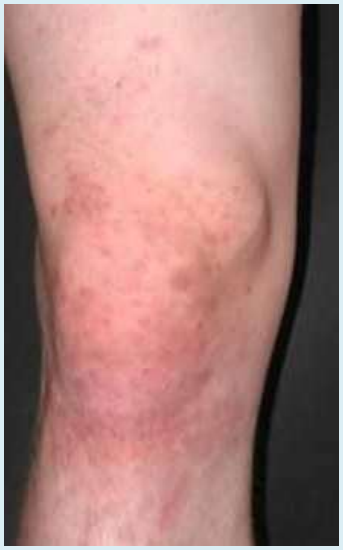
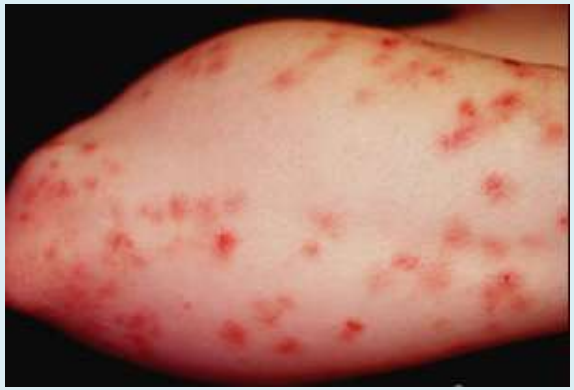
Chronic diarrhea with microcytic anemia

A **38-year-old man** without a significant medical history presents for an office evaluation. He reports a 9 to 12-month history of **intermittent diarrhea**, associated with some mild cramping. He says the **stools are usually large in volume**, are nonbloody, and sometimes **look greasy**. He has **lost more than 9 kg** during this period **without trying**, but says that **his appetite and oral intake have been good**. He has tried taking a proton pump inhibitor daily for the last several months, but it has not improved his symptoms. He also **tried refraining from any intake of dairy products, but that did not affect the diarrhea**, either. He has not experienced fever or any other constitutional symptoms. He does not smoke and drinks an occasional beer on the weekends, but not regularly. He is married and monogamous, and he was adopted and does not know his family medical history.

His hemoglobin level is 9.8 g/dl, the MCV is 75 fL. On examination, he is afebrile and normotensive and comfortable appearing. He has some **glossitis**, but no other oral lesions. His chest is clear to auscultation, and his heart is regular in rate and rhythm. On abdominal examination, his bowel sounds are active and there is no tenderness, and no masses or organomegaly. Rectal examination is negative for occult blood. **He has a few papulovesicular lesions on his elbows and knees with some excoriations.**

What is the most likely diagnosis?
What is the best diagnostic test? **:**





CFIM n° 55

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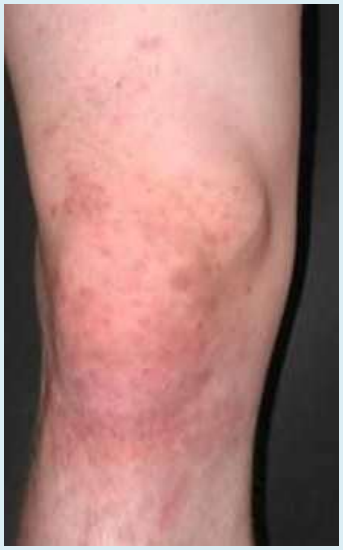
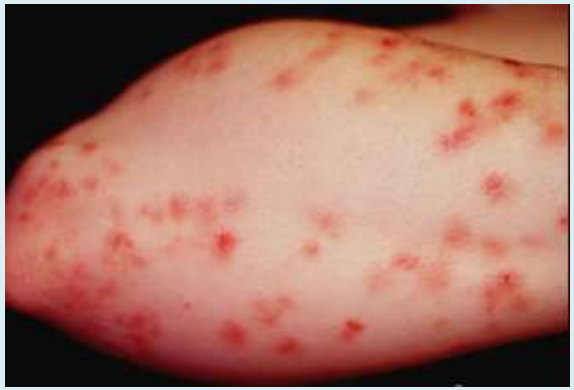




What is the most likely diagnosis? **Chronic diarrhea due to celiac disease.**

What is the best diagnostic test? **: Serology (IgA tissue ransglutaminase antibody, IgA tTG) and endoscopic examination with small bowel biopsy.**

Ineffective oral iron in a woman with sideropenic anemia

A 46-year-old woman presents with* **fatigue** and is found to have* **iron deficiency** with **anaemia**. She has experienced **intermittent episodes of mild diarrhoea for many years**, previously diagnosed as irritable bowel syndrome and lactose intolerance. She has no current significant gastrointestinal symptoms. Examination reveals 2 **oral aphthous ulcers** and pallor. Abdominal examination is normal and results of faecal testing for occult blood are negative. Upper and lower GI endoscopies were negative- **Oral iron supplementation was*ineffective.**

Other presentations

Atypical presentations include an asymptomatic patient, elevated liver enzymes, vitamin D deficiency, osteoporosis, constipation, aphthous stomatitis, nausea or vomiting, heartburn or gastro-oesophageal reflux disease, hyposplenia or asplenia, myalgias, arthralgias, peripheral neuropathy, alopecia, headaches, infertility, and adverse pregnancy outcomes.

Celiac Disease

- *Typical symptoms*: weight loss, chronic diarrhea, abdominal distention, growth retardation.
- *Atypical symptoms*: dermatitis herpetiformis, iron deficiency anemia, osteoporosis.
- Abnormal serologic test results.
- Abnormal small bowel biopsy.
- Clinical improvement on gluten-free diet.

Celiac disease (also called sprue, celiac sprue, and gluten enteropathy) is a permanent dietary disorder caused by an immunologic response to gluten, a storage protein found in certain grains, that results in diffuse damage to the proximal small intestinal mucosa with malabsorption of nutrients. Although symptoms may manifest between 6 months and 24 months of age after the introduction of weaning foods, the majority of cases present in childhood or adulthood. Population screening with serologic tests suggests that the disease is present in 1:100 whites of Northern European ancestry, in whom a clinical diagnosis of celiac disease is made in only 10%, suggesting that most cases are undiagnosed or asymptomatic. Celiac disease

grano, orzo, segale, avena

Coeliac disease

►Suspect this in all those with diarrhoea + weight loss or anaemia (esp. if iron or B_{12} ↓). It is a T-cell-mediated autoimmune disease of the small bowel in which prolamin (alcohol-soluble proteins in wheat, barley, rye ± oats) intolerance causes villous atrophy and malabsorption (including of bile acids).[2,3] *Associations:* HLA DQ2 in 95%; the rest are DQ8; autoimmune disease; dermatitis herpetiformis. *Prevalence:* 1 in 300–1500 (commoner if Irish). *Typical age:* Any (peaks in infancy and 50–60yrs). ♀:♂ >1:1. There is a 10% prevalence in 1st-degree relatives and a 30% relative risk for siblings.

Presentation Stinking stools/steatorrhoea; diarrhoea; abdominal pain; bloating; nausea + vomiting; aphthous ulcers; angular stomatitis (p321, fig 2); weight ↓; fatigue; weakness; osteomalacia; failure to thrive (children). ⅓ are asymptomatic.

Diagnosis Hb↓; RCDW↑ (p319); B_{12}↓, ferritin↓. Antibodies: α-gliadin, transglutaminase and anti-endomysial—an IgA antibody, 95% specific unless patient is IgA-deficient. Duodenal biopsy done at endoscopy (p256—as good as jejunal biopsy if ≥4 taken): subtotal villous atrophy, ↑intra-epithelial WBCs + crypt hyperplasia, reversing on gluten-free diet (along with ↓symptoms & antibodies). ►Exclude coeliac in all labelled as IBS (p276).

Treatment Lifelong gluten-free diet (ie no prolamins)—patients become experts. Rice, maize, soya, potatoes, oats (≤50g/d),[260] and sugar are OK. Gluten-free biscuits, flour, bread, and pasta are prescribable. Verify diet by endomysial antibody tests.

Complications Anaemia; 2° lactose-intolerance[4]; GI T-cell lymphoma (rare; suspect if refractory symptoms or ↓weight); ↑risk of malignancy (gastric, oesophageal, bladder, breast, brain); myopathies; neuropathies; hyposplenism; osteoporosis.

7. What Should Be Assessed in the Patient With Newly Diagnosed Celiac Disease?

Vitamin and mineral deficiencies should be sought, and bone health should be assessed. Patients with overt malabsorption may have multiple deficiencies of fat soluble vitamins, minerals, and micronutrients.

Iron deficiency anemia (IDA) is a very common manifestation of CD, affecting up to 32% of adults; CD is frequent in patients undergoing endoscopy for IDA.[50] A complete blood count and ferritin should be assessed in newly diagnosed CD, and CD should be considered in all patients with IDA without documented bleeding.

Vitamin B_{12} deficiency occurs in CD because of (1) terminal ileal involvement, (2) pancreatic insufficiency, or (3) concomitant autoimmune gastritis, which causes B_{12} deficiency in 10.5% of CD patients.[51] Vitamin B_{12} deficiency occurs in 12%–41% of patients with CD,[51] yet the true prevalence may be higher because most studies use serum B_{12} levels without methylmalonic acid (MMA) levels. Because of the potential irreversible neurologic sequelae from untreated deficiency, all patients with CD should have vitamin B_{12} levels checked, with follow-up MMA levels when B_{12} is low normal.

Folate is also absorbed in the proximal intestine, and although low levels of folate have been found in 35%–49% of CD patients, resultant anemia is less common. Serum folate levels may be normal to elevated in CD with concomitant bacterial overgrowth. Folate levels should be measured in CD, and emphasis should be placed on folate supplementation in women of childbearing age.

Copper deficiency occurs in 6.8%–33% with CD[52] and can cause microcytic anemia, neutropenia, and thrombocytopenia and rarely myeloneuropathy.[53] Because copper deficiency may occur without anemia, levels should be checked in newly diagnosed patients to prevent neurologic sequelae. Zinc deficiency affects 20%–31% of patients with CD and can cause poor tissue healing, dermatitis, or dysgeusia.[52]

Bone disease is frequent in CD, resulting from malabsorption of calcium and/or vitamin D, with subsequent osteopenia, osteoporosis, or osteomalacia. In newly diagnosed patients, the prevalence of osteoporosis is approximately 28% in the spine and 15% in the hip. Bone mineral density improves on a GFD, especially in the first year[54,55]; however, fracture risk is increased both before and after diagnosis.[56] Although vitamin D deficiency is common in CD, the prevalence of osteomalacia is unknown.[54] All patients with CD should have calcium and 25-hydroxyvitamin D levels at baseline, and many recommend bone densitometry for adults at diagnosis[3] or after 1 year to allow stabilization.[54]

Practical Suggestion

Patients with newly diagnosed CD should have a complete blood count, ferritin, vitamin B_{12}, folate, copper, zinc, calcium, and 25-hydroxy vitamin D checked. Parenteral vitamin B_{12} should be given with severe deficiency, neurologic features, or ongoing malabsorption. Bone densitometry should be performed in adults with CD.

DISEASES ON THE AUTOIMMUNE SPECTRUM

Organ Specific	
Graves' disease	Vitiligo
Hashimoto's thyroiditis	Autoimmune hemolytic anemia
Autoimmune polyglandular syndrome	Autoimmune thrombocytopenic purpura
Type 1 diabetes mellitus	Pernicious anemia
Insulin-resistant diabetes mellitus	Myasthenia gravis
Immune-mediated infertility	Multiple sclerosis
Autoimmune Addison's disease	Guillain-Barré syndrome
Pemphigus vulgaris	Stiff-man syndrome
Pemphigus foliaceus	Acute rheumatic fever
Dermatitis herpetiformis	Sympathetic ophthalmia
Autoimmune alopecia	Goodpasture's syndrome
Organ Nonspecific (Systemic)	
Systemic lupus erythematosus	Granulomatosis with polyangiitis
Rheumatoid arthritis	Antiphospholipid syndrome
Systemic necrotizing vasculitis	Sjögren's syndrome

MECHANISMS OF TISSUE DAMAGE IN AUTOIMMUNE DISEASE

Effector	Mechanism	Target	Disease
Autoantibody	Blocking or inactivation	α Chain of the nicotinic acetylcholine receptor	Myasthenia gravis
		Phospholipid–β_2-glycoprotein I complex	Antiphospholipid syndrome
		Insulin receptor	Insulin-resistant diabetes mellitus
		Intrinsic factor	Pernicious anemia
	Stimulation	TSH receptor (LATS)	Graves' disease
		Proteinase-3 (ANCA)	Granulomatosis with polyangiitis
		Epidermal cadherin	Pemphigus vulgaris
		Desmoglein 3	
	Complement activation	α_3 Chain of collagen IV	Goodpasture's syndrome
	Immune complex formation	Double-stranded DNA	Systemic lupus erythematosus
		Immunoglobulin	Rheumatoid arthritis
	Opsonization	Platelet GpIIb:IIIa	Autoimmune thrombocytopenic purpura
		Rh antigens, I antigen	Autoimmune hemolytic anemia
	Antibody-dependent cellular cytotoxicity	Thyroid peroxidase, thyroglobulin	Hashimoto's thyroiditis
T cells	Cytokine production	?	Rheumatoid arthritis, multiple sclerosis, type 1 diabetes mellitus
	Cellular cytotoxicity	?	Type 1 diabetes mellitus

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; LATS, long-acting thyroid stimulator; TSH, thyroid-stimulating hormone.

The spectrum of autoimmune disease

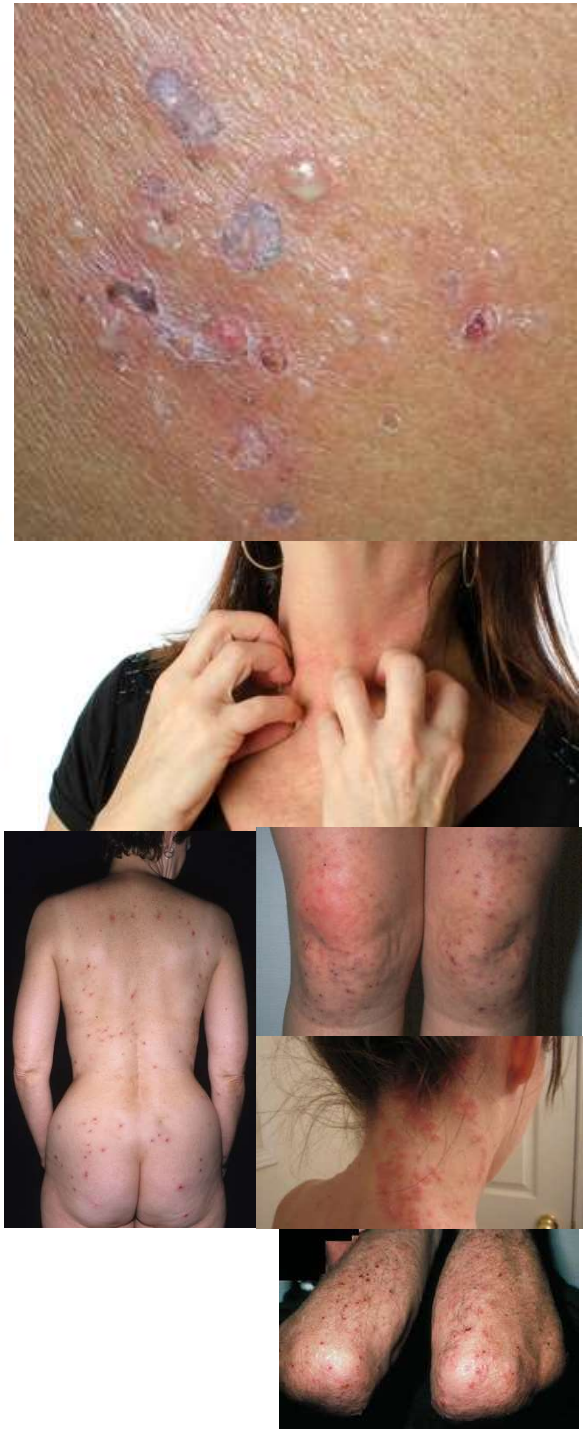
Organ Specific Autoimmune Diseases

- Graves Disease (Thyroid: TSHR Abs, TPO Abs)
- Hashimoto Thytreoiditis (Thyroid: TPO Abs, Tg Abs)
- Diabetes Type I (Pankreas: GAD II Abs, IA2 Abs, ICA)
- Goodpasture Syndrome (Kidney: GBM Abs)
- Pernicious Anemia (Stomach: Parietal Cell Abs)
- Primary Biliary Cirrhosis (Liver, Bile: AMAbs)
- Myasthenia Gravis (Muscles: AChR Abs)
- Dermato-/Polymyositis (Skin / Muscles: Jo 1 Abs)
- Vasculitis (Vessels: ANCA)
- Rheumatoid Arthritis (Joints: CRP, RF, RA33 Abs, Sa Abs)
- MCTD (RNP Abs)
- Scleroderma (Scl 70 Abs, CENP Abs, PM/Scl Abs)
- SLE (ANA, Cardiolipin Abs, Beta 2 GP I Abs)

Multi-systemic Autoimmune Diseases

DERMATITIS HERPETIFORMIS

Dermatitis herpetiformis is an uncommon disease manifested by pruritic papules, vesicles, and papulovesicles mainly on the elbows, knees, buttocks, posterior neck, and scalp. It appears to have its highest prevalence in Northern Europe and is associated with HLA antigens -B8, -DR3, and -DQ2. The histopathology is distinctive. Circulating antibodies to tissue transglutaminase are present in 90% of cases. NSAIDs may cause flares. Patients have gluten-sensitive enteropathy, but it is subclinical in the great majority. However, ingestion of gluten is the cause of the disease, and strict long-term avoidance of dietary gluten has been shown to decrease the dose of dapsone (usually 100–200 mg daily) required to control the disease and may even eliminate the need for treatment. Patients with dermatitis herpetiformis are at increased risk for development of gastrointestinal lymphoma, and this risk is reduced by a gluten-free diet.



Serologic tests

•Serologic tests should be performed in all patients in whom there is a suspicion of celiac disease.

•The recommended test is the **IgA tissue transglutaminase (IgA tTG) antibody**, which has a 95% sensitivity and 95% specificity for the diagnosis of celiac disease.

•Antigliadin antibodies are not recommended because of their lower sensitivity and specificity.

•IgA antiendomysial antibodies are no longer recommended due to the lack of standardization among laboratories.

•An **IgA level** should be obtained in patients with a negative IgA tTG antibody when celiac disease is strongly suspected because up to 3% of patients with celiac disease have **IgA deficiency**.

•A test that measures **IgG antibodies to deamidated gliadin** has excellent sensitivity and specificity and is useful in patients with IgA deficiency and young children.

•**Levels of all antibodies become undetectable after 3–12 months of dietary gluten withdrawal** and may be used to monitor dietary compliance, especially in patients whose symptoms fail to resolve after institution of a gluten-free diet.

NOMENCLATURE

- **Gluten** (from Latin gluten, "glue") is a general name given to a mixture of plant storage proteins present in cereal grains as wheat, rye, barley and oats. (grano, orzo, segale, avena).
- Gluten includes **prolamins**, proteins having a high proline and glutamine content and found in wheat (**gliadin**), barley (hordein), rye (secalin), and oats (avenin). Some prolamins may induce coeliac disease in genetically predisposed individuals.
- **Deamidated gliadin** is produced by enzymatic treatment of gluten. The enzyme **tissue transglutaminase** converts some of the abundant glutamines to glutamic acid. Deamidated gliadin is soluble in water. The immune reaction to deamidated gliadin is much greater than that to gliadin.
- The **endomysium** is a layer of connective tissue that ensheaths a muscle fiber. The endomysium contains a form of transglutaminase called tissue transglutaminase (tTG) and antibodies that bind to this form of transglutaminase are called endomysial autoantibodies (EmA)

Tropical sprue: Villous atrophy + malabsorption occurring in the Far and Middle East and Caribbean—the cause is unknown. *Tetracycline* 250mg/6h PO + *folic acid* 15mg/d PO + optimum nutrition may help.[259]

Endoscopic mucosal biopsy of the proximal duodenum (bulb) and distal duodenum is the standard method for confirmation of the diagnosis in patients with a positive serologic test for celiac disease.

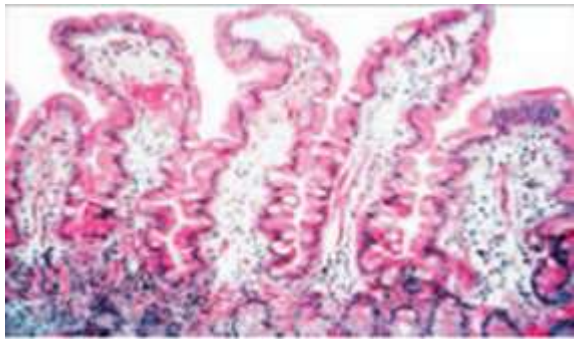
•Mucosal biopsy should also be pursued in patients with negative serologies when symptoms and laboratory studies are strongly suggestive of celiac disease.

•At endoscopy, atrophy or scalloping of the duodenal folds may be observed.

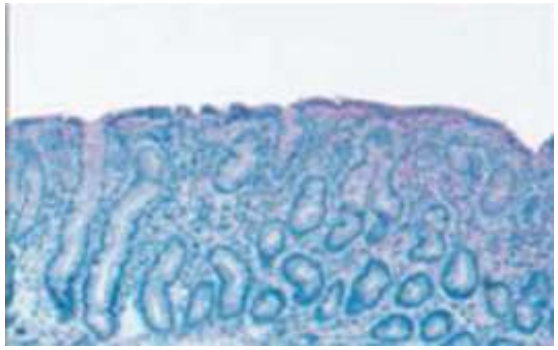
•**An adequate normal biopsy excludes the diagnosis**.

•**Partial or complete reversion of these abnormalities occurs within 3–24 months after a patient is placed on a gluten-free diet**, but symptom resolution remains incomplete in 50% of patients.

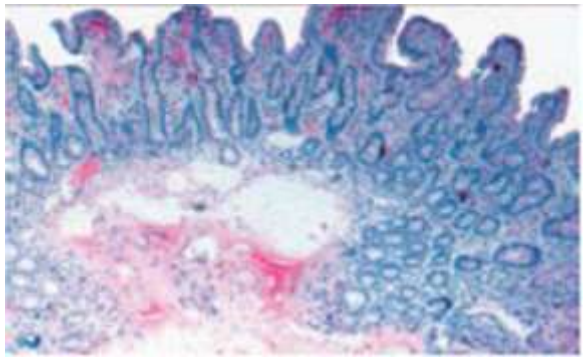
•If a patient with a compatible biopsy demonstrates prompt clinical improvement on a gluten-free diet and a decrease in antigliadin antibodies, a repeat biopsy is unnecessary.



Normal



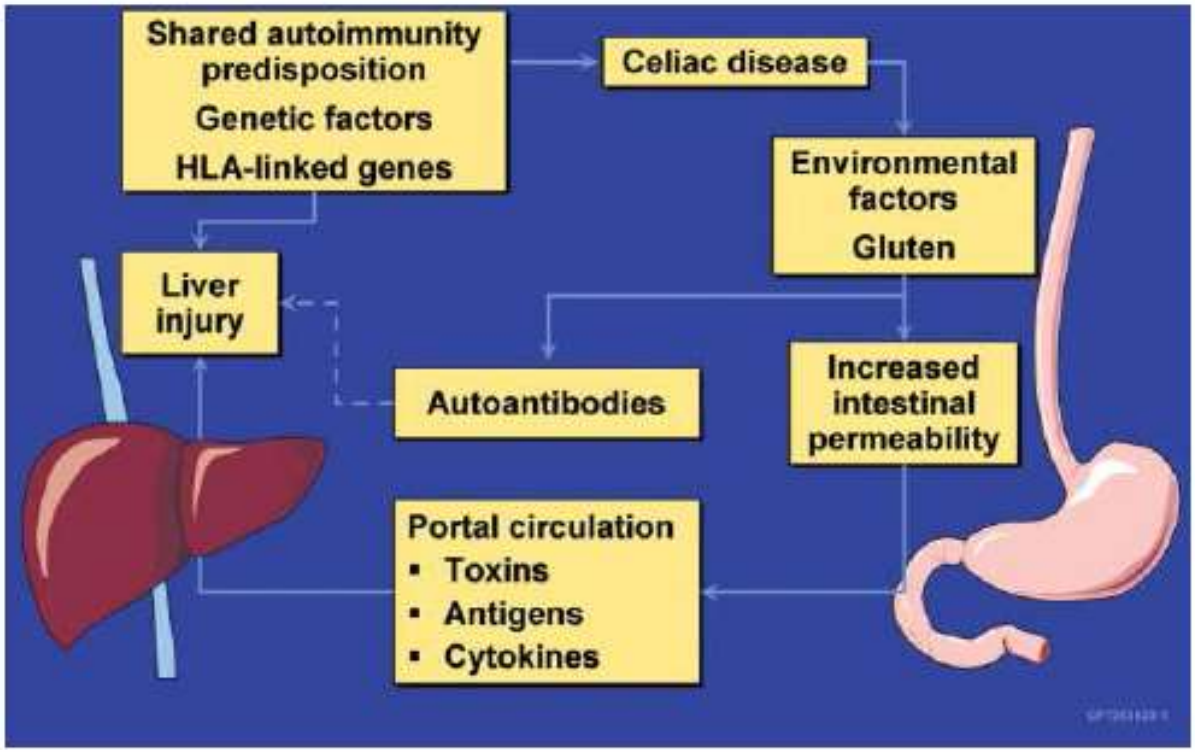
Untreated celiac sprue



Treated celiac sprue

Meta-analysis: coeliac disease and hypertransaminasaemia

Aliment Pharmacol Ther 2011; 34: 33–40



Conclusions

Undetected coeliac disease is a potential cause for cryptogenic hypertransaminasaemia in 3% to 4% of cases. More than 20% of individuals with newly diagnosed coeliac disease may have abnormal serum transaminases and these normalise on a gluten-free diet in the majority of cases.

Nonceliac gluten sensitivity

Nonceliac gluten sensitivity (NCGS) is the clinical term used to describe gastrointestinal (GI) and/or extraintestinal symptoms associated with gluten ingestion. The prevalence of NCGS is unknown. The condition has clinical features that overlap with those of celiac disease (CD) and wheat allergy (WA).

The pathophysiologic process in NCGS is thought to be through an innate immune mechanism,whereas CD and WA are autoimmune- and allergen mediated, respectively. However, dietary triggers other than gluten, such as the fermentable oligosaccharides, disaccharides, monosaccharides, and polyols, have been implicated. Currently, no clinical biomarker is available to diagnose NCGS. Exclusion of CD and WA is necessary in the evaluation of a patient suspected to have NCGS.

The onset of symptoms in patients with NCGS can occur within hours or days of gluten ingestion. **Patients with NCGS have GI and extraintestinal symptoms that typically disappear when gluten-containing grains are eliminated from their diets**. However, most patients suspected to have NCGS have already initiated a gluten-free diet at the time of an evaluation. A gluten elimination diet followed by a monitored open challenge of gluten intake to document recurrence of GI and/or extraintestinal symptoms can sometimes be helpful. If NCGS is strongly suggested, then a skilled dietitian with experience in counseling on gluten-free diets can provide proper patient education. Additional research studies are warranted to further our understanding of NCGS, including its pathogenesis and epidemiology, and to identify a biomarker to facilitate diagnosis and patient selection for proper management.

Mayo Clinic Proceedings 2015

Symptoms

Gastrointestinal
Bloating
Diarrhea
Constipation
Abdominal pain
Nausea
Vomiting
Anal fissures
Extraintestinal
"Foggy" mind
Tiredness
Fatigue
Joint pain
Depression
Numbness
Loss of balance
Eczema
Anemia
Weight fluctuations
Rash
Headaches

Comparison of Gluten-Related Disorders

Variable	Celiac disease	Nonceliac gluten sensitivity	Wheat allergy
Symptom onset	Days to weeks	Hours to days	Minutes to hours
Pathogenesis	Autoimmunity and innate immunity	Innate immunity?	Allergic immunity
HLA	HLA-DQ2/HLA-DQ8 restricted	Not HLA-DQ2/HLA-DQ8 restricted	Not HLA-DQ2/HLA-DQ8 restricted
Autoantibodies	Almost always present	Always absent	Always absent
Enteropathy[a]	Almost always present	Always absent	Always absent
Features	Intestinal and extraintestinal	Intestinal and extraintestinal	Intestinal and extraintestinal
Complications	Comorbidities, long-term complications	Comorbidities, long-term complications?	No comorbidities, anaphylaxis

[a]Enteropathy is defined histologically by villous atrophy and crypt hyperplasia.

Small Bowel Disease

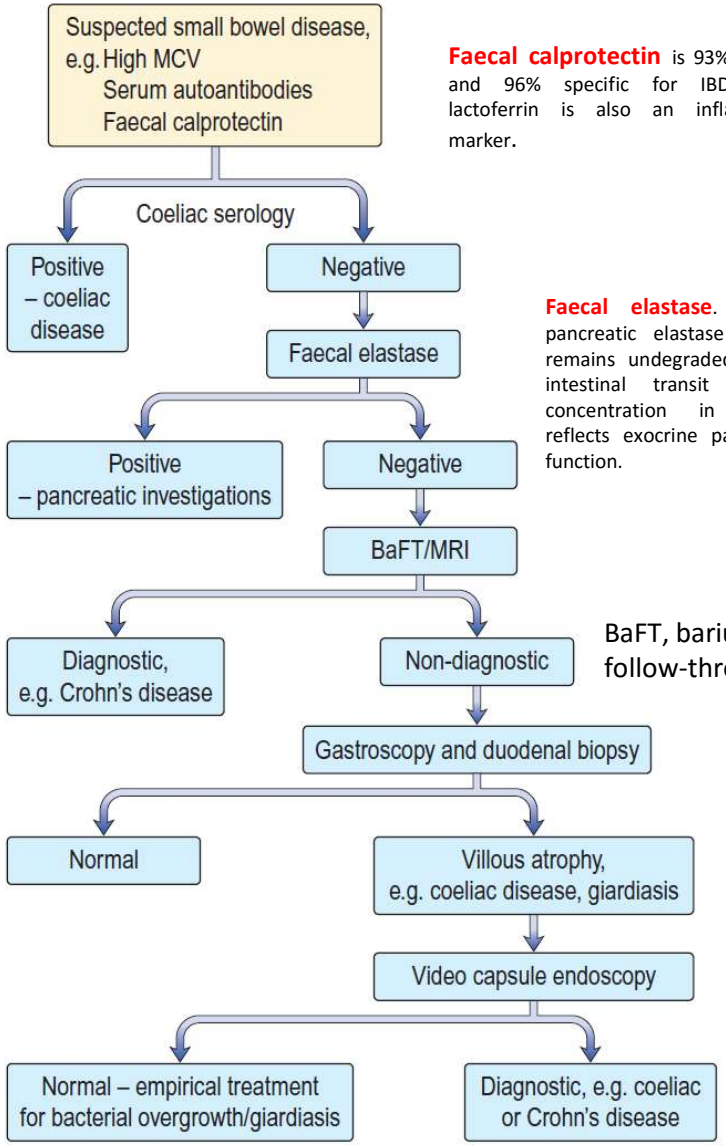
Disorders of the small intestine causing malabsorption

- **Coeliac disease**
- Dermatitis herpetiformis
- Tropical sprue
- **Crohn's disease**
- **Bacterial overgrowth**
- Intestinal resection (short bowel syndrome)
- Whipple's disease
- Radiation enteropathy
- Parasite infestation (e.g. Giardia intestinalis)

Presenting features of small bowel disease

- **Diarrhoea**
- **Steatorrhoea**
- **Abdominal pain and discomfort**
- **Weight loss**
- Nutritional deficiencies
  - common: **iron**, **B12**, **folate** (anemia)
  - uncommon) **vitamin K** (bruising), **calcium** (tetany), **vitamin D** (osteomalacia), multiple vitamin deficiencies (stomatitis, sore tongue and aphthous ulceration) hypoalbuminemia (oedema due to intestinal loss of albumin, protein-losing enteropathy).

Flow diagram for investigation of patients with suspected small bowel disease



Faecal calprotectin is 93% sensitive and 96% specific for IBD. Faecal lactoferrin is also an inflammatory marker.

Faecal elastase. Human pancreatic elastase 1 (E1) remains undegraded during intestinal transit so its concentration in faeces reflects exocrine pancreatic function.

BaFT, barium follow-through

CHRONIC DIARRHEA

more than 4-week duration

(may be termed persistent diarrhea if symptoms continue for 2 to 4 weeks)

Secretory
Bacterial infections, eg, cholera
Hormone-producing tumors (carcinoid, VIPoma, medullary cancer of thyroid, gastrinoma)
Exogenous stimulant laxatives
Endogenous laxatives (dihydroxy bile acids)
Idiopathic secretory diarrhea
Bowel resection, disease, or fistula (inadequate absorptive surface)
Congenital electrolyte absorption defects
Cholerrheic diarrhea (excess bile acid entering colon stimulates secretion)

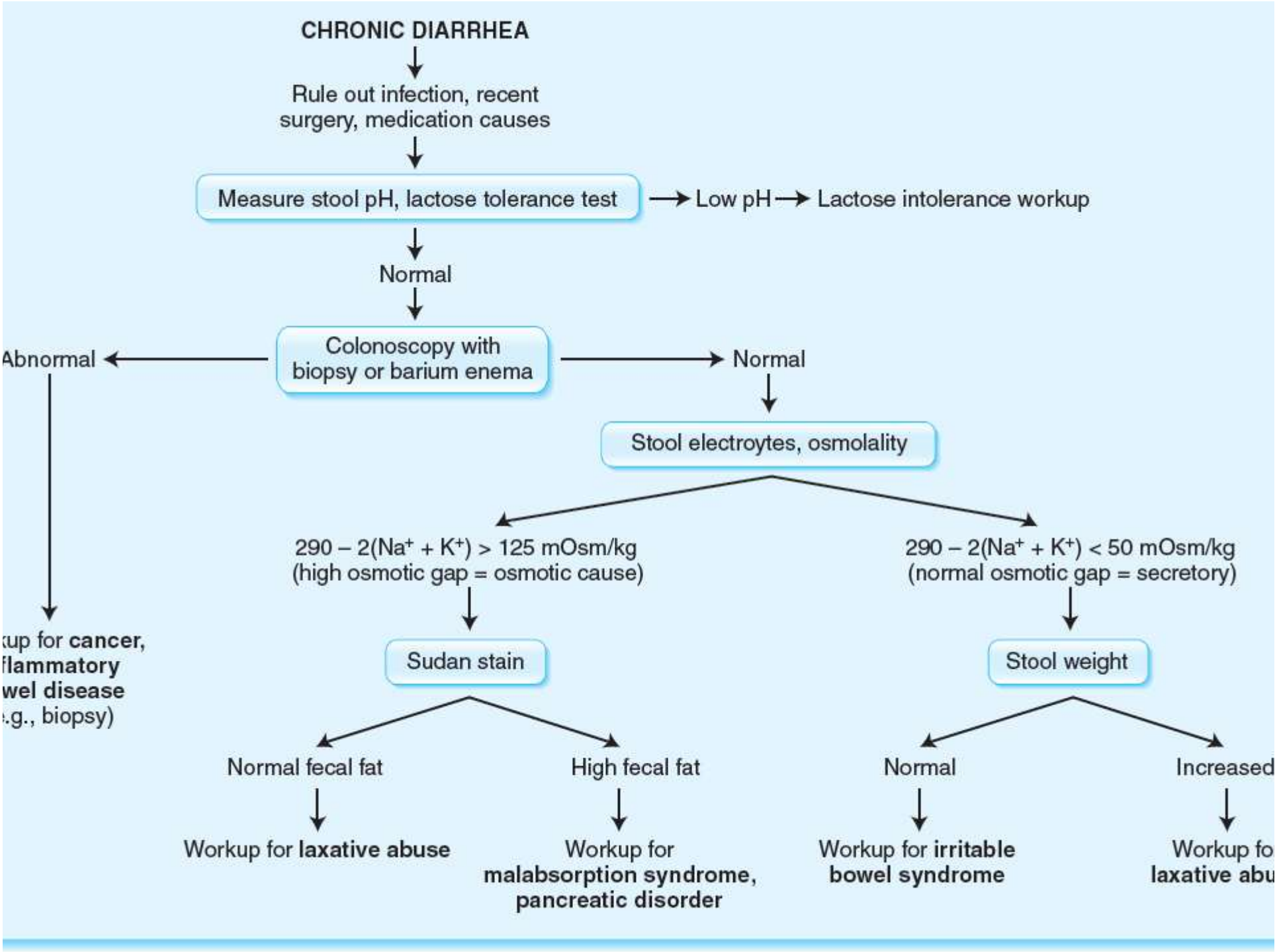
Osmotic
Osmotic laxatives (magnesium, phosphate, sulfate)
Lactase deficiencies
Nonabsorbable carbohydrates (sorbitol, lactulose, polyethylene glycol)

Steatorrhea
Chronic pancreatitis (exocrine insufficiency)
Cystic fibrosis
Crohn's disease
Bacterial overgrowth
Celiac disease
Whipple disease
Tropical sprue
Mycobacterium avium-intracellulare (AIDS patients)
Amyloidosis
First- or second-degree lymphatic obstruction

Inflammatory causes
Inflammatory bowel disease (Crohn, ulcerative colitis)
Lymphocytic and collagenous colitis
Eosinophilic gastroenteritis
Graft-vs-host disease
Infections (invasive bacteria, viruses, and parasites, Brainerd diarrhea)
Radiation enteritis

Dysmotility
Irritable bowel syndrome
Visceral neuromyopathies (diabetic diarrhea)
Hyperthyroidism
Drugs (prokinetic agents)

Unlike acute diarrhea, most cases of chronic diarrhea are not infectious. In order to evaluate and manage patients with chronic diarrhea, it is useful to classify them into their pathophysiologic mechanism (see Table 55–1).


CHRONIC DIARRHEA
Rule out infection, recent surgery, medication causes
Measure stool pH, lactose tolerance test
Low pH
Lactose intolerance workup
Normal
Colonoscopy with biopsy or barium enema
Abnormal
Normal
Stool electroytes, osmolality
290 – 2(Na+ + K+) > 125 mOsm/kg (high osmotic gap = osmotic cause)
290 – 2(Na+ + K+) < 50 mOsm/kg (normal osmotic gap = secretory)
kup for cancer, flammatory wel disease .g., biopsy)
Sudan stain
Stool weight
Normal fecal fat
High fecal fat
Normal
Increased
Workup for laxative abuse
Workup for malabsorption syndrome, pancreatic disorder
Workup for irritable bowel syndrome
Workup fo laxative abu

Irritable bowel syndrome is characterized by **intermittent diarrhea** and **crampy abdominal pain** often **relieved with defecation**, but **no** **weight loss** or abnormal **blood in the stool**. **Constipation and diarrhea may alternate.** It is a diagnosis of exclusion once other conditions, such as infl ammatory bowel disease and parasitic infection (eg, giardiasis), have been excluded.

Irritable bowel syndrome (IBS)

IBS denotes a mixed group of abdominal symptoms for which no organic cause can be found. Most are probably due to disorders of intestinal motility or enhanced visceral perception (the 'brain-gut' axis: see BOX). Several diagnostic criteria exist that evaluate symptoms and their duration (eg Manning, Rome II/III);[223,224] but they are not always helpful in practice because of complex interactions between IBS and chronic pain syndromes (BOX).[225] *Prevalence:* 10–20%; age at onset: ≤40yrs; ♀:♂ ≥2:1.

Diagnosis Only diagnose IBS if abdominal pain (or discomfort) is either relieved by defecation *or* associated with altered stool form or bowel frequency (constipation and diarrhoea may alternate) *and* there are ≥2 of: urgency; incomplete evacuation; abdominal bloating/distension; mucous PR; worsening of symptoms after food. Other symptoms: nausea, bladder symptoms, backache. Symptoms are chronic (>6 months), and exacerbated by stress, menstruation, or gastroenteritis (post-infection IBS). *Signs:* Examination is often normal, but general abdominal tenderness is common. Insufflation of air during sigmoidoscopy (*not* usually needed) may reproduce the pain. *Think of other diagnoses if:* Age >40yrs (esp male); history <6 months; anorexia; weight↓; waking at night with pain/diarrhoea; mouth ulcers; abnormal CRP, ESR, Hb, coeliac serology. ►Investigate PR bleeding urgently. **Management** See BOX.

Managing IBS

Make a *positive* diagnosis (OPPOSITE) but also try to exclude other diagnoses, so:

- If the history is classic, FBC, ESR, CRP, LFT & coeliac serology (p280) are sufficient.
- If ≥50yrs or any marker or organic disease (T°↑, blood PR, weight↓): colonoscopy.
- Have a low threshold for referring if family history of ovarian or bowel cancer.
- Excluding ovarian cancer may need serum CA-125 (*OHCS* p281; if >35 do US scan).
- If diarrhoea is prominent do: LFT; stool culture; B_{12}/folate; anti-endomysial antibodies (coeliac, p280); TSH; consider referral ± barium follow-through (if symptoms suggest small bowel disease) ± rectal biopsy.

Further investigation should be guided by symptoms and include:

- Upper GI endoscopy (dyspepsia, reflux) or small bowel radiology (Crohn's).
- Duodenal biopsy (coeliac disease), eg if anti-endomysial antibodies +ve.
- Giardia tests, p436 (it often triggers IBS; antiparasitic Rx may not help).[230]
- ERCP (p756, eg chronic pancreatitis) or MRCP (p756) if active pancreatitis.
- Transit studies and anorectal physiological studies—rarely used.

Refer if: 1 Diagnosis unsure 2 If changing symptoms in 'known IBS' 3 *To surgeon* if rectal mucosal prolapse 4 *To dietician* if food intolerance[1] 5 *To psycho- or hypnotherapist* if stress or depression (seen in ≥50%) or refractory symptoms (here, NICE favours cognitive therapy, *OHCS* p372) 6 *To gynaecologist* if cyclical pain, dyspareunia, dysmenorrhoea; CA-125↑; endometriosis (*OHCS* p288) often mimics IBS 7 *To dermatologist* if co-existing atopy (IBS is 3-fold more common in atopy)[231] 8 *To yourself* (wearing a different hat) or *pain clinic* if *chronic pain overlap syndromes* (fibromyalgia + chronic fatigue + chronic pelvic pain) or detrusor problems.

Rx Treatment is rarely 50% successful, so aim to make symptoms less intrusive by forging a *therapeutic alliance*. *Explanation* and *reassurance* are vital as is *interdisciplinary teamwork* (interdisciplinary implies a harmonized approach, not just multidisciplinary with each specialist ploughing his own furrow).[232] Ensure a healthy diet; fibre, lactose, fructose, wheat, starch, caffeine, sorbitol, alcohol and fizzy drinks may worsen symptoms. Probiotics and water-soluble fibre may be OK. Many IBS patients report food intolerance[2], but few clinicians consider food hypersensitivity to be a cause of IBS. No tests can identify food intolerance reliably.[NICE 2012] Dietary elimination and food challenge data are contradictory. Further Rx depends on which symptoms predominate:

- *Constipation:* The standard healthy diet (p236) may be problematic: ↑fibre intake can worsen flatulence/bloating; avoid insoluble fibre, such as bran (oats are better). *Bisacodyl* and *sodium picosulfate*[233] can help constipation. *Ispaghula* has non-fermentable water-soluble fibre—better than *lactulose* which ferments (↑gas production is hard to distinguish from bloating).[234]
- *Diarrhoea:* Avoid sorbitol sweeteners; try a bulking agent ± *loperamide* 2mg after each loose stool; max 16mg/d (NNT=5); SE: colic, bloating, ileus.
- *Colic/bloating:* Oral antispasmodics: *mebeverine* 135mg/8h (over the counter); *alverine citrate* 60–120mg/8h;[235] *dicycloverine* 10–20mg/8h.[236 MET] Adding *simeticone* (=dimeticone; it's in Imodium Plus®) improves spasm.[237 MET] Once-daily *Bacillus coagulans* GBI-30, *B. infantis* 35624, *E. coli* DSM17252 and *L. acidophilus*.[238, 239]
- *Psychological symptoms/visceral hypersensitivity:* Emphasize the positive! In 50% symptoms go or improve after 1yr; <5% worsen. Consider cognitive behaviour therapy (*OHCS* p372), hypnosis,[1] and tricyclics, eg *amitriptyline* 10–50mg at night (SE: dry mouth[etc]); explain that it's for chronic pain (± depression).[240, 241] NNT=6. Explain that all forms of abuse (sexual, physical, verbal) perpetuate IBS.

The future Interest is being expressed in modulating the brain-gut axis by 5-HT3 antagonists (eg alosetron; 2012 data show it can ↑ quality of life and ↓ restriction of daily activities in women with severe diarrhoea-predominant IBS, but it has a chequered regulatory history owing to SE, eg ischaemic colitis).[242]

1 Food intolerance: dietary fibre and lactose (milk and dairy foods). Wheat resistant starch, caffeine, fructose, sorbitol, alcohol and fizzy drinks.

2 12wks of hypnosis helps abnormal sensory perception:[243] ►Do not think of hypnosis as dubious; it is a neat way to influence the brain-gut axis, reducing doctor dependency and stopping patients from being patients (passive recipients of suffering). Benefits may last ≥5yrs:[244, 245]

Lactase Deficiency

Diarrhea, bloating, flatulence, and abdominal pain after ingestion of milk-containing products.

Diagnosis supported by symptomatic improvement on lactose-free diet.

Diagnosis confirmed by hydrogen breath test.

Lactase is a brush border enzyme that hydrolyzes the disaccharide lactose into glucose and galactose. The concentration of lactase enzyme levels is high at birth but declines steadily in most people of non-European ancestry during childhood and adolescence and into adulthood. As many as 90% of Asian Americans, 70% of African Americans, 95% of Native Americans, 50% of Mexican Americans, and 60% of Jewish Americans are lactose intolerant compared with less than 25% of white adults. Lactase deficiency may also arise secondary to other gastrointestinal disorders that affect the proximal small intestinal mucosa. These include Crohn disease, sprue, viral gastroenteritis, giardiasis, short bowel syndrome, and malnutrition. Malabsorbed lactose is fermented by intestinal bacteria, producing gas and organic acids. The nonmetabolized lactose and organic acids result in an increased stool osmotic load with an obligatory fluid loss.

BACTERIAL OVERGROWTH SYNDROMES

Increased amounts of a colonic-type bacterial flora in the small intestine (e.g., *E. coli* or *Bacteroides).*
This bacterial proliferation is due to stasis caused by impaired peristalsis (**functional stasis**), changes in intestinal anatomy (**anatomic stasis**), or **direct communication between the small and large intestine.** These conditions have also been referred to as stagnant bowel syndrome or blind loop syndrome.
Macrocytic anemia is due to cobalamin—not folate—deficiency (most bacteria require cobalamin for growth).
Steatorrhea is due to impaired micelle formation as a consequence of a reduced intraduodenal concentration of conjugated bile acids (*Bacteroides* deconjugate conjugated bile acids)
Diarrhea is due to steatorrhea and/or bacterial enterotoxins production increasing fluid secretion,

Diagnosis; (a) bacterial overgrowth syndrome may be suspected from the **combination of a low serum cobalamin level and an elevated serum folate level,** as enteric bacteria frequently produce folate compounds that are absorbed in the duodenum; (b) jejunal cultures;(c) breath tests; (d) small bowel barium radiography or CT enterography study should be obtained to look for mechanical factors predisposing to intestinal stasis.

Therapy: where possible, the anatomic defect that has potentiated bacterial overgrowth should be corrected. Otherwise, treatment as follows for 1–2 weeks with oral broad-spectrum **antibiotics** effective against enteric aerobes and anaerobes usually leads to dramatic improvement .

ABNORMALITIES CONDUCIVE TO BACTERIAL OVERGROWTH
STRUCTURAL
Afferent loop syndrome after gastrojejunostomy
Ileocecal valve resection
End-to-side intestinal anastomoses
Duodenal and jejunal diverticula
Strictures (Crohn disease, radiation enteritis)
Adhesions (postsurgical)
Gastrojejunocolic fistulas
MOTOR
Scleroderma
Diabetes mellitus
Idiopathic pseudo-obstruction
HYPOCHLORHYDRIA
Atrophic gastritis
Proton pump inhibitors
Acquired immunodeficiency syndrome
Acid-reducing surgery for peptic ulcer disease
MISCELLANEOUS
Immunodeficiency states
Pancreatitis
Cirrhosis
Chronic renal failure

Chronic pancreatitis

Epigastric pain 'bores' through to back, eg relieved by sitting forward or hot water bottles on epigastrium/back (look for *erythema ab igne*'s mottled dusky greyness); bloating; steatorrhoea; ↓weight; brittle diabetes. Symptoms relapse and worsen.

Causes: Alcohol; rarely: familial; cystic fibrosis; haemochromatosis; pancreatic duct obstruction (stones/tumour); ↑PTH; congenital (*pancreas divisum*).

Tests *Ultrasound* ± *CT* (pancreatic calcifications confirm the diagnosis), *MRCP* + *ERCP* (risks acute attack); *AXR:* speckled calcification; ↑glucose; breath tests, eg ^{13}C-hiolien.[261]

Treatment *Drugs:* Give analgesia (coeliac-plexus block may give brief relief);[262] lipase, eg Creon®; fat-soluble vitamins (eg Multivite®). Insulin needs may be high or variable (beware hypoglycaemia). *Diet:* No alcohol; low fat may help. Medium-chain triglycerides (MCT oil®) may be tried (no lipase needed for absorption, but diarrhoea may be worsened). *Surgery:* For unremitting pain; narcotic abuse (beware of this); weight↓: eg pancreatectomy or pancreaticojejunostomy (a duct drainage procedure).

Complications Pseudocyst; diabetes; biliary obstruction; local arterial aneurysm; splenic vein thrombosis; gastric varices; pancreatic carcinoma.

Laboratory studies:

- Serum amylase and lipase may be normal
- 72h quantitative fecal fat determination (cumbersome)
- Fecal elastase (random stool sample; 93% sensitivity and specificity)

The differential diagnosis for colitis includes ischemic colitis, infectious colitis (*C difficile*, *E coli*, *Salmonella*, *Shigella*, *Campylobacter*), radiation colitis, and IBD (Crohn disease vs ulcerative colitis). Mesenteric ischemia usually is encountered in people older than 50 years with known atherosclerotic vascular disease or other cause of hypoperfusion. The pain usually is acute in onset following a meal ("intestinal angina") and not associated with fevers. Infectious colitis is usually characterized by an acute onset of symptoms, often in patients with a recent history of foreign travel, or recent use of antibiotics.

Inflammatory bowel disease (IBD) is most commonly diagnosed in young patients between the ages of 15 and 25 years. There is a second peak in the incidence of IBD (usually Crohn disease) between the ages of 60 and 70 years. IBD may present with a low-grade fever. The chronic nature of this patient's disease (several months) is typical of IBD. Anemia may be present, either due to iron deficiency from chronic GI blood loss, or anemia of chronic disease. Patients with IBD may also report fatigue and weight loss.

Gastrointestinal malabsorption

Symptoms Diarrhoea; ↓weight; lethargy; steatorrhoea (stool fat↑; hard to flush away) bloating.

Deficiency signs Anaemia (↓Fe, B_{12}, folate); bleeding disorders (↓vit K); oedema (↓protein); metabolic bone disease (↓vit D); neurological features, eg neuropathy.

Tests FBC (↓ or ↑MCV); ↓Ca^{2+}; ↓Fe; ↓B_{12} + folate; ↑INR; lipid profile; coeliac tests (below). *Stool:* Sudan stain for fat globules; stool microscopy (infestation); α_1AT (p264), elastase. *Ba follow-through:* Diverticula; Crohn's; radiation enteritis. *Breath hydrogen analysis:* for bacterial overgrowth.[1] Take samples of end-expired air; give glucose; take more samples at ½h intervals; ↑exhaled hydrogen = overgrowth. *Endoscopy + small bowel biopsy, ERCP:* (p756) biliary obstruction; chronic pancreatitis. **Causes** See BOX.

1 Bacterial overgrowth proximal to the colon causes diarrhoea, abdominal pain, vitamin malabsorption and possibly malnutrition. Causes: old age, chronic pancreatitis; HIV; bacteria not killed by gastric acid (PPI; achlorhydria); fistulae; post-gastrectomy/Roux-en-Y; jejunal diverticula; amyloidosis; autonomic neuropathy. Diagnosis: breath test or culture of duodenal aspirate (>10^5 colonies/mL). *OHGH* p226.

Table 15–11. Clinical manifestations and laboratory findings in malabsorption of various nutrients.

Manifestations	Laboratory Findings	Malabsorbed Nutrients
Steatorrhea (bulky, light-colored stools)	Increased fecal fat; decreased serum cholesterol; decreased serum carotene, vitamin A, vitamin D	Triglycerides, fatty acids, phospholipids, cholesterol. Fat soluble vitamins: A, D, E, K
Diarrhea (increased fecal water)	Increased stool volume and weight; increased fecal fat; increased stool osmolality gap	Fats, carbohydrates
Weight loss; muscle wasting	Increased fecal fat; decreased carbohydrate (D-xylose) absorption	Fat, protein, carbohydrates
Microcytic anemia	Low serum iron	Iron
Macrocytic anemia	Decreased serum vitamin B_{12} or red blood cell folate	Vitamin B_{12} or folic acid
Paresthesia; tetany; positive Trousseau and Chvostek signs	Decreased serum calcium or magnesium	Calcium, vitamin D, magnesium
Bone pain; pathologic fractures; skeletal deformities	Osteopenia on radiograph; osteoporosis (adults); osteomalacia (children)	Calcium, vitamin D
Bleeding tendency (ecchymoses, epistaxis)	Prolonged prothrombin time or INR	Vitamin K
Edema	Decreased serum total protein and albumin; increased fecal loss of alpha-1-antitrypsin	Protein
Milk intolerance (cramps, bloating, diarrhea)	Abnormal lactose tolerance test	Lactose

INR, international normalized ratio.

Causes of gastrointestinal malabsorption

Common in the UK Coeliac disease; chronic pancreatitis; Crohn's disease.

Rarer

- ↓*Bile:* Primary biliary cirrhosis; ileal resection; biliary obstruction; colestyramine.
- *Pancreatic insufficiency:* Pancreatic cancer; cystic fibrosis.
- *Small bowel mucosa:* Whipple's disease (p730); radiation enteritis; tropical sprue; small bowel resection; brush border enzyme deficiencies (eg lactase insufficiency); drugs (metformin, neomycin, alcohol); amyloid (p364).
- *Bacterial overgrowth:* Spontaneous (esp. in elderly); in jejunal diverticula; post-op blind loops. DM & PPI use are also risk factors. Try *metronidazole* 400mg/8h PO or *oxytetracycline* 250mg/6h. Don't confuse with afferent loop syndrome (p624).
- *Infection:* Giardiasis; diphyllobothriasis (B_{12} malabsorption); strongyloidiasis.
- *Intestinal hurry:* Post-gastrectomy dumping; post-vagotomy; gastrojejunostomy.

Deficiency syndromes and the sites of nutrient absorption

Vitamin/nutrient	Site of absorption	Deficiency syndrome
A[F]	Small intestine	Xerophthalmia (p278)
B_1 (thiamine)	Small intestine	Beriberi (p278); Wernicke's encephalopathy (p728)
B_2 (riboflavin)	Proximal small intestine	Angular stomatis; cheilitis (p238)
B_6 (pyridoxine)	Small intestine	Polyneuropathy
B_{12}	Terminal ileum	Macrocytic anaemia (p326); neuropathy; glossitis
C	Proximal ileum	Scurvy (p278)
D[F]	Jejunum as free vitamin	Rickets (p698); osteomalacia (p698)
E[F]	Small intestine	Haemolysis; neurological deficit
K[F]	Small intestine	Bleeding disorders (p338)
Folic acid	Jejunum	Macrocytic anaemia (p326)
Nicotinamide	Jejunum	Pellagra (p278)
Mineral		
Calcium	Duodenum + jejunum	p690
Copper	Stomach + jejunum	Menkes' kinky hair syndrome
Fluoride	Stomach	Dental caries
Iodide	Small intestine	Goitre; cretinism
Iron	Duodenum + jejunum	Microcytic anaemia (p320)
Magnesium	Small intestine	p693
Phosphate	Small intestine	Osteoporosis; anorexia; weakness
Selenium	Small intestine	Cardiomyopathy (p693)
Zinc	Jejunum	Acrodermatitis enteropathica; poor wound healing (p693)

[F] = fat-soluble vitamin, thus deficiency is likely if there is fat malabsorption.

Nutritional disorders

►Always consider that more than one nutritional disorder is likely to be present.

Scurvy is due to lack of vitamin C.[1] Is the patient poor, pregnant, or on an odd diet? *Signs:* 1 Listlessness, anorexia, cachexia (p29). 2 Gingivitis, loose teeth, and foul-breath (halitosis). 3 Bleeding from gums, nose, hair follicles, or into joints, bladder, gut. 4 Muscle pain/weakness. 5 Oedema.[246, 247] *Diagnosis:* No test is completely satisfactory. WBC ascorbic acid↓. *℞:* Dietary education; *ascorbic acid* ≥250mg/24h PO.

Beriberi There is heart failure with general oedema (wet beriberi) or neuropathy (dry beriberi) due to lack of vitamin B_1 (thiamine). For treatment and diagnostic tests, see Wernicke's encephalopathy (p728).

Pellagra = lack of nicotinic acid. Classical triad: **d**iarrhoea, **d**ementia, **d**ermatitis (Casal's necklace) ± neuropathy, depression, insomnia, tremor, rigidity, ataxia, fits. It may occur in carcinoid syndrome and anti-TB drugs (isoniazid). It is endemic in China and Africa. *℞:* Education, electrolyte replacement, *nicotinamide* 100mg/4h PO.[248] See BOX.

Xerophthalmia This vitamin A deficiency syndrome is a big cause of blindness in the Tropics. Conjunctivae become dry and develop oval/triangular spots (Bitôt's spots). Corneas become cloudy and soft. Give *vitamin A* (*OHCS* p450). ►Get special help if pregnant: vitamin A embryopathy must be avoided. Re-educate and monitor diet.

Wernicke's encephalopathy Thiamine (vitamin B_1) deficiency with a classical triad of 1 confusion 2 ataxia (wide-based gait; fig 2) and 3 ophthalmoplegia (nystagmus, lateral rectus or conjugate gaze palsies). There is inadequate dietary intake, ↓ GI absorption and impaired utilization of thiamine resulting in focal areas of brain damage, including periaqueductal punctate haemorrhages (mechanism unclear). Always consider this diagnosis in alcoholics: it may also present with memory disturbance, hypotension, hypothermia, or reduced consciousness. *Recognized causes:* Chronic alcoholism, eating disorders, malnutrition, prolonged vomiting, eg with chemotherapy, GI malignancy or hyperemesis gravidarum. *Diagnosis:* Primarily clinical. Red cell transketolase activity is decreased (rarely done). *Treatment:* Urgent replacement to prevent irreversible Korsakoff's syndrome (p718). Give ***thiamine*** (Pabrinex®) 2 pairs of high-potency ampoules IV/IM/8h over 30min for 2d, then 1 pair OD for a further 5d. Oral supplementation (100mg OD) should continue until no longer 'at risk' (+ give other B vitamins). Anaphylaxis is rare. If there is coexisting hypoglycaemia (often the case in this group of patients), make sure thiamine is given before glucose, as Wernicke's can be precipitated by glucose administration to a thiamine-deficient patient. *Prognosis:* Untreated, death occurs in 20%, and Korsakoff's psychosis occurs in 85%—a quarter of whom will require long-term institutional care.

Karl Wernicke, 1848–1905
(German neurologist)

55.1 Which of the following features is *not* consistent with the diagnosis of irritable bowel syndrome?

A. Abdominal pain relieved with defecation

B. Sensation of incomplete evacuation

C. Passage of mucus

D. Nocturnal awakening with pain or diarrhea

E. Normal bowel habits alternating with either diarrhea or constipation

55.2 Which of the following findings is more consistent with an osmotic, rather than a secretory, diarrhea?

A. The diarrhea persists despite a 48-hour fast.

B. Stool osmolality = 290 mOsm, stool Na = 95 mOsm, stool K = 15 mOsm.

C. Diarrhea is large volume and watery, and is accompanied by paroxysms of flushing and wheezing.

D. Profuse, painless "rice-water" stool in a patient in a cholera-endemic area.

55.3 Which of the following patients is not a good candidate for evaluation for celiac disease, with either endoscopy or serologic testing?

A. A 26-year-old woman who experiences with intermittent abdominal bloating but no diarrhea and is found to have osteopenia and vitamin D deficiency.

B. A 19-year-old college freshman with bulky, foul-smelling, floating stools and excessive flatulence, who has lost 20 lb unintentionally.

C. A thin, 39-year-old man with a family history of celiac disease, who has been adhering to a gluten-free vegetarian diet for the last 3 years, and now complains of gassiness and reflux.

D. A 42-year-old man who was found to have iron deficiency anemia, but has no gastrointestinal symptoms, and recently had a negative colonoscopy.

55.1 **D.** Nocturnal diarrhea is not typically associated with IBS, and should prompt further investigation, for example, with imaging or colonoscopy. The other symptoms listed are included in commonly used diagnostic criteria for IBS. It should be remembered that IBS is essentially a diagnosis of exclusion, and is established when patients have typical symptoms, but other conditions with similar clinical presentations have been excluded in a cost-effective manner.

55.2 **B.** Normal stool osmolality is equal to plasma, about 290 mOsm. In secretory diarrhea, most of the osmotically active particles are electrolytes, and can be calculated as 2 × [Na + K]. The size of osmotic gap (the difference between calculated and directly measured osmolality) is equivalent to the concentration of the poorly absorbed unmeasured solute in the fecal water. This patient has a stool osmotic gap of 70 (gap >50 is indicative of osmotic diarrhea). Answers C and D are suggestive of carcinoid syndrome and cholera infection, respectively, both causes of secretory diarrhea.

55.3 **C.** While GI symptoms in a patient with a family history of celiac disease are reasonable to investigate, the fact that he has been on a gluten-free diet for a prolonged period greatly diminishes the sensitivity of both endoscopic and serologic testing. Unexplained osteopenia and vitamin D deficiency in a young woman, unexplained iron deficiency anemia in any patient, and the classic presentation with steatorrhea and weight loss should all be investigated.

ACUTE DIARRHEA

Diarrhea of less than 14-day duration.

Diarrheal illnesses are extremely common, affecting nearly one in three people in the United States each year. In developing countries, acute infectious diarrhea is one of the leading causes of mortality. In the developed world, **90% of cases of acute diarrhea are infectious**, but the large majority of those illnesses are mild and self-limited. High-risk groups include travelers, immunocompromised patients, and patients who are hospitalized or institutionalized, but those groups are outside the scope of this discussion.

Most patients with mild to moderate illness do not require specific evaluation, and their symptoms can be managed with an oral sugar-electrolyte solution, or with antimotility agents such as loperamide. Bismuth subsalicylate can also reduce symptoms of nausea and diarrhea.

A more severe illness is suggested by any of the following findings: profuse watery diarrhea with signs of hypovolemia, grossly bloody stools, fever, symptoms >48 hours, severe abdominal pain, age >70 years, or hospitalized patients or recent use of antibiotics.

For these patients, an evaluation should be performed to **distinguish between inflammatory and noninflammatory** causes of diarrhea. Routine evaluation includes:

- Testing for **fecal leukocytes**,
- **Routine stool culture** (performed for *Salmonella*, *Shigella*, and *Campylobacter*).

Additional testing might include:

- Examination of **stool for ova and parasites**, which may be considered in cases of persistent diarrhea, especially if patient has exposure to infants in a day care setting (*Giardia*, *Cryptosporidium*), or if there is a known community waterborne outbreak of these infections.
- Nonroutine cultures, such as for ***E coli* O157:H7**, may be performed in cases of acute bloody diarrhea, especially when there is a known local outbreak, or if the patient develops hemolytic uremic syndrome (HUS).
- Stool may also be tested for the ***C difficile* toxin** in patients with recent antibiotic use.

If testing suggests a **noninflammatory diarrhea**, most cases are due to viral infection (Norwalk, rotavirus), food poisoning (*S aureus*, *B cereus*, *C perfringens*) or giardiasis. Viral infections and food poisoning are generally self-limited and are treated with **supportive care**. Giardiasis is treated with metronidazole or tinidazole.

If testing suggests an **inflammatory diarrhea**, **empiric therapy** is usually instituted, often with **quinolone antibiotics** such as ciprofloxacin or norfloxacin. An exception to this strategy is in patients with suspected **enterohemorrhagic *E coli* (EHEC)** infection. There is no evidence of benefit from antibiotics for EHEC infections such as the O157:H7 strain, and there is concern about increased risk of hemolytic uremic syndrome due to an increase in the production of Shiga toxin when antibiotics are administered, so **antibiotics are not recommended.**

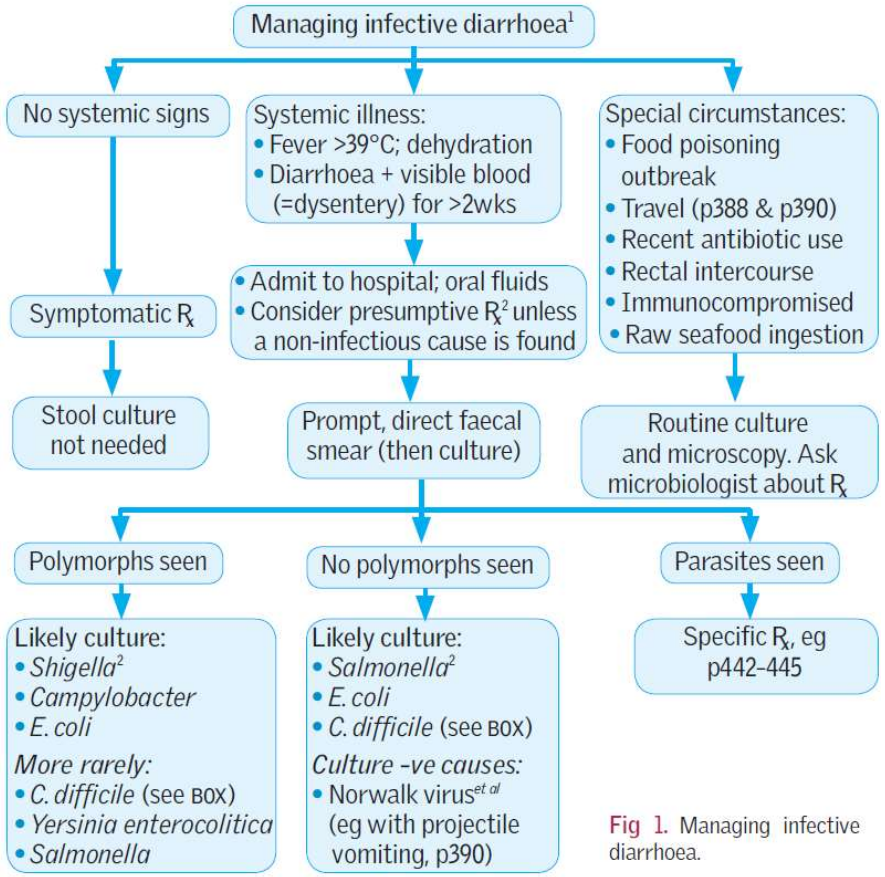
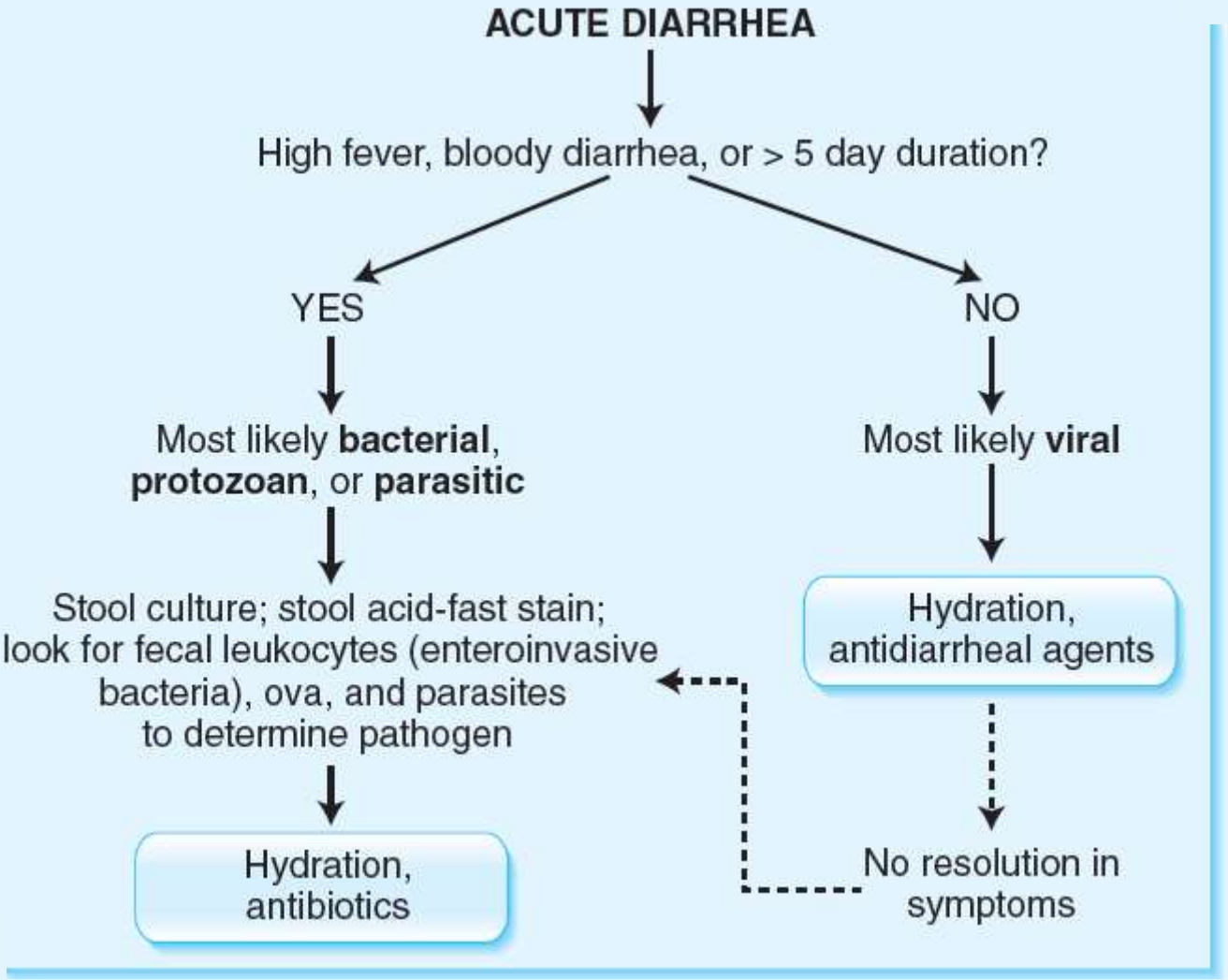


Fig 1. Managing infective diarrhoea.

1 Be aware of your local pathogens, and be prepared to close wards and hospitals if contagion is afoot.
2 Prompt specific Rx: eg **ciprofloxacin** 500mg/12h PO for 6d may be needed before sensitivities are known. Metronidazole is also tried, as giardia is a common cause of watery diarrhoea (no leukocytes) in travellers.


ACUTE DIARRHEA
High fever, bloody diarrhea, or > 5 day duration?
YES
NO
Most likely **bacterial**, **protozoan**, or **parasitic**
Most likely **viral**
Stool culture; stool acid-fast stain; look for fecal leukocytes (enteroinvasive bacteria), ova, and parasites to determine pathogen
Hydration, antidiarrheal agents
Hydration, antibiotics
No resolution in symptoms

Clostridium difficile: the cause of pseudomembranous colitis

C. difficile is a Gram +ve 'superbug' whose spores are contagious (faecal-oral or from the environment, where spores can live for ages and are hard to eradicate).

Signs: T°↑; colic; mild diarrhoea—or serious bloody diarrhoea with systemic upset—CRP↑↑, WCC↑, albumin↓, and colitis (with yellow adherent plaques on inflamed non-ulcerated mucosa—the pseudomembrane) and multi-organ failure.

Asymptomatic carriage: 1–3% of all adults (∴ broad-spectrum/IV antibiotic use).

Predictors of fulminant C. diff colitis: >70yrs, past *C. diff* infection; use of antiperistaltic drugs; Girotra's triad: **1** Increasing abdominal pain/distention and diarrhoea **2** Leukocytosis >18,000 **3** Haemodynamic instability.[69] *Deaths:* 6500/yr[uk].

Toxins: Tissue culture, ELISA, and PCR help defect *C. difficile* toxins (CDT). Some strains produce no toxin and are non-pathogenic; most produce toxins A and B. Some strains are hypervirulent, eg NAP1/027.

℞: Stop the causative antibiotic (if possible). Treatment is not usually needed if asymptomatic (use of antibiotics for *C. difficile* is controversial). If symptomatic, give metronidazole ≤400mg/8h PO for ≤10d (vancomycin 125mg/6h PO is better in severe disease; if complications, up to 2g/day).[70]

► Urgent colectomy may be needed if toxic megacolon, LDH↑, or if deteriorating.

Recurrent disease: Repeat metronidazole once only (overuse causes irreversible neuropathy). NB: probiotics may prevent recurrences (*Saccharomyces boulardii* 500mg/12h, unless immunosuppressed or CVP line *in situ*). Administration of stools (via NGT or colonoscope) from healthy subjects may have a role.[70]

Preventing spread: Meticulous cleaning, use of disposable gloves, not using rectal thermometers, hand-washing, and ward protocols (eg 'bare below elbows').

History Work (is he a chef?—don't work until an infective cause is ruled out) *Acute or chronic?* If acute (<2wks) suspect gastroenteritis—any risk factors? HIV; achlorhydria, eg PA, p328, or on acid suppressants, eg PPI? Travel? Diet change? Contact with D&V? Any fever/pain? Chronic diarrhoea alternating with constipation suggests irritable bowel (p276). Weight↓, nocturnal diarrhoea and anaemia mandate close follow-up (UC/Crohn's^{etc}?).

Bloody diarrhoea: *Campylobacter*, *Shigella*/*Salmonella* (p426), *E. coli*, amoebiasis (p436), UC, Crohn's, colorectal cancer (p618), colonic polyps, pseudomembranous colitis, ischaemic colitis (p622). *Fresh PR bleeding:* p631.

Mucus occurs in IBS(p276), colorectal cancer, and polyps.

Frank pus suggests IBD, diverticulitis, or a fistula/abscess. White cells are microscopically *absent* in amoebiasis, cholera, *E. coli* and viruses.

Explosive: Eg cholera; giardia; yersinia (p422); rotavirus.

Large bowel: (*Salmonella*, *Shigella*, *C. diff* & entamoeba). Watery stool ± blood/mucus; pelvic pain relieved by defecation; tenesmus; urgency.

Small bowel symptoms: Periumbilical (or RIF) pain not relieved by defecation.

Look for Dehydration—dry mucous membranes, ↓skin turgor; capillary refill >2s; shock (►►think of cholera, p426). Any fever, weight↓, clubbing, anaemia, oral ulcers (p238), rashes or abdominal mass or scars? Any goitre/hyperthyroid signs? Do rectal exam for masses (eg rectal cancer) or impacted faeces (if you don't put your finger in, you'll put your foot in it by missing this diagnosis that never responds to codeine!)

- **Blood** *FBC:* MCV↓/Fe deficiency, eg coeliac or colon ca; MCV↑ if alcohol abuse or B_{12} absorption↓, eg in coeliac or Crohn's; eosinophilia if parasites. *ESR/CRP↑:* Infection, Crohn's/UC, cancer. *U&E:* K^+↓≈severe D&V. *TSH↓:* Thyrotoxicosis. *Coeliac serology:* p280.
- **Stool** *MC&S:* Bacterial pathogens, ova cysts, parasites *C. diff* toxin (see BOX). *Faecal fat excretion* or *^{13}C-hiolein (highly labelled triolein) breath test* (nicer and reliable) if symptoms of chronic pancreatitis, malabsorption, or steatorrhoea.[67]
- **Rigid sigmoidoscopy** With biopsy of normal and abnormal looking mucosa: ~15% of patients with Crohn's disease have macroscopically normal mucosa.
- **Colonoscopy/barium enema** (malignancy? colitis?) ►Avoid in acute episode. If normal, consider small bowel radiology (eg Crohn's) ± ERCP (chronic pancreatitis).

Management Treat causes. Food handlers: no work until stool samples are -ve. If a hospital outbreak, wards may need closing. *Oral rehydration* is better than IV, but if impossible, give 0.9% saline + 20mmol K^+/L IVI. ►If dehydrated and bloody diarrhoea for ≥2wks, IV fluids may well be needed. *Codeine phosphate* 30mg/8h PO or *loperamide* 2mg PO after each loose stool (max 16mg/day) ↓stool frequency (avoid in colitis; both may precipitate toxic megacolon).[68] Avoid antibiotics unless infective diarrhoea is causing systemic upset (fig 1) to avoid selecting resistant strains. *Antibiotic-associated diarrhoea*[3] may respond to probiotics (eg lactobacilli).

3 Erythromycin is prokinetic, others cause overgrowth of bowel organisms, or alter bile acids.

Pigmented Whipple's disease

A 48 year old man presents with episodic watery diarrhea for five months, which was predominantly nocturnal. He had also lost 8 kg of weight during the preceding year. His medical history is unremarkable, and he is not on any drugs. There is no significant history of travel. His serum albumin is found to be 2.5 g/dL (normal: 3.5 to 5.5 g/dL).

Select Relevant Investigations

❖ Serum Electrolytes

Na+: 132 mEq/L (135 - 145) K+: 3.4 mEq/L (3.5 - 5.5) Cl-: 97 mEq/L (95 - 105)

❖ Stool Analysis

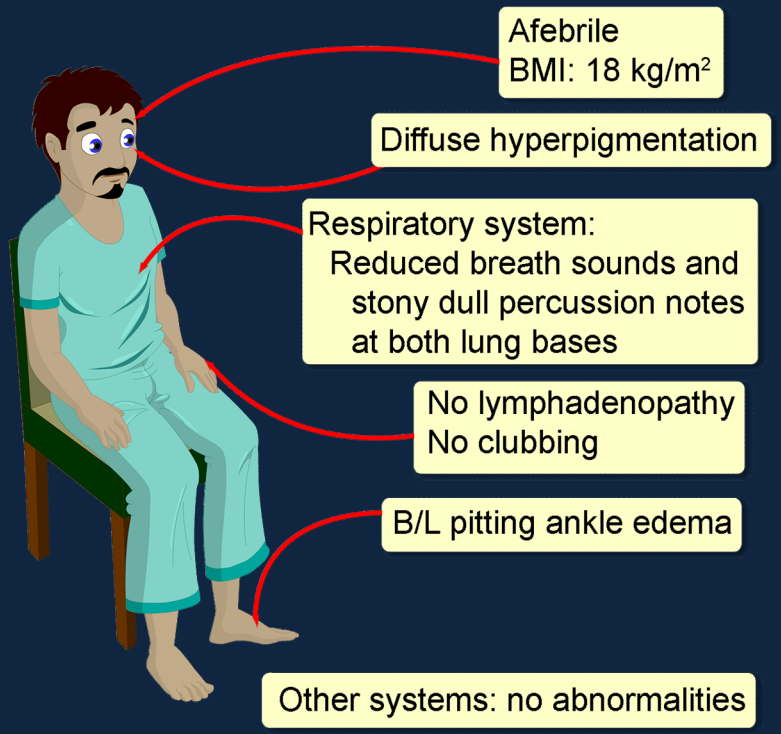
No amoeba, ova or cysts identified No pus cells or erythrocytes Fecal fat analysis: 9 g/24h (normal: 2 - 6) Bacterial and protozoal cultures: negative

❖ Morning Cortisol

22 mcg/dl (<3: adrenal insufficiency; 3-19: indeterminate; 19-25: unambiguously normal)

❖ Upper GI Endoscopy + Biopsy

The duodenal mucosa shows pale yellow shaggy areas alternating with erythematous regions. Biopsies reveal expanded villi containing macrophages which stain positive to the Periodic Acid-Schiff (PAS) stain.



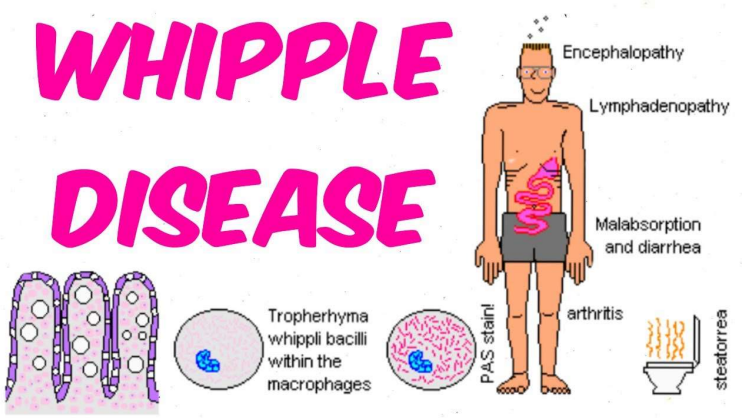
- Antibiotics
- Steroids
- Surgical resection
- Dietary restrictions

Diagnosis and reasoning

This middle aged gentleman has presented with **chronic watery diarrhea** - a very common condition which may be due to a myriad of causes.
The first step in his evaluation should be to determine if the diarrhea is organic or functional in origin (keeping in mind that the majority of such cases are functional).
In this patient's case, the profound **weight loss** (of over 5 kg) strongly suggests an organic cause, as does the predominantly nocturnal nature of the diarrhea.
The organic causes of chronic diarrhea can be broadly classified into **inflammatory** conditions (such as Crohn's disease), **malabsorptive** conditions (such as giardiasis, coeliac disease and Whipple's disease), and **secretory** conditions (such as diabetes, adrenal insufficiency, and hypo-or-hyperthyroidism).
In most patients, differentiating between these etiologies requires a systematic and at times protracted workup.
However, this patient's examination reveals a valuable clue which helps short-circuit the diagnostic pathway: the presence of **generalized hyperpigmentation**.
Very few etiologies causing chronic diarrhea give rise to generalized hyperpigmentation; in this patient, the two most plausible are Whipple's disease and adrenal insufficiency.
A diagnostic workup initially aimed at these two etiologies is perhaps the most efficient way forward.
First of all, note that Whipple's disease gives rise to a malabsorptive diarrhea, while that of Adrenal insufficiency is secretory in origin.
Thus the **stool analysis** showing increased fecal fat (i.e. malabsorption) is a pointer towards Whipple's disease; the **hypoalbuminemia** coupled with examination findings of peripheral edema and bilateral pleural effusions provide further supportive evidence in this regard.
Note also that adrenal insufficiency is typically associated with **hyponatremia and hyperkalemia**; the mild hyponatremia and hypokalemia in this patient is more suggestive of chronic electrolyte loss secondary to the diarrhea.
Estimation of **morning cortisol** definitively rules out adrenal insufficiency by demonstrating levels which are unambiguously normal.
The diagnosis of Whipple's disease requires **endoscopy and biopsy of the duodenal mucosa**. This is justifiable now in this patient, and reveals consistent histopathological findings, clinching the diagnosis.
Antibiotics are the mainstay of treatment in patients with Whipple's disease. Steroids, dietary restrictions and surgical resection have no place in the management.

Whipple's disease[122] A rare disease featuring GI malabsorption which usually occurs in middle-aged white males, most commonly in Europe. It is fatal if untreated and is caused by *Tropheryma whippelii*, which, combined with defective cell-mediated immunity, produces a systemic disease. *Features:* Often starts insidiously with arthralgia (chronic, migratory, seronegative arthropathy affecting mainly peripheral joints). GI symptoms commonly include colicky abdominal pain, weight loss, steatorrhea/diarrhoea, which leads to malabsorption (p280). Systemic symptoms such as chronic cough, fever, sweats, lymphadenopathy and skin hyperpigmentation also occur. Cardiac involvement may lead to endocarditis, which is typically blood culture negative. CNS features include a reversible dementia, ophthalmoplegia, and facial myoclonus (if all together, they are highly suggestive)—also hypothalamic syndrome (hyperphagia, polydipsia, insomnia). NB: CNS involvement may occur without GI involvement. *Tests:* Diagnosis requires a high level of clinical suspicion. Jejunal biopsy shows stunted villi. There is deposition of macrophages in the lamina propria-containing granules which stain positive for Periodic Acid-Schiff (PAS). Similar cells may be found in affected samples, eg CSF, cardiac valve tissue, lymph nodes, synovial fluid. The bacteria may be seen within macrophages on electron microscopy. PCR of bacterial RNA can be performed on serum or tissue. MRI may demonstrate CNS involvement. *℞:* Should include antibiotics which cross the blood–brain barrier. Current recommendations: IV *ceftriaxone* (or penicillin+streptomycin) for 2wks then oral *co-trimoxazole* for some months. Shorter courses risk relapse. A rapid improvement in symptoms usually occurs.

George Hoyt Whipple, 1878–1976 (US pathologist)



Clinical suspicion for Whipple's disease*

Suggestive syndromes include the following:

- **Syndrome of arthralgias, abdominal pain, diarrhea, and weight loss**
- **RF-negative migratory polyarthritis nonresponsive to immunosuppressive therapy**
- **Unexplained progressive CNS disease/early onset cognitive deficits**
- **Fever unknown origin, chronic serositis, or unexplained generalized lymphadenopathy**

Rule out more common causes of symptoms¶

In particular:

- **Inflammatory bowel disease**
- **Infectious causes of chronic diarrhea**
- **Connective tissue disease**
- **Advanced HIV infection**
- **Tuberculosis**
- **Hyperthyroidism**

Feature	Patients with Whipple's Disease
	no./total no. (%)
Male sex	770/886 (87)
Arthralgia or arthritis	244/335 (73)
Diarrhea	272/335 (81)
Weight loss	223/240 (93)
Fever	128/335 (38)
Adenopathy	174/335 (52)
Melanoderma	99/240 (41)
Neurologic signs†	33/99 (33)
Ocular signs†	6/99 (6)
Pleural effusion	26/190 (14)

* Data are from reports on seven case series, all published since 1960, by Chears et al.,[22] Enzinger and Helwig,[16] Kelly and Weisiger,[23] Maizel et al.,[24] Dobbins,[15] Fleming et al.,[25] and Durand et al.[21] Total numbers refer to the total number of patients evaluated for Whipple's disease. The ages of the patients at diagnosis ranged from 1 to 83 years.

† Supranuclear ophthalmoplegia is included as a neurologic sign but not as an ocular sign. Two patients presented with supranuclear ophthalmoplegia.

Explosive Giardiasis

A 35 year old man presents with watery diarrhea and nausea for 4 weeks. During this time, his bowel movements changed from once a day to 4 to 6 times a day with foul smelling, loose, urgent stools associated with a crampy abdominal pain. He had lost 8 kg of weight during the same time period. The symptoms started around 1 week after returning from a holiday to Turkey, where he had gone camping and drunk water from a natural spring. His medical and surgical histories are unremarkable but his family history is significant for a sister with celiac disease.

Select Relevant Investigations

- **Stool Microscopy** Fresh stool examination for leucocytes, erythrocytes and trophozoites is negative. Fixed stool examination for enteric parasites is negative. Routine stool examination for enteric parasites is negative.

- **Stool Culture and Antigen Assay** Positive for Giardia. Negative for routine bacteria, rotavirus/adenovirus antigen and Clostridium difficile antigen. The Cryptosporidium antigen is not detected by a Lateral Flow Test (LFT).

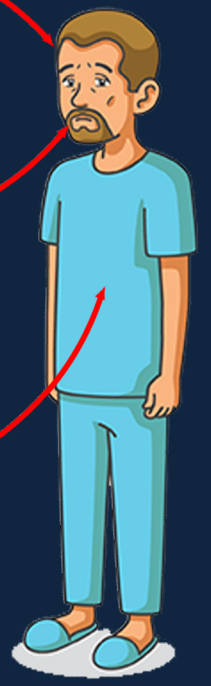
- **Serology for Gluten Antibodies** EMA (Immunoglobulin A anti-endomysium antibodies): negative AGA (IgA anti-gliadin antibodies): negative tTGA (IgA anti-tissue transglutaminase): negative
- **Endoscopy & Duodenal Biopsy** No macroscopic features suggestive of celiac disease. Biopsies indicated partial villous atrophy. No crypt hyperplasia or intraepithelial lymphocytes. Heavy colonization with G. lamblia trophozoites noted.

Averagely built, not emaciated
Afebrile
Mild pallor
Not icteric

Not dehydrated
No pedal edema
No features suggestive of a nutritional deficiency
Pulse: 68 bpm, regular
BP: 110/80 mmHg
RR:16/ min

Abdomen:
Not distended
Generalized mild tenderness
No organomegaly
No free fluids

Heart, Lungs,CNS: no abnormalities



(+) Metronidazole
(-) Gluten Free Diet
(+) Health Education
(-) Isolation

Diagnosis and reasoning

This patient has presented with diarrhea, nausea and weight loss, in a background of recent foreign travel, where he consumed untreated water; this is strongly suggestive of an infectious etiological agent causing travelers' diarrhea. Note also the persistence of symptoms for several weeks; while most cases of travelers' diarrhea are due to bacteria and viruses, such episodes are usually short and self-limiting. Thus, considering the duration of symptoms in this patient, a protozoan parasitic etiology becomes more likely; of these, Giardia is the most commonly implicated organism, followed by Cryptosporidium and E. histolytica. Other causes of persistent travelers' diarrhea include sequential infection with diarrheal pathogens (which is very unlikely, given that he has been in the country throughout); and immunosuppression (for which there is no evidence). The family history of celiac disease raises the possibility of an alternate etiology, as first-degree relatives of affected individuals are at high risk of developing the condition; furthermore, recent studies suggest that a person can develop celiac disease at any age. Irritable bowel syndrome (IBS), despite being a diagnosis of exclusion is another consideration. The history does not provide any more diagnostically useful information, while his physical examination findings are inconclusive. Therefore, the microscopy of a fresh stool sample is a good first step, as it is cheap and fast to perform; note that the negative results seen here do not exclude an infectious agent, given the relatively low specificity and sensitivity. Further investigations to detect pathogens are warranted; a subsequent stool antigen assay tests positive for Giardia, while simultaneously excluding the other likely infectious agents. A stool antigen assay has both a sensitivity and specificity of more than 90% for detection of giardiasis; in combination with the supportive history, this is sufficient to clinch the diagnosis. While there exists the low possibility that co-existent celiac disease may also be present, it is probably most logical to treat the giardiasis with antibiotics first, and then assess the patient's response to therapy. A poor response should elicit a detailed workup for celiac disease, inclusive of antibody levels and if indicated, an intestinal biopsy. Metronidazole is the drug of choice for management of giardiasis; education of the patient about water-borne diseases is important for prevention in the future. A gluten free diet is not indicated at the current time; in fact, if he does turn out to have celiac disease, this might even hinder the diagnosis. Patients with giardiasis need not be isolated.

Giardia lamblia (fig 1) is a flagellate protozoon that lives in the duodenum and jejunum. Spread: faecal–oral (↑ risk if, eg immunosuppression, travel, anal sex, achlorhydria, playgroups,[391] and swimming)—or from pets or birds. Drinking water may be contaminated.

The patient is often asymptomatic. Lassitude, bloating, flatulence, abdominal pain, loose stools ± explosive diarrhoea are typical. Malabsorption, weight loss, and lactose intolerance may occur.

Δ: • Stool microscopy for cysts and trophozoites may be –ve so repeat ≳ 3 times • Duodenal fluid aspirate analysis • Stool ELISA/PCR • Therapeutic trial. *ΔΔ:* Any cause of diarrhoea (p246), sprue (p280), coeliac.

℞: Scrupulous hygiene. Tinidazole 2g PO stat (avoid alcohol); if pregnant, paromomycin 500mg/6h PO for 7d. If this fails, check compliance and consider treating *all* the family. If diarrhoea persists, avoid milk as lactose intolerance may persist for 6wks.

Entamoeba histolytica (amoebiasis; figs 2–5) affects 50 million people worldwide; ~100,000 die annually.[392] Spread: faecal–oral (eg oral–anal sex).[393] Boil water and infected food to destroy cysts. Most symptoms are from involvement of the colon, but 1% present with potentially fatal invasive liver disease. Distinguishing invasive forms (*E. histolytica*) from a morphologically identical but *usually*[394] non-invasive *E. dispar* requires PCR *et al*.

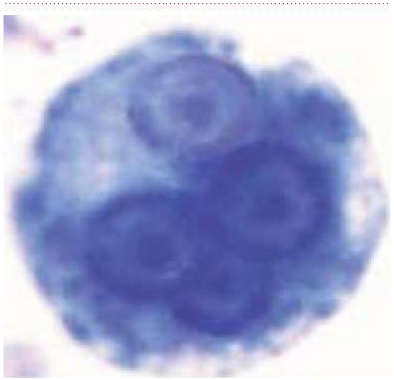


Fig 2. *E. histolytica* cyst with an endosome inside each of its 4 nuclei.

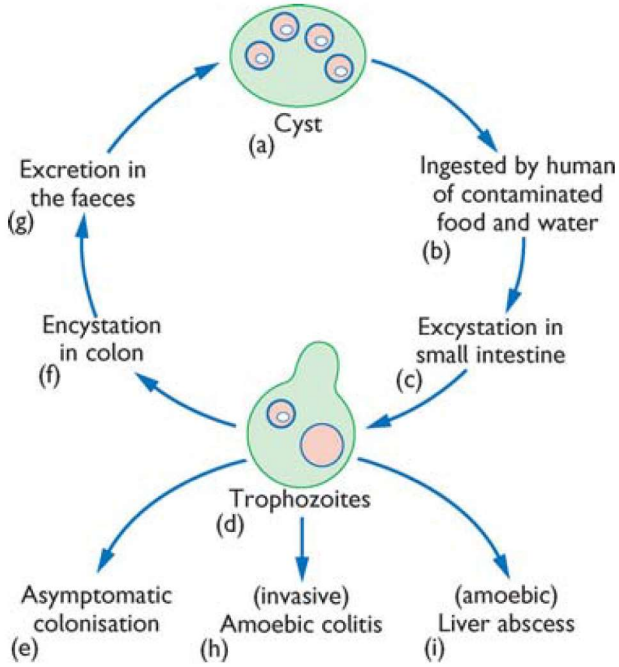
Amoebic dysentery[ND] may occur some time after initial infection. Diarrhoea starts slowly, becoming profuse & bloody. An acute febrile prostrating illness can occur but high fever, colic, and tenesmus are rare. May remit and relapse. *Δ:* Stool microscopy: trophozoites, blood, pus cells. Faecal antigen detection also helps. Serology indicates previous or current infection and may be unhelpful in acute infection. *ΔΔ: Bacillary dysentery* often starts more suddenly, is more dehydrating, and stools are more watery. *Acute ulcerative colitis* is more gradual and stools are bloodier. Other causes of bloody diarrhoea: p426 & p246.

Amoebic colonic abscesses may perforate causing peritonitis.

Amoebomas are inflammatory masses, eg in the caecum (a cause of RIF masses).

Amoebic liver abscess is often a single mass in the right lobe containing 'anchovy-sauce' pus. *Signs:* High swinging fever, sweats, RUQ pain/tenderness ± chest pain (eg if intrapleural rupture). WCC↑. LFT normal or ↑ (cholestatic). 50% have no history of amoebic dysentery. *Δ:* PCR; ultrasound/CT ± aspiration; don't rely on microscopy.

℞: **Metronidazole** 800mg/8h PO for 5d for acute amoebic dysentery (active against vegetative amoebae), then **diloxanide furoate** 500mg/8h PO for 10d to destroy gut cysts (it's a luminal agent to prevent recurrence; SE rare); **diloxanide** is also best in chronic disease when *Entamoeba* cysts, not vegetative forms, are in stools. Amoebic liver abscess/severe infections: **tinidazole** 2g/24h for 5d ± ultrasound-guided aspiration (by an expert in theatre) if not improving within days, eg via catheter (not needle) if >10cm across.[395] Check INR/clotting pre-op. Give **diloxanide** post-metronidazole.



The lifecycle of Entamoeba histolytica is in 2 stages: cysts and trophozoites. Cysts (10–15µm across) typically contain 4 nuclei. During excystation in the gut lumen, nuclear division is followed by cytoplasmic division, giving rise to 8 trophozoites. Tropho zoites (10–50µm across) contain one nucleus with a central karyosome; they live in the caecum and colon. ~90% of individuals infected with E. histolytica are asymptomatic. Re-encystation of the trophozoites occurs in the colon, and excretion of cysts in faeces perpetuates the lifecycle. Trophozoites may also invade colon epithelium, causing amoebic colitis in ~10%. E. histolytica can spread haematogenously after breaching colon epithelium and can establish persistent extra-intestinal infection (eg amoebic liver abscess).

Gastroenteritis

Ingesting certain bacteria, viruses, and toxins is a common cause of D&V (p56 & p246). Contaminated food and water are common sources, but often no specific cause is found. Ask about details of food and water taken, cooking method, time until onset of symptoms, and whether fellow-diners were affected. Ask about swimming, canoeing, etc. NB: food poisoning is a notifiable disease (p373) in the UK.

Tests *Stool microscopy/culture* if from abroad, an institution, or in day care, or an outbreak is suspected. In these circumstances culture of the food source may help.

Prevention Hygiene; if abroad, avoid unboiled/unbottled water, ice cubes, salads, and peel own fruit. Eat only freshly prepared hot food (or *thoroughly* rewarmed, p377).[20] Household water treatment and safe storage technologies can ↑ water quality and ↓ rates of diarrhoea, eg chlorine or solar disinfection, and ceramic or biosand filtration.[1 82]

Management Usually symptomatic. Maintain *oral fluid* intake (±oral rehydration sachets). For severe symptoms (but not in dysentery), give *anti-emetics,* eg ***prochlorperazine*** 12.5mg/6h IM + *antidiarrhoeals* (***codeine phosphate*** 30mg PO/IM or ***loperamide*** 4mg stat, then 2mg after each loose stool). *Antibiotics are only indicated if systemically unwell, immunosuppressed or elderly;* resistance is common.
Cholera: ***tetracycline*** reduces transmission.
Salmonella: ***ciprofloxacin*** 500mg/12h PO, 200–400mg/12h IVI over 60min (remember that antibiotic therapy in salmonella enteritis may ↑ number of chronic carriers).
Shigella and Campylobacter: ***ciprofloxacin*** as above.

Organism/source	Incubation	Clinical features	Notes/sources of infection
Staph. aureus	1–6h	D&V, P, hypotension	Meat
Bacillus cereus	1–5h	D&V	Rice
Red beans	1–3h	D&V	
Heavy metals, eg zinc	5min–2h	V, P (?work exposure)	(Delayed fever ± flu-like features)
Scrombotoxin	10–60min	D, flushing, sweating	Fish (NB may report hot mouth)
Mushrooms	15min–24h	D&V, P, fits, coma (LFT↑↑)	Image: p251 (hepatic & renal failure)
Salmonella	12–48h	D&V, P, fever, septicaemia	Meat, eggs, poultry
C. perfringens	8–24h	D, P afebrile	Meat
C. botulinum	12–36h	V, paralysis	Processed food
C. difficile	1–7d	Bloody D, P, gut perforation; toxic megacolon; hospital-acquired (1000 deaths/yr^{UK})	Antibiotic-associated; getting more virulent (eg strain BI/NAP1 with 20-fold ↑ in toxin A and B production)[76]
Vibrio cholerae	2h–5d	See p426	Water*
Vib. parahaemolyticus	12–24h	Profuse D; P, V	Seafood
Campylobacter	2–5d	Bloody D, P, T°↑, peritonism	Milk, poultry, water*
Listeria		Meningoencephalitis; "I've got flu"; miscarriages	Cheese, pâtés
E. coli type O157	12–72h	Cholera/typhoid-like;*	Haemolytic-uraemic sy., p308
Y. enterocolitica	24–36h	D, P, fever	Milk*
Cryptosporidium (fig1)	4–12d	D in HIV	Cow→water→man
Giardia lamblia	1–4wks	p436 (D, malabsorption)	*Nappies, cats;[77] dogs, crows[78]
Entamoeba histolytica	1–4wks	See p436	*
Noroviruses, eg Norwalk SRVS (small round structured virus)	12–48h[79] mean≈34h	Fever, P, D & projectile V;[80] 'winter vomiting illness'. Δ: no leucocytes in faeces; PCR	*Fecal-oral (vomit is infectious); very contagious, and common. Infectious for ≤48h after symptoms resolve[81]
Rotavirus	1–7d	D&V, fever, malaise	*(Vaccine available for infants aged from 6 weeks, 2 doses)
Shigella	2–3d	Bloody D, P, fever	Any food

V = vomiting; D = diarrhoea; P = abdominal pain. *May be food- or water-borne.

Abdominal pain

Varies depending on the underlying cause. Examples: irritation of the mucosa (acute gastritis), smooth muscle spasm (acute enterocolitis), capsular stretching (liver congestion in CCF), peritoneal inflammation (acute appendicitis) and direct splanchnic nerve stimulation (retroperitoneal extension of tumour). The *character* (constant or colicky, sharp or dull), *duration,* and *frequency* depend on the mechanism of production. The *location* and *distribution* of referred pain depend on the anatomical site. *Time of occurrence* and *aggravating* or *relieving factors* such as meals, defecation, and sleep also have special significance related to the underlying disease process. The site of the pain may provide a clue:

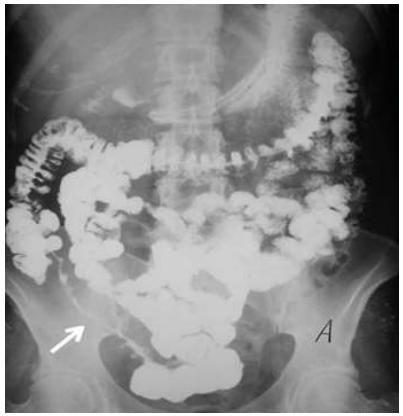
- **Epigastric** Pancreatitis, gastritis/duodenitis, peptic ulcer, gallbladder disease, aortic aneurysm.
- **Left upper quadrant** Peptic ulcer, gastric or colonic (splenic flexure) cancer, splenic rupture, subphrenic or perinephric abscess, renal (colic, pyelonephritis).
- **Right upper quadrant** Cholecystitis, biliary colic, hepatitis, peptic ulcer, colonic cancer (hepatic flexure), renal (colic, pyelonephritis), subphrenic/perinephric abscess.
- **Loin** (lateral ⅓ of back between thorax and pelvis—merges with the flank, p567) Renal colic, pyelonephritis, renal tumour, perinephric abscess, pain referred from vertebral column. Causes of *flank pain* are similar (see index for fuller list).
- **Left iliac fossa** Diverticulitis, volvulus, colon cancer, pelvic abscess, inflammatory bowel disease, hip pathology, renal colic, urinary tract infection (UTI), cancer in undescended testis; zoster—wait for the rash! (p458). *Gynae:* Torsion of ovarian cyst, salpingitis, ectopic pregnancy.
- **Right iliac fossa pain** All causes of left iliac fossa pain plus appendicitis and Crohn's ileitis, but usually excluding diverticulitis.
- **Pelvic** *Urological:* UTI, retention, stones. *Gynae:* Menstruation, pregnancy, endometriosis (*OHCS* p288), salpingitis, endometritis (*OHCS* p274), ovarian cyst torsion.
- **Generalized** Gastroenteritis, irritable bowel syndrome, peritonitis, constipation.
- **Central** Mesenteric ischaemia, abdominal aneurysm, pancreatitis.

Remember referred pain: Myocardial infarct → epigastrium; pleural pathology.

Mechanism

Crampy abdominal pain, diarrhea and weight loss in a young woman smoker

Janine, a 22-year-old woman, comes to your office with a **6-week** history of **5 loose, nonbloody stools daily**, **right lower quadrant crampy abdominal pain** (especially after eating), **9-kg weight loss**, and **bilateral knee and ankle pains**. Janine **has smoked 1 pack of cigarettes daily** for the past 5 years. Findings from the physical examination show a **definite and moderately tender 5-cm mass in the right lower quadrant of her abdomen**. No joint effusion or skin lesions are noted. Results from the stool studies are negative for enteric pathogens, and the results from her blood work show **mild anemia (hemoglobin, 11.2 g/dL**), with a normal metabolic panel and normal thyroid-stimulating hormone levels. Radiographic findings (small bowel enema) demonstrate a **10-cm narrowing in the terminal ileum (string sign)** with a separation of bowel loops around the terminal ileum



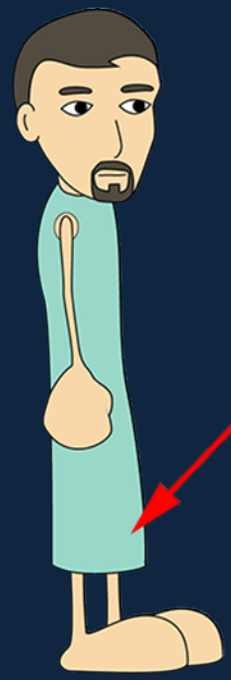
What is the most likely diagnosis? ***Crohn disease***

What is your next step? Janine has developed an ***inflammatory mass***, as demonstrated radiographically and upon physical examination. The mass is formed by indurated loops of bowel that may contain internal ***fistulas*** and even a small ***abscess***. Because most of this mass effect is due to inflammation, an antiinflammatory agent such as ***prednisone*** is indicated. The short-term effect of prednisone is rapid, with some patients showing a remarkable response within 1 to 2 weeks. Janine is started on prednisone, 40 mg daily. Strategies to maintain corticosteroid-induced remission with long-term therapy such as with ***azathioprine*** are essential to maintain steroid-free remission and to minimize the number of bowel resections over a lifetime. Most patients who have an inflammatory mass at the time of diagnosis will require ***surgical resection*** at some point in their lives, but ***delaying surgery as long as possible is preferable*.**

A 28-year-old woman arrives in the urgent care clinic complaining of **cramping abdominal pain**. She has had the pain intermittently over the past 5 months, accompanied by **diarrhea**. During this time period, **she lost 7 kg** and had significant malaise. On examination, she has a diffusely tender abdomen, worst in the right lower quadrant (RLQ), but no rebound or guarding. Complete blood count (CBC) reveals **anemia**, and her **serum vitamin B12 level is low.** Her stool culture and ova and parasites examination results are negative. She is referred for colonoscopy, partly to exclude inflammatory bowel disease (IBD).

Bilateral foot numbness and tingling associated with steatorrea

A 42 year old man presents with numbness and a tingling sensation in both lower limbs, associated with generalised weakness and fatigability for 3 months. He also experienced occasional malodorous, bulky stools and lost 8 kg of weight during the preceding year. There was no history of alcohol abuse, rectal bleeding, or joint pains.



BMI:19.5 kg/m2
Pale

Lower limbs:
- Normal tone and power
- Normal ankle and knee jerks with flexor plantar responses
- B/L reduced sensation to touch and pinprick below ankles
- Normal position and vibration sense
- No cerebellar signs
- Normal gait

Remainder of CNS normal

Vital signs: stable
No lymphadenopathy
Heart, Lungs, Abdomen:
- no abnormalities

Mechanisms of damage to peripheral nerves

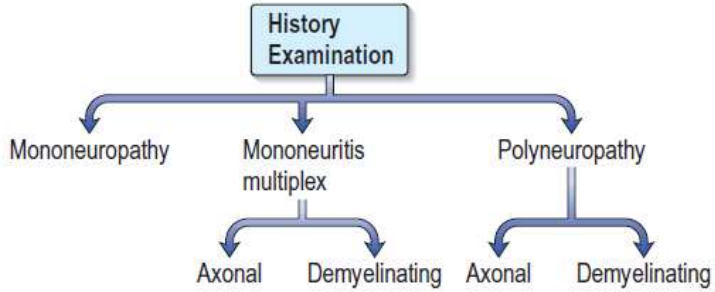
Peripheral nerves consist of two principal cellular structures – the nerve nucleus with its axon and the myelin sheath, which is produced by Schwann cells between each node of Ranvier. Blood supply is via vasa nervorum. Several mechanisms, some co-existing, cause nerve damage.

- **Demyelination**: Schwann cell damage leads to myelin sheath disruption. This causes marked slowing of conduction, seen for example in ***Guillain–Barré syndrome***
- **Axonal degeneration**: axon damage leads to the nerve fibre dying back from the periphery. A wide range of ***toxic and metabolic disorders*** damage peripheral nerves as their long axons (requiring cellular transport of proteins from cell body to nerve terminals) make them uniquely vulnerable. This explains the concept of length dependent neuropathy with the longest, most vulnerable axons (to the toes) being affected first.
- **Compression**: focal demyelination at the point of compression causes disruption of conduction. This occurs typically in ***entrapment neuropathies***, e.g. carpal tunnel syndrome).
- **Infarction**: microinfarction of vasa nervorum occurs in ***diabetes*** and ***arteritis***, e.g. polyarteritis nodosa, Churg–Strauss syndrome.
- **Infiltration**: infiltration of peripheral nerves by inflammatory cells occurs in ***leprosy*** and granulomas, e.g. ***sarcoid***, and by ***neoplastic cells***.

Types of peripheral nerve disease

- ***Neuropathy*** simply means a pathological process affecting a peripheral nerve or nerves.
- ***Mononeuropathy*** means a process affecting a single nerve.
- ***Mononeuritis multiplex,*** several individual nerves are affected.
- ***Polyneuropathy*** describes diffuse, symmetrical disease, usually commencing peripherally. The course may be acute, chronic, static, progressive, relapsing or towards recovery. Polyneuropathies are motor, sensory, sensorimotor and autonomic. They are classified broadly into demyelinating and axonal types, depending upon which principal pathological process predominates. It is often impossible to separate these clinically. Many systemic diseases cause neuropathies. Widespread loss of tendon reflexes is typical, with distal weakness and distal sensory loss.
- ***Radiculopathy*** means disease affecting nerve roots and *plexopathy*, the brachial or lumbosacral plexus.

Diagnosis is made by clinical pattern, nerve conduction/ EMG, nerve biopsy, usually sural or radial, and identification of systemic or genetic disease.



Peripheral neuropathies. The type of neuropathy (axonal or demyelinating) can be assessed by electrical nerve studies

Polyneuropathies

Polyneuropathies are disorders of peripheral or cranial nerves, whose distribution is usually symmetrical and widespread, often with distal weakness and sensory loss ('glove and stocking'). They are classified by course (*acute* or *chronic*), by function (*sensory, motor, autonomic, mixed*), or by pathology (*demyelination, axonal degeneration*, or *both*). For example, Guillain-Barré syndrome (p716) is an acute, predominantly motor, demyelinating neuropathy, whereas chronic alcohol abuse leads to a chronic, initially sensory then mixed, axonal neuropathy.

Diagnosis The history is vital: be clear about the time course, the precise nature of the symptoms, and any preceding or associated events (eg D&V before Guillain-Barré syndrome; weight↓ in cancer; arthralgia from a connective tissue disease). Ask about travel, alcohol and drug use, sexual infections, and family history. If there is palpable nerve thickening think of leprosy or Charcot-Marie-Tooth. Examine other systems for clues to the cause, eg alcoholic liver disease.

Mostly sensory
Diabetes mellitus
Renal failure
Leprosy

Mostly motor
Guillain-Barré syndrome

Sensory neuropathy: Numbness; pins & needles, "feels funny" or "burning"; affects extremities 1st ('glove & stocking' distribution—map out each modality, p450). There may be difficulty handling small objects such as buttons. Signs of trauma (eg finger burns) or joint deformation may indicate sensory loss. Diabetic and alcoholic neuropathies are typically painful.

Motor neuropathy: Often progressive (may be rapid); weak or clumsy hands; difficulty in walking (falls, stumbling); difficulty in breathing (vital capacity↓). Signs: LMN lesion: wasting and weakness most marked in the distal muscles of hands and feet (foot or wrist drop). Reflexes are reduced or absent.

Cranial nerves: Swallowing/speaking difficulty; diplopia.

Autonomic system

Tests FBC, ESR, glucose, U&E, LFT, TSH, B_{12}, electrophoresis, ANA & ANCA (p555), CXR, urinalysis, and consider an LP ± specific genetic tests for inherited neuropathies (eg for PMP22 in Charcot-Marie-Tooth),[318] lead level, antiganglioside antibodies. Nerve conduction studies help distinguish demyelinating from axonal causes.

Management Treat the cause. Involve physio & OT (p449). Foot care and shoe choice are important in sensory neuropathies to minimize trauma. Splinting joints helps prevent contractures in prolonged paralysis. In Guillain-Barré and CIDP[2] IV immunoglobulin helps.[319] For vasculitic causes, steroids/immunosuppressants may help. Treat neuropathic pain with amitriptyline or nortriptyline (10-25mg at night; may not work in HIV neuropathy).[320] If this fails, try gabapentin[3] or pregabalin.[321]

Causes

Metabolic
Diabetes mellitus
Renal failure
Hypothyroidism
Hypoglycaemia
Mitochondrial disorders

Vasculitides (p558)
Polyarteritis nodosa
Rheumatoid arthritis
Wegener's granulomatosis

Malignancy
Paraneoplastic syndromes
Polycythaemia rubra vera

Inflammatory
Guillain-Barré syndrome
Sarcoidosis; CIDP[2]

Infections Leprosy
HIV, syphilis
Lyme disease (p430)

Nutritional
↓ vit B_1, B_{12} (eg EtOH abuse)
↓ vit E, folate
↑ vit B_6 (if >100mg/d)

Inherited syndromes
Charcot-Marie-Tooth (p710)
Refsum's syndrome (p724)
Porphyria (p706)
Leucodystrophy

Toxins Lead, arsenic

Drugs
Alcohol
Isoniazid
Phenytoin
Vincristine
Cisplatin
Nitrofurantoin
Metronidazole

Others
Paraproteinaemias
Amyloidosis (p364)

Autonomic neuropathy

Sympathetic and **P**arasympathetic neuropathies may be isolated or part of a generalized sensorimotor peripheral neuropathy.

Causes: DM, amyloidosis, Guillain–Barré and Sjögren's syndrome, HIV, leprosy, SLE,[322] toxic, genetic (eg porphyria), or paraneoplastic, eg paraneoplastic encephalomyeloneuropathies and Lambert–Eaton myasthenic syndrome (LEMS, p516).

Signs: Postural hypotension[s] (faints on standing, eating, or hot bath), erectile dysfunction[p]/ejaculatory failure[s] (remember '**p**oint & **s**hoot'), sweating↓[s], constipation, nocturnal diarrhoea, urine retention[p], Horner's[s] (p716), Holmes–Adie pupil[p] (p79).[323]

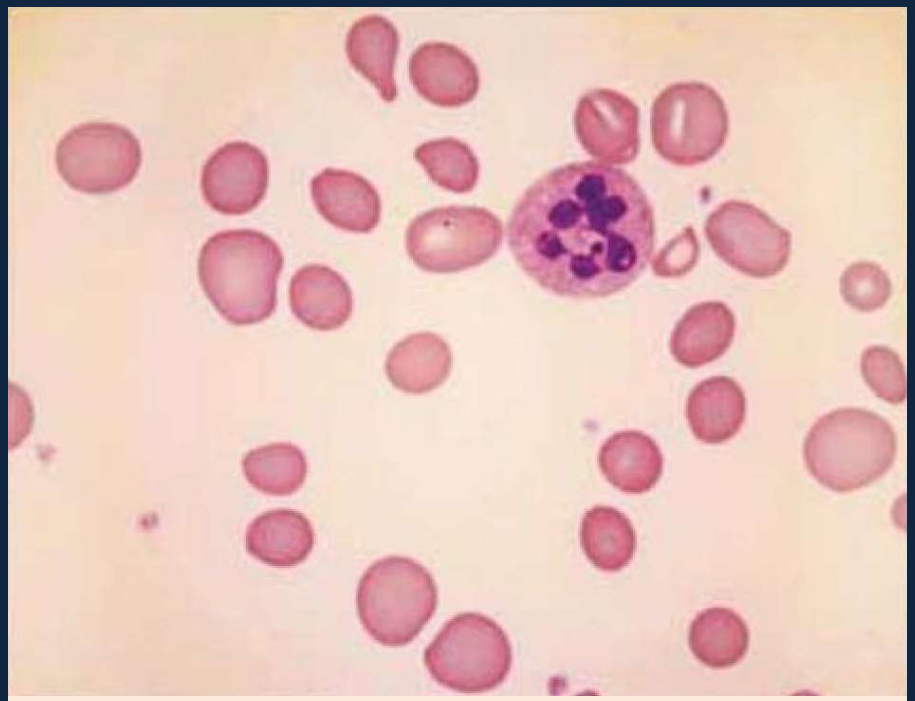
Autonomic function tests • *Postural drop* of ≥20/10mmHg is abnormal. *Rx:* p39.

- *ECG:* A variation of <10bpm with respiration is abnormal.
- *Cystometry:* Bladder pressure studies.
- *Pupils:* Instil 0.1% epinephrine (dilates if post-ganglionic sympathetic denervation, not if normal); 2.5% cocaine (dilates if normal; not if sympathetic denervation); 2.5% methacholine (constricts if parasympathetic lesion)—rarely used.
- *Paraneoplastic antibodies:* Anti-Hu, anti-Yo, anti-Ri, antiamphiphysin, anti-CV2, anti-Ma2). *Other ab:* Antiganglionic acetylcholine receptor antibody presence shows that the cause may be autoimmune autonomic ganglionopathy.[324]

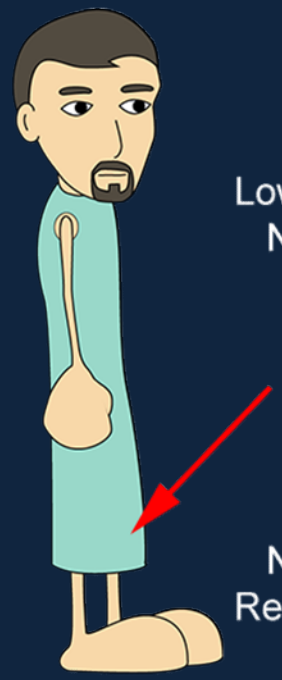
Primary autonomic failure Occurs alone (autoimmune autonomic ganglionopathy), as part of multisystem atrophy (MSA, p499), or with Parkinson's disease, typically in a middle-aged/elderly man. Onset: insidious; symptoms as above.

Bilateral foot numbness and tingling associated with steatorrea

A 42 year old man presents with numbness and a tingling sensation in both lower limbs, associated with generalised weakness and fatigability for 3 months. He also experienced occasional malodorous, bulky stools and lost 8 kg of weight during the preceding year. There was no history of alcohol abuse, rectal bleeding, or joint pains. His full blood count shows a Hb of 8.7 g/dL and MCV of 112 fL. A blood film shows a megaloblastic anemia with hypersegmented neutrophils.



Megaloblastic anaemia:
peripheral blood film showing many macrocytes and one hypersegmented neutrophil (normally there should be ≤5 segments).



BMI:19.5 kg/m2
Pale

Lower limbs:
Normal tone and power
Normal ankle and knee jerks
with flexor plantar responses
B/L reduced sensation to touch
and pinprick below ankles
Normal position and vibration sense
No cerebellar signs
Normal gait
Remainder of CNS normal

Vital signs: stable
No lymphadenopathy
Heart, Lungs, Abdomen:
no abnormalities

Macrocytic anaemia

Macrocytosis (MCV >96fL) is common, often due to alcohol excess without any accompanying anaemia. Although only ~5% are due to B_{12} deficiency, pernicious anaemia is the most common cause of a macrocytic anaemia in Western countries. B_{12} and folate deficiency are megaloblastic anaemias. A megaloblast is a cell in which nuclear maturation is delayed compared with the cytoplasm. This occurs with B_{12} and folate deficiency, as they are both required for DNA synthesis.

Causes of macrocytosis

- *Megaloblastic:* (fig 1) B_{12} deficiency, folate deficiency, cytotoxic drugs.
- *Non-megaloblastic:* Alcohol, reticulocytosis (eg in haemolysis), liver disease, hypothyroidism, pregnancy.
- *Other haematological disease:* Myelodysplasia (fig 2), myeloma, myeloproliferative disorders, aplastic anaemia.

Tests: B_{12} and folate deficiency result in similar blood film and bone marrow biopsy appearances.

Blood film: Hypersegmented polymorphs (fig 1) in B_{12} and folate deficiency (target cells if liver disease; see fig 8, p323 and fig 3, p337).

Other tests: LFT (include γGT), TFT, serum B_{12} and serum folate (or red cell folate—a more reliable indicator of folate status, as serum folate only reflects *recent* intake).

Bone marrow biopsy is indicated if the cause is not revealed by the above tests. It is likely to show one of the following 4 states:

1. Megaloblastic.
2. Normoblastic marrow (eg in liver disease, hypothyroidism).
3. Abnormal erythropoiesis (eg sideroblastic anaemia, p320, leukaemia, aplasia).
4. Increased erythropoiesis (eg haemolysis).

Folate is found in green vegetables, nuts, yeast and liver; it is synthesized by gut bacteria. Body stores can last for 4 months. Maternal folate deficiency causes fetal neural tube defects. It is absorbed by duodenum/proximal jejunum. *Causes of deficiency:*

- Poor diet, eg poverty, alcoholics, elderly.
- Increased demand, eg pregnancy or ↑cell turnover (seen in haemolysis, malignancy, inflammatory disease and renal dialysis).
- Malabsorption, eg coeliac disease, tropical sprue.
- Drugs, alcohol, anti-epileptics (phenytoin, valproate), methotrexate, trimethoprim.

Treatment: Assess for an underlying cause, eg poor diet, malabsorption. Treat with folic acid 5mg/day PO for 4 months, ►never without B_{12} unless the patient is known to have a normal B_{12} level, as in low B_{12} states it may precipitate, or worsen, subacute combined degeneration of the cord (p328). In pregnancy prophylactic doses of folate (400µg/day) are given from conception until at least 12wks; this helps prevent spina bifida, as well as anaemia. NB: if ill (eg CCF) with megaloblastic anaemia, it may be necessary to treat before serum B_{12} and folate results are known. Do tests then treat with large doses of hydroxocobalamin, eg 1mg/48h IM—see *BNF*, with folic acid 5mg/24h PO. Blood transfusions are very rarely needed, but see p318.

Folate and ischaemic heart disease Previous observational studies have indicated that higher homocysteine concentrations are associated with a greater risk of coronary heart disease. It has been suggested that folic acid supplementation may have a role in prevention of cardiac disease by lowering homocysteine levels. However, trials are disappointing (further studies awaited).[20] One meta-analysis also showed no causal relationship between high homocysteine concentrations and coronary heart disease risk in Western populations.[21]

Folate and cognition If borderline folate deficiency (as shown by ↑homocysteine), 800µg folic acid/d for 3yrs has been found to benefit cognition.[22] The FACIT trial 2007

B_{12} deficiency and pernicious anaemia

Vitamin B_{12} is found in meat, fish, and dairy products, but not in plants. Body stores are sufficient for 4yrs. It is protein-bound and released during digestion. B_{12} then binds to intrinsic factor in the stomach, and this complex is absorbed in the terminal ileum. In B_{12} deficiency, synthesis of thymidine, and hence DNA, is impaired, so RBC production is slow. *Causes of deficiency:* • Dietary (eg vegans) • Malabsorption: *stomach* (lack of intrinsic factor): pernicious anaemia, post gastrectomy; *terminal ileum:* ileal resection, Crohn's disease, bacterial overgrowth, tropical sprue, tapeworms (*diphyllobothrium*) • Congenital metabolic errors.

Features *General*: Symptoms of anaemia (p318), 'lemon tinge' to skin due to combination of pallor (anaemia) and mild jaundice (due to haemolysis), glossitis (beefy-red sore tongue; fig 1), angular cheilosis (also known as stomatitis, p320).

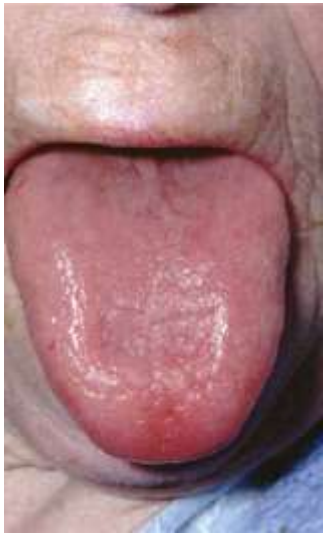
* *Neuropsychiatric:* Irritability, depression, psychosis, dementia.

Neurological: Paraesthesiae, * peripheral neuropathy. Also:

* *Subacute combined degeneration of the spinal cord:* Onset is insidious (*subacute*) with peripheral neuropathy due to ↓B_{12}. There is a *combination* of symmetrical posterior (dorsal) column loss, causing sensory and LMN signs, and symmetrical corticospinal tract loss, causing motor and UMN signs (p450). Joint-position and vibration sense are often affected first leading to ataxia, followed by stiffness and weakness if untreated. The classical triad is: • Extensor plantars (UMN) • Absent knee jerks (LMN) • Absent ankle jerks (LMN). It may present with falls at night-time, due to a combination of ataxia and reduced vision, which is also seen with ↓B_{12}. Pain and temperature sensation may remain intact even in severe cases, as the spinothalamic tracts are preserved. ►Neurological signs of B_{12} deficiency can occur without anaemia.

The **neurological changes**, if left untreated for a long time, can be irreversible. and occasionally occur in patients who are not clinically anaemic. The classical neurological features are those of a **polyneuropathy** progressively involving the peripheral nerves and the posterior and eventually the lateral columns of the spinal cord (subacute combined degeneration). Patients present with symmetrical paraesthesiae in the fingers and toes, early loss of vibration sense and proprioception, and progressive weakness and ataxia. Paraplegia may result.

Dementia and psychiatric problems, hallucinations, delusions, and optic atrophy may occur from vitamin B12 deficiency.



Atrophic glossitis due to B12 deficiency ;

Pernicious anaemia (PA) This is caused by an autoimmune atrophic gastritis, leading to achlorhydria and lack of gastric intrinsic factor secretion.

Incidence 1:1000; ♀:♂≈1.6:1; usually >40yrs; higher incidence if blood group A.

Associations Other autoimmune diseases (p555): thyroid disease (~25%), vitiligo, Addison's disease, hypoparathyroidism. Carcinoma of stomach is ~3-fold more common in pernicious anaemia, so have a low threshold for upper GI endoscopy.

Tests • Hb↓ (30–110g/L) • MCV↑ • WCC and platelets ↓ if severe • Serum B_{12}↓[1] • Reticulocytes ↓ or normal as production impaired • Hypersegmented polymorphs (p326) • Megaloblasts in the marrow • Specific tests for PA: 1 Parietal cell antibodies: found in 90% with PA, but also in 3–10% without. 2 Intrinsic factor (IF) antibodies: specific for pernicious anaemia, but lower sensitivity. These target B_{12} binding sites (in 50%) or ileal binding sites (in 35%).

Treatment Treat the cause if possible. If a low B_{12} is due to malabsorption, injections are required. Replenish stores with hydroxocobalamin (B_{12}) 1mg IM alternate days, eg for 2wks (or, if CNS signs, until improvement stops). Maintenance: 1mg IM every 3 months for life (child's dose: as for adult). If the cause is dietary, then oral B_{12} can be given after the initial acute course (see BOX). Initial improvement is heralded by a transient marked reticulocytosis and hence ↑MCV, after 4–5 days.

Practical hints • Beware of diagnosing PA in those under 40yrs old: look for GI malabsorption (small bowel biopsy, p280).
- Watch for hypokalaemia as treatment becomes established.
- Transfusion is best avoided, but PA with high output CCF may require exchange transfusion (p318), after doing tests for FBC, folate, B_{12}, and marrow sampling.
- As haemopoiesis accelerates on treatment, additional iron may be needed.
- Hb rises ~10g/L per week; WCC and platelet count should normalize in 1wk.

Prognosis Supplementation usually improves peripheral neuropathy within the first 3–6 months, but has little effect on cord signs. Patients do best if treated as soon as possible after the onset of symptoms: don't delay!

When a low B_{12} is not due to pernicious anaemia

B_{12} deficiency is common, eg up to 15% of older people. If untreated, it can lead to megaloblastic anaemia and irreversible CNS complications. In the UK, the usual regimen is regular (eg 3-monthly) IM hydroxocobalamin (1mg). Elsewhere, ***high-dose oral B_{12} regimen*** (cyanocobalamin 1mg/day) is standard, less costly, and obviates the need for repeat visits to nurses. This use is not yet licensed in the UK[24] Passive absorption of B_{12} occurs throughout the gut—but only 1–2% of an oral dose is absorbed this (non-terminal ileum) way. The dietary reference range is ~2µg/d.

That a low B_{12} is not due to PA can usually be determined by serology testing for parietal cell and intrinsic factor antibodies (but -ve in 50% of those with PA), and plasma response to oral B_{12}, and IM B_{12} if no response to oral doses. The oral dose may be given as cyanocobalamin 50–150µg/daily, between meals (in the NHS, mark the prescription 'SLS', p223, to justify/communicate this special indication). This *low-dose regimen* is often sufficient for B_{12} deficiency of dietary origin.[25] NB: foods of non-animal origin contain no B_{12} unless fortified or contain bacteria. This information is important for vegans and their breastfed offspring.

Non-dietary, non-autoimmune causes of a low B_{12}: Crohn's and coeliac disease; after gastric surgery; acid-suppressors (eg ranitidine); metformin; pancreatic insufficiency; false-low reading (seen in ≥20% so do 2 readings in isolated low B_{12}). NB: normal serum B_{12} is documented in overt deficiency, which is confusing. Measuring holotranscobalamin and homocysteine or methylmalonic acid (↑ if B_{12} low) may be better, but have their own problems, and are non-standard tests.

NB: Schilling tests are not done as the radioisotope they use is not available.

Bilateral foot numbness and tingling associated with steatorrea

A 42 year old man presents with numbness and a tingling sensation in both lower limbs, associated with generalised weakness and fatigability for 3 months. He also experienced occasional malodorous, bulky stools and lost 8 kg of weight during the preceding year. There was no history of alcohol abuse, rectal bleeding, or joint pains. His full blood count shows a Hb of 8.7 g/dL and MCV of 112 fL. A blood film shows a megaloblastic anemia with hypersegmented neutrophils.

Select Relevant Investigations

♦ **Serum B12 + Folate**

Serum Vitamin B12: 150 pg/ml (200-900)

Serum Folate: 5 ng/ml (5-16)

♦ **Stool full report**

No amoeba, ova or cysts identified

No pus cells or erythrocytes

Bacterial and protozoal cultures: negative

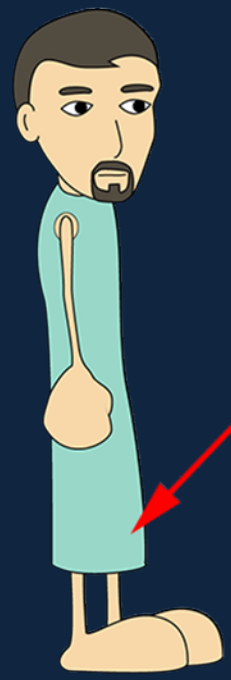
Fecal fat analysis: 7g/24h (2-6)

♦ **Lower GI endoscopy & biopsy**

There is mucosal inflammation with friability and granularity from the ileum to ascending colon. There are multiple, deep serpiginous ulcerations located transversely and longitudinally. The biopsies are suggestive of Crohn's disease.

♦ **Serum Albumin**

30 g/L (35-55)



BMI:19.5 kg/m2
Pale

Lower limbs:
- Normal tone and power
- Normal ankle and knee jerks with flexor plantar responses
- B/L reduced sensation to touch and pinprick below ankles
- Normal position and vibration sense
- No cerebellar signs

Normal gait
Remainder of CNS normal

Vital signs: stable
No lymphadenopathy
Heart, Lungs, Abdomen: no abnormalities

Select Relevant Management

- Budesonide
- NSAIDS
- Vitamin B12
- Surgical Resection

Diagnosis and reasoning

This middle aged gentleman has presented with a complex constellation of symptoms and signs.

In such patients, the first step of the diagnostic approach should be to attempt to classify these findings into discrete (and logical) groups; this gives us the following:

- There is evidence of a sensory neuropathy affecting the distal lower limbs in a bilateral and symmetric manner.
- The history of malodorous and bulky stools is suspicious of steatorrhea.
- There is a background of constitutional symptoms such as weakness, fatigability and significant weight loss.

Note that the above symptoms involve multiple organ systems - the peripheral system and the gastrointestinal tract (GI).

If we consider the differential diagnosis of symmetric (distal) sensory neuropathy, the list of conditions is wide indeed.

However, in practice, the most common are diabetes mellitus, hypothyroidism, alcoholism, deficiency of vitamins such as cobalamin, thiamine or folate, and connective tissue disorders.

The list of diseases causing steatorrhea is similarly wide; however, the most common causes are diseases of the pancreas such as chronic pancreatitis, pancreatic tumors or exocrine pancreatic insufficiency; and diseases of the small bowel such as inflammatory bowel disease or celiac disease.

When these disparate lists are considered together, several potential diagnoses become apparent:

- This could be a malabsorptive condition. Thus, malabsorption of fat would result in steatorrhea, while malabsorption of water soluble vitamins would result in a deficiency of thiamine, folate or cobalamin.

- Diabetes in association with chronic pancreatitis; here, the pancreatic insufficiency would explain the impaired fat digestion, while diabetic neuropathy would account for the CNS findings.

- Alcoholism complicated by chronic pancreatitis; note that alcohol reduces gastrointestinal absorption of cobalamin.

However, observe the presence of a megaloblastic anemia with hypersegmented neutrophils in the blood film; this is strongly suggestive of either cobalamin or folate deficiency, making the second diagnosis above unlikely.

In addition, there is no history of alcohol abuse or a previous history suggestive of episodes of pancreatitis; this makes the third diagnosis unlikely.

Thus, a malabsorptive disorder is the most likely underlying etiology.

Assaying the serum cobalamin and folate levels demonstrates the presence of vitamin B12 deficiency; the fecal fat analysis gives objective evidence of steatorrhea. Thus the clinical diagnosis gains further credence.

Cobalamin is absorbed from the terminal ileum; unfortunately, many diseases can affect this region of the bowel, including celiac disease, Crohn's disease, intestinal tuberculosis, Whipples disease and tropical sprue.

However, the terminal ileum is amenable to endoscopic inspection - thus an ileoscopy and biopsy is a good path towards rapid resolution of the diagnosis.

Endoscopy reveals inflammation and multiple ulcerations involving the ileum and proximal ascending colon, indicating the presence of inflammatory bowel disease (IBD). The biopsy findings are suggestive of Crohn's disease, clinching the diagnosis.

Controlled-release oral glucocorticoids (such as Budesonide) are recommended as the primary therapy in patients with mild to moderate active Crohn's disease which is localized to the ileum and/or the right colon.

Note that NSAIDs are probably best avoided in these individuals, as they may provoke disease activity (via mechanisms which are unclear).

Vitamin B12 should be administered in view of the deficiency. Surgical resection is not indicated right now.

Discussion

Crohn's disease (CD) is an inflammatory bowel disease of unclear etiology, characterized by transmural inflammation and 'skip' lesions (i.e. isolated lesions) which may involve the entire gastrointestinal tract from the mouth to the perianal region.

Ulcerative Colitis (UC) is the other major form of inflammatory bowel disease; in this, there is superficial and diffuse inflammation of the colonic mucosa and submucosa, which almost invariably affects the rectum and extends proximally and contiguously along the colon.

CD is a chronic relapsing disease which is almost always incurable, with most patients requiring lifelong therapy.

The incidence and prevalence in the United States are estimated to be 20.2 cases per 100,000 person-years and 201 per 100,000 person-years respectively.

While the disease may occur at any age, the incidence is bimodal, with one peak in the second and third decades of life, and a smaller peak in the fifth decade.

Simultaneous involvement of both the ileum and colon is the most common clinical pattern, being found in 35% of patients; isolated colonic involvement (32%), isolated small bowel involvement (28%) and gastroduodenal disease (5%) are the next most common.

Although the pathogenesis of CD is poorly understood, a number of risk factors such as genetic susceptibility, immunoregulatory defects, smoking, diet (processed, fried, and sugary foods), and Nonsteroidal Anti Inflammatory Drugs (NSAIDs) have been identified.

Due to the insidious nature of the disease, patients can have symptoms for many years prior to diagnosis; fatigue, prolonged diarrhea with abdominal pain, fever, weight loss, and gastrointestinal bleeding are the most common.

Approximately one third of patients have perianal disease (which is quite uncommon in UC); these include abscesses, anal fissures, anorectal fistulas, and perianal skin tags.

Extraintestinal manifestations include anemia, inflammatory arthropathies, aphthous ulcers of the mouth, cholelithiasis, ocular involvement (such as uveitis or scleritis), erythema nodosum, osteoporosis, nephrolithiasis, and venous thromboembolism.

Crohn's disease is often tricky to diagnose clinically, because of the heterogeneous presentation, often insidious onset, and overlap of symptoms with other forms of inflammatory bowel disease.

The diagnosis is usually established via the presence of supportive endoscopic or imaging findings, in a patient with a compatible clinical picture.

Characteristic endoscopic findings include skip lesions, cobblestoning (serpiginous and linear ulcers), strictures, and aphthous ulcers of the distal ileum or colon; these are distinct from those of UC.

Wireless capsule endoscopy can be used for evaluation of CD affecting the small bowel; however, this should be avoided in suspected cases of intestinal stricture.

Imaging is most useful in the evaluation of upper GI disease; endoscopic ultrasonography (EUS) and MRI are valuable for the diagnosis of perirectal complications.

Laboratory tests help in assessing disease activity, identifying complications, and monitoring the response to therapy.

Key therapeutic goals include control of symptoms, induction of clinical remission, maintenance of remission with minimal adverse effects, and improvement of quality of life.

Two main strategies are currently employed in the management of CD; the conventional "step up" approach begins with corticosteroids or 5-aminosalicylate (5-ASA), and advances to immunomodulators or anti–tumor necrosis factor (TNF) agents based on severity of disease,

The early, aggressive, "top-down" approach begins with tumour necrosis factor (TNF) alfa inhibitors in combination with immunomodulators.

Note that the which of the above strategies is optimal is still a matter of controversy.

In the step-up approach, glucocorticoids, 5-aminosalicylate (5-ASA) and antibiotics are currently recommended for achieving remission in mild to moderate disease; immunomodulators (such as azathioprine, mercaptopurine or methotrexate) can be used as add on drugs to induce remission and maintenance.

Note that (long term therapy with) corticosteroids should not be used for maintenance of remission.

TNF-alfa inhibitors (Infliximab and adalimumab) decrease mucosal production of inflammatory cytokines, and are used in patients with severe active CD, who have not responded to complete and adequate therapy with a corticosteroid or an immunosuppressive agent.

Patients on TNF-alfa inhibitors should have their disease reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate.

Abscesses should be drained as appropriate; chronic fistulae and perianal fissures are usually treated with antibiotics and immunosuppressives or anti-TNF agents.

Note that most patients with CD will eventually require surgery for refractory disease, intractable hemorrhage, perforation, obstruction, abscesses, intestinal dysplasia, bowel cancer or unresponsive fulminant disease.

It is essential to properly educate the patients and their families about the disease, side effects, complications, and importance of nutrition.

As mentioned earlier, CD can affect almost any site in the gastrointestinal tract. However, once established, the location of disease does not tend to change over time, although it's behavior may.

Thus, surgery may be curative in a limited population of patients, in whom CD is limited to the colon - if the entire colon is removed.

The complications of CD are linked to it's transmural inflammatory nature; these include deep ulceration leading to fistulization (by way of the sinus tracts penetrating the serosa), micro perforations, abscess formation, adhesions, malabsorption, and acute or subacute intestinal obstruction.

Poor prognostic indicators include a young age at diagnosis, perianal disease, upper GI tract involvement, multiple extraintestinal manifestations, active tobacco use, and perforating (ie. fistulizing disease); these patients are believed to benefit from "top down" therapy.

At least half of patients will require surgical treatment in the first ten years of the disease; approximately 80% will require surgery within their lifetime.

Around 10% to 20% of patients experience prolonged remission after the initial presentation; less than 5% of patients will have a continuous course of active disease.

The lifetime risk of fistula development has been reported to range from 20% to 40%.

Estimates from different population-based studies show these individuals to have a mortality ranging from no increased risk to a five-fold increase compared to the general population; this is higher in the first 2 years following diagnosis, and in patients with upper GI disease.

The risk of developing colorectal cancer is similar to that for individuals with UC who have the same extent of colonic involvement.

Take home messages

1. CD is a chronic, relapsing IBD which is usually incurable.
2. Clinical diagnosis is often tricky, due to the insidious nature of symptoms and overlap with other forms of IBD.
3. While CD can affect almost any site in the GI tract, once established, the location of disease usually does not tend to change over time, although the behavior may.
4. The "step up" approach and "top down" approach are the two main management strategies; which is more effective is still a matter of controversy.

Low grade fever with bloody diarrhea

A 23 year old woman presents with blood and mucus diarrhea, low grade fever, lethargy, and malaise for 1 week. She experienced around 3 to 4 bowel movements daily. She had several such episodes over the last 4 months, which were unsuccessfully treated with multiple courses of antibiotics. She had gone backpacking around South Asia 6 months earlier. An x-ray of her abdomen is found to be normal.

Select Relevant Investigations

♦ **Full Blood Count**

WBC/DC: 8,700/mm3 N: 75% L: 23% Hb: 10.5 g/dl
MCV: 88 fl MCH: 31.2 pg MCHC: 30 g/dl
Platelets: 517,000/mm3

♦ **Tuberculin Test**

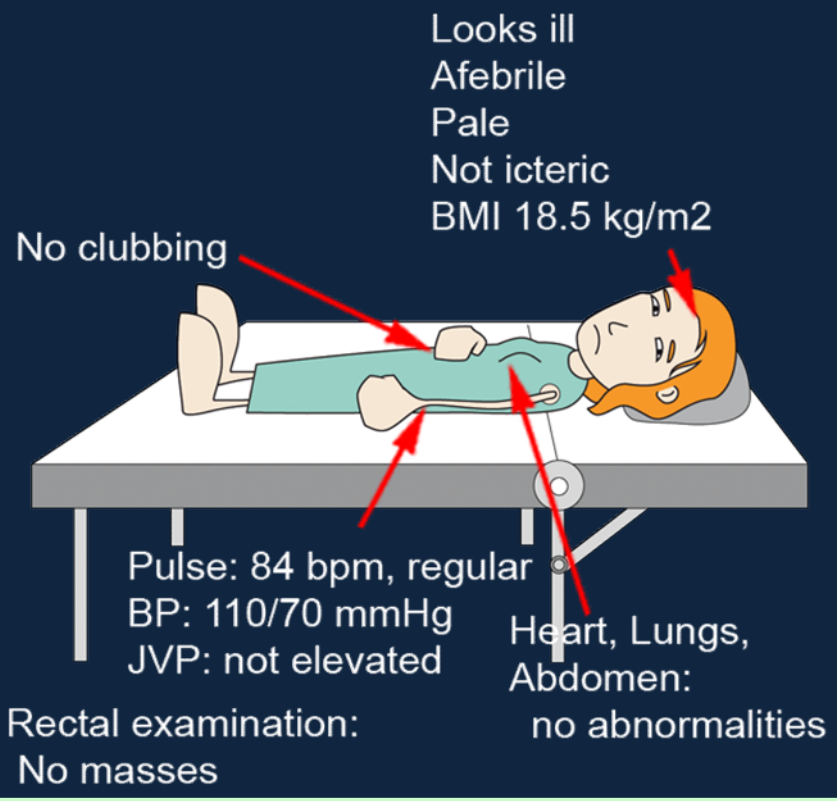
The tuberculin test is negative.

♦ **Lower GI Endoscopy**

The mucosa of the rectum and sigmoid colon appear uniformly inflamed, with multiple erosions. There is no contact bleeding. Biopsies show inflammation of the mucosa and submucosa only, with distortion of the crypts, crypt abscesses and lymphoid aggregates.

♦ **Stool Microscopy + Culture**

Appearance: semi solid Pus cells: field full / hpf
RBC: field full / hpf No amoeba, ova or cysts identified
The stool cultures are negative



Assessing severity in UC (Truelove & Witts criteria modified to include CRP)[190]

Variable	Mild UC	Moderate UC	Severe UC
Motions/day	<4	4-6	>6
Rectal bleeding	Small	Moderate	Large
T°C at 6AM	Apyrexial	37.1-37.8°C	>37.8°C
Resting pulse	<70 beats/min	70-90 beats/min	>90 beats/min
Haemoglobin	>110g/L	105-110g/L	<105g/L
ESR (do CRP too)	<30 (<16 might be better)[191]		>30 (or CRP >45mg/L)

The differential diagnosis for colitis includes ischemic colitis, infectious colitis (*C difficile*, *E coli*, *Salmonella*, *Shigella*, *Campylobacter*), radiation colitis, and IBD (Crohn disease vs ulcerative colitis). Mesenteric ischemia usually is encountered in people older than 50 years with known atherosclerotic vascular disease or other cause of hypoperfusion. The pain usually is acute in onset following a meal ("intestinal angina") and not associated with fevers. Infectious colitis is usually characterized by an acute onset of symptoms, often in patients with a recent history of foreign travel, or recent use of antibiotics.

Inflammatory bowel disease (IBD) is most commonly diagnosed in young patients between the ages of 15 and 25 years. There is a second peak in the incidence of IBD (usually Crohn disease) between the ages of 60 and 70 years. IBD may present with a low-grade fever. The chronic nature of this patient's disease (several months) is typical of IBD. Anemia may be present, either due to iron deficiency from chronic GI blood loss, or anemia of chronic disease. Patients with IBD may also report fatigue and weight loss.

Low grade fever with bloody diarrhea

A 23 year old woman presents with blood and mucus diarrhea, low grade fever, lethargy, and malaise for 1 week. She experienced around 3 to 4 bowel movements daily. She had several such episodes over the last 4 months, which were unsuccessfully treated with multiple courses of antibiotics. She had gone backpacking around South Asia 6 months earlier. An x-ray of her abdomen is found to be normal.

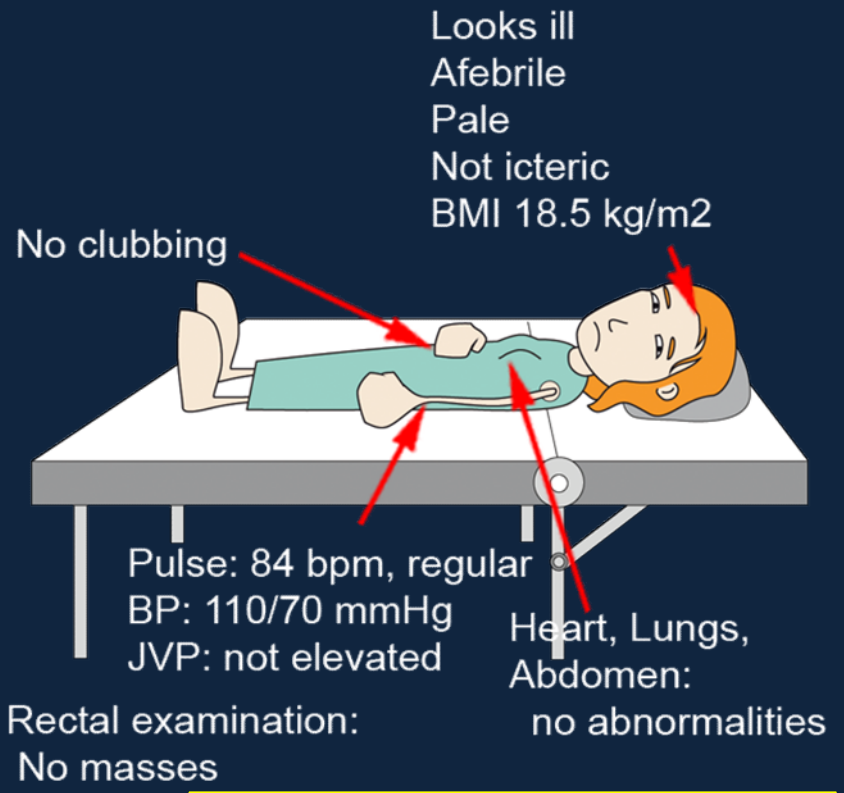
Select Relevant Investigations

♦ **Full Blood Count**
WBC/DC: 8,700/mm3 N: 75% L: 23% Hb: 10.5 g/dl
MCV: 88 fl MCH: 31.2 pg MCHC: 30 g/dl
Platelets: 517,000/mm3

♦ **Tuberculin Test**
The tuberculin test is negative.

♦ **Lower GI Endoscopy**
The mucosa of the rectum and sigmoid colon appear uniformly inflamed, with multiple erosions. There is no contact bleeding. Biopsies show inflammation of the mucosa and submucosa only, with distortion of the crypts, crypt abscesses and lymphoid aggregates.

♦ **Stool Microscopy + Culture**
Appearance: semi solid Pus cells: field full / hpf
RBC: field full / hpf No amoeba, ova or cysts identified
The stool cultures are negative



Select Relevant Management

- **Mesalazine stat (rectal+oral)**
- Azathioprine stat
- Antituberculous therapy
- Vancomycin stat

Diagnosis and reasoning

Chronic diarrhea is a relatively common complaint, and may be due to a myriad of causes.
However, the presence of blood and mucus in this patient narrows the likely etiologies into a few key groups : infectious diarrhea, inflammatory diarrhea and antibiotic associated diarrhea.
Her history of recent travel to South Asia makes infectious diarrhea a possibility - especially intestinal tuberculosis and amoebiasis.
Inflammatory diarrhea secondary to inflammatory bowel disease (IBD) is also compatible with her age and presentation.
Antibiotic associated diarrhea (such as pseudomembranous colitis) is unlikely given that antibiotics were commenced only after she became symptomatic.
Her full blood count reveals normochromic normocytic anemia and thrombocytosis - in this context, this is suggestive of a chronic inflammatory process.
The negative tuberculin test argues against tuberculosis (although it does not exclude it definitively).
The stool culture and microscopy provides several important clues. The negative cultures and absence of ova and parasites argue against bacterial infections and amoebiasis. However, the presence of fecal leukocytes confirms the presence of bowel inflammation - making inflammatory diarrhea the most likely etiology.
Thus, a colonoscopy is probably the next best step in the diagnostic workup - and in this patient reveals proctosigmoiditis. In addition, the biopsies obtained show that this is superficial inflammation, with features suggestive of ulcerative colitis (UC).
Considering her clinical and biochemical parameters, this can be classified as a moderate episode of UC.
UC primarily involving the left colon is best treated with a combination of a mesalazine suppository and oral mesalazine. While Azathioprine is an option down the line, it is not indicated immediately.
Vancomycin would have been indicated if she had pseudomembranous colitis. Anti-tuberculous therapy is not indicated.

Assessing severity in UC (Truelove & Witts criteria modified to include CRP)[190]

Variable	Mild UC	Moderate UC	Severe UC
Motions/day	<4	4–6	>6
Rectal bleeding	Small	Moderate	Large
T°C at 6AM	Apyrexial	37.1–37.8°C	>37.8°C
Resting pulse	<70 beats/min	70–90 beats/min	>90 beats/min
Haemoglobin	>110g/L	105–110g/L	<105g/L
ESR (do CRP too)	<30 (<16 might be better)[191]		>30 (or CRP >45mg/L)

Discussion

UC is one of the major manifestations of inflammatory bowel disease (the other is Crohn's disease). UC typically displays a chronic, protracted, relapsing and remitting course.

The onset is bimodal, with one peak at 15 to 25 years and another smaller one at 55 to 65 years. The incidence is 1.2 to 20.3 cases per 100,000 persons per year.

The precise etiology of UC is poorly understood, although genetics, immune reactions and environmental factors have been implicated in the pathogenesis.

UC is characterized by diffuse inflammation of the colonic mucosa. The inflammation almost invariably affects the rectum and extends proximally along variable lengths of the colon. Note that there are no intervening areas of normal mucosa (which is important in distinguishing UC from Crohn's disease).

The Montreal classification identifies three main patterns of distribution: proctitis, left sided colitis, and pancolitis. The inflammation is limited to the mucosa and submucosa and spares the deeper layers of the bowel wall.

The cardinal symptoms of UC are intermittent bloody diarrhea, rectal urgency, and tenesmus. The onset is typically gradual, often followed by periods of spontaneous remission and subsequent relapses.

Fever, malaise, and weight loss may also occur - but are less common than in Crohn's disease.

Episodes of UC are classified as mild, moderate or severe based on the Truelove and Witts criteria, which utilizes both biochemical and clinical features. The Mayo score is an alternative classification of severity.

Extra-intestinal manifestations are also frequent. These include uveitis, pyoderma gangrenosum, pleuritis, erythema nodosum, ankylosing spondylitis and other spondyloarthropathies.

UC may result in several important complications. One such important acute complication is severe life threatening inflammation of the colon, which may result in severe bleeding and toxic megacolon.

Patients with UC are also at an increased risk of colon cancer - as high as 20% to 30% after 30 years following diagnosis.

Colonoscopy and biopsy is the test of choice to diagnose UC. If endoscopy is not readily available or when colonic strictures prevent a thorough evaluation, a double-contrast barium enema and small-bowel barium follow-through may be performed to demonstrate fine mucosal detail.

While laboratory measurements are not diagnostic, they are often are helpful in assessing and monitoring disease activity and in differentiating UC from other forms of colitis.

Routine radiographic testing is not recommended.

UC can be treated medically or surgically. Medical therapy is aimed at acute treatment of the inflammatory symptoms, followed by maintenance of remission.

Mesalazine (5-aminosalicylic acid) is the first line agent used in UC. It suppresses the production of proinflammatory mediators in the colonic lumen, thereby reducing the inflammation.

Second line treatments include oral and IV corticosteroids, while immunosuppressive therapy (such as azathioprine or IV cyclosporine) may be required in patients unresponsive to other measures.

Approximately two-thirds of patients achieve clinical remission with medical therapy, and the vast majority maintain remission.

After remission has been achieved, the goal is to maintain the symptom-free status, which can be accomplished with various medications, with the exception of glucocorticoids (which have no place in maintenance therapy, given the marked side effects associated with their long-term use).

Surgical treatment is most commonly indicated in patients who do not respond to medical management.

Other indications for surgery include intractable fulminant colitis, toxic megacolon, perforation, uncontrollable bleeding, intolerable side effects of medications, high-grade or multifocal dysplasia, dysplasia-associated lesions or masses, and cancer.

Approximately 66% of patients with extensive disease eventually require surgery.

Traditional proctocolectomy with ileostomy is curative and technically straightforward. However, possible complications include small-bowel obstruction, fistulas, persistent pain, sexual and bladder dysfunction, and infertility.

Total proctocolectomy with ileal pouch-anal anastomosis (IPAA) is currently the procedure of choice for most patients who require elective surgery, since it has the distinct advantage of preserving anal-sphincter function. Pouchitis is the most common and clinically important long-term complication of IPAA.

As patients with long standing colitis have a higher risk of colorectal cancer screening for colorectal cancer must be offered to all patients with longstanding, extensive UC.

Take home messages

1. The main causes of chronic blood and mucus diarrhea are infectious diarrhea, inflammatory diarrhea and antibiotic associated diarrhea.

2. The life threatening complications of UC are significant bleeding, toxic megacolon and colonic perforation.

3. The severity of each episode of colitis may be gauged by clinical and biochemical parameters, allowing preemptive action.

4. Colonoscopy and biopsy is the diagnostic test of choice.

5. These patients are at a high risk of colonic cancer later in life. Regular screening is essential.

Abdominal pain with bloody diarrhea

A 28-year-old man comes to the emergency room complaining of 2 days of abdominal pain and **diarrhea**. He describes his stools as **frequent**, with **10 to 12 per day**, small volume, sometimes with **visible blood** and **mucus**, and preceded by a sudden urge to defecate. The **abdominal pain** is **crampy**, diffuse, and moderately severe, and it is not relieved with defecation. In the **past 6 to 8 months**, he has experienced **similar episodes** of abdominal pain and loose mucoid stools with some bleeding, but the episodes were milder and resolved within 24 to 48 hours. He has no other medical history and takes no medications. He has neither traveled out of the United States nor had contact with anyone with similar symptoms. He works as an accountant and does not smoke or drink alcohol. No member of his family has gastrointestinal problems.

On examination, his temperature is **37.2°C**, heart rate **98 bpm**, and blood pressure 118/74 mm Hg. He appears uncomfortable and is lying still on the stretcher. His sclerae are anicteric, and his oral mucosa is pink and clear without ulceration. His chest is clear, and his heart rhythm is regular, without murmurs. His abdomen is soft and mildly distended, with hypoactive bowel sounds and minimal diffuse tenderness but no guarding or rebound tenderness.

Laboratory studies are significant for a **white blood cell count of 15800/mm^3** with 82% polymorphonuclear leukocytes, **hemoglobin 10.3 g/dL**, and platelet count 754 000/mm^3. The HIV (human immunodeficiency virus) assay is negative. Renal function and liver function tests are normal. A **plain film radiograph** of the abdomen shows a mildly dilated air-filled colon with a 4.5-cm diameter and no pneumoperitoneum or air/fluid levels.

What is the most likely diagnosis?
What is your next step?

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What is the most likely diagnosis? Colitis, probably ulcerative colitis.

What is your next step? Admit to the hospital, obtain stool samples to exclude infection, and begin therapy with corticosteroids.

Assessing severity in UC (Truelove & Witts criteria modified to include CRP)[190]

Variable	Mild UC	Moderate UC	Severe UC
Motions/day	<4	4-6	>6
Rectal bleeding	Small	Moderate	Large
T°C at 6AM	Apyrexial	37.1-37.8°C	>37.8°C
Resting pulse	<70 beats/min	70-90 beats/min	>90 beats/min
Haemoglobin	>110g/L	105-110g/L	<105g/L
ESR (do CRP too)	<30 (<16 might be better)[191]		>30 (or CRP >45mg/L)

Depending on the rate of blood loss, GI bleeding can manifest in several forms and can be classified as overt, occult or obscure. Overt GI bleeding, otherwise known as acute GI bleeding, is visible and can present in the form of hematemesis, "coffee-ground" emesis, melena, or hematochezia. Occult or chronic GI bleeding as a result of microscopic hemorrhage can present as Hemoccult-positive stools with or without iron deficiency anemia[9,10]. The American Gastroenterological Association defines occult GI bleeding as the initial presentation of a positive fecal occult blood test (FOBT) result and/or iron-deficiency anemia when there is no evidence of visible blood loss to the patient or clinician[11]. Obscure GI bleeding refers to recurrent bleeding in which a source is not identified after upper endoscopy and colonoscopy. Obscure bleeding may be either overt or occult[10-12].

gastrointestinal bleeding

Overt (acute) vs occult (chronic) vs obscure

gastrointestinal bleeding

Upper vs lower

Upper GI bleeding includes hemorrhage originating from the esophagus to the ligament of Treitz, at the duodenojejunal flexure[13]. Lower GI bleeding is defined as bleeding that originates from a site distal to the ligament of Treitz[14]. In recent years upper GI bleeding has been redefined as bleeding above the ampulla of Vater within reach of an upper endoscopy; lower GI bleeding has been further subdivided into mid GI bleeding coming from the small bowel between the ampulla of Vater to the terminal ileum, and lower GI bleeding coming from the colon[11].

Upper gastrointestinal bleeding

Common causes

- Peptic ulcers
- Mallory-Weiss tear
- Oesophageal varices
- Gastritis/gastric erosions
- Drugs (NSAIDs, aspirin, steroids, thrombolytics, anticoagulants)
- Oesophagitis
- Duodenitis
- Malignancy
- No obvious cause

Rare causes

- Bleeding disorders
- Portal hypertensive gastropathy
- Aorto-enteric fistula[2]
- Angiodysplasia
- Haemobilia
- Dieulafoy lesion[3]
- Meckel's diverticulum
- Peutz-Jeghers' syndrome
- Osler-Weber-Rendu synd.

Rectal bleeding

Typical causes

- Diverticulitis, p630
- Colorectal cancer, p618
- Haemorrhoids, p634
- Crohn's, UC, p272-275
- Perianal disease, p632
- Angiodysplasia, p630
- Rarities—trauma, also:
  - ischaemic colitis, p622
  - radiation proctitis
  - aorto-enteric fistula

Colorectal carcinoma

This is the 3rd most common cancer and 2nd most common cause of UK cancer deaths (16,000 deaths/yr). Usually adenocarcinoma. 86% of presentations are in those >60yrs old.[114] Lifetime UK incidence: ♂ = 1:15; ♀ = 1:19.

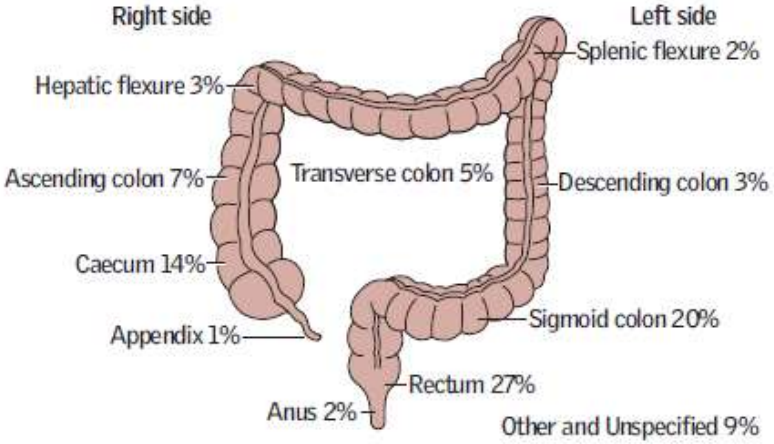
Predisposing factors Neoplastic polyps (see below, & p525); IBD (UC and Crohn's); genetic predisposition (<8%), eg FAP and HNPCC (see p524); diet (low-fibre; ↑red and processed meat); ↑alcohol[115]; smoking[116]; previous cancer. *Prevention:* Aspirin ≥75mg/d reduces incidence and mortality—it is thought to inhibit polyp growth. Benefit ↑ with duration of use and is greatest for proximal lesions. Widespread chemoprevention is not currently recommended due to gastrointestinal SEs.[117]

Presentation depends on site: *Left-sided:* Bleeding/mucus PR; altered bowel habit or obstruction (25%); tenesmus; mass PR (60%). *Right:* Weight↓; Hb↓; abdominal pain; obstruction less likely. *Either:* Abdominal mass; perforation; haemorrhage; fistula. See p532 for a guide to urgent referral criteria. See fig 1 for distribution.

Tests FBC (microcytic anaemia); faecal occult blood (FOB, see BOX); sigmoidoscopy; barium enema or colonoscopy (figs 2 & 3, p257), which can be done 'virtually' by CT (fig 1, p757); LFT, CT/MRI; liver USS. CEA (p535) may be used to monitor disease and effectiveness of treatment. If family history of FAP, refer for DNA test once >15yrs old.

Spread Local, lymphatic, by blood (liver, lung, bone) or transcoelomic. The TNM system (Tumour, Node, Metastases; p527) is most commonly used to stage disease and is largely replacing Dukes' classification (BOX).

Polyps are lumps that appear above the mucosa. 1 *Inflammatory:* Ulcerative colitis, Crohn's, lymphoid hyperplasia. 2 *Hamartomatous:* Juvenile polyps, Peutz-Jeghers (p722). 3 *Neoplastic:* Tubular or villous adenomas: malignant potential, esp. if >2cm. Polyps should be biopsied and removed if they show malignant change. Most can be reached by flexible colonoscope; diathermy can avoid morbidity of colectomy.



Distribution of colorectal carcinomas.

screening for colorectal cancer
Faecal Occult Blood
colonoscopy

Dukes' classification for the staging of colorectal cancer

Stage	Description	Treated 5yr survival rate
A	Limited to muscularis mucosae	93%
B	Extension through muscularis mucosae	77%
C	Involvement of regional lymph nodes	48%
D	Distant metastases	6.6%

Surgery
aims to cure and may ↑survival times by up to 50%

Radiotherapy
is mostly used in palliation for colonic cancer.

Chemotherapy
Adjuvant chemotherapy reduces Dukes' C mortality by ~25%.

. Estimated 10 most common cancer cases in the United States in males and females (all races).

Rank	Males Total Cases = 855,220 (percent)	Females Total Cases = 810,320 (percent)
1	Prostate (27)	Breast (29)
2	Lung and bronchus (14)	Lung and bronchus (13)
3	Colon and rectum (8)	Colon and rectum (8)
4	Urinary bladder (7)	Uterine corpus (6)
5	Melanoma (5)	Thyroid (6)
6	Lymphoma (5)	Lymphoma (5)
7	Kidney and renal pelvis (5)	Melanoma (4)
8	Oral cavity and pharynx (4)	Kidney and renal pelvis (3)
9	Leukemia (4)	Pancreas (3)
10	Liver and intrahepatic bile duct (3)	Leukemia (3)
	Other sites (18)	Other sites (20)

Data from the American Cancer Society, 2013.

INFLAMMATORY BOWEL DISEASE

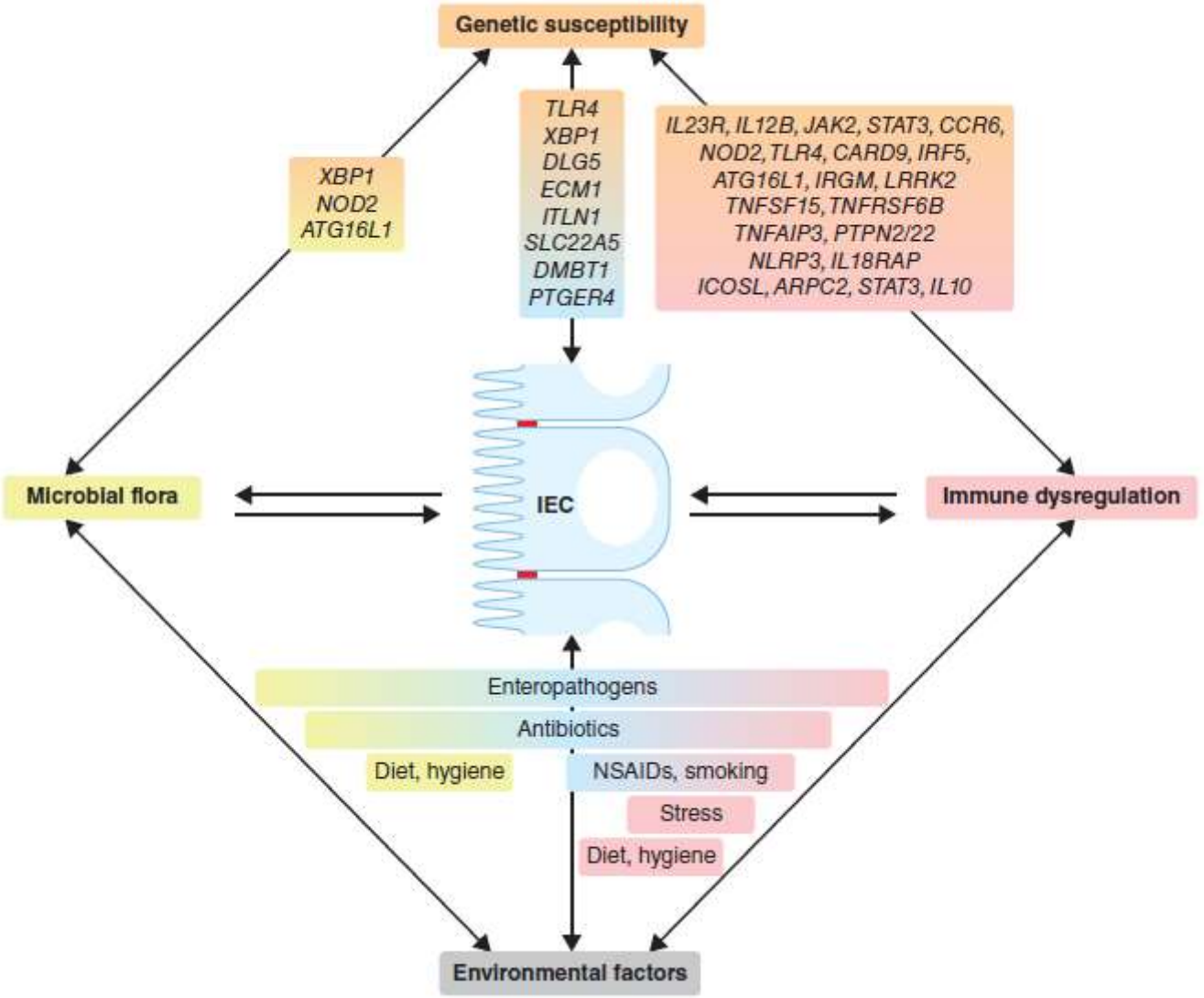
The term "inflammatory bowel disease" includes ulcerative colitis and Crohn disease. Ulcerative colitis is a chronic, recurrent disease characterized by diffuse mucosal inflammation involving only the colon. Ulcerative colitis invariably involves the rectum and may extend proximally in a continuous fashion to involve part or all of the colon. Crohn disease is a chronic, recurrent disease characterized by patchy transmural inflammation involving any segment of the gastrointestinal tract from the mouth to the anus.

Crohn disease and ulcerative colitis may be associated in 50% of patients with a number of extraintestinal manifestations, including oral ulcers, oligoarticular or polyarticular nondeforming peripheral arthritis, spondylitis or sacroiliitis, episcleritis or uveitis, erythema nodosum, pyoderma gangrenosum, hepatitis and sclerosing cholangitis, and thromboembolic events.

Diagnosing 'indeterminate colitis'

After full investigation, IBD may not obviously be Crohn's or UC. Indeterminate colitis more often resembles UC, and may be due to unrecognized variants of UC with transmural inflammation or skip lesions. Colectomy + pouch formation may be needed (see MINIBOX), though pouch failure rate is higher than in UC.[203]

FIGURE 351-1 Pathogenesis of inflammatory bowel disease (IBD). In IBD, the tridirectional relationship between the commensal flora (microbiota), intestinal epithelial cells (IEC), and mucosal immune system is dysregulated, leading to chronic inflammation. Each of these three factors is affected by genetic and environmental factors that determine risk for the disease. NSAIDs, nonsteroidal anti-inflammatory drugs. *(Adapted from A Kaser et al: Annu Rev Immunol 28:573, 2010.)*



Ulcerative colitis (UC)

UC is a relapsing and remitting inflammatory disorder of the colonic mucosa. It may affect just the rectum (proctitis, as in ~50%) or extend to involve part of the colon (left-sided colitis, in ~30%) or the entire colon (pancolitis, in ~20%). It 'never' spreads proximal to the ileocaecal valve (except for backwash ileitis). *Cause:* Unknown;[1] there is some genetic susceptibility. *Pathology:* Hyperaemic/haemorrhagic granular colonic mucosa ± pseudopolyps formed by inflammation. Punctate ulcers may extend deep into the lamina propria—inflammation is normally not transmural. Mucosal disease differentiates it from Crohn's disease. *Histology:* See biopsy, below. *Prevalence:* 100–200/100,000. *Incidence:* 10–20/100,000/yr. ♀:♂ >1:1. Most present aged 15–30yrs. UC is 3-fold as common in non-smokers (the opposite is true for Crohn's disease)—symptoms may relapse on stopping smoking.

Symptoms Episodic or chronic diarrhoea (± blood & mucus); crampy abdominal discomfort; bowel frequency relates to severity (see TABLE); urgency/tenesmus≈rectal UC. Systemic symptoms in attacks: fever, malaise, anorexia, weight↓.

Signs May be none. In acute, severe UC there may be fever, tachycardia, and a tender, distended abdomen. *Extraintestinal signs:* Clubbing; aphthous oral ulcers; erythema nodosum (p275); pyoderma gangrenosum; conjunctivitis; episcleritis; iritis; large joint arthritis; sacroiliitis; ankylosing spondylitis; fatty liver; PSC (p266); cholangiocarcinoma; nutritional deficits; amyloidosis (p266).[189]

Tests *Blood:* FBC, ESR, CRP, U&E, LFT, blood culture. *Stool* MC&S/CDT (p247) to exclude *Campylobacter, C. difficile, Salmonella, Shigella, E. coli,* amoebae. *AXR:* No faecal shadows; mucosal thickening/islands (fig 2, p743); colonic dilatation (below). *Erect CXR:* Perforation. *Ba enema* (fig 1): Never do during severe attacks or for diagnosis. *Colonoscopy* shows disease extent and allows biopsy (p256, fig 5)—look for inflammatory infiltrate; goblet cell depletion; glandular distortion; mucosal ulcers; crypt abscesses.

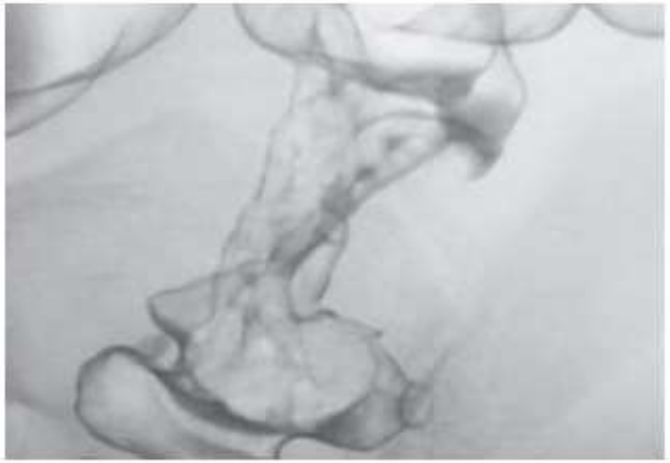
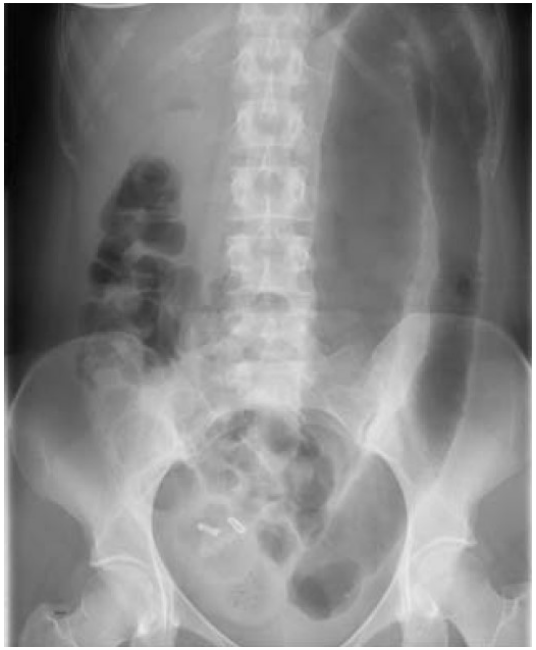


Fig 1. Ba enema: ulcers + loss of haustral pattern. ©OTM.



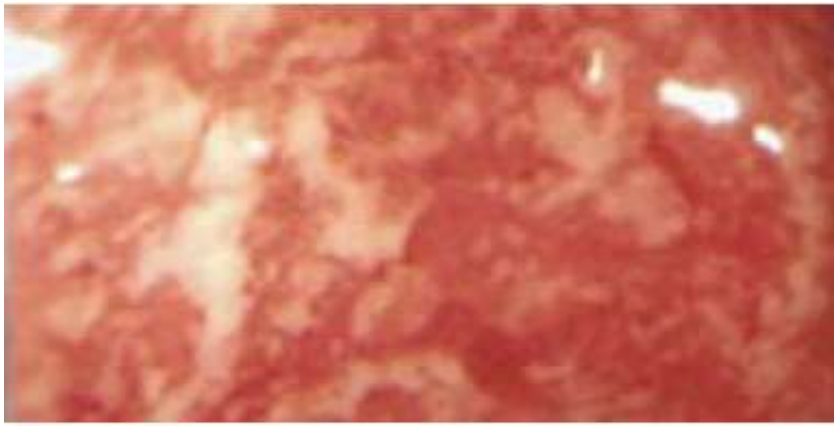


Fig 5. Colonic mucosa in active UC (p272); it is red, inflamed and friable (bleeds on touching). Signs of severity: mucopurulent exudate, mucosal ulceration ± spontaneous bleeding. If quiescent, there may only be a distorted or absent mucosal vascular pattern.

Fig 2. Abdominal film showing toxic megacolon associated with ulcerative colitis, note bowel wall thickening and loss of mucosal folds in the colon.

Assessing severity in UC (Truelove & Witts criteria modified to include CRP)[190]			
Variable	**Mild UC**	**Moderate UC**	**Severe UC**
Motions/day	<4	4–6	>6
Rectal bleeding	Small	Moderate	Large
T°C at 6AM	Apyrexial	37.1–37.8°C	>37.8°C
Resting pulse	<70 beats/min	70–90 beats/min	>90 beats/min
Haemoglobin	>110g/L	105–110g/L	<105g/L
ESR (do CRP too)	<30 (<16 might be better)[191]		>30 (or CRP >45mg/L)

Complications ►Perforation and bleeding are 2 serious dangers, also:

- Toxic dilatation of colon (mucosal islands, colonic diameter >6cm).
- Venous thrombosis: give prophylaxis to all inpatients (p344).[192] Colonic cancer: risk≈15% with pancolitis for 20yrs. Intra-epithelial neoplasms may occur in flat, normal-looking mucosa. To spot these, surveillance colonoscopy is done, eg 2–4yrs, with 4 random biopsies/10cm. Endomicroscopy (expensive!) may ↑ detection rates.[2]

Inducing remission *Mild UC:* • 5-ASA[3], eg sulfasalazine (SSZ) or mesalazine (=mesalamine) or olsalazine are the mainstay for remission-induction/maintenance. SSZ is cheapest and often as good (unless sulfa-allergic).[193] Once-a-day regimen: Mezavant XL®, 2 gastro-resistant 1.2g tabs once daily.[194]

- Steroids help remission induction, eg *prednisolone* ~20mg/d PO ± twice-daily steroid foams PR (eg *hydrocortisone* as Colifoam®), or *prednisolone* 20mg retention enemas (Predsol®).[4] If improving in 2wks, ↓steroids slowly. If not treat as moderate UC.

Moderate UC: If 4–6 motions/day, but otherwise well, try oral *prednisolone* 40mg/d for 1wk, then 30mg/d for 1wk, then 20mg for 4 more weeks + 5-ASA[3] (eg 4 Mezavent 1.2g tabs once daily) + twice-daily steroid enemas.[4] If improving, ↓steroids gradually. If no improvement after 2 weeks, treat as severe UC.

Severe UC: If unwell and ≥6 motions/d, admit for nil by mouth & IV hydration (eg 1L of 0.9% saline + 2L dextrose-saline/24h, + 20mmol K^+/L for maintenance; less if elderly).

- *Hydrocortisone* 100mg/6h IV.
- Rectal steroids, eg *hydrocortisone* 100mg in 100mL 0.9% saline/12h PR.
- Monitor T°, pulse, and BP—and record stool frequency/character on a stool chart.
- Twice-daily exam: document distension, bowel sounds, and tenderness.
- Daily FBC, ESR, CRP, U&E ± AXR. Consider blood transfusion (eg if Hb <90–100g/L). NB: day 3 CRP >45 or bowels open >8×/day = 85% chance of colectomy on this admission.
- Parenteral nutrition is only very rarely required (eg if severely malnourished).
- If improving in 5d, transfer to *prednisolone* PO (40mg/24h) with a 5-ASA (eg *sulfasalazine* 500mg/6h) to maintain remission.
- If on day 3 CRP >45 or >6 stools/d, ►►action is probably needed, eg colectomy or *rescue therapy* with *ciclosporin* or *infliximab*, which can avoid urgent colectomy in steroid-refractory patients (the need for elective colectomy in the long-term is not modified).[190, 195]

Topical therapies Proctitis may respond to *suppositories* (*prednisolone* 5mg or *mesalazine*, eg Asacol® 250mg/8h or Pentasa® 1g at bedtime). Topical 5-ASAs work better than topical steroids.[196] Procto-sigmoiditis may respond to *foams* PR (20mg Predfoam®/12-24h or 5-ASA, eg Asacol® 1g/d); disposable applicators aid accurate delivery. Retention enemas may be needed in left-sided colitis.

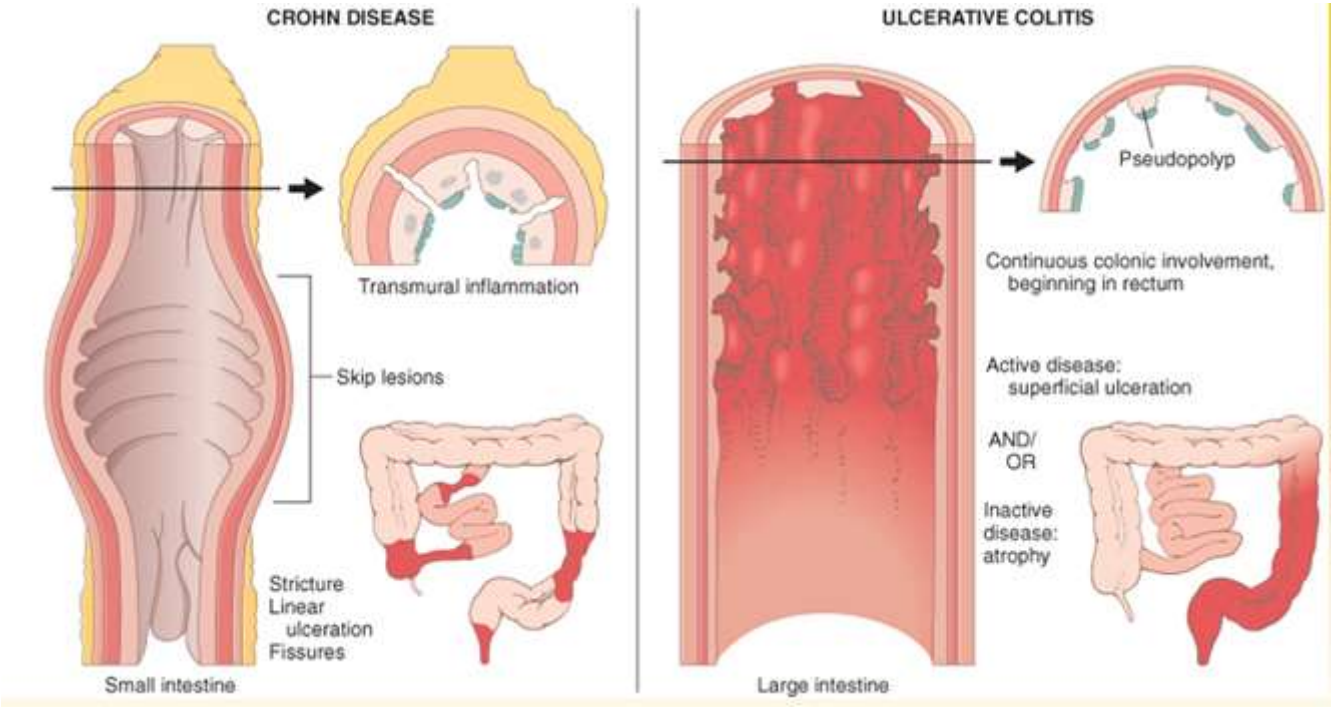
Surgery This is needed at some stage in ~20%, eg *proctocolectomy + terminal ileostomy:* It may be possible to retain the ileocecal valve, and hence reduce liquid loss.[197] *Colectomy* with *ileo-anal pouch* later. *Surgical mortality:* 2-7%, higher if perforation. *Pouchitis* may improve with antibiotics (eg *metronidazole* + *ciprofloxacin* for 2wks) and immunosuppressants.[198]

Indications:
- Perforation
- Massive haemorrhage
- Toxic dilatation
- Failed medical therapy

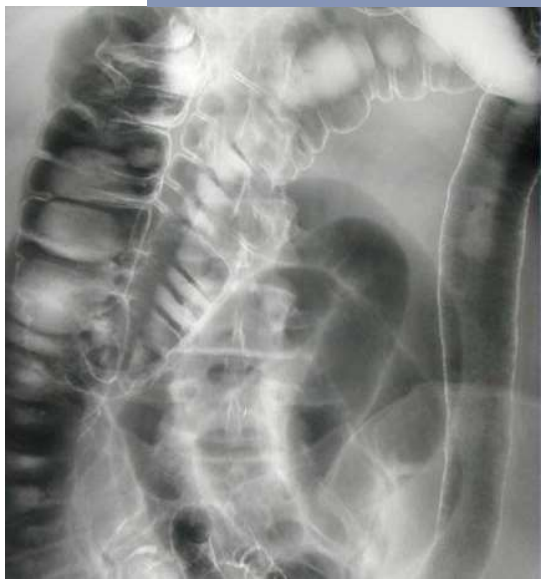
It's time for immunomodulation if... no remission comes with steroids, or if prolonged use is required. Agents: azathioprine, methotrexate, infliximab, adalimumab or calcineurin inhibitors (ciclosporin; tacrolimus).[199] Dose example: *Azathioprine* (2-2.5mg/kg/d PO after food).[200] Treat for several months, and monitor FBC every 4-6wks.

Maintaining remission All *5-ASAs* ↓relapse rate from 80% to 20% at 1yr—examples are *sulfasalazine*, *mesalazine*, and *olsalazine*.[4] Maintenance continues for life. *Sulfasalazine* (500mg/6h PO) is 1st-line. SEs relate to sulfapyridine intolerance (headache, nausea, anorexia). Warn of SEs: T°↑, rash, haemolysis (►monitor FBC and U&E at start, then at 3 months, then annually), hepatitis, pancreatitis, paradoxical worsening of colitis, and reversible oligospermia.[201] *Newer 5-ASAs* (eg *mesalazine* 400-800mg/8h PO or *olsalazine* 500mg/12h PO) are as good at maintaining remission, have fewer SEs, but are more expensive. They are indicated in *sulfasalazine* intolerance and young men in whom fertility is a concern (less effect on sperm).[202]

	Crohn Disease	Ulcerative Colitis
Site of origin	Terminal ileum	Rectum
Pattern of progression	"Skip" lesions/irregular	Proximally contiguous
Thickness of inflammation	Transmural	Submucosa or mucosa
Symptoms	Crampy abdominal pain	Bloody diarrhea
Complications	Fistulas, abscess, obstruction	Hemorrhage, toxic megacolon
Radiographic findings	String sign on barium x-ray	Lead pipe colon on barium x-ray
Risk of colon cancer	Slight increase	Marked increase
Surgery	For complications such as stricture	Curative

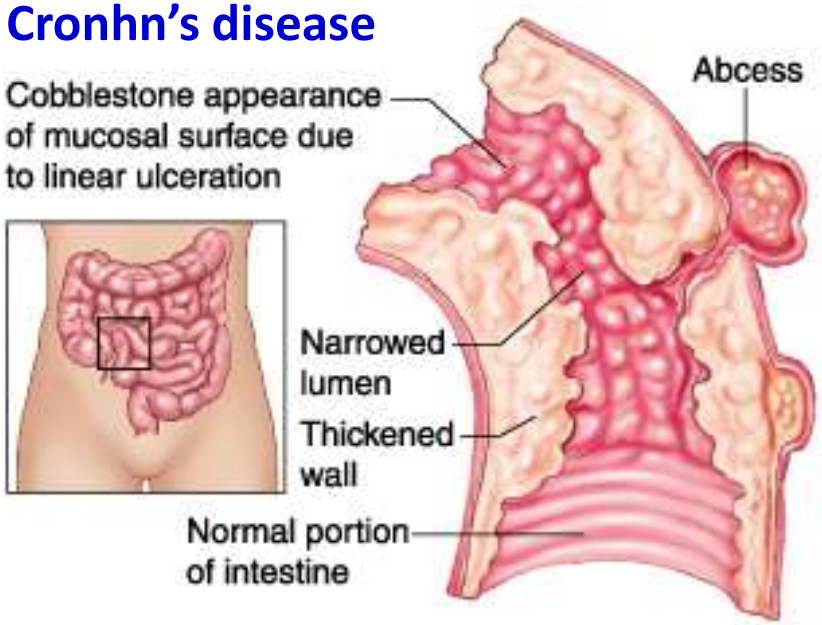


- Shortening of colon secondary to fibrosis
- Loss of haustration



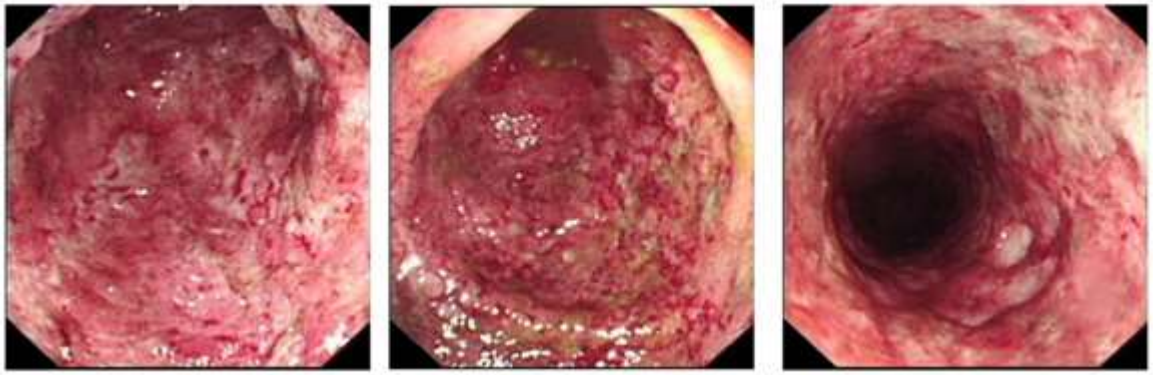
COLONSCOPY

Cronhn's disease



Skip lesions

Strictures



Pseudopolyps

Ulcerative colitis-inflammation and continuous ulceration throughout the colonic mucosa

FEATURES	CROHN'S DISEASE	ULCERATIVE COLITIS
Location	Any part of gastrointestinal tract	Colonic
Inflammation	Transmural	Mucosal/submucosal
Smoking	Smokers higher than expected	Appears to be protective
Risk of colorectal cancer	Elevated in colonic Crohn's	Elevated
Risk of intestinal cancer	Elevated in small-bowel Crohn's disease	NA
hsCRP	Elevation common	Elevation not common
Serology	ASCA, OmpC, CBir1	pANCA
Surgery	Recurrence common	Total proctocolectomy may be curative
Fistulas	Common	Very rare
FDA-approved biologic agents	Infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), natalizumab (Tysabri), vedolizumab (Entyvio)	Infliximab, adalimumab, golimumab, vedolizumab (Entyvio)
Immunomodulator therapy	Azathioprine (AZA, Imuran),[1] 6-mercaptopurine (6MP, Purinethol),[1] methotrexate (MTX, Trexall)[1]	AZA, 6MP, cyclosporine (Sandimmune, Neoral)[1]
Endoscopic features	Skip lesions	Contiguous involvement
Strictures	Common	Colorectal cancer unless proven otherwise
Genetic markers*	NOD2, ATG16L1, IRGM, IL23R, IL12B, STAT3, NKX2-3	IL12B, STAT3. NKX2-3

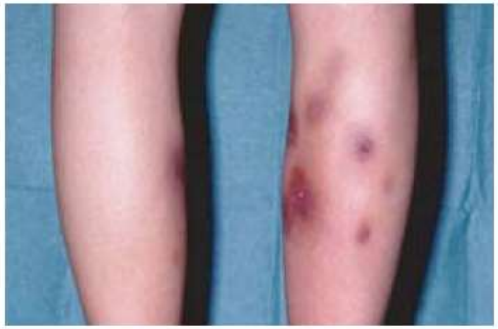
[1]Not FDA approved for this indication.
*Not approved for diagnosis. More than 50 genes have been associated with susceptibility to IBD.
Abbreviations: ASCA = anti–*Saccharomyces cerevisiae* antibodies; CBir1 = anti-flagellin antibody; FDA = U.S. Food and Drug Administration; hsCRP = high-sensitivity C-reactive protein; NA = not applicable; OmpC = anti-porin antibody; pANCA = perinuclear antineutrophilic cytoplasmic antibody.

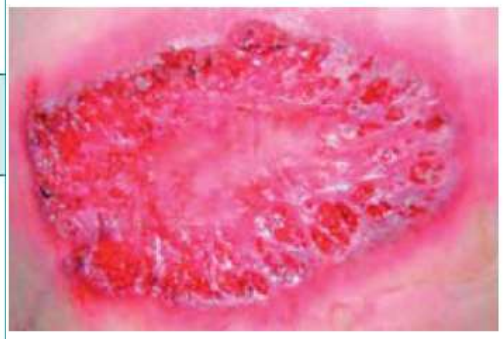
Serology studies, such as anti–*Saccharomyces cerevisiae* antibodies (ASCA), perinuclear antineutrophilic cytoplasmic antibody (pANCA), anti-porin antibody (OmpC), and anti-flagellin antibody (CBir1), are occasionally useful to predict disease behavior.

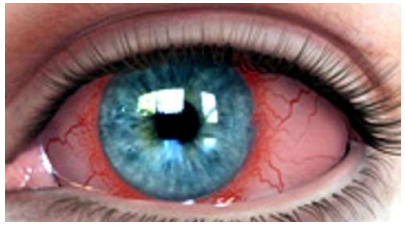
Lactoferrin and Calprotectin, which are inflammatory markers found in stool, can be used to assess for postoperative recurrence in patients with Crohn's disease. A few studies have demonstrated the utility of elevated inflammatory markers in predicting future clinical flares.

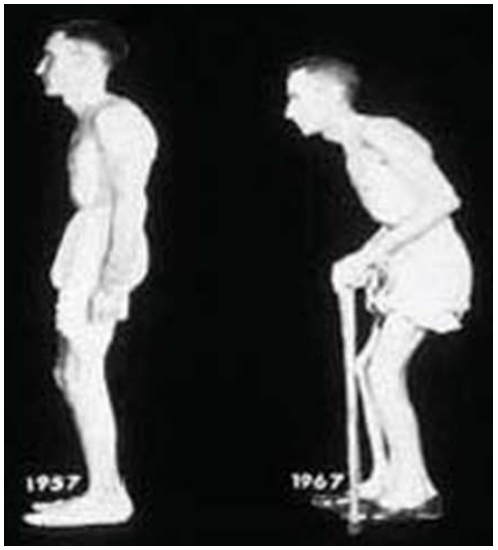
Table 16–2 • EXTRAINTESTINAL MANIFESTATIONS OF INFLAMMATORY BOWEL DISEASE

	CROHN DISEASE	ULCERATIVE COLITIS
Skin manifestations	Erythema nodosum: 15% Pyoderma gangrenosum: rare	Erythema nodosum: 10% Pyoderma gangrenosum: 1%-12%
Rheumatologic	Arthritis (polyarticular, asymmetric): common Ankylosing spondylitis: 10%	Arthritis: less common Ankylosing spondylitis: less common
Ocular	Uveitis: common (photophobia, blurred vision, headache)	Uveitis: common (photophobia, blurred vision, headache)
Hepatobiliary	Cholelithiasis fatty liver: common Primary sclerosing cholangitis: rare	**Fatty liver: common** **Primary sclerosing cholangitis: uncommon but more often than Crohn**
Urologic	Nephrolithiasis (10%-20%) after small bowel resection or ileostomy	









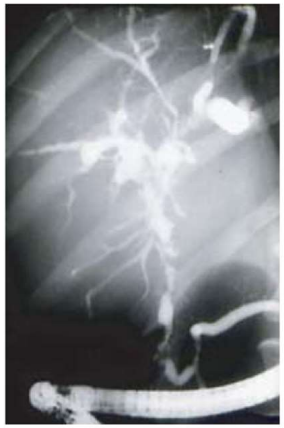


Fig 1. ERCP showing many strictures in the biliary tree with a characteristic 'beaded' appearance. *MRCP* (fig 2) is more cost effective.

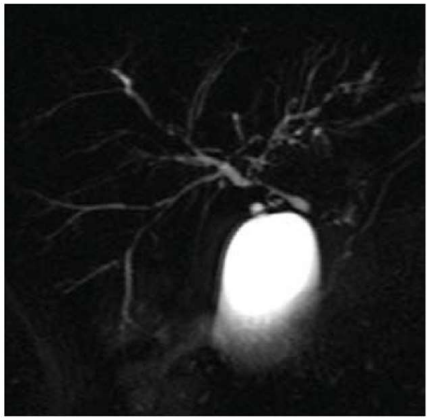


Fig 2. MRCP showing features of PSC. The intrahepatic ducts show multifocal strictures. (MRCP = magnetic resonance cholangiopancreatography). Strictures can be hard to differentiate from cholangiocarcinoma (coexistence of UC may promote this development). Stenting may be needed.

Calcium oxalate monohydrate.

Table 16–2 • EXTRAINTESTINAL MANIFESTATIONS OF INFLAMMATORY BOWEL DISEASE

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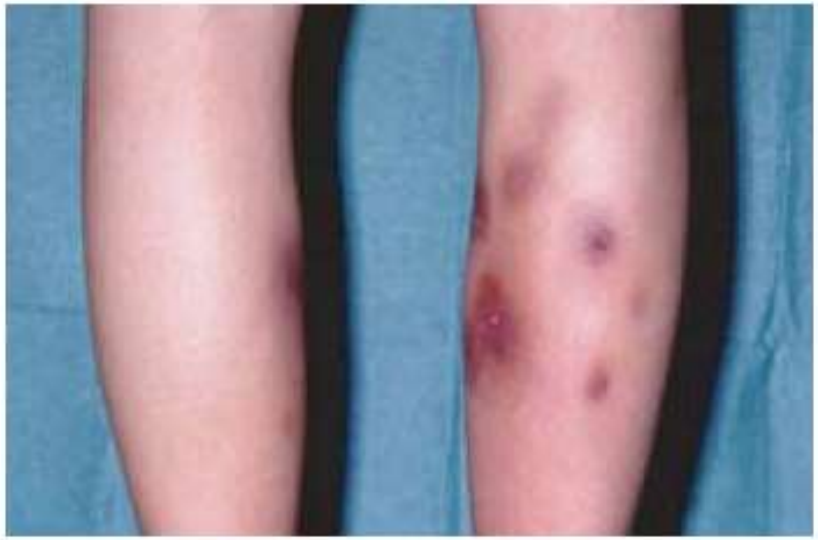
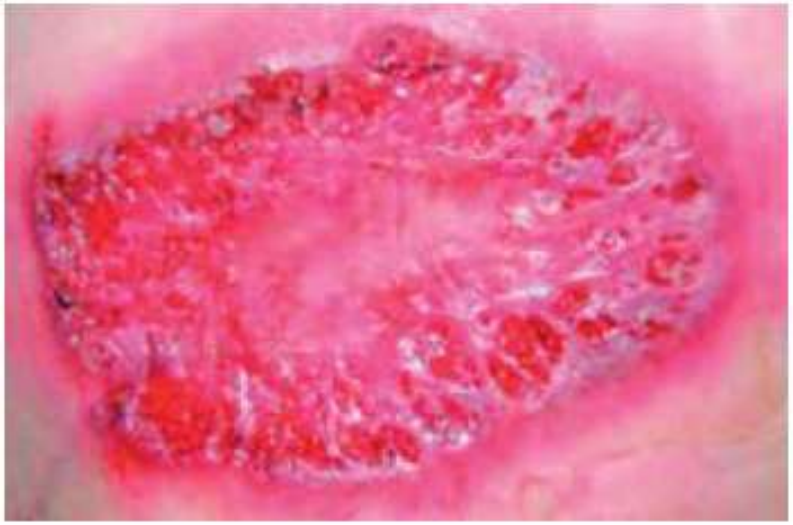
Urologic	Nephrolithiasis (10%-20%) after small bowel resection or ileostomy	

Skin manifestations of systemic diseases

Crohn's Perianal/vulval/oral ulcers; erythema nodosum; pyoderma gangrenosum.

Erythema nodosum (fig 1) Painful, blue-red, raised lesions on shins (± thighs/arms). *Causes:* sarcoidosis, drugs (sulfonamides, the Pill, dapsone), streptococcal infection. *Less common:* Crohn's/UC, BCG vaccination, leptospirosis, *Mycobacterium* (TB, leprosy), *Yersinia* or various viruses and fungi. Cause unknown in 30–50%.



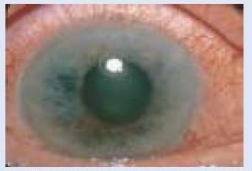
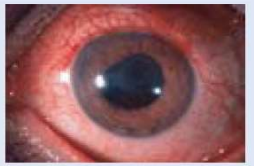
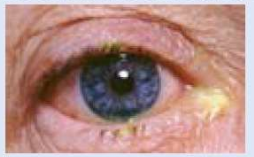


Pyoderma gangrenosum (fig 2) Recurring nodulo-pustular ulcers, ~10cm wide, with tender red/blue overhanging necrotic edge, purulent surface, and healing with cribriform scars on leg, abdomen, or face. *Associations:* UC/Crohn's, autoimmune hepatitis, Wegener's■, myeloma, neoplasia. ♀>♂. *Treatment:* Get help. Oral steroids ± ciclosporin should be 1st-line therapy.[78]

Systemic conditions causing eye signs

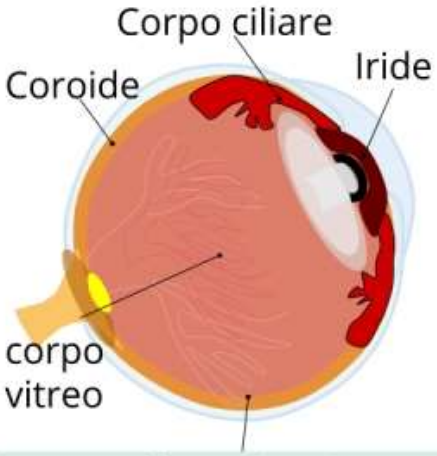
Systemic inflammatory diseases may manifest as iritis in ankylosing spondylitis and Reiter's■; *conjunctivitis* in Reiter's; *scleritis* or *episcleritis* in RA, vasculitis and SLE. Scleritis in RA and Wegener's■ may damage the eye. Refer urgently if eye pain. Giant cell arteritis causes optic nerve ischaemia presenting as sudden blindness.

Differential diagnosis of a red eye

	Conjunctiva	Iris	Pupil	Cornea	Anterior chamber	Intraocular pressure	Treatment	Appearance
Acute glaucoma	Both ciliary and conjunctival vessels injected. Entire eye is red. See *OHCS* p430.	Injected	Dilated, fixed, oval	Steamy, hazy	Very shallow	Very high	Refer. IV acetazolamide + pilocarpine drops (miotic); Peripheral iridotomy.	
Anterior uveitis (iritis)	Redness most marked around cornea, which doesn't blanch on pressure. Usually unilateral. *Causes:* AS, RA, Reiter's■, sarcoidosis, herpes simplex, herpes zoster, and Behçet's disease. NB: a similar scleral appearance but without papillary or anterior chamber involvement may be *scleritis* (eg RA, SLE, vasculitis).	Injected	Small, irregular due to adhesions between the anterior lens and the pupil margin	Normal	Turgid	Normal	Refer. Steroid eye drops (eg 0.5% prednisolone) + mydriatic (eg cyclopentolate 0.5%).	
Conjunctivitis	Often bilateral. Conjunctival vessels injected, greatest toward fornices, but blanching on pressure. Mobile over sclera. Purulent discharge.	Normal	Normal	Normal	Normal	Normal	Most do not require treatment. Consider chloramphenicol ointment or drops.	
Subconjunctival haemorrhage	Bright red sclera with white rim around limbus. *Causes:* BP↑; leptospirosis; bleeding disorders; trauma; snake venom; haemorrhagic fevers.	Normal	Normal	Normal	Normal	Normal	Looks alarming but resolves spontaneously. Check BP if elderly; Refer if traumatic; On warfarin?	

After RD Judge, GD Zuidema, FT Fitzgerald *Clinical diagnosis* 5/e, Little Brown, Boston. Images courtesy of Prof. Jonathan Trobe and ADB.

Uveite: infiammazione dell'uvea



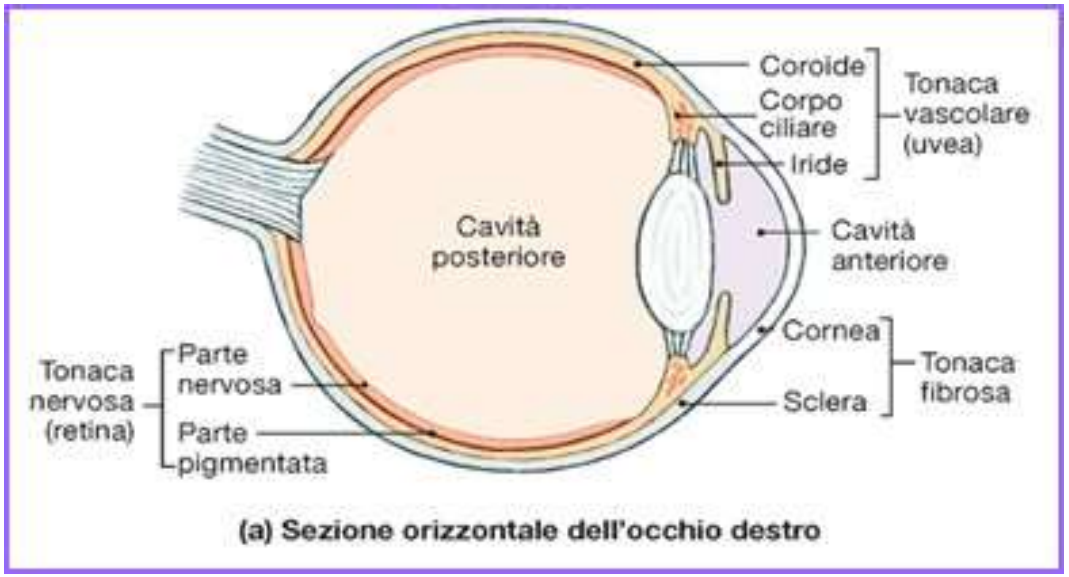
L'uvea è un rivestimento dell'occhio formato da coroide, corpo ciliare ed iride

L'uveite anteriore è l' infiammazione di iride e corpo ciliare

L'uveite posteriore è l' infiammazione della coroide

L'uveite intermedia è l' infiammazione della coroide e del corpo vitreo

L'uveite totale è l' infiammazione dell'intera uvea



(a) Sezione orizzontale dell'occhio destro

Pharmacologic Therapy

Although ulcerative colitis and Crohn disease appear to be distinct entities, the same pharmacologic agents are used to treat both. Despite extensive research, there are still no specific therapies for these diseases. The mainstays of therapy are 5-aminosalicylic acid derivatives, corticosteroids, immunomodulating agents (such as mercaptopurine or azathioprine and methotrexate), and biologic agents.

Ulcerative Colitis

Proctitis

- Initial treatment choices
  - Mesalamine suppositories (Canasa) or enemas (Rowasa) to induce remission
  - Steroid foam enemas (Cortifoam) to induce remission
  - Mesalamine suppositories or enemas to maintain remission
- Second-line treatment choices
  - Oral mesalamine in combination with local therapy
  - Adjunctive treatment with antibiotics: ciprofloxacin (Cipro),[1] metronidazole (Flagyl),[1] or rifaximin (Xifaxan)[1]
  - Probiotics

Left-Sided Colitis

- Initial treatment choices
  - Oral mesalamine product with or without local therapy
- Second-line treatment choices
  - Oral or intravenous steroids budesonide (Uceris)
  - Immunomodulator therapy
  - Infliximab (IFX, Remicade), adalimumab (Humira), golimumab (Simponi)
  - Cyclosporine (Sandimmune)[1] on an inpatient basis (avoid cyclosporine after IFX therapy due to risk of severe immunosuppression)

Pancolitis

- Initial treatment choices
  - Oral mesalamine with a short course of oral or intravenous steroids including colonic-release budesonide
- Second-line treatment choices
  - Immunomodulator therapy
  - Infliximab, adalimumab, golimumab
  - Cyclosporine on an inpatient basis (avoid cyclosporine after IFX therapy due to risk of severe immunosuppression)

Crohn's Disease

Ileocecal Inflammatory Crohn's Disease

- First-line treatment
  - Oral mesalamine (ileo-colonic release mesalamine product for ileal disease; Pentasa for more proximal small-bowel disease)[1]
  - Budesonide (Entocort EC) 9 mg PO qd
  - Immunomodulator therapy
  - Biologic agents with or without concomitant immunomodulators

Ileal Stricturing Disease

- No proximal dilation
  - Trial with budesonide or biologic agents (patients with elevated hsCRP are more likely to respond)
- Proximal small-bowel dilation
  - Consider surgical approach

Internally Fistulizing Disease without Intraabdominal Abscess

- Stricture immediately distal to fistula
  - Surgical approach
- No stricture
  - Biologic agents with or without concomitant immunomodulators

Externally Fistulizing Disease without Intraabdominal Abscess

- Biologic agents with or without concomitant immunomodulators

Fistulizing Disease with Intraabdominal Abscess

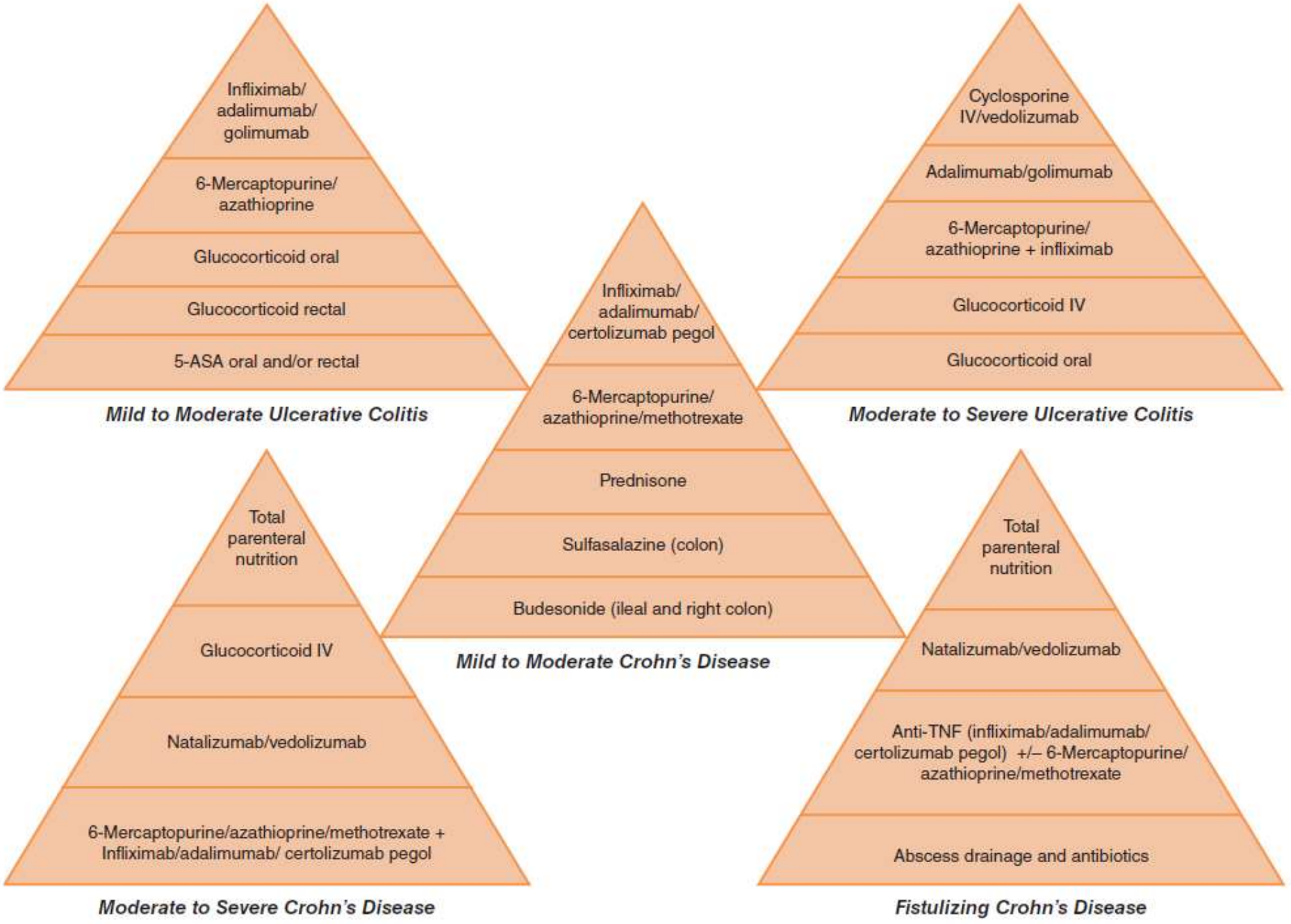
- Intravenous antibiotics as appropriate
- Percutaneous drainage if appropriate
- Surgical drainage if indicated
- Biologic agents with or without concomitant immunomodulators once infectious process has been treated

Perianal Crohn's Disease without Abscess Formation

- Antibiotics: Ciprofloxacin (Cipro),[1] metronidazole (Flagyl),[1] rifaximin (Xifaxan)[1]
- Immunomodulators
- Biologic agents with or without concomitant immunomodulators
- Seton placement
- Diverting ostomy

Colonic Crohn's Disease

- Oral steroids to induce remission
- Immunomodulator therapy
- Biologic agents with or without concomitant immunomodulator therapy



Harrison's 2015

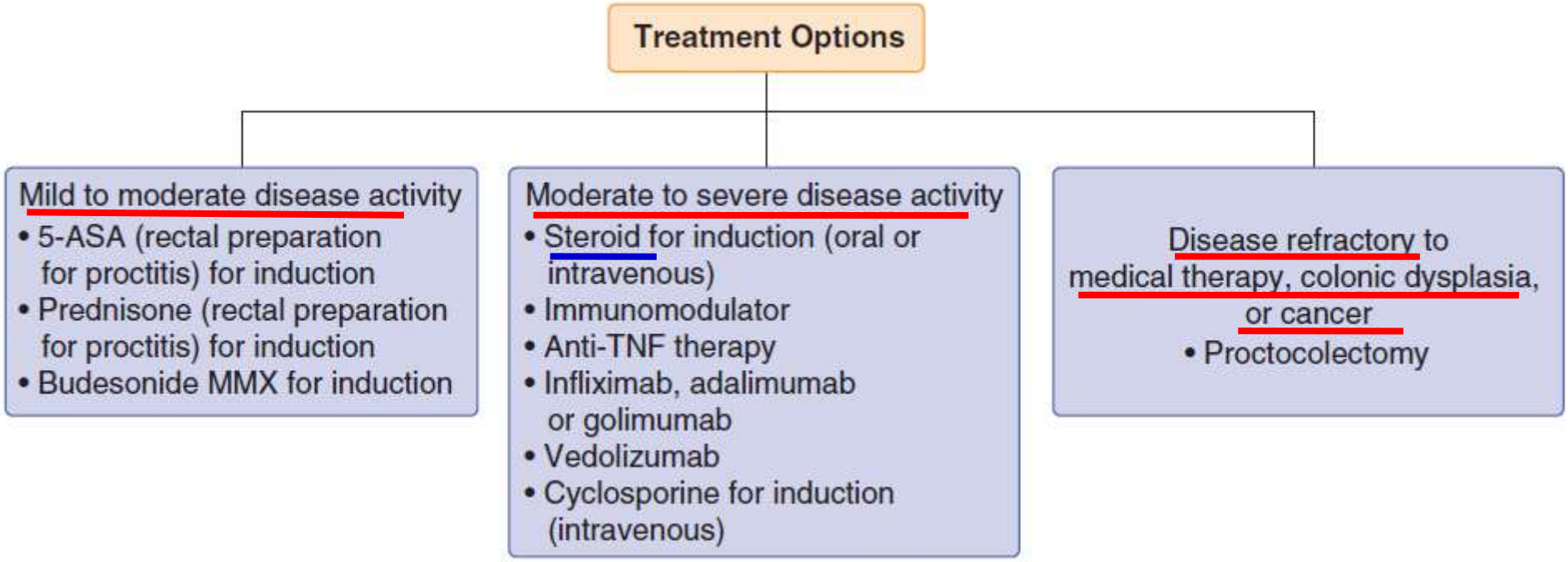


FIGURE 141-4. Ulcerative colitis treatment algorithm.

Cecil's 2016

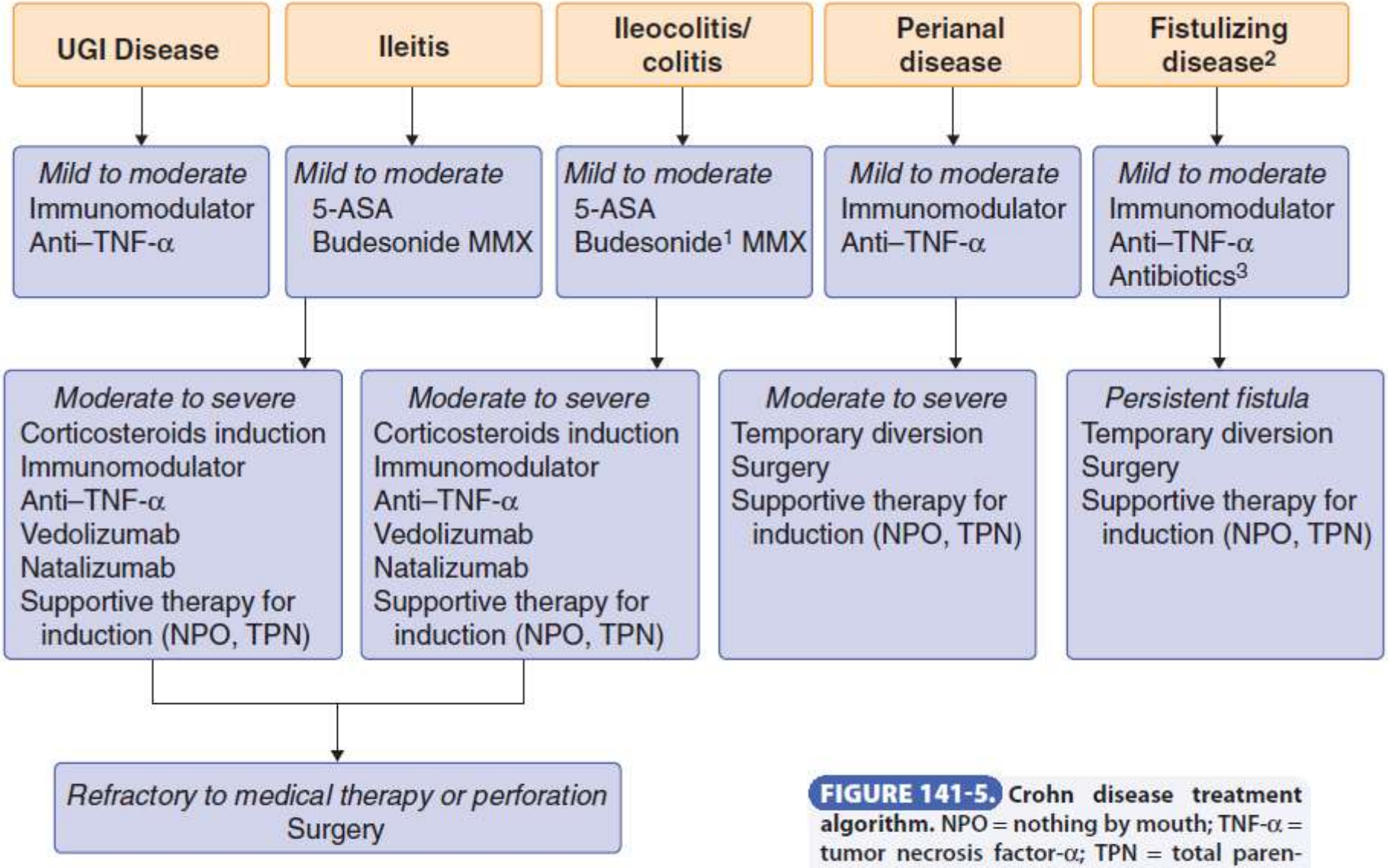


FIGURE 141-5. Crohn disease treatment algorithm. NPO = nothing by mouth; TNF-α = tumor necrosis factor-α; TPN = total parenteral nutrition; UGI = upper gastrointestinal.

[1]Proximal colon disease involvement.
[2]Abscess should be excluded before initiating medical therapy.
[3]Perianal location.

Cecil's 2016

16.1 A 32-year-old woman has a history of chronic diarrhea and gallstones and now has rectovaginal fistula. Which of the following is the most likely diagnosis?

A. Crohn disease
B. Ulcerative colitis
C. Systemic lupus erythematosus
D. Laxative abuse

16.2 A 45-year-old man with a history of ulcerative colitis is admitted to the hospital with 2 to 3 weeks of right-upper quadrant abdominal pain, jaundice, and pruritus. He has no fever and a normal WBC count. Endoscopic retrograde cholangiopancreatography (ERCP) shows multifocal strictures of both the intrahepatic and extrahepatic bile ducts with intervening segments of normal and dilated ducts. Which of the following is the most likely diagnosis?

A. Acute suppurative cholangitis
B. Cholangiocarcinoma
C. Primary sclerosing cholangitis (PSC)
D. Choledocholithiasis with resultant biliary strictures

16.3 A 25-year-old man is hospitalized for ulcerative colitis. He has now developed abdominal distention, fever, and transverse colonic dilation of 7 cm on x-ray. Which of the following is the best next step?

A. 5-ASA
B. Steroids
C. Antibiotics and prompt surgical consultation
D. Infliximab

16.4 A 35-year-old woman has chronic crampy abdominal pain and intermittent constipation and diarrhea, but no weight loss or gastrointestinal bleeding. Her abdominal pain is usually relieved with defection. Colonoscopy and upper endoscopy with biopsies are normal, and stool cultures are negative. Which of the following is the most likely diagnosis?

A. Infectious colitis
B. Irritable bowel syndrome
C. Crohn disease
D. Ulcerative colitis

16.1 **A.** Fistulas are common with Crohn disease because of its transmural nature but are uncommon in ulcerative colitis. Gallstones are common in patients with Crohn disease due to ileal bile salt malabsorption and depletion, causing the formation of more cholesterol-rich lithogenic bile.

16.2 **C.** The ERCP shows the typical appearance for primary sclerosing cholangitis (PSC), which is associated with IBD in 75% of cases. Stone-induced strictures should be extrahepatic and unifocal. Cholangiocarcinoma is less common but may develop in 10% of patients with PSC.

16.3 **C.** With toxic megacolon, antibiotics and surgical intervention are often necessary and life saving. Medical therapy is usually ineffective.

16.4 **B.** Irritable bowel syndrome is characterized by intermittent diarrhea and crampy abdominal pain often relieved with defecation, but no weight loss or abnormal blood in the stool. It is a diagnosis of exclusion once other conditions, such as inflammatory bowel disease and parasitic infection (eg, giardiasis), have been excluded.

REVIEW QUESTIONS

1. Which one of the following complications is a known consequence of long-standing ulcerative colitis?

   A. Fecaluria (as a manifestation of fistula formation to the bladder from adjacent loops of bowel)
   B. Perianal abscess formation
   C. Colonic stricture formation with subsequent small bowel obstruction
   D. Development of dysplasia and carcinoma
   E. Development of left-sided hydoureter

Answer: D The transmural inflammatory process of Crohn disease (but not ulcerative colitis) predisposes to the formation of fistulas, and the presence of fistulae signifies that the transmural inflammation has penetrated into adjacent organs, tissue, or skin. Ulcerative colitis is limited to the colon and, unlike Crohn disease, does not cause perianal abscesses. In Crohn disease, inflammation can lead to ileal or colonic strictures, and marked inflammation can cause local reactions that have a mass effect and lead to obstruction of the right ureter, where the ileum and the ureter cross anatomically. Patients with ulcerative colitis do not develop strictures or hydroureter. Dysplasia and carcinoma may develop in patients with longstanding Crohn disease but are much more typical of ulcerative colitis. This risk provides the rationale for endoscopic surveillance of patients with long-standing inflammatory bowel disease.

2. Which one of the following features is most typical for ulcerative colitis?

   A. Deep serpiginous ulcers
   B. Aphthous ulcers
   C. Pseudopolyps
   D. Fistulas
   E. Colonic stricturing

Answer: C Pseudopolyps are typically found in patients with ulcerative colitis, not in patients with Crohn disease. Typical radiologic and endoscopic features of Crohn disease include deep linear ulcers and superficial or aphthous ulcers overlying lymphoid follicles. The presence of fistulas should signal the presence of Crohn disease. Patients with Crohn disease may have strictures, which are not classically seen in ulcerative colitis. When strictures are observed in patients with ulcerative colitis, coexisting colorectal cancer should be suspected.

3. Which one of the following statements regarding mesalamine (5-ASA) is true?

   A. Oral mesalamine is effective for the induction and for the maintenance of remission in patients who have Crohn disease with a colonic disease distribution.
   B. Topical mesalamine for ulcerative proctitis (suppositories) and for left-sided ulcerative colitis (enemas) is effective for the induction and maintenance of remission.
   C. Mesalamine is first-line therapy for patients with moderate to severe ulcerative colitis.
   D. Mesalamine is efficacious as primary therapy for perianal fistulizing Crohn disease when active disease is present in the rectum.
   E. A combination of topical and oral mesalamine therapy in patients with left-sided Crohn disease is more effective than topical or oral mesalamine alone.

Answer: B Oral mesalamine is effective for inducing and maintaining remission in mild to moderate ulcerative colitis. Mesalamine suppositories treat the lower 10 to 20 cm of the colon but do not reach the left colon or splenic flexure; they are extremely effective for inducing and maintaining remission in ulcerative proctitis. In contrast, mesalamine liquid enemas will reach the left colon and as high as the splenic flexure; they are extremely effective for inducing and maintaining remission in left-sided ulcerative colitis. Both oral and topical therapies are effective for treating patients with active ulcerative colitis, and the combination of topical and oral mesalamine therapy is more effective than either mesalamine therapy alone in patients with left-sided ulcerative colitis. Mesalamine is no more effective than placebo for inducing or maintaining remission in Crohn disease patients.

Test characteristics of anti-saccaromyces cervisiae antibodies (ASCA) and perinuclear antineutrophil cytoplasmic antibodies (pANCA) in the diagnosis of inflammatory bowel disease (IBD)

Antibody	Sensitivity, percent	Specificity, percent	PPV, percent
Sensitivity, specificity, and positive predictive value (PPV) in patients with IBD compared to non-IBD controls			
ASCA +	60	91	88
pANCA +	50	95	69
ASCA +/pANCA -	56	94	91
pANCA +/ASCA -	44	97	78
Sensitivity, specificity, and positive predictive value in differentiating ulcerative colitis (UC) from Crohn disease (CD) in patients with IBD*			
ASCA +/CD +	60	86	92
pANCA +/UC +	50	94	76
ASCA +/pANCA -/CD +	56	92	95
pANCA +/ASCA -/UC +	44	98	88

* Where CD + or UC +, the control group for comparison is the other type of IBD.

Data from: Peeters M, Joosens S, Vermeire S, et al. Diagnostic value of anti-Saccharomyces cerevisiae and antineutrophil cytoplasmic autoantibodies in inflammatory bowel disease. Am J Gastroenterol 2001; 96:730.

Positive Predictive Value (PPV).
It is the percentage of patients with a positive test who actually have the disease

Calprotectin in stool

- Calprotectin is a protein belonging to the S100 family and occurring in large amounts in neutrophil granulocytes, where it accounts for 5% of total proteins and 60% of cytoplasm proteins.
- When inflammatory processes occur, **calprotectin is released** due to the **degranulation of neutrophil granulocytes.** In bowel inflammation, calprotectin may be detected in the stool. The faecal assay provides direct information about the inflammation site, whereas with serum or plasma, inflammation might be located anywhere.
- **An increased Calprotectin concentration in stool** is the direct consequence of neutrophil degranulation due to mucosal damage. Faecal Calprotectin assay offers a number of advantages in the **detection of bowel inflammation.** In IBD patients, i.e. patients affected by **ulcerative colitis**, **Crohn's disease** and in the so-called **indeterminate colitis,** the calprotectin level **is generally very high**. In IBS subjects, the calprotectin level is lower if compared to patients with the active IBD, sometimes higher than the cut-off value but always higher than healthy subjects.

Laboratory evidence of nutritional deficiences reported in adults with inflammatory bowel disease

	Percent
Hypoalbuminemia	25 to 80
Anemia	60 to 80
Iron deficiency	39 to 81
Vitamin B12 deficiency•	20 to 60
Folic acid deficiency	36 to 54
Calcium deficiency	13
Magnesium deficiency	14 to 33
Potassium deficiency	6 to 20
Vitamin A deficiency	11
Vitamin D deficiency	75
Vitamin E deficiency	*
Vitamin K deficiency	*
Zinc deficiency	40 to 50
Copper deficiency	*
Vitamin C deficiency	*
Vitamin B1 (thiamine) deficiency[1]	32
Niacin deficiency	*

* Cases reported but prevalence not described.
• Frequency of vitamin B12 deficiency depends on extent of ileal involvement or ileal resection.
Adapted from: Perkal MF, Seashore JH. Nutrition and inflammatory bowel disease. Gastroenterol Clin N Am 1989; 18(3):567.

1. *Hwang C, Ross V, Mahadevan U. Micronutrient deficiencies in inflammatory bowel disease: from A to zinc. Inflamm Bowel Dis 2012; 18:1961.*

Iron Supplementation in IBD — Patients with IBD present unique challenges regarding iron supplementation. **Oral iron supplementation can potentially worsen symptoms and/or IBD activity.** The available data suggest that while many patients tolerate oral supplementation without worsening of disease activity, some develop gastrointestinal side effects, a subset of which may be attributable to worsening IBD disease activity . The percentage of patients who will be intolerant of oral iron has not been extensively studied, although some data suggest it may be as high as 25 percent. However, there are no established definitions or predictors of tolerance in IBD patients. Non-absorbed iron can worsen IBD symptoms and aggravate intestinal inflammation through the Fenton reaction, which releases reactive oxygen species. **Oral iron therapy also may be limited by malabsorption**, particularly in patients with intestinal mucosal disease. Together, these issues of intolerance and malabsorption can significantly limit the utility of oral iron for repletion of iron stores in patients with IBD, particularly in the face of ongoing losses. Finally, there is a **theoretical concern that oral iron might increase oxidative stress and thereby contribute to carcinogenesis in IBD** by augmenting oxidative damage and epithelial proliferation due to inflammation. This concern is mainly based on animal models. Whether these observations are clinically important in humans with IBD is unclear.

Throughout Europe and Great Britain, **intravenous (IV) rather than oral iron replacement is preferred for the treatment of iron deficiency complicating IBD**. IV iron is more effective, better tolerated, and improves quality of life to a greater extent with far fewer adverse events than oral iron.

A. 5-Aminosalicylic Acid (5-ASA)

5-ASA is a topically active agent that has a variety of anti-inflammatory effects. It is used in the active treatment of ulcerative colitis and Crohn disease and during disease inactivity to maintain remission. It is readily absorbed from the small intestine but demonstrates minimal colonic absorption. A number of oral and topical compounds have been designed to target delivery of 5-ASA to the colon or small intestine while minimizing absorption. Commonly used formulations of 5-ASA are sulfasalazine, mesalamine, and azo compounds. Side effects of these compounds are uncommon but include nausea, rash, diarrhea, pancreatitis, and acute interstitial nephritis.

	Systemic Activity
Prednisone	4–5
Triamcinolone	5
Triamcinolone acetonide	5
Dexamethasone	30–120
Betamethasone	30
Betamethasone valerate	—
Methylprednisolone	5
Fluocinolone acetonide	—
Flurandrenolide	—
Deflazacort	3–4

[1]Hydrocortisone = 1 in potency.

Conversione degli Steroidi

Idrocortisone **flebocortid**	20	40	60	80	100	120	140	160	200	400	625	2.500	5.000	10.000
Prednisone **deltacortene**	**5**	10	15	20	25	30	35	40	50	100	156	625	1.250	2.500
Prednisolone	5	10	15	20	25	30	35	40	50	100	156	625	1.250	2.500
Triamcinolone **ledercort**	4	8	12	16	20	24	28	32	40	80	125	500	1.000	2.000
Metilprednisolone **depo-medrol** **solu-medrol** **medrol** **urbason**	4	8	12	16	20	24	28	32	40	80	125	500	1.000	2.000
Betametasone **bentelan** **celestone**	0.75	1.5	2.25	3	3.75	4.5	5.25	6	7.5	15	23.5	94	188	375
Desametasone **soldesam**	0.7	1.5	2.25	3	3.75	4.5	5.25	6	7.5	15	23.5	94	188	375
Deflazacort **flantadin** **deflan**	6	12	18	24	30	36	42	48	60	120	188	750	1.500	3.000

Management of patients receiving systemic corticosteroids.

Recommendations for prescribing

- Do not administer corticosteroids unless absolutely indicated or more conservative measures have failed.
- Keep dosage and duration of administration to the minimum required for adequate treatment.

Monitoring recommendations

- Screen for tuberculosis with a purified protein derivative (PPD) test or chest radiograph before commencing long-term corticosteroid therapy.
- Screen for diabetes mellitus before treatment and at each clinician visit.
  - Have patient test urine weekly for glucose.
  - Teach patient about the symptoms of hyperglycemia.
- Screen for hypertension before treatment and at each clinician visit.
- Screen for glaucoma and cataracts before treatment, 3 months after treatment inception, and then at least yearly.
- Monitor plasma potassium for hypokalemia and treat as indicated.
- Obtain bone densitometry before treatment and then periodically. Treat osteoporosis.
- Weigh daily. Use dietary measures to avoid obesity and optimize nutrition.
- Measure height frequently to document the degree of axial spine demineralization and compression.
- Watch for fungal or yeast infections of skin, nails, mouth, vagina, and rectum, and treat appropriately.
- With dosage reduction, watch for signs of adrenal insufficiency or corticosteroid withdrawal syndrome.

Patient information

- Prepare the patient and family for possible adverse effects on mood, memory, and cognitive function.
- Inform the patient about other possible side effects, particularly weight gain, osteoporosis, and aseptic necrosis of bone.
- Counsel to avoid smoking and excessive ethanol consumption.

Prophylactic measures

- Institute a vigorous physical exercise and isometric regimen tailored to each patient's disabilities.
- Administer calcium (1 g elemental calcium) and vitamin D_3, 400–800 international units orally daily.
  - Check spot morning urines for calcium; alter dosage to keep urine calcium concentration < 30 mg/dL (< 7.5 mmol/L).
  - If the patient is receiving thiazide diuretics, check for hypercalcemia, and administer only 500 mg elemental calcium daily.
  - Consider a bisphosphonate such as alendronate (70 mg orally weekly) or periodic intravenous infusions of pamidronate or zoledronic acid.
- Avoid prolonged bed rest that will accelerate muscle weakness and bone mineral loss. Ambulate early after fractures.
- Avoid elective surgery, if possible. Vitamin A in a daily dose of 20,000 units orally for 1 week may improve wound healing, but it is not prescribed in pregnancy.
- Avoid activities that could cause falls or other trauma.
- For ulcer prophylaxis, if administering corticosteroids with nonsteroidals, prescribe a proton pump inhibitor (not required for corticosteroids alone). Avoid large doses of antacids containing aluminum hydroxide (many popular brands) because aluminum hydroxide binds phosphate and may cause a hypophosphatemic osteomalacia that can compound corticosteroid osteoporosis.
- Treat hypogonadism.
- Treat infections aggressively. Consider unusual pathogens.
- Treat edema as indicated.

Abdominal pain

Varies depending on the underlying cause. Examples: irritation of the mucosa (acute gastritis), smooth muscle spasm (acute enterocolitis), capsular stretching (liver congestion in CCF), peritoneal inflammation (acute appendicitis) and direct splanchnic nerve stimulation (retroperitoneal extension of tumour). The *character* (constant or colicky, sharp or dull), *duration,* and *frequency* depend on the mechanism of production. The *location* and *distribution* of referred pain depend on the anatomical site. *Time of occurrence* and *aggravating* or *relieving factors* such as meals, defecation, and sleep also have special significance related to the underlying disease process. The site of the pain may provide a clue:

- **Epigastric** Pancreatitis, gastritis/duodenitis, peptic ulcer, gallbladder disease, aortic aneurysm.
- **Left upper quadrant** Peptic ulcer, gastric or colonic (splenic flexure) cancer, splenic rupture, subphrenic or perinephric abscess, renal (colic, pyelonephritis).
- **Right upper quadrant** Cholecystitis, biliary colic, hepatitis, peptic ulcer, colonic cancer (hepatic flexure), renal (colic, pyelonephritis), subphrenic/perinephric abscess.
- **Loin** (lateral ⅓ of back between thorax and pelvis—merges with the flank, p567) Renal colic, pyelonephritis, renal tumour, perinephric abscess, pain referred from vertebral column. Causes of *flank pain* are similar (see index for fuller list).
- **Left iliac fossa** Diverticulitis, volvulus, colon cancer, pelvic abscess, inflammatory bowel disease, hip pathology, renal colic, urinary tract infection (UTI), cancer in undescended testis; zoster—wait for the rash! (p458). *Gynae:* Torsion of ovarian cyst, salpingitis, ectopic pregnancy.
- **Right iliac fossa pain** All causes of left iliac fossa pain plus appendicitis and Crohn's ileitis, but usually excluding diverticulitis.
- **Pelvic** *Urological:* UTI, retention, stones. *Gynae:* Menstruation, pregnancy, endometriosis (*OHCS* p288), salpingitis, endometritis (*OHCS* p274), ovarian cyst torsion.
- **Generalized** Gastroenteritis, irritable bowel syndrome, peritonitis, constipation.
- **Central** Mesenteric ischaemia, abdominal aneurysm, pancreatitis.

Remember referred pain: Myocardial infarct → epigastrium; pleural pathology.

INFLAMMATORY BOWEL DISEASE

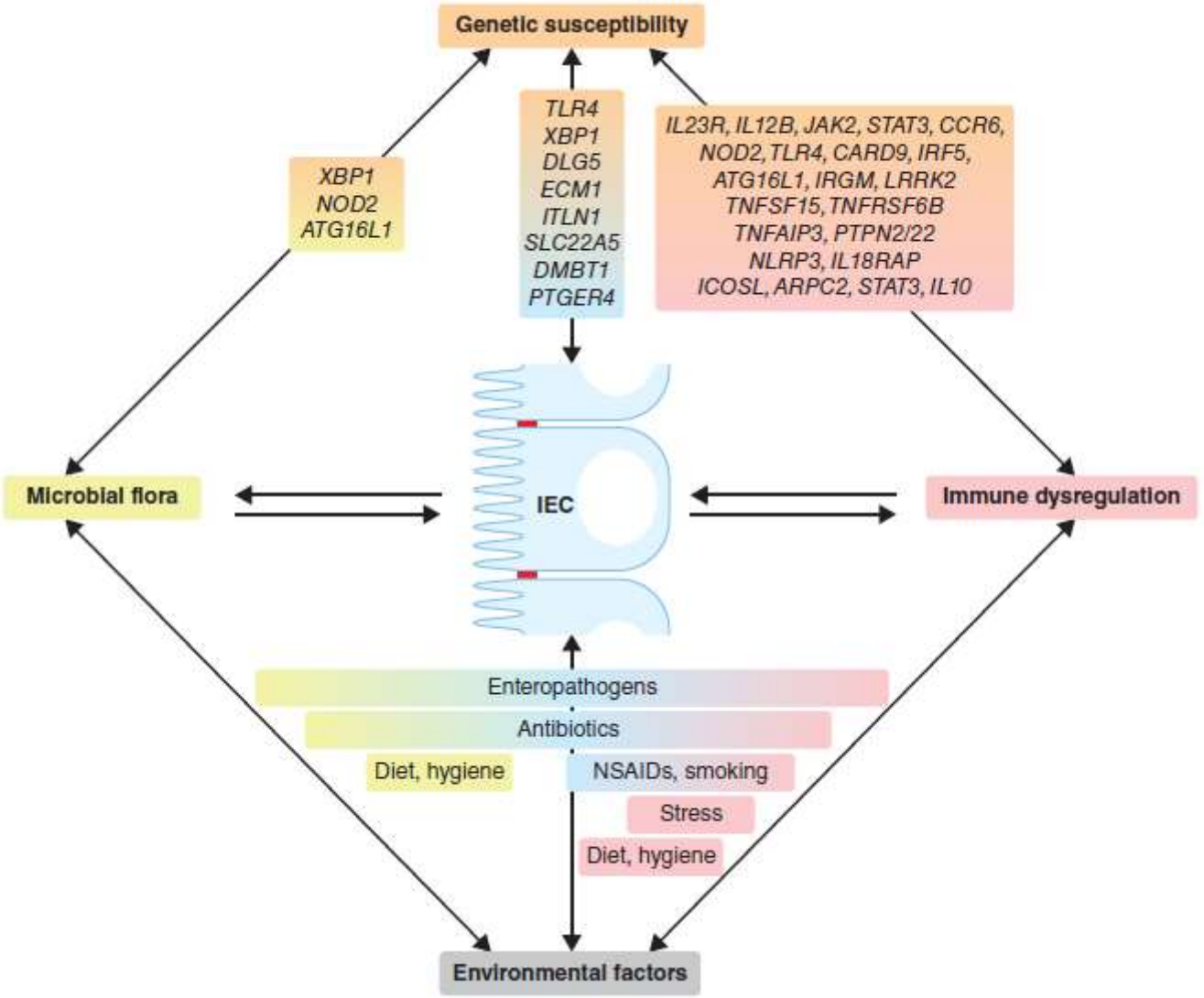
The term "inflammatory bowel disease" includes ulcerative colitis and Crohn disease. Ulcerative colitis is a chronic, recurrent disease characterized by diffuse mucosal inflammation involving only the colon. Ulcerative colitis invariably involves the rectum and may extend proximally in a continuous fashion to involve part or all of the colon. Crohn disease is a chronic, recurrent disease characterized by patchy transmural inflammation involving any segment of the gastrointestinal tract from the mouth to the anus.

Crohn disease and ulcerative colitis may be associated in 50% of patients with a number of extraintestinal manifestations, including oral ulcers, oligoarticular or polyarticular nondeforming peripheral arthritis, spondylitis or sacroiliitis, episcleritis or uveitis, erythema nodosum, pyoderma gangrenosum, hepatitis and sclerosing cholangitis, and thromboembolic events.

Diagnosing 'indeterminate colitis'

After full investigation, IBD may not obviously be Crohn's or UC. Indeterminate colitis more often resembles UC, and may be due to unrecognized variants of UC with transmural inflammation or skip lesions. Colectomy + pouch formation may be needed (see MINIBOX), though pouch failure rate is higher than in UC.[203]

FIGURE 351-1 Pathogenesis of inflammatory bowel disease (IBD). In IBD, the tridirectional relationship between the commensal flora (microbiota), intestinal epithelial cells (IEC), and mucosal immune system is dysregulated, leading to chronic inflammation. Each of these three factors is affected by genetic and environmental factors that determine risk for the disease. NSAIDs, nonsteroidal anti-inflammatory drugs. *(Adapted from A Kaser et al: Annu Rev Immunol 28:573, 2010.)*



Crohn's disease

A chronic inflammatory GI disease characterized by transmural granulomatous inflammation affecting any part of the gut from mouth to anus (esp terminal ileum (in ~70%) and proximal colon). Unlike UC, there is unaffected bowel between areas of active disease (skip lesions). *Cause:* Unknown.[1] Mutations of the NOD2/CARD15 gene ↑risk. *Prevalence:* 0.5–1/1000; less if Asian. ♀/♂ >1. *Incidence:* 5–10/100,000/yr. Presentation is mostly at ~20–40yrs. *Associations:* Altered cell-mediated immunity. Smoking ↑risk ×3–4; NSAIDs may exacerbate disease. *Classification:* Complex![2]

1 **Environmental agents** are implicated. **Genetics:** colon involvement goes with ↑CARD15 gene expression in macrophages & intestinal epithelial cells.[208] **Dysregulated immune responses** might be primary or from infecting gut commensals, eg *Mycobacterium avium para*-TB;[209] *E. coli* adhesins, p273, may have a role.
2 Vienna classification into 24 groups depending on age (> or <40yrs), site affected, and behaviour.

- Insidious onset.
- Intermittent bouts of low-grade fever, diarrhea, and right lower quadrant pain.
- Right lower quadrant mass and tenderness.
- Perianal disease with abscess, fistulas.
- Radiographic or endoscopic evidence of ulceration, stricturing, or fistulas of the small intestine or colon.

Crohn's disease

Symptoms Diarrhoea/urgency ("I get up at 4AM, go 5-6 times in the next 45mins..."), abdominal pain, weight loss/failure to thrive. Fever, malaise, anorexia. "I can be fine one minute, and deathly ill the next. The vomiting, the pain, the diarrhoea that smells so bad it could clear Grand Central Station in 0.5 seconds...I have even been attacked after I came out of the bathroom by 3 guys because I stunk up the place."

Signs Aphthous ulcerations; abdominal tenderness/mass; perianal abscess/fistulae/skin tags; anal strictures. *Beyond the gut:* (fig 1) clubbing, skin, joint & eye problems.

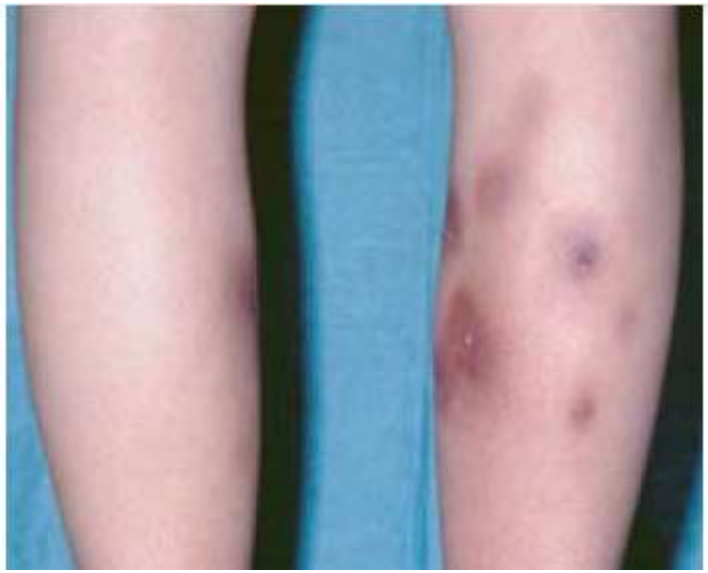


Fig 1. *Beyond the gut...* "I hate how this stupid illness is crippling me..." As well as erythema nodosum on the shins (above; also caused by sarcoid, drugs, streptococci and TB) Crohn's can associate with sero-ve arthritis of big joints, spondyloarthropathy, ankylosing spondylitis, sacroiliitis, pyoderma gangrenosum, conjunctivitis, episcleritis, and iritis.

Complications Small bowel obstruction; toxic dilatation (colonic diameter >6cm, toxic dilatation is rarer than in UC); abscess formation (abdominal, pelvic, or ischio-rectal); fistulae (present in ~10%), eg colovesical (bladder), colovaginal, perianal, enterocutaneous; perforation; rectal haemorrhage; colon cancer; fatty liver, PSC (p266), cholangiocarcinoma, renal stones, osteomalacia, malnutrition, amyloidosis.

Tests *Blood:* FBC, ESR, CRP, U&E, LFT, INR, ferritin, TIBC, B_{12}, folate. *Stool* MC&S and CDT (p247) to exclude *C. difficile*, *Campylobacter*, *E. coli* *et al*. *Colonscopy + rectal biopsy* even if mucosa looks normal (20% have microscopic granulomas). *Small bowel enema* detects ileal disease. *Capsule endoscopy* (p256, dummy patency capsule 1st that disintegrates if it gets stuck). *Barium enema* (rarely used): cobblestoning, 'rose thorn' ulcers ± colon strictures. *Colonoscopy* (fig 2) is preferred to barium enema to assess disease extent. *MRI* can assess pelvic disease and fistulae (as good as EUA). Small bowel *MRI* assesses disease activity and shows site of strictures.

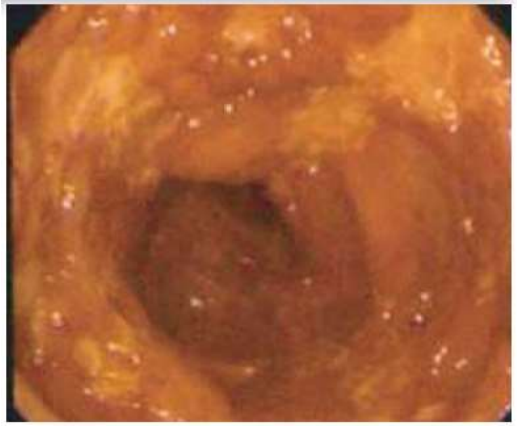
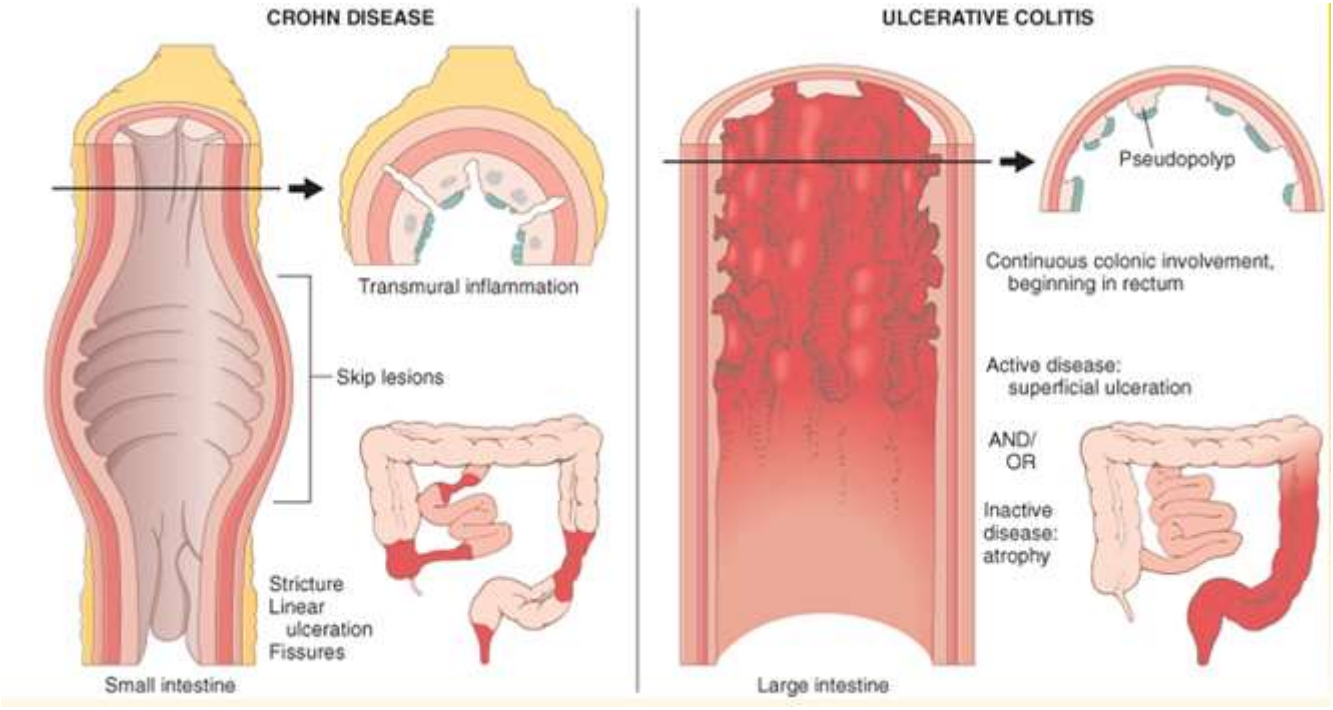
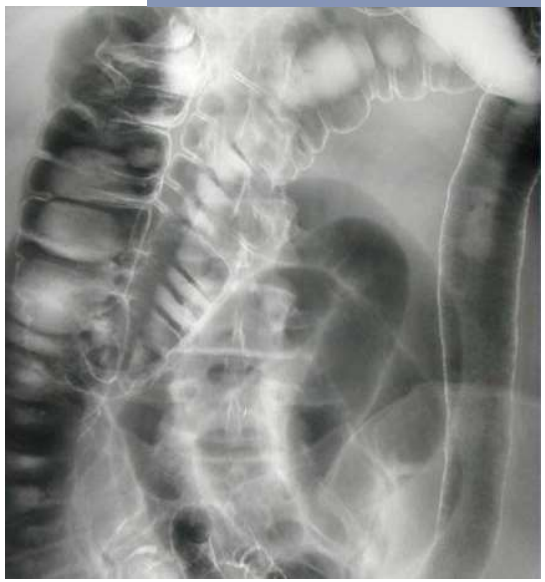


Fig 2. Deep fissured ulcers seen at colonoscopy. The end result? "My family does not or will not even talk to me about the disease ... I don't know when urgency to race for the bathroom will happen so I don't go out and have been living a hermit life..." ©Dr A Mee.

	Crohn Disease	Ulcerative Colitis
Site of origin	Terminal ileum	Rectum
Pattern of progression	"Skip" lesions/irregular	Proximally contiguous
Thickness of inflammation	Transmural	Submucosa or mucosa
Symptoms	Crampy abdominal pain	Bloody diarrhea
Complications	Fistulas, abscess, obstruction	Hemorrhage, toxic megacolon
Radiographic findings	String sign on barium x-ray	Lead pipe colon on barium x-ray
Risk of colon cancer	Slight increase	Marked increase
Surgery	For complications such as stricture	Curative

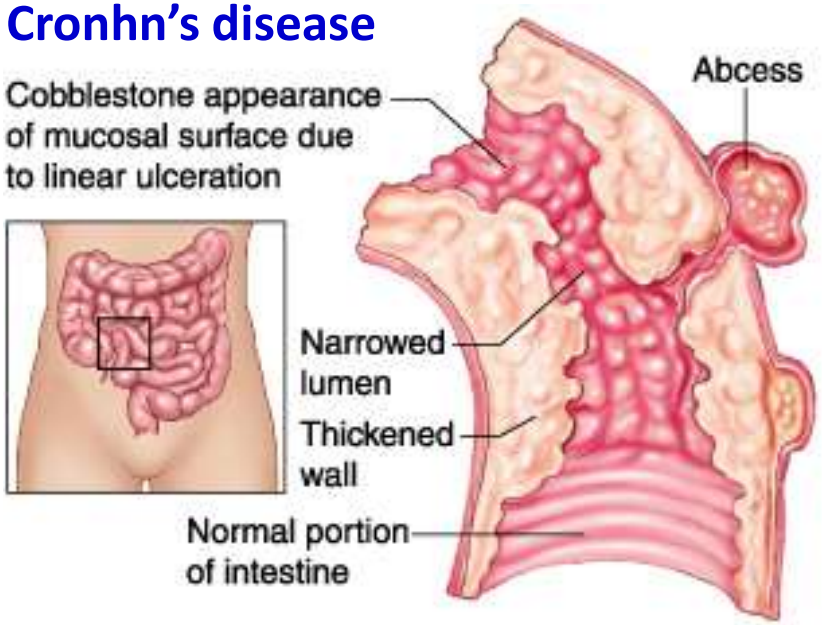


- Shortening of colon secondary to fibrosis
- Loss of haustration



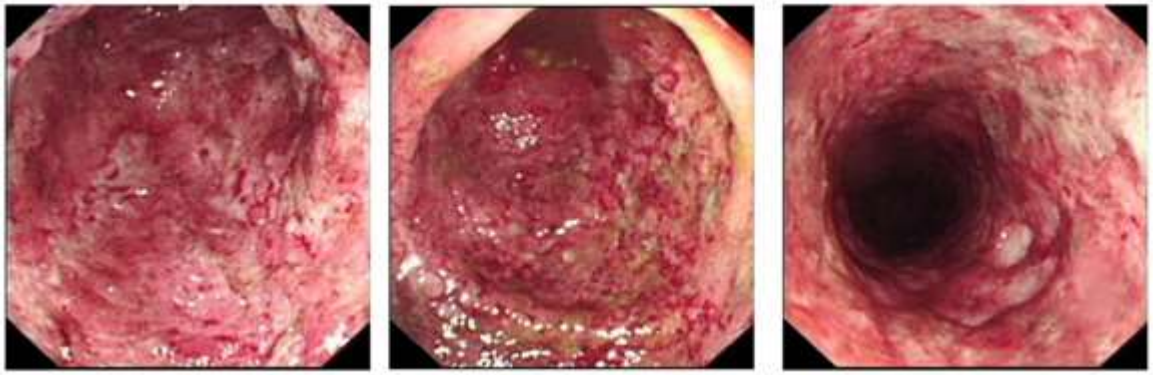
COLONSCOPY

Cronhn's disease



Skip lesions

Strictures



Pseudopolyps

Ulcerative colitis-inflammation and continuous ulceration throughout the colonic mucosa

FEATURES	CROHN'S DISEASE	ULCERATIVE COLITIS
Location	Any part of gastrointestinal tract	Colonic
Inflammation	Transmural	Mucosal/submucosal
Smoking	Smokers higher than expected	Appears to be protective
Risk of colorectal cancer	Elevated in colonic Crohn's	Elevated
Risk of intestinal cancer	Elevated in small-bowel Crohn's disease	NA
hsCRP	Elevation common	Elevation not common
Serology	ASCA, OmpC, CBir1	pANCA
Surgery	Recurrence common	Total proctocolectomy may be curative
Fistulas	Common	Very rare
FDA-approved biologic agents	Infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), natalizumab (Tysabri), vedolizumab (Entyvio)	Infliximab, adalimumab, golimumab, vedolizumab (Entyvio)
Immunomodulator therapy	Azathioprine (AZA, Imuran),[1] 6-mercaptopurine (6MP, Purinethol),[1] methotrexate (MTX, Trexall)[1]	AZA, 6MP, cyclosporine (Sandimmune, Neoral)[1]
Endoscopic features	Skip lesions	Contiguous involvement
Strictures	Common	Colorectal cancer unless proven otherwise
Genetic markers*	NOD2, ATG16L1, IRGM, IL23R, IL12B, STAT3, NKX2-3	IL12B, STAT3. NKX2-3

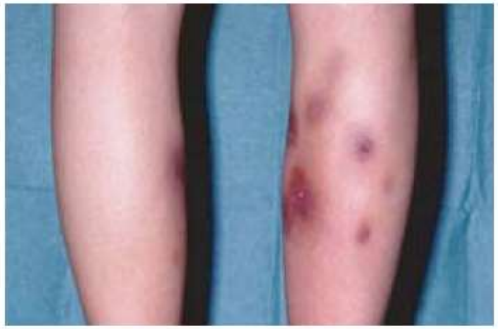
[1]Not FDA approved for this indication.
*Not approved for diagnosis. More than 50 genes have been associated with susceptibility to IBD.
Abbreviations: ASCA = anti–*Saccharomyces cerevisiae* antibodies; CBir1 = anti-flagellin antibody; FDA = U.S. Food and Drug Administration; hsCRP = high-sensitivity C-reactive protein; NA = not applicable; OmpC = anti-porin antibody; pANCA = perinuclear antineutrophilic cytoplasmic antibody.

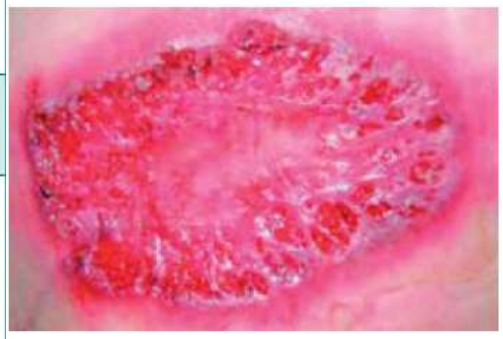
Serology studies, such as anti–*Saccharomyces cerevisiae* antibodies (ASCA), perinuclear antineutrophilic cytoplasmic antibody (pANCA), anti-porin antibody (OmpC), and anti-flagellin antibody (CBir1), are occasionally useful to predict disease behavior.

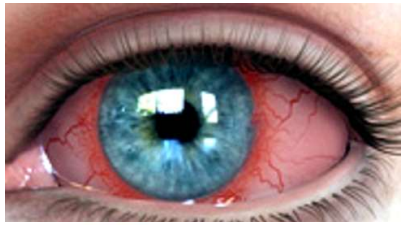
Lactoferrin and Calprotectin, which are inflammatory markers found in stool, can be used to assess for postoperative recurrence in patients with Crohn's disease. A few studies have demonstrated the utility of elevated inflammatory markers in predicting future clinical flares.

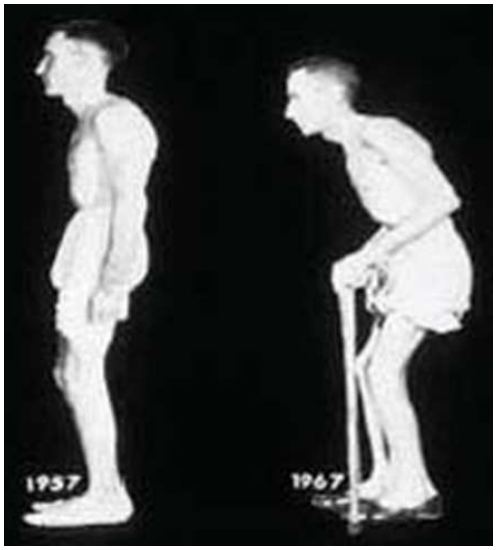
Table 16–2 • EXTRAINTESTINAL MANIFESTATIONS OF INFLAMMATORY BOWEL DISEASE

	CROHN DISEASE	ULCERATIVE COLITIS
Skin manifestations	Erythema nodosum: 15% Pyoderma gangrenosum: rare	Erythema nodosum: 10% Pyoderma gangrenosum: 1%-12%
Rheumatologic	Arthritis (polyarticular, asymmetric): common Ankylosing spondylitis: 10%	Arthritis: less common Ankylosing spondylitis: less common
Ocular	Uveitis: common (photophobia, blurred vision, headache)	Uveitis: common (photophobia, blurred vision, headache)
Hepatobiliary	Cholelithiasis fatty liver: common Primary sclerosing cholangitis: rare	**Fatty liver: common** **Primary sclerosing cholangitis: uncommon but more often than Crohn**
Urologic	Nephrolithiasis (10%-20%) after small bowel resection or ileostomy	









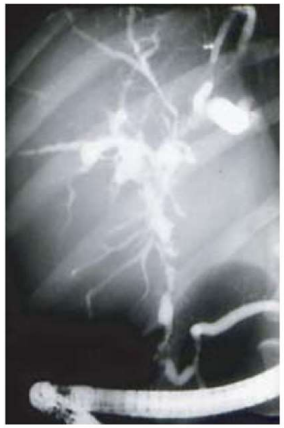


Fig 1. ERCP showing many strictures in the biliary tree with a characteristic 'beaded' appearance. *MRCP* (fig 2) is more cost effective.

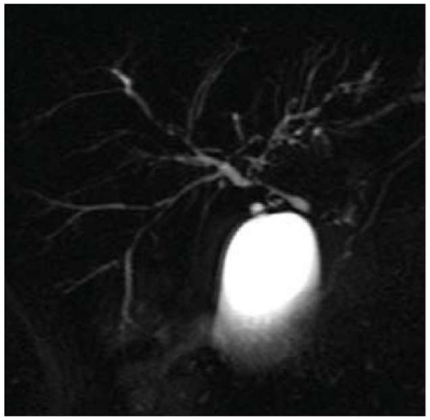


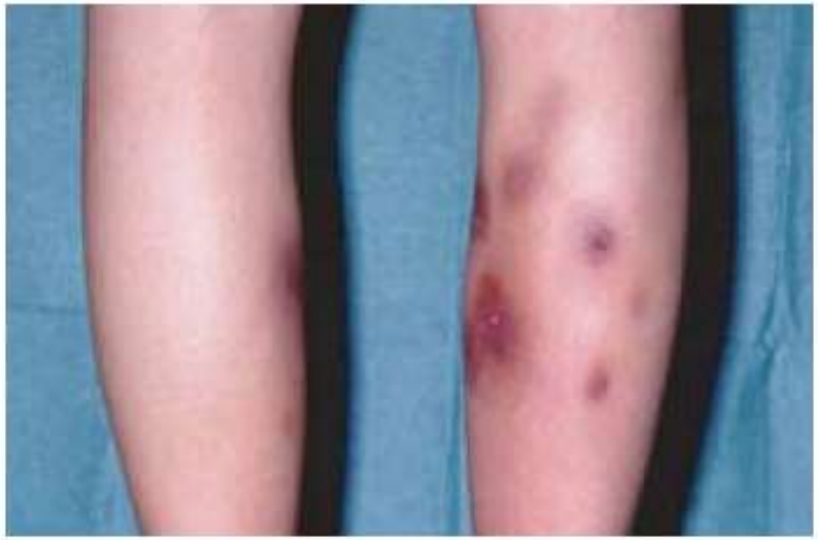
Fig 2. MRCP showing features of PSC. The intrahepatic ducts show multifocal strictures. (MRCP = magnetic resonance cholangiopancreatography). Strictures can be hard to differentiate from cholangiocarcinoma (coexistence of UC may promote this development). Stenting may be needed.

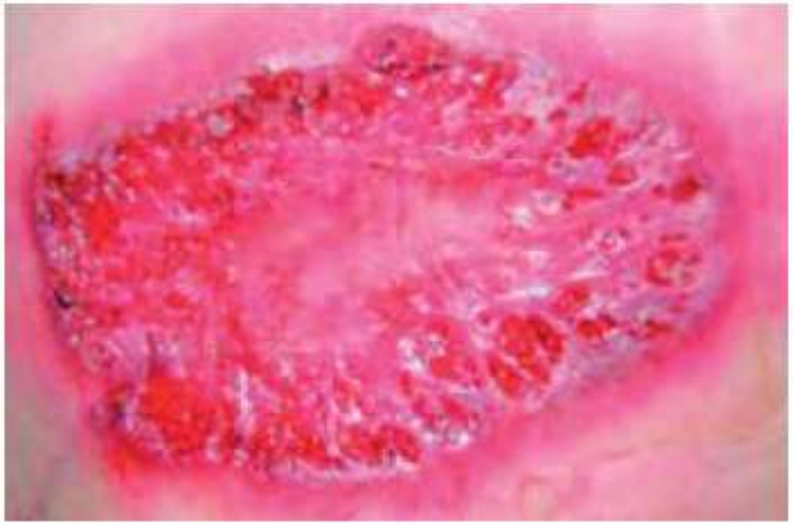
Calcium oxalate monohydrate.

Skin manifestations of systemic diseases

Crohn's Perianal/vulval/oral ulcers; erythema nodosum; pyoderma gangrenosum.

Erythema nodosum (fig 1) Painful, blue-red, raised lesions on shins (± thighs/arms). *Causes:* sarcoidosis, drugs (sulfonamides, the Pill, dapsone), streptococcal infection. *Less common:* Crohn's/UC, BCG vaccination, leptospirosis, *Mycobacterium* (TB, leprosy), *Yersinia* or various viruses and fungi. Cause unknown in 30–50%.



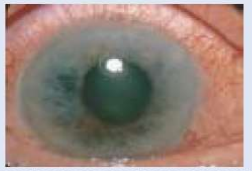
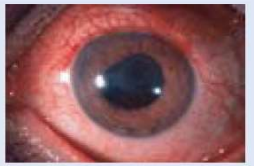
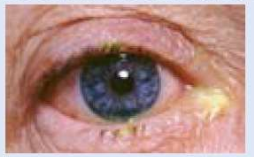


Pyoderma gangrenosum (fig 2) Recurring nodulo-pustular ulcers, ~10cm wide, with tender red/blue overhanging necrotic edge, purulent surface, and healing with cribriform scars on leg, abdomen, or face. *Associations:* UC/Crohn's, autoimmune hepatitis, Wegener's■, myeloma, neoplasia. ♀>♂. *Treatment:* Get help. Oral steroids ± ciclosporin should be 1st-line therapy.[78]

Systemic conditions causing eye signs

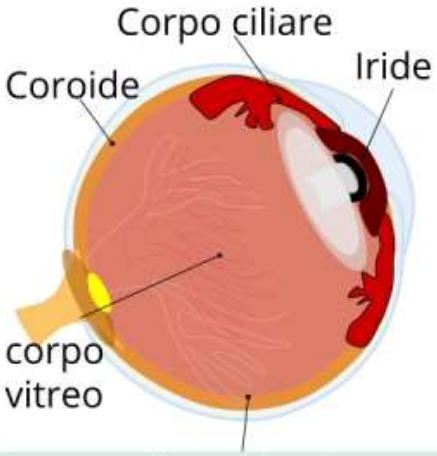
Systemic inflammatory diseases may manifest as iritis in ankylosing spondylitis and Reiter's■; *conjunctivitis* in Reiter's; *scleritis* or *episcleritis* in RA, vasculitis and SLE. Scleritis in RA and Wegener's■ may damage the eye. Refer urgently if eye pain. Giant cell arteritis causes optic nerve ischaemia presenting as sudden blindness.

Differential diagnosis of a red eye

	Conjunctiva	Iris	Pupil	Cornea	Anterior chamber	Intraocular pressure	Treatment	Appearance
Acute glaucoma	Both ciliary and conjunctival vessels injected. Entire eye is red. See *OHCS* p430.	Injected	Dilated, fixed, oval	Steamy, hazy	Very shallow	Very high	Refer. IV acetazolamide + pilocarpine drops (miotic); Peripheral iridotomy.	
Anterior uveitis (iritis)	Redness most marked around cornea, which doesn't blanch on pressure. Usually unilateral. *Causes:* AS, RA, Reiter's■, sarcoidosis, herpes simplex, herpes zoster, and Behçet's disease. NB: a similar scleral appearance but without papillary or anterior chamber involvement may be *scleritis* (eg RA, SLE, vasculitis).	Injected	Small, irregular due to adhesions between the anterior lens and the pupil margin	Normal	Turgid	Normal	Refer. Steroid eye drops (eg 0.5% prednisolone) + mydriatic (eg cyclopentolate 0.5%).	
Conjunctivitis	Often bilateral. Conjunctival vessels injected, greatest toward fornices, but blanching on pressure. Mobile over sclera. Purulent discharge.	Normal	Normal	Normal	Normal	Normal	Most do not require treatment. Consider chloramphenicol ointment or drops.	
Subconjunctival haemorrhage	Bright red sclera with white rim around limbus. *Causes:* BP↑; leptospirosis; bleeding disorders; trauma; snake venom; haemorrhagic fevers.	Normal	Normal	Normal	Normal	Normal	Looks alarming but resolves spontaneously. Check BP if elderly; Refer if traumatic; On warfarin?	

After RD Judge, GD Zuidema, FT Fitzgerald *Clinical diagnosis* 5/e, Little Brown, Boston. Images courtesy of Prof. Jonathan Trobe and ADB.

Uveite: infiammazione dell'uvea



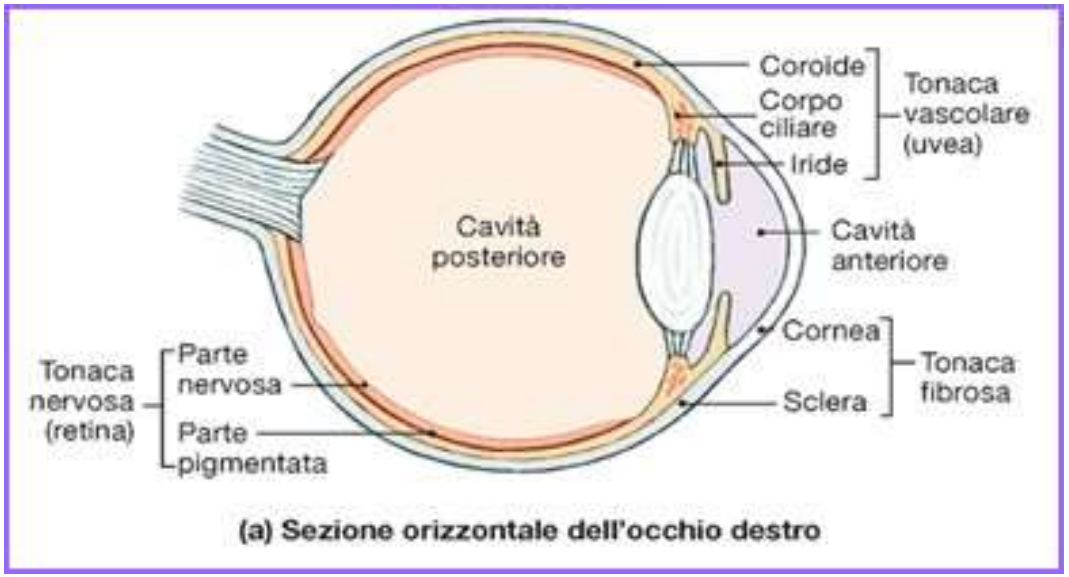
L'uvea è un rivestimento dell'occhio formato da coroide, corpo ciliare ed iride

L'uveite anteriore è l' infiammazione di iride e corpo ciliare

L'uveite posteriore è l' infiammazione della coroide

L'uveite intermedia è l' infiammazione della coroide e del corpo vitreo

L'uveite totale è l' infiammazione dell'intera uvea



(a) Sezione orizzontale dell'occhio destro

Test characteristics of anti-saccaromyces cervisiae antibodies (ASCA) and perinuclear antineutrophil cytoplasmic antibodies (pANCA) in the diagnosis of inflammatory bowel disease (IBD)

Antibody	Sensitivity, percent	Specificity, percent	PPV, percent
Sensitivity, specificity, and positive predictive value (PPV) in patients with IBD compared to non-IBD controls			
ASCA +	60	91	88
pANCA +	50	95	69
ASCA +/pANCA -	56	94	91
pANCA +/ASCA -	44	97	78
Sensitivity, specificity, and positive predictive value in differentiating ulcerative colitis (UC) from Crohn disease (CD) in patients with IBD*			
ASCA +/CD +	60	86	92
pANCA +/UC +	50	94	76
ASCA +/pANCA -/CD +	56	92	95
pANCA +/ASCA -/UC +	44	98	88

* Where CD + or UC +, the control group for comparison is the other type of IBD.

Data from: Peeters M, Joosens S, Vermeire S, et al. Diagnostic value of anti-Saccharomyces cerevisiae and antineutrophil cytoplasmic autoantibodies in inflammatory bowel disease. Am J Gastroenterol 2001; 96:730.

Positive Predictive Value (PPV).
It is the percentage of patients with a positive test who actually have the disease

Calprotectin in stool

- Calprotectin is a protein belonging to the S100 family and occurring in large amounts in neutrophil granulocytes, where it accounts for 5% of total proteins and 60% of cytoplasm proteins.
- When inflammatory processes occur, **calprotectin is released** due to the **degranulation of neutrophil granulocytes.** In bowel inflammation, calprotectin may be detected in the stool. The faecal assay provides direct information about the inflammation site, whereas with serum or plasma, inflammation might be located anywhere.
- **An increased Calprotectin concentration in stool** is the direct consequence of neutrophil degranulation due to mucosal damage. Faecal Calprotectin assay offers a number of advantages in the **detection of bowel inflammation.** In IBD patients, i.e. patients affected by **ulcerative colitis**, **Crohn's disease** and in the so-called **indeterminate colitis,** the calprotectin level **is generally very high**. In IBS subjects, the calprotectin level is lower if compared to patients with the active IBD, sometimes higher than the cut-off value but always higher than healthy subjects.

Laboratory evidence of nutritional deficiences reported in adults with inflammatory bowel disease

	Percent
Hypoalbuminemia	25 to 80
Anemia	60 to 80
Iron deficiency	39 to 81
Vitamin B12 deficiency•	20 to 60
Folic acid deficiency	36 to 54
Calcium deficiency	13
Magnesium deficiency	14 to 33
Potassium deficiency	6 to 20
Vitamin A deficiency	11
Vitamin D deficiency	75
Vitamin E deficiency	*
Vitamin K deficiency	*
Zinc deficiency	40 to 50
Copper deficiency	*
Vitamin C deficiency	*
Vitamin B1 (thiamine) deficiency[1]	32
Niacin deficiency	*

* Cases reported but prevalence not described.
• Frequency of vitamin B12 deficiency depends on extent of ileal involvement or ileal resection.
Adapted from: Perkal MF, Seashore JH. Nutrition and inflammatory bowel disease. Gastroenterol Clin N Am 1989; 18(3):567.

1. *Hwang C, Ross V, Mahadevan U. Micronutrient deficiencies in inflammatory bowel disease: from A to zinc. Inflamm Bowel Dis 2012; 18:1961.*

Iron Supplementation in IBD — Patients with IBD present unique challenges regarding iron supplementation. **Oral iron supplementation can potentially worsen symptoms and/or IBD activity.** The available data suggest that while many patients tolerate oral supplementation without worsening of disease activity, some develop gastrointestinal side effects, a subset of which may be attributable to worsening IBD disease activity . The percentage of patients who will be intolerant of oral iron has not been extensively studied, although some data suggest it may be as high as 25 percent. However, there are no established definitions or predictors of tolerance in IBD patients. Non-absorbed iron can worsen IBD symptoms and aggravate intestinal inflammation through the Fenton reaction, which releases reactive oxygen species. **Oral iron therapy also may be limited by malabsorption**, particularly in patients with intestinal mucosal disease. Together, these issues of intolerance and malabsorption can significantly limit the utility of oral iron for repletion of iron stores in patients with IBD, particularly in the face of ongoing losses. Finally, there is a **theoretical concern that oral iron might increase oxidative stress and thereby contribute to carcinogenesis in IBD** by augmenting oxidative damage and epithelial proliferation due to inflammation. This concern is mainly based on animal models. Whether these observations are clinically important in humans with IBD is unclear.

Throughout Europe and Great Britain, **intravenous (IV) rather than oral iron replacement is preferred for the treatment of iron deficiency complicating IBD**. IV iron is more effective, better tolerated, and improves quality of life to a greater extent with far fewer adverse events than oral iron.

Hyperoxaluria - Renal stones

- **Dietary calcium can decrease oxalate absorption in the gut by the formation of insoluble calcium oxalate salts in the intestinal lumen**.
- **When less calcium is available in the intestinal lumen to bind oxalate, oxalate absorption and urinary oxalate excretion increase.**

Relatively common settings in which this occurs include:

- low-calcium diet,
- increased intestinal calcium absorption as seen in hypercalciuria
- **malabsorption syndromes,** as with small bowel disease (eg, Crohn's disease), surgical bowel resection or diversion, including jejunoileal bypass for obesity (bariatric surgery), or cystic fibrosis

This last situation leads to the malabsorption of fatty acids and bile salts, and is called **enteric hyperoxaluria**. The increase in oxalate absorption and subsequent excretion is due both to **(a)** binding of free calcium to fatty acids in the intestinal lumen and to **(b)** increased colonic permeability to small molecules such as oxalate induced by exposure of the colon to nonabsorbed bile salts .

Patients with malabsorption may have additional factors predisposing to stone formation other than increased oxalate excretion (which can be as high as 80 to 200 mg [0.9 to 2.2 mmol] per day). The **(c)** diarrheal fluid losses can lead both to a reduction in urine volume and, **(d)** if the patient has a metabolic acidosis, a low urine pH and a marked decrease in citrate excretion; these changes can promote uric acid as well as calcium oxalate stone formation.

Crohn’s disease: Calcium oxalate and uric acid kidney stones can result from steatorrhea and diarrhea . Uric acid stones can result from dehydration and metabolic acidosis.

Pharmacologic Therapy

Although ulcerative colitis and Crohn disease appear to be distinct entities, the same pharmacologic agents are used to treat both. Despite extensive research, there are still no specific therapies for these diseases. The mainstays of therapy are 5-aminosalicylic acid derivatives, corticosteroids, immunomodulating agents (such as mercaptopurine or azathioprine and methotrexate), and biologic agents.

Treatments for Crohn disease

Medications

- Loperamide, atropine, or tincture of opium for symptomatic diarrhea
- Broad-spectrum antibiotics if bacterial overgrowth or microperforations with exacerbations
- 5-Aminosalicylic acid agents such as mesalamine work for colonic but not small bowel disease
- Ileal-release preparation budesonide
- Corticosteroids such as prednisone are the mainstay for treatment of severe exacerbations
- Immunomodulatory drugs such as azathioprine, mercaptopurine, infliximab, or methotrexate

Surgery

- Indications for surgery: intractability to therapy, intraabdominal abscess, bleeding, obstruction

Therapeutic Procedures

- Diet high in fiber and low in fat and lactose; vitamin B_{12} supplementation

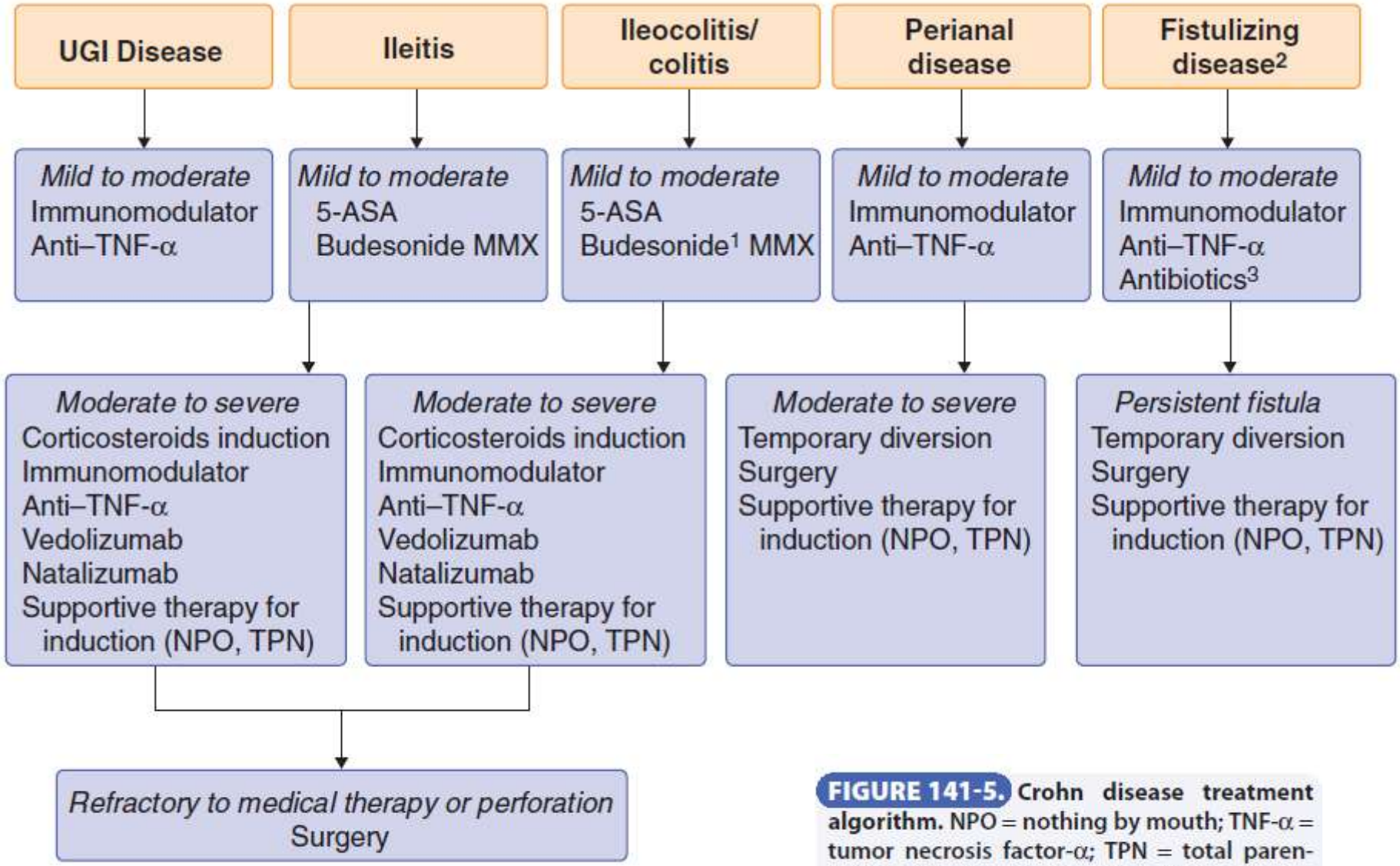


FIGURE 141-5. Crohn disease treatment algorithm. NPO = nothing by mouth; TNF-α = tumor necrosis factor-α; TPN = total parenteral nutrition; UGI = upper gastrointestinal.

[1]Proximal colon disease involvement.
[2]Abscess should be excluded before initiating medical therapy.
[3]Perianal location.

Cecil's 2016

Ulcerative Colitis

Proctitis

- Initial treatment choices
  - Mesalamine suppositories (Canasa) or enemas (Rowasa) to induce remission
  - Steroid foam enemas (Cortifoam) to induce remission
  - Mesalamine suppositories or enemas to maintain remission
- Second-line treatment choices
  - Oral mesalamine in combination with local therapy
  - Adjunctive treatment with antibiotics: ciprofloxacin (Cipro),[1] metronidazole (Flagyl),[1] or rifaximin (Xifaxan)[1]
  - Probiotics

Left-Sided Colitis

- Initial treatment choices
  - Oral mesalamine product with or without local therapy
- Second-line treatment choices
  - Oral or intravenous steroids budesonide (Uceris)
  - Immunomodulator therapy
  - Infliximab (IFX, Remicade), adalimumab (Humira), golimumab (Simponi)
  - Cyclosporine (Sandimmune)[1] on an inpatient basis (avoid cyclosporine after IFX therapy due to risk of severe immunosuppression)

Pancolitis

- Initial treatment choices
  - Oral mesalamine with a short course of oral or intravenous steroids including colonic-release budesonide
- Second-line treatment choices
  - Immunomodulator therapy
  - Infliximab, adalimumab, golimumab
  - Cyclosporine on an inpatient basis (avoid cyclosporine after IFX therapy due to risk of severe immunosuppression)

Crohn's Disease

Ileocecal Inflammatory Crohn's Disease

- First-line treatment
  - Oral mesalamine (ileo-colonic release mesalamine product for ileal disease; Pentasa for more proximal small-bowel disease)[1]
  - Budesonide (Entocort EC) 9 mg PO qd
  - Immunomodulator therapy
  - Biologic agents with or without concomitant immunomodulators

Ileal Stricturing Disease

- No proximal dilation
  - Trial with budesonide or biologic agents (patients with elevated hsCRP are more likely to respond)
- Proximal small-bowel dilation
  - Consider surgical approach

Internally Fistulizing Disease without Intraabdominal Abscess

- Stricture immediately distal to fistula
  - Surgical approach
- No stricture
  - Biologic agents with or without concomitant immunomodulators

Externally Fistulizing Disease without Intraabdominal Abscess

- Biologic agents with or without concomitant immunomodulators

Fistulizing Disease with Intraabdominal Abscess

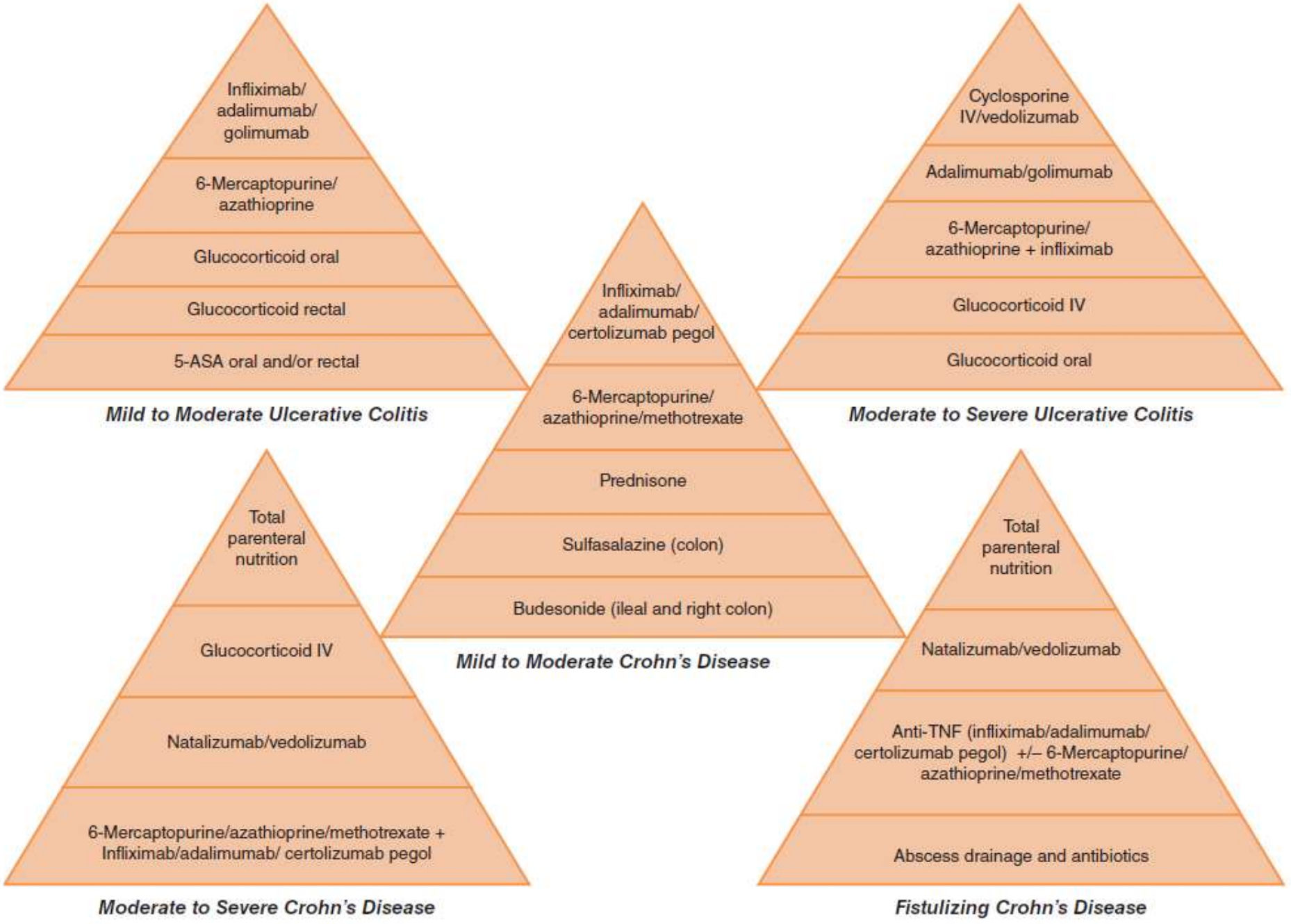
- Intravenous antibiotics as appropriate
- Percutaneous drainage if appropriate
- Surgical drainage if indicated
- Biologic agents with or without concomitant immunomodulators once infectious process has been treated

Perianal Crohn's Disease without Abscess Formation

- Antibiotics: Ciprofloxacin (Cipro),[1] metronidazole (Flagyl),[1] rifaximin (Xifaxan)[1]
- Immunomodulators
- Biologic agents with or without concomitant immunomodulators
- Seton placement
- Diverting ostomy

Colonic Crohn's Disease

- Oral steroids to induce remission
- Immunomodulator therapy
- Biologic agents with or without concomitant immunomodulator therapy



Harrison's 2015

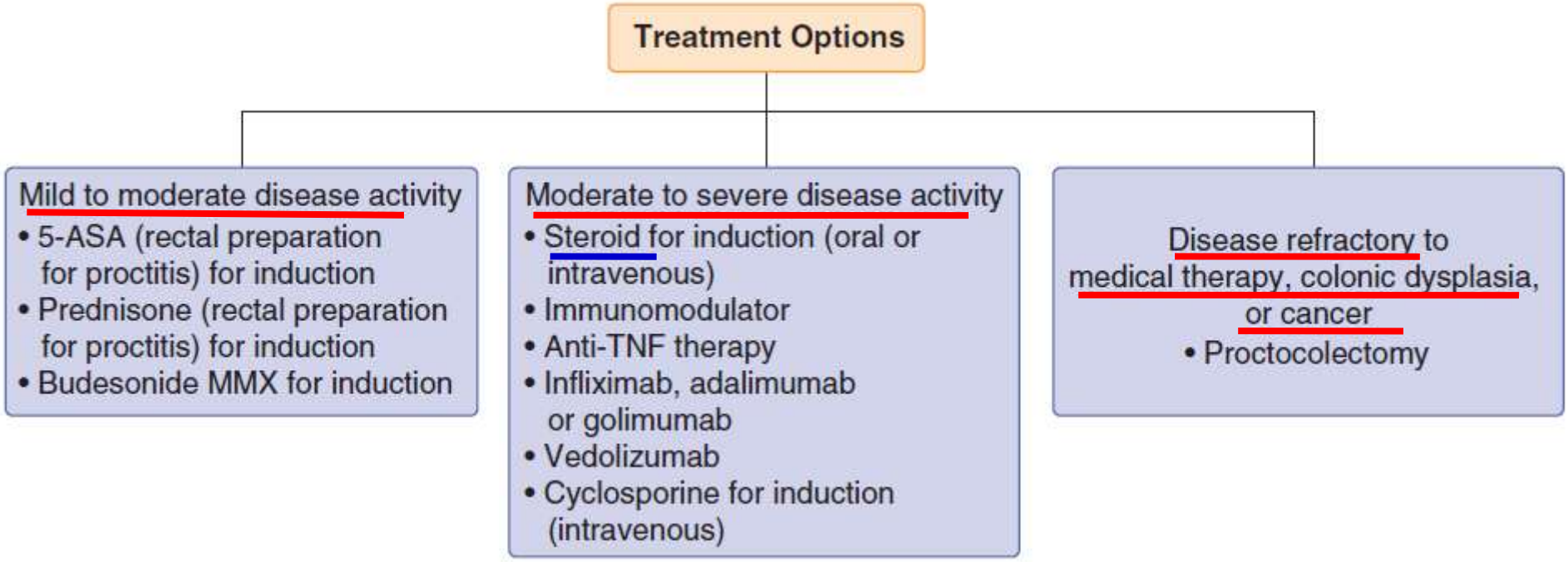


FIGURE 141-4. Ulcerative colitis treatment algorithm.

Cecil's 2016

16.1 A 32-year-old woman has a history of chronic diarrhea and gallstones and now has rectovaginal fistula. Which of the following is the most likely diagnosis?

A. Crohn disease
B. Ulcerative colitis
C. Systemic lupus erythematosus
D. Laxative abuse

16.2 A 45-year-old man with a history of ulcerative colitis is admitted to the hospital with 2 to 3 weeks of right-upper quadrant abdominal pain, jaundice, and pruritus. He has no fever and a normal WBC count. Endoscopic retrograde cholangiopancreatography (ERCP) shows multifocal strictures of both the intrahepatic and extrahepatic bile ducts with intervening segments of normal and dilated ducts. Which of the following is the most likely diagnosis?

A. Acute suppurative cholangitis
B. Cholangiocarcinoma
C. Primary sclerosing cholangitis (PSC)
D. Choledocholithiasis with resultant biliary strictures

16.3 A 25-year-old man is hospitalized for ulcerative colitis. He has now developed abdominal distention, fever, and transverse colonic dilation of 7 cm on x-ray. Which of the following is the best next step?

A. 5-ASA
B. Steroids
C. Antibiotics and prompt surgical consultation
D. Infliximab

16.4 A 35-year-old woman has chronic crampy abdominal pain and intermittent constipation and diarrhea, but no weight loss or gastrointestinal bleeding. Her abdominal pain is usually relieved with defection. Colonoscopy and upper endoscopy with biopsies are normal, and stool cultures are negative. Which of the following is the most likely diagnosis?

A. Infectious colitis
B. Irritable bowel syndrome
C. Crohn disease
D. Ulcerative colitis

16.1 **A.** Fistulas are common with Crohn disease because of its transmural nature but are uncommon in ulcerative colitis. Gallstones are common in patients with Crohn disease due to ileal bile salt malabsorption and depletion, causing the formation of more cholesterol-rich lithogenic bile.

16.2 **C.** The ERCP shows the typical appearance for primary sclerosing cholangitis (PSC), which is associated with IBD in 75% of cases. Stone-induced strictures should be extrahepatic and unifocal. Cholangiocarcinoma is less common but may develop in 10% of patients with PSC.

16.3 **C.** With toxic megacolon, antibiotics and surgical intervention are often necessary and life saving. Medical therapy is usually ineffective.

16.4 **B.** Irritable bowel syndrome is characterized by intermittent diarrhea and crampy abdominal pain often relieved with defecation, but no weight loss or abnormal blood in the stool. It is a diagnosis of exclusion once other conditions, such as inflammatory bowel disease and parasitic infection (eg, giardiasis), have been excluded.

REVIEW QUESTIONS

1. Which one of the following complications is a known consequence of long-standing ulcerative colitis?

   A. Fecaluria (as a manifestation of fistula formation to the bladder from adjacent loops of bowel)
   B. Perianal abscess formation
   C. Colonic stricture formation with subsequent small bowel obstruction
   D. Development of dysplasia and carcinoma
   E. Development of left-sided hydoureter

Answer: D The transmural inflammatory process of Crohn disease (but not ulcerative colitis) predisposes to the formation of fistulas, and the presence of fistulae signifies that the transmural inflammation has penetrated into adjacent organs, tissue, or skin. Ulcerative colitis is limited to the colon and, unlike Crohn disease, does not cause perianal abscesses. In Crohn disease, inflammation can lead to ileal or colonic strictures, and marked inflammation can cause local reactions that have a mass effect and lead to obstruction of the right ureter, where the ileum and the ureter cross anatomically. Patients with ulcerative colitis do not develop strictures or hydroureter. Dysplasia and carcinoma may develop in patients with longstanding Crohn disease but are much more typical of ulcerative colitis. This risk provides the rationale for endoscopic surveillance of patients with long-standing inflammatory bowel disease.

2. Which one of the following features is most typical for ulcerative colitis?

   A. Deep serpiginous ulcers
   B. Aphthous ulcers
   C. Pseudopolyps
   D. Fistulas
   E. Colonic stricturing

Answer: C Pseudopolyps are typically found in patients with ulcerative colitis, not in patients with Crohn disease. Typical radiologic and endoscopic features of Crohn disease include deep linear ulcers and superficial or aphthous ulcers overlying lymphoid follicles. The presence of fistulas should signal the presence of Crohn disease. Patients with Crohn disease may have strictures, which are not classically seen in ulcerative colitis. When strictures are observed in patients with ulcerative colitis, coexisting colorectal cancer should be suspected.

3. Which one of the following statements regarding mesalamine (5-ASA) is true?

   A. Oral mesalamine is effective for the induction and for the maintenance of remission in patients who have Crohn disease with a colonic disease distribution.
   B. Topical mesalamine for ulcerative proctitis (suppositories) and for left-sided ulcerative colitis (enemas) is effective for the induction and maintenance of remission.
   C. Mesalamine is first-line therapy for patients with moderate to severe ulcerative colitis.
   D. Mesalamine is efficacious as primary therapy for perianal fistulizing Crohn disease when active disease is present in the rectum.
   E. A combination of topical and oral mesalamine therapy in patients with left-sided Crohn disease is more effective than topical or oral mesalamine alone.

Answer: B Oral mesalamine is effective for inducing and maintaining remission in mild to moderate ulcerative colitis. Mesalamine suppositories treat the lower 10 to 20 cm of the colon but do not reach the left colon or splenic flexure; they are extremely effective for inducing and maintaining remission in ulcerative proctitis. In contrast, mesalamine liquid enemas will reach the left colon and as high as the splenic flexure; they are extremely effective for inducing and maintaining remission in left-sided ulcerative colitis. Both oral and topical therapies are effective for treating patients with active ulcerative colitis, and the combination of topical and oral mesalamine therapy is more effective than either mesalamine therapy alone in patients with left-sided ulcerative colitis. Mesalamine is no more effective than placebo for inducing or maintaining remission in Crohn disease patients.

Find out how your patient deals with what may be a brutal disease (no intimacy...no sex...no hope..."I live with this alone and will die alone"). With a collaborative approach, courage, attention to detail and a dose of humour, this can change. Help quit smoking. ►*Optimize nutrition* (BOX). Assess severity: T°↑, pulse↑, ↑ESR, ↑WCC, ↑CRP + ↓albumin may merit admission (esp. if he looks ill). NB: the liver often switches to making CRP-type proteins rather than albumin. Specific options: aminosalicylates, steroids, immunosuppressants, TNF inhibitors, antibiotics, diet/supplements.

Mild attacks: (Symptomatic but systemically well). *Prednisolone* 30mg/d PO for 1wk, then 20mg/d for 4wks. See in clinic 3-weekly. If symptoms resolve, ↓prednisolone by 5mg every 2–4 weeks; stop steroids when parameters are normal (see also BOX).

Severe: Looks ill. Admit for IV steroids, nil by mouth, and IVI (eg 1L 0.9% saline + 2L dextrose-saline/24h, + 20mmol K^+/L, less if elderly). *Hydrocortisone* 100mg/6h IV.

- Treat rectal disease: steroids, eg *hydrocortisone* 100mg in 100mL 0.9% saline/12h PR.
- *Metronidazole* 400mg/8h PO, or 500mg/8h IV, helps (esp. in perianal disease or superadded infection). SEs: alcohol intolerance; irreversible neuropathy.
- Monitor T°, pulse, BP, and record stool frequency/character on a stool chart.
- Physical examination daily. Daily FBC, ESR, CRP, U&E, and plain AXR.
- Consider need for blood transfusion (if Hb <100g/L) and parenteral nutrition.
- If improving after 5d, transfer on to oral *prednisolone* (40mg/d). If not, *infliximab* and *adalimumab* have a role (esp. in fistulizing Crohn's). CI: CCF; infection. NICE 2010
- Consider abdominal sepsis complicating Crohn's disease especially if abdominal pain (ultrasound, CT & MRI are often required to assess this). Seek surgical advice.

Perianal disease occurs in about 50%. MRI and examination under anaesthetic (EUA) are an important part of assessment. Treatment includes oral antibiotics, immunosuppressant therapy ± *infliximab*, and local surgery ± seton insertion.[207]

Additional therapies in Crohn's disease (useful in ≤50% of patients)

Azathioprine (AZA) (2–2.5mg/kg/d PO) can be a used as a steroid-sparing agent, eg if steroid SEs, and if there are multiple/rapid relapses. It takes 6–10 weeks to work.[210] Steroids are so disappointing in the long term that *early combined immunosuppression* (azathioprine + infliximab ± steroids) is a tempting early option ('reversing the pyramid'). But evidence is scant; get expert advice.[211, 212]

Sulfasalazine Efficacy of 5-ASA in Crohn's is unproven but high-dose PENTASA post-op in patients with ileal resection may ↓recurrent disease.

TNFα inhibitors TNFα plays an important role in pathogenesis of Crohn's disease, therefore TNFα inhibitors, eg *infliximab* and *adalimumab*, can ↓disease activity. They counter neutrophil accumulation and granuloma formation, activate complement, and cause cytotoxicity to CD4+ T-cells, thus clearing cells driving the immune response. Response may be short-lived, but it may be repeated at 8wks. Trials have also shown it to be effective as maintenance therapy.[213] CI: Sepsis, ↑LFT >3-fold above top end of normal, concurrent *ciclosporin* or *tacrolimus*. SE: Rash. Avoid in people with known underlying malignancy.[214] TB may reactivate when on infliximab, so screen patients before starting the treatment (CXR, PPD). Cost per QALY: (see p10) £6700 (higher in fistulizing Crohn's).[215] According to SONIC trial, combined AZA and infliximab can ↑ efficacy of Rx at 12 months, but there are long-term safety issues (eg hepatosplenic T cell lymphomas).

Methotrexate A large randomized trial recommended 25mg IM weekly for remission induction, enabling complete withdrawal from steroids in patients with refractory Crohn's. NNT ≈ 5—see p669. There was no evidence for lower doses, and no substantial SE were found.[216] Methotrexate is contraindicated in pregnancy.

Nutrition Enteral is preferred (eg polymeric diet); consider TPN as a last resort. *Elemental diets* (E028®) contain amino acids and can give remission.[217, 218] Low residue diets help control Crohn's activity, but won't on their own give remission.

Antibiotics such as rifaximin EIR (extended intestinal release) 800mg/d PO gave a remission in one RCT.[219] Probiotics (eg lactobacilli): no randomized data.[220]

IV immunoglobulin Small series report rapid benefit (no randomized trials).[221]

Surgery 50–80% need ≥1 operation in their life. It never cures. In the severely affected, it can become a devastating cycle of deterioration. Indications: drug failure (most common); GI obstruction from stricture; perforation; fistulae; abscess. Surgical aims are: 1 to defunction (rest) distal disease, eg with a temporary ileostomy or 2 resection of the worst areas—but see short bowel syndrome, p582.[222] Bypass and pouch surgery is not done in Crohn's (∴ ↑risk of recurrence).

Poor prognosis if: Age <30yrs (onset age is bimodal: peaks 20–30yrs and 60–70); steroids needed at 1st presentation; perianal disease; diffuse small bowel disease.

A. 5-Aminosalicylic Acid (5-ASA)

5-ASA is a topically active agent that has a variety of anti-inflammatory effects. It is used in the active treatment of ulcerative colitis and Crohn disease and during disease inactivity to maintain remission. It is readily absorbed from the small intestine but demonstrates minimal colonic absorption. A number of oral and topical compounds have been designed to target delivery of 5-ASA to the colon or small intestine while minimizing absorption. Commonly used formulations of 5-ASA are sulfasalazine, mesalamine, and azo compounds. Side effects of these compounds are uncommon but include nausea, rash, diarrhea, pancreatitis, and acute interstitial nephritis.

	Systemic Activity
Prednisone	4–5
Triamcinolone	5
Triamcinolone acetonide	5
Dexamethasone	30–120
Betamethasone	30
Betamethasone valerate	—
Methylprednisolone	5
Fluocinolone acetonide	—
Flurandrenolide	—
Deflazacort	3–4

[1]Hydrocortisone = 1 in potency.

Conversione degli Steroidi

Idrocortisone **flebocortid**	20	40	60	80	100	120	140	160	200	400	625	2.500	5.000	10.000
Prednisone **deltacortene**	**5**	10	15	20	25	30	35	40	50	100	156	625	1.250	2.500
Prednisolone	5	10	15	20	25	30	35	40	50	100	156	625	1.250	2.500
Triamcinolone **ledercort**	4	8	12	16	20	24	28	32	40	80	125	500	1.000	2.000
Metilprednisolone **depo-medrol** **solu-medrol** **medrol** **urbason**	4	8	12	16	20	24	28	32	40	80	125	500	1.000	2.000
Betametasone **bentelan** **celestone**	0.75	1.5	2.25	3	3.75	4.5	5.25	6	7.5	15	23.5	94	188	375
Desametasone **soldesam**	0.7	1.5	2.25	3	3.75	4.5	5.25	6	7.5	15	23.5	94	188	375
Deflazacort **flantadin** **deflan**	6	12	18	24	30	36	42	48	60	120	188	750	1.500	3.000

Management of patients receiving systemic corticosteroids.

Recommendations for prescribing

- Do not administer corticosteroids unless absolutely indicated or more conservative measures have failed.
- Keep dosage and duration of administration to the minimum required for adequate treatment.

Monitoring recommendations

- Screen for tuberculosis with a purified protein derivative (PPD) test or chest radiograph before commencing long-term corticosteroid therapy.
- Screen for diabetes mellitus before treatment and at each clinician visit.
  - Have patient test urine weekly for glucose.
  - Teach patient about the symptoms of hyperglycemia.
- Screen for hypertension before treatment and at each clinician visit.
- Screen for glaucoma and cataracts before treatment, 3 months after treatment inception, and then at least yearly.
- Monitor plasma potassium for hypokalemia and treat as indicated.
- Obtain bone densitometry before treatment and then periodically. Treat osteoporosis.
- Weigh daily. Use dietary measures to avoid obesity and optimize nutrition.
- Measure height frequently to document the degree of axial spine demineralization and compression.
- Watch for fungal or yeast infections of skin, nails, mouth, vagina, and rectum, and treat appropriately.
- With dosage reduction, watch for signs of adrenal insufficiency or corticosteroid withdrawal syndrome.

Patient information

- Prepare the patient and family for possible adverse effects on mood, memory, and cognitive function.
- Inform the patient about other possible side effects, particularly weight gain, osteoporosis, and aseptic necrosis of bone.
- Counsel to avoid smoking and excessive ethanol consumption.

Prophylactic measures

- Institute a vigorous physical exercise and isometric regimen tailored to each patient's disabilities.
- Administer calcium (1 g elemental calcium) and vitamin D_3, 400–800 international units orally daily.
  - Check spot morning urines for calcium; alter dosage to keep urine calcium concentration < 30 mg/dL (< 7.5 mmol/L).
  - If the patient is receiving thiazide diuretics, check for hypercalcemia, and administer only 500 mg elemental calcium daily.
  - Consider a bisphosphonate such as alendronate (70 mg orally weekly) or periodic intravenous infusions of pamidronate or zoledronic acid.
- Avoid prolonged bed rest that will accelerate muscle weakness and bone mineral loss. Ambulate early after fractures.
- Avoid elective surgery, if possible. Vitamin A in a daily dose of 20,000 units orally for 1 week may improve wound healing, but it is not prescribed in pregnancy.
- Avoid activities that could cause falls or other trauma.
- For ulcer prophylaxis, if administering corticosteroids with nonsteroidals, prescribe a proton pump inhibitor (not required for corticosteroids alone). Avoid large doses of antacids containing aluminum hydroxide (many popular brands) because aluminum hydroxide binds phosphate and may cause a hypophosphatemic osteomalacia that can compound corticosteroid osteoporosis.
- Treat hypogonadism.
- Treat infections aggressively. Consider unusual pathogens.
- Treat edema as indicated.