MINISTRY OF HEALTH OF THE REPUBLIC OF MOLDOVA

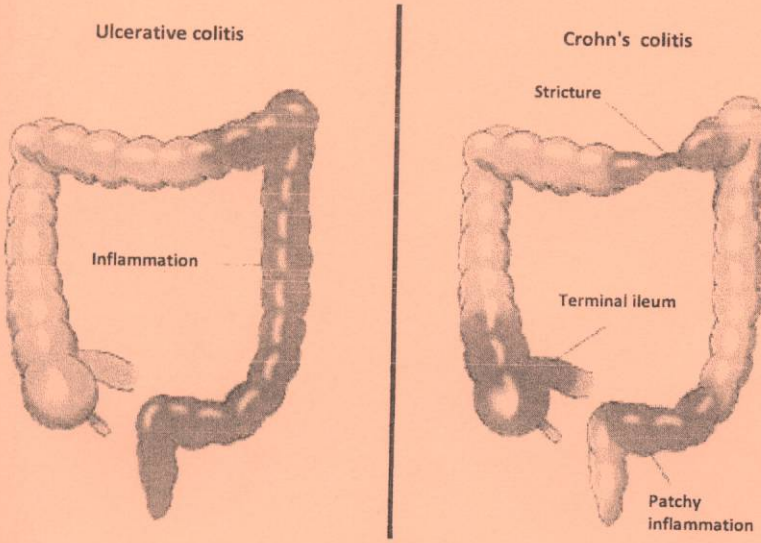
PUBLIC INSTITUTION
STATE UNIVERSITY OF MEDICINE AND PHARMACY
NICOLAE TESTEMITANU

Angela PELTEC Adela TURCANU

INFLAMMATORY BOWEL DISEASE

BASIC FACTS

Guideline for students



CHISINAU
2014

MINISTRY OF HEALTH OF THE REPUBLIC OF MOLDOVA

PUBLIC INSTITUTION
STATE UNIVERSITY OF MEDICINE AND PHARMACY
NICOLAE TESTEMITANU

Angela PELTEC Adela TURCANU

INFLAMMATORY BOWEL DISEASE

BASIC FACTS

Guideline for students

CHISINAU
CEP *Medicina*
2014

CZU 616.34-002(075.8)
P 49

Recommended for publishing by Central Methodical Council of the PI State University of Medicine and Pharmacy *Nicolae Testemiţanu*, protocol no 3 from 06.03.2014

Authors:
Angela Peltec, MD, associate professor
Adela Turcanu, MD, associate professor

Referenced:
Tudor Timiş, MD, associate professor
Elina Berliba, MD, associate professor

Redactor: *Nadejda Şamşurina*
Type-setting: *Iulia Don*

DESCRIEREA CIP A CAMEREI NAŢIONALE A CĂRŢII

Peltec, Angela.
Inflammatory bowel disease. Basic facts: Guideline for students / Angela Peltec, Adela Turcanu; Public Inst. State Univ. of Medicine and Pharmacy *Nicolae Testemiţanu*. – Chişinău: CEP *Medicina*, 2014. – 88 p.
Bibliogr.: p. 74-80. 50 ex.
ISBN 978-9975-118-45-3.
616.34-002(075.8)
P 49

ISBN 978-9975-118-45-3

BACKGROUND

Inflammatory bowel disease (IBD) is an idiopathic disease caused by a dysregulated immune response to host intestinal microflora, probably involving an immune reaction of the body to its own intestinal tract

The 2 major types of IBD are ***ulcerative colitis*** (UC), which is limited to the colon, and ***Crohn`s disease*** (CD), which can involve any segment of the gastrointestinal (GI) tract from the mouth to the anus, involves "skip lesions," and is transmural. There is a genetic predisposition to IBD, and patients with this condition are more prone to the development of malignancy.

Although both ulcerative colitis and Crohn`s disease have distinct pathologic findings, approximately 10-15% of patients cannot be classified definitively into either type; in such patients, the disease is labeled as ***indeterminate colitis***.

The rectum is always involved in ulcerative colitis, and the disease primarily involves continuous lesions of the mucosa and the submucosa. Severe colitis noted during colonoscopy in a patient with inflammatory bowel disease. The mucosa is grossly denuded, with active bleeding noted. Stricture in the terminal ileum is noted during colonoscopy in a patient with inflammatory bowel disease.

When the patient is symptomatic due to active inflammation, the disease is considered to be in an active stage (the patient is having a flare of IBD). Both ulcerative colitis and Crohn`s disease usually have waxing and waning intensity and severity. In many cases, symptoms correspond well to the degree of inflammation present for either disease, although this is not universally true.

Ulcerative colitis and Crohn`s disease share many extraintestinal manifestations. Eye-skin-mouth-joint extraintestinal manifestations (eg, oral aphthae, erythema nodosum, large-joint arthritis, and episcleritis) reflect active disease, whereas pyoderma gangrenosum, primary sclerosing cholangitis (PSC), ankylosing spondylitis, uveitis, kidney stones,

and gallstones may occur in quiescent disease. (1) Systemic symptoms are common in IBD and include fever, sweats, malaise, and arthralgias.

EPIDEMIOLOGY

International statistics

Before 1960, the incidence of ulcerative colitis was several times higher than that of Crohn's disease. More recent data suggest that the incidence of Crohn's disease is approaching that of ulcerative colitis. (*Figure 1, 2*). Internationally, the incidence of IBD is approximately 0.5-24.5 cases per 100,000 person-years for ulcerative colitis and 0.1-16 cases per 100,000 person-years for Crohn's disease. Overall, the prevalence for IBD is 396 cases per 100,000 persons annually (2).

The highest rates of IBD are assumed to be in ***developed countries***, and the lowest are considered being in developing regions; ***colder-climate regions*** and ***urban areas*** have a greater rate of IBD than those of warmer climates and rural areas.

Annually, an estimated 700,000 physician visits and 100,000 hospitalizations are due to IBD (2). In the United States approximately 1-2 million people have ulcerative colitis or Crohn's disease.

Time-trend analyses showed statistically significant increases in the incidence of IBD over time (3). The prevalence and incidence of Crohn's disease and ulcerative colitis in different regions of the word is showen in Table 1.

Table 1

Prevalence and incidence of Crohn's disease and ulcerative colitis in different regions of the word (3)

	Crohn's disease		Ulcerative colitis	
	Prevalence (No per 100.000 persons)	**Annual incidence (No per 100.000 persons)**	**Prevalence**	**Incidence**
North America	319	20,0	249	19,2
Europe	322	12,7	505	24,3
Asia and Middle East		5,0		6,3

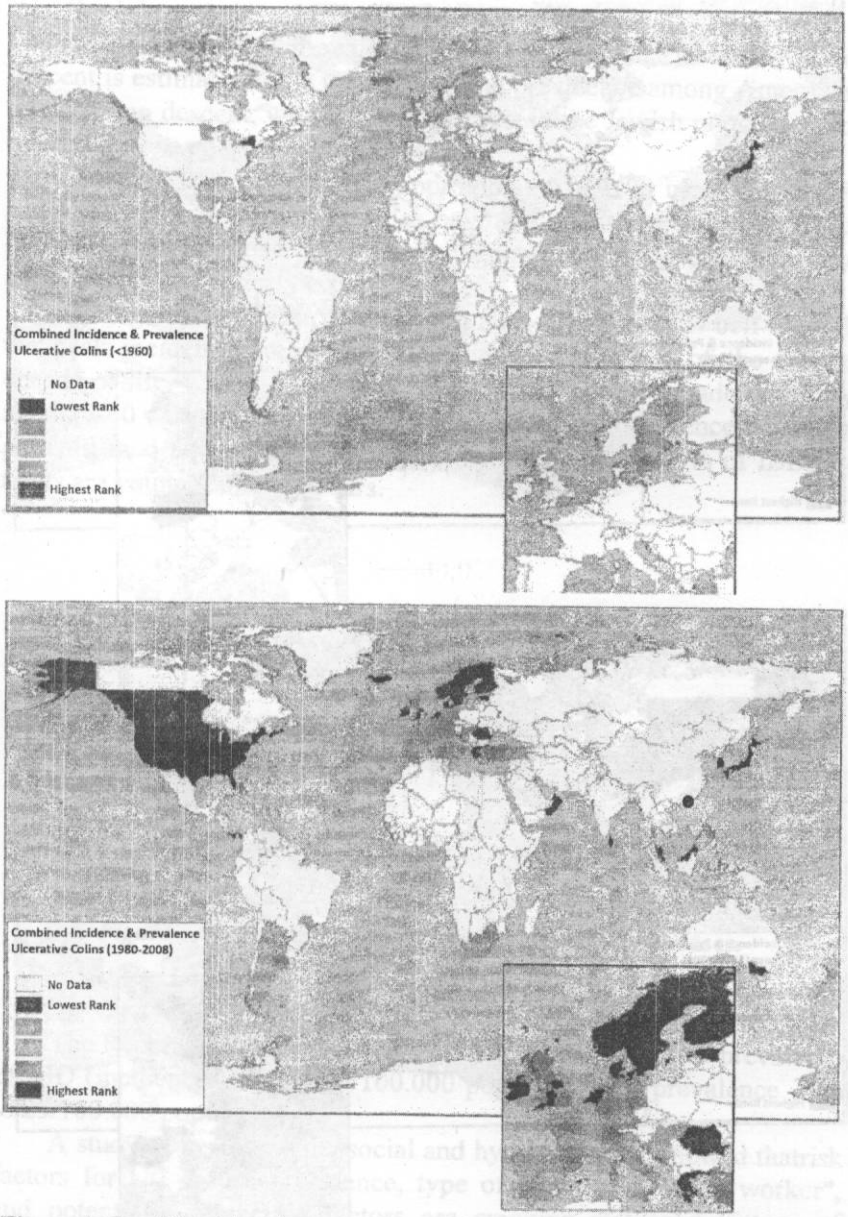


Figure 1. **Combined incidence and prevalence of ulcerative colitis before 1960 and nowadays** (Source: Gastroenterology 2012, AGA institute).

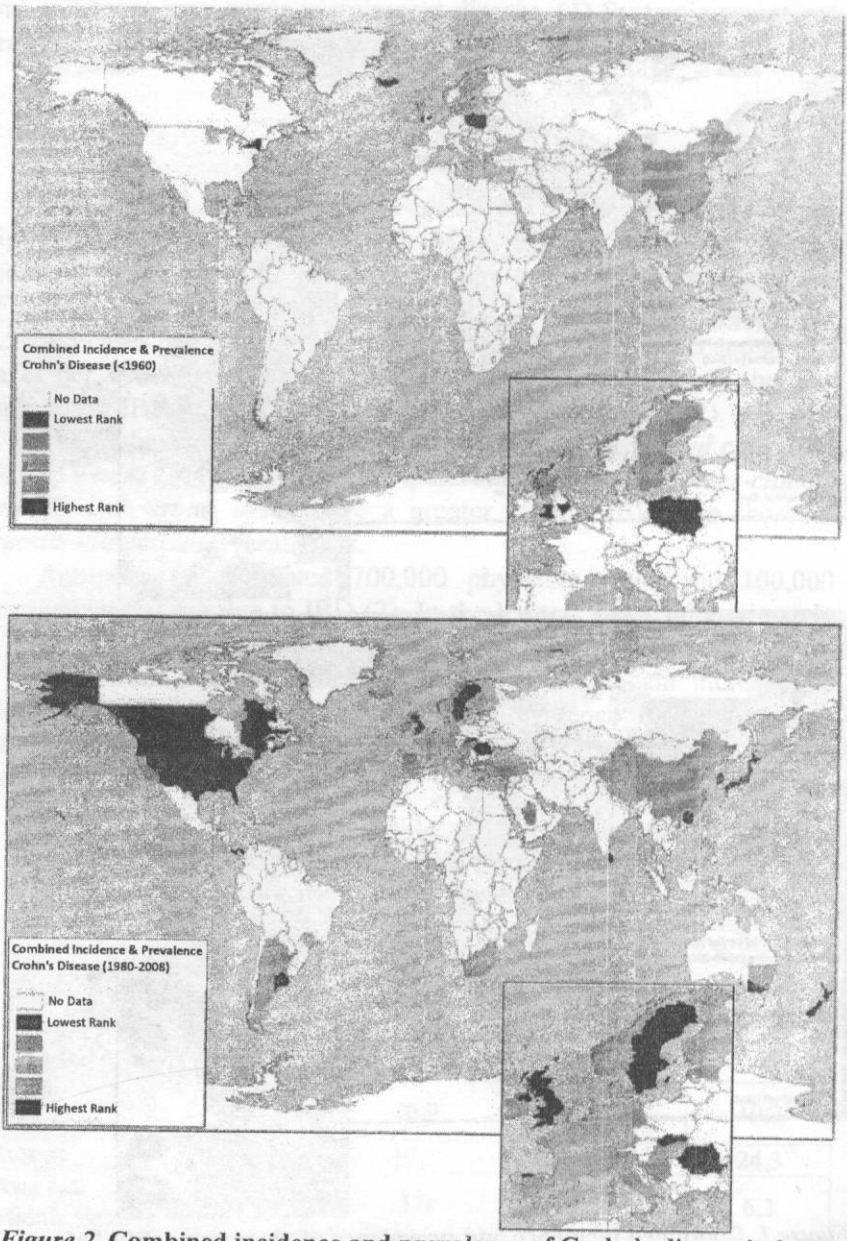


Figure 2. **Combined incidence and prevalence of Crohn`s disease before 1960 and nowadays** (Source: Gastroenterology 2012, AGA institute).

Racial, sexual, and age-related differences

The incidence and prevalence of IBD among Americans of African descent is estimated to be the same as the prevalence among Americans of European descent, with the highest rates in the Jewish populations of middle European extraction (4).

The male-to-female ratio is approximately 1:1 for ulcerative colitis and Crohn's disease, with females having a slightly greater incidence. Both diseases are most commonly diagnosed in young adults (ie, late adolescence to the third decade of life).

The age distribution of newly diagnosed IBD cases is bell-shaped; the peak incidence occurs in people in the early part of the second decade of life, with the vast majority of new diagnoses made in people aged 15-40 (*Figure 3*). A second, smaller peak in incidence occurs in patients aged 55-65 and is increasing. Approximately 10% of IBD patients are younger than 18 years.

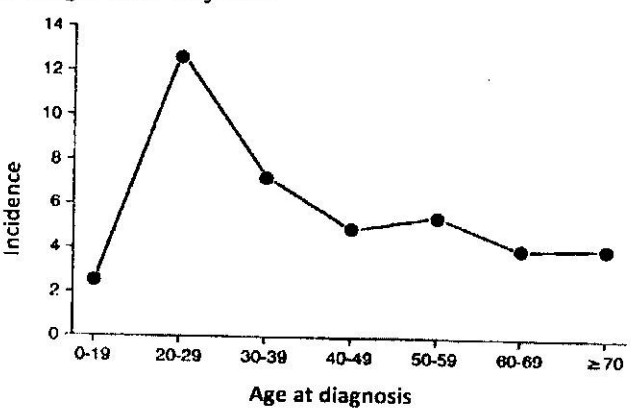


Figure 3. **Age distribution of newly diagnosed IBD cases.**

Statistics from the Republic of Moldova

The Republic of Moldova is a regionwitha relatively low prevalence of IBD (incidence – up to 4,6/100.000 population and prevalence – up to 25/100.000 population).

A study of demographic, social and hygienic factorsshowed thatrisk factors for UC areurbanresidence, type of activity – "office worker", and potentially protective factors are smoking statusand history of appendectomy.

Evaluation ofclinical features of onset showed that more than half of patients had of a gradual onset with minimal activity, resulting in a delayed diagnosis, which delayed specific treatment.

In the last decadeno significant increase ofin the incidence and prevalence of IBD was noted. The recorded average age at onset of deviation peak incidence was increased from 21-40 years to 31-50 yearsin last three decades (5).

ETIOLOGY

Three characteristics define the etiology of IBD:

1) Genetic predisposition;

2) An altered, dysregulated immune response; and

3) An altered response to gut microorganisms.

However, the triggering event for the activation of the immune response in IBD has yet to be identified. Possible factors related to this event include a pathogenic organism (as yet unidentified) or an inappropriate response (ie, failure to downgrade the inflammatory response to an antigen, such as an alteration in barrier function).

Environmental risk factor

Several environmental risk factors have been proposed to contribute to IBD pathogenesis, but the results are inconsistent. The most consistent association described has been smoking, which increases the risk of Crohn's disease. However, current smoking protects against ulcerative colitis, whereas former smoking increases the risk of ulcerative colitis.

Dietary factors have also been inconsistently described. In some studies, high fiber intake and high intake of fruits and vegetables appear protective against IBD (6). High animal protein intake (meat or fish) carried a higher risk of IBD (7) (*Table 2*).

Table 2

Environmental risk factors

Risk factors	Characteristics
Pathogenic organism	as yet unidentified
Intraluminal antigen	cow's milk protein (breast feeding – protector factors)
Appropriate immune response to an *intraluminal antigen* and an *inappropriate response* to a similar *antigen* is present on *intestinal epithelial* cells	alteration in barrier function
High animal protein intake (meat or fish)	associated with a higher risk of inflammatory bowel disease

Genetics

Persons with IBD have a genetic susceptibility for the disease (8). These genes appear to be permissive, they are not causative (the present of the genedoes not necessarily mean the disease will develop) (*Table 3*).

Table 3

Genes with functions associated with inflammatory bowel disease

Gene	Chromosome (human)	Function
Crohn's disease		
CARD15	16	NFkB activation and/or regulation, killing of intracellular pathogens. Paneth-cell function, (α-defensin production)
SLC22A4 & SLC22A5	5	Organic cation, carnitine transporters, possibly transport xenobiotic substances
DLG5	10	Epitheliel scaffolding protein
PPARG	3	Intracellular inhibitor of NFkB and cellular activation
Ulcerative colitis		
MDR1	7	Efflux transporter for drugs and, possibly, xenobiotic compounds

Abbreviations: *CARD15*, caspase recruitment domain family, member 15 (formerly NOD2); *DLG5*, discs large homolog 5 (Drosophila); *MDR1*, multigrug resistance 1; *PPARG*, peroxisome proliferative-activated gamma; *SLC22A4* and *SLC22A5*, solute carrier family 22 (organic cation transporter), membres 4 and 5 (formerly OCTN1 and OCTN2).

First-degree relatives have a 5- to 20-fold increased risk of developing IBD, as compared with persons from unaffected families (9). ***Twin studies*** show a concordance of approximately 70% in identical twins, versus 5-10% in nonidentical twins. ***Monozygous twin studies*** show a high concordance for Crohn's disease but less so for ulcerative colitis.

Crohn's disease

An early discovery of chromosome 16 (*IBD1* gene) led to the identification of 3 single nucleotide polymorphisms (2 missense, 1 frameshift) in the *NOD2* gene (now called *CARD15*) as the first gene (*CARD15*) clearly associated with IBD (as a susceptibility gene for Crohn's disease).

CARD15 is a polymorphic gene involved in the innate immune system. The CARD15 genotype is associated not only with the onset of disease but also with its natural history. These gene products appear to be involved in the intracellular innate immune pathwaysthat recognize microbial products in the cytoplasm.

Another early genome-wide association study dealt with at Jewish and non-Jewish case-control cohorts and identified 2 single nucleotide polymorphisms in the ***IL23R*** gene, which encodes 1 subunit of the interleukin-23 receptor protein (10). These gene products appear to be involved in regulating adaptive immunity.

The interlectin gene (*ITLN1*) is expressed in the small bowel and colon, and it is also involved in recognition of certain microorganisms in the intestine. An association was found with the ***ATG16L1 gene,*** which encodes the autophagy-related 16-like protein, which is involved in the autophagosome pathway that processes intracellular bacteria (11).

Ulcerative colitis

The genetic predisposition for ulcerative colitis appears to be lesser in magnitude than Crohn's disease but consists of a set of genetic susceptibilities that shows significant overlap with Crohn's disease

Additional susceptibility loci for ulcerative colitis have been found on 1p36 and 12q15. The 1p36 single nucleotide polymorphism is near the ***PLA2G2E*** **gene**, which is involved in releasing arachidonic acid from membrane phospholipids, leading to other proinflammatory lipids. The first 12q15 signal is located near the ***interferon (IFN)-gamma, interleukin (IL)-26, and IL-22 genes,*** whereas the second 12q15 signal is located in IL-26. These genes play roles in the immune response to pathogens as well as the tissue inflammation processes. (12)

Smoking

The risk of developing ulcerative colitis is higher in nonsmokers and former smokers than in current smokers. The onset of ulcerative colitis occasionally appears to coincide with smoking cessation; however, this does not imply that smoking would improve the symptoms of ulcerative colitis. There has been limited success with the use of nicotine patches. Crohn's disease patients have a higher incidence of smoking than the general population, and smoking appears to lessen the response to medical therapy.

PATHOPHYSIOLOGY

The common end pathway of ulcerative colitis is inflammation of the mucosa of the intestinal tract, causing ulceration, edema, bleeding, and fluid and electrolyte loss (13) In several studies, genetic factors appeared to influence the risk of IBD by causing a disruption of epithelial barrier integrity, deficits in autophagy, (14) deficiencies in innate pattern recognition receptors, and problems with lymphocyte differentiation, especially in Crohn`s disease (*Figure 4*).

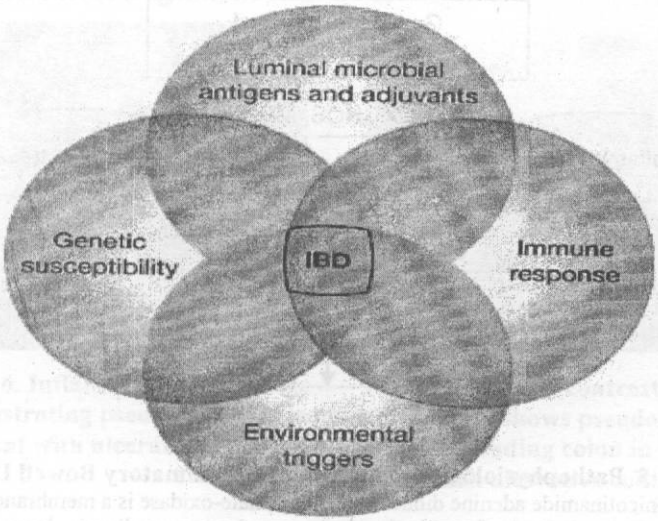


Figure 4. **Interaction of various factors contributing to chronic intestinal inflammation in a genetically susceptible host.**

Genetic susceptibility is influenced by the luminal microbiota, which provide antigens and adjuvants that stimulate either pathogenic or protective immune responses. Environmental triggers are necessary to initiate or reactivate disease expression. Abbreviation: IBD, inflammatory bowel diseases. (SartorRB(2006) Mechanisms of Disease: pathogenesis of Crohn's disease and ulcerative colitis *Nat Clin Pract Gastroenterol Hepatol* 3: 390–407 doi:10.1038/ncpgasthep0528).

Inflammatory mediators have been identified in IBD, and considerable evidence suggests that these mediators play an important role in the pathologic and clinical characteristics of these disorders. Cytokines, which are released by macrophages in response to various antigenic stimuli, bind to different receptors and produce autocrine, paracrine, and endocrine effects (*Figure 5*). Cytokines differentiate lymphocytes into different types of T-cells. Helper T-cells, type 1 (Th-1), are associated

principally with Crohn's disease, whereas Th-2 cells are associated principally with ulcerative colitis. The immune response disrupts the intestinal mucosa and leads to a chronic inflammatory process (15).

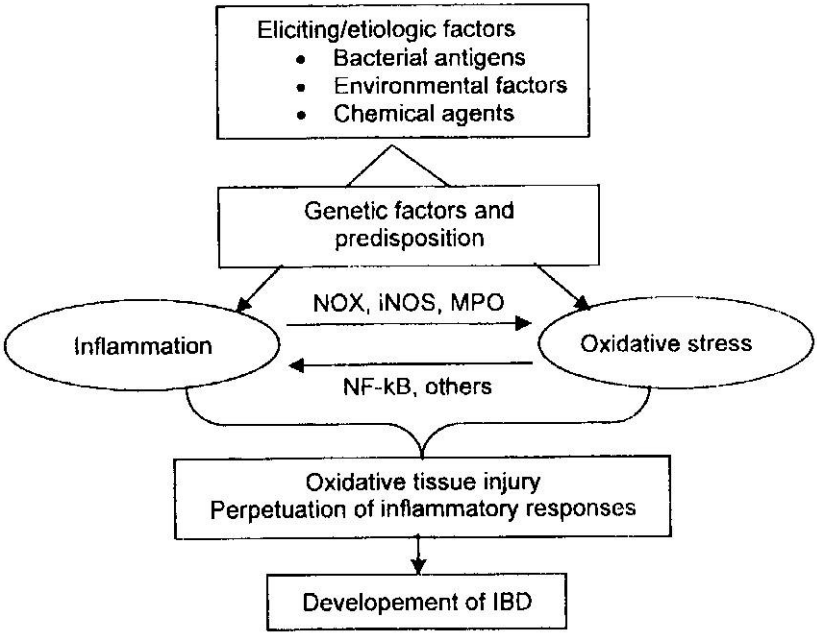


Figure 5. **Pathophysiology mechanism of Inflammatory Bowell Disease** (NOX –nicotinamide adenine dinucleotide phosphate-oxidase is a membrane-bound enzymecomplex, it can be found in the plasma membrane as well as in the membranes ofphagosomesused byneutrophilwhite blood cell – NADPH oxidase; iNOS – inducible nitric oxide synthase enzymes – exposure to microbial products, such as lipopolysaccharide (LPS) and dsRNA or proinflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) induces the expression of iNOS gene in various inflammatory and tissue cells; MPO - mieloperoxidaza; NF-kB –nuclear factor B – play a crucial role in inflammatory disorders).

Ulcerative colitis

In **ulcerative colitis**, inflammation begins in the rectum and extends proximally in an uninterrupted fashion to the proximal colon and could eventually involve the entire length of the large intestine. The rectum is always involved in ulcerative colitis; and unlike in Crohn's disease, there are no "skip areas" (ie, normal areas of the bowel interspersed with diseased areas).

The disease remains confined to the rectum in approximately 25% of cases, and in the remainder of cases, ulcerative colitis spreads proximally and contiguously. Pancolitis occurs in 10% of patients. The distal terminal ileum may become inflamed in a superficial manner, referred to as backwash ileitis. Even with less than total colonic involvement, the disease is strikingly and uniformly continuous. As ulcerative colitis becomes chronic, the colon becomes a rigid foreshortened tube that lacks its usual haustral markings, leading to the lead-pipe appearance observed on barium enema (*Figure 6, 7*).

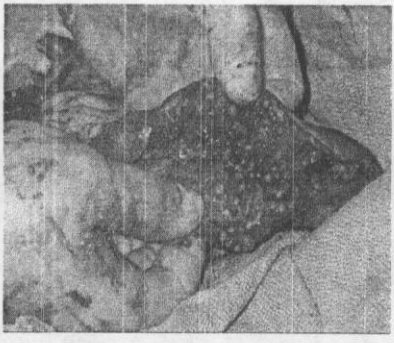


Figure 6. **Inflamed colonic mucosa demonstrating pseudopolyps in a patient with ulcerative colitis.**

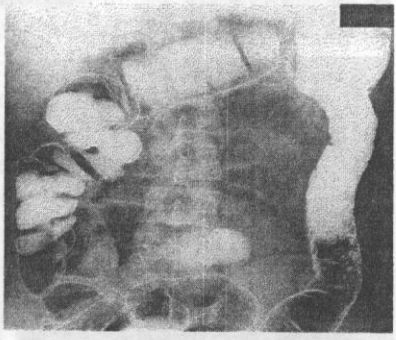


Figure 7. **Double-contrast barium enema study shows pseudopolyposis of the descending colon in a patient with ulcerative colitis.**

Crohn`s disease

Crohn`s disease can affect any portion of the gastrointestinal tract, from the mouth to the anus, and causes 3 patterns of involvement: inflammatory disease, strictures, and fistulas. This disease consists of segmental involvement by a nonspecific granulomatous inflammatory process. The most important pathologic feature of Crohn`s disease is that it is transmural, involving all layers of the bowel, not just the mucosa and the submucosa, which is characteristic of ulcerative colitis. Furthermore, Crohn`s disease is discontinuous, with skip areas interspersed between 2 or more involved areas.

In 35% of cases, Crohn`s disease occurs in the ileum and colon; in 32%, solely in the colon; in 28%, in the small bowel; and in 5%, in the gastroduodenal region. (16) Late in the disease, the mucosa develops a

cobblestone appearance, which results from deep, longitudinal ulcerations interlaced with intervening normal mucosa (*Figure 8*).

Diarrhea, cramping, and abdominal pain are common symptoms of Crohn`s disease in all of the above locations, except for the gastroduodenal region, in which anorexia, nausea, and vomiting are more common.

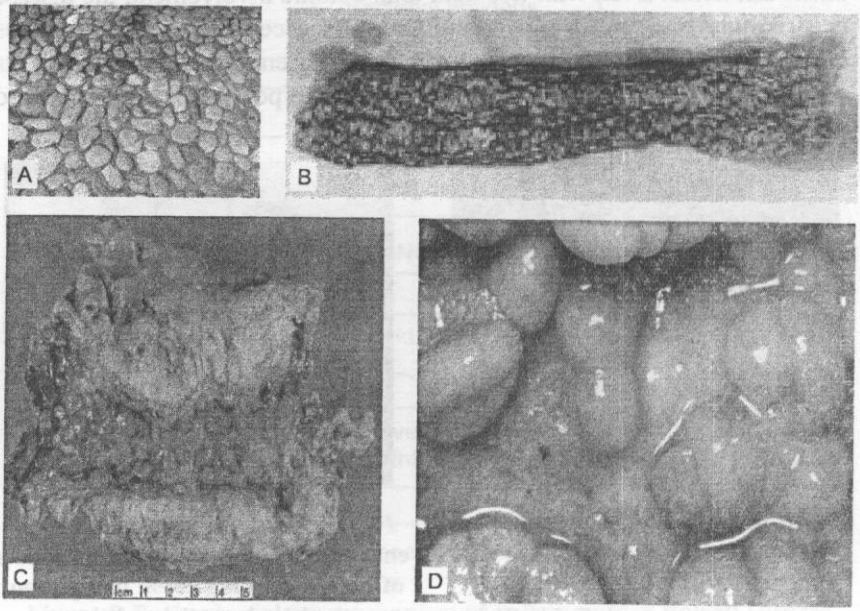


Figure 8. **The mucosa develops a cobblestone appearance of the mucosa of the terminal ileum in a patient with Crohn`s disease.**
(*A* – cobblestone, Luisburg Square, Beacom Hill Boston USA; *B* – resected jejunum in a patient with known Crohn`s disease demonstrating prominent cobblestone appearance image courtesy of Jaroslav Cehovssky; *C* – cobblestone change of the mucosa of the terminal ileum in a patient with Crohn`s disease, communicating fissures and crevices in the mucosa separate islands of more intact, edematous epithelium; *D* – endoscopic pattern of cobblestone appearance, tissues may develop shallow, crater like areas or deeper sores and a cobblestone pattern).

Rectal sparing is a typical but not constant feature of Crohn`s disease. However, anorectal complications (eg, fistulas, abscesses) are common. Much less commonly, Crohn`s disease involves the more proximal parts of the GI tract, including the mouth, tongue, esophagus, stomach, and duodenum.

Cholelithiasis and nephrolithiasis

The incidence of gallstones and kidney stones is increased in Crohn`s disease because of malabsorption of fat and bile salts. Gallstones are formed because of increased cholesterol concentration in the bile, which is caused by a reduced bile salt pool.

Patients who have Crohn`s disease with ileal disease or resection are also likely to form calcium oxalate kidney stones. With the fat malabsorption, unabsorbed long-chain fatty acids bind calcium in the lumen. Oxalate in the lumen is normally bound to calcium. Calcium oxalate is poorly soluble and poorly absorbed; however, if calcium is bound to malabsorbed fatty acids, oxalate combines with sodium to form sodium oxalate, which is soluble and is absorbed in the colon (enteric hyperoxaluria). The development of calcium oxalate stones in Crohn`s disease requires an intact colon to absorb oxalate. Patients with ileostomies generally do not develop calcium oxalate stones, but they may develop uric acid or mixed stones (17).

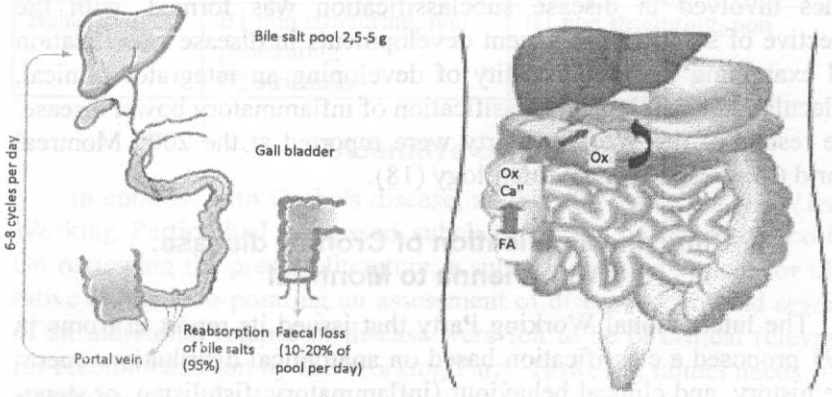


Figure 9. **Pathophysiology mechanisms of cholelithiasis and nephrolithiasis in case of IBD.**

CLASSIFICATION

Inflammatory bowel disease encompasses two idiopathic, chronic, inflammatory diseases: Crohn's disease and ulcerative colitis. Crohn's disease and ulcerative colitis are disorders of unknown cause, involving genetic and immunological influence on the gastrointestinal tract's ability

to distinguish foreign from self-antigens. They share many overlapping epidemiological, clinical, and therapeutic characteristics. In some patients it is not possible to distinguish which form of inflammatory bowel disease is present (*Figure 10*).

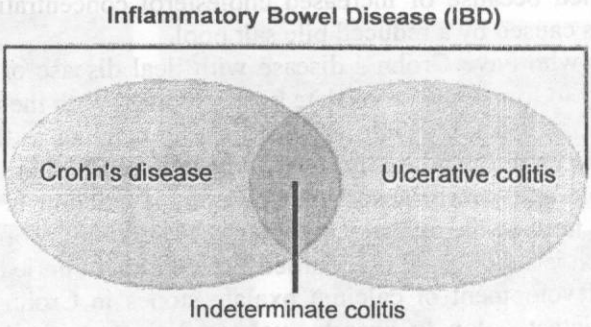


Figure 10. **Classification of IBD.**

In 2003, a Working Party of investigators with an interest in the issues involved in disease subclassification was formed, with the objective of summarising recent developments in disease classification and examining the practicability of developing an integrated clinical, molecular, and serological classification of inflammatory bowel disease. The results of the Working Party were reported at the 2005 Montreal World Congress of Gastroenterology (18).

Clinical classification of Crohn's disease: from Vienna to Montreal

The International Working Party that issued its report in Rome in 1991 proposed a classification based on anatomical distribution, operative history, and clinical behaviour (inflammatory, fistulising, or stenotic disease). However, this classification was felt inappropriate for clinical application in the following years, and the World Congress of Gastroenterology in Vienna in 1998 provided an opportunity for reconsidering and reanalysis of this classification (19). The resulting Vienna classification of Crohn's disease considered age of onset (A), disease location (L), and disease behaviour (B) as the predominant phenotypic elements. The Montreal revision of the Vienna classification has not changed the

three predominant parameters of age at diagnosis, location, and behaviour, but modifications within each of these categories have been made (20).

With respect to age of onset, the Montreal classification allows for early onset of disease to be categorized separately as a new A1 category for those with age of diagnosis at 16 years or younger, whereas A2 and A3 account for age of diagnosis at 17–40 years and >40 years, respectively (*Table 4*).

Table 4

Vienna and Montreal classification for Crohn's disease

	Vienna	Montreal
Age at diagnosis	A1 below 40 y A2 above 40 y	A1 below 16 y A2 between 17 and 40 y A3 above 40 y
Location	L1 ileal L2 colonic L3 ileocolonic L4 upper	L1 ileal L2 colonic L3 ileocolonic L4 isolated upper disease*
Behaviour	B1 non stricturing, non penetrating B2 stricturing	B1 non stricturing, non penetrating B2 stricturing

Ulcerative colitis

In contrast with Crohn's disease, neither the Rome nor the Vienna Working Parties had addressed subclassification of ulcerative colitis. On reviewing the present literature, a subclassification system for ulcerative colitis incorporating an assessment of disease extent and severity of an individual relapse of disease were felt to be of critical relevance for recommendation by the Working Party. However, unmet needs were clearly apparent in discussion, of which the most acute appeared to be the need for a classification of longitudinal disease progression, or disease behaviour over time-that is, the frequency of disease relapse and course of disease during the natural history.

The Montreal classification of disease extent of ulcerative colitis allows extent to be defined into three subgroups (*Table 5*).

The subclassification was felt to have clear biological relevance in terms of the response of patients to medical therapy (differential response to topical therapy), and also to be validated by the natural history

of the disease, with respect to rates of medication usage, hospitalization, or colectomy. Moreover, the risk of colorectal malignancy was also felt to provide further validation for this subclassification. In addition, numerous studies show association of specific serological and genetic markers with extensive ulcerative colitis, making this subset of particular importance in the study of its pathophysiology (21, 22).

Table 5

Montreal classification of extent of ulcerative colitis (UC)

Extent		Anatomy
E1	Ulcerative proctitis	Involvement limited to the rectum (that is, proximal extent of inflammation is distal to the rectosigmoid junction)
E2	Left sided UC (distal UC)	Involvement limited to a proportion of the colorectum distal to the splenic flexure
E3	Extensive UC (pancolitis)	Involvement extends proximal to the splenic flexure

The major drawback of the extent based classification system was clearly identified to be instability of disease extent over time, once again underlining the dynamic nature of inflammatory bowel disease. Progression of disease extent over time, together with regression, has been well identified and accepted. The actual risk of proximal extension of proctitis over 10 years is estimated to be as great as 41–54% (18). Progression of left sided colitis may be even higher. The contrary observation is also valid-that disease extent may regress over time, with regression rates estimated from a crude rate of 1.6% to an actual rate of 71% after 10 years (18). In light of this, the Montreal classification proposes the maximal extent of involvement as the critical parameter.

The Working Party has suggested the classification of severity of relapse into four disease activity/severity categories (*Table 6*).

The term fulminant colitis is in variable use, and the Working Party felt that the research agenda in ulcerative colitis must address whether this term has prognostic, value or clinical utility, contrasted with severe relapse of ulcerative colitis, or should be abandoned.

At the present time, evidence to introduce age of onset as a separate subgroup in ulcerative colitis was felt to be unproven, either with respect to clinical utility or in a basic research agenda. Other issues that

clearly require consideration in a research agenda would be the need for separate classification of colonic disease associated with sclerosing cholangitis.

Table 6

Montreal classification of severity of ulcerative colitis (UC)

Severity		Definition
S0	Clinical remission	Asymptomatic
S1	Mild UC	Passage of four or fewer stools/day (with or without blood), absence of any systemic illness, and normal inflammatory markers (ESR)
S2	Moderate UC	Passage of more than four stools per day but with minimal signs of systemic toxicity
S3	Severe UC	Passage of at least six bloody stools daily, pulse rate of at least 90 beats per minute, temperature of at least 37,5°C, haemoglobin of less than 10,5 g/100 ml, and ESR of at least 30 mm/h

ESR erythrocyte sedimentation rate.

Indeterminate colitis

There is considerable confusion about the appropriate use of the term indeterminate colitis. The Working Party reviewed the initial definition introduced by *Ashley Price* in 1978 (23). *Price* suggested that the diagnosis be made only following colectomy in patients in whom the features were not sufficient to allow a diagnosis of either Crohn's disease or ulcerative colitis but were sufficient to allow a diagnosis of inflammatory bowel disease affecting the colon. In subsequent years, the use of the term has been widened by clinicians to allow for patients in whom inflammatory bowel disease affecting the colon is apparent on clinical and endoscopic features but in whom histology and all other clinical parameters do not allow a clear diagnosis of either Crohn's disease or ulcerative colitis.

The Montreal Working Party has recommended that the term "indeterminate colitis" should be reserved only for those cases where colectomy has been performed and pathologists are unable to make a definitive diagnosis of either Crohn's disease or ulcerative colitis after full examination. In contrast, the term "inflammatory bowel disease,

type unclassified" (IBDU) is suggested for patients in whom there is evidence on clinical and endoscopic grounds for chronic inflammatory bowel disease affecting the colon, without small bowel involvement, and no definitive histological or other evidence to favour either Crohn's disease or ulcerative colitis. In these patients, clearly infection would have been ruled out before the term IBDU might be applied.

The Working Party discussed the prospects for the use of serological and genetic markers in refining the classification of indeterminate colitis and IBDU further. Both established serological markers (anti-Saccharomyces cerevisiae antibody (ASCA), antineutrophil cytoplasmic autoantibody (ANCA)) and novel markers currently emerging (OmpC, cBir flagellin, I2) were felt to carry the potential for helping further the understanding of the classification of these entities (22). In addition, it was felt strongly that the increasing use of capsule endoscopy, and novel diagnostic methods in the relatively near future, lead to a further need to revisit this classification scheme.

PRESENTATION

History

The manifestations of IBD generally depend on the area of the intestinal tract involved. The *commonly experienced symptoms of Crohn's disease* include *recurrent abdominal pain and diarrhea.* Sometimes, the diagnosis may be delayed by several months to a few years, as these symptoms are not specific for IBD. Patients with IBD have irritable bowel syndrome (IBS), cramping, irregular bowel habits, and passage of mucus without blood or pus.Fifty percent of patients with Crohn's disease may present with *perianal disease* (eg, fistulas, abscesses). Occasionally, *acute right lower quadrant pain and fever,* mimicking appendicitis or intestinal obstruction, may be noted.

Grossly bloody stools, occasionally with tenesmus, although typical of ulcerative colitis, are less common in Crohn's disease. Stools may be formed, but loose stools predominate if the colon or the terminal ileum is involved extensively.

Systemic symptoms are common in IBD and include *weight loss, fever, sweats, malaise, and arthralgias.* A low-grade fever may be the first warning sign of a flare. Patients are commonly fatigued, which is often related to the pain, inflammation, and anemia that accompany disease activity. Weight loss is observed more commonly in Crohn's

disease than in ulcerative colitis because of the malabsorption associated with small bowel disease, or small bowel disease may act as an appetite deterrent. In addition, patients may reduce their food intake in an effort to control their symptoms.

Recurrences may occur with *emotional stress, infections* or other *acute illnesses, pregnancy, dietary problems, use of cathartics or antibiotics, or nonadherence to therapy.*

The World Gastroenterology Organization (WGO) indicates the following symptoms may be associated with inflammatory damage in the digestive tract (24):

- Diarrhea: mucus or blood may be present in the stool; can occur at night; incontinence may occur.
- Constipation: this may be the primary symptom in ulcerative colitis and limited to the rectum; obstipation may occur and may proceed to bowel obstruction.
- Bowel movement abnormalities: pain or rectal bleeding may be present, as well as severe urgency and tenesmus.
- Abdominal cramping and pain: commonly present in the right lower quadrant in Crohn's disease; occur periumbilically or in the left lower quadrant in moderate to severe ulcerative colitis.
- Nausea and vomiting: occurs more often in Crohn's disease than in ulcerative colitis).

Physical Examination

Fever, tachycardia, dehydration, and toxicity may occur in patients with IBD. Pallor may also be noted, reflecting anemia. The prevalence of these factors is directly related to the severity of the attack.

Toxic megacolon is a medical emergency. Patients appear septic; have high fever, lethargy, chills, and tachycardia; and have increasing abdominal pain, tenderness, and distention.

Patients with Crohn's disease may develop a mass in the right lower quadrant. Perianal complications (eg, perianal fissures or fistulas, abscesses, rectal prolapse) may be observed in up to 90% of patients with this disease. Common presenting signs include occult blood loss and low-grade fever, weight loss, and anemia. The rectal examination often reveals bloody stool or positive Hemoccult examination.

Growth retardation may be the only presenting sign of IBD in young patients. The physical examination should also include a search for extraintestinal manifestations, such as iritis, episcleritis, arthritis, and dermatologic involvement.

WORKUP

Approach Considerations

Several laboratory studies are of value in assisting with the management of IBD and provide supporting information. However, no laboratory test is specific enough to adequately and definitively establish the diagnosis of IBD. Laboratory values may be used as surrogate markers for inflammation and nutritional status and to look for deficiencies of necessary vitamins and minerals. Serologic studies have been proposed to help diagnose IBD and to differentiate Crohn's disease from ulcerative colitis, but such studies are not recommended for routine diagnosis of Crohn's disease or ulcerative colitis.

In individuals who are immunosuppressed, are from third world countries, or have a history of travel, intestinal tuberculosis (TB) may need to be excluded. In such cases, tuberculin purified protein derivative (PPD) or interferon-gamma assays (eg, QuantiFERON-TB, T-SPOT, TB test) may be indicated, as well as culture for amebiasis, giardiasis, *Strongyloides* infection, and studies for histoplasmosis and coccidioidomycosis.Chest radiography may exclude pulmonary TB, but this imaging modality does not exclude extrapulmonary TB (24).

Laboratory Studies

Hematologic tests

Complete blood cell count

The components of the complete blood cell (CBC) count can be useful indicators of disease activity and iron or vitamin deficiency. An elevated white blood cell (WBC) count is common in patients with active inflammatory disease and does not necessarily indicate infection.

Anemia is common and may be either an anemia of chronic disease (usually normal mean corpuscular volume [MCV]) or an iron deficiency anemia (MCV is often low). Anemia may result from acute or chronic blood loss malabsorption (iron, folate, and vitamin B12) or may reflect the chronic disease state. Note that the MCV can be elevated in patients taking azathioprine (Imuran) or 6-mercaptopurine (6-MP). Generally,

the platelet count is normal, or it may be elevated in the setting of active inflammation.

Nutritional evaluation: Vitamin B12 evaluation, iron studies, RBC folate, nutritional markers.

Vitamin B12 deficiency can occur in patients with Crohn's disease who have significant terminal ileum disease or in patients who have had terminal ileum resection. The standard replacement dose of vitamin B12 is 1000 mg subcutaneously (SC) every month, because oral replacement is often insufficient.

Serum iron studies should be obtained at the time of diagnosis, because active IBD is a source for GI blood loss, making ***iron deficiency*** common. A microcytic hypochromic anemia suggests iron deficiency; if confirmed with serum iron/total iron-binding capacity (TIBC), iron can be replaced either enterally or parenterally. For parenteral replacement, intravenous (IV) iron sucrose can be used, and dosing is based on the table in the package insert, with a maximum of 30 mL (1500 mg) at once.

Although ***folate deficiency*** is not common in persons with IBD, several concerns have been raised regarding this vitamin. Sulfasalazine is a folate reductase inhibitor and may inhibit normal uptake of folate; thus, many practitioners commonly administer folate supplements in patients taking sulfasalazine. Folate supplements are indicated in all women who are pregnant to help prevent neural tube defects; this is particularly true for patients with IBD, and supplementation with 2 mg/day or more (rather than the usual 1 mg/day) should be considered in those on sulfasalazine.

Nutritional status can be assessed by serum albumin, prealbumin, and transferrin levels. However, note that transferrin is an acute-phase reactant that can be falsely elevated in persons with active IBD. Hypoalbuminemia may reflect malnutrition because of poor oral intake or because of the protein-losing enteropathy that can coexist with active IBD.

ESR and CRP levels

The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level are often used as serologic markers for inflammation, but they are not specific for IBD. However, measuring such inflammatory markers also aids in monitoring disease activity and response to treatment. A small but significant number of patients with Crohn's disease or ulcerative colitis may not have elevated ESR or CRP levels

even in the setting of significant active inflammation. In addition, inflammatory markers may be elevated in the setting of superimposed intestinal or extraintestinal infections.

Serologic Studies

pANCA and ASCA tests

Perinuclear antineutrophil cytoplasmic antibodies (pANCA) have been identified in some patients with ulcerative colitis, and anti-*Saccharomyces cerevisiae* antibodies (ASCA) have been found in patients with Crohn's disease. The combination of positive pANCA and negative ASCA has high specificity for ulcerative colitis, whereas the inverse pattern-positive ASCA, negative pANCA-is more specific for Crohn's disease (24). However, false-positive (and false-negative) results are not uncommon; therefore, at this time, serologic markers cannot be used to definitively rule in or exclude IBD. Patients with Crohn's disease who have a greater number of positive ASCA may be at a greater risk for complications such as strictures and fistulas, and they may also be at a higher risk for surgery.

Fecal calprotectin levels

Fecal calprotectin has been proposed as a noninvasive surrogate marker of intestinal inflammation in IBD (25). As colorectal neoplasia and gastrointestinal infection also increase fecal calprotectin, this marker is not in widespread use. Note that relatives of patients with IBD may also have elevated levels of fecal calprotectin (with unknown degrees of inflammation).

Stool Studies

Before making a definitive diagnosis of idiopathic inflammatory bowel disease, perform a stool culture, ova and parasite studies, bacterial pathogens culture, and evaluation for *Clostridium difficile* infection (26). At a minimum, a *C difficile* toxin assay should be performed on any patient hospitalized with a flare of colitis, because pseudomembranous colitis is commonly superimposed on IBD colitis. Note that the level of the inflammatory marker calprotectin in feces correlates significantly with colonic inflammation in both ulcerative colitis and Crohn's disease (27).

Assessment for *Cytomegalovirus* colitis should be performed in cases refractory to steroids (24). Amebiasis can be difficult to identify from the stool; therefore, consider serologic testing.

As many as 50-80% of cases of acute terminal ileitis may be due to *Yersinia* enterocolitis infections. This produces a picture of pseudoappendicitis. As with IBD, yersiniosis has a high frequency of secondary manifestations, such as erythema nodosum and monoarticular arthritis. Thus, in the right clinical setting, a suspicion for *Yersinia* should be considered.

Radiography

Upright chest and abdominal radiography

Abdominal radiography may allow for assessment of the kidneys, ureters, and bladder for nephrolithiasis and the vertebral bodies for osteopenia or osteoporosis and sacroileitis. If severe fulminant colitis is present, abdominal radiography may reveal an edematous, irregular colon with thumbprinting (*Figure 11*). Occasionally, pneumatosis coli (air in the colonic wall) may be present.

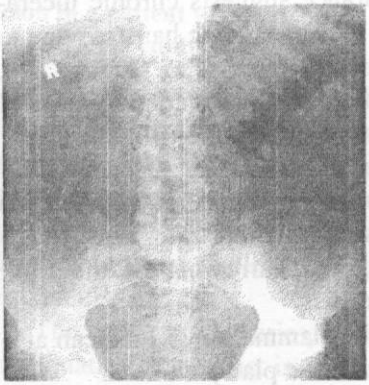


Figure 11. **Plain abdominal radiograph from a patient with known ulcerative colitis who presented with an acute exacerbation of his symptoms. This image shows thumbprinting in the region of the splenic flexure of the colon.**

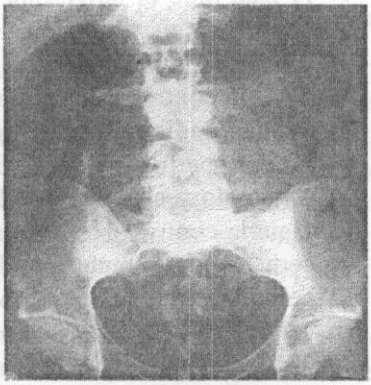


Figure 12. **Toxic megacolon - a long continuous segment of air-filled colon greater than 6 cm in diameter** (Image courtesy of Dr. Pauline Chu).

Toxic megacolon is a life-threatening complication of ulcerative colitis and requires urgent surgical intervention. This condition occurs predominantly in the transverse colon, probably because air collects there in the supine position. The transverse colon is dilated, usually more than 8 cm (dilation more than 6 cm is considered abnormal). Free air, which appears as a long continuous segment of air-filled colon greater than 6 cm in diameter, indicates a surgical emergency (*Figure 12*). A colectomy is required if no improvement occurs within 24-48 hours. Repeat radiographs are required at 12- to 24-hour intervals to monitor the course of dilatation and to assess the need for emergency colectomy.

Barium double - contrast enema radiographic studies

The barium enema imaging technique was one of the first studies that allowed characterization of the typical findings associated with inflammatory bowel disease (IBD). Barium enemas may be useful in cases of limited or no access to endoscopy, in cases of incomplete colonoscopy, or to measure stricture length (24).

Several terms have been used to describe abnormalities found after barium studies of the colon, including the following:

- A lead-pipe or stove-pipe appearance suggests chronic ulcerative colitis that has resulted in a loss of colonic haustrae due to the colon becoming a rigid foreshortened tube (*Figure 13*). Double-contrast barium enema study shows pseudopolyposis of the descending colon in a patient with ulcerative colitis.
- Rectal sparing suggests Crohn's colitis in the presence of inflammatory changes in other portions of the colon (*Figure 14*) Double-contrast barium enema study demonstrates marked ulceration, inflammatory changes, and narrowing of the right colon in a patient with Crohn's colitis.
- Thumbprinting indicates mucosal inflammation (which can also be seen frequently on the abdominal flat plate)
- Skip lesions suggest areas of inflammation alternating with normal-appearing areas, again suggesting Crohn's colitis

Barium can be refluxed into the terminal ileum in many cases, which can assist in the diagnosis of Crohn's disease. The string sign (a narrow band of barium flowing through an inflamed or scarred area) in the terminal ileum is typical of one form of ileal Crohn's disease observed on radiographs. Barium enema is contraindicated in patients with

moderate to severe colitis, because it risks perforation or precipitation of a toxic megacolon.

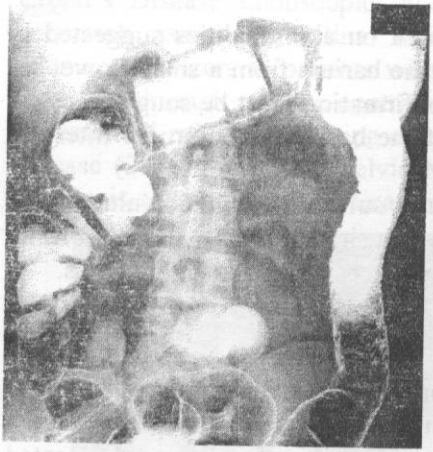


Figure 13. **Double-contrast barium enema study shows pseudopolyposis of the descending colon in a patient with ulcerative colitis.**

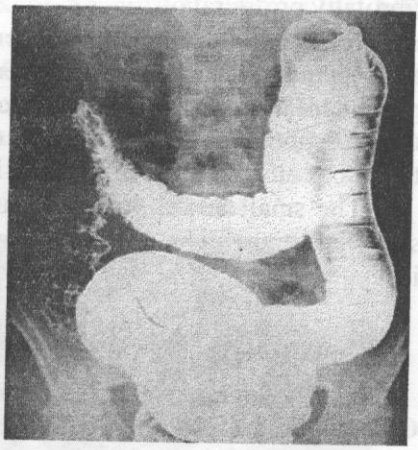


Figure 14. **Double-contrast barium enema study demonstrates marked ulceration, inflammatory changes, and narrowing of the right colon in a patient with Crohn`s colitis.**

In Crohn`s disease, areas of segmental narrowing with loss of normal mucosa, fistula formation, and the string sign (a narrow band of barium flowing through an inflamed or scarred area) in the terminal ileum are typically observed on radiographs. Some patients with ulcerative colitis also demonstrate inflammatory changes in the terminal ileum (ileitis), but these findings lack the skip pattern that is characteristic of Crohn`s disease.

The small bowel series, or small bowel follow-through, can reveal inflammation, can assist in the assessment of stricture length and severity, and can help determine the most appropriate surgical approach. Fistulas may be demonstrated on films from a small bowel series, even if they are not suggested on the basis of the clinical evaluation.

Cobblestoning in Crohn`s disease. Spot view of the terminal ileum from a small bowel follow-through study demonstrates linear longitudinal and transverse ulcerations that create a cobblestone appearance. Also, note the relatively greater involvement of the mesenteric side of

the terminal ileum and the displacement of the involved loop away from the normal small bowel secondary to mesenteric inflammation and fibrofatty proliferation

Although radiologists may remark on abnormalities suggested in the cecum or ascending colon when the barium from a small bowel series enters the colon, independent confirmation must be sought because the presence of stool and dilution of the barium make proper interpretation of colon findings difficult.

The small bowel series is usually sufficient for the evaluation of small intestine Crohn's disease; however, in rare cases, it can afford an inadequate view of the terminal ileum, necessitating an enteroclysis.

Ultrasonography

Ultrasonography (US) is a noninvasive technique in diagnosing Crohn's disease. Although this technique has a sensitivity of 84% and a specificity of 92%, it has less accuracy when the disease is located proximal to the terminal ilium.Ultrasonography, magnetic resonance imaging (MRI), and computed tomography (CT) scanning have similar accuracy for the entire bowel and are reliable in identifying fistulas, abscesses, and stenosis; however, US may lead to false positives for abscesses. US and MRI are often preferred over CT scanning because of the lack of radiation, especially in younger patients (28).

CT Scanning and MRI

CT scanning of the abdomen and pelvis findings may be very suggestive of IBD. Wall thickening on CT scans is nonspecific and may occur from smooth muscle contraction alone, especially in the absence of other extraintestinal inflammatory changes; however, the presence of inflammatory changes (eg, mesenteric fat stranding, wall enhancement, increased vascularity ["comb sign"]) significantly increases the predictive value of the CT scan.

CT scanning is the ideal study to determine if the patient has abscesses, and it can be used to guide percutaneous drainage of these abscesses. Fistulas may also be detected on CT scans. CT scanning is best for demonstrating intra-abdominal abscesses, mesenteric inflammation, and fistulas (*Figure 15*).

The use of magnetic resonance imaging (MRI) was validated in a prospective study that compared this imaging modality to the standard Crohn's Disease Endoscopic Index of Severity (CDEIS) (29). MRI accurately assessed intestinal wall thickness, presence and degree of edema, and ulcers in patients with Crohn`s disease. This study confirmed that through relative contrast enhancement (RCE), MRI can play an essential role in predicting disease activity and severity in Crohn`s disease (29). In addition, pelvic MRI has a higher sensitivity for the diagnosis of perirectal complications of Crohn`s disease.

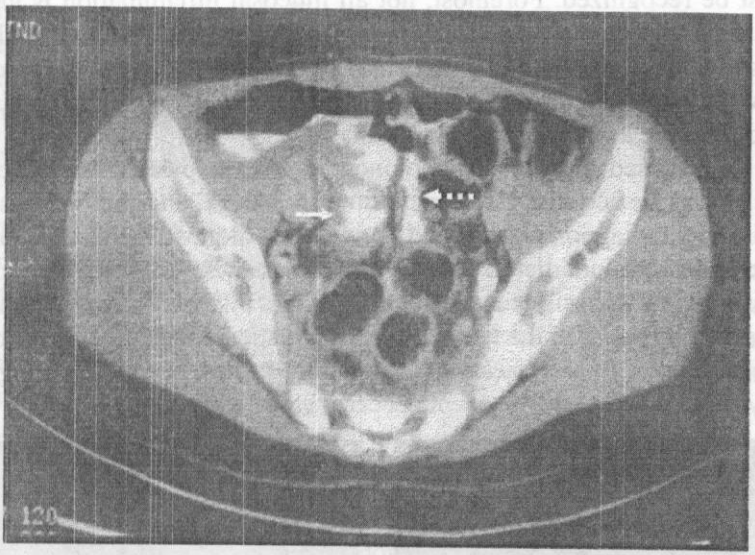


Figure 15. **Computed tomography scan from a patient with terminal ileal Crohn`s disease shows an enteroenteral fistula (arrow) between loops of diseased small intestine.**

CT enterography

A newer CT technique (called CT enterography) is a contrast CT technique in which larger than normal amounts of oral contrast are ingested by the patient. This technique, which requires a skilled radiologist, allows for better visualization of the small bowel mucosa and is considered by some to be superior to the small bowel x-ray series because of its ability to identify extraintestinal lesions; for diagnosing intestinal disease, it compares favorably with capsule enterography,

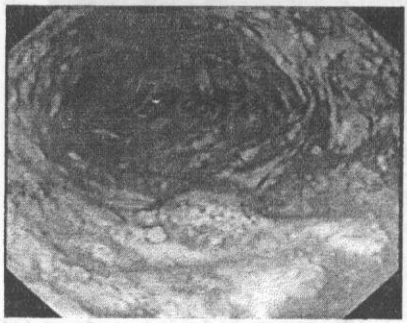
ileocolonoscopy, and small bowel follow-through x-ray. In situations where repeated studies are needed, MR enterography may be considered to avoid excess radiation exposure (30-32).

Colonoscopy and Flexible Sigmoidoscopy

Colonoscopy

Colonoscopy is one of the most valuable tools available to the physician for the diagnosis and treatment of IBD, although its limitations must be recognized. Foremost, not all mucosal inflammation is idiopathic IBD. Infectious causes of inflammation must always be considered, as should diverticulitis and ischemia (which are far more common as new diagnoses in an elderly population than IBD, despite the similar colonoscopic and histologic appearance).

When used appropriately, colonoscopy can help determine the extent and severity of colitis, assist in guiding treatment, and provide tissue to assist in the diagnosis. In skilled hands, the colonoscope can frequently reach the terminal ileum and permit assessment of inflammation to assist in the diagnosis or exclusion of Crohn`s disease. Inflammation may occasionally occur in the terminal ileum in patients with ulcerative colitis; this is referred to as a backwash ileitis and is mild, is nonulcerating, and may occur when a widely patent ileocecal valve is present (*Figure 16, 17*).



Figures 16. **Severe colitis noted during colonoscopy in a patient with inflammatory bowel disease. The mucosa is grossly denuded, with active bleeding noted.**

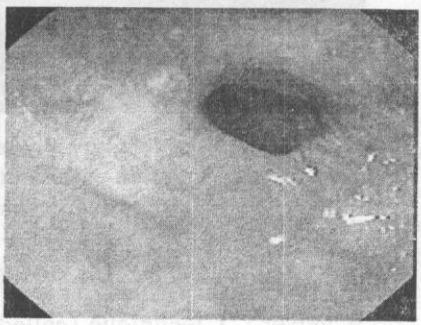


Figure 17. **Stricture in the terminal ileum - a narrowed segment visible upon intubation of the terminal ileum with the colonoscope. Relatively little active inflammation is present, indicating that this is a cicatrix stricture.**

Colonoscopy or sigmoidoscopy reveals that the rectum is almost always involved in ulcerative colitis, but it is frequently spared in Crohn's disease. The disease can be limited to the rectum (proctitis); to the rectum, sigmoid, and descending colon (left-sided colitis); or to the entire colon (pancolitis). Ulcerative colitis does not involve any other segment of the GI tract. Colectomy is curative.

Colonoscopy can also be used for therapeutic intervention in patients with IBD. The most common therapeutic use is stricture dilation in persons with Crohn's disease. Colonic, anastomotic, and even small bowel strictures can often be dilated using pneumatic through-the-scope dilators. Intralesional injection of steroids (eg, triamcinolone at 5 mg in 4 quadrants) may help, but it is usually of transient value and has yet to be demonstrated in controlled trials.

Flexible sigmoidoscopy

Flexible sigmoidoscopy is useful for a preliminary diagnosis in patients with chronic diarrhea or rectal bleeding; however, because of the limited length of the scope (60 cm), it can only help diagnose distal ulcerative colitis or proctitis. Rarely, Crohn colitis can be diagnosed based on flexible sigmoidoscopy findings. Note that sigmoid inflammation, particularly in older patients, may be confused with diverticulitis or ischemia.

Upper GI Endoscopy

Esophagogastroduodenoscopy (EGD) is used for the evaluation of upper gastrointestinal tract symptoms, particularly in patients with Crohn's disease. Aphthous ulceration occurs in the stomach and duodenum in 5-10% of patients with Crohn's disease. The diagnosis of Crohn's disease may be made after gastric or duodenal ulcers fail to heal with acid suppression alone but is usually accompanied by ileal or ileocolonic Crohn's disease.

Enteroscopy

Capsule enteroscopy

In capsule enteroscopy, the patient swallows an encapsulated video camera that transmits images to a receiver outside the patient. It is most commonly used for finding obscure sources of gastrointestinal (GI) blood loss, the images can find ulcerations associated with Crohn's disease if upper endoscopy and colonoscopy are unrevealing. Capsule

enteroscopy may also aid in the diagnosis of small bowel Crohn's disease when the standard diagnostic workup with a colonoscopy and upper endoscopy is negative (24). The major risk is the potential for the camera to become lodged at the point of a stricture, which may necessitate operative intervention for removal.

Double balloon enteroscopy

Double balloon enteroscopy, or deep small bowel enteroscopy, is a technique whereby a long enteroscope is passed into the intestine using an overtube. Both the endoscope and the overtube have balloons that can be inflated and deflated sequentially as the endoscope is advanced in an "inchworm" fashion.

Histologic Findings

Ulcerative colitis

Ulcerative colitis is a superficial inflammation of the bowel wall almost entirely limited to the large bowel (when the cecum is involved, there may be some inflammation in the distal-most ileum, the so-called "backwash ileitis"). Only in complicated cases such as evolution into toxic megacolon are the deeper layers of the bowel wall involved with the inflammatory process.

Ulcerative colitis primarily involves the mucosa and the submucosa, with formation of crypt abscesses and mucosal ulceration. The mucosa typically appears granular and friable. In more severe cases, pseudopolyps form, consisting of areas of hyperplastic growth with swollen mucosa surrounded by inflamed mucosa with shallow ulcers. In severe ulcerative colitis, inflammation and necrosis can extend below the lamina propria to involve the submucosa and the circular and longitudinal muscles.

In ulcerative colitis inflammation almost always involves the rectum and is contiguous, regardless of the extent of the colon involved. The exception to this rule is that the initial inflammation may appear patchy during colonoscopy that is performed very early in the ulcerative colitis process, although biopsy specimens of intervening normal-appearing mucosa often do reveal inflammation. The intestinal inflammation of ulcerative colitis only involves the colon. Biopsy specimens demonstrate neutrophilic infiltrate along with crypt abscesses and crypt distortion. Granulomas do not occur in ulcerative colitis (*Figure 18, 19*).

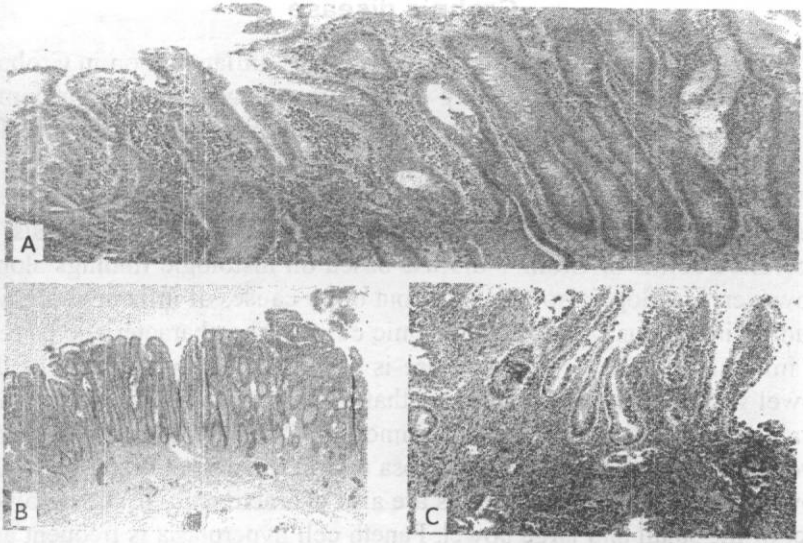


Figure 18. A – chronic architectural changes in ulcerative colitis. Note the crypt branching and irregularity of size and shape, with an increase in chronic inflammatory cells in the lamina propria; *B* – low-power image from a colon biopsy in a patient with ulcerative colitis illustrates changes limited to the mucosa. These changes include chronic alteration of the crypt architecture and an increase in chronic inflammatory cells in the lamina propria; *C* – chronic architectural changes in ulcerative colitis. Note the trifid crypt.

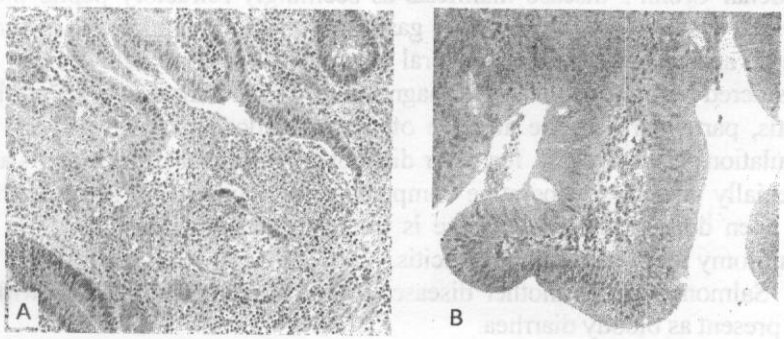


Figure 19. A – high-power view of a crypt abscess in ulcerative colitis shows the crypt to be dilated and filled with neutrophils and debris; *B* – This is an example of low-grade glandular dysplasia in a patient with longstanding ulcerative colitis. Note the loss of mucin, nuclear hyperchromasia, and nuclear pseudostratification.

Crohn's disease

The entire intestinal wall is involved with inflammation in Crohn's disease. Biopsy specimens may demonstrate granulomas (approximately 50% of the time). The presence of granulomas is often helpful for making the diagnosis but is not necessary. Because biopsy specimens obtained at colonoscopy are generally superficial mucosal tissue samples, the pathologist may have difficulty making a definitive diagnosis of ulcerative colitis or Crohn's disease based on histologic findings alone. However, histology also helps rule out other causes of inflammation, including infectious colitis and ischemic colitis. The characteristic pattern of inflammation in Crohn's disease is a transmural involvement of the bowel wall by lymphoid infiltrates that contains sarcoidlike granulomas in about half of the cases (most commonly in the submucosa). Proliferative changes in the muscularismucosa and in the nerves scattered in the bowel wall and myenteric plexus are also characteristic. In the involved foci of the small and large bowel, Paneth cell hyperplasia is frequent and areas of pyloric metaplasia may be seen. In full-blown cases, long and deep fissurelike ulcers form (*Figure 20, 21*).

DIFFERENTIAL DIAGNOSES

Approximately 90% of patients with Crohn's disease have involvement of the terminal ileum and/or right colon. Occasionally, gastric or duodenal Crohn's disease manifests as seemingly refractory peptic ulcer disease. Due to the nonspecific gastrointestinal symptoms of Crohn's disease and ulcerative colitis, several other diagnoses (see below) must be considered before establishing a diagnosis of Crohn's disease or ulcerative colitis, particularly in the absence of typical endoscopic findings and in populations at higher risk for other diagnoses. Note that historically – and especially when a preoperative computed tomography (CT) scanning has not been done – Crohn's disease is frequently diagnosed at the time of laparotomy for presumed appendicitis.

Salmonellosis is another disease in the differential diagnosis, which can present as bloody diarrhea.

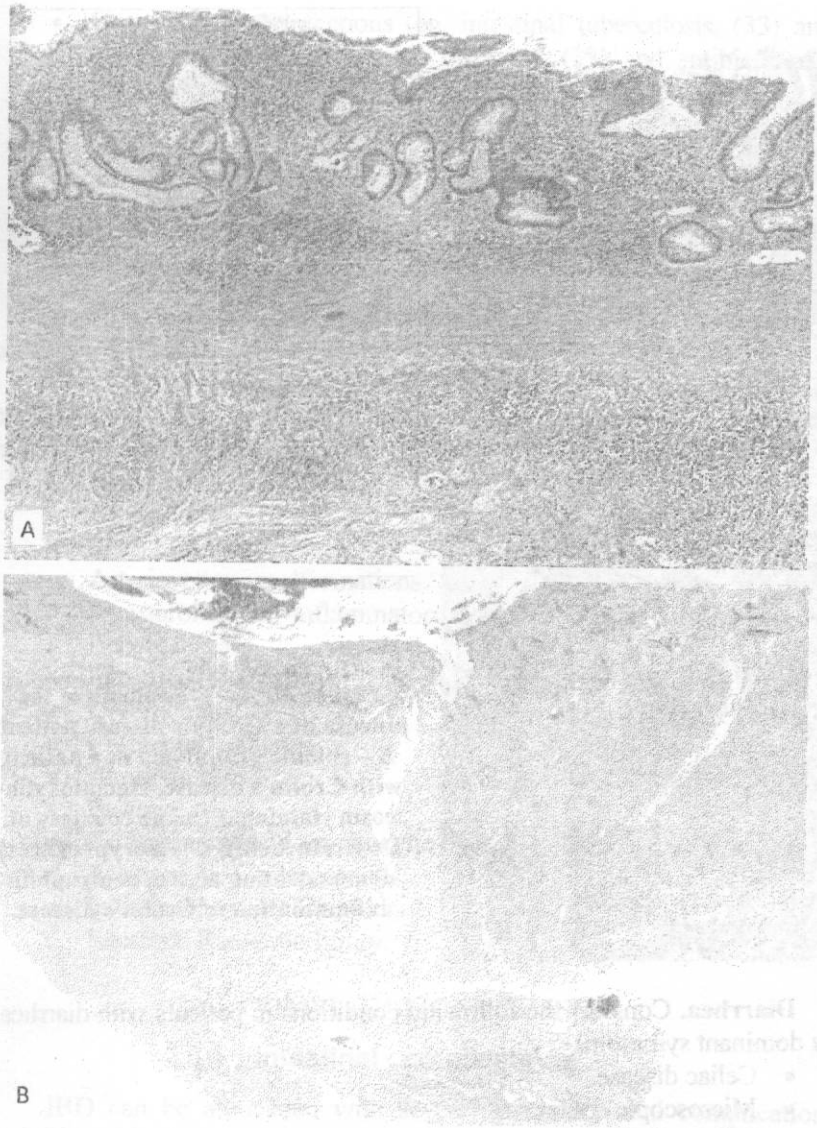


Figure 20. A – **Histologic features of chronic Crohn colitis with crypt atrophy and branching, as well as lymphocytic infiltrate. Hematoxylin-eosin staining. Courtesy of Dr E. Ruchelli;** ***B*** **– Deep knifelike, fissuring, transmural ulcer in Crohn`s disease.**

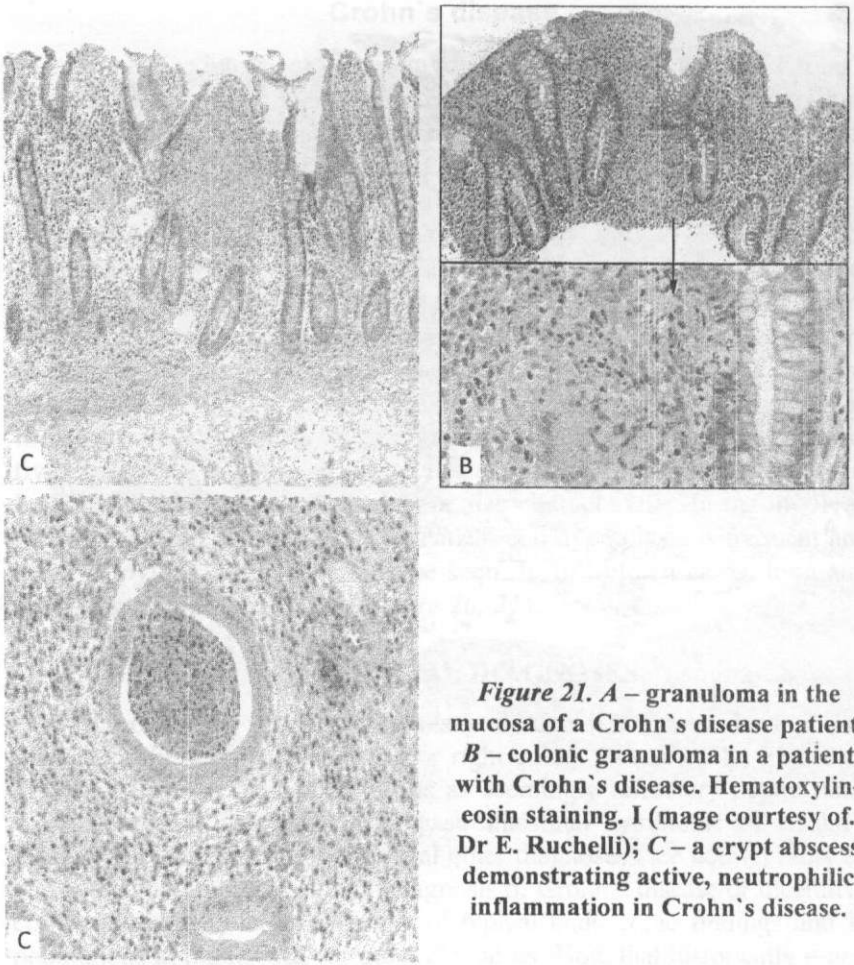


***Figure 21. A* – granuloma in the mucosa of a Crohn`s disease patient; *B* – colonic granuloma in a patient with Crohn`s disease. Hematoxylin-eosin staining. I (mage courtesy of. Dr E. Ruchelli); *C* – a crypt abscess demonstrating active, neutrophilic inflammation in Crohn`s disease.**

Diarrhea. Consider the following conditions in patients with diarrhea as a dominant symptom:

- Celiac disease.
- Microscopic colitis.
- Irritable bowel syndrome.
- Lactose intolerance.
- Functional diarrhea.
- Giardiasis.

- Gastrointestinal infections (eg, intestinal tuberculosis, (33) amebiasis, (33) chronic *Yersinia* infection, (33) and antibiotic-associated colitis/*Clostridium difficile* infection, Salmonellosis).
- Gastroenteritis, Viral (Cytomegalovirus).
- Food Poisoning.
- Behcet disease (33).
- AIDS.
- C1 esterase deficiency, hereditary angioedema.
- Colorectal malignancy (eg, adenocarcinoma, lymphoma).

Abdominal pain, gastrointestinal bleeding, and/or intestinal ulceration.

In patients with predominant abdominal pain, gastrointestinal bleeding, and/or intestinal ulceration, consider the following conditions in the differential diagnosis:

- Ischemic colitis.
- Appendicitis.
- Radiation-induced colitis.
- Arteriovenous malformations.
- Nonsteroidal anti-inflammatory drug (NSAID) enteropathy.
- Behcet disease.
- Intestinal tuberculosis.
- Diverticulitis.
- Colorectal malignancy.
- Anorexia Nervosa.
- Bulimia.
- Collagenous and Lymphocytic Colitis.
- Eosinophilic Gastroenteritis.
- Intestinal Motility Disorders.
- Intestinal Radiation Injury.

COMPLICATIONS OF IBD

Intestinal complications

IBD can be associated with several gastrointestinal complications, including risk of hemorrhage, perforation, strictures, and fistulas – as well as perianal disease and related complications, such as perianal or pelvic abscesses, toxic megacolon (complicated acute severe colitis), and malignancy (colorectal cancer, cholangiocarcinoma complicating primary sclerosing cholangitis).

Extraintestinal complications

Extraintestinal complications occur in approximately 20-25% of patients with IBD (24) (*Table 7*). In some cases, they may be more symptomatic than the bowel disease itself. These include osteoporosis (usually a consequence of prolonged corticosteroid use), hypercoagulability resulting in venous thromboembolism, anemia, gallstones, primary sclerosing cholangitis, aphthous ulcers, iritis (uveitis) and episcleritis, and skin complications (pyoderma gangrenosum, erythema nodosum) (*Figure 22*).

Table 7

Common Extraintestinal Complications of IBD in US and Europe (35)

Complication	Prevalence
Scleritis	18%
Anterior uveitis	17%
Gall stones (particularly in Crohn`s disease)	13-34%
Inflammatory arthritis	10-35%
Anemia	9-74%
Aphthous stomatitis	4-20%
Osteoporosis	2-20%
Erythema nodosum	2-20%

Source: Larson S, Bendtzen K, Nielsen OH. Extraintestinal manifestations of inflammatory bowel disease: epidemiology, diagnosis and management. *Ann Med* 2010;42:97-114.

Table 8

Extraintestinal Complications of IBD in Swiss Patients (34)

Complication	Crohn`s disease	Ulcerative Colitis
Arthritis	33%	4%
Aphthous stomatitis	10%	4%
Uveitis	6%	3%
Erythema nodosum	6%	3%
Ankylosing spondylitis	6%	2%
Psoriasis	2%	1%
Pyoderma gangrenosum	2%	2%
Primary sclerosing cholangitis	1%	4%

Source: Vavricka SR, Brun L, Ballabeni P, et al. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. Am J Gastroenterol. 2011;106:110-9.

The Swiss National IBD Cohort Study also demonstrated the risks of extraintestinal complications of IBD; their results are summarized in Table 5 (34). The risk factors of having complications included family history and active disease for Crohn`s disease only; no significant risk factors were noted in patients with ulcerative colitis (34).

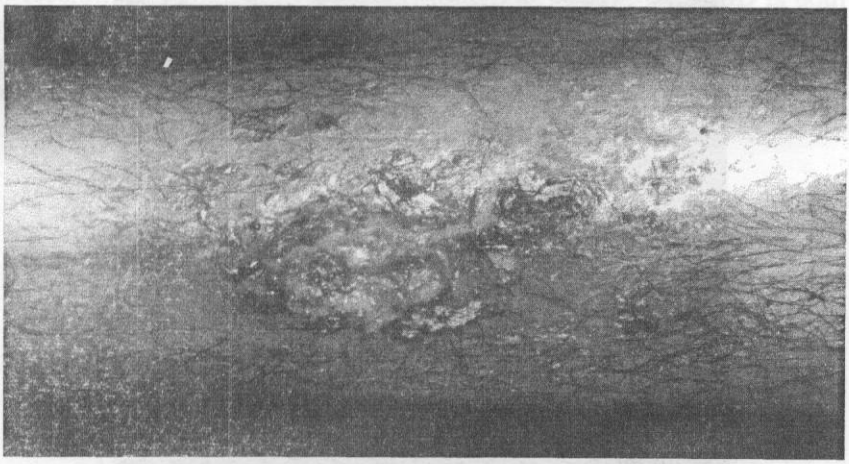


Figure 22. **Pyoderma gangrenosum.**

TREATMENT AND MANAGEMENT

Although ulcerative colitis and Crohn`s disease have significant differences, many, but not all, of the treatments available for one condition are also effective for the other. Surgical intervention for ulcerative colitis is curative for colonic disease and potential colonic malignancy, but it is not curative for Crohn`s disease.

The current standard approach for treating IBD is the "bottom-up" approach. This involves assessing how severe a patient's symptoms are, and choosing treatment based on that severity.So, for instance, a patient who has mild symptoms probably would be started on aminosalicylates or antibiotics. A patient who has more severe symptoms or hasn't responded to the first-line of treatment might be prescribed corticosteroids. But many doctors now think that some patients – particularly those with Crohn's disease – would benefit from the "top-down" treatment approach. This involves treating the disease more aggressively early on, and with

a combination of treatments. The goal here is to induce remission (absence of symptoms) and then maintain remission (*Figure 23*).

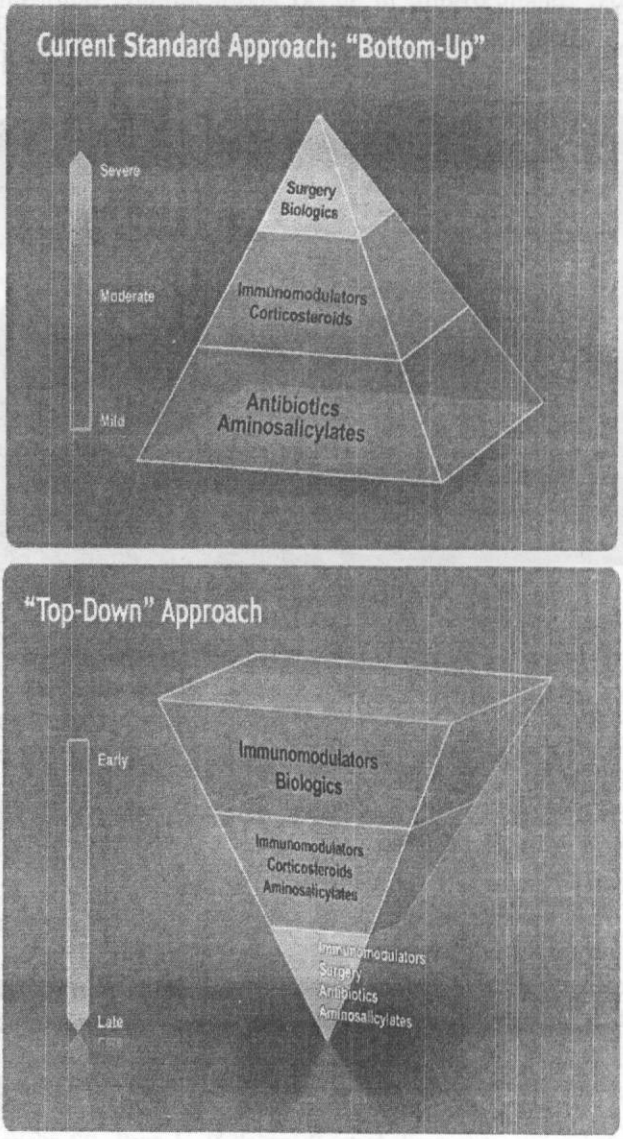


***Figure 23*. Different treatment approaches.**

Approach Considerations

The care of a patient with IBD can be either medical or surgical in nature or, in many patients, a combination of both. The management algorithm is also dependent on whether the diagnosis is Crohn's disease or ulcerative colitis. The medical approach for patients with IBD is both symptomatic care (ie, relief of symptoms) and mucosal healing following a stepwise approach to medication, with escalation of the medical regimen until a response is achieved (*Figure 24*).

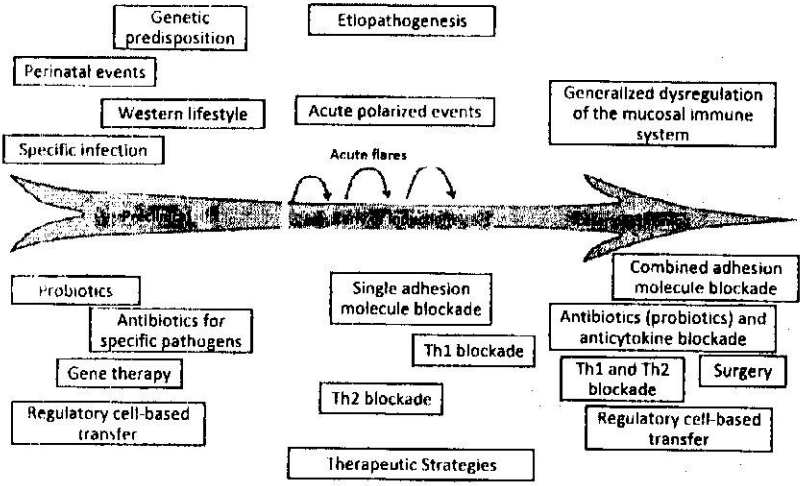


Figure 24. **Therapeutic strategies.**

The 2 *goals of therapy* are the *achievement of remission* (induction) and the *prevention of disease flares* (maintenance). Note that a top-down approach, with earlier introduction of biologics and immunomodulators, is frequently advocated to forestall complications.

The concept of deep mucosal healing, particularly in Crohn's disease, is becoming increasingly advocated. There are several studies, primarily involving anti-TNF agents (and occasionally immune modifiers); that have shown that the elimination of inflammation (as demonstrated by endoscopic and histologic criteria) results in a decrease in the rate of surgery, the use of corticosteroids, and the rate of hospitalization (36-42). This supports the use of immune-modifying agents (mercaptopurine or azathioprine) or one of the anti-TNF agents earlier in the course of IBD (36-42).

Diet, Lifestyle Modifications, and Activity

No known dietary or lifestyle changes prevent inflammatory bowel disease (IBD), and no known dietary substances have been consistently shown to cause activation of IBD. Tobacco use has been linked to increases in the number and severity of flares of Crohn's disease, and smoking cessation can help achieve remission in patients with Crohn's disease. Lactose intolerance is common in persons with Crohn's disease or ulcerative colitis and can mimic symptoms of IBD.

Diet

Although diet has been well demonstrated to have little or no influence on inflammatory activity in persons with ulcerative colitis, it may influence symptoms. For this reason, patients are often advised to make a variety of dietary modifications, especially adaptation of a low-residue diet, although the evidence does not support a *low-residue diet* as beneficial in the treatment of ulcerative colitis. Such a diet, however, might decrease the frequency of bowel movements.

Unlike in patients with ulcerative colitis, diet can influence inflammatory activity in persons with Crohn's disease. *Nothing by mouth* (NPO) can hasten the reduction of inflammation, as may the use of a liquid or predigested formula for enteral feeding. Although a meta-analysis in 1995 demonstrated that steroids were superior to liquid diet alone for Crohn's disease, a liquid diet seemed superior to a regular diet for reducing inflammation. The problem with using enteral liquid diets, especially the predigested formulations, is that palatability limits the intake of adequate energy (calories) to meet patient requirements. Parenteral alimentation may be needed.

Multivitamin supplementation is recommended in patients with IBD. For patients with vitamins B12 or vitamin D deficiency, supplementation of these vitamins should be given. Patients receiving steroid therapy should receive vitamin D and calcium supplementation. Parenteral iron (IM weekly or IV) may be used in patients with chronic iron-deficiency anemia who are unable to tolerate the oral formulation (24).

Activity

Generally, patients do not need to limit activity when IBD is quiescent. During flares of disease activity, activity is limited only by the extent of fatigue and the abdominal pain or diarrhea the patient is

experiencing. When abdominal pain persists beyond medical therapy – induced resolution of the active inflammation, other causes of pain must be considered, including abscess, stricture, nephrolithiasis, IBS, and psychiatric disease.

In most instances, diarrhea limits activity primarily because of the lack of immediate access to toilet facilities in many locations and/or occupations. Dehydration may be an issue, often requiring IV hydration or the use of oral rehydration solutions.

Moderate to vigorous physical activity for as long as 12 weeks has been shown to improve symptom scores and many specific quality-of-life dimensions, including energy, sleep, emotion, and physical functioning (43). This degree of activity was defined as 20-60 minutes of intense exercise 3-5 days per week. The improvements occur despite lack of change in body weight, oral-anal transit time, bowel movements per week, or stool consistency. This study also highlights that symptomatic deterioration is more likely in physically inactive individuals.

Symptomatic Therapy

In addition to treatment of the underlying inflammation, patients with IBD may require symptomatic therapy, particularly when their symptoms are not related to active inflammation. Treatment with antidiarrheal agents such as loperamine or diphenoxylate/atropine should generally be avoided in patients with active inflammation, as these drugs can precipitate toxic megacolon in individuals with significant colonic inflammation. Similarly, other agents that may have anticholinergic effects should be avoided, although antispasmodic medications may sometimes be useful for symptomatic relief. In patients with Crohn's disease who have significant ileal disease or who have had an ileal resection, diarrhea may sometimes be due to bile salt malabsorption. In such patients, treatment with bile-binding resins, such as cholestyramine, may be helpful in managing the diarrhea.

Overview of Stepwise Therapy

A stepwise approach may be taken in mild to very moderateIBD.

The first step in medication therapy for IBD is usually *aminosalicylates*. There are several different aminosalicylates, but none has

been consistently demonstrated to be superior to the others for all patients. These agents appear to have greater efficacy for the treatment of ulcerative colitis than for Crohn's disease, for which efficacy data are limited. For Crohn's disease, metronidazole or ciprofloxacin is occasionally used, particularly for perianal disease or an inflammatory mass.

If the patient's condition fails to respond to an adequate dose of aminosalicylates, *the second step* is often *corticosteroids*, which tend to provide rapid relief of symptoms and a significant decrease in inflammation (44). The most common range for moderate flares of IBD is oral prednisone at 10-40 mg/day; for more severe flares, the higher end of the range is used (occasionally doses up to 60 mg/day are required). Once a clinical response is seen, the dose is tapered. Most patients who use oral corticosteroids can tolerate a relatively rapid taper after a response is achieved; occasionally, a very prolonged steroid taper is necessary to prevent relapse in patients who have had prolonged exposure to steroids in the past. Inability to taper down the steroids without recurrence of symptoms should trigger discussion regarding the use of alternative drugs (immunomodulators or anti-TNF therapy).

Immune-modifying agents are *step III* drugs and are used if corticosteroids fail or are required for prolonged periods. *Anti-TNF monoclonal antibody therapies* are also step III drugs that are effective in both Crohn's disease and ulcerative colitis; some studies have demonstrated that they have a greater efficacy than azathioprine.

Drugs from different therapeutic classes may be used additively. In some patients with high-risk disease, a step-down approach with early introduction of stronger agents such as the anti-TNF agents has been advocated to prevent complications and improve patient outcomes. There are many situations, especially in patients with more severe disease, where the step-down approach is clearly in the patient's best interest.

In general, *one major goal* is to wean the patient off steroids as soon as possible to prevent long-term adverse effects from these agents. *Ardizzone et al* suggest that a lack of mucosal healing after corticosteroid therapy is the only factor associated with negative outcomes at 5 years (45).

Step I – Aminosalicylates

The 5 oral aminosalicylate preparations available for use are sulfasalazine (Azulfidine), mesalamine (Asacol, Asacol HD, Pentasa, Lialda, Apriso), balsalazide (Colazal), and olsalazine (Dipentum). Enema and suppository formulations are also available. All of these are derivatives of 5-aminosalicylic acid (5-ASA); the major differences are in the mechanism and site of delivery. Some of these agents also have unique adverse effects lacking in other agents of this class (*Table 9, Figure 25*).

All of the aminosalicylates are useful for treating flares of IBD and for maintaining remission. None of the aminosalicylates has been proven to have greater efficacy than any of the others for the treatment of ulcerative colitis. As a class, these agents appear to be more effective in persons with ulcerative colitis than in persons with Crohn's disease; in persons with mild Crohn's disease, the primary utility is for colonic disease (as is the case with sulfasalazine (24); administer folic acid if sulfasalazine is used). Aminosalicylates have only a weak effect in preventing recurrence after surgery in patients with Crohn's disease (46).

For patients in remission from distal ulcerative colitis, oral or rectal 5-ASA can be used to manage this disease, as well as a combination regimen of oral and topical 5-ASA. In treating rectal disease, rectal 5-ASA is preferred over rectal steroids. A dose response has been described regarding the use of these agents for ulcerative colitis. For moderate disease, a dose of 4,8 g/day of mesalamine has been shown to be more efficacious than 2,4 g/day.

5-aminosalicylic acid formulations

(*Baumgart D.C., Sandborn W.J.* Inflammatory bowel disease: clinical aspects and established and evolving therapies. Lancet 2007; 369: 1641-57)

Generic name	Proprietary name	Formulation	Sites of delivery	Unit strength
Mesalazine	North American Asacol[1]	Eudragit-S coated tablets (release at pH≥7-0)	Terminal ileum, colon	400 mg
Mesalazine	Asacol 800	Eudragit-S coated tablets (release at pH>7-0)	Terminal ileum, colon	800 mg
Mesalazine	Mesavant (EU), Lialda (USA) (SDP 476)	Advanced, multimatrix system	Terminal ileum, colon	1200 mg
Mesalazine	UK, Italy, Netherlands Asacol[2]	Eudragit-S coated tablets (release at pH≥7-0)	Terminal ileum, colon	400 mg
Mesalazine	Salofalk[3], Mesasal, Claversal[3]	Eudragit-L coated tablets (release at pH>6-0)	Distal ileum, colon	250 mg, 500 mg
	Salofalc Granu-Stix[3]	Eudragit-L100, poly-acrylate-dispersion, povidone K (Eudragit-NE 40 D, Nonoxinol 100), simeticone	80% colon, sigmoid colon, rectum	500 mg, 1000 mg

5-ASA-5-aminosalicylic acid.

[1]North American Asacol: originally developed by Tillotts Laboratories, Colpermin, UK (later changed name to Tillotts Pharma AG, Ziefen, Switzerland), then Norwich Eaton, Norwich, NY, USA, currently Procter and Gamble, Cincinnati, Ohio, USA. Marketed by Procter and Gamble in North America. Manufactured with original Tillotts Laboratories manufacturing process.

[2]UK, Italy, Netherlands Asacol: purchased from Tillotts Laboratories by Smith Kline French Laboratories (later changed name to Smith Kline Beecham and then GlaxoSmithKline), Gitliani, and Byk-Gulden. Differences might exist in Eudragit-S coating thickness, excipients, and manufacturing processes. No published data establishing the biocquivalence of North American Asacol and UK, Italy, Netherlands Asacol.

[3]Manufactured by Dr Falk Pharma in Germany.

Table 9 continues

	Claversal Micropellets[4]	Eudragit L-100-55, Eudragit S-100, dispersible cellulose	Ileocaecal valve, colon, left-sided colon	1500 mg
	Claversal Foam[4]	Eudragit L-100-55, Eudragit S-100, dispersible cellulose		5 g foam (1000 mg 5-ASA)
Mesalazine	Pentasa[5]	Ethylcellulose-coated microgranules (time dependent release) available as a tablet, capsule or sachet	Duodenum, ileum, colon	250 mg and 500 mg tablets; 500 mg capsules; 1000 mg sachets
Olsalazine	Dipentum	5-aminosalicylic acid dimer linked by azo-bond, available as a gelatin capsule	Colon	250 mg
Sulfasalazine	Azulfidine, Salazopyrin	5-aminosalicylic acid linked to sulfapyridine by azo-bond available as a tablet	Colon	500 mg (200 mg 5-ASA)
Sulfasalazine	Azulfidine/ Salazopyrin EN-tabs	5-aminosalicylic acid linked to sulfapyridine by azo-bond, available as a tablet coated with cellulose acetate phthalate	Colon	500 mg (200 mg 5-ASA)
Balsalazide	Colazide, Colazal	5-aminosalicylic acid linked to 4-amino-benzoyl-β-alanine by azo-bond, available as a capsule	Colon	750 mg (262 mg 5-ASA)

[4]Manufactured by Merckle Recordati in Germany.

[5]United States Pentasa: 250 mg capsule from Shire Pharmaceuticals (previously developed and marketed by Marion Laboratories, which later merged into Hoechst-Marion-Roussel, then Aventis and now Sanofi). Pentasa is manufactured and distributed by Ferring Pharmaceuticals.

Probiotic agents

Supplementation of the high-potency probiotic mixtures (eg, VSL#3 (47, 48) have been shown in some reports to reduce ulcerative colitis disease activity index scores in patients with mild to moderate relapsing ulcerative colitis who are being treated with 5-ASA. Studies in patients with Crohn`s disease have been much less promising.

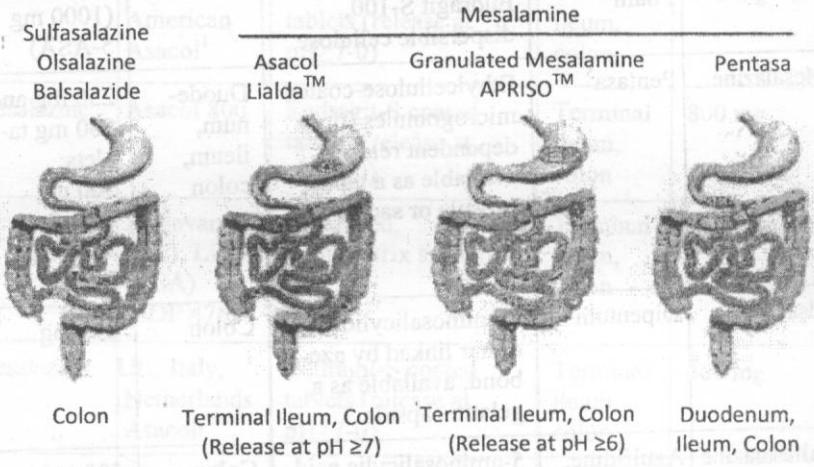


Figure 25. **Oral 5-ASA formulations: sites of delivery** (Adapted from Baumgart D.C., Sandborn W.J. Lancet. 2007; 369:1641–1657. And from Sandborn W.J. J Clin Gastroenterol. 2008; 42:338–344).

Step IA – Antibiotics

The antibiotics metronidazole and ciprofloxacin are the most commonly used antibiotics in persons with IBD. According to a systemic review, antituberculosis therapy, macrolides, fluoroquinolones, 5-nitroimidazoles, and rifaximin (alone or in combination) have not consistently been shown to induce remission in selective active Crohn`s disease and have rarely been shown to induce remission in ulcerative colitis (49).

Antibiotics are used only sparingly in persons with ulcerative colitis because of limited treatment efficacy and because of an increased risk of developing antibiotic-associated pseudomembranous colitis. In persons with Crohn`s disease, antibiotics are used for various indica-

tions, most commonly for perianal disease, fistulas, and intra-abdominal inflammatory masses.

Antibiotics have potential adverse effects, including nausea, anorexia, diarrhea, and monilial (candidal) infections. Peripheral neuropathy can be observed in association with metronidazole and, when present, requires discontinuation of therapy with that drug. Finally, antibiotics can also increase the risk of *Clostridium difficile* colitis.

Step II – Corticosteroids

Corticosteroids are rapid-acting anti-inflammatory agents used in the treatment of IBD. These drugs are indicated for acute flares of disease only and have no role in the maintenance of remission.

Corticosteroids may be administered by various routes depending on the location and severity of disease; they may be administered intravenously (ie, methylprednisolone, hydrocortisone), orally (ie, prednisone, prednisolone, budesonide, dexamethasone), or topically (ie, enema, suppository, or foam preparations).Corticosteroids are limited by their adverse effects, particularly with prolonged use.

The potential complications of corticosteroid use include fluid and electrolyte abnormalities, osteoporosis, avascular necrosis, peptic ulcers, cataracts, glaucoma, neurologic and endocrine dysfunctions, infectious complications, and occasional psychiatric disorders (including psychosis).

The consensus regarding treatment with these agents is that they should be tapered once remission has been induced. Corticosteroids do not have a role in maintaining remission.

Patients who are concerned about immunosuppressive therapies, including immunomodulators or anti-tumor necrosis factor (TNF) agents, should be educated about the potential greater incidence of complications occurring with long-term steroid use and with undertreated disease. Patients with prolonged use of steroids may also require ophthalmologic examination because of the risk of development of glaucoma and cataracts.

Periodic assessment of bone mineral density is recommended for patients taking steroids for more than 3 months.Agents used for osteoporosis prevention and treatment (eg, the bisphosphonates) are useful for preventing the bone loss associated with corticosteroid use.

Intravenous corticosteroids

Intravenous corticosteroids are often used for patients who are severely ill and hospitalized; few data have been published on the optimum dosage of IV or oral corticosteroids. The upper end of dosing generally includes IV methylprednisolone at 20 mg every 6 hours or IV hydrocortisone at 100 mg every 8 hours. Typically, once a clinical response is observed (usually within 3-5 days), the dose of the IV corticosteroid can be tapered. Before hospital discharge, conversion to an oral corticosteroid is made with dosage tapering in an outpatient setting.

Oral corticosteroids

When oral corticosteroids are used, dosing is variable, and few data have been published to guide optimal dosing. The most common range for moderate flares of IBD is prednisone at 10-40 mg/day. For more severe flares, doses up to 60 mg/day may be used, but there are no supportive data. Once a clinical response is seen, the dose is tapered. Most patients who use oral corticosteroids can only occasionally tolerate a relatively rapid taper after a response is achieved; a prolonged steroid taper is rarely necessary to prevent relapse. When the latter situation occurs, consider escalation of therapy with the use of alternative drugs (immune modifiers or anti-TNF therapy).

Budesonide (Entocort EC), a synthetic corticosteroid, is available for Crohn's disease with ileal or ileocecal involvement.Budesonide has extensive first-pass metabolism, which limits systemic adverse effects. (50)However, some absorption occurs over a prolonged period of exposure. Budesonide is also less effective than other standard glucocorticosteroids for the treatment of ileal Crohn's disease and has not demonstrated efficacy in maintaining therapy beyond 12 months.

According to the American Gastroenterological Association (AGA) guidelines, ileal-release preparations of budesonide are indicated for the treatment of patients with mild to moderate ileal and right-sided colonic Crohn's disease.These preparations have not been demonstrated to be effective in patients with ulcerative colitis, but clinical trials in this setting are under way.

Topical corticosteroids

Topical corticosteroids are used in persons with distal colonic disease in a manner similar to that of topical mesalamine; the major difference is that even though topical mesalamine may be used to help

maintain remission, topical corticosteroids are used for active disease and have only a small role in the maintenance of remission. According to AGA guidelines, topical therapy with either hydrocortisone (grade A recommendation) or budesonide (grade B recommendation) is effective for distal colonic inflammation in patients with mild to moderate IBD (50).

Patients with ulcerative colitis with predominantly distal disease may be treated with topical budesonide, a synthetic steroid which has local anti-inflammatory effects and limited systemic effects (51). Although topical budesonide is effective, novel oral controlled-release formulations have been developed to enable treatment of the entire colon.

Rectal corticosteroids

Cortenema, Cortifoam, and Anusol-HC suppositories are useful in treating distal disease (proctitis and proctosigmoiditis).

Step III – Immunomodulators

Immune modifiers have a slower onset of action (typically, a 2- to 3-month lag) and, consequently, are not used for induction of remission. However, these agents have shown effectiveness for their steroid-sparing action in persons with refractory disease; they are also used as primary treatment for fistulas and maintenance of remission in patients intolerant of or not responsive to aminosalicylates.

The immunomodulators 6-mercaptopurine (6-MP) and azathioprine (AZA) are used in patients with inflammatory bowel disease (IBD) in whom remission is difficult to maintain with the aminosalicylates alone. Calcineurin inhibitors such as cyclosporin A (CSA) and tacrolimus, as well as methotrexate (MTX), are also immune-modifying agents (24); CSA is almost exclusively limited to acute severe colitis, whereas tacrolimus has been used in both perianal Crohn's disease and ulcerative colitis.

Thiopurine agents

The American Gastroenterological Association (AGA), in accordance with the US Food and Drug Administration (FDA), recommends that patients undergo assessment of the thiopurine methyltransferase (TPMT) genotype or phenotype before starting therapy with AZA or 6-MP (50). Individuals who have low enzyme activity or are homozy-

gous deficient in the TPMT mutation are at risk of very severe leukopenia, with potential septic complications, and may not be good candidates for therapy with these drugs.

About 11% of individuals with heterozygous TPMT activity respond well to therapy but are prone to myelotoxicity, although this can be minimized with the use of lower doses. These patients, as well as those with wild-type TPMT activity, require monitoring for complications (50).

Adverse effects and monitoring

Use of immune modifiers mandates monitoring of blood parameters; they can cause significant neutropenia or pancytopenia that warrants a dose reduction or discontinuation. Routine complete blood cell (CBC) counts with differentials and platelet counts are checked monthly, and liver function tests (LFTs) can be performed intermittently. After a year of stable dosing with no difficulties with blood counts (except the expected lymphopenia), the intervals between blood count monitoring can be increased.

The cytopenic effect is typically dose dependent, although some patients are more sensitive than others. The typical AZA dose is 2-2.5 mg/kg/day, whereas the dose of 6-MP is 1-1.5 mg/kg/day. In some studies, blood levels of 6-thioguanine has been shown to guide dosing, but such tests offer little advantage, at a much greater cost for routine monitoring and dose adjustment, over CBC counts and liver function tests. In independent studies, metabolite levels have not shown any correlation with clinical efficacy, but they may help in monitoring compliance.

Other adverse effects of immune modifiers include fever, rash, infectious complications, hepatitis, pancreatitis, and bone marrow depression. The most common reason for discontinuing the immune modifiers within the first few weeks is the development of abdominal pain; occasionally, a biochemically demonstrable pancreatitis occurs.

Concerns have been raised about the development of malignancy in patients taking 6-MP and azathioprine. These agents have been associated with a 2- to 4-fold greater incidence of lymphoma and an increase in nonmelanoma skin cancers, but curiously, there is a 3,5-fold decrease in colorectal carcinoma.

Anti-TNF-alpha monoclonal antibodies

Infliximab

Infliximab (Remicade) is an anti-TNF-alpha monoclonal antibody that is administered by infusion for the treatment of Crohn`s disease.

Infliximab neutralizes the biological activity ofTNFα by binding with highaffinityto the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors (*Figure 26*). Infliximab does not neutralize TNFβ (lymphotoxin-α), a relatedcytokinethat utilizes the same receptors as TNFα.

Biological activities attributed to TNFα include:

1. induction of pro- inflammatory cytokines such asinterleukins (IL) 1 and 6;
2. enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes;
3. activation ofneutrophilandeosinophilfunctional activity;
4. induction of acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by synoviocytes and/or chondrocytes.

Infliximab is FDA approved for both ulcerative colitis and Crohn`s disease; it appears to have a higher efficacy rate in Crohn`s disease. Infliximab is generally administered as 3 separate infusions of 5 mg/kg for the induction of remission of moderate to severe IBD at weeks 0, 2, and 6, followed by infusions every 8 weeks for maintenance of remission.

A systemic review of the efficacy of biologic therapies in IBD confirmed that anti-TNF-alpha antibodies was effective in inducing remission of active Crohn`s disease (44). For Crohn`s disease, the response rate may be as high as 80%, and the induction of remission rate is 30-50% after a single dose; with multiple dosing, higher rates of remission are attained. For ulcerative colitis, the response rates may be as high as 50-70%.

Patients with moderate to severe Crohn`s disease who have documented active inflammation, dependence on corticosteroids and an inability to taper these agents, or disease refractory to steroids are most likely to benefit from anti-TNF therapy. Before anti-TNF agents are administered, screening should be done for coexistent infection with perianal and abdominal abscess (including *Mycobacterium tuberculosis*), and caution is advised if a patient is a carrier for the hepatitis B virus (52).

Infliximab is also indicated for the treatment of fistulizing Crohn`s disease. For this indication, the fistula responds (closes) in 68% of patients treated with infliximab, although 12% may develop an abscess. The response can be maintained by continuing regular dosing (ie, every 8 weeks) after the induction dose.

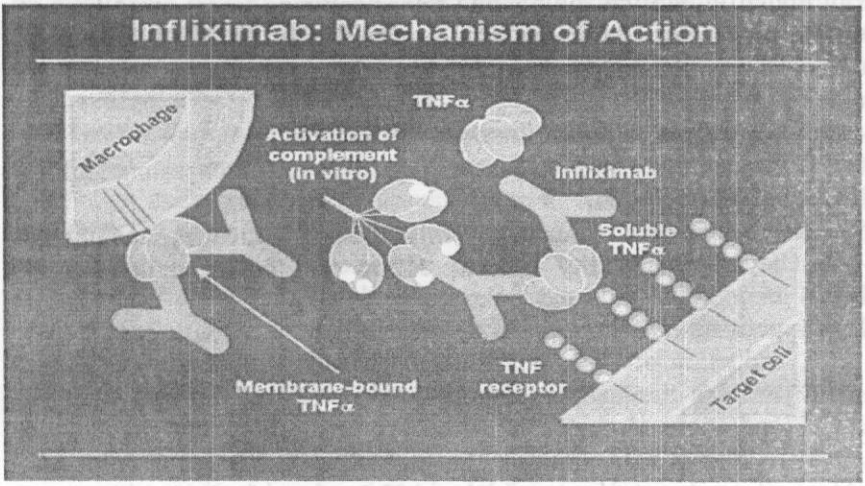


Figure 26. **Infliximab bindings of TNF to membranes of T-cells and macrophages, induces apoptosis and has a potent biological effect.**

Adverse effects of infliximab

The adverse effects of infliximab are uncommon but can include hypersensitivity and flu-like symptoms; the latter can often be avoided by pretreatment with acetaminophen and diphenhydramine. There have been rare reports of lupus-like reactions and lymphoproliferative malignancies, although whether the malignancies are related to the drug or to the underlying disease process remains uncertain; they are more likely due to concomitant use of immunomodulators.

Adalimumab, certolizumab, natalizumab

Other anti-TNF agents include adalimumab (Humira), which is given by subcutaneous (SC) injection every 2 weeks after a loading dose of 6 injections over 4 weeks,and certolizumab pegol (Cimzia), which is given by SC injection every 4 weeks. Natalizumab (Tysabri), an agent aimed at preventing the accumulation of lymphocytes in the diseased bowel by blocking the effects of integrin. Natalizumab is an intravenous medication that has shown efficacy in Crohn`s disease.

Step IV – Clinical Trial Agents

Clinical trial agents tend to be disease-specific (ie, an agent works for Crohn's disease but not for ulcerative colitis, or vice versa). These include anti-adhesion molecules and anticytokine therapies (24). In Crohn's disease, additional agents include T-cell marker therapies and mesenchymal stem cells; in ulcerative colitis, anti-inflammatory proteins have also been studied (24).

Experimental agents used in persons with Crohn's disease include thalidomide (50-300 mg/day PO) and interleukin (IL)-11 (1 mg/wk SC). Experimental agents used in persons with ulcerative colitis include the nicotine patch (14-21 mg/day via topical patch), butyrate enema (100 mL per rectum twice daily), and heparin (10000 U SC twice daily). Multiple contraindications, interactions, and precautions are associated with these drugs (*Figure 27*).

Inflammatory Bowel Disease

1. **Antigen processing and presentation, activation of macrophages**
   - Antibiotics
   - Probiotics
2. **Antigen recognition, activation of CD4+ T cells**
   - CyA
   - Tacrolimus
   - ?MTX
3. **Generation of Th1/Th2 response**
   - IL-10
4. **Production of proinflammatory cytokines**
   - Anti TNF antibodies
   - Thalidominde
   - Corticosteroids
   - IL-11
5. **Recruitment, migration, and adhesion**
   - Antisense oligonucleotide to ICAM-1
   - Anti-α4 integrin antibody
   - ?Heparin
6. **Inflammation and injury**
   - Aminosalicylates
   - Corticosteroids
   - ?Local anesthetics
7. **Repair and restitution**
   - ?Heparin
   - ?IL-11
   - ?Nicotine

Figure 27. **Experimental agents.**

SUPPORTIVE CARE

IBD flares in patients with mild to moderate disease are usually managed in an outpatient setting. However, an important and sometimes overlooked concern in the management of IBD is the dosing and duration of use of corticosteroid therapy. For a flare of moderate severity, a dose of prednisone of 20-40 mg/day or equivalent is often sufficient to treat the flares. Once symptoms are controlled, a dedicated tapering progression of the steroid follows.

Patients are candidates for immunomodulators (azathioprine, 6-mercaptopurine, methotrexate) or anti-TNF agents (infliximab, adalimumab, certolizumab pegol) and biologic agents if flares are frequent (>1-2 times), if the duration of steroid use is prolonged (more than a few weeks per year), if reduction of the steroid dose causes recurrence of symptoms (steroid dependent), or if steroids do not appear to be working (steroid refractory).

A health maintenance issue of particular importance to patients with IBD is a reduction in bone density because of decreased calcium absorption (due to the underlying disease process) or corticosteroid use. Osteoporosis is a very serious complication, approaching 40% of patients with IBD, and increases the risk for fractures. All patients who have been using steroids for longer than 3 months, as well as postmenopausal women, should undergo testing with bone-density studies; treatment with bisphosphonates and calcium supplements can be initiated in patients with significantly low bone density.

MANAGEMENT

Management of ulcerative colitis

Mild to moderately active ulcerative colitis in outpatients with left-sided (distal colitis and proctitis) or extensive disease

Mild to moderately active ulcerative colitis is initially managed with oral 5-aminosalicylic acid compounds. Topical 5-aminosalicylic acid, either alone or in combination with oral 5-aminosalicylic acid, is an alternative therapeutic approach for patients with left-sided disease. For patients with left-sided disease. If topical therapy is used, suppositories are most appropriate for proctitis, whereas more extended disease affecting the sigmoid or greater parts of the left colon need the addition of enemas or foams. Oral or topical 5-aminosalicylic acid doses of more

than 1500 mg per day are sufficient to induce remission. Oral or topical 5-aminosalicylic acid should be continued as maintenance therapy in patients who respond to induction therapy with 5-aminosalicylic acid.

Moderately active ulcerative colitis that does not respond to 5-aminosalicylic acid and severe (but not fulminant) disease requires treatment with oral corticosteroids given at a dose of 40–60 mg of prednisolone per day (or equivalent). Patients who often require steroid therapy should be started on azathioprine at 2-5 mg/kg bodyweight per day or mercaptopurine at 1-5 mg/kg bodyweight per day.

Induction therapy with infliximab at a dose of 5 mg/kg at 0, 2, and 6 weeks followed by maintenance therapy every 8 weeks could be considered in outpatients with steroid dependent or refractory disease or and should be used in patients failing azathioprine or 6-mercaptopurine monotherapy. Alternatives to infliximab are adalimumab given subcutaneously as a loading dose of 160 mg at week 0 and 80 mg at week 2, followed by a maintenance dose of 40 mg every other week and, in the near future, certolizumab pegol given subcutaneously as a loading dose of 400 mg at weeks 0, 2, and 4, followed by a maintenance dose of 400 mg every 4 weeks.

Severe or fulminant colitis in inpatients

Fulminant colitis requires close interaction of gastroenterologists and surgeons to ensure a timely referral for emergency colectomy if indicated. Medical therapy is indicated in patients with severe ulcerative colitis who do not seem toxic (focal abdominal tenderness, suspected or known sepsis). Intravenous corticosteroids at a dose of 60 mg up to 1 mg/kg bodyweight are the first line of treatment accompanied by supportive therapy with intravenous fluids. Bowel rest or parenteral nutrition are not indicated in patients with severe ulcerative colitis, but should be prescribed in patients with toxic megacolon where surgery might be imminent. Routine broad-spectrum antibiotics are not indicated in the absence of abdominal infection. For patients who do not respond to 5 days of intravenous corticosteroids, several medical alternatives exist in addition to colectomy. Ciclosporin, tacrolimus, and infliximab are all effective. Ciclosporin is given intravenously as a 24-h continuous infusion at doses of 2–4 mg/kg per day. Tacrolimus is dosed orally to achieve serum trough concentrations of 5–15 ng/mL (*Figure 28*).

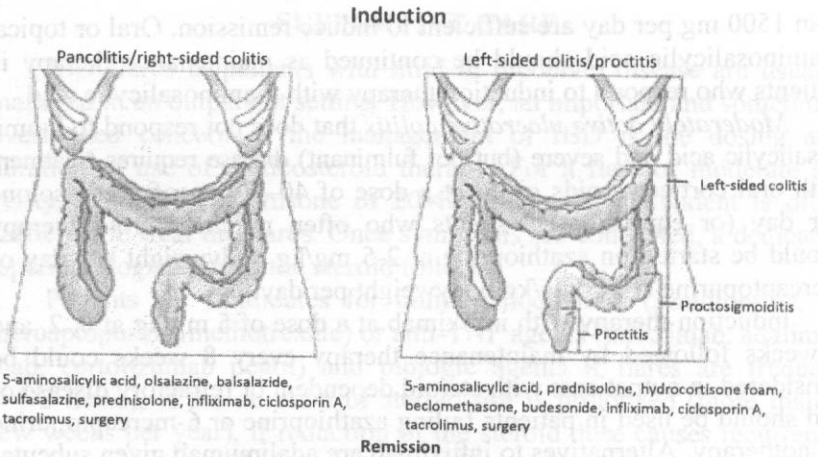


Figure 28. **Stepwise approaches to the management of ulcerative colitis** (from Baumgart D.C., Sandborn W.J. Inflammatory bowel disease: clinical aspects and established and evolving therapies. *Lancet* 2007; 369: 1641–57) (53).

Management of Crohn's disease

Inflammatory Crohn's disease in outpatients

The optimum first-line therapy for *mild Crohn's disease* is dependent on the disease location. Patients with ileal or ileocaecal disease might be induced into remission with budesonide at 9 mg daily. In patients with mild ileocaecal or colonic disease, remission might be induced with sulfasalazine at 4000 mg per day.The use of sulfasalazine is limited by its toxicity. The efficacy of mesalazine at doses of 3200 mg or more per day for first-line induction therapy is not evidence based and is controversial among experts, but is widely used in clinical practice.

Patients who do not respond to first-line therapy should receive induction therapy with 40–60 mg oral prednisolone per day. In general, infliximab at 5 mg/kg bodyweight at weeks 0, 2, and 6 is reserved for patients who do not enter remission with prednisolone. An alternative to infliximab is adalimumab given subcutaneously as a loading dose of 160 mg at week 0 and 80 mg at week 2 and certolizumab pegol given subcutaneously as a loading dose of 400 mg at weeks 0, 2, and 4.

Azathioprine and mercaptopurine are not ideal induction agents because of their slow onset of action. 5-aminosalicylic acid is not effective for maintenance of remission in patients with Crohn's disease. Budesonide maintenance therapy modestly prolongs the time to relapse. The main maintenance agents for Crohn's disease are azathioprine 2,5 mg/kg or mercaptopurine 1,5 mg/kg. An alternative to azathioprine or 6-mercaptopurine is maintenance therapy with methotrexate at 15 to25 mg per week given intramuscularly or subcutaneously. Maintenance therapy of 5 mg/kg infliximab every 8 weeks, alternatively adalimumab given subcutaneously at 40 mg every other week, or in near future also certolizumab pegol given subcutaneously at 400 mg every 4 weeks, therapies can be added to immunosuppressive therapy with azathioprine, 6-mercaptopurine, or methotrexate if needed to maintain a steroid-free remission. Surgery should beconsidered in patients with obstructive complications and those who have not responded to medical therapy.

Fulminant and refractory inflammatory Crohn's disease in inpatients

In patients with fulminant inflammatory Crohn's disease, remission might be induced with intravenous corticosteroids, such as methylprednisolone at a dose of 1,0–1,5 mg/kg bodyweight per day. Intravenous infliximab at a dose of 5 mg/kg bodyweight at weeks 0, 2, and 6 is an alternative as main therapy in thesepatients and can be used in patients who do not respond to intravenous corticosteroids. An alternative to infliximab is adalimumab given subcutaneously as aloading dose of 160 mg at week 0 and 80 mg at week 2 and, in the near future, certolizumab pegol given subcutaneously as a loading dose of 400 mg at weeks 0, 2, and 4. Surgery might be an appropriate initial therapy for patients with fulminant ileocaecal disease with obstructive complication or those unable totolerate medical therapy.

Fistulising Crohn's disease

Fistulising Crohn's disease requires close interaction between surgeons and gastroenterologists. Remission might be induced with antibiotics (ciprofloxacin at1000 mg per day or metronidazole at 1000–1500 mg per day), infliximab at a dose of 5 mg/kg at weeks 0, 2, and 6, or fistulotomy or drainage with setons orboth. An alternative to infliximab is adalimumab, which is given subcutaneously as 160 mg at week 0 and 80 mg at week 2, and then 40 mg subcutaneouslyevery other week beginning at week 4. Patients with fi stulising Crohn's disease can

be maintained on azathioprine 2,5 mg/kg or 6-mercaptopurine at 1,5 mg/kg monotherapy or combined with infliximab 5 mg/kg every 8 weeks maintenance therapy (*Figure 29*).

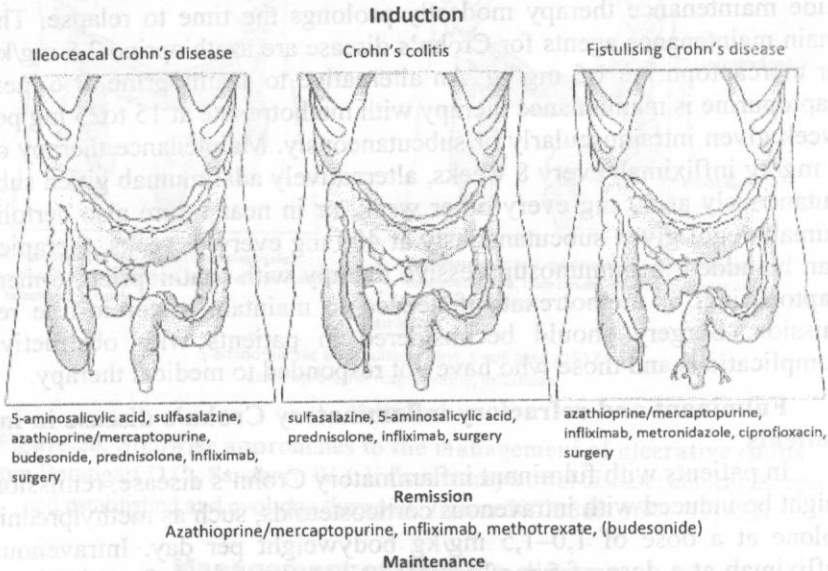


Figure 29. **Stepwise approach to the management of Crohn's disease** (from Baumgart D.C., Sandborn W.J. Inflammatory bowel disease: clinical aspects and established and evolving therapies. *Lancet* 2007; 369: 1641–57) (53).

Inpatient Management

Patients should be admitted to the hospital if surgical intervention is anticipated or if their condition does not respond to outpatient treatment, if they are dehydrated, or if they have uncontrolled pain or diarrhea. Start IV hydration. If indicated, obtain an abdominal flat-plate image to exclude obstruction or megacolon. If the patient is nauseous or vomiting or has evidence of obstruction or megacolon, nasogastric intubation may be helpful. Consider early consultation with a surgeon in the setting of severe colitis or bowel obstruction.

If the patient has active colitis, send a stool sample for *Clostridium difficile* toxin assay and routine microbiologic culture. Laboratory studies to be considered include a CBC count with differential; erythrocyte sedimentation rate; levels of albumin, glucose, calcium, magnesium,

phosphate, and BUN/creatinine; electrolyte status; and a pregnancy test in females of childbearing age.

Patients with acute severe colitis are treated with IV corticosteroids. Antibiotics may not be routinely indicated but may be indicated in select patients. Electrolyte correction and, potentially, transfusion can be performed if indicated on the basis of laboratory findings.

Patients with suspected bowel obstruction should be kept on a diet of nothing by mouth, except for medications. Most patients with ulcerative colitis may maintain a regular (or low-fiber) diet, unless megacolon is present or surgery is being contemplated.

Although a colonoscopic evaluation may also be contemplated, consider the increased risk of perforation in persons with acute colitis. Assess and correct the posthydration CBC count and electrolyte levels, as indicated. Depending on the response to the initial interventions, advancement of the diet may be considered.

By the second or third hospital day, most patients should be showing clear evidence of clinical improvement from IV steroids. Assess the electrolyte status if IV fluids are still being administered. Consider advancement of the diet. The corticosteroid dose can be tapered. If the patient is not improving, consider other treatment options; these may include hyperalimentation, other medical therapies, surgical intervention, or transfer to a tertiary care facility.

Continue to advance the diet, as tolerated, on hospital day 4. Continue the switch to oral medications. Many patients with a flare of Crohn's disease or ulcerative colitis may be discharged by this time (occasionally even sooner); some may require another day of IV therapy.

If no progress has been made in the patient's condition since admission, additional treatments are necessary, including surgery or more aggressive medical treatments. Again, consider transfer to a tertiary care facility. If the patient has been unable to tolerate an oral diet, initiate hyperalimentation and/or reconsider surgical intervention.

Most patients should be able to be discharged on or before the fifth hospital day. A regular diet should be tolerated, with some restrictions if strictures are present. An ESR level may be obtained to assist in future disease assessment, but its result is unlikely to alter current management.

Discharge the patient on oral medications, with appropriate follow-up as an outpatient, typically within a few weeks.

Management of Refractory Disease

Step-down therapy should be considered early in the management of patients with difficult or refractory disease. This approach uses immune modifiers or anti-TNF agents earlier in the treatment of the IBD patient than the step-up approach described earlier (*Figure 23*).

Immune modifiers

If it is difficult to reduce the dose of corticosteroids, if the disease is refractory to corticosteroid therapy, or if patients are corticosteroid dependent, the use of immune modifiers 6-MP or azathioprine should be used. The typical dosing of 6-MP or azathioprine is 1-2 mg/kg/day. At higher doses, closer monitoring is warranted, including measurement of the thiopurine methyltransferase (TPMT) enzyme; obtaining 6-TG and 6-MMP levels; doing a CBC; and determining liver, kidney, pancreatic function.

These agents are not used for acute flares, because the time from the initiation of treatment to the onset of significant action may be as long as 2-3 months. Response to immune modifiers may be dose dependent; monitoring of blood counts is required to protect the patient from the hematologic toxicity associated with these agents.

Monoclonal antibodies

An alternative agent is infliximab, a monoclonal antibody against TNF-alpha. A randomized, controlled trial demonstrated that adalimumab can induce remission in patients with Crohn's disease that is refractory to treatment with infliximab.Note that in September 2011, the US Food and Drug Administration issued a notification regarding updates to the Black Box Warning for the entire class of tumor necrosis factor-alpha blockers (54). The advisory included the risk of *Legionella* and *Listeria* infections, as well as consistency of the information in the Boxed Warning and the Warnings and Precautions sections regarding the risk of serious infections and the associated disease-causing organisms.

Smoking cessation

A lifestyle change that may benefit patients with Crohn's disease is smoking cessation. Tobacco use has been linked to increases in the number and severity of flares of Crohn's disease, and smoking cessation alone is occasionally sufficient to achieve remission of refractory Crohn's disease.

Management in Remission

The top-down approach (ie, earlier use of immunomodulators and biologics) includes the need for steroid-enhanced mucosal healing and achieves an earlier and more complete remission than step-up therapy (*Figure 23*). A general rule of thumb is that once remission is achieved, the medications used to achieve remission should be continued, except steroids, which should be tapered off, because they have no role in maintaining remission (55) and their use may lead to debilitating illness, particularly after long-term use. Home infusion of IV hyperalimentation is becoming increasingly available for those rare patients with Crohn's disease who need prolonged bowel rest is necessary (eg, cases of severe fistulizing disease). The short bowel may require prolonged hyperalimentation.

Management of the Older IBD Patients

Diseases of the lung (primarily chronic obstructive pulmonary disease) in Crohn's disease are common comorbidities, primarily because of smoking; however, cardiovascular disease, although common in the older patient, does not have any direct link with IBD. IBD may also be a factor in the treatment of prostate cancer (to avoid rectal injury), but is generally not a factor in breast cancer.

Most of the concerns regarding the interaction of other disease processes and IBD revolve around the medications used to treat various conditions; therefore, the physician treating the older patient must continually be aware of the potential for medication interactions. Although the advent of electronic medical records makes it easier to check for such interactions easier, it remains up to the physician to determine which interactions are clinically significant.

Aspirin and nonsteroidal anti-inflammatory drugs are frequently used for cardiovascular and rheumatologic disorders; these agents and cyclooxygenase type 2 (COX-2) inhibitors are known to cause flares in IBD (not universally, but often enough to be clinically important) (56).

Most aminosalicylates do not have substantial interactions with non-IBD agents. The side effects of corticosteroids may be exacerbated in the older population, particularly in those with diabetes, accelerated bone loss, and cataract formation. The anti-TNF agents are generally contraindicated in patients with congestive heart failure (CHF) but can be used once the CHF is controlled. The immune-modifying agents have

a clinically important interaction with allopurinol, as allopurinol tremendously increases the serum levels of mercaptopurine and azathioprine to the point where these agents can quickly manifest toxicity.

Surgical intervention

Ulcerative colitis is a surgically curable disease. However, Crohn's disease can involve any segment of the gastrointestinal tract from the mouth to the anus; surgical resection is not curative, as recurrence is the norm. In addition, repeated need for surgery and bowel resection may result in short gut syndromeand dependence on parenteral nutrition.

Ulcerative colitis

Consider surgical intervention for patients in whom medical therapy fails, as it is curative for colonic disease, and for those with colonic dysplasia or malignancy (26). Approximately 25-30% of patients may require operative management (24).

Emergency surgery is indicated in patients with lifethreatening complications:

- perforation;
- refractory rectal bleeding; and
- toxic megacolon not responsive to medical management (57).

Elective surgeryis indicated in patients with:

- dysplasia or cancer;
- ulcerative colitis refractory to medical management; or
- intolerance to long-term immunosuppression or other medical therapies (58, 59).

Elective surgery can sometimes be performed laparoscopically. For fulminant colitis, the surgical procedure of choice consists of a subtotal colectomy with end ileostomy and creation of a Hartmann pouch.

The surgical options for ulcerative colitis vary. Currently, the 2 most common choices are proctocolectomy with ileostomy and total proctocolectomy with ileal J-pouch-anal anastomosis (*Figure 30*).

The most common operation performed to treat ulcerative colitis is *ileal pouch/anal anastomosis* (IPAA). In this multistage procedure, a diverting ileostomy is performed and an ileal pouch is created and anastomosed directly to the anus, with complete removal of the rectal mucosa. After the ileoanal anastomosis is healed, the ileostomy is taken down, and flow through the anus is reestablished.

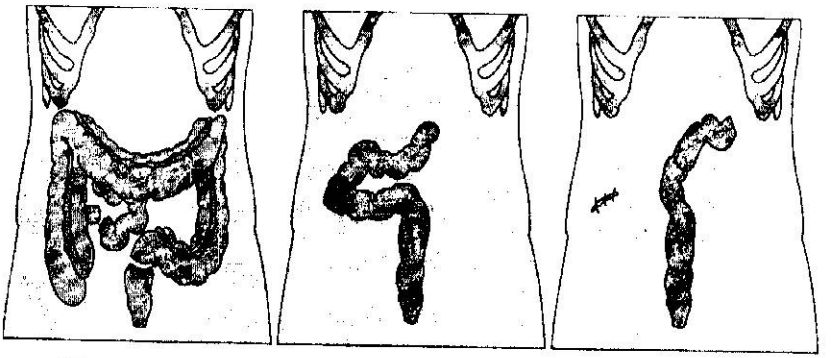


Figure 30. **Scheme of the proctocolectomy with ileo-pouch anal anastomosis surgical procedure** (from Baumgart D.C., Sandborn W.J. Inflammatory bowel disease: clinical aspects and established and evolving therapies. *Lancet* 2007; 369: 1641 -57) (53).

Debate exists about the technical aspects of this procedure, such as mucosectomy versus doublestaple technique, the role of temporary diverting ileostomy, the optimum patient age, the role of ilealJ-pouch-anal anastomosis in indeterminate colitis, andthe advantages of laparoscopic versus open surgery. Very rarely, particularly in those with a preoperative diagnosis of indeterminate colitis, Crohn's disease of the pouch may develop. An alternative to the ileal J-pouch-anal anastomosis is proctocolectomy with Brooke ileostomy (58).

Proctocolectomy with ileal J-pouch-anal anastomosis might be complicated by the development of pouchitis, high stool frequency, faecal incontinence, reduced fertility, and need for reoperation.

IPAA offers an excellent option for younger patients with ulcerative colitis and concerns about body image. However, IPAA is also associated with a substantial rate of infertility (due to pelvic dissection). For patients who plan to become pregnant, a subtotal colectomy is preferred to avoid the 48% decrease in fecundity with the IPAA procedure.

Crohn's disease

Although surgery might be necessary to induce remission or to treat complications in some patients, it will not cure Crohn's disease. Surgery for Crohn's disease is most commonly performed in cases of complications of the disease (ie, strictures, fistulas). Approximately 70% of patients with ileocolonic Crohn's disease require surgical intervention

(although rates as high as 70-75% have been reported from certain cohorts (24)). In general, conservative resection is advocated (including potential stricturoplasty, as opposed to resective surgery) to preserve bowel length in case additional surgery is needed in the future.

In general, in patients with colonicdisease, indications for emergency and elective surgery aresimilar to those for ulcerative colitis. Specific indications for surgery include formation of fibrotic strictures leadingto symptoms of part or complete bowel obstruction, internal fistulas complicated by abdominal abscess, enterovesical fistulas, and enterocutaneous fistulas (58).

Although surgery is an important treatment option for Crohn's disease, patients should be aware that it is not curative and that disease recurrence after surgery is the rule. Disease recurrence generally mimics the original disease pattern at the surgical anastomosis. Endoscopic evidence of recurrent inflammation is present in 93% of patients 1 year after surgery.

In segmental resection, a segment of intestine with active Crohn's disease or a stricture is resected, and the remaining bowel is reanastomosed. In general, as little bowel as possible is resected, because the risk of disease recurrence is significant.

In patients with a very short cicatrix stricture, a bowel-sparing stricturoplasty can be performed. In this procedure, a longitudinal incision is made across the stricture, and then the incision is repaired with a vertical suture. All mucosa is spared, and the obstruction is relieved. As many as 6-8 stricturoplasties can be performed in a single operative session.

Stricturoplasty is associated with a 6-8% rate of septic complications (2-3% of patients require reoperation); this may be prevented with optimal preoperative management to control the inflammatory component of the stricture before surgical intervention.

Ileorectal or ileocolonic anastomosis is an option available to some patients who have distal ileal or proximal colonic disease. In patients with severe perianal fistulas, a diverting ileostomy or colostomy is an option. In this procedure, the distal colon is defunctionalized and a temporary ileostomy or colostomy is created. The ileostomy or colostomy is then taken down after 6 months or longer. Many patients who pursue this option choose to forego reanastomosis after placement of a stoma and a consequent improvement in quality of life. Approximately 50% of

patients who have the reanastomosis performed have recurrences of perianal disease.

Symptomatic enteroenteric fistulas are generally resected, although recurrence is common. Postoperative medical therapy often prevents recurrence, although data are lacking regarding efficacy. 5-ASA preparations provide a very modest benefit for maintenanceofremission in patients with Crohn'sdisease (46). Budesonide and conventional corticosteroidsare not effective. Mesalazine at doses of 3000–4000 mg per day has a modest effect. The preferred program of prevention varies between immunomodulators and biologic therapy. Azathioprine and mercaptopurine mightbe effective, but the controlled trials showed inconsistent results and only modest efficacy (60). Metronidazole showedshort-term efficacy, and ordnidazole given for a year was effective (*Table 10*) (61).

Contraception in the perioperative setting

Before undergoing major elective surgery, women with IBD should stop using combined oral contraception for a minimum of 4 weeks before the surgery, and alternative methods of contraception should be used (61). Advise each patient when oral contraception can be restarted.

If a woman with IBD is considering sterilization, counsel her and her partner regarding alternative contraceptive methods (eg, long-acting reversible contraception, vasectomy). Note that in women with a history of pelvic or abdominal surgery, laparoscopic sterilization may not be considered an appropriate contraceptive method (62).

Tapering corticosteroids in the postoperative setting

If possible, the use of corticosteroids should be minimized before surgery. Poor postoperative outcomes have been associated with prednisone doses greater than 30 mg/day (24).

The World Gastroenterology Organization (WGO) recommendations for tapering corticosteroids depend on the duration of corticosteroid use, as follows (24):

- Less than 1 month: abrupt cessation postoperatively is allowed.
- 1-3 months, with a dose of 20 mg/day or greater: taper by 5 mg/day per week after surgery.
- 3-6 months: taper by 2,5 mg/day per week.
- More than 6 months: taper slowly, at 1 mg/wk or less once the dose is 10 mg/day.

Crohn's disease – evidence-based indications for treatment

(from Baumgart D.C., Sandborn W.J. Inflammatory bowel disease: clinical aspects and established and evolving therapies. *Lancet* 2007; 369: 1641–57) (53)

Drug	Dose	Mildly to moderately active		Refractory and severely active		Perianal fistulas		Postoperative maintenance
		Induction	Maintenance	Induction	Maintenance	Induction	Maintenance	
Oral sulfasalazine	Induction 3–6 g per day	Yes[64,65]	No[64,65]					No[69]
Oral mesalazine		No[66,68]	No[72,73,1]					No[70,72,1]
Oral corticosteroids prednisone	Induction 0·25 mg per kg to 0·75 mg per kg	Yes[64]	No[64]	Yes[64]	No[64]			No[73]
Oral corticosteroids methyl-prednisolone	Induction 48 mg per day	Yes[65]	No[65]	Yes[65]	No[65]			
Intravenous corticosteroids prednisone	Prednisone 60 mg per day			Yes[74]				
Budesonide	Induction 9 mg per day Maintenance 6 mg per day	Yes[75,76]	No[77,2]		Yes			No
Metronidazole†	Induction 10–20 mg per kg per day	No[4,78,1]				Yes[3]		No[84,4]
Azathioprine	Azathioprine 2–3 mg per kg per day	No[5]	No[6]	No[5]	Yes[81]	No[5]	Yes[81]	Yes[82]
Mercaptopurine	Maintenance 1·1,5 mg/kg per day	No[5]	No[6]	No[5]	Yes[81]	No[5]	Yes[81]	Yes[83]
Methotrexate	Induction 25 mg per week Maintenance 15–25 mg per week			Yes[84,4]	Yes[85]			
Infliximab	Induction 5 or 10 mg/kg at weeks 0, 2, and 6 Maintenance 5 or 10 mg/kg every 8 weeks			Yes[86]	Yes[87]	Yes[88]	Yes[89]	
Adalimumab	Induction 160 mg at week 0 and 80 mg at week 2 Maintenance 40 mg every other week or weekly			Yes[90]	Yes[91]	Yes in a subgroup analysis[91]	Yes in a subgroup analysis[91]	
Certolizumab pegol	Induction 400 mg at weeks 0, 2, and 4 Maintenance 400 mg every 4 weeks			Yes[92]	Yes[93]	No data	No data	

[1]Recommended in current practice guidelines and widely used in clinical practice. Evidence for controlled clinical trials does not consistently support efficacy. [2]Budesonide 6 mg per day significantly increases time to relapse, but does not meet conventional criteria for maintenance of remission at 1 year in patients with medically induced remission. Budesonide 6 mg is effective as a steroid-sparing agent in patients who are dependent on prednisone or prednisolone. [3]Recommended in current practice guidelines and widely used in clinical practice. Evidence based on uncontrolled studies only, no controlled trials ever done. [4]Studies show short-term reduction in recurrence of severe endoscopic lesions, no difference in clinical remission rates at 1 year. [5]Slow onset of action precludes or limits use as induction agent. [6]Toxicity profile of agent precludes use for this indication.

Reproduction and pregnancy

Clinicians are advised to review the prescribing information for medications in women who are attempting to conceive, are pregnant, or are breastfeeding (62). All of the aminosalicylates (sulfasalazine, mesalamine, olsalazine, balsalazide) and corticosteroids appear to be safe in women in all phases of fertility, pregnancy, and lactation. Men should avoid sulfasalazine during periods when they and their mates are attempting to become pregnant.

Reproduction

In women with IBD, fertility is normal or only minimally impaired. The majority of case reports and small series show no adverse outcomes of pregnancies in patients with IBD who are taking immune modifiers. Birth defects have not been reported at a rate higher than that of the general population. If a patient is taking an immune modifier and becomes pregnant, current data support the consensus that continuing the immune modifier throughout the pregnancy is the safest course of action for both the mother and the fetus (63).

The only agent that is contraindicated in women considering pregnancy is methotrexate (MTX), which has demonstrated teratogenic effects. MTX should be discontinued 3 months prior to planned conception.

For men with IBD, sulfasalazine can decrease sperm counts and sperm motility, causing a functional azoospermia; the other aminosalicylates do not have this effect. The sperm effects are reversible by discontinuing the sulfasalazine. No firm evidence indicates that the use of immune modifiers in the father leads to increased birth defects.

Pregnancy

Most infants born to parents with IBD are healthy. The prevalence of prematurity, stillbirth, and birth defects is similar to that of the general population. The prevalence of spontaneous abortion is slightly higher in patients with IBD (12,2%) than in the general population (9,9%). Previous proctocolectomy or ileostomy is not an impediment to successful pregnancy; however, controversy exists regarding the type of delivery (cesarean or vaginal) that is most appropriate when a woman

has had ileal pouch/anal anastomosis surgery (62). Women who have undergone such a procedure should consult with their obstetricians and gastroenterologists (62).

Aminosalicylates, including sulfasalazine, are safe during pregnancy. Folate supplements should be taken. Corticosteroids are also safe, but if high doses are needed near the end of the pregnancy, monitor the infant for signs of adrenal suppression. Continuation of immune modifiers (ie, 6-MP, azathioprine) appear to be safe in pregnancy, (56, 64) as well as metronidazole and ciprofloxacin.

It is considered safe to continue TNF-alpha inhibitors during pregnancy (FDA category B), but concerns have been raised about high levels of maternally administered anti-TNF agents being found in the fetal circulation (65-68). The manufacturers of infliximab and adalimumab recommend that these 2 agents be discontinued during the third trimester of pregnancy, although there is no documentation of fetal harm. Certolizumab does not cross the placenta (65-68).

Effective contraception must be used with certain drug therapy. Both male and female partners receiving methotrexate should use effective contraception for a minimum of 3 months following treatment with this agent.

Other concerns that have been raised include the potential reduction of fertility with total abdominal colectomy with ileal pouch/anal anastomosis (IPAA) surgery (primarily because of adhesions). This possibility can likely be avoided by using a laparoscopic approach, and if infertility occurs, fertility can often be normalized by lysis of adhesions.

According to the Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit in the United Kingdom, women with IBD should plan for conception when their disease is stable and well controlled (62). Male and female patients require prepregnancy counseling to help them with the best management of their condition before conception occurs.

Contraception precautions

Advise women who have Crohn's disease and small bowel disease and malabsorption that oral contraception may have reduced effectiveness (62). Additional contraception is recommended for women on combined hormonal contraception who are also receiving antibiotic regimens for less than 3 weeks, as well as for 7 weeks following cessa-

tion of the antibiotic. Note that certain medications prescribed for rectal or genital use may adversely affect the efficacy of condoms (62). In addition, consider whether contraceptive agents may have an effect on diseases associated with IBD (eg, osteoporosis, venous thromboembolism, primary sclerosing cholangitis).

In women with IBD who will undergo major elective surgery, combined oral contraception should be discontinued for a minimum of 4 weeks before the procedure.These women should use alternative contraception.

Breastfeeding

Sulfasalazine metabolites can be detected in breast milk. Low concentrations of mesalamine and higher concentrations of its metabolites can also be detected in breast milk, but the significance of this is unknown. In addition, corticosteroids can also be detected in breast milk.

Immune modifiers are excreted in breast milk and should be considered only on a case-by-case basis; either the immune modifier should be discontinued or the infant should be bottle fed.

Antibiotics (metronidazole, ciprofloxacin) should generally be avoided during lactation, because they are excreted in breast milk; either breastfeeding or the drugs should be discontinued. These agents are probably safe for fertility and during pregnancy.

Anti-TNF agents (ie, infliximab, adalimumab) traverse the placenta, whereas certolizumab does not, because of the absence of the Fc fragment. They are found in the cord blood but not in breast milk.

Although small amounts of the topical agents are absorbed and thus may be excreted in breast milk, the concentrations are much lower than those with the oral forms of the same medications. These medications are probably reasonably safe in breastfeeding.

CONSULTATIONS

In patients with severe IBD, with complications such as strictures or fistulas, and with flares requiring hospitalization, consultation with a surgeon is often required. Early consultation with a surgeon is particularly important in patients with severe disease or extraluminal complications, because delayed surgery can be associated with poorer outcomes.

An interventional radiologist may be consulted when percutaneous drainage of an abscess is desired. Specialty consultation is best for

managing extracolonic manifestations (ie, uveitis, arthritis, dermatitis, sclerosing cholangitis). Also consider arranging consultations for patients with a registered dietitian and a stoma nurse, if indicated.

PROGNOSIS

The standardized mortality ratio for IBD ranges from approximately 1,4 times the general population (Sweden) to 5 times the general population (Spain). Most of this increase appears to be in the Crohn's disease population; the ulcerative colitis population appears to have the same mortality rate as the general population.

The majority of studies indicate a small but significant increase in mortality associated with IBD (69). A frequent cause of death in persons with IBD is the primary disease (70); infections and COPD/respiratory illness are other major causes of death (71). IBD is not a risk factor for cardiovascular mortality (72).

Patients with IBD are more prone to the development of malignancy. Persons with Crohn's disease have a higher rate of small bowel malignancy. Patients with pancolitis, particularly ulcerative colitis, are at a higher risk of developing colonic malignancy after 8-10 years of disease. The current standard of practice is to screen patients with colonoscopyat 1-2 year intervals once they have had the disease for greater than 10 years.

In addition to long-term, disease-related complications, patients can also experience morbidity from prolonged medical therapy, particularly as a consequence of steroid exposure.

Ulcerative colitis

The average patient with ulcerative colitis has a 50% probability of having another flare during the next 2 years; however, patients may have only one flare over 25 years, and others may have almost persistent active disease. A small percentage of patients with ulcerative colitis have a single attack and no recurrence. Typically, remissions and exacerbations are characteristic of this disease, with acute attacks lasting weeks to months.

Patients with ulcerative colitis limited to the rectum and sigmoid have a 50% chance of progressing to more extensive disease over 10

years and a 7,5% rate of colectomy over 5 years.Approximately 10% of patients presenting with proctitis will develop a pancolitis (73).

Crohn`s disease

The clinical course of Crohn`s disease is much more variable than that of ulcerative colitis, and it is dependent on the anatomic location and extent of the disease. Periodic remissions and exacerbations are the rule in Crohn`s disease. The relapse rate over 10 years is 90%, and the cumulative probability of requiring surgery over 10 years is approximately 38%. Terminal ileum location, fistulizing, and structuring disease are all independent risk factors for subsequent surgery (74).

A review of the literature indicates that approximately 80% of patients who are in remission for 1 year will remain in remission over subsequent years.Patients with active disease in the past year have a 70% chance of having clinical disease activity in the following year. Approximately 20% of patients will have annual relapses, and 13% will have a course free of relapses. Less than 5% of patients with Crohn`s disease will have continually active disease (75).

Overall, the patient's quality of life with Crohn`s disease is generally lower than that of individuals with ulcerative colitis. Studies support evidence that specific *CARD15* mutations are associated with the intestinal location of the disease, as well as course and prognosis, (9) and are correlated with the propensity for developing ileal strictures and with an early onset of disease.

Bibliography

1. Agrawal D., Rukkannagari S., Kethu S. Pathogenesis and clinical approach to extraintestinal manifestations of inflammatory bowel disease.*Minerva Gastroenterol Dietol.* Sep 2007;53(3):233-48.
2. Centers for Disease Control and Prevention. Inflammatory bowel disease (IBD). Available athttp://www.cdc.gov/ibd/#epidIBD
3. Molodecky N.A., Soon I.S., Rabi D.M., Ghali W.A., Ferris M., Chernoff G., et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review.*Gastroenterology.* Jan 2012; 142(1):46-54.e42; quiz e30.
4. Roth M.P., Petersen G.M., McElree C., Feldman E., Rotter J.I. Geographic origins of Jewish patients with inflammatory bowel disease. *Gastroenterology.* Oct 1989;97(4):900-4.
5. Ţurcan S. Colita ulceroasă. Universitatea de Stat de Medicină şi Farmacie "Nicolae Testemiţanu". Chişinău: CEP Medicina, 2012. 192 p
6. Amre D.K., D'Souza S., Morgan K., Seidman G., Lambrette P., Grimard G., et al. Imbalances in dietary consumption of fatty acids, vegetables, and fruits are associated with risk for Crohn's disease in children. *Am J Gastroenterol.* Sep 2007;102(9):2016-25.
7. Jantchou P., Morois S., Clavel-Chapelon F., Boutron-Ruault M.C., Carbonnel F. Animal protein intake and risk of inflammatory bowel disease: The E3N prospective study. *Am J Gastroenterol.* Oct 2010;105(10):2195-201.
8. Bengtson M.B., Solberg I.C., Aamodt G., Jahnsen J., Moum B., Vatn M.H. Relationships between inflammatory bowel disease and perinatal factors: both maternal and paternal disease are related to preterm birth of offspring. *Inflamm Bowel Dis.* May 2010; 16(5):847-55.
9. Tsianos E.V., Katsanos K.H., Tsianos V.E. Role of genetics in the diagnosis and prognosis of Crohn's disease. *World J Gastroenterol.* Jan 14 2012; 18(2):105-18.
10. Glas J., Seiderer J., Wetzke M., Konrad A., Török H.P., Schmechel S., et al. rs1004819 is the main disease-associated IL23R variant in German Crohn's disease patients: combined analysis of IL23R, CARD15, and OCTN1/2 variants. *PLoS One.* Sep 5 2007;2(9):e819.
11. Hampe J., Franke A., Rosenstiel P., Till A., Teuber M., Huse K., et al. A genome-wide association scan of nonsynonymous SNPs identifies a susceptibility variant for Crohn's disease in ATG16L1. *Nat Genet.* Feb 2007; 39(2):207-11.
12. Silverberg M.S., Cho J.H., Rioux J.D., McGovern D.P., Wu J., Annese V., et al. Ulcerative colitis-risk loci on chromosomes 1p36 and 12q15 found by genome-wide association study. *Nat Genet.* Feb 2009; 41(2):216-20.

13. Thoreson R., Cullen J.J. Pathophysiology of inflammatory bowel disease: an overview. *Surg Clin North Am.* Jun 2007; 87(3):575-85.
14. Rioux J.D., Xavier R.J., Taylor K.D., Silverberg M.S., Goyette P., Huett A., et al. Genome-wide association study identifies new susceptibility loci for Crohn's disease and implicates autophagy in disease pathogenesis. *Nat Genet.* May 2007;39(5):596-604.
15. Lashner B. Inflammatory bowel disease. In: Carey W.D., ed. *Cleveland Clinic: Current Clinical Medicine - 2009.* Philadelphia, Pa: Saunders; 2009.
16. Wilkins T., Jarvis K., Patel J. Diagnosis and management of Crohn's disease. *Am Fam Physician.* Dec 15 2011; 84(12):1365-75.
17. Trinchieri A., Lizzano R., Castelnuovo C., Zanetti G., Pisani E. Urinary patterns of patients with renal stones associated with chronic inflammatory bowel disease. *Arch Ital Urol Androl.* Jun 2002; 74(2):61-4.
18. Silverberg M.S., Satsangi J., Ahmad T., et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: Report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol 2005; 19(suppl A):5 36.
19. Gasche C., Scholmerich J., Brynskov J., et al. A simple classification of Crohn's disease: report of the Working Party for the World Congresses of Gastroenterology, Vienna 1998. Inflamm Bowel Dis 2000;6:8–15.
20. Satsangi J., Silverberg M.S., Vermeire S., Colombel J.-F. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut 2006; 55:749–753. doi: 10.1136/gut. 2005. 082909.
21. Ho G.T., Nimmo E.R., Tenesa A., et al. Allelic variations of the multidrug resistance gene determine susceptibility and disease behavior in ulcerative colitis. Gastroenterology 2005; 128:288–96.
22. Joossens S., Reinisch W., Vermeire S., et al. The value of serologic markers in indeterminate colitis: a prospective follow-up study. Gastroenterology 2002; 122:1242–7.
23. Price A.B. Overlap in the spectrum of non-specific inflammatory bowel disease – 'colitis indeterminate'. J Clin Pathol 1978; 31:567–77.
24. World Gastroenterology Organisation (WGO). World Gastroenterology Organisation Global Guideline. Inflammatory bowel disease: a global perspective. Munich, Germany: World Gastroenterology Organisation (WGO); 2009.
25. Gisbert J.P., McNicholl A.G. Questions and answers on the role of faecal calprotectin as a biological marker in inflammatory bowel disease. *Dig Liver Dis.* Jan 2009; 41(1):56-66.
26. Kornbluth A., Sachar D.B. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol.* Mar 2010; 105(3):501-23; quiz 524.

27. D'Incà R., Dal Pont E., Di Leo V., Ferronato A., Fries W., Vettorato M.G., et al. Calprotectin and lactoferrin in the assessment of intestinal inflammation and organic disease. *Int J Colorectal Dis.* Apr 2007; 22(4):429-37.
28. Panés J., Bouzas R., Chaparro M., García-Sánchez V., Gisbert J.P., Martínez de Guereñu B., et al. Systematic review: the use of ultrasonography, computed tomography and magnetic resonance imaging for the diagnosis, assessment of activity and abdominal complications of Crohn's disease. *Aliment Pharmacol Ther.* Jul 2011; 34(2):125-45.
29. Rimola J., Ordás I., Rodriguez S., García-Bosch O., Aceituno M., Llach J., et al. Magnetic resonance imaging for evaluation of Crohn's disease: validation of parameters of severity and quantitative index of activity. *Inflamm Bowel Dis.* Aug 2011; 17(8):1759-68.
30. Paulsen SR, Huprich JE, Fletcher JG, Booya F, Young BM, Fidler JL, et al. CT enterography as a diagnostic tool in evaluating small bowel disorders: review of clinical experience with over 700 cases.*Radiographics.* May-Jun 2006;26(3):641-57; discussion 657-62.
31. Guimarães L.S., Fidler J.L., Fletcher J.G., Bruining D.H., Huprich J.E., Siddiki H., et al. Assessment of appropriateness of indications for CT enterography in younger patients. *Inflamm Bowel Dis.* Feb 2010; 16(2):226-32.
32. Solem C.A., Loftus E.V. Jr., Fletcher J.G., Baron T.H., Gostout C.J., Petersen B.T., et al. Small-bowel imaging in Crohn's disease: a prospective, blinded, 4-way comparison trial.*Gastrointest Endosc.* Aug 2008; 68(2):255-66..
33. [Guideline] Bernstein C.N., Fried M., Krabshuis J.H., Cohen H., Eliakim R., Fedail S., et al. World Gastroenterology Organization Practice Guidelines for the diagnosis and management of IBD in 2010. *Inflamm Bowel Dis.* Jan 2010; 16(1):112-24.
34. Vavricka S.R., Brun L., Ballabeni P., Pittet V., Prinz Vavricka B.M., Zeitz J., et al. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. *Am J Gastroenterol.* 2011; 106:110-119.
35. Larsen S., Bendtzen K., Nielsen O.H. Extraintestinal manifestations of inflammatory bowel disease: epidemiology, diagnosis, and management. *Ann Med.* Mar 2010;42(2):97-114.
36. Frøslie K.F., Jahnsen J., Moum B.A., Vatn M.H. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. *Gastroenterology.* Aug 2007; 133(2):412-22.
37. Schnitzler F., Fidder H., Ferrante M., Noman M., Arijs I., Van Assche G., et al. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. *Inflamm Bowel Dis.* Sep 2009; 15(9):1295-301.

38. Baert F., Moortgat L., Van Assche G., Caenepeel P., Vergauwe P., De Vos M., et al. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease.*Gastroenterology*. Feb 2010; 138(2):463-8; quiz e10-1.
39. Colombel J.F., Sandborn W.J., Reinisch W., Mantzaris G.J., Kornbluth A., Rachmilewitz D., et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med*. Apr 15 2010; 362(15):1383-95.
40. Ha C., Kornbluth A. Mucosal healing in inflammatory bowel disease: where do we stand? *Curr Gastroenterol Rep*. Dec 2010; 12(6):471-8.
41. Feagan B.G., Lémann M., Befrits R., Connell W., D'Haens G., Ghosh S., et al. Recommendations for the treatment of Crohn's disease with tumor necrosis factor antagonists: an expert consensus report. *Inflamm Bowel Dis*. Jan 2012; 18(1):152-60.
42. Hanauer S.B. Crohn's disease: step up or top down therapy. *Best Pract Res Clin Gastroenterol*. Feb 2003; 17(1):131-7.
43. Johannesson E., Simren M., Strid H., Bajor A., Sadik R. Physical activity improves symptoms in irritable bowel syndrome: a randomized controlled trial. *Am J Gastroenterol*. May 2011; 106(5):915-22.
44. Ford A.C., Bernstein C.N., Khan K.J., et al. Glucocorticosteroid therapy in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol*. Apr 2011;106(4):590-9; quiz 600.
45. Ardizzone S., Cassinotti A., Duca P., et al. Mucosal healing predicts late outcomes after the first course of corticosteroids for newly diagnosed ulcerative colitis. *Clin Gastroenterol Hepatol*. Jun 2011; 9(6):483-489.e3.
46. Gordon M., Naidoo K., Thomas A.G., Akobeng A.K. Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease. *Cochrane Database Syst Rev*. 2011; (1):CD008414.
47. Tursi A., Brandimarte G., Papa A., et al. Treatment of relapsing mild-to-moderate ulcerative colitis with the probiotic VSL#3 as adjunctive to a standard pharmaceutical treatment: a double-blind, randomized, placebo-controlled study. *Am J Gastroenterol*. Oct 2010; 105(10):2218-27.
48. Mach T. Clinical usefulness of probiotics in inflammatory bowel diseases.*J Physiol Pharmacol*. Nov 2006;57 Suppl 9:23-33.
49. Khan K.J., Ullman T.A., Ford A.C., et al. Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis. *Am J Gastroenterol*. Apr 2011; 106(4):661-73.
50. [Guideline] Lichtenstein G.R., Abreu M.T., Cohen R., Tremaine W. American Gastroenterological Association Institute medical position statement on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. *Gastroenterology*. Mar 2006; 130(3):935-9.

51. Silverman J., Otley A. Budesonide in the treatment of inflammatory bowel disease. *Expert Rev Clin Immunol.* Jul 2011; 7(4):419-28.
52. Rubin D.T., Panaccione R., Chao J., Robinson A.M. A practical, evidence-based guide to the use of adalimumab in Crohn's disease. *Curr Med Res Opin.* Sep 2011; 27(9):1803-13.
53. Baumgart D.C., Sandborn W.J. Inflammatory bowel disease: clinical aspects and established and evolving therapies. *Lancet* 2007; 369: 1641–57.
54. US Food and Drug Administration. Tumor Necrosis Factor-alpha (TNFα) Blockers: Label Change - Boxed Warning Updated for Risk of Infection from Legionella and Listeria Posted September 7, 2011. Available at http://www.fda.gov /Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ ucm 270 977.htm.
55. Mokrowiecka A., Daniel P., Slomka M., Majak P., Malecka-Panas E. Clinical utility of serological markers in inflammatory bowel disease. *Hepatogastroenterology.* Jan-Feb 2009; 56(89):162-6.
56. Kefalakes H., Stylianides T.J., Amanakis G., Kolios G. Exacerbation of inflammatory bowel diseases associated with the use of nonsteroidal anti-inflammatory drugs: myth or reality? *Eur J Clin Pharmacol.* Oct 2009; 65(10):963-70.
57. Berg D.F., Bahadursingh A.M., Kaminski D.L., Longo W.E. Acute surgical emergencies in infl ammatory bowel disease. *Am J Surg* 2002; 184: 45–51.
58. Larson D.W., Pemberton J.H. Current concepts and controversies in surgery for IBD. *Gastroenterology* 2004; 126: 1611–19.
59. Itzkowitz S.H., Present D.H., Crohn's, Colitis Foundation of America Colon Cancer in IBDSG. Consensus conference: colorectal cancer screening and surveillance in infl ammatory bowel disease. *Infl amm Bowel Dis* 2005; 11: 314 21.
60. Hanauer S.B., Korelitz B.I., Rutgeerts P., et al. Postoperative maintenance of Crohn's disease remission with 6-mercaptopurine, mesalamine, or placebo: a 2-year trial. *Gastroenterology.* 2004; 127: 723–29.
61. Rutgeerts P., Van Assche G., Vermeire S., et al. Ornidazole for prophylaxis of postoperative Crohn's disease recurrence: a randomized, double-blind, placebo-controlled trial. *Gastroenterology.* 2005; 128: 856 61.
62. Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit. Sexual and reproductive health for individuals with inflammatory bowel disease. London (UK): Faculty of Sexual and Reproductive Healthcare (FSRH); 2009.
63. Gisbert J.P. Safety of immunomodulators and biologics for the treatment of inflammatory bowel disease during pregnancy and breast-feeding. *Inflamm. Bowel Dis.* May 2010; 16(5):881-95.

64. Pew Research Center. The Databank: 10,000 - Baby Boomers retire. Available athttp://pewresearch.org/databank/dailynumber/?NumberID=1150.
65. Schnitzler F., Fidder H., Ferrante M., Ballet V., Noman M., Van Assche G., et al. Outcome of pregnancy in women with inflammatory bowel disease treated with antitumor necrosis factor therapy. *Inflamm Bowel Dis.* Sep 2011; 17(9):1846-54.
66. Zelinkova Z., de Haar C., de Ridder L., Pierik M.J., Kuipers E.J., Peppelenbosch M.P., et al. High intra-uterine exposure to infliximab following maternal anti-TNF treatment during pregnancy. *Aliment Pharmacol Ther.* May 2011; 33(9):1053-8.
67. Roux C.H., Brocq O., Breuil V., Albert C., Euller-Ziegler L. Pregnancy in rheumatology patients exposed to anti-tumour necrosis factor (TNF)-alpha therapy. *Rheumatology (Oxford).* Apr 2007; 46(4):695-8.
68. O'Donnell S., O'Morain C. Review article: use of antitumour necrosis factor therapy in inflammatory bowel disease during pregnancy and conception. *Aliment Pharmacol Ther.* May 2008; 27(10):885-94.
69. Card T., Hubbard R., Logan R.F. Mortality in inflammatory bowel disease: a population-based cohort study. *Gastroenterology.* Dec 2003; 125(6):1583-90.
70. Jess T., Loftus E.V. Jr., Harmsen W.S., Zinsmeister A.R., Tremaine W.J., Melton L.J. 3rd, et al. Survival and cause specific mortality in patients with inflammatory bowel disease: a long term outcome study in Olmsted County, Minnesota, 1940-2004. *Gut.* Sep 2006; 55(9):1248-54.
71. Hutfless S.M., Weng X., Liu L., Allison J., Herrinton L.J. Mortality by medication use among patients with inflammatory bowel disease, 1996-2003. *Gastroenterology.* Dec 2007; 133(6):1779-86.
72. Dorn SD, Sandler RS. Inflammatory bowel disease is not a risk factor for cardiovascular disease mortality: results from a systematic review and meta-analysis. *Am J Gastroenterol.* Mar 2007;102(3):662-7.
73. Meucci G., Vecchi M., Astegiano M., Beretta L., Cesari P., Dizioli P., et al. The natural history of ulcerative proctitis: a multicenter, retrospective study. Gruppo di Studio per le Malattie Infiammatorie Intestinali (GSMII). *Am J Gastroenterol.* Feb 2000; 95(2):469-73.
74. Solberg I.C., Vatn M.H., Høie O., Stray N., Sauar J., Jahnsen J., et al. Clinical course in Crohn's disease: results of a Norwegian population-based ten-year follow-up study. *Clin Gastroenterol Hepatol.* Dec 2007; 5(12):1430-8.
75. Lichtenstein G.R., Hanauer S.B., Sandborn W.J. Management of Crohn's disease in adults. *Am J Gastroenterol.* Feb 2009; 104(2):465-83; quiz 464, 484.

Further reading:

1. AGA medical position statement on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. 2010. http://www.gastrojournal.org/article/S0016-5085(09)02202-1/fulltext.
2. Dorn S.D., Sandler R.S. Inflammatory bowel disease is not a risk factor for cardiovascular disease mortality: results from a systematic review and meta-analysis. *Am J Gastroenterol.* Mar 2007; 102(3):662-7.
3. [Guideline] Farraye F.A., Odze R.D., Eaden J., Itzkowitz S.H., McCabe R.P., Dassopoulos T., et al. AGA medical position statement on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. *Gastroenterology.* Feb 2010; 138(2):738-45.
4. Colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas. (National Institute for Health and Clinical Excellence (NICE), London). http://guideline.gov/content.aspx?id=34830.
5. Colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas. London, UK: National Institute for Health and Clinical Excellence (NICE); 2011. Available athttp://guideline.gov/content.aspx?id=34830.

Test

Simple - Choice Test

1. S.C. Which of the following statement about Crohn's disease (CD) is NOT correct?
   A. CD is a transmural process
   B. CD can affect any part of the gastrointestinal tract from the mouth to the anus
   C. "Cobblestone" appearance is characteristic of CD
   D. Active CD is characterized by focal inflammation and formation of fistula tracts
   E. In long-standing disease, inflammatory polyps (pseudopolyps) may be present as a result of epithelial regeneration

2. S.C. Crohn's disease can affect:
   A. Only the colon
   B. Only the esophagus
   C. Any part of the gastrointestinal tract from the mouth to the anus
   D. Only the small intestine
   E. Only the stomach

3. S.C. The mainstay of therapy for mild to moderate Ulcerative Colitis and Crohn's colitis is:
   A. Sulfasalazine and the other 5-ASA agents
   B. Glucocorticoids
   C. Azathioprine and 6-mercaptopurine
   D. Methotrexate
   E. Infliximab

4. S.C. Ulcerative colitis is characterized by the presence of:
   A. Small bowel significant abnormalitis
   B. Continuous colitis
   C. "Cobblestoning" patterns
   D. Granuloma on biopsy
   E. Segmental colitis

Multiple - Choice Test

1. M.C. Clinical manifestations of Crohn's disease with Ileocolitis are:
   A. Chronic history of recurrent episodes of right lower quadrant pain
   B. Intestinal Malabsorption (hypoalbuminemia, hypocalcemia, hypomagnesemia, coagulopathy)

C. Diarrhea
D. Low-grade fever
E. Weight loss

2. M.C. Complications ofCrohn's disease are:
   A. Fistula formation
   B. Toxic megacolon
   C. Free perforation
   D. Intraabdominal and pelvic abscesses
   E. Intestinal obstruction

3. M.C. Clinical manifestations of Crohn's disease depend of site of disease, that are following:
   A. Ileocolitis
   B. Jejunoileitis
   C. Proctitis
   D. Colitis and Perianal Disease
   E. Gastroduodenal Disease

4. M.C. The major symptoms of UC are:
   A. Diarrhea
   B. Rectal bleeding
   C. Tenesmus
   D. Passage of mucus and crampy abdominal pain
   E. Chronic history of recurrent episodes of right lower quadrant pain

5. M.C. Clinical, endoscopic, and radiographic features characteristic for Ulcerative Colitis are:
   A. Gross blood in stool
   B. Response to antibiotics
   C. Mucus
   D. Recurrence after surgery
   E. Continuous disease

6. M.C.Medical management of Ulcerative Colitis includes:
   A. 5-ASA agents
   B. Glucocorticoids
   C. Antibiotics
   D. Azathioprine
   E. 6-mercaptopurine

Answers

Simple - Choice Test

1. E (**HARRISON'S** Gastroenterology and Hepatology. Derived from Harrison's Principles of Internal Medicine, 17th Edition Ed. Dan L. Longo, 2010, p 178).
2. C (**HARRISON'S** Gastroenterology and Hepatology. Derived from Harrison's Principles of Internal Medicine, 17th Edition Ed. Dan L. Longo, 2010, p 178).
3. A (**HARRISON'S** Gastroenterology and Hepatology. Derived from Harrison's Principles of Internal Medicine, 17th Edition Ed. Dan L. Longo, 2010, p 191).
4. B (**HARRISON'S** Gastroenterology and Hepatology. Derived from Harrison's Principles of Internal Medicine, 17th Edition Ed. Dan L. Longo, 2010, p 184).

Multiple - Choice Test

1. A, C, D, E (**HARRISON'S** Gastroenterology and Hepatology. Derived from Harrison's Principles of Internal Medicine, 17th Edition Ed. Dan L. Longo, 2010, p. 199).
2. A, C, D, E (**HARRISON'S** Gastroenterology and Hepatology. Derived from Harrison's Principles of Internal Medicine, 17th Edition Ed.Dan L. Longo, 2010, p. 199).
3. A, B, D, E (**HARRISON'S** Gastroenterology and Hepatology. Derived from Harrison's Principles of Internal Medicine, 17th Edition Ed. Dan L. Longo, 2010, p. 180).
4. A, B, C, D (**HARRISON'S** Gastroenterology and Hepatology. Derived from Harrison's Principles of Internal Medicine, 17th Edition Ed. Dan L. Longo, 2010, p. 179).
5. A, C, E (**HARRISON'S** Gastroenterology and Hepatology. Derived from Harrison's Principles of Internal Medicine, 17th Edition Ed. Dan L. Longo, 2010, p. 184).
6. A, B, D (**HARRISON'S** Gastroenterology and Hepatology. Derived from Harrison's Principles of Internal Medicine, 17th Edition Ed. Dan L. Longo, 2010, p. 188-192).

Case-based self-assessment questions

1. Which of the following statements regarding the epidemiology of inflammatory bowel disease is correct?

A. Monozygotic twins are highly concordant for ulcerative colitis.
B. Oral contraceptive use decreases the incidence of Crohn's disease.
C. Persons of Asian descent have the highest rates of ulcerative colitis and Crohn's disease.
D. Smoking may decrease the incidence of ulcerative colitis.
E. Typical age of onset for Crohn's disease is 40–50 years old.

2. A 24-year-old woman is admitted to the hospital with a 1-year history of severe abdominal pain and chronic diarrhea, which has been bloody for the past 2 months. She reports a 20-lb weight loss, frequent fevers, and night sweats. She denies vomiting. Her abdominal pain is crampy and primarily involves her right lower quadrant. She is otherwise healthy. Examination is concerning for an acute abdomen with rebound and guarding present. CT shows free air in the peritoneum. She is urgently taken to the operating room for surgical exploration, where she is found to have multiple strictures and a perforation of her bowel in the terminal ileum. The rectum was spared and a fissure from the duodenum to the jejunum is found. The perforated area is resected and adhesions lysed. Which of the following findings on pathology of her resected area confirms her diagnosis?

A. Crypt abscesses.
B. Flat villi.
C. Noncaseating granuloma throughout the bowel wall.
D. Special stain for Clostridium difficile toxin.
E. Transmural acute and chronic inflammation.

3. A 45-year-old man with ulcerative colitis has been treated for the past 5 years with infliximab with excellent resolution of his bowel symptoms and endoscopic evidence of normal colonic mucosa. He is otherwise healthy. He is evaluated by a dermatologist for a lesion that initially was a pustule over his right lower extremity but has since progressed in size with ulceration. The ulcer is moderately painful. He does not recall any trauma to the area. On examination the ulcer measures 15 cm by 7 cm and central necrosis is present. The edges of the ulcer are violaceous. No other lesions are identified. Which of the following is the most likely diagnosis?

A. Erythema nodosum.
B. Metastatic Crohn's disease.
C. Psoriasis.
D. Pyoderma gangrenosum.
E. Pyoderma vegetans.

4. Inflammatory bowel disease (IBD) may be caused by exogenous factors. Gastrointestinal flora may promote an inflammatory response or may inhibit inflammation. Probiotics have been used to treat IBD. Which of the following organisms has been used in the treatment of IBD?
A. Campylobacter spp.
B. Clostridium difficile
C. Escherichia spp.
D. Lactobacillus spp.
E. Shigella spp.

5. Your 33-year-old patient with Crohn's disease (CD) has had a disappointing disease response to glucocorticoids and 5-ASA agents. He is interested in steroid-sparing agents. He has no liver or renal disease. You prescribe once-weekly methotrexate injections. In addition to monitoring hepatic function and complete blood count, what other complication of methotrexate therapy do you advise the patient of?
A. Disseminated histoplasmosis.
B. Lymphoma.
C. Pancreatitis.
D. Pneumonitis.
E. Primary sclerosing cholangitis.

Answers

1. **The answer is D.** The incidence of inflammatory bowel disease is highly influenced by ethnicity, location, and environmental factors. Both conditions have their highest incidence in the United Kingdom and North America, and the peak incidence has a bimodal distribution of age of presentation: 15–30 years and 60–80 years. The incidence of both ulcerative colitis and Crohn's disease is highest among persons of the Ashkenazi Jewish population. Prevalence decreasesprogressively in non-Jewish white, African-American, Hispanic, and Asian populations. Cigarettesmoking is associated with a decreased incidence of ulcerative

colitis, but may cause Crohn's disease.Oral contraceptive use is associated with a slightly higher incidence of Crohn's disease, but notulcerative colitis. Monozygotic twins are highly concordant for Crohn's disease, but not ulcerativecolitis.

2. **The answer is C**. Chronic bloody diarrhea associated with weight loss andsystemic symptoms in a young person is highly suggestive of inflammatory bowel disease. Her surgicalfindings suggest discontinuous lesions, which is typical of Crohn's disease. Ulcerative colitis, incontrast, typically affects the rectum and proceeds caudally from there without normal mucosa until thearea of inflammation terminates. The presence of strictures and fissures further supports the diagnosis of Crohn's disease, as these are not features of ulcerative colitis. Microscopically, both ulcerative colitis and Crohn's disease may have crypt abscess and, although Crohn's disease is more often transmural, full thickness disease may be present in ulcerative colitis. The hallmark of Crohn's diseaseis granulomas that may be present throughout the bowel wall and involve the lymph nodes, mesentery, peritoneum, liver, and pancreas. Although pathognomonic for Crohn's disease, granulomas are onlyfound in about half of surgical resections. Flat villi are not always present in either disease and aremore commonly found in isolation with celiac disease.

3. **The answer is D**. There are a number of dermatologic manifestations ofinflammatory bowel disease (IBD), and each type of IBD has a particular predilection for differentdermatologic conditions. This patient has pyoderma gangrenosum. Pyoderma gangrenosum can occur inup to 12% of patients with ulcerative colitis and is characterized by a lesion that begins as a pustuleand progresses concentrically to surrounding normal skin. The lesions ulcerate with violaceous, heapedmargins and surrounding erythema. They are typically found on the lower extremities. Often the lesionsare difficult to treat and respond poorly to colectomy; similarly, pyoderma gangrenosum is notprevented by colectomy. Treatment commonly includes IV antibiotics, glucocorticoids, dapsone, infliximab, and other immunomodulatory agents. Erythema nodosum is more common in Crohn'sdisease, and attacks correlate with bowel symptoms. The lesions are typically multiple red hot, tendernodules measuring 1–5 cm and are found on the lower legs and arms. Psoriasis is more common inulcerative colitis. Finally, pyoderma vegetans is a

rare disorder in intertriginous areas reported to be amanifestation of inflammatory bowel disease in the skin.

4. The **answer is D**. Despite beingdescribed as a clinical entity for over a century, the etiology of IBD remains cryptic. Current theory isrelated to an interplay between inflammatory stimuli in genetically predisposed individuals. Recentstudies have identified a group of genes or polymorphisms that confer risk of IBD. Multiplemicrobiologic agents, including some that reside as "normal" flora, may initiate IBD by triggering aninflammatory response. Anaerobic organisms (e.g., Bacteroides and Clostridia spp.) may beresponsible for the induction of inflammation. Other organisms, for unclear reasons, may have theopposite effect. These "probiotic" organisms include Lactobacillus spp., Bifidobacterium spp., Taeniasuis, and Saccharomyces boulardii. Shigella, Escherichia, and Campylobacter spp. are known topromote inflammation. Studies of probiotic therapy in adults and children with IBD have shownpotential benefit for reducing disease activity.

5. **The answer is D**. Methotrexate, azathioprine, cyclosporine, tacrolimus, and antitumornecrosis factor (TNF) antibody are reasonable options for patients with CD, depending on theextent of macroscopic disease. Pneumonitis is a rare but serious complication of methotrexate therapy. Primary sclerosing cholangitis is an extraintestinal manifestation of inflammatory bowel disease (IBD). Pancreatitis is an uncommon complication of azathioprine, and IBD patients treated with azathioprineare at a fourfold increased risk of developing a lymphoma. Anti-TNF antibody therapy is associatedwith an increased risk of tuberculosis, disseminated histoplasmosis, and a number of other infections.

(**HARRISON'S** Gastroenterology and Hepatology. Derived from Harrison's Principles of Internal Medicine, 18th Edition Ed. Dan L. Longo, 2012, (Chap. 295))

CONTENTS