

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 (Cyclosporin 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. Cyclosporin.				
				Exclude infection				
				Blood tests helpful but not diagnostic				

UC vs CD (cont)			Aetiology (cont)		Histopathology of UC (cont)		Ciclosporin – side effects								
JOINTS	Serone-	Serone	Genetics	47 loci associated with UC (and counting)	The most intense inflammation begins :	the lower right in the sigmoid colon and extends upward and around to the ascending colon. At the lower left is the ileocecal valve with a portion of terminal ileum that is not involved.	Tremor								
	gative	gative					Paraesthesia								
	polyarthritis	polyar-	Malaise												
	(blood test –ve for	thritis	Headache												
	rheumatoid factor		Abnormal liver function tests												
	protein and		Histopathology of UC		Repeated ulceration and healing cycles result in:	Granulation tissue resembling polyps	Hirsutism								
	cyclic-citru-						Gingival hyperplasia								
	linated		Superficial diffuse inflammation in the lamina propria affecting the colon only	Chara			Continuous from the rectum up to the caecum								
	peptide)							Crypt abscesses, goblet cell depletion and crypt distortion							
									Can affect the distal few cm of small bowel – ‘backwash ileitis’						
Aetiology				Non-smokers	Anti-TNFs adverse effects										
Inappr- opriate immune response	Increased pro-in-				Infections	Steroids/Immunosuppressa-									
	flammatory						Two or more therapies in combination increases risk 15 fold	Active infection/abscesses must be excluded before commencing anti-TNF treatment							
Breakdown in tolerance to gut microbial load	cytokines eg TNF-								Patients should be screened for exposure to TB (CXR/Tuberculin skin test)	Malignancy					
	α, IL-1β, IL-6										Increased risk of lymphoma (but overall risk still v low)	Heart failure			
	Altered gut flora.												Anti-TNFs contraindicated in severe heart failure		
Defects in				Azathioprine (Aza)	Mercaptopurine (6-MP)	Purine antimetabolites inhibiting DNA synthesis									Aza is metabolised to 6-MP
mucosal							Doses mg/kg/day	6-MP 0.75-1mg/kg/day							
immunity.															
Combini- ation of factors	Enviromental														
	factors. Triggered														

Treatment – Crohn's		Distribution of Crohn's disease (cont)		Corticosteroids (cont)		Differential Diagnosis of UC (cont)	
Initial diagnosis if mild to moderate:	5-ASA's less effective but may have a chemoprotective effect against cancer risk. Glucocorticosteroids	Anus	33% have anal disease. Other (gastroduodenal, oesophageal, oral). Rare.	Side effects:	Skin thinning. Osteoporosis. Osteonecrosis. Easy bruising. Cushing's syndrome (moon face, acne, hirsutism, striae). Cataracts. Diabetes. Hypertension. Psychosis.		<i>Yersinia</i>
Severe active Crohn's (including fistulising Crohn's)	Immunosuppressants Azathioprine, Mercaptopurine, Methotrexate. Anti-TNF therapy (Infliximab) (severe active Crohn's)	Treatment		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.			<i>Amoebic Dysentery</i>
For perianal Crohn's:	Antibiotics (Metronidazole, Ciprofloxacin) –	UC and Crohn's are lifelong relapsing-remitting conditions		Ciclosporin & Tacrolimus (FK506)		Ischaemic Colitis	
Smoking cessation		Treatment is not curative but aims to suppress inflammation and thereby maintain normal gut structure and function		Ciclosporin	Inhibits dephosphorylation of nuclear factor of activated T cells (NFATc)	<i>*Pseudomembranous Colitis</i>	Clostridium difficile infection
Nutritional Support		Corticosteroids		Tacrolimus (FK506)	Binds to FK-506 binding protein (FKBP). Calcineurin inhibitor.	Anti-TNF Therapy	
Surgey		Oral	Prednisolone (eg 40mg od, 8 week reducing course). Budesonide (lower systemic effects). Beclomethasone (Clipper). Used for moderate flares of UC/Crohn's.	Both prevent	interleukin 2 release and clonal expansion of T cell subsets	Tumour Necrosis Factor α Inflammatory cytokine involved in pathogenesis of Crohn's (and UC)	
Emotional support: possible delayed growth and onset of puberty in young people		Intravenous:	For severe UC or Crohn's Hydrocortisone (eg 100mg qds)	Differential Diagnosis of UC		You tube TNF McAB Therapy	
Possibility of requiring surgery		Topical	Steroid Suppositories/Enemas (eg Predsol supps, Predfoam enemas). Less effective than topical 5-ASA but can be used in combination.	Crohn's Colitis		Monoclonal anti-TNF antibodies	
Distribution of Crohn's disease				Infective colitis:		Infliximab –	
Small Bowel	80% of cases small bowel involved. Majority distal ileum. 1/3 exclusively ileitis.			<i>E.coli</i>		Route: IV	
Ileo-colonic	50% have ileocolitis			<i>Campylobacter</i>		Licensed for Refractory Crohn's or UC/Fistulating Crohn's	
Colonic	20% colonic disease only			<i>Salmonella</i>		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, eicosapentanoic 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 alicyclic acid (Mesalazine) Moderate inflammatory cells and cytokine release from epithelial cells. Mechanism not fully understood but involves inhibition of cyclooxygenase and prostanoic acid 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 Features:	Abdominal Pain. Diarrhoea. Weight loss. Anorexia.	Malignant change common	Malignant change rare
Abdominal pain	Perianal disease	Obstruction secondary to strictures Abscesses, Fistulae Depends on portion of GI tract involved		Fistulae less common	10% have fistulae
Continuous, always begins in rectum	Bloody diarrhoea			25% have anal involvement	60% have anal involvement
No strictures	Skip lesions	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.		Muscular shortening of the colon	Fibrous shortening
Stricture and fistula formation with perianal disease				No skip lessons	Skip lesions
Mucosal inflammation	Transmural inflammation throughout bowel wall, lymphoid aggregates and non-necrotising granulomas. Can develop fissuring ulcers, crypt abscesses, goblet cell depletion and crypt distortion	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		No fat or vitamin malabsorption	Fat & vitamin malabsorption
Diffuse inflammation in the lamina propria				No granulomas (collection of macrophages)	Granulomas in 50%
Patchy ulceration with crypt abscesses, goblet cell depletion and crypt distortion		UC AND CROHNS Ulcerative Colitis Only affects colon No fissures, horizontal ulcers		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	Crohn's Disease Affects mouth to anus Deep ulcers & fissures		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