users.
 - Routine multivitamin supplementation for all.
 - For chronic iron deficiency anemia use parenteral iron (either as weekly intramuscular shots or dosing with IV iron) if oral iron is not tolerated.

Disease Status and Drug Therapy

See Table 9.

Surgical Treatment

IBD patients may require hospitalization for surgery or medically refractory disease—this accounts for at least half of direct costs attributable to IBD.

Surgery in CD

- 70%–75% of CD patients require surgery at some point to relieve symptoms if drug treatment fails or to correct complications.
- Surgery is rarely curative in CD—it recurs frequently after surgery.
- Surgery can, however, lead to long-lasting remission in some with CD.
- Surgical options are

TABLE 9. Overview Disease Status and Drug Therapy

	Distal UC	Extensive UC	CD
Mild	Rectal or oral 5-ASA Rectal GCS	Topical and Oral 5-ASA	Sulfasalazine or other 5-ASA for colonic disease only metronidazole or ciprofloxacin for perineal disease BUD for ileal and/or right colon disease
Moderate	Rectal or oral 5-ASA Rectal GCS	Topical and Oral 5-ASA	Oral GCS AZA or 6-MP MTX Anti-TNF
Severe	Rectal and oral 5-ASA Oral or intravenous GCS Rectal GCS	I.V. GCS I.V. CsA or I.V. infliximab	Oral or I.V. GCS Subcutaneous (sc) or I.M. MTX I.V. infliximab or s.c. adalimumab or s.c. certolizumab
Refractory	Oral or I.V. GCS + AZA or 6-MP	Oral or I.V. GCS + AZA or 6-MP or infliximab or CsA	I.V. infliximab s.c adalimumab s.c certolizumab
Quiescent	Oral or rectal 5-ASA Oral AZA or 6-MP	Oral 5-ASA Oral AZA or 6-MP	AZA or 6-MP or MTX
Perianal			Oral antibiotics AZA or 6-MP I.V. infliximab

5-ASA, 5-aminosalicylic acid; 6-MP, 6-mercaptopurine; AZA, azathioprine; BUD, budesonide; CsA, cyclosporine A; GCS, glucocorticosteroid; MTX, methotrexate.

Note: Budesonide only for mild-moderate ileal and/or proximal colon disease.

- Drainage of abscesses.
- Segmental resection.
- Bowel-sparing stricturoplasty.
- Ileorectal or ileocolonic anastomosis.
- Temporary diverting ileostomy/colostomy in severe perianal fistula.

Surgery in UC

- 25%–30% of UC patients may require surgery if medical treatment is not completely successful or in the presence of dysplasia.
- Surgical resection in UC is considered curative for the disease.
- Surgical options are
 - Temporary ileostomy.
 - Total proctocolectomy plus permanent ileostomy.
 - Ileal pouch–anal anastomosis (IPAA).

Surgery and Medication

- Corticosteroids: gradually reduce dosage to prevent surgical complications
 - Corticosteroids for <1 month: may stop abruptly after surgery.

- Corticosteroids (≥ 20 mg/day) for 1–3 months: reduce dose 5 mg/day each week after surgery.
- Corticosteroids for 3–6 months: reduce dose 2.5 mg/day each week.
- Corticosteroids for >6 months: reduce dose slowly with ≤ 1 mg/week once at 10 mg/day.
- Aim to minimize steroid dose prior to surgery when possible. Prednisone doses greater than 30 mg/day preoperatively are associated with poorer postoperative outcomes.
- Azathioprine: no increased risk in a perioperative setting.
- Perioperative anti-TNF α therapy with infliximab, adalimumab, or certolizumab
 - Suspect increased risk for emergency colectomy for acute severe colitis.
 - No increased risk in CD.
- Postoperative maintenance in CD with oral 5-ASA or 6-MP/AZA to reduce frequency and severity of recurrences. Best data for maintenance are for metronidazole: it is cheap and can be considered in resource-poor settings (although limited by dysgeusia and neuropathy side effects). By contrast, the data for 5-ASA are weak and it is more expensive.
- Stress importance of smoking cessation—the single most effective approach patients can take to reduce recurrence in CD.

Cascades: IBD Management

Cascade 2: UC Management[†]

Level 1: Limited resources.

1. In endemic area and limited access to diagnostics give a course of antiamoeba therapy.
2. In endemic area for TB consider trial of anti-TB therapy for 1 month to determine response.
3. Sulfasalazine (cheapest) for all mild to moderate colitis and for maintenance of remission. Different mesalazine preparations are available including Asacol 800 mg, Mezavant 1200 mg pills, and Pentasa 2 g sachet. These larger doses can facilitate better adherence and no sulfa SEs.
4. Steroid enemas for distal colon disease.[‡]
5. Oral prednisone for moderate to severe disease (acute severe disease requires IV steroids).
6. If acute severe colitis unresponsive to steroids IV or chronic steroid-resistant or -dependent colitis consider colectomy. This decision needs to be made in timely fashion in acute severe UC. Consider either Oxford or Sweden predictors of outcome on day 3 of IV steroids.
7. CMV should be actively sought in refractory disease.
8. 5-ASA for failure to maintain remission. Azathioprine for steroid dependence. Methotrexate can be considered if azathioprine not available or intolerance.

Level 2: If resources available then:

1. Treat TB and parasites when diagnosed first.
2. Sulfasalazine can be used for mild to moderate colitis.
3. Asacol 800 mg, Mezavant 1200 mg pills, and Pentasa 2 g sachet now available and can facilitate better adherence and no sulfa SEs.
4. 5-ASA enemas or suppositories for distal disease. Can be used for maintenance of remission in distal disease in lieu of oral 5-ASA. Steroid enemas are also an option but typically not for maintenance.
5. Combination therapy with oral and rectal 5-ASA may be more effective in active distal disease or even active proctitis.
6. If patients fail to maintain remission with 5-ASA then consider azathioprine or 6-MP/AZA; in case of azathioprine failures consider methotrexate.

[†]Steroid enemas can sometimes be made with locally available resources, sometimes at lower cost.

[‡]Some traditional Chinese medicines are deemed useful as an alternative medicine for anemia in China. These are not typically used in the West. Some Chinese agents suggested include powder of natural indigo, powder for treating throat disease (Xilei powder), Yunnan white drug, or oral prescription such as pulsatilla decoction, and some single component of Chinese medicine, such as Pulsatilla root, Coptis root, Amur corktree bark, Baikal skullcap root, and curcumin.

Level 3: If greater resources available:

1. Cyclosporine can be considered in acute severe colitis and
2. Infliximab can be considered for acute severe colitis or moderately severe steroid-dependent or resistant colitis.
3. Azathioprine or 6-MP.

Cascade 3: CD Management[†]

Level 1: Limited resources.

1. In endemic area and limited access to diagnostics give a course of antiamoeba therapy.
2. In endemic area for TB consider trial of anti-TB therapy for 1 month to determine response.
3. Sulfasalazine (cheapest) for all mild to moderate colitis and for maintenance of remission.
4. Steroid enemas[‡] for distal colon disease.
5. Trial of metronidazole for ileocolonic or colonic disease.
6. Oral prednisone for moderate to severe disease.
7. If short segment of small bowel disease, consider surgery.
8. Azathioprine or methotrexate.
9. Metronidazole for postoperative maintenance.

Level 2: If resources available then:

1. Treat TB and parasites when diagnosed first.
2. Sulfasalazine for mild to moderate active colonic CD.
3. Budesonide can be used for mild ileal or ileocolonic disease (right colon).
4. If patients fail to maintain remission after course of steroids then consider azathioprine (or 6-MP/AZA), in case of azathioprine failures, consider methotrexate.

Level 3: If greater resources available:

1. Infliximab or adalimumab or certolizumab can be considered for moderate to severe steroid-dependent or -resistant disease.
2. Immunosuppressive drugs like 6MP and AZA can also be very helpful in the treatment of fistula in CD.
3. Tacrolimus can be considered in anti-TNF failures.

[†]Steroid enemas can sometimes be made with locally available resources, sometimes at lower cost.

[‡]Some traditional Chinese medicines are deemed useful as an alternative medicine for anemia in China. These are not typically used in the West. Some Chinese agents suggested include powder of natural indigo, powder for treating throat disease (Xilei powder), Yunnan white drug, or oral prescription such as pulsatilla decoction, and some single component of Chinese medicine, such as Pulsatilla root, Coptis root, Amur corktree bark, Baikal skullcap root, and curcumin.

Cascade 4: Perineal Fistulas

Level 1: Limited resources.

1. Metronidazole.
- 1a. Surgery if abscess is present.
2. Ciprofloxacin.
3. Combination of metronidazole and ciprofloxacin. These antibiotics can be used for maintenance of fistula closure if tolerated over the long term.
4. Surgery—should be considered early and if long-term maintenance of antibiotics is required.

Level 2: More resources available.

1. Metronidazole.
- 1a. Surgery if abscess is present.
2. Ciprofloxacin.
3. Combination of metronidazole and ciprofloxacin. These antibiotics can be used for maintenance of fistula closure if tolerated over the long term.

4. Surgery should be considered early and if long-term maintenance of antibiotics is required.
5. AZA/6MP for maintenance of fistula closure.

Level 3: If greater resources available:

1. Metronidazole.
- 1a. Surgery if abscess is present.
2. Ciprofloxacin.
3. Combination of metronidazole and ciprofloxacin. These antibiotics can be used for maintenance of fistula closure if tolerated over the long term.
4. Surgery—should be considered early and if long-term maintenance of antibiotics is required and particularly if fistula is simple.
5. AZA/6MP for maintenance of fistula closure.
6. Infliximab.
7. Adalimumab for infliximab failures or as an alternative to infliximab primarily.
8. Surgery for complex fistulas.