

Independent work

Gastroenterology – Crohn's Disease

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Crohn's Disease

Aim of this module

To increase the understanding of Crohn's disease by looking at the underlying pathology and causes and then moving on to use this information to understand the different clinical presentations and subsequent treatment options.

Learning outcomes

By the end of this module, you should understand:

- *The pathological features of Crohn's disease
- *The epidemiology and natural history of the disease
- *The complex aetiology of the disease
- *The varying clinical presentations of the disease as well as how to make a diagnosis
- *The principles of managing the disease both medically and surgically.

How to use this module

This module is designed by a student for students. The data is up-to-date and the references and reading list are at the end.

The module is divided into sections to allow for the content to be tackled in bite-sized chunks. At the end of each section is a set of questions such as true/false, multiple choice and fill in the blanks. Please have paper and a pen handy to write down your answers. This is designed to see how well you have understood the section to allow you to gauge the depth of your learning.

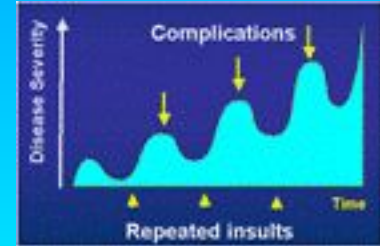
At the end of the module is a series of clinical case studies and extended matching questions for you to put the information you have learnt into practise and see how you do.

I hope you enjoy it!

Epidemiology & Pathology of Crohn's Disease

Epidemiology

- Crohn's disease (CD) is a chronic relapsing inflammatory condition usually with flare-ups alternating with periods of remission, and an increasing disease severity and incidence of complications as time goes on.
- It can affect any part of the gastrointestinal tract from the mouth to the anus. For typical sites & proportion of patients affected see below:



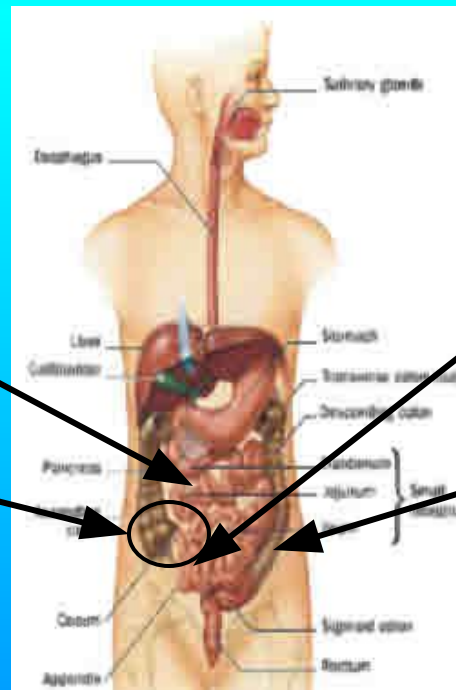
Extensive Small
Bowel – 5%

Ileocaecal – 45%

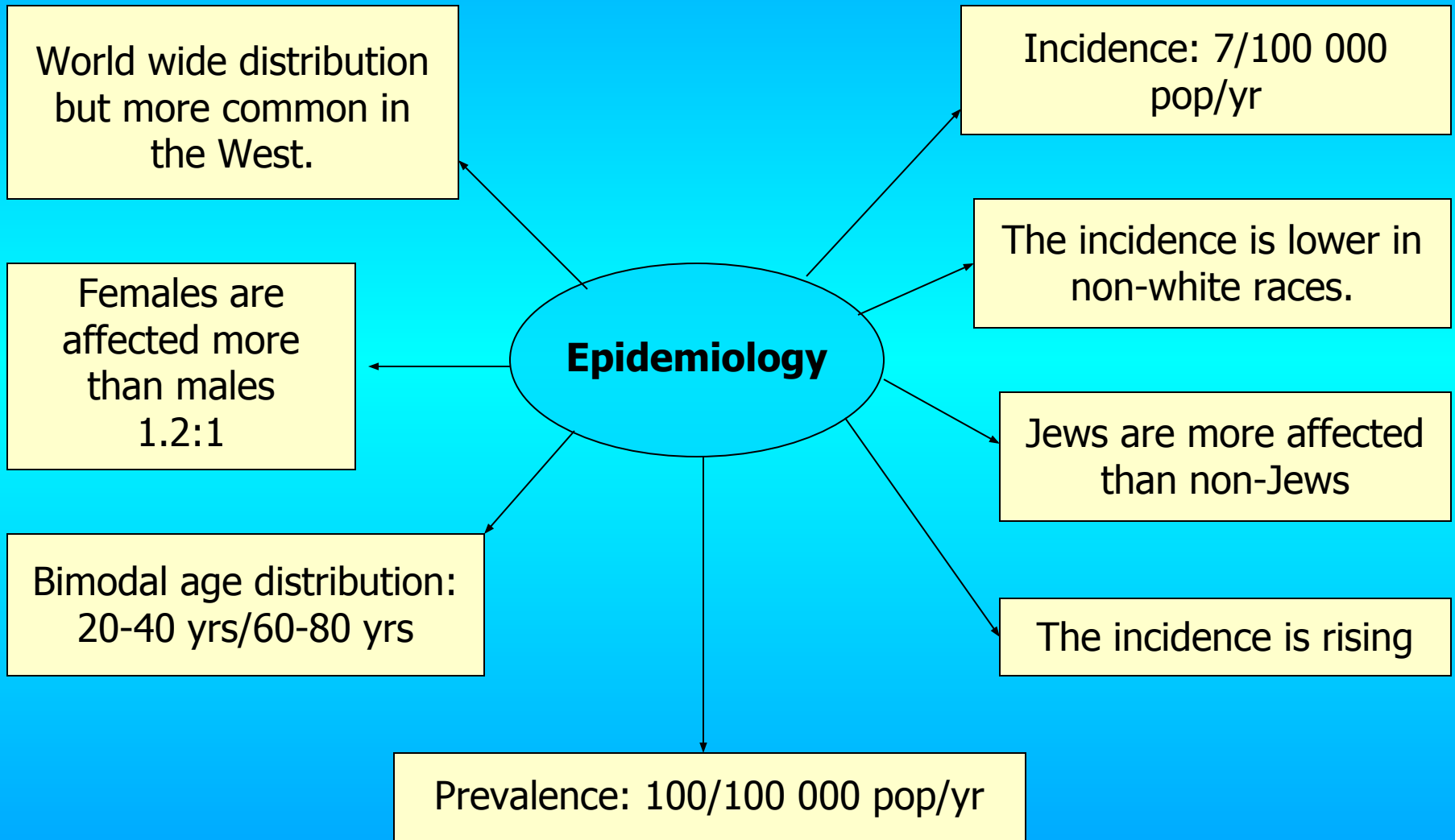
Terminal Ileum
only – 20%

Colon only – 25%

Other: anorectal,
gastroduodenal, oral only
– 5%



Epidemiology



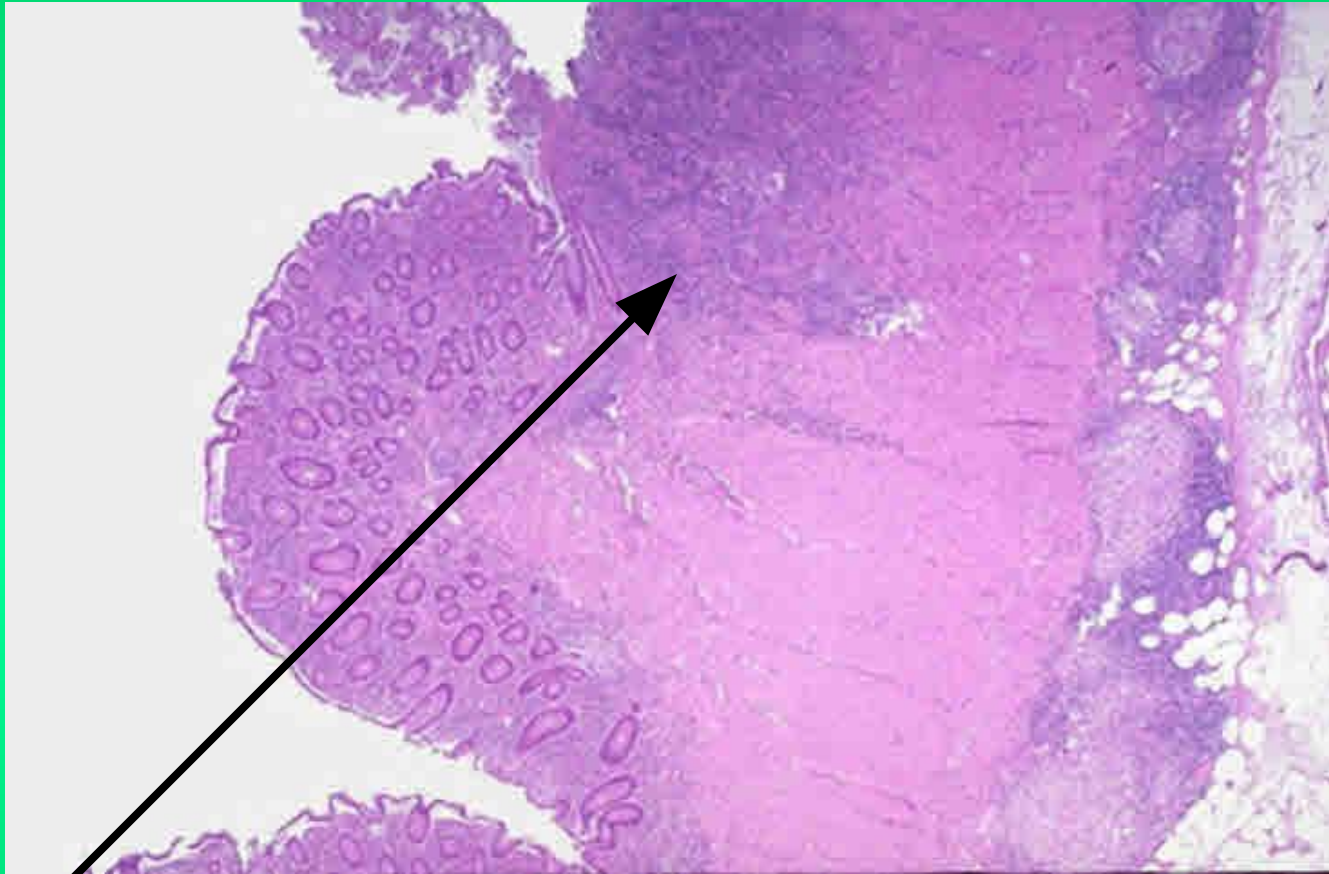
Pathology

CLICK ON THE PICTURES FOR A LARGER VIEW & DESCRIPTION

- ❖ It is characterised by patchy transmural inflammation.
- ❖ The chronic inflammatory process leads to thickening of the bowel wall and can cause a narrowed lumen.
- ❖ In early CD there are prominent lymphoid follicles followed by aphthoid ulceration. Later this progresses to larger deep fissuring ulcers separated by normal looking mucosa (cobble-stoning), fibrosis, stricturing and fistulation. These changes are often segmentally distributed (skip lesions).



Histology: Transmural Inflammation



Here, inflammatory cells extend from mucosa through submucosa and muscularis and appear as nodular infiltrates on the serosal surface with pale granulomatous centres.

Gross view: Terminal Ileum

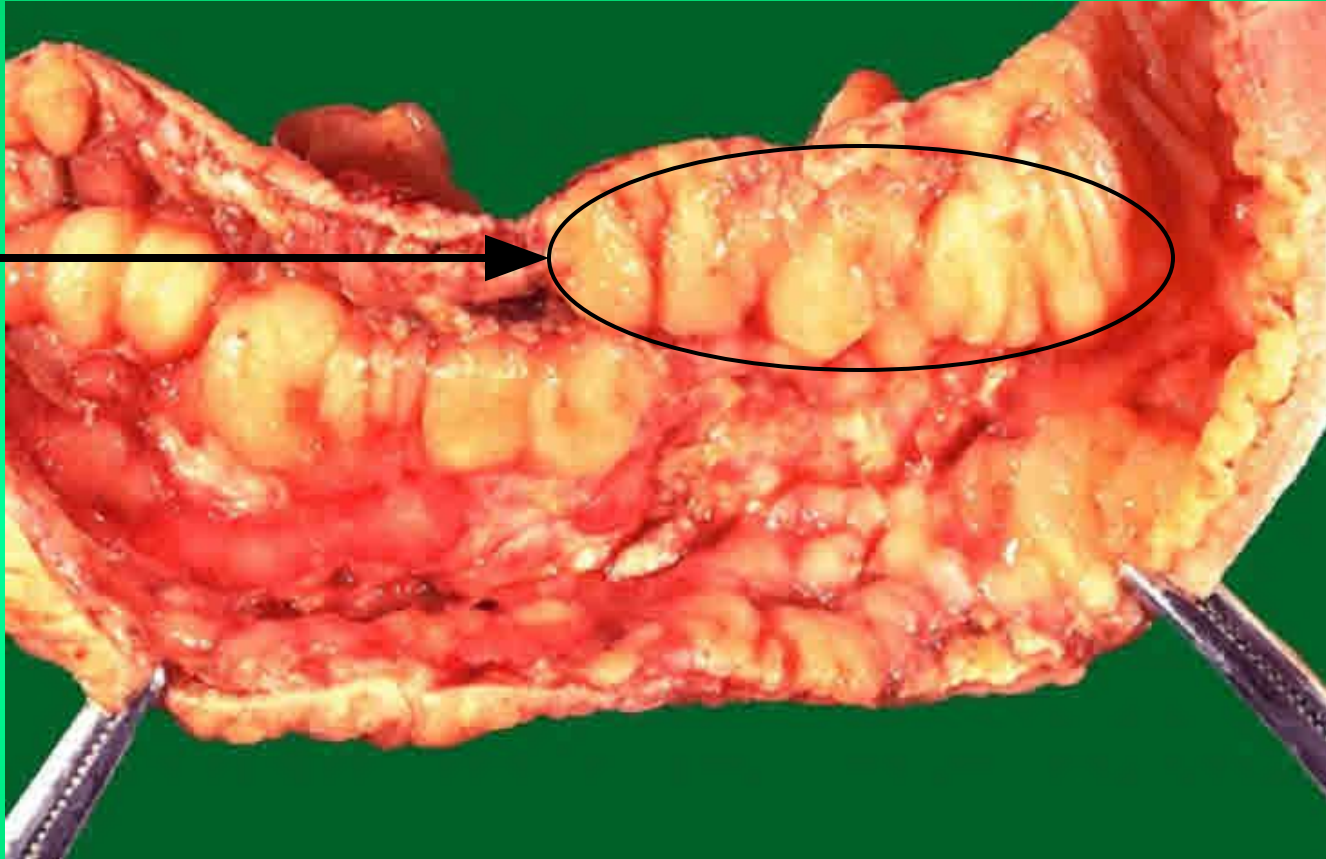


Here the middle portion of small bowel has a greatly thickened wall and the mucosa has lost the typical plicae circulares.

This diagram also hints as to the discontinuous nature of Crohn's disease there the area of inflammation is surrounded by normal mucosa. This is known as a skip lesion.

BACK

Gross view: Small intestine



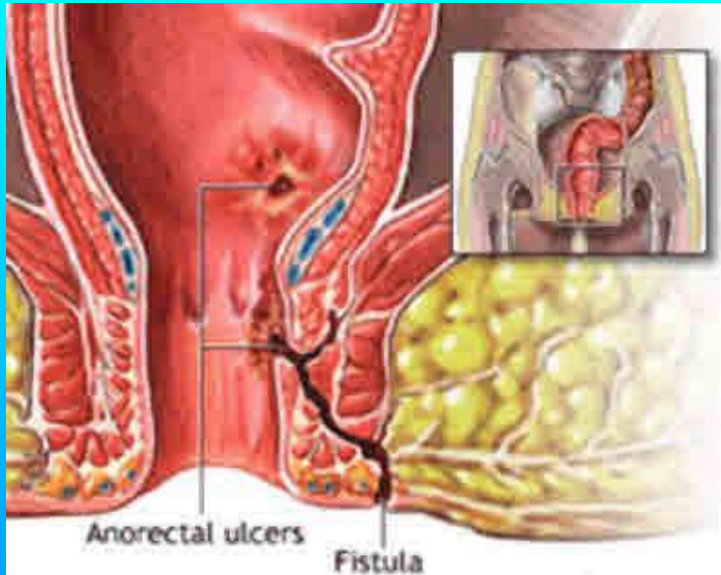
Here, the mucosal surface demonstrates an irregular nodular appearance and aphthoid ulceration.

A cobble-stone effect is also visible.

Pathology

Some of the complications of CD are outlined below:

Fistula formation – abnormal channels of communication can form in CD between loops of bowel, bladder and skin. If the CD is in the colon, fistulae can form between the colon and vagina or between the colon and perineum. The diagram on the right shows the beginning of a fistula formation with a fissure extending through mucosa towards the muscular wall. Below is a cartoon representation of a fistula starting from an area of ulceration



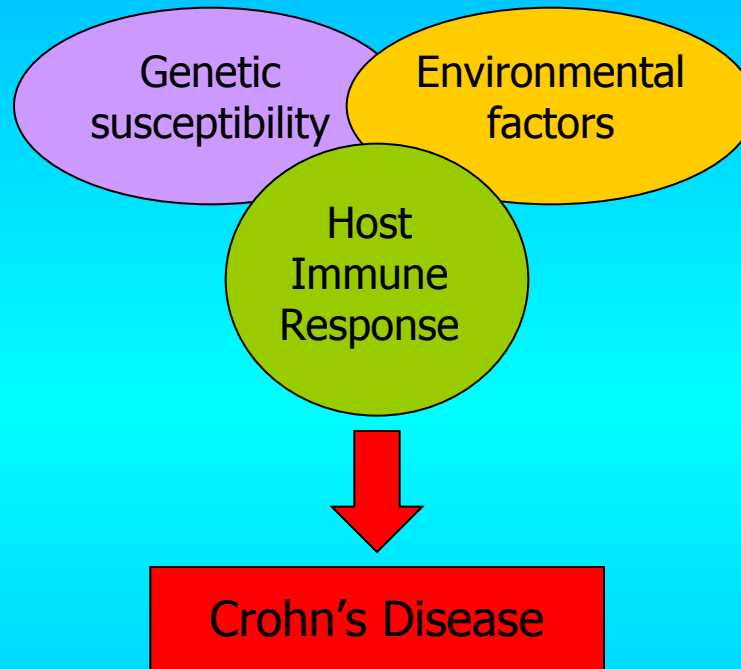
Obstruction - typically occurs from strictures or adhesions which narrow the lumen, blocking the passage of the intestinal contents. This can be seen in the barium follow-through to the right.



Aetiology and Pathogenesis of Crohn's Disease

Aetiology & Pathogenesis

The aetiology of Crohn's disease is unknown. There are many proposed pathogenic mechanisms, some of which are represented in this diagram.



As there is no one cause, it is likely that Crohn's disease is an outcome of interactions between genetic predisposition, environmental factors and the subsequent reaction of the host immune system.

Genetic Factors

Genetic
susceptibility

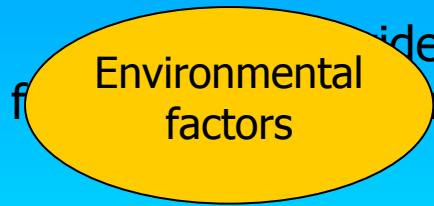
There are 3 mutations on the CARD15 gene on chromosome 5 that are associated with some forms of Crohn's Disease (CD). The risk of developing CD is increased forty-fold if you are homozygous for all three mutations.

The mutations appear to alter monocyte recognition of the constituent flora of the gut. It is possible that functional defects in CARD15 prevent innate immunity from balancing resistance to the microbes in the gut in CD patients, leading to uncontrolled inflammation and mucosal damage.

However the CARD15 mutations only account for 20-30% of cases of CD and CD is not found in oriental populations who have the mutations. Therefore this gene is not necessary for CD.

It is likely that there are other susceptibility genes that influence how the immune system interacts with the gut flora which may be discovered in the future. Putative loci have been mapped to chromosome 12 (IBD2), 6 (IBD3) and 14 (IBD4).

Environmental Factors



A wide range of environmental factors have been

- ☐ Smoking – Patients with CD are more likely to have been smokers and smoking may worsen CD and increase the risk of relapse/surgical intervention.
- ☐ Diet – Active CD may improve when a normal diet is changed to a liquid formula diet.
- ☐ Bacterial infection – There is some evidence implicating *E. coli*, *M. paratuberculosis*, the measles virus and *L. monocytogenes* in the pathogenesis of CD. This data is controversial and requires further research to clarify.
- ☐ Drugs – the oral contraceptive pill has been linked epidemiologically with CD. Relapse may be precipitated by NSAIDs.

Immune response

Both the potential genetics underlying CD and the environmental and host factors surrounding the patient may be considered as initiating factors for CD, but the exact aetiology is unknown.

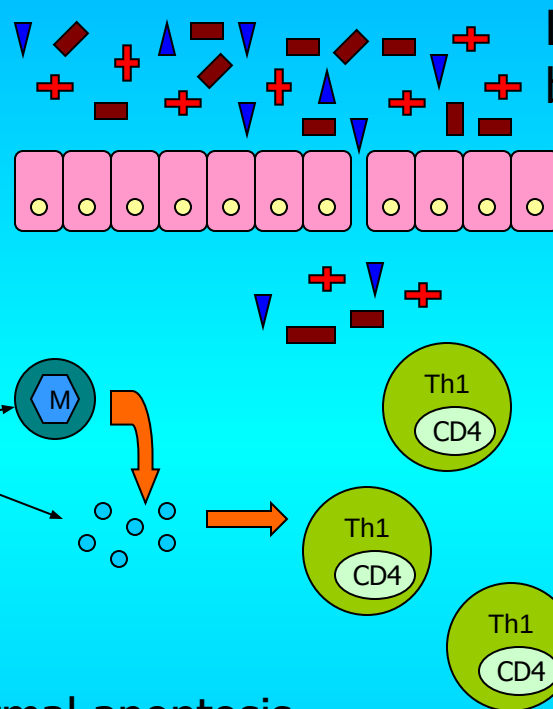
What is known is that mucosal immunity is dysregulated in CD leading to a prolonged inflammatory response in the gut.

In CD, a dominant CD4 Th1 reaction is induced. The mechanisms for this are displayed diagrammatically on the next page.

The immune system and CD

CD mucosal macrophages produce large amounts of cytokines IL-12 & IL-18 which induce the recruitment of Th1 cells

Th1 also have abnormal apoptosis sustained by these cytokines.

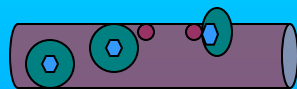


Luminal antigen's (from bacteria/food)

Gut epithelium – limits but doesn't exclude antigens from entering the lamina propria. In CD there is an increased permeability.

□ Interferon- γ - recruits leukocytes to the site resulting in increased inflammation.

□ TNF- α - causes increased inflammation.



Adhesins (•) are important in assisting the migration of leukocytes through endothelial cells to the area

Clinical features of Crohn's Disease

Clinical Features

The clinical presentation can be very variable depending upon the site and predominant pathology of that site.

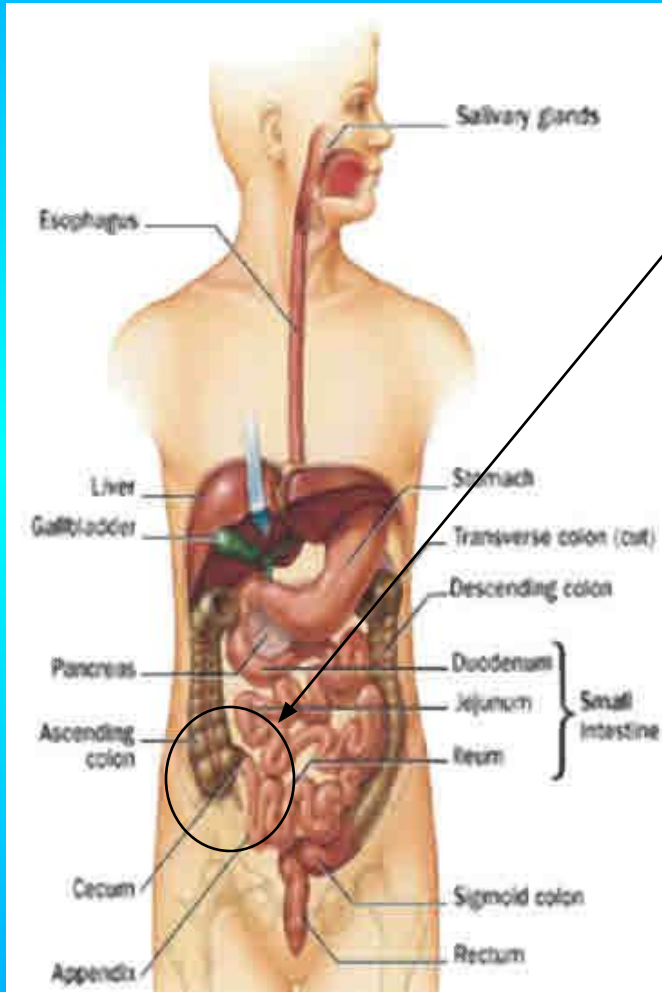
Major symptoms include:

- Diarrhoea (can be bloody with colonic involvement, or steatorrhoea in small bowel disease)
- Abdominal pain
- Weight loss
- Constitutional symptoms such as malaise, anorexia, nausea, vomiting and a low grade fever.

To make things more complicated – 15% of patients have no gastrointestinal symptoms at all!

To make things a little clearer, the following pages show the clinical presentation for CD of different sites.

Clinical Features



Ileocecal (45%) & terminal ileum (20%)

Patients present with pain and/or tender mass in right iliac fossa with or without diarrhoea and weight loss.

The nature of the pain can distinguish between the underlying pathology: constant pain with fever suggests inflammation and abscess; fibrosis/stricture formation has more generalised, intermittent colicky pain with signs of bowel obstruction.

CD here can sometimes present as an emergency with acute right iliac fossa pain which mimics appendicitis.

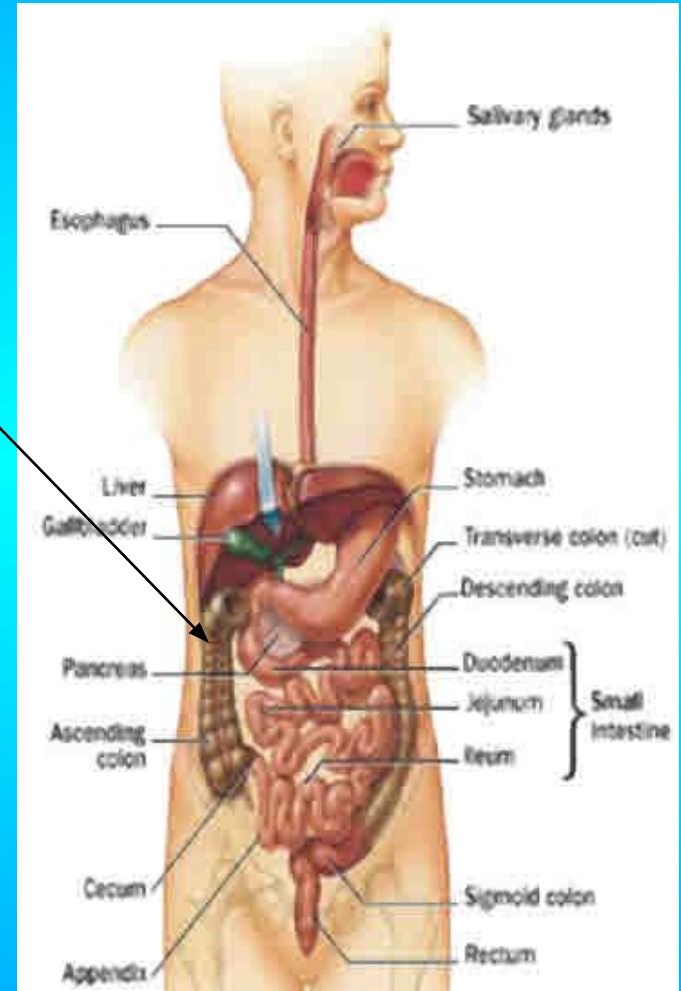
Clinical Features

Crohn's colitis (25%)

Symptoms such as diarrhoea (mucous/blood), sense of urgency and occasionally abdominal pain/malaise.

Similar to ulcerative colitis but less blood in the diarrhoea.

Extra-intestinal features are more common in CD of the colon than CD of the small bowel.



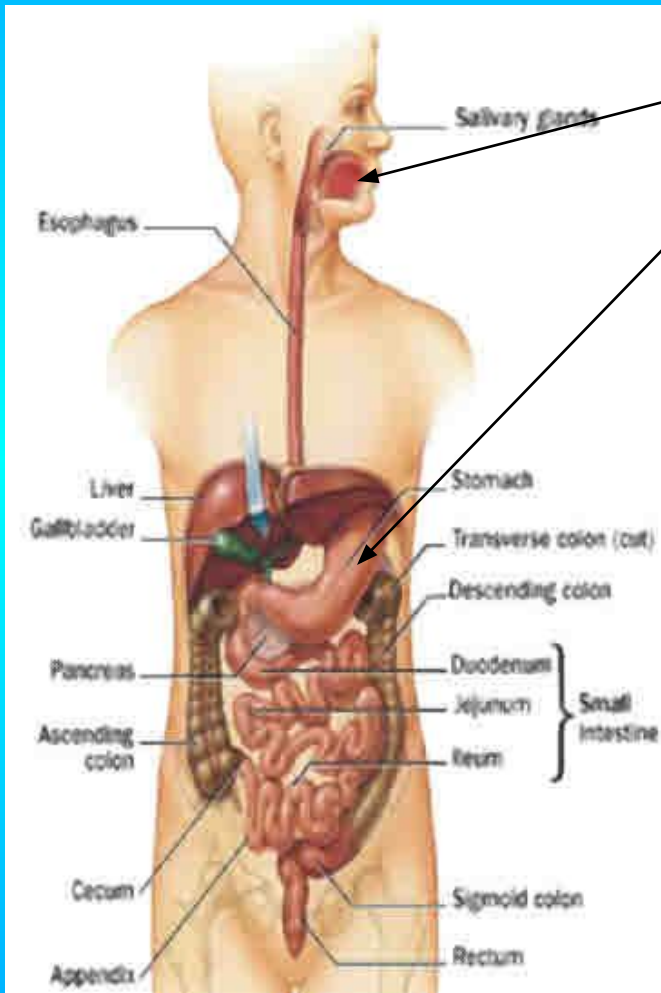
Clinical Features

Gastroduodenal & oral (5%)

Very rare.

The former presents with upper abdominal pain or dyspepsia with anorexia, nausea and weight loss.

The latter presents with mouth ulcers or induration.

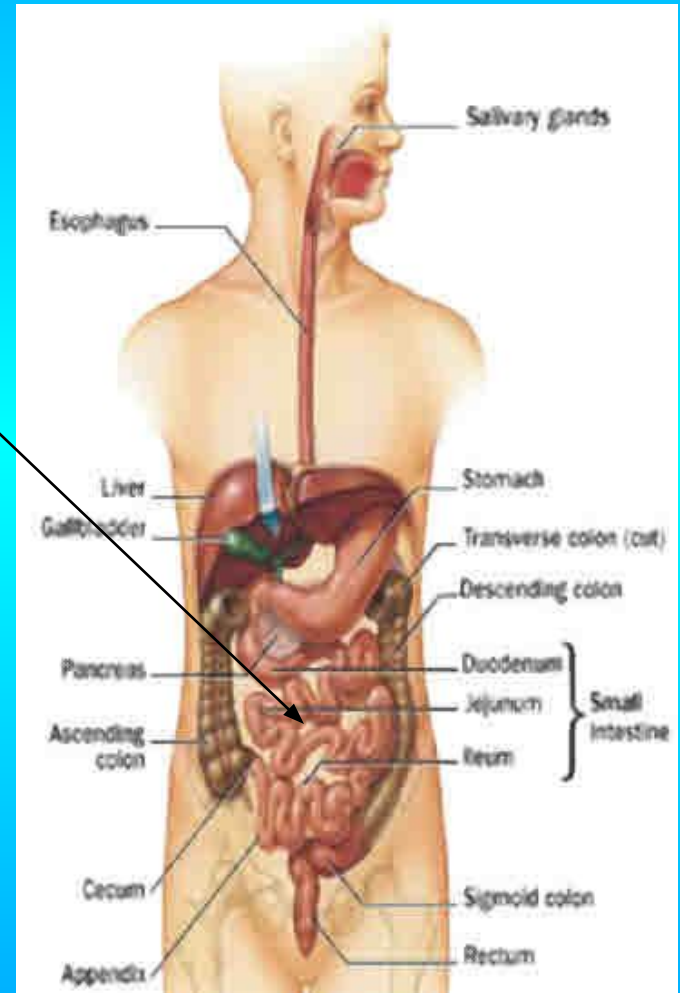


Clinical Features

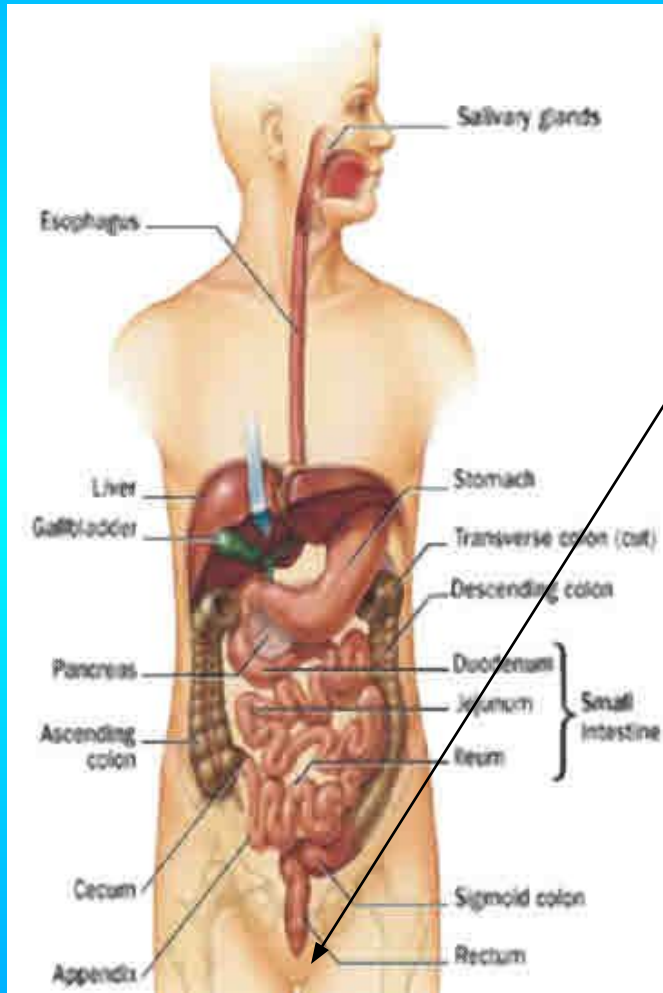
Extensive small bowel (5%)

Presents with typical pain, diarrhoea and weight loss in addition to features of malabsorption (e.g. steatorrhoea) and anaemia.

Due to the malabsorption, undernutrition is frequently a problem



Clinical Features



Perianal CD – complication

Characterised by perianal pain and/or discharge. It's due to fistula, fissure or abscess formation and can be confirmed by examination. It is not as painful as it looks but sedation is often needed for sigmoidoscopy.

Direct questions about pneumaturia (air bubbles in the urine) and faeculent vaginal discharge may be needed to elicit this when taking a history.

Intestinal Complications

Anal and perianal complications

- Fissure in ano or fistula in ano
- Haemorrhoids
- Skin tags
- Perianal or ischiorectal abscess
- Anorectal fistulae

Undernutrition

- Caused by reduced food intake, malabsorption, increased protein loss from inflamed bowel and the increased metabolic demands of being sick.

Short bowel syndrome

- Develops when extensive bowel resection leads to excessive malabsorption of fluids, electrolytes and nutrients.

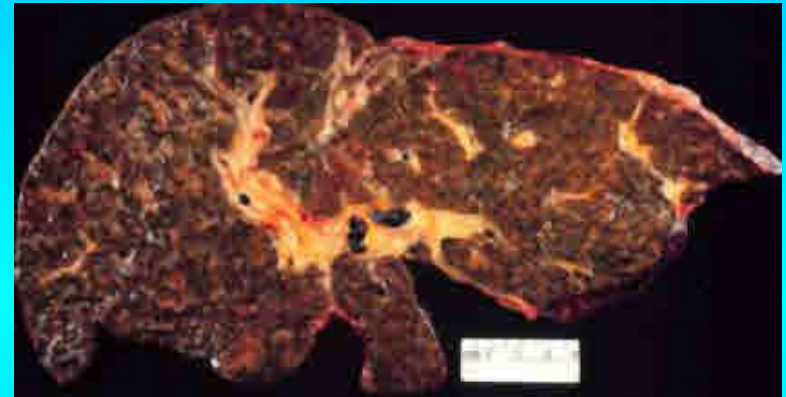
Cancer

- With Crohn's colitis, there is an increased risk of colorectal carcinoma
- There is a small increased risk of rarer small intestinal and anal cancers occurring in sites of prolonged inflammation.

Extra-intestinal complications

There are many systemic associations and complications of CD, most affecting the liver and biliary tree, joints, skin and eyes:

Sclerosing Cholangitis – occurs in a small proportion of patients. The pathogenesis is unknown and the condition is characterised by an inflammatory obliterative fibrosis of the biliary tree (the white in the diagram->). It progresses slowly and a liver transplant is the only cure.



Ankylosing spondylitis – affects about 5% of patients with Crohn's colitis. The patient presents with back pain and stiffness and the diagnosis can come years before the CD.

Extra-intestinal complications



Erythema nodosum – occurs in ~8% of Crohn's colitis patients when disease is active. Hot, red tender nodules appear on the arms and legs and subside after a few days.

Pyoderma gangrenosum – occurs in ~2% of CD patients, starting as a small pustule, then developing into a painful, enlarging ulcer, most commonly on the leg.



In addition to these conditions, other complications and associations include episcleritis and uveitis (occurring in 5% of patients with active disease), osteoporosis (as a consequence of chronic inflammation, malabsorption and treatment with corticosteroids) and arthropathy.

Diagnosis and Management of Crohn's Disease

Diagnosis

Radiology and imaging

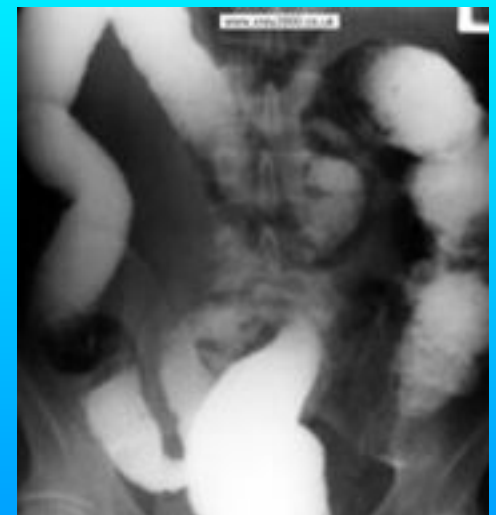
Colonoscopy, terminal ileoscopy & biopsy: These allow direct visualisation and allows for a biopsy of the mucosa to be taken. This is central to macroscopic and microscopic diagnosis.



Barium follow-through – findings consistent with Crohn's include an asymmetrical alteration in mucosal pattern with deep ulceration and areas of narrowing or stricturing.



Ultrasound & CT scanning: Can help define thickness of the bowel and mesentery and can be useful to evaluate disease progress & chart fistula formation.



Diagnosis

Blood tests

Haematology: results suggesting anaemia, \downarrow platelet count & \uparrow ESR suggests an inflammatory bowel condition.

Biochemistry: \uparrow C-reactive protein and \downarrow serum albumin suggests active CD. Liver biochemistry may be abnormal.

Stool cultures

Faecal calprotectin: provides accurate marker of inflammatory activity. Calprotectin is a neutrophil-derived cytosolic protein that is resistant to bacterial degradation and if present in the stools provides an accurate index of intestinal inflammatory activity. It is not routinely available but has the potential to be a simple, cheap, non-invasive marker.

Stool cultures should be done to rule out infection as a differential diagnosis.

Differential Diagnosis

There are many differential diagnosis for Crohn's disease, complicated further by the differing presentations of CD depending upon the site and pathology. Some major differential diagnoses are outlined below:

- *Yersinia* infections and appendicitis cause an acute ileitis
- If diarrhoea is bloody (as it sometimes is with colonic CD), other causes could be ulcerative colitis, infective colitis, colorectal cancer, ischaemia or iatrogenic causes (NSAIDs or antibiotics)
- Causes of abdominal pain, diarrhoea and weight loss include ulcerative colitis, infective colitis and other forms of colitis, cancer (of pancreas, colorectal, small bowel lymphomas or endocrine tumours), ischaemia coeliac disease and irritable bowel disease.

Management

Management is best if a MDT approach is adopted, including physicians, surgeons, specialist nurses, dieticians and counsellors.

Treatment depends upon the disease activity and site but should also be tailored to the clinical presentation and underlying pathology. The aim is to induce and maintain remission.

Risk factors outlined earlier (such as smoking) should be avoided.

Full explanation and psychosocial support should be given to the patient as CD is a lifelong chronic condition and this may not be fully understood by the patient at the time of diagnosis.

Patient education is very important.



Medical management

- Dietary advice and nutritional support including vitamin supplementation to counter-act any deficiencies that develop.
- Diarrhoea can be controlled by anti-diarrhoeals such as loperamide, codeine phosphate or co-phenotrope. If the diarrhoea is due to bile acid malabsorption, then this can be treated with colestyramine.
- Likely to be beneficial in inducing remission:
 - Corticosteroids (oral)
 - Aminosalicylates
 - (azathioprine/mercaptopurine – trade off between benefits and harms)
 - Methotrexate
 - Infliximab
- Likely to maintain remission:
 - Smoking cessation
 - (Unknown if the following are effective: enteral nutrition, fish oil, probiotics)
- The BNF information about the drugs on this page can be seen [HERE](#)

Drug Information

Class	Name	Side effects	Contra-indications
Aminosalicylates	Balsalazide, mesalazine, olsalazine, sulfasalazine	Diarrhoea, nausea, vomiting, abdo pain, headache, hypersensitivity reactions. Rarely – acute pancreatitis, hepatitis, myocarditis, pericarditis, lung disorders	Avoid in salicylate hypersensitivity and use with caution in renal impairment, pregnancy and breastfeeding. Blood disorders can occur
Corticosteroids	Prednisolone	Numerous. Too many to list here but they include gastro-intestinal effects, musculoskeletal effects, endocrine effects, neuropsychiatric effects & ophthalmic effects	Avoid in systemic infection. Avoid live vaccines. Caution in adrenal suppression, children, adolescents and the elderly.
Infliximab	Infliximab	Infections, nausea, abdo pain, hypersensitivity reaction, worsening of heart failure, fever among others	Pregnancy, breast-feeding. Caution in hepatic or renal impairment.
Methotrexate	Methotrexate	Myelosuppression, mucositis, pneumonitis, anorexia, abdo discomfort, intestinal ulceration	Severe renal or hepatic impairment, pregnancy, breast feeding

BACK

Surgical management

- Surgery is indicated for perforation or haemorrhage (emergency) or for small-bowel obstruction, Crohn's colitis, abscess (intra-abdo and perianal), fistulas and inflammation unresponsive to medical therapy.
- Approximately 80% of patients with CD will require surgery at some point.
- The principle of surgery is to conserve as much bowel as possible as 60% of patients need further surgery.
- Surgery is not curative.

In small bowel CD – resection is likely to be beneficial whereby discrete sections are removed and an end-to-end anastomosis created. The benefits of strictureplasty to widen a narrowed lumen are unknown at this time.

In colonic CD – segmental and subtotal colectomy is likely to be beneficial. In a segmental colectomy the part of the colon affected is removed and an end-to-end anastomosis created in remaining colon and in a subtotal colectomy the ileum is sewn/stapled to the sigmoid colon as seen in diagram.



Prognosis

Mortality

The cumulative mortality is approximately twice that of the general population. Death is primarily due to sepsis, pulmonary embolism and complications of the surgery or immunosuppressive agents used as treatments.

Morbidity

The pattern of CD is a lifelong duration with periods of active disease alternating with periods of remission. The disease causes significant disability with only 75% of patients being fully capable of work in the first year of disease and 15% of patients unable to work after 5-10years of the disease.

People with CD are also more at risk of developing certain cancers and other complications as mentioned under the clinical features section of this module.

Summary

- Crohn's disease is a chronic inflammatory condition of the gastrointestinal tract characterised by transmural inflammation, skip lesions and fistula formation.
- It is a recurring condition alternating between active disease and remission. The disease is more common in males and in the west.
- It is caused by an interaction between genetic susceptibility, environmental factors and the host immune system.
- The clinical presentation and subsequent treatments depend upon the site of inflammation and the type of pathology underlying it. For example, the most common site is the ileocaecal area which presents typically with pain and/or tender mass in right iliac fossa with or without diarrhoea and weight loss. On the other hand oral CD presents with mouth ulcers and induration.
- Treatment involves a multi-disciplinary team and working closely with the patient is very important.
- Drug therapies include aminosalicylates, oral corticosteroids , Infliximab and Methotrexate.
- Surgical options include small bowel resection or segmental/subtotal colectomy.

The different sections

If you want to revisit any of the sections of this module please use the list below. Clicking on a section will return you to that part of the presentation.

[Introduction](#)

[Epidemiology and Pathology](#)

[Aetiology and Pathogenesis](#)

[Clinical Features](#)

[Diagnosis and management](#)

Case Study

30-year-old woman was admitted with a 4-week history of increasing bloody diarrhoea and abdominal pain; she had lost 3kg in weight. She smoked 25 cigarettes a day. On examination, she was not clinically anaemic and, apart from a temperature of 37.8°C and some tenderness over the right iliac fossa, there were no abnormal physical signs.

The perineum was normal but sigmoidoscopy to 15cm showed a red, granular mucosa with mucopus and contact bleeding. Laboratory investigations showed a low haemoglobin (108g/l) with a raised CRP (67 mg/l) but a normal white-cell count. Urea and electrolytes, serum vitamin B₁₂, folate, iron, ferritin and iron-binding capacity were normal. Her total serum proteins were 54g/l (NR 62-82) with a serum albumin of 29g/l (NR 35-50). Faecal examination and culture revealed no ova or *Campylobacter*. *Clostridium difficile* toxin was absent from the stools.

Case Study

The rectal biopsy taken at sigmoidoscopy showed a small area of ulceration of the surface epithelium with considerable mucopus. Many crypt abscesses were present. The lamina propria contained a heavy infiltrate of lymphocytes, plasma cells and macrophages. Two non-caseating granulomas were present.

The appearances were those of *Crohn's disease affecting the colon*. A small-bowel barium infusion and a colonoscopy were performed to assess the extent of disease. Inflammatory strictures were seen at a number of separate sites (skip lesions) in the ascending and transverse colons. She was treated with corticosteroids and a 3-month course of metronidazole with symptomatic improvement. She was strongly advised to stop smoking.

Thank you

I hope this has been of some help
to your studies!

Reading list

Books

- Rampton, D.S., & Shanahan, F., *Fast Facts: Inflammatory Bowel Disease*. 2nd ed. 2006, Oxford: Health Press.
- Kumar, P., & Clark, M., *Clinical Medicine*. 6th ed. 2005. Spain: Elsevier.
- BMJ, *Clinical Evidence consise*, Vol 16, December 2006.

Websites

- <http://www.emedicine.com/>
- <http://www.clinicalevidence.com/ceweb/conditions/index.jsp>
- <http://www.bnf.org/bnf/>

Patient-centred websites

- <http://www.nacc.org.uk/content/home.asp>
- <http://www.ccfa.org/>