

Treatment – Ulcerative Colitis		IBD and Cancer		Immunosuppressants (cont)		UC vs CD		
Mild-Moderate disease	5-Aminosalicylates (suppository or enema possibly combined with oral aminosalicylates) If unable to tolerate aminosalicylates: Steroids (topical corticosteroid or oral prednisolone)	Increased risk of colorectal cancer (CRC) in UC and Crohn's colitis 20-30% risk at 30 years from diagnosis Regular surveillance colonoscopy performed from 8-10 years post-diagnosis 5-ASAs are protective		BSG guidelines advise use in following situations	Severe relapse or frequently relapsing disease. 2 or more steroid course required within 12 months. Relapse below 15mg prednisolone. Relapse within 6 weeks of stopping steroids.		UC	CD
Resistant Disease	Immunosuppressants (eg Azathioprine, Mercaptopurine) Anti-TNF monoclonal Ab (Infliximab, Adalimumab)	Risk of CRC particularly high in patients with UC + Primary Sclerosing Cholangitis PSC also carries a high risk of cholangiocarcinoma		Pathology of UC		SKIN	Erythema nodosum Pyoderma gangrenosum	Erythema nodosum Pyoderma gangrenosum
Severe colitis	Intravenous corticosteroids Cyclosporin Infliximab (5 mg/kg infused over 2 hours at 2 and 6 week intervals) (Assuming 3 doses, average cost per patient = £5,035) Surgery	Ciclosporin		Idiopathic chronic inflammatory disorder of the colonic mucosa, with the potential for extraintestinal inflammation.		EYE	Iritis Episcleritis (inflammation of the episclera : white of the eye)	Iritis Episcleritis
Therapeutic Pyramid for Active UC		Calcineurin inhibitor Prevents clonal expansion of T cell subsets Rapid onset of action		The disease extends proximally from the anal verge in an uninterrupted pattern to involve all or part of the colon		KIDNEY	Calculi (kidney stones) Pyelonephritis (inflammation of the kidney due to bacterial infection)	Calculi pyelonephritis
Mild:	Topical Steroids: Aminosalicylates	Used as salvage therapy for severe UC not responding to IV steroids Usually introduced on day 3 of steroids IV 2mg/kg/day Responders converted to oral Cyclosporin for 3-6 months and switched to Azathioprine/6-MP (Ciclosporin not used long-term)		Diagnosis of IBD		LIVER	Sclerosing cholangitis (inflammation of bile ducts: impeding bile flow)	Systemic amyloidosis (deposition of amyloid proteins)
Moderate:	Infliximab, Systemic Corticosteroids, Oral steroids	Requires regular monitoring of Drug levels/Full blood count/-Renal function/Blood pressure		Endoscopy and biopsy				
Severe:	Surgery, Cyclosporine, Infliximab	Immunosuppressants		Radiology				
		Indicated for severe or refractory IBD		Thiopurines. Methotrexate. Ciclosporin.				
				Exclude infection				
				Blood tests helpful but not diagnostic				



Treatment – Crohn's

Initial diagnosis if mild to moderate: 5-ASA's less effective but may have a chemoprotective effect against cancer risk. Glucocorticosteroids

Severe active Crohn's (including fistulising Crohn's) Immunosuppressants Azathioprine, Mercaptopurine, Methotrexate
Anti-TNF therapy (Infliximab) (severe active Crohn's)

For perianal Crohn's: Antibiotics (Metronidazole, Ciprofloxacin) –

Smoking cessation
Nutritional Support
Surgey
Emotional support: possible delayed growth and onset of puberty in young people
Possibility of requiring surgery

Distribution of Crohn's disease

Small Bowel 80% of cases small bowel involved. Majority distal ileum. 1/3 exclusively ileitis.

Ileo-colonic 50% have ileocolitis

Colonic 20% colonic disease only

Distribution of Crohn's disease (cont)

Anus 33% have anal disease. Other (gastroduodenal, oesophageal, oral). Rare.

Treatment

UC and Crohn's are lifelong relapsing-remitting conditions

Treatment is not curative but aims to suppress inflammation and thereby maintain normal gut structure and function

Corticosteroids

Oral Prednisolone (eg 40mg od, 8 week reducing course). Budesonide (lower systemic effects). Beclomethasone (Clipper). Used for moderate flares of UC/Crohn's.

Intravenous: For severe UC or Crohn's Hydrocortisone (eg 100mg qds)

Topical Steroid Suppositories/Enemas (eg Predsol supps, Predfoam enemas). Less effective than topical 5-ASA but can be used in combination.

Corticosteroids (cont)

Side effects: Skin thinning. Osteoporosis. Osteonecrosis
Easy bruising.
Cushing's syndrome (moon face, acne, hirsutism, striae).
Cataracts. Diabetes.
Hypertension.
Psychosis.

Corticosteroids are very effective at inducing remission
They are not a long-term maintenance therapy because of the effect on cortisol levels on the hypothalamus and anterior pituitary.

Ciclosporin & Tacrolimus (FK506)

Ciclosporin Inhibits dephosphorylation of nuclear factor of activated T cells (NFATc)

Tacrolimus (FK506) Binds to FK-506 binding protein (FKBP). Calcineurin inhibitor.

Both prevent interleukin 2 release and clonal expansion of T cell subsets

Differential Diagnosis of UC

Crohn's Colitis

Infective colitis: *E.coli*

Campylobacter

Salmonella

Differential Diagnosis of UC (cont)

Yersinia

Amoebic Dysentery

Ischaemic Colitis

**Pseudomonas Colitis* Clostridium difficile infection

Anti-TNF Therapy

Tumour Necrosis Factor α Inflammatory cytokine involved in pathogenesis of Crohn's (and UC)

You tube TNF McAB Therapy
Monoclonal anti-TNF antibodies
Infliximab –
Route: IV
Licensed for Refractory Crohn's or UC/Fistulating Crohn's
Also used for severe UC

Adalimumab (Humira)
Subcutaneous
Licensed for refractory Crohn's

Pathology of Crohns Disease

Idiopathic chronic inflammatory disorder of the full thickness of the intestine Most commonly the ileum and the colon, with the potential to involve the gastrointestinal tract at any level from the mouth to the anus and perianal region.

Pathology of Crohns Disease (cont)

Typically there is patchy disease in the gastro-intestinal tract with intervening areas of normal mucosa "Skip lesions"

Transmural inflammation with lymphoid aggregates (clusters of lymphoid cells- include T-cells, B-cells and NK cells.)

Non caseating granulomas (60% cases) Caseating "turning to cheese"

Skip Leisons

**Strictures and fistula formation* In Crohn's, strictures make the bowel too tight, and fistulas create unnatural pathways—both are serious complications.

Perianal disease

Can affect any part of the GI tract

Smokers

Treatments Summary

Crohn's & Ulcerative Colitis

Salicylates

5-Amino salicylic acid (5-ASA); mesalamine (Asacol)

Steroids (glucocorticoids): Methylprednisolone (Medrol)

Immunosuppressants: Azathioprine & mercaptopurine

Treatments Summary (cont)

Ciclosporin A (Sandimmun or Neoral) Tacrolimus (FK-506, Fujimycin) (Prograf, Advagraf, Protopic)

NOVEL TREATMENTS

Nicotine: useful in UC?

LTB4 antagonists eg zileuton.

Fish oils, eicosopentanoic acid diverts LT production towards LTB5 production.

IL1 receptor antagonists (UC).

Short Chain fatty acids.

CuZnSOD and desferrioxamine (Peroxyl scavenger).

Epidemiology

Crohn's disease	Ulcerative Colitis
Incidence 8-10/100,000 in UK	Incidence 15/100,000 in UK
Prevalence ~150 per 100,000 (1 in 660 people)	Prevalence 200 per 100,000 (1 in 500 people)

Peak age at diagnosis 20-40, second smaller peak aged ~60

5-ASAs

5 Aminos alicylic acid (Mesalazine) Moderate inflammatory cells and cytokine release from epithelial cells. Mechanism not fully understood but involves inhibition of cyclooxygenase and prostanoid formation and N-acetyl-5-ASA through PPAR gamma (Peroxisome Proliferator Alpha Receptor gamma)

5-ASAs (cont)

Uses - UC Maintenance of remission – mainstay of long-term treatment for UC. Treatment of mild-moderate flares. Chemoprotective effect against colorectal cancer.

Uses – Crohn's Limited effectiveness compared to UC. Limited effectiveness in active Crohn's or maintaining remission. May reduce risk of relapse after surgery.

5-ASAs (cont)

Side Effects: Diarrhoea! Nausea. Headache Rash (rarely Stevens-Johnson syndrome). Nephrotoxicity (Interstitial nephritis & Nephrotic syndrome). Agranulocytosis (low white blood cell count). Pancreatitis.

Oral

pH dependent resin (Asacol, Salofalk, Mesren)
Time-controlled (Pentasa)
Multimatrix pH dependent delivery (Mezavant)
Carrier molecules split by colonic bacterial enzymes (Sulfasalazine, Olsalazine, Balsalazide)

Dose

1.6-4.8g/per day
Single daily dosing seems as effective as traditional bd/tds

Topical

Suppositories - Proctitis
Foam or Liquid enemas - Distal colitis (rectum and sigmoid)
Check FBC/Renal function annually

UC vs CD

Ulcerative colitis	Crohn's disease
Affects the colon only	Affects any part of the GI tract
Male:F-emale 1:1	Male: Female 1:2

UC vs CD (cont)		Clinical Presentation – Crohn's		UC AND CROHNS (cont)	
Bloody diarrhoea	Abdominal pain	Typical Abdominal Pain.		Malignant change common	Malignant change rare
Abdominal pain	Weight loss	Features: Diarrhoea. Weight loss. Anorexia.		Fistulae less common	10% have fistulae
Continuous, always begins in rectum	Perianal disease	Obstruction secondary to strictures		25% have anal involvement	60% have anal involvement
No strictures	Bloody diarrhoea	Abscesses, Fistulae		Muscular shortening of the colon	Fibrous shortening
Mucosal inflammation	Skip lesions	Depends on portion of GI tract involved		No skip lessons	Skip lesions
Diffuse inflammation in the lamina propria	Stricture and fistula formation with perianal disease			No fat or vitamin malabsorption	Fat & vitamin malabsorption
Patchy ulceration with crypt abscesses, goblet cell depletion and crypt distortion	Transmural inflammation throughout bowel wall, lymphoid aggregates and non-necrotising granulomas. Can develop fissuring ulcers, crypt abscesses, goblet cell depletion and crypt distortion			Mild lymphoid reaction	Marked lymphoid reaction (increased WBC)
Terminal ileum in 10% cases	Often affects the terminal ileum (80%) Any part of alimentary tract can be affected			Mild fibrosis	Fibrosis
No fistulas	Fistulas			Mild Serositis	Serositis (inflammation, serous membranes)
				Raised ANCA (antineutrophil cytoplasmic antibodies. Autoantibodies directed against own neutrophils.)	ANCA normal
				More common in non-smokers or ex smokers	Increased incidence in smokers

Histopathology Crohn's Disease of Ileum

Inflammatory cells (the bluish infiltrates) extend from mucosa through submucosa and muscularis.

On the serosal surface inflammatory cells appear as nodular infiltrates with pale granulomatous centres.

Clinical Presentation of UC

'Bloody diarrhoea' and passage of mucus

Urgency

Abdominal Discomfort (pain unusual)

Usually insidious onset

Can be severe with systemic upset, fever

Requires hospitalisation

May need urgent surgery

UC AND CROHNS

Ulcerative Colitis	Crohn's Disease
Only affects colon	Affects mouth to anus
No fissures, horizontal ulcers	Deep ulcers & fissures

