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Inflammatory Bowel Disease, 2016 update

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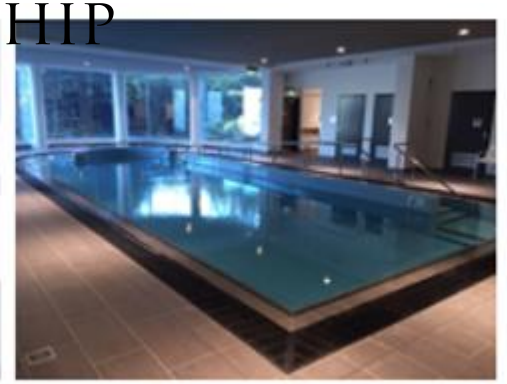
University of Toronto Inflammatory Bowel Disease fellowship

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CASE

- 24F with intermittent abdominal pain(5/10) since 4 years ago
  - RLQ
  - Bloating can be anything from 1 to 4 hrs post prandial
  - Occasional diarrhoea up to 4BM a day(2-3 weeks each time) at least 4-6 times a year sometimes with minimal rectal bleeding
  - Symptoms can be worse with certain foods
  - Intermittent constipation
  - Tiredness
  - Occasional Lower back pain
  - No skin lesions
  - No weight loss

PAST HISTORY

- Seasonal allergic rhinitis
- Occasional Migraines
- Regular menstrual periods with no heavy periods

SOCIAL HISTORY

- Lives with family
- 1 brother (15yo)
- In a happy relationship with her boyfriend
- Smokes 10 cigarettes a day
- Smokes occasional marijuana
- Works in a retail shop with a stable job
- No recent psychosocial stressors
- No recent travel. Last travel was 2 years ago to Vietnam
- Australian born to Aussie parents
- No FHx of CRC

MEDICATIONS

- Occasional Neurofen for headaches
- No other medications

- No known drug allergies

Review Of Systems

- Lightheadedness recently, No other constitutional symptoms
- Only positives:
  - Abdominal pain
  - Possible lower leg red raised tender rash at times
  - Occasional oral aphthous ulcers
  - Lower back pain
- CVS, Resp, Neuro, Urogenital systems otherwise unremarkable

On Examination

- BP: Lying 100/60 Standing: 95/60,
- HR:72/min, T=36.5, O2sat: 98%on RA,
- Pale Conjunctivae, No conjunctivitis
- CVS/Resp/Neuro/Joints/Skin Unremarkable
- Abdo: RLQ tenderness, Rectal examination unremarkable

DIFFERENTIAL DIAGNOSES

- IBS
- Lactose intolerance
- Infectious colitis
  - Yersinia, E-Coli, Shigella, Salmonella, Amoeba, C. diff, CMV, TB, HIV
- Crohn's Disease
- Ulcerative Colitis
- NSAID enteropathy/Colitis
- Rarer causes
  - Appendicitis
  - Diverticulitis
  - Diverticular Colitis (SCAD)
  - Ischaemic colitis
  - Perforating or obstructing carcinoma
  - Ovarian pathologies
- Lymphoma
- Endometriosis
- Carcinoid

INVESTIGATIONS

- Hb: **105** (119-160)
- MCV:**80** (80-100)
- WCC:**11.2** (4-11)
- Neut:**7.8** (2-7.5)
- Platelet: **465** (150-450)

- UEC: Unremarkable
- LFTs: N except
- Alb: **32**
- Coags: Unremarkable

- Negative coeliac serology

- Vit D: **30**(>50)
- Ferritin: **12**(30-300)
- Tsat: **8%**(10%-45%)
- TFT: N
- CRP:**15**(<5.0)
- ESR: **35**(<20)
- B12: 140(135-650), Active B12: **20**(>35)
- RC Folate: 30(>7.0)

INVESTIGATIONS

- Stool MCS repeated 3 times:

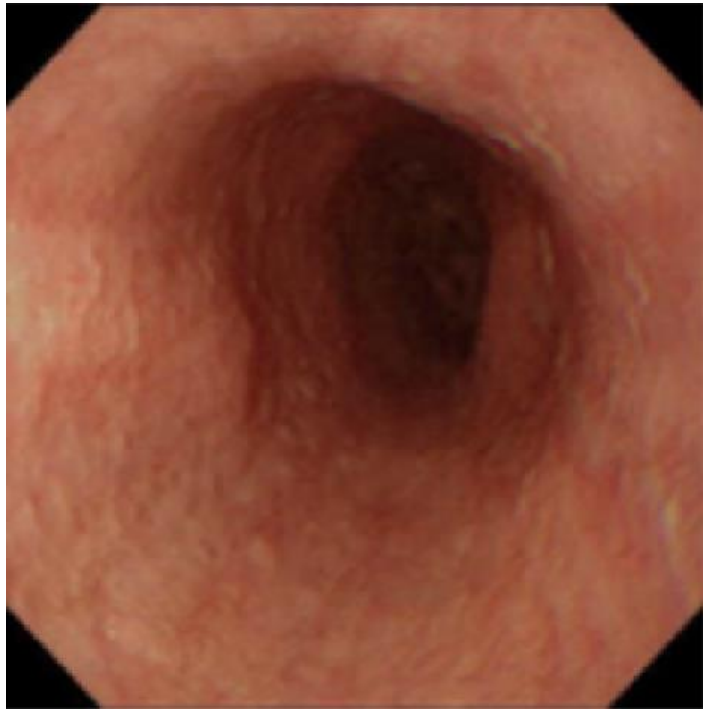
  No infection, No RBC, No WC. No Ova/cyst/Parasites

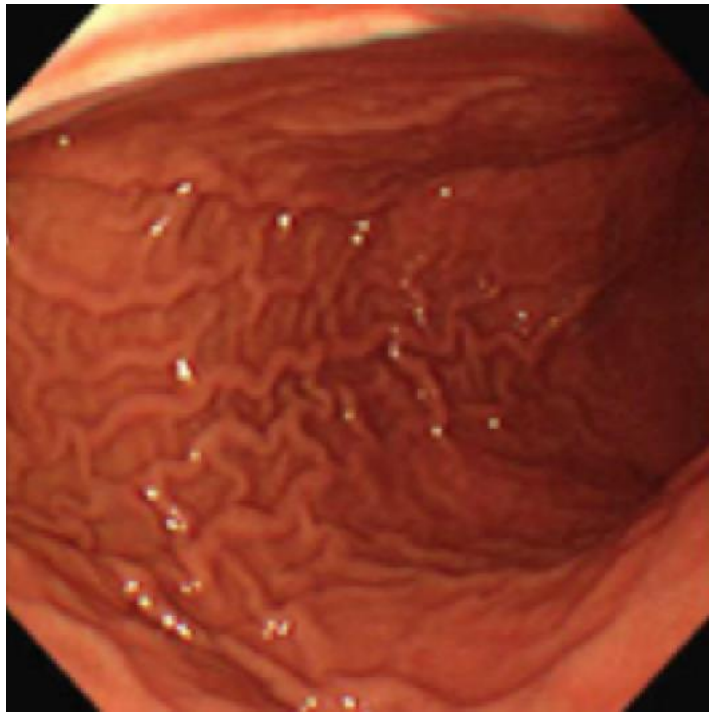
- Abdominal US: Essentially unremarkable
- Sacroiliac Xray: N

What shall we do next?

GASTROSCOPY

- Normal Oesophagus
- Normal Stomach
- Normal Duodenum





- Biopsies and Disaccs:
- No H Pylori
- No Coeliac disease
- Normal Diaccharidase results

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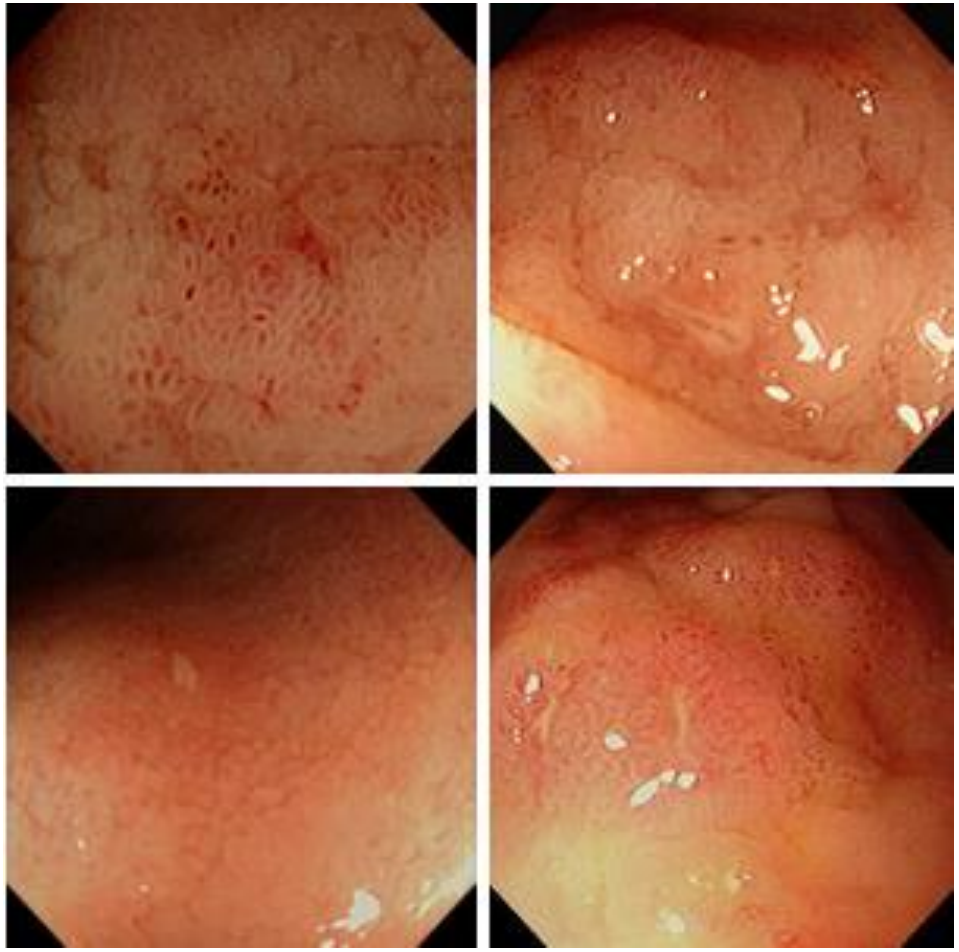
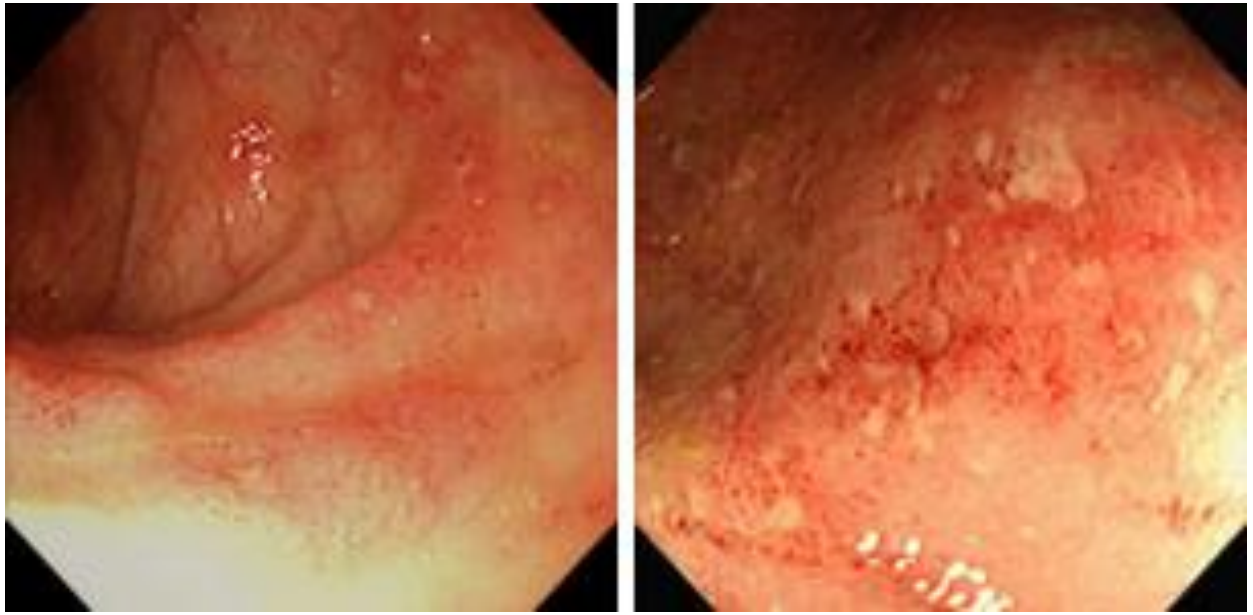
Colonoscopy





COLONOSCOPY

- Discontinuous inflammation,
- Aphthoid ulcers,
- Cobble stone appearance,
- Rectum sparing,

- Anal lesions,
- Fistula

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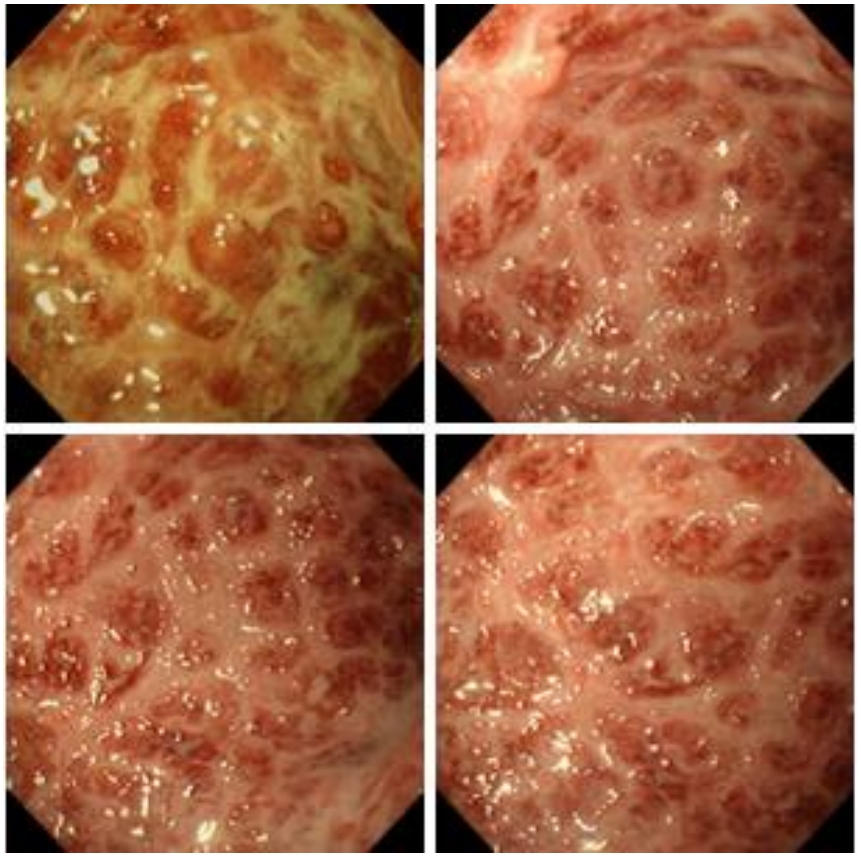
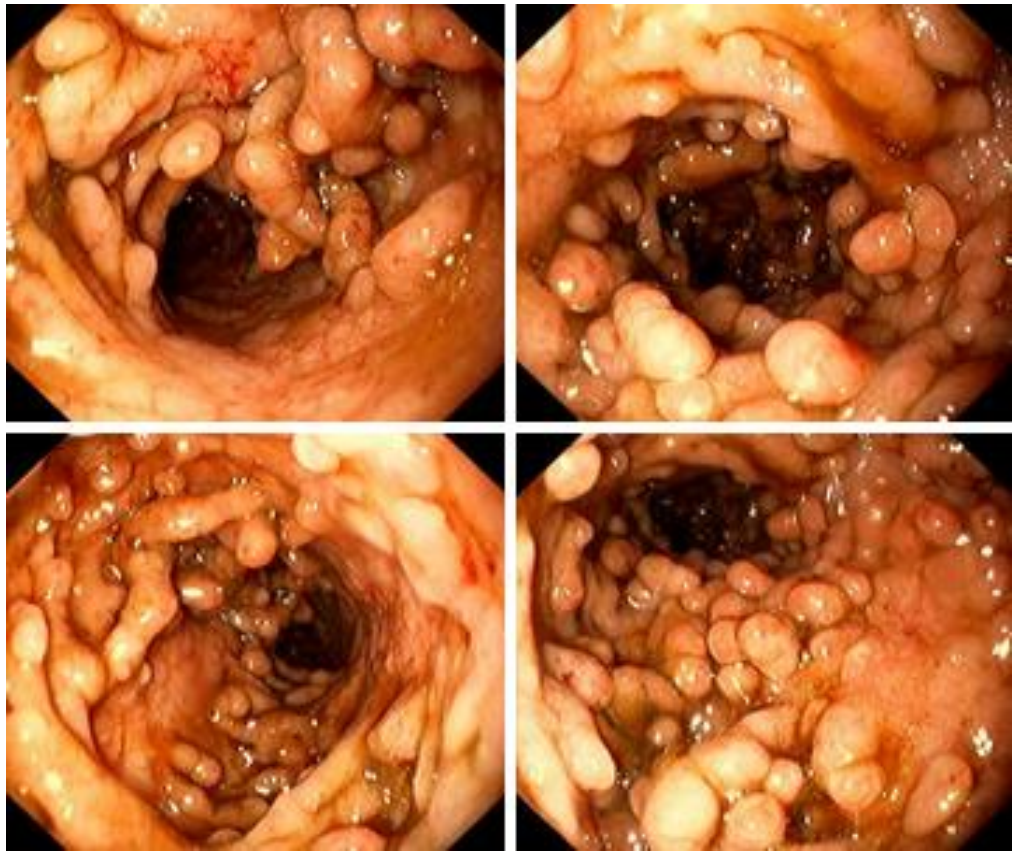
Colonoscopy findings





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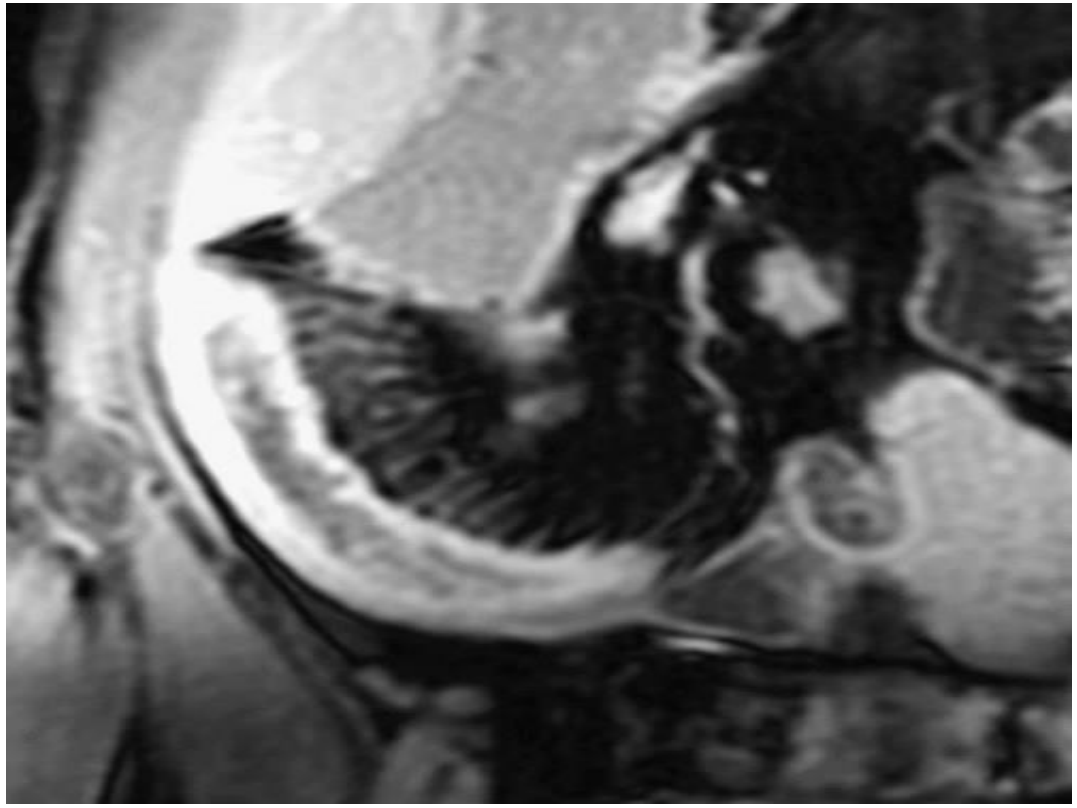
HISTOPATHOLOGY

- Granulomas are highly characteristic of CD

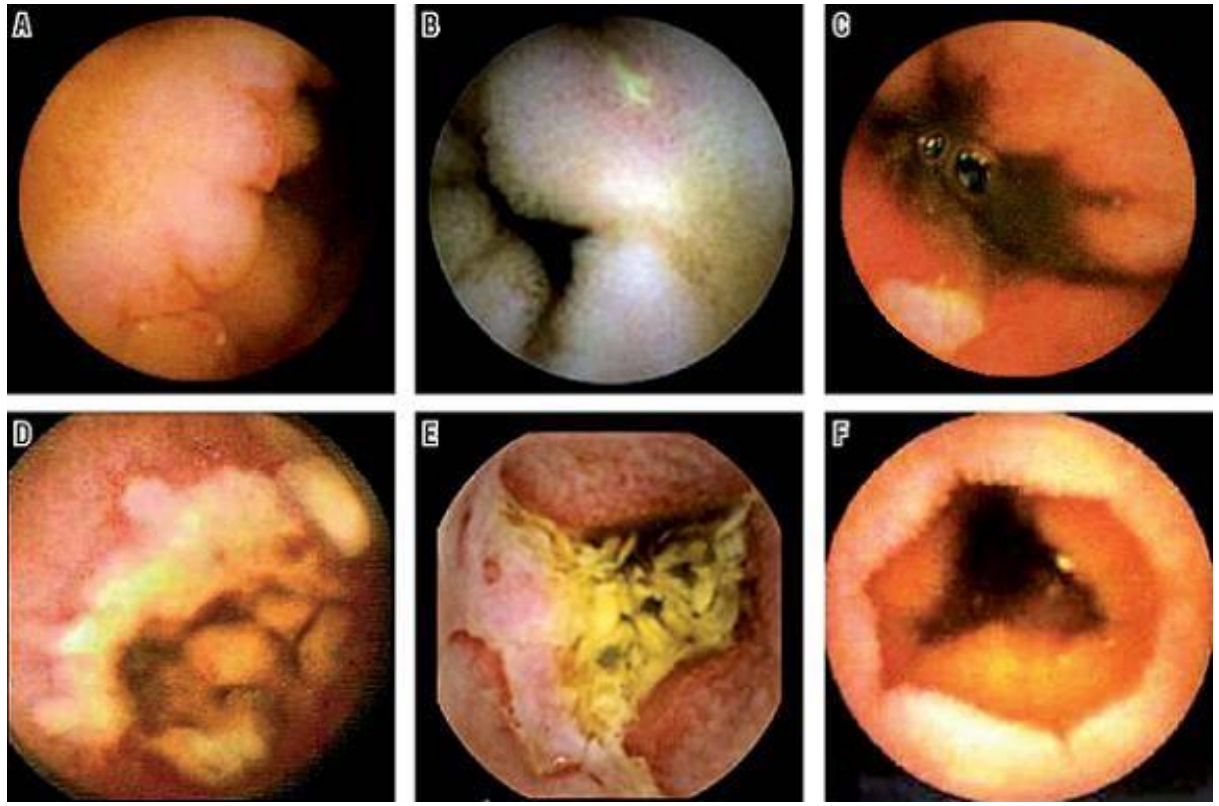
- Prevalence of granulomas in CD
  - 15% in endoscopic series
  - 70% in surgical series
- The presence of lymphoid aggregates in the submucosa and external to the muscularis propria is a reliable sign of CD even when granulomas are not seen
- TNF is the key cytokine in the formation of granulomas

Do we need any more investigations?

- Consider MR/CT enterography for further assessment of Small bowel if any concerns



ANY MORE INVESTIGATIONS?



- Video Capsule Endoscopy

ASSESSMENT OF SEVERITY(CDAI)

Variable	Multiplication Factor
Number of liquid or soft stools (over 7 days)	2
Abdominal pain (sum of scores over 7 days) 0=none, 1 or 2=intermediate, 3=severe	5
General well-being (sum of scores over 7 days) 0=good to 4=terrible	7
Number of complications (on day of assessment except for fever) arthalgias or arthritis iritis or uveitis erythema nodosum, pyoderma gangrenosum, or aphthous stomatits anal fissure, fistula, or abscess other fistula fever (>37.8°C, over 7 days)	20
Use of opiates for diarrhea 0=no, 1=yes	30
Abdominal Mass (on day of assessment) 0=none, 2=questionable, 5=definite	10
47 minus hematocrit (men), 42 minus hematocrit (women) (day of assessment)	6
Percentage deviation above or below standard weight (on day of assessment) according to the Metropolitan Life Insurance Height and Weight Tables for Men and for Women	1

- In remission <150
- Mild-moderate 150-220
- Moderate-severe 220-450
- Fulminant >450

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Endoscopic Assessment

CDEIS

	Deep ulcerations *12 points*	Superficial ulcerations *6 points*	Surface of ulcerations *(0-10 *)*	Surface of lesions *(0-10 *)*
Ileum	0 or 12	0 or 6	0–10	0–10
Right colon	0 or 12	0 or 6	0–10	0–10
Transverse	0 or 12	0 or 6	0–10	0–10
Left colon	0 or 12	0 or 6	0–10	0–10
Rectum	0 or 12	0 or 6	0–10	0–10

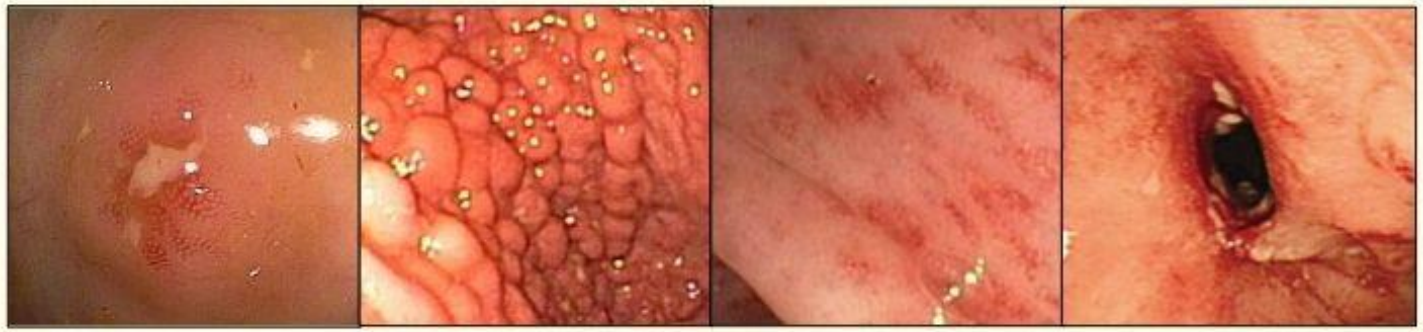
TOTAL (sum of all cases)	N
TOTAL/number of explored segments	N/1–5
+ 3 if ulcerated stenosis	0–3
+ 3 if non-ulcerated stenosis	0–3
CDEIS:	**0 to 44**

*0-10 cm refers to a visual analogue scale

Mary JY, *et al. Gut* 1989;30:983–9

SES-Score

Variable	0	1	2	3
Size of ulcer (diameter in cm)	None	Aphthous ulcers (0.1-0.5)	Large ulcers (0.5-2)	Very large ulcers (>2)
Ulcerated surface (%)	None	<10	10-30	>30
Affected surface (%)	Unaffected segment	<50	50-75	>75
Presence of strictures	None	Single, can be passed	Multiple, can be passed	Cannot be passed



Aphthous ulcer | Cobblestone appearance | Patchy erythema | Deep ulcerations and stricture formation

BIOCHEMICAL ASSESSMENT

- FBE :Anaemia, Thrombocytosis, Leukocytosis
- UEC: Electrolyte disturbance due to diarrhoea
- LFT: PSC, PBC, DILI, AIH
- Albumin: Good marker of general nutritional status in chronic conditions (Not helpful in acute settings)
- CRP: (30% CD have N CRP at diagnosis, 15-25% do not have CRP rise with mild-moderate active disease) 75-80% sesitivity in general for IBD
- ESR
- Micronutrients: Iron, B12, Folate, Vit D

FAECAL TESTS

- MCS/OCP low sensitivity

- Calprotectin:
  - High sensitivity
  - low specificity
  - Needs to be interpreted carefully in the context of patients symptoms and previous results

TREATMENT GOAL IN 2016?

- Treat to target (Deep remission)

- Biochemical remission
- Endoscopic remission
- Histologic remission
- Radiologic remission

PATIENT EDUCATION

- Prognosis of IBD
- Importance of compliance with medication esp in young patients
- Long-term risks of uncontrolled disease
- Risk factors for flare up
- Need for ongoing follow up and micronutrient assessment
- Check vaccinations (esp live vaccines before immunosuppression)
- Assess and prevent complications of immunosuppression
- Follow up surveillance colonoscopy

COMPLICATIONS OF CD

- ✓Perforation
- ✓Abscess formation
- ✓Stricture & small bowel obstruction
- ✓Nutritional deficiencies
- ✓Cancer: small bowel adenocarinoma
- ✓Cancer: colon if crohn's colitis

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IBD Treatment options in 2016

- Medications used in treatment
  - 5- ASA (NOT for CD anymore in 2016 except selective cases of CD colitis)
  - Antibiotics only in acute settings/selective cases with Perianal disease
  - Glucocorticoids
  - Immune modulators
  - **Biologics**

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MANAGEMENT OF FLARE UPS

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- Assess the need for hospitalization
- Corticosteroids IV/O
- Antibiotics
- Imaging to rule out Toxic megacolon/Abscess/Fistula
- VTE prophylaxis
- Surgical consult
- Low residue diet
- Assess for flare up risk factors
  - Poor compliance
  - Acute infection
  - C. diff
  - CMV
  - NSAIDs
  - Smoking
  - Psychosocial stress

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Side effects of sulfasalazine and aminosalicylates

	Common (>10 percent)	Uncommon (1 to 10 percent)	Rare (<1 percent)
Sulfasalazine	Nausea/headache Rash Male infertility Headache	Abdominal pain Hemolytic anemia Leukopenia Thrombocytopenia	Hepatitis Pneumonitis Neutropenia Pancreatitis Agranulocytosis Otalgia
Aminosalicylates	Watery diarrhea Abdominal pain Headache Nausea	Pancreatitis Colitis exacerbation Fever/rash Rash	Pneumonitis Pericarditis Nephritis Thrombocytopenia

AZATHIOPRINE AND 6MP

- ✓Pts should undergo an assessment of the thiopurine methyltransferase genotype before starting therapy with AZA or 6-MP.

- ✓Individuals who have low enzyme activity or are homozygous deficient in the TPMT mutation are at risk of very severe leukopenia, with potential septic complications, and are not be good candidates for therapy with these drugs.

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WHAT'S NEW ABOUT AZT AND 6MP

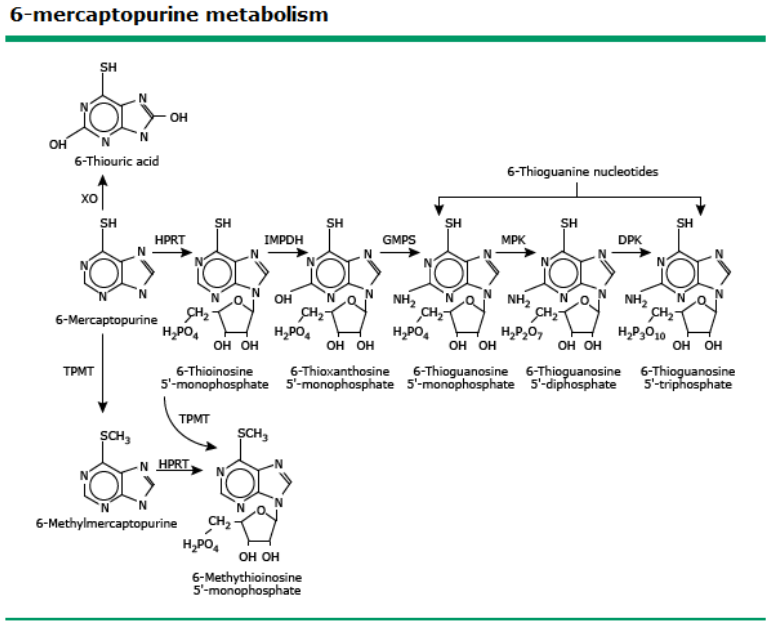
- Check levels 8-12 weeks after dose adjustments
  - 6TG
    - Best therapeutic effects at level of 230-400 pmol/10^8 RBC
    - a/w Bone marrow toxicity at levels higher than 400
  - 6MMP
    - High levels of >5700 is a/w liver toxicity

6MMP:6TG ratio (Old)

<11: suboptimal

11-20: satisfactory

>20: Shunting to 6MMP, may benefit from Allopurinol



WITHDRAWAL OF AZT/6MP

- 21% relapse rate in 18/12 after withdrawal of AZT
- 40% EXTRA risk of recurrence in 5 years compared to placebo
- Normally 40% risk of recurrence in 5 years

- Remember the extra risk of need for surgery with each relapse

AZT/6MP SIDE EFFECTS

- ✓Abnormal liver biochemical test results
- ✓Bone marrow suppression
- ✓Hypersensitivity reactions (fever, rash, arthralgia)
- ✓Infections
- ✓Lymphoma (esp if EBV-ve in males)
- ✓Nausea, abdominal pain, diarrhea
- ✓Pancreatitis
- ✓Skin cancer

MTX

- ✓IM or SC MTX (25 mg/week) is effective in inducing remission and reducing glucocorticoid dosage;
- ✓15 mg/week is effective in maintaining remission in CD .
- ✓Potential toxicities include leukopenia, hepatic fibrosis and Hypersensitivity pneumonitis

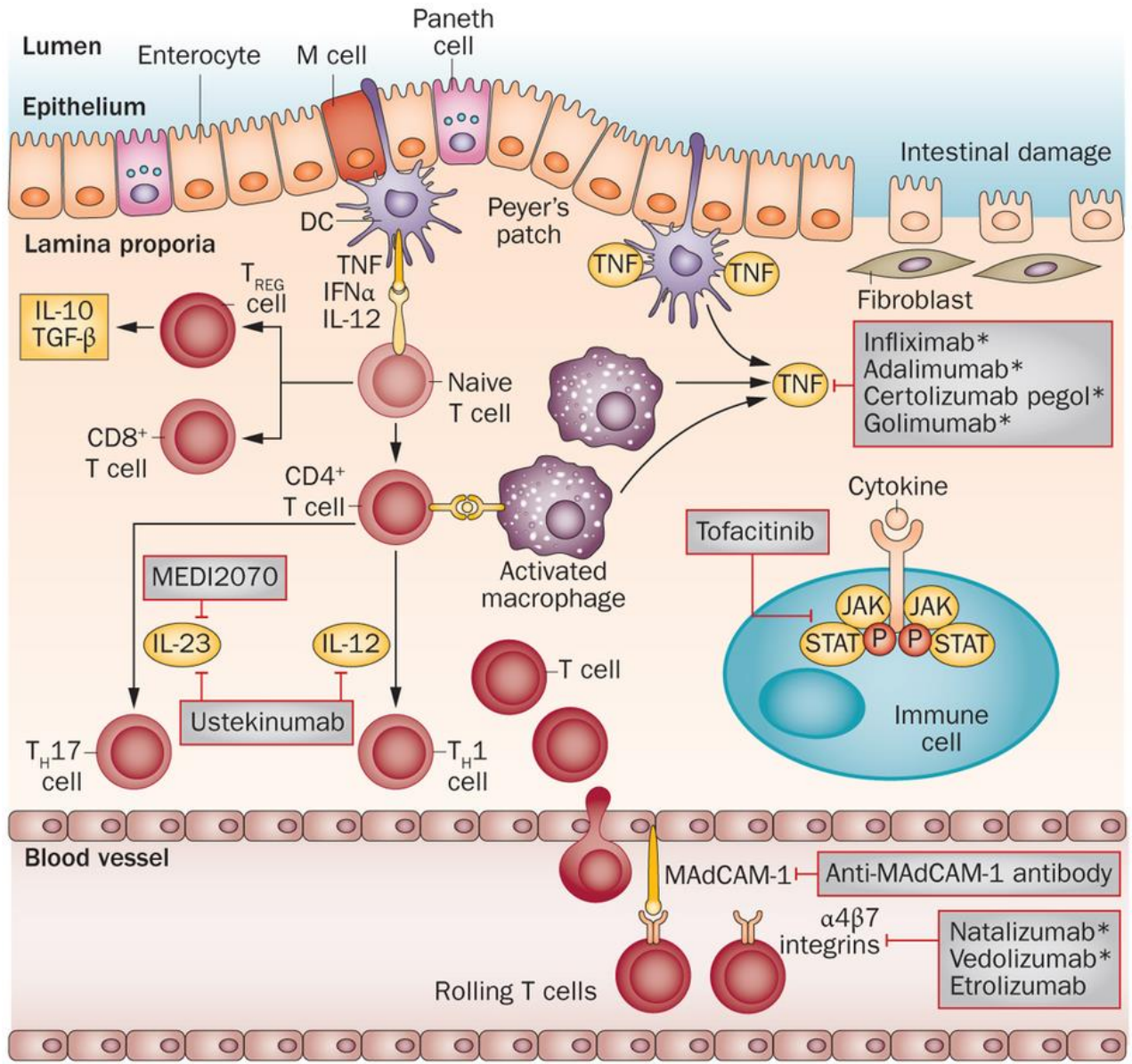
- Stop 3 months before conception

BIOLOGICS (MONOCLONAL ANTIBODIES)

- Biologics are genetically-engineered proteins derived from human genes.
- Designed to inhibit specific components of the immune system that play pivotal roles in fueling inflammation

BIOLOGICS (MONOCLONAL ANTIBODIES)

- Infliximab (TNFα inhibitor)- Remicade
- Adalimumab (TNFα inhibitor)- Humira, PBS for Juvenile Arthritis, CD
- Certolizumab (TNFα inhibitor)- Cimzia, Not on PBS
- Golimumab (TNFα inhibitor)- Simponi, PBS for RA, Psoriasis, AS
- Vedolizumab (α4β7 integrin inhibitor)- Entyvio, Mod-severe UC, Severe CD
- Ustekinumab(IL-12/23 inhibitor)- Stelara, PBS for RA
- Tofacitinib (JAK inhibitor) Xeljanz, PBS for RA
- Biosimilars (Inflectra, Exemptia)



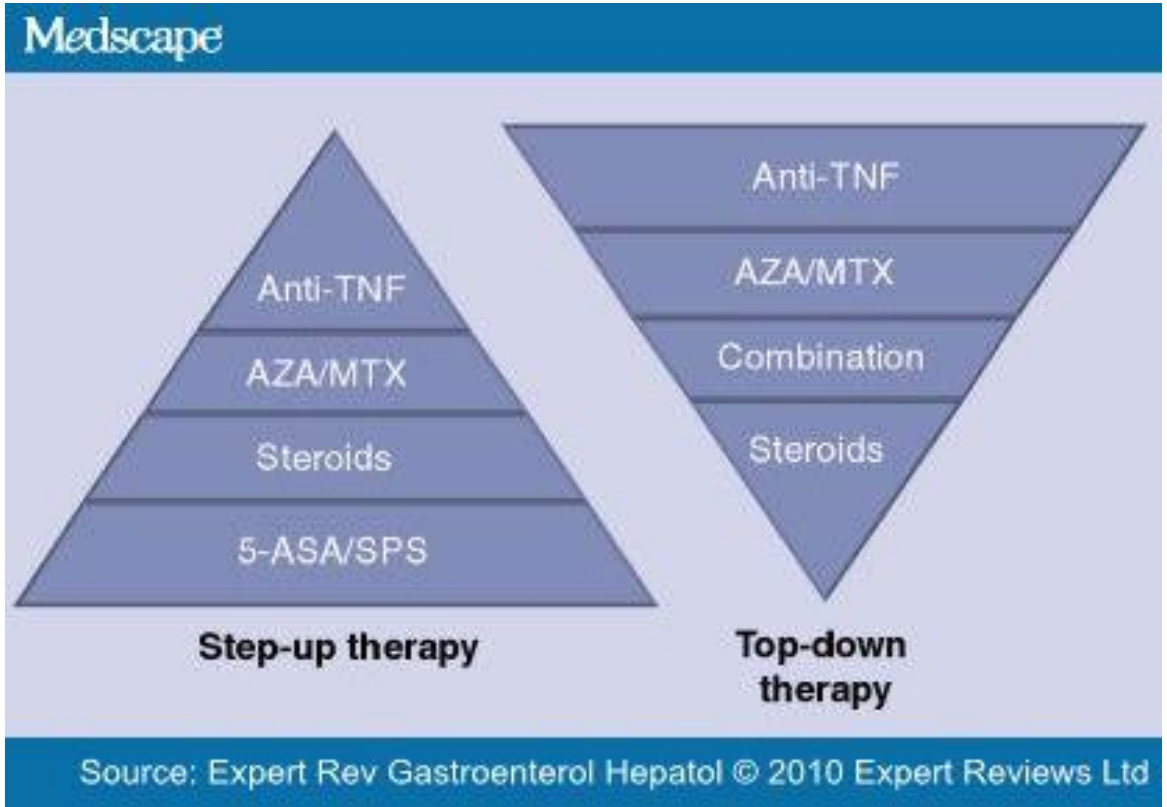
Nature Reviews | Gastroenterology & Hepatology

BIOLOGICS

✓Treatment of moderate to severe active CD or UC

✓Effective in CD patients with refractory perianal and enterocutaneous fistulas

- Different regimens
  - High dose vs standard dose induction
  - Topdown vs step up therapy
- Monitoring of trough levels
- Monitoring for Antibodies to biologics



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PRE-BIOLOGICS WORK UP

- Routine blood tests(FBE, UEC, LFT, CRP, ESR)
- Hepatitis B serology (Including HepB cAb/sAg/sAb)
- Quantiferon gold/CXR/Tuberculin test (Rule out Latent TB)
- Assess vaccinations
- Assess for any active infections
- Patient education

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VACCINATION REQUIREMENTS FOR ALL IBD PATIENTS

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INFECTION	VACCINE	VACCINATION REGIME	FURTHER INSTRUCTIONS
Hepatitis B Virus	Twinrix (HBV+ HAV) If Hep A immune Engerix-B may be substituted	**Standard schedule**: Week 0, 4, and 6 months **Rapid schedule**: Week 0, week 1, week 3, month 12.	Check HBsAb 6 months after last injection: >100 IU/L no booster required, check HBsAb 12 monthly (pts on immunosuppressants only)
Hepatitis A Virus		**Standard schedule**: Week 0, 4, and 6 months	Low/moderate response – consider booster (pts on immunosuppressants) <10 IU/L – not detected – administer booster **After booster:** 10 - >100 IU/L no booster required, check HBsAb 12 monthly (pts on immunosuppressants only) <10 IU/L – not detected – administer H-B-VAX II dialysis formulation (40Mcg/mL) Check HBsAb 6 months after booster
Pneumococcal	Pneumovax 23	Administer 2 weeks prior to immunosuppressant if possible.	Revaccinate every 5 years
Diphtheria Tetanus Pertussis	Boostrix	One vaccine required every 10 years, 5 if exposed to tetanus	No further action required
Influenza	Fluvax	Annual, March to April	Counsel patients to avoid infected persons
HPV	Gardasil	Week 0, month 2, month 6	For all females not immunised

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OTHER VACCINES – LIVE (NOT FOR IMMUNOSUPRESSED PATIENTS)			
Varicella zoster	Varilrix Varivax Zostavax	Week 0 then week 6	Immunise non immune patients ONLY if **NOT** on immunosuppressants
Tuberculosis	BCG		BCG vaccination is no longer recommended in Australia.
Yellow fever Virus	Stamaril	I dose provides protection for 10 years	Only consider for patient **NOT** on immunosuppressants who plan to enter endemic areas
ADDITIONAL RECCOMENDATIONS FOR TRAVEL			
Japanese Encephalitis	Jspect	2 doses 28 days apart, > 7 days prior to potential exposure	Inactivated vaccine. Vaccination required if travelling to Japan
Salmonella typhi	Tpherix Typhim VI	1 dose > 2 weeks prior to possible exposure	Inactivated vaccine
REFER ALL PATIENTS INTENDING TO TRAVEL TO A DOCTOR SPECIALISING IN TRAVEL MEDICINE			

Biologics side effects

	Vedolizumab	Anti-TNF therapy
Serious Infection	-	+/-
Opportunistic	-	+
Demyelinating	-	+
Autoimmune (SLE, vasculitis)	-	+
Dermatology (psoriasis)	-	+
Cardiac (CHF)	-	+
Pulmonary (Sarcoidosis, ILD)	-	+

Caveat: most new drugs have additional toxicities identified during post-marketing surveillance

Kopylov U. *GCNA* 2014
Feuerstein JD. *GCNA* 2014

WITHDRAWAL OF BIOLOGICS

- 50% recurrence risk in 24 months
- Patient education

- Rechallenge with the same biologics is >90 successful.

What to do when patient is undergoing a surgical procedure for an unrelated condition while on biologics?

- Refer to a Gastroenterologist
  - Individual assessment on a case by case basis

PREGNANCY AND BIOLOGICS

- Try to be in remission before conception
- If Patient has to remain on biologics, it can safely be continued till late stages of pregnancy and preferably stopped at 32 weeks.

- Detectable low levels of IFX/ADA has been reported in baby's blood up until 6-12 months after delivery.

- Avoid Live vaccines for the baby(esp Rotavirus)

BACK TO OUR PATIENT

- Impression: Moderate Crohn's Ileocolitis
- After vaccinations were all checked and TPMT was normal she decided to have Treatment with AZT/Prednisolone
- MRE showed no evidence of more proximal SB involvement
- Initially bloods checked Q2/52 until the target dose of 2.5mg/kg was achieved.
- MRI spine/sacroiliac joints showed no AS/Sacroiliitis.
- Patient's symptoms resolved after 2 months
- Repeat Colonoscopy confirmed Mucosal healing, but with Multiple Inflammatory polyps

FOLLOW UP

- Prednisolone was weaned over 8 weeks
- 3-6 Monthly FBE/Iron studies/LFT/UEC/B12/Folate
- Vit D/Ca supplements/ Iron Pills/ B12 injections
- Finally stopped smoking ☺
- Annual Influenza vaccine
- Pneumovax as per guidelines(Q5yrs or 2 doses)
- Bone densitometry Q2-3 years.
- Surveillance Colonoscopy (+/- Chromoendoscopy) Q2 years 8-10 years after first symptoms of Colitis
- Early referral to Gastroenterologist in case of flare up

ULCERATIVE COLITIS

- ✓The hallmark of UC is continuous inflammation that begins in the rectum.
- ✓ The earliest endoscopic sign of UC is mucosal erythema and oedema
- ✓ As disease progresses, the mucosa becomes granular and friable.
- ✓In severe inflammation, the mucosa may be covered by yellow-brown mucopurulent exudates associated with mucosal ulcerations.

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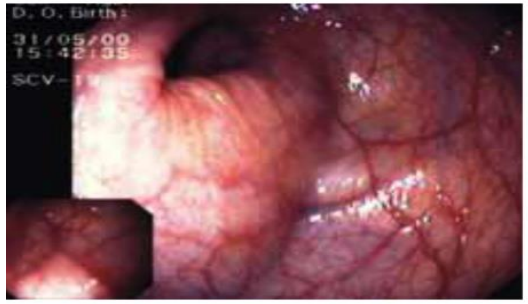
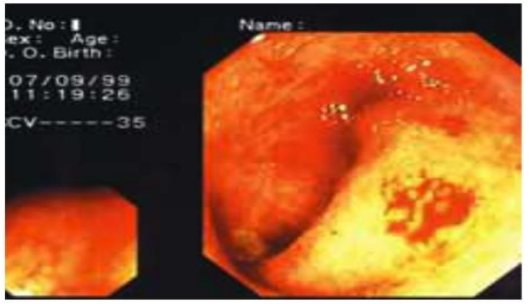
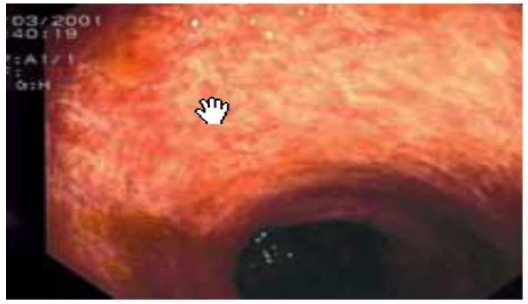
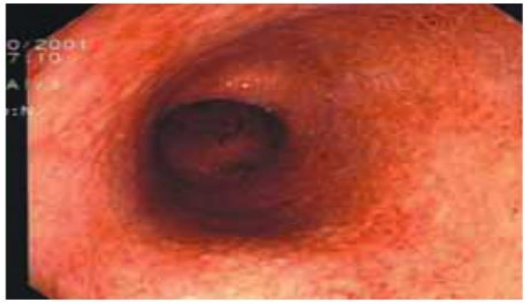
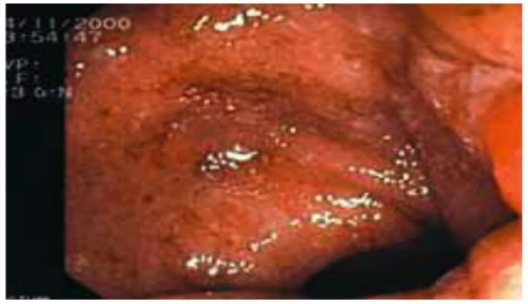
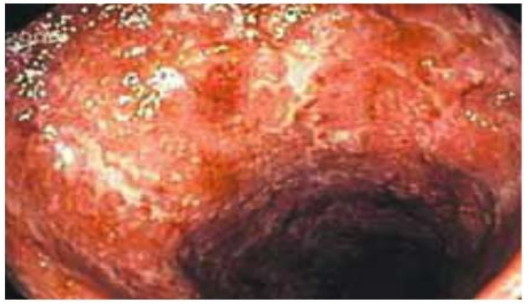
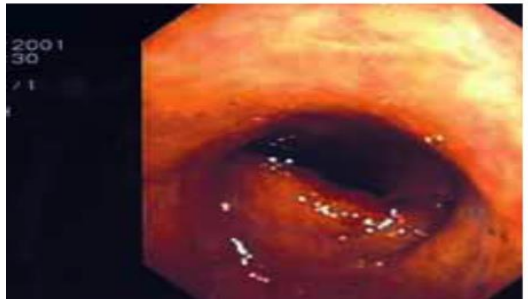
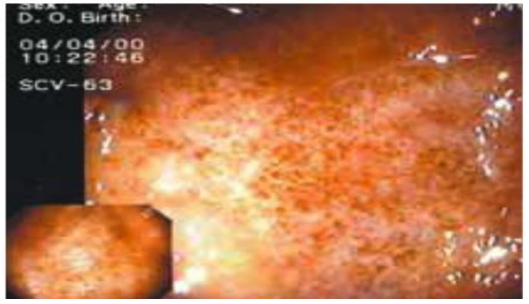
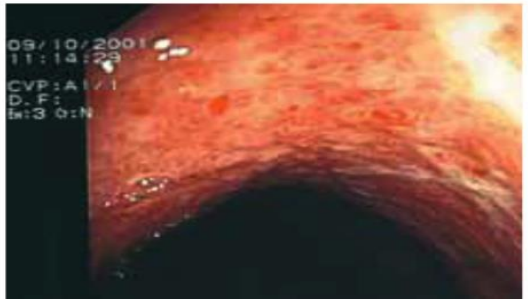
Mayo UC Endoscopic Score = 0 (Normal or inactive disease)	Mayo UC Endoscopic Score = 1 (Mild disease: erythema, decreased vascular pattern, mild friability)	Mayo UC Endoscopic Score = 2 (Moderate disease: marked erythema, absent vascular pattern, friability, erosions)	Mayo UC Endoscopic Score = 3 (Severe disease: spontaneous bleeding, ulceration)
			
			
			

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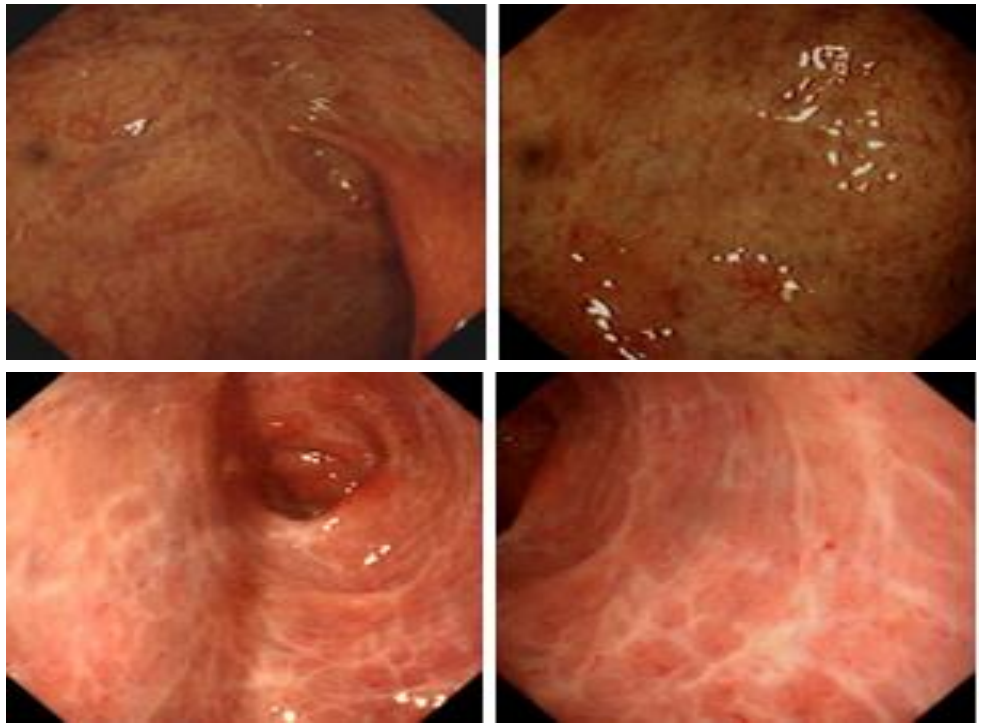

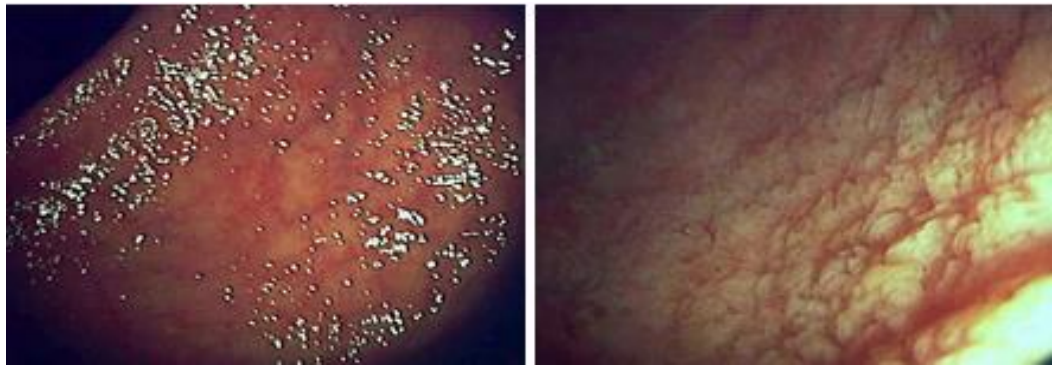

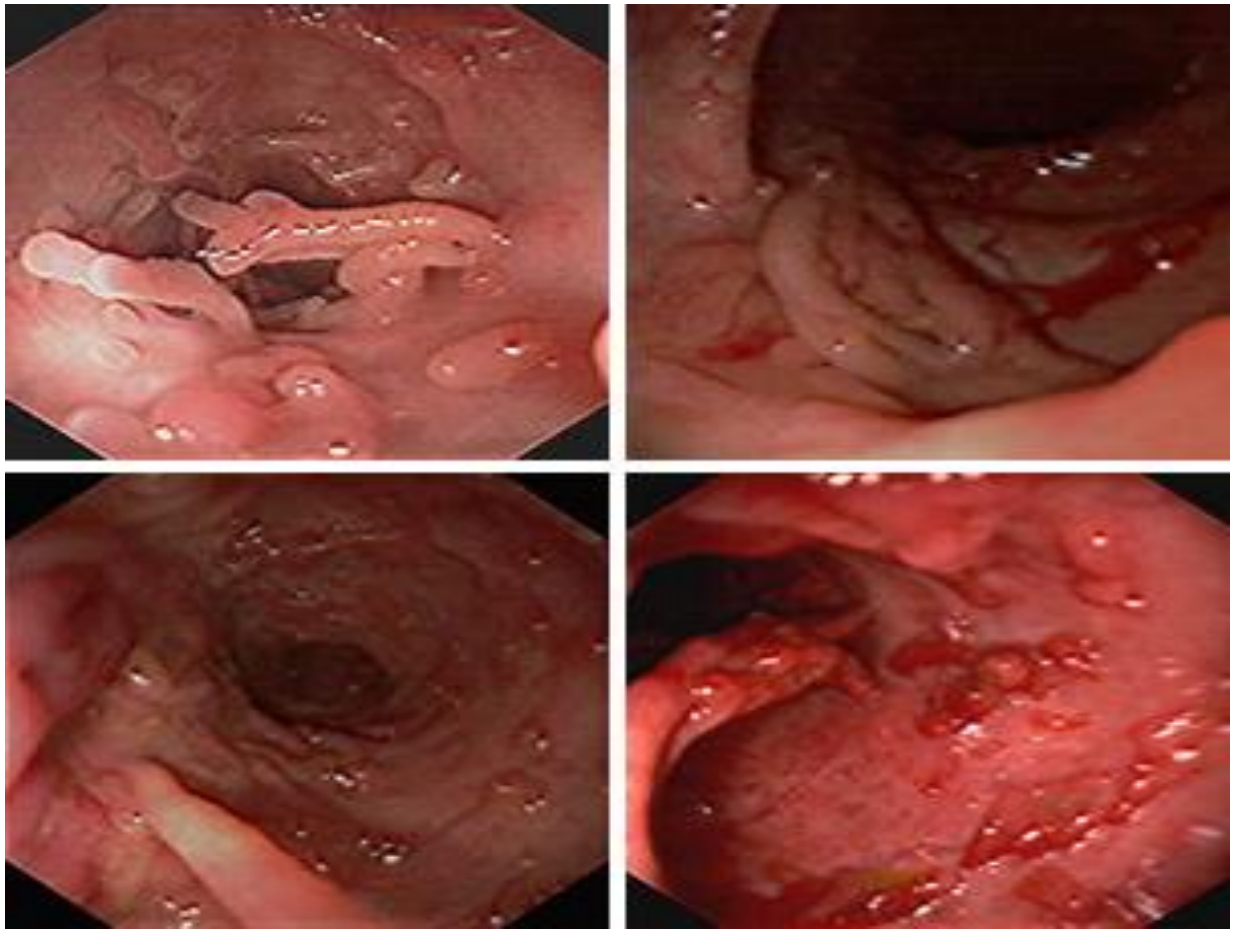

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UC

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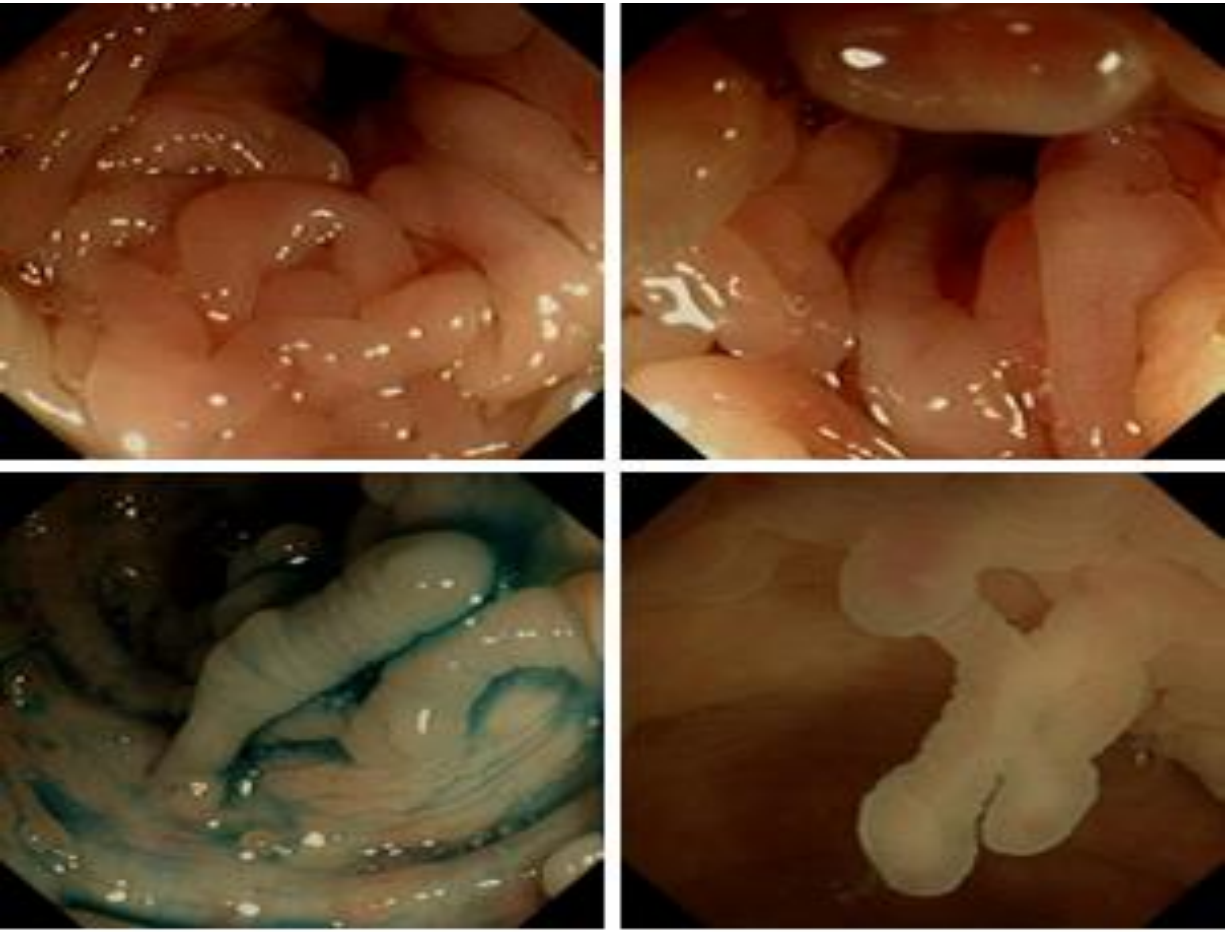

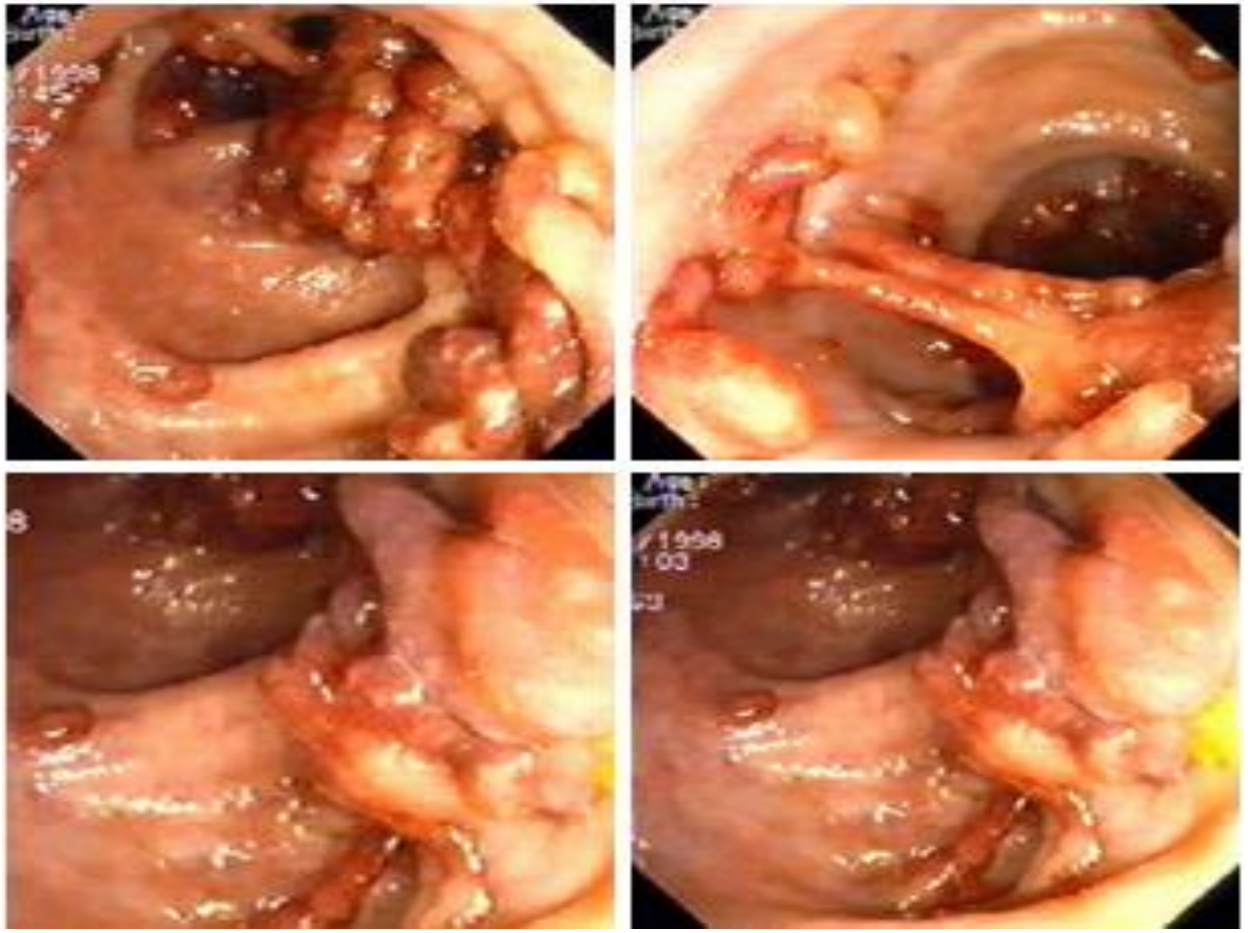

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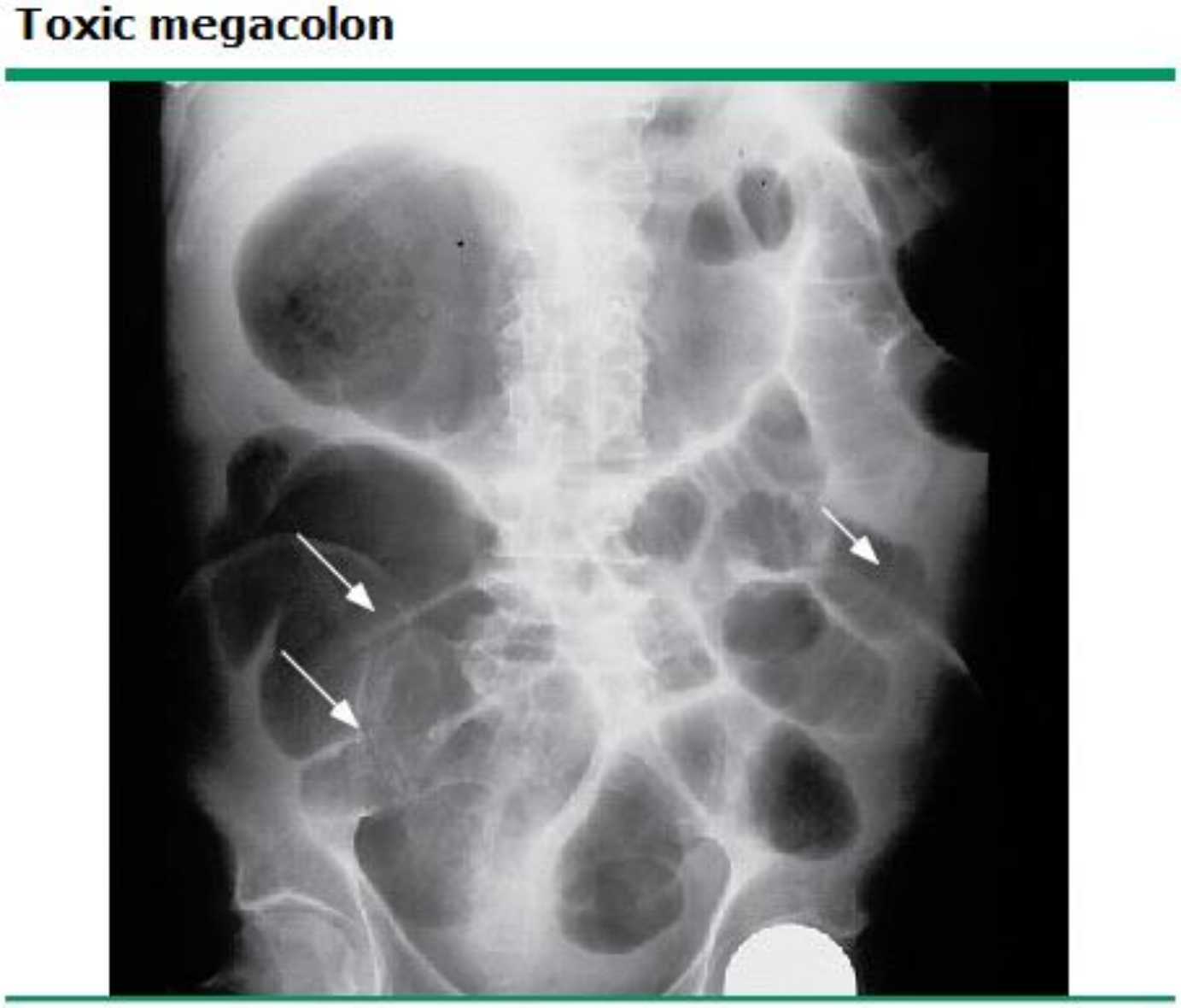
Tox

- ✓Def … >6 cm, with … UC.
- ✓It o …
- ✓It c… … ics.
- ✓Abc… … herapy alon…
- ✓Urg… … ve



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CHROMOENDOSCOPY

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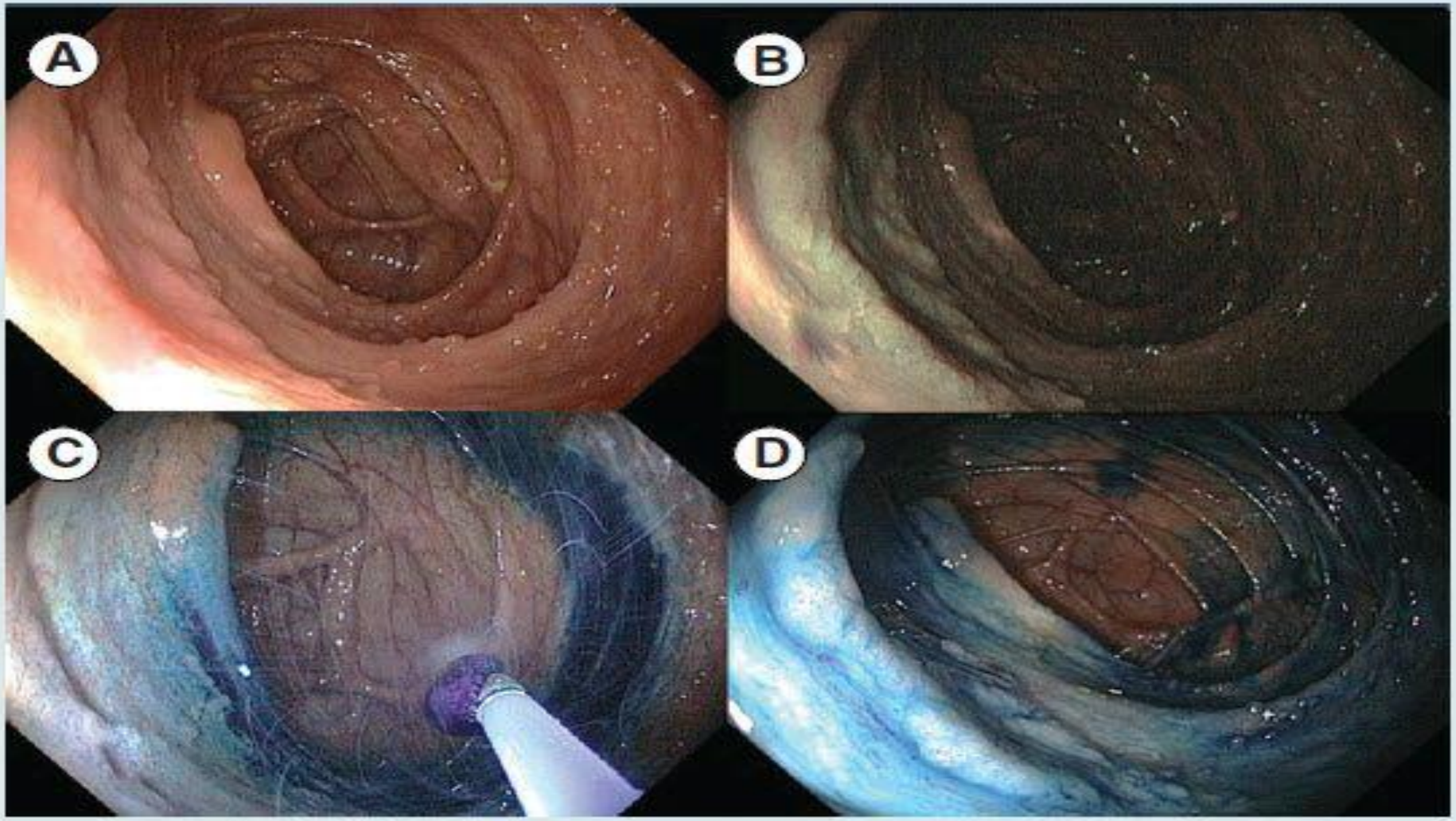

Mild-Mod UC

- Proctitis/Proctosigmoiditis
  - Induction: Topical 5-ASA+/- topical steroids if needed
  - Maintenance: 5-ASA enema +/- oral 5-ASA if needed

- Left-sided colitis-Pancolitis
  - Induction: oral and topical 5-ASA+/- topical/oral steroids
  - Maintenance: oral and topical 5-ASA

SEVERE UC

- If >2 flare a year or steroid dependent despite maximum dose of 5-ASAs then
  - AZT/6MP
  - Biologics

- If stroid refractory or no response to IV steroids for 7-10 days consider
  - Cyclosporin just short term as a bridge
  - Biologics
  - Some advocate empirical Abx therapy before consideration of colectomy
  - Colectomy

VEDOLIZUMAB FOR UC

- 6 week remission rate of 47% vs 26% for Placebo
- 52 weeks remission rate of 42% vs 16% for Placebo
- Low side effect profile

- Not ideal for fulminant disease or salvage therapy
- It takes 6-12 weeks to work (Can you keep patient well with Steroids in the meantime)

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Right Diagnosis, Right Treatment, Right Dose, Refractory?

Ulcerative Colitis	
Agent	Remission
Mesalamine	50%
Corticosteroids	54%
Thiopurines	58%
Infliximab	34.7%
Golimumab	18.7%
Adalimumab	17.3%
Cyclosporine	46.6%
Vedolizumab	41.8%

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Right Diagnosis, Right Treatment, Right Dose, Refractory?

Crohn's Disease	
Agent	Remission
Rifaxamin	52%
Corticosteroids	58%
Thiopurines	44%
Methotrexate	39%
Infliximab	28%
Adalimumab	36%
Ustekinumab	41.7%
Certolizumab	48%
Natalizumab	61%
Vedolizumab	39%

SURGERY

- Indications for urgent surgery

✓Toxic megacolon refractory to medical management

✓Fulminant attack refractory to medical management

✓Uncontrolled colonic bleeding

- Indications for elective surgery

✓Long-term steroid dependence

✓Dysplasia or adenocarcinoma found on surveillance biopsy for colonic disease present 7-10 years

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SURGICAL INTERVENTION IN IBD

- UC: Proctocolectomy with ileostomy, total proctocolectomy with ileoanal anastomosis, UC is surgically curable

- Fulminant colitis: Surgical procedure of choice is subtotal colectomy with end ileostomy and creation of a Hartmann pouch

- CD: Surgery (not curative) most commonly performed in cases of disease complications

FUTURE THERAPIES

- Tofacitinib (JAK-2 inhibitor)
- Various other monoclonal antibodies
- Mongersen for CD
- Faecal transplant
- Probiotics
- Stem cells therapy

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THANK YOU

DR OMID ZARGHOM

SYDNEY NORWEST GASTROENTEROLOGY

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