Inflammatory Bowel Disease

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Queensland Government

Case Study

A 25-year old woman, with history of Irritable Bowel Syndrome since childhood, presents with rectal bleeding and moderate abdominal cramping. On physical exam she is of medium build and looks well. Blood work and stool studies are performed. Which of the following findings would help differentiate irritable bowel syndrome with hemorrhoidal bleeding from mild ulcerative colitis?

A.Normal CRP level of 2

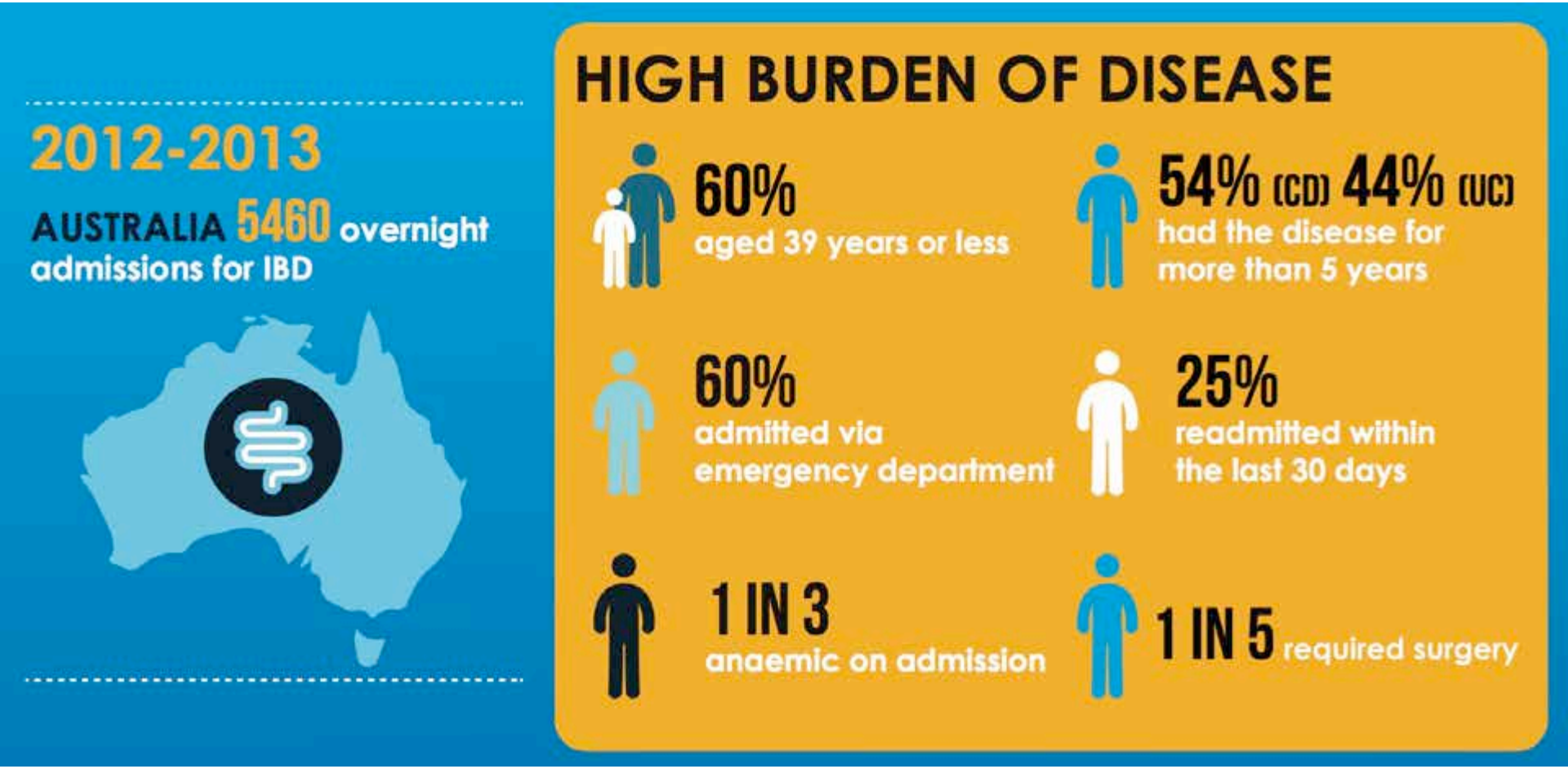
B.Normal ESR level of 5

C.Elevated fecal calprotectin level of 1000ug/ml

D.Normal haematocrit of 34.5

E.Positive assay for ASCA

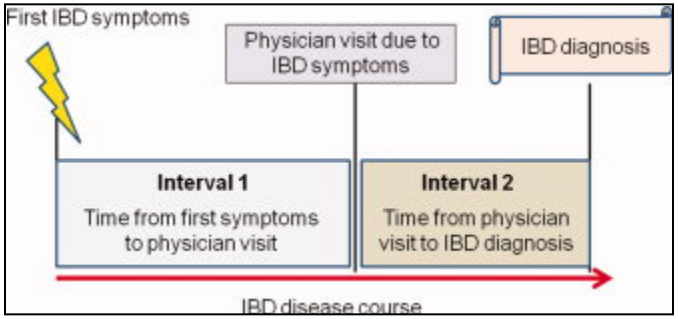
Snapshot: IBD patients presenting to Australian hospital in recent times



2012 Hospital Cost: $100 million, Productivity Lost: $361 million
2017: Estimated 80,000 Australians live with Inflammatory Bowel Disease

Inflammatory Bowel Disease Audit: Final report of the first audit of the organisation and provision of IBD services in Australia 2016; Crohn's & Colitis Australia

Diagnostic Lag Time in Inflammatory Bowel Disease Can increase Morbidity and Complications



	CD	UC	IC	*P*-value
Number of patients	932	625	34	
Time from first symptoms to IBD diagnosis (median, IQR)	9, 3-24	4, 1-12	3, 2-6	CD vs. UC: $P < 0.001$ CD vs. IC: $P < 0.001$ UC vs. IC: $P = 0.441$
Time from first symptoms to physician visit (median, IQR)	2, 0-6	1, 0-4	1, 0-2	CD vs. UC: $P = 0.002$ CD vs. IC: $P = 0.025$ UC vs. IC: $P = 0.181$
Time from physician visit to IBD diagnosis (median, IQR)	4, 0-18	1, 0-5	1, 0-4	CD vs. UC: $P < 0.001$ CD vs. IC: $P = 0.003$ UC vs. IC: $P = 0.429$

The biggest delay in making a diagnosis of IBD is a result of not suspecting it

Systematic evaluation of risk factors for diagnostic delay in inflammatory bowel disease.; Inflamm Bowel Dis. 2012 Mar;18(3):496-505; Swiss IBD Cohort

Inflammatory Bowel Disease has distinct red flag symptoms

Irritable Bowel Syndrome	Inflammatory Bowel Disease
• chronic abdominal pain and discomfort • urgency and bloating • diarrhoea • alternating bouts of diarrhoea and constipation • changes in bowel habit	• ***All Symptoms on left but also:* • weight loss (>5% in last 6m) • nocturnal diarrhoea • blood in stools • Fever • symptoms of bowel obstruction, abdominal/perianal mass • Family history of IBD • New symptoms in patient ≥50 years • elevated CRP (>25) • anemia (Hb<100) • iron deficiency, low albumin • Faecal Calprotectin ↑ (>200)

There is no single test that confirms diagnosis of IBD

Tests	Comment
Faeces	1. Faecal M/C/S, OCP, Multiplex PCR 2. Clostridium difficile toxin + PCR 3. Faecal Calprotectin – useful when diarrhoea > 1/12 ** *FOBT should not be used for IBD diagnosis*
Serological	1. FBE: ↓Hb, ↓MCV, ↑Plt, ↑WCC 2. Biochemistry: ↓albumin, ↑creatinine/urea 3. Iron Studies ↓Ferritin 4. CRP/ESR – note normal values does not exclude inflammation ** *Special Antibody Tests: not recommended for initial testing*
Imaging	1. AXR: may establish whether UC is present, excludes toxic megacolon in ASC, can show small bowel dilation in CD 2. Cross-Sectional Imaging: • USS/MRI – preferred • CT – not ideal ***Barium Studies – rarely used as insensitive and unnecessary*

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Faecal Calprotectin (FC)

- Neutrophil-derived proteins: FC, elastase, lysozyme, and lactoferrin– FC most sensitive
- Selection of patients for further diagnostic investigation and Assessing severity of colonic inflammation
  - **FC levels <50 µg/g have a NPV >92% to exclude organic gastrointestinal disease.**
  - **Levels >250 µg/g correlate with endoscopic IBD disease activity**; Sens 90%.
- Does not differentiate between the types of inflammation
- Marker of relapse in patients with inactive inflammatory bowel disease
  - Doubling FC levels associated with an increased risk of relapse [HR]: 2.01; 95% [CI]: 1.52–2.65)
- ** No Medicare Rebate in Australia: Costs: $70-80

Schoepfer: Inflamm Bowel Dis. 2008 Jan;14(1):32-9.
NICE. Faecal Calprotectin diagnostic tests for inflammatory diseases of the bowel. NICE diagnostic guidance (DG11). 2013
Dhaliwal, Frontline Gastroenterol 2015;6:14–19

Referral pathways: urgent referral for severe symptoms

Refer to hospital admission for treatment

- Bloody Diarrhoea (≥6x/day) & >1 of:
- Fever >37.8° C
- Anaemia (Hb <10.5 g/dL)
- Tachycardia (pulse rate >90 bpm)
- ESR >30 mm/h or CRP >25 mg/L

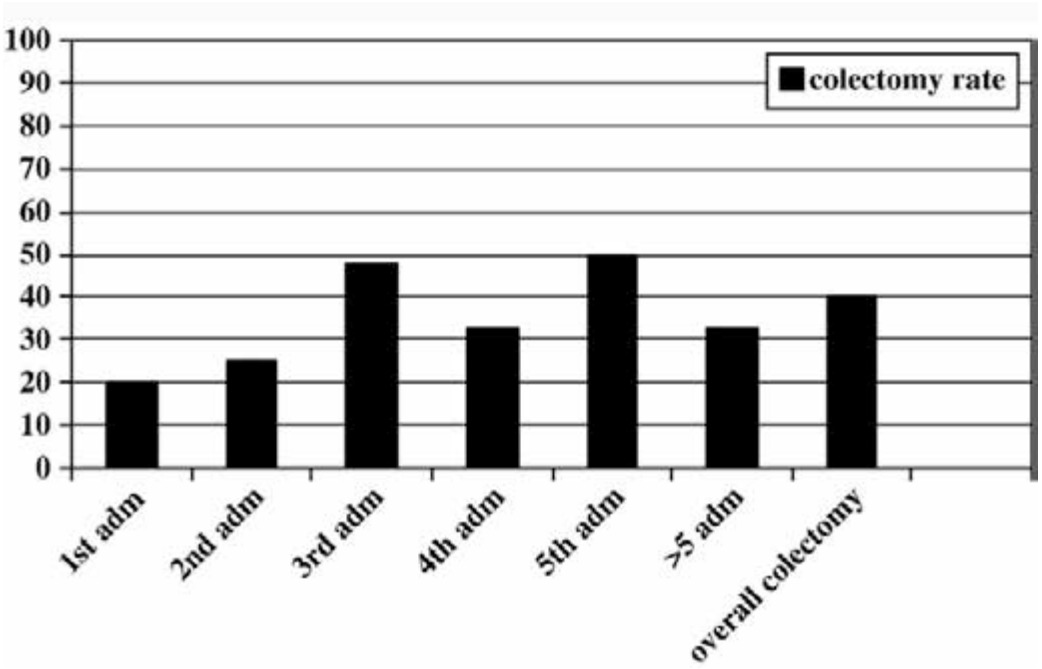
Acute Severe Colitis (ASC) is potentially life-threatening: Needs Emergency Assessment and immediate Gastroenterologist Input

Refer to a gastroenterologist:

- IBD Symptoms previously mentioned
- Early Investigations

1. Magro F *et al*. *J Crohn's Colitis* 2017. doi:10.1093/ecco-jcc/jjx008. 2. 2013 Clinical Insights Steering Committee. Clinician's guide to ulcerative colitis (UC) management. June 2014 V1

Acute Severe Colitis is a marker for Colectomy



- Quarter of all UC patients experience ASC
- 40% ASC patients undergo surgery vs 3% of non-ASC UC patients
- More TW criterion associated with higher colectomy rates (Fever, Anemia, Tachycardia, CRP>25/ESR>8)

The pattern and outcome of acute severe colitis ; Lotte C. Dinesen Simon P.L. Travis; Journal of Crohn's and Colitis, Volume 4, Issue 4, 1 October 2010

Suggested GP role in managing Established inflammatory bowel disease

Shared decision making

Smoking cessation

Adherence

Ensure remission

Nutritional status

Regular monitoring
e.g. vaccinations, Pap smears, bone mineral density

Colorectal cancer surveillance

Psychological stress

Annual specialist review

1. Gastroenterological Society of Australia (GESA). Australian Guidelines for General Practitioners and Physicians: Inflammatory Bowel Disease (IBD). Third Edition. Melbourne: Digestive Health Foundation; 2013. 2. Ooi S-Y, Andrews JM. *Med Today* 2014; 15:36–44.

Identifying Patients in need of Early Specialist Help or Aggressive Therapy

Impact of Demographics:

- IBD patients are young and itinerant, too busy, poor response, medication SE
- Vast regional area serviced by surgeons and non-gastroenterologist
- >90% UC have mild-moderate disease: can be managed by GP with focus on maintaining remission

Poor Outcome Predictors

Loss of Weight > 5kg at presentation
Poor appetite: decreased oral intake
Unable to manage usual activities
Need for steroids at first visit
Hospital admission at first visit
Young age onset (<40y)
Widespread disease: ileal/perianal disease in CD or pancolitis in UC
Intolerance/non compliance to medication

Refer all IBD patients – At minimum: 6-12monthly gastroenterologist review for stable patients

Tindall WN et al. J Manage Care Pharm 2007; 13 (7 Suppl. S-a):S2–S12
Bennett AL et al. World J Gastroenterol 2015; 21:4457–65.

Patient Reported Outcomes (PRO) in Treat-to-Target Approach

Mucosal Healing (Endoscopic Remission) as Goal: Absence of Inflammation and Ulceration ie MAYO endoscopic subscore 0/1 in UC and absence of ulceration in CD.

	Treat-to-Target PROs
CD	resolution of abdominal pain and normalization of bowel habit
UC	resolution of rectal bleeding and normalization of bowel habit

And…

•Resolution of symptoms alone is not a sufficient target. Objective evidence of inflammation of the bowel is necessary when making clinical decisions

•Available biomarkers including CRP and fecal calprotectin are not targets: they are are adjunctive measures of inflammation for monitoring in CD.

Failure of achieving PROs or persistence of inflammation biomarkers despite maximising therapy requires referral/discussion with specialist

Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target; Am J Gastroenterol 2015; 110:1324–1338, L Peyrin-Biroulet

Question

In which of the following patients would smoking cessation be the most likely to improve long term disease course?

A. 35 year old male smoker with ulcerative colitis reasonably well controlled on mesalamine

B. 62 year old female smoker with watery diarrhoea and colonic biopsy finding a thickened band of subepitheilial collagen

C. 27 year old male smoker who is recovering from 2nd small bowel resection for medically refractory ileitis

D. 42 year old female smoker with acute diarrhoea after returning from a trip to Bolivia

E. 61 year old male alcoholic smoker with chronic malabsorptive diarrhoea

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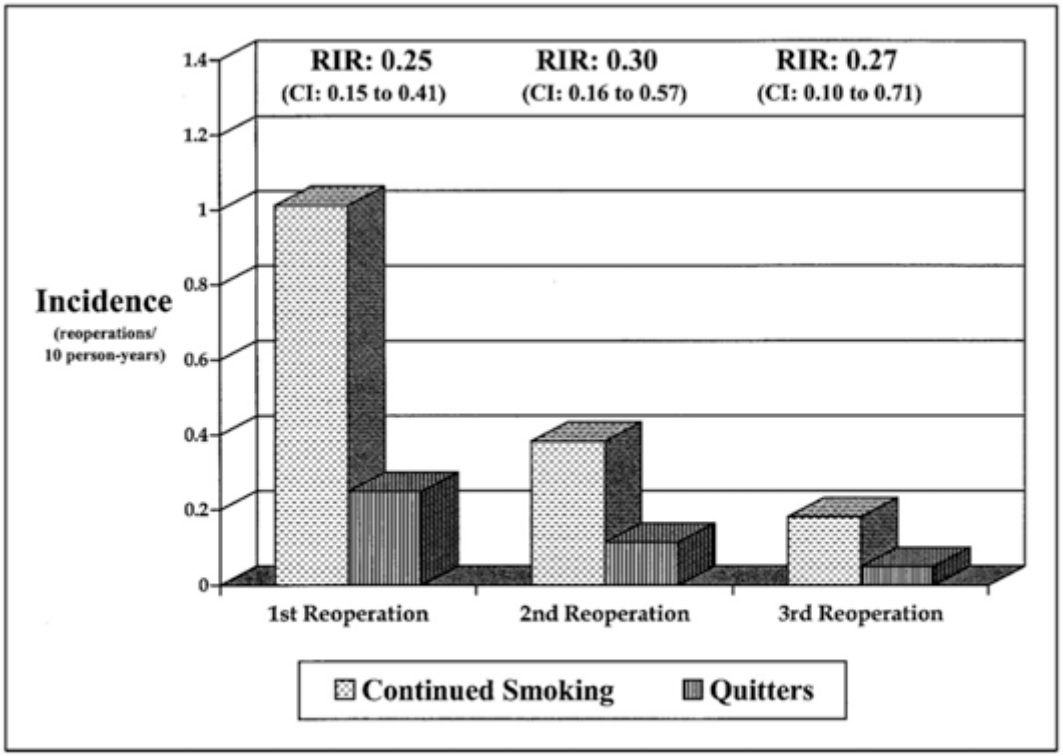
Smoking is the most important modifiable risk factor for progression in Crohn's Disease, more flares, need for 1st operation, and surgical recurrence



Crohn's disease patients who quit smoking have a reduced risk of reoperation for recurrence; William R. Ryan; The American Journal of Surgery 187 (2004) 219–225

Case Study

A 26year old woman presents with a new diagnosis of active Crohn's disease involving the terminal ileum and colon. During her initial evaluation she was found to have a positive pregnancy test. She is moderately ill and starting to lose a small amount of weight. She is anemic and hypoalbuminemic. She is concerned about fetal exposure to medications used to treat her IBD. Which of the following approaches to disease management is most appropriate at this point?

A. Wait until the 1st trimester is over and initiate prednisolone and 6-mercaptopurine at that time

B. Start prednisolone and hold off on the 6-MP until the 3rd trimester

C. Use mesalamine only until the pregnancy is over and then start more aggressive therapy if needed

D. Initiate anti-TNF therapy

E. Start prednisolone and methotrexate

Pregnancy & IBD

- Lower birth rate among men and women with quescent IBD due to avoidance of pregnancy rather than inability to conceive:
  - Exception:
    - Proctocolectomy/IPAA pouch formation in women: x3 fold risk; active CD
    - Reversible reduced sperm motility/count in men using sulfasalzine
- Goal: remission ideally for 6m prior to conception: Active IBD increase preterm deliveries, intrauterine growth restriction, and low birth weight
  - 30% of CD pts in remission at time of pregnancy will flare
    - if conception occurs at a time of active disease, two thirds have persistent activity and of these, two thirds will deteriorate
    - Fetal Mortality is high as 18-20% when emergency CD Surgery is required
- Ressurance that risk of children having IBD low as 6-8%

Ferguson, Inflammatory bowel disease in pregnancy. BMJ. 2008;337

- Nearly all UC/CD medications can be continued during pregnancy and breast-feeding (despite TGA warnings)

Mesalazine/5-ASA	C
Azathioprine/Mercaptopurine (TP)	D
Steroids/Prednisolone	A
Anti-TNF: Infliximab, Adalimumab	C
Vedolizumab	Unclassified – early limited data safe
**Methotrexate: teratogenic; never use	

Continuing 5-ASA/Immunosuppression and specialist notification/referral during new pregnancy or family planning is vital

Anti-TNF/Thiopurine usage during pregnancy

Anti-TNF/Thiopurine (TP) was safe in PIANO registry (multinational prospective study, n=1052)

- TP and anti-TNF agents not associated with increase in complication: spontaneous abortion, congenital abnormality, preterm birth, intrauterine growth retardation, caesarean section, NICU stays
- Slightly higher risk of mild childhood infections in infants of mothers on combination TP and anti-TNF
- The majority (72%) of newborns were breastfed:
  - Breastfeeding was not associated with an increase or decrease in infection risk among drug exposures and within each drug category

	IFX concentration µg/ml			ADA concentration µg/ml		
	Last infusion < GW 30	Last infusion ≥ GW 30	*P* value	Last injection < GW 30	Last injection ≥ GW 30	*P* value
Total number	18 (41%)	26 (59%)		7 (19%)	29 (81%)	
Maternal blood	0.6 (0.0-3.3)	4.0 (0.0-22.2)	< .0001	0.3 (0.0-0.7)	2.1 (0.0-10.0)	.0006
Cord blood	2.2 (0.1-8.9)	10.0 (1.9-28.7)	< .0001	0.2 (0.0-1.2)	2.5 (0.0-12.1)	.0047

GW = gestational week

Avoid use of live vaccine in Infants for first 12months: Rotavirus, MMR (measles-mumps-rubella), oral polio, small pox, Varicella, BCG (Bacille Calmette-Guerin), Yellow Fever

Uma Mahadevan, PIANO: A 1000 Patient Prospective Registry of Pregnancy Outcomes in Women With IBD Exposed to Immunomodulators and Biologic Therapy
Juulsgaard, Concentrations of Adalimumab and Infliximab in Mothers and Newborns, and Effect on Infection, Accepted Manuscript Gastroenterology

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A 28 year old man with a 10year history of Crohn's disease is very stable on 5mg/kg Infliximab every 8 weeks and 100mg of Azathioprine. He is planning on going to South America to work in a native clinic for 2 months and then plans on trekking through the rain forests. He goes to a travel clinic for an immunization review. Which of the following recommended immunizations should be avoid based on his clinical and medication history?

A.Malaria prophylaxis

B.Hepatitis B vaccination

C.Yellow fever immunization

D.Pneumococcal immunization

E.Influenza immunization

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Vaccinations

Following 5 to be Considered for all people with IBD
Influenza vaccine (trivalent inactivated vaccine) annually
Pneumococcal vaccine (booster may be needed after 3-5y)
Hepatitis B vaccine
Varicella zoster vaccine
Human Papilloma Virus/HPV vaccine

Rahier JF, ECCO J Corhns Colitis 2009; 3:47-91

Question

Which of the following patients has the highest risk of IBD associated colorectal cancer?

A. Patient with Crohn's disease x25 years with 10cm of sigmoid colon and 10cm of ileal involvement

B. Patient with ulcerative colitis x15 years and Primary Sclerosing Cholangitis

C. Patient with ulcerative colitis x 15 years and extensive post-inflammatory polyps

D. Patient with ulcerative colitis x 15 years and a family history of adenoma

E. Patient with ulcerative colitis x 15 years and chronic active inflammation on all surveillance colonoscopies

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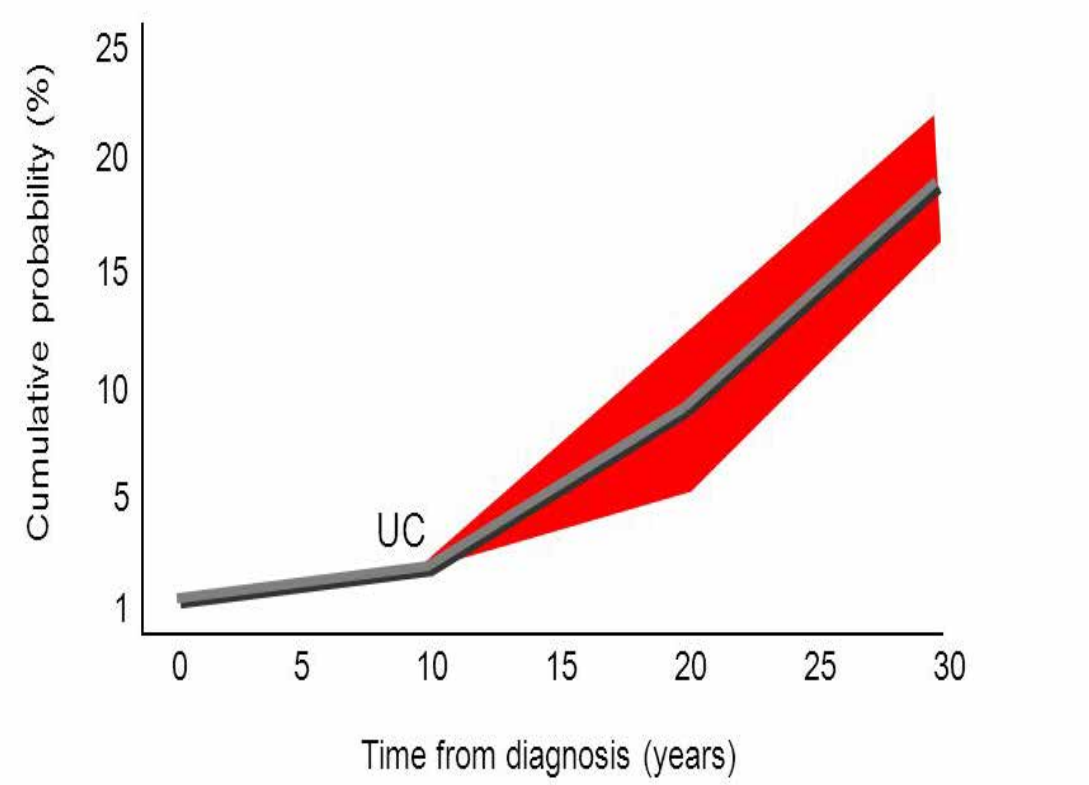
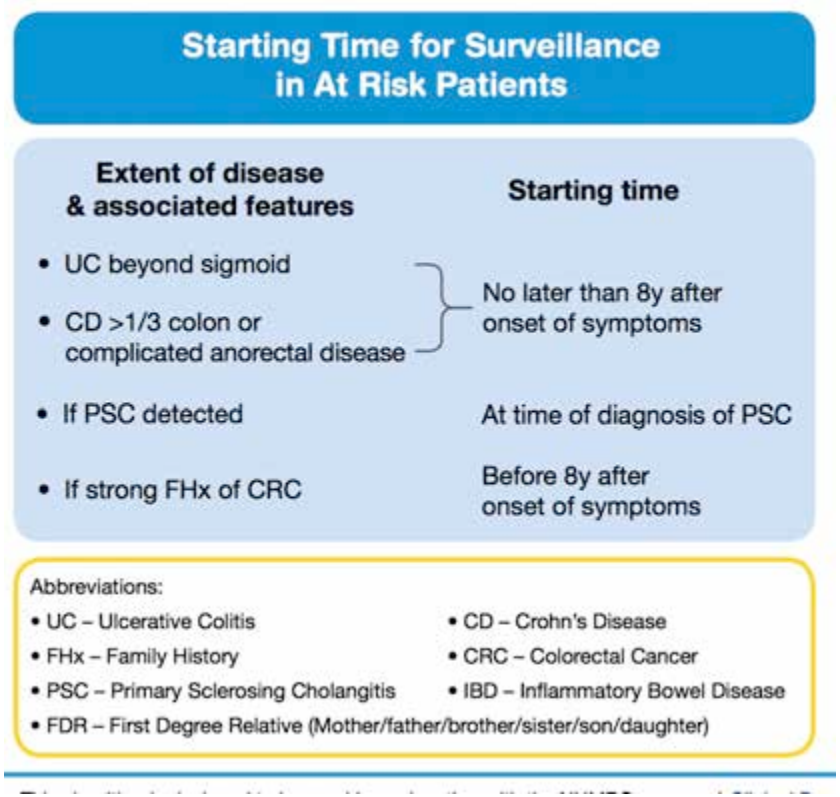
UC and Risk of Developing Colorectal Cancer Over Time



Eaden JA, et al. Gut 2001 48:526

High Risk Features stratifying CRC risk



Starting Time for Surveillance in At Risk Patients

Extent of disease & associated features	Starting time
• UC beyond sigmoid • CD >1/3 colon or complicated anorectal disease	No later than 8y after onset of symptoms
• If PSC detected	At time of diagnosis of PSC
• If strong FHx of CRC	Before 8y after onset of symptoms

Abbreviations:

- UC – Ulcerative Colitis
- CD – Crohn's Disease
- FHx – Family History
- CRC – Colorectal Cancer
- PSC – Primary Sclerosing Cholangitis
- IBD – Inflammatory Bowel Disease
- FDR – First Degree Relative (Mother/father/brother/sister/son/daughter)

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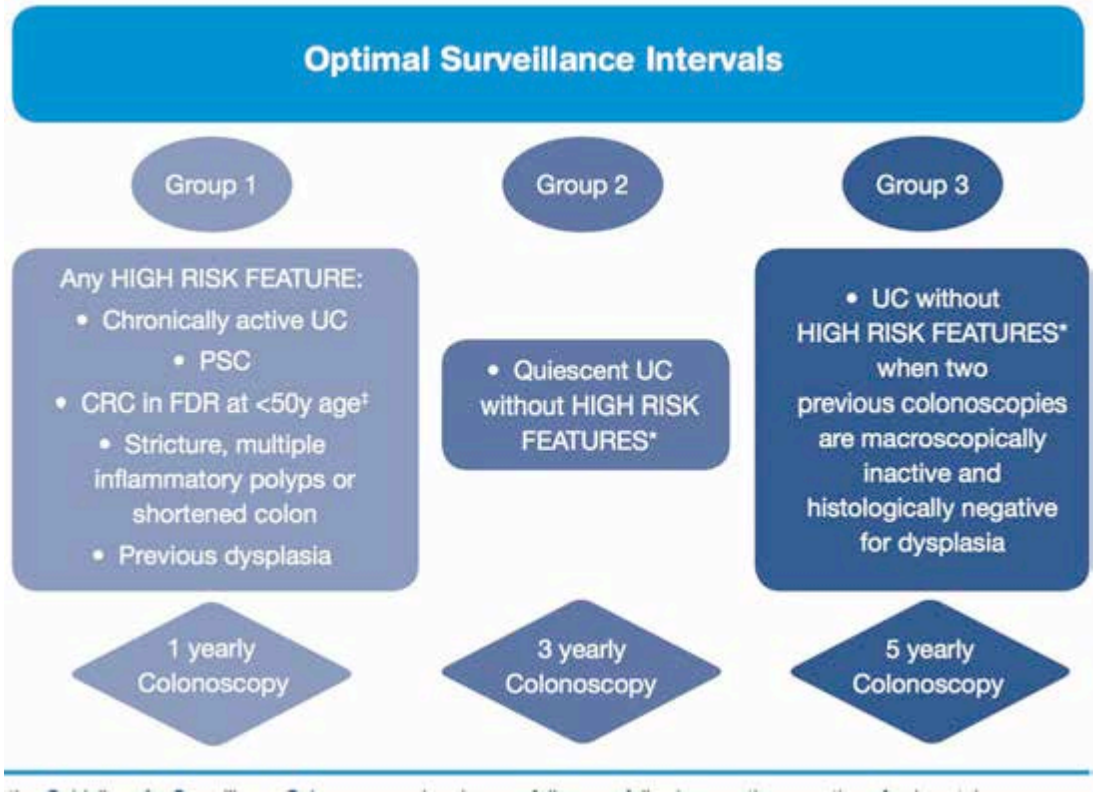

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Which of the following statements is **incorrect** regarding the use of 5-aminosalicylates in inflammatory bowel disease?

- A. Mesalamine is efficacious in induction of remission in patients with ulcerative colitis
- B. Mesalamine treatment can be associated with interstitial nephritis
- C. There is a dose response relationship of mesalamine in treatment of ulcerative colitis
- D. The incidence of nausea and malaise is similar among patients taking sulfasalazine and mesalamine
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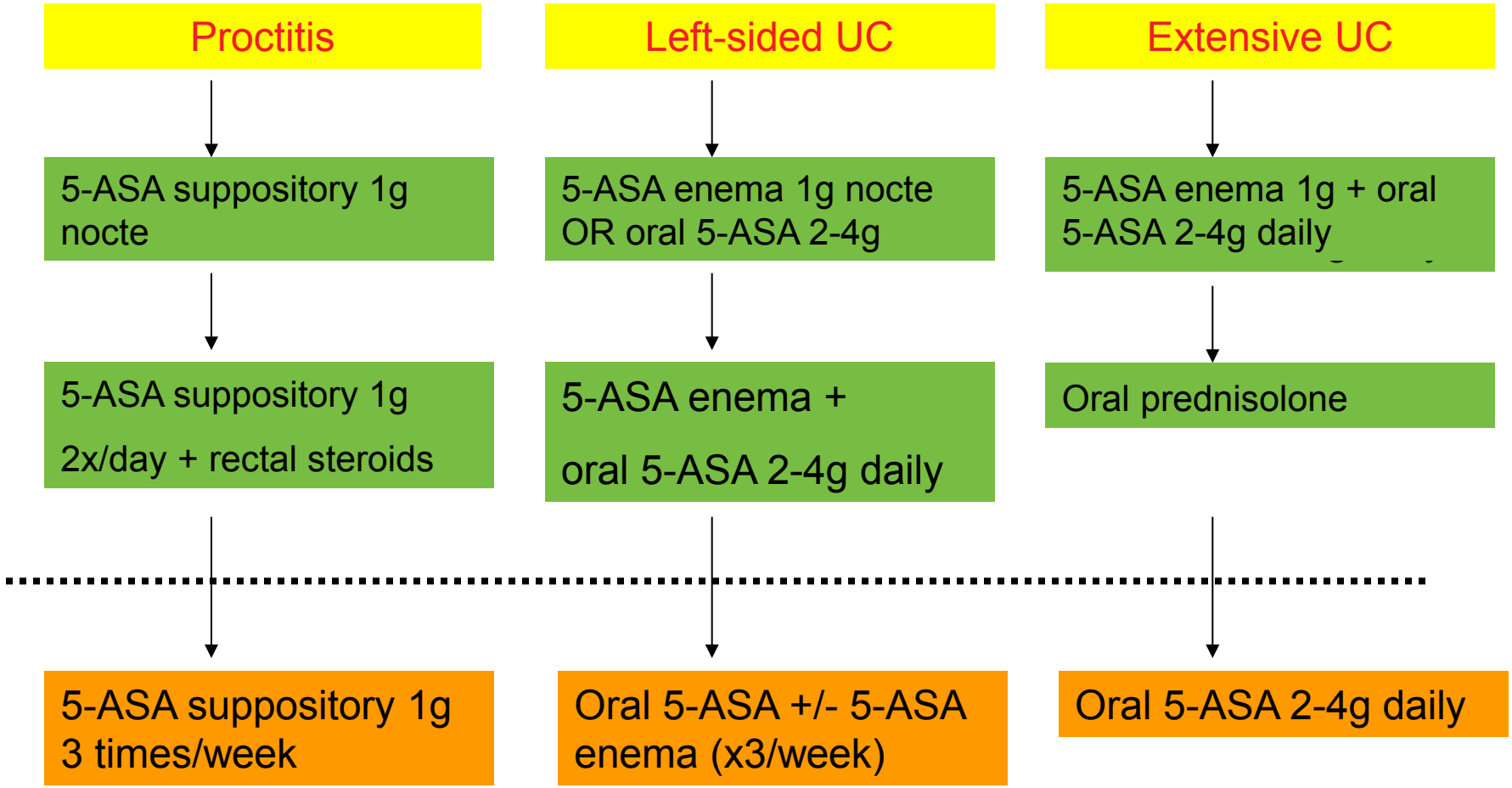
Therapeutic Strategies for Mild-Moderate UC



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Which of the following is true regarding 5-aminosalicylate use in IBD?

A. Response rates to 5-aminosyalicylates are about the same for ulcerative colitis and Crohn's disease

B. Side effects include renal dysfunction and pancreatitis

C. The onset action of 5-aminosalicylates is approximately 12 weeks

D. Mesalamine is contraindicated in men trying to conceive due to adverse effects on sperm

E. 5-aminosalicylates are thought to work both systemically and topically in ulcerative colitis

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IBD Team and Support for GPs in MetroNorth Public Hospitals

Gastroenterologists contributing to MN IBD Services:

- Dr Graham Radford-Smith (RBWH and Bundaberg)
- Dr Mariko Howlett (RBWH)
- Dr Georgia Hume (RBWH)
- Dr Soong Ooi (RBWH, North Lakes Clinics)
- Dr Richard Cheng (Redcliffe Hospital, North Lakes Clinics)
- Dr Anthony Pan (Redcliffe Hospital, North Lakes Clinics)
- Dr Ruth Hodgson (TPCH)

Specialist IBD nurses:

- Ms Anna McMahon (telehealth; RBWH/MN)
- Ms Karen Sewell (RBWH/MN)
- Ms Madonna McIntyre (research, Northlakes Clinic)

- De-identified questions to:
  - rbwh-crohnscolitis@health.qld.gov.au
- Phone IBD helpline on 07 3646 7020 (Mon - Fri from 0800am – 1630pm)
- GP referral guidelines (next page)

Referring to MetroNorth IBD Services

https://www.health.qld.gov.au/metronorth/refer/services/gastroenterology/inflammatory-bowel-disease