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Inflammatory bowel disease

WHAT'S NEW?

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Outline

- CASE 1.
  - Acute severe UC (anything new?)
  - Faecal transplantation
  - Newer treatments

- CASE 2
  - Atypical presentation Crohn's disease
  - Mucosal healing as treatment target
  - Faecal calprotectin
  - Drug monitoring

Case FL

- 33 year old female
- UC diagnosed **2006** – proctitis only
- PMH: anxiety, high BMI
- Responded to combination of mesalazine tablets and suppositories for 4 years
- **Clinic** : multiple flares over past year, BO 20 times/day, 1 ½ stone weight loss
  - HR 110, Temp 36.8
  - Hb 102, CRP 13 (TFT/TTG normal)

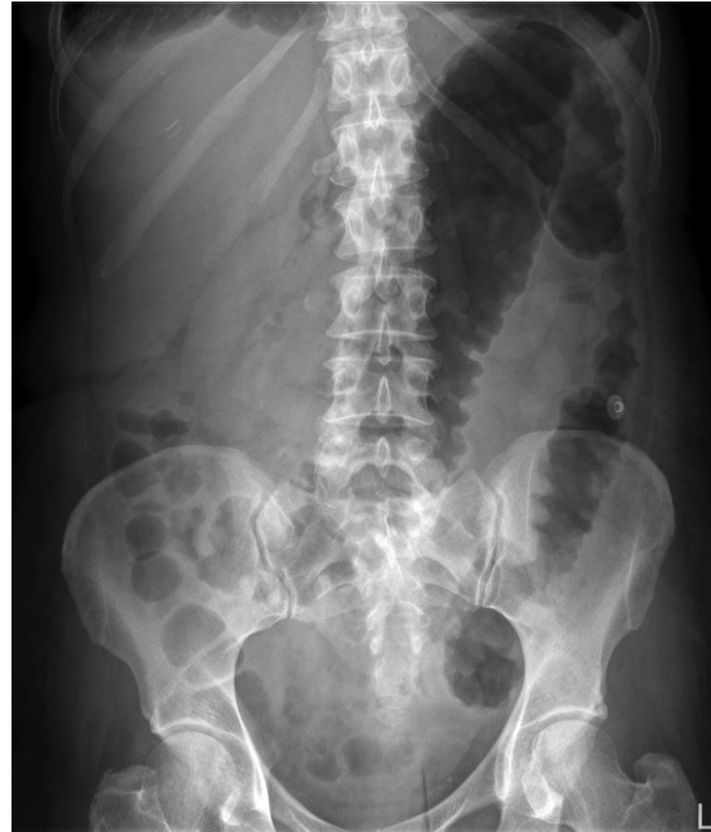
Probability for progression of proctosigmoiditis (sigmoidoscopy and radiology): 53% after 25 years

Langholz et al 1996

Case 1: ASUC-Anything new?

- Definition of ASUC, Truelove and Witts -
  - bloody diarrhoea ≥6/day and any of:
  - systemic toxicity (HR >90/min, temp 37.8 °C)
  - Hb <10.5
  - ESR >30 mm/h

- Hydrocortisone 100 mg QDS
- Fluids, replace K+
- Nutrition
- VTE
- Stool MC&S
- Sigmoidoscopy CMV



Mortality-79 % in 1933, down to 23 % with better supportive care, less than 7% with steroids

The largest meta-analysis of steroid use for UC included 32 studies and 1991 patients between 1974 and 2006, mortality rates were reduced to 1% and colectomy rates to 27%.

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Case 1: ASUC-Anything new?

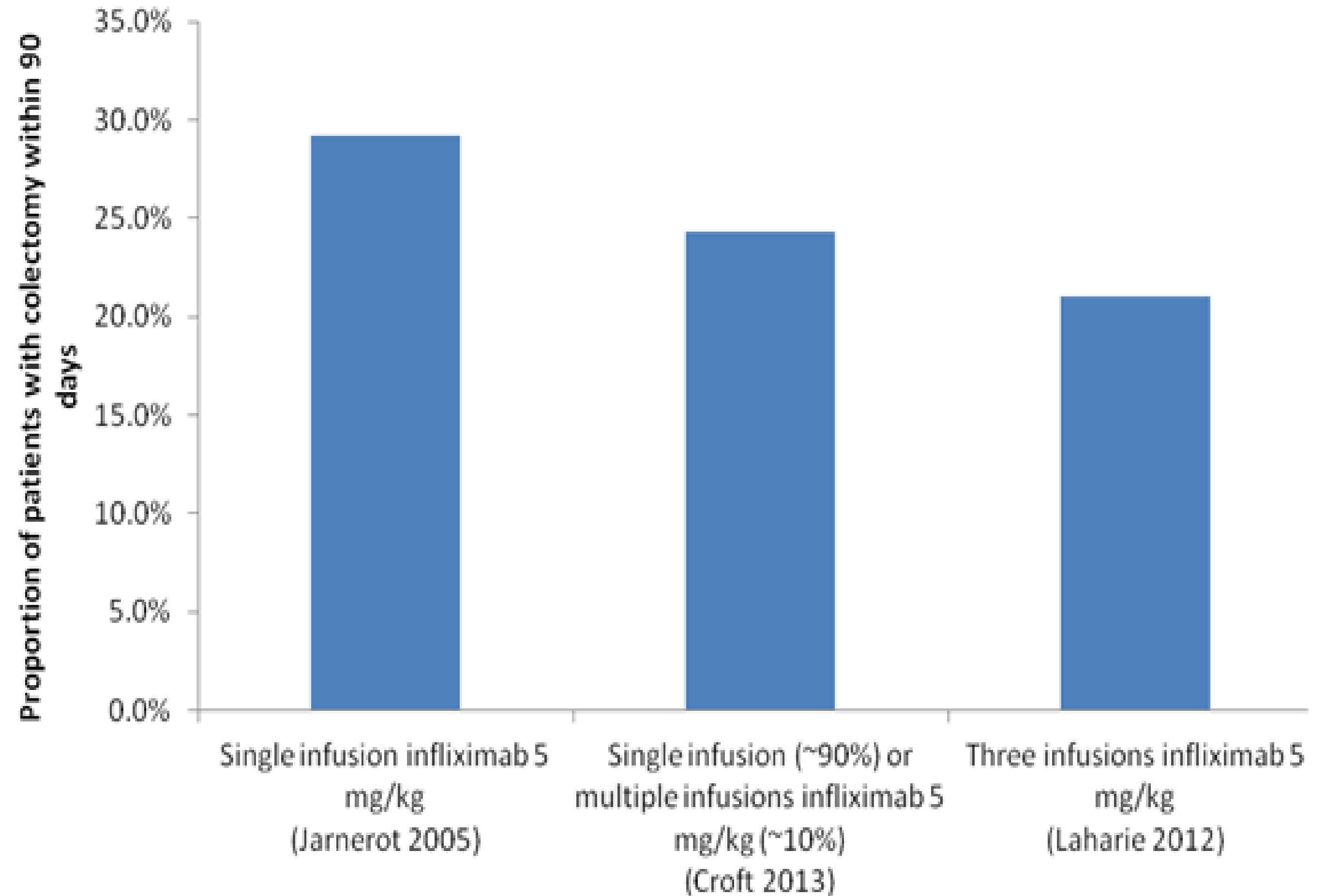
- Reassessed at 72 hours of Hydrocortisone- Stool frequency >8/day, C-reactive protein (CRP) >45 mg/L
- What Next?
- CYcloSporine versus InFliximab (**CYSIF**) – first head-to-head trial (110 patients)
  - No significant difference. 86% patients in the ciclosporin group had a clinical response at day 7 compared with 84% of patients in the infliximab group (p=0.76). Day 98 colectomy rates were 17% in the ciclosporin group and 21% in the infliximab group (p=0.60). Laharie, D Bourreille A et al Lancet *2012;380:1909–15.*
- The UK IBD audit may provide a guide for real-world outcomes and reported response rates of 52.6% (2008) and 63.8% (2010) for ciclosporin compared with 80.4% (2008) and 85.5% (2010) for infliximab, when used for inpatients with steroid refractory UC

Case 1: Day 3 escalation of therapy

	Ciclosporin	Infliximab
Mechanism	Calcineurin inhibitor	Anti-TNF
SEs/risks	• ↑ Fluid, BP, K^+, creatinine, lipids, hair, gums, glucose, cholesterol • ↓ Mg • Hepatic toxicity • Neurotoxicity/seizures (more likely if low cholesterol/Mg levels)	• Reactivation of latent TB • Increased susceptibility to infection • Exacerbation of demyelination • Reactivation of malignancy • Heart failure
Monitoring	• Weekly ciclosporin • 1-2x week U+Es (at first) • Mg, LFTs • Blood pressure • Lipids (0m and 1m)	• Exclude active/latent TB prior • Close observation for infection

Case 1: Day 3 escalation of therapy

- NICE Guidance Feb 2015 :
  - Infliximab, adalimumab,golimumab recommended in moderately to severely active ulcerative colitis in adults whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who cannot tolerate, or have medical contraindications for, such therapies.

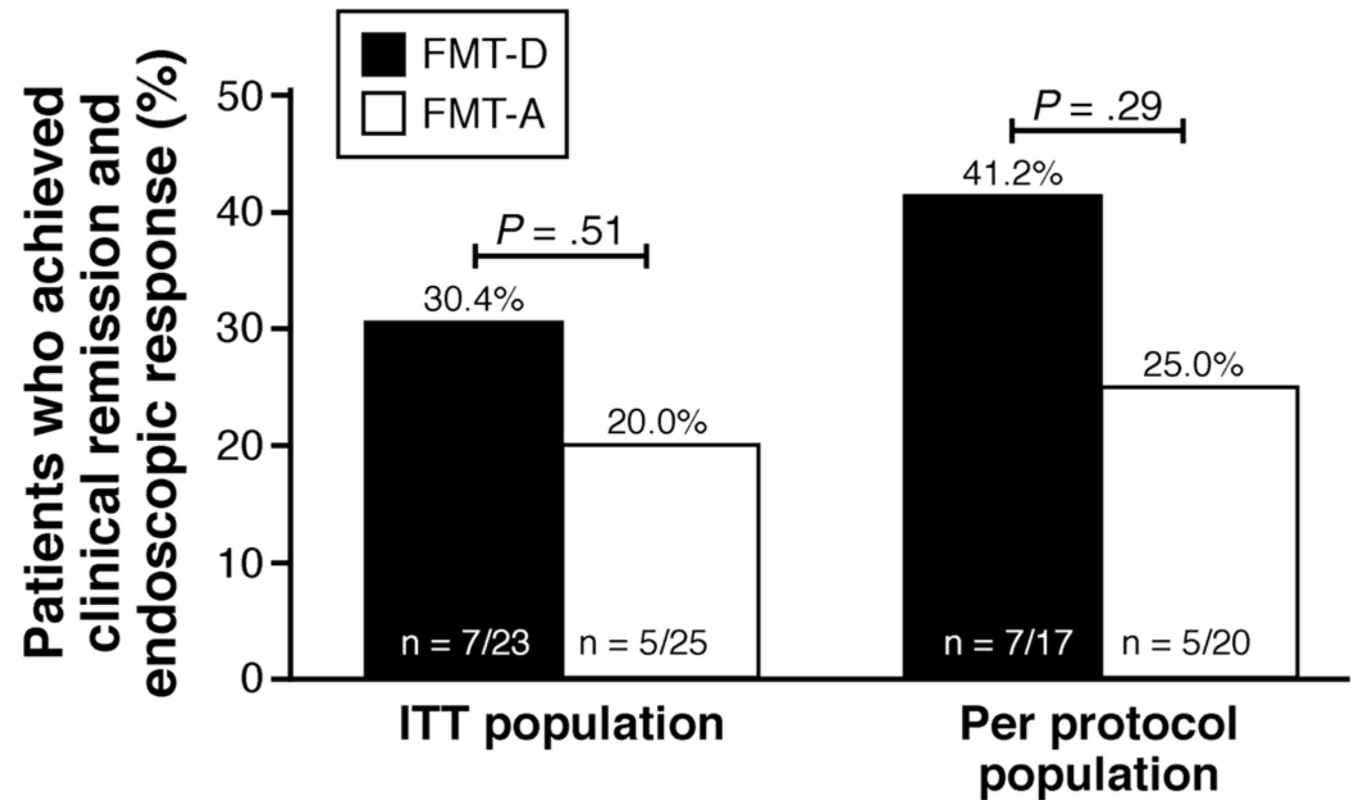


Case 2

- Received rescue infliximab
- Met with surgeons
- Any alternative available?

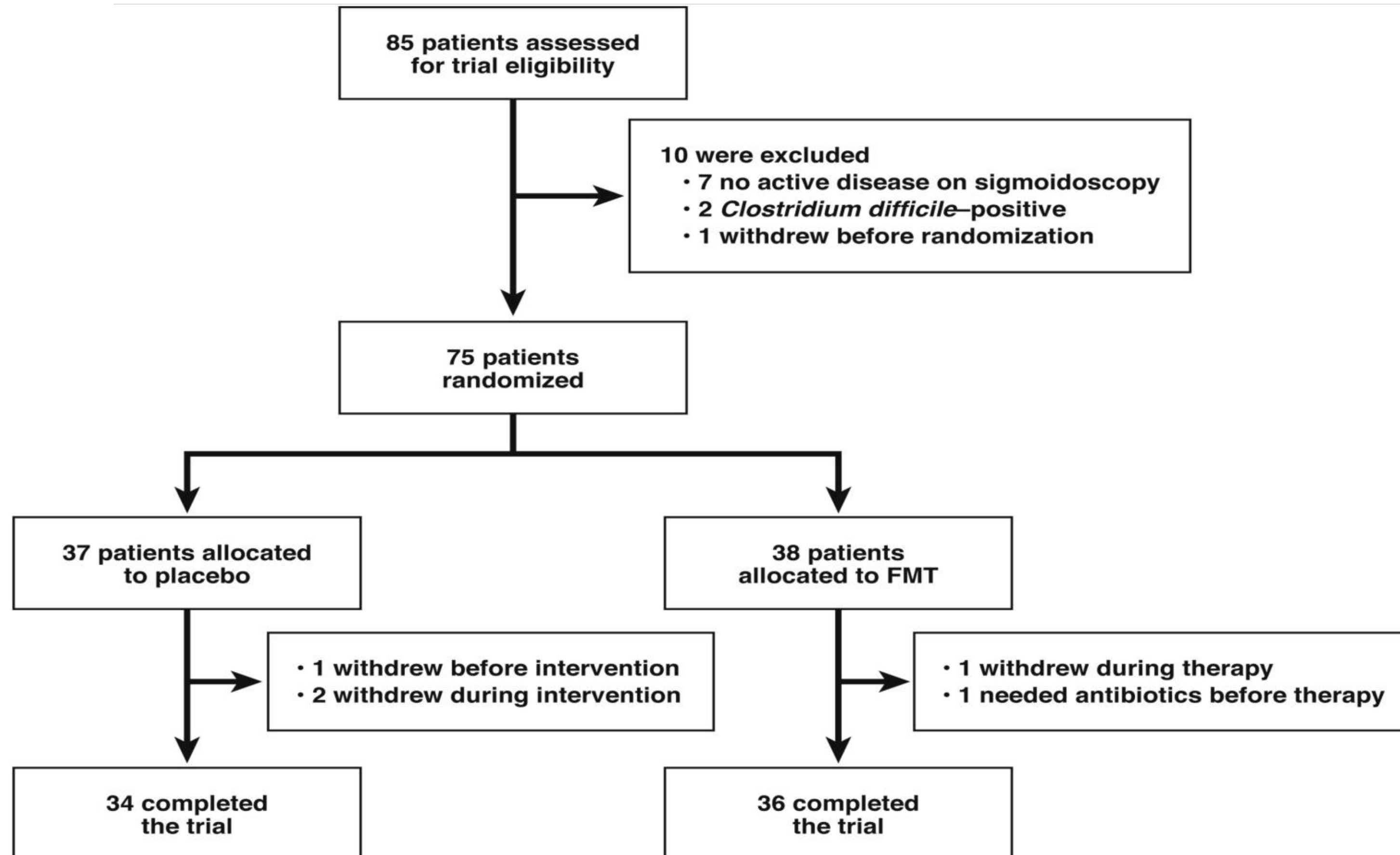
Faecal Transplantation in UC : TURN trial

Patients with mild to moderately active UC (n = 50) were assigned to groups that underwent FMT with faeces from healthy donors or were given autologous faecal microbiota (control); each transplant was administered via nasoduodenal tube at the start of the study and 3 weeks later.



Rossen N, Fuentes S et al Gastroenterology 149; 1,110-118.e4 (July 2015)

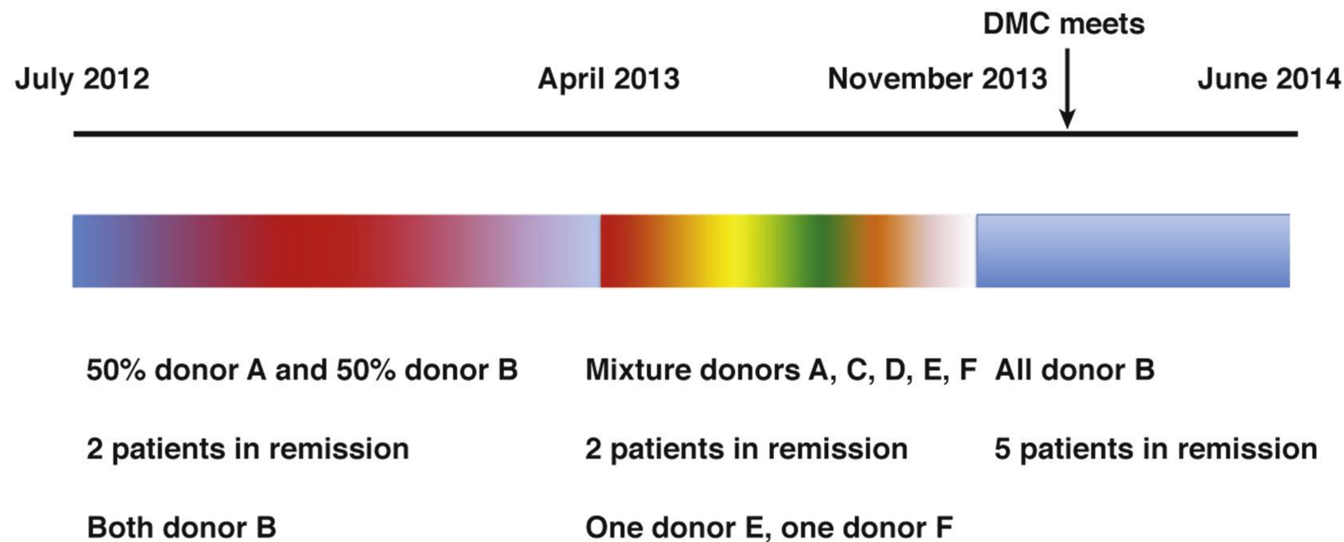
Faecal Transplantation in UC: US Trial



FT given by weekly enema
Placebo- water

Moayyedi P, Surette M et al, Gastroenterology 149;1102-109.e6 (July 2015)

Faecal transplantation in UC



There were 38 patients randomized to FMT. Treatment successes attributable to donor B were 7 of 18 (39%) vs 2 of 20 (10%) with other donors (P = .06, Fisher's exact test), suggesting statistical evidence for donor dependence.

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%

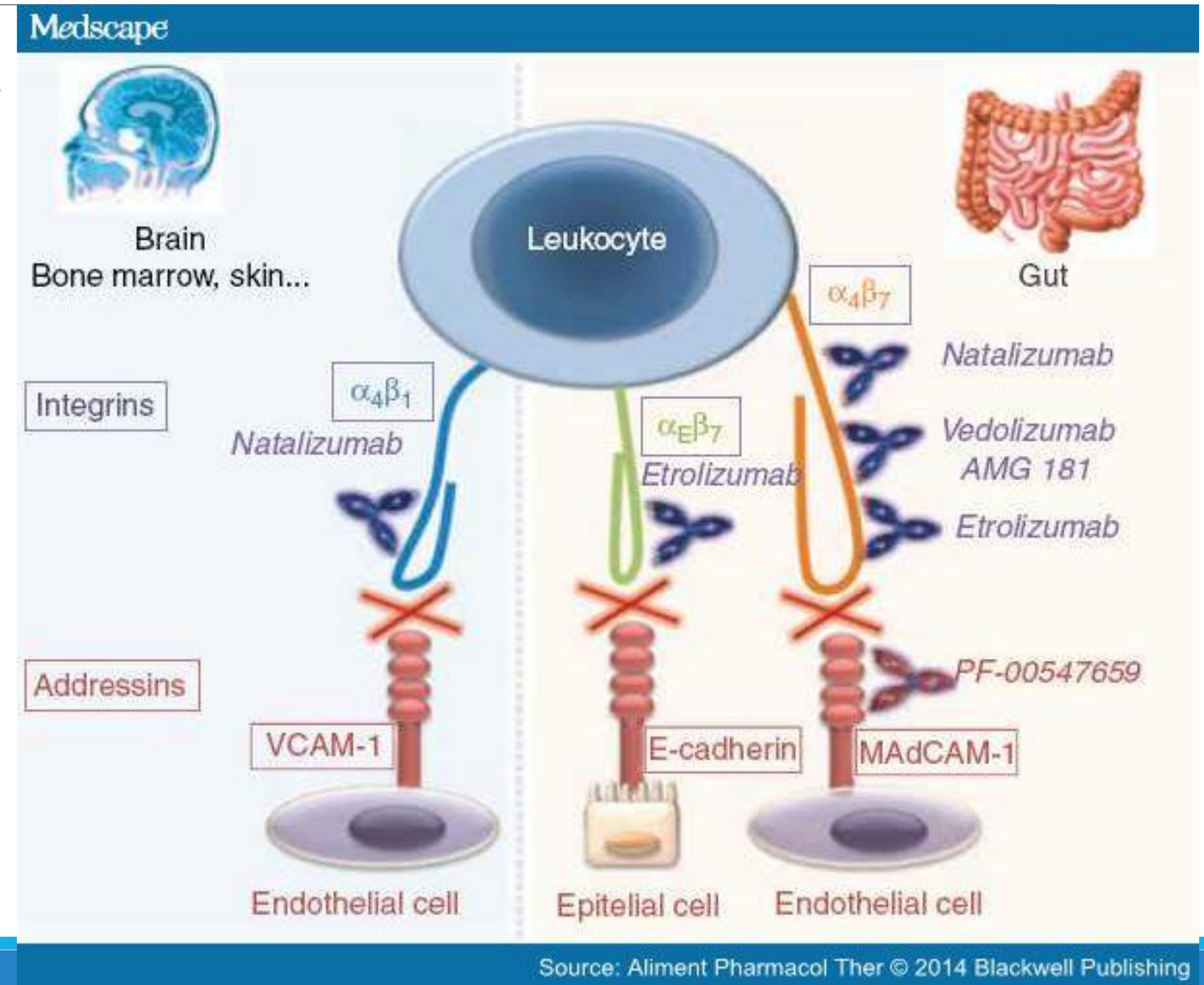
A B C D E F

Donor

f_Lachnospiraceae
g_Blautia
g_Faecalibacterium
f_Ruminococcaceae
f_Clostridiaceae
g_Subdoligranulum
g_Bacteroides
g_Prevotella
g_Lachnospira
o_Clostridiales
f_Erysipelotrichaceae
f_Ruminococcaceae
g_Oscillospira
g_Ruminococcus
g_Eubacterium

Newer Treatments: Anti Adhesion molecules

- Natalizumab- Prog. Multifocal leuko.
- Nice 2015 Approved Vedolizumab
- Initial induction 0,2,8 weeks
- Then i/v every 8 weeks
- Approved for UC alongside Anti TNF
- Approved for CD in Anti-TNF failure



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- Gemini studies
- *Feagan et al 2013 NEJM*

Table 3. Outcome Measures in the Trial of Maintenance Therapy.

Outcome	Placebo (N=126)	Vedolizumab Every 8 Wk (N=122)	Vedolizumab Every 4 Wk (N=125)	Between-Group Difference*			
				Every 8 Wk vs. Placebo	P Value	Every 4 Wk vs. Placebo	P Value
	number/total number (percent)			*percentage points (95% CI)*		*percentage points (95% CI)*	
Clinical remission at wk 52	20/126 (15.9)	51/122 (41.8)	56/125 (44.8)	26.1 (14.9–37.2)	<0.001	29.1 (17.9–40.4)	<0.001
Durable clinical response†	30/126 (23.8)	69/122 (56.6)	65/125 (52.0)	32.8 (20.8–44.7)	<0.001	28.5 (16.7–40.3)	<0.001
Durable clinical remission‡	11/126 (8.7)	25/122 (20.5)	30/125 (24.0)	11.8 (3.1–20.5)	0.008	15.3 (6.2–24.4)	0.001
Mucosal healing at wk 52	25/126 (19.8)	63/122 (51.6)	70/125 (56.0)	32.0 (20.3–43.8)	<0.001	36.3 (24.4–48.3)	<0.001
Glucocorticoid-free remission at wk 52§	10/72 (13.9)	22/70 (31.4)	33/73 (45.2)	17.6 (3.9–31.3)	0.01	31.4 (16.6–46.2)	<0.001

* Between-group differences in percentage points were adjusted for three stratification factors: cohort, concomitant use or nonuse of glucocorticoids, and concomitant use or nonuse of immunosuppressive agents or prior use or nonuse of TNF antagonists.

† A durable clinical response was defined as a response at both weeks 6 and 52.

‡ Durable clinical remission was defined as remission at both weeks 6 and 52.

§ This outcome was assessed in patients receiving oral glucocorticoids at baseline.

Case 2 : Referral

Dear Haematology,

Please see this 33yr old man with weight loss and night sweats.

He also has a rash on his hands.

I am concerned he has a malignancy.

Yours,

A GP

Case 2:Initial Assessment – 5/2013

Weight loss

Non specific abdo pain and vomiting

Night sweats

Joint pain, back pain and stiffness

Unable to work (restaurant worker)

From Bangladesh, in UK since Jan 2013

No history / FHx TB

Previously fit and well

No meds, no alcohol, no smoking

O/E

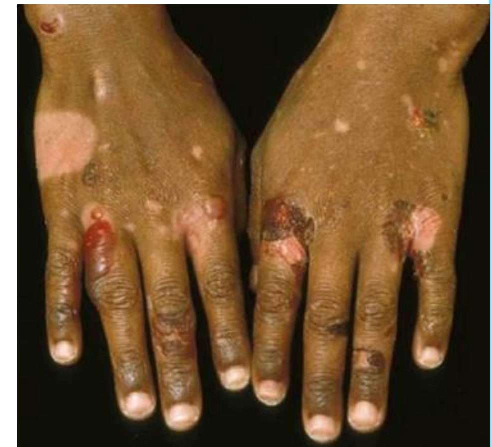
Ill looking, generalised pain

No lymphadenopathy

Rash over both knuckles – pink/keratotic, no joint swelling

<u>Impression</u>

Infective process rather than malignancy



Case 2 : 6/2013

Symptoms ongoing…

Normal FBC

ESR 90

CRP 160

Mild elevation ALP

Normal CXR

Urine AFB negative

MPS negative

XR Spine normal

Impression

Rheumatological / Autoimmune condition

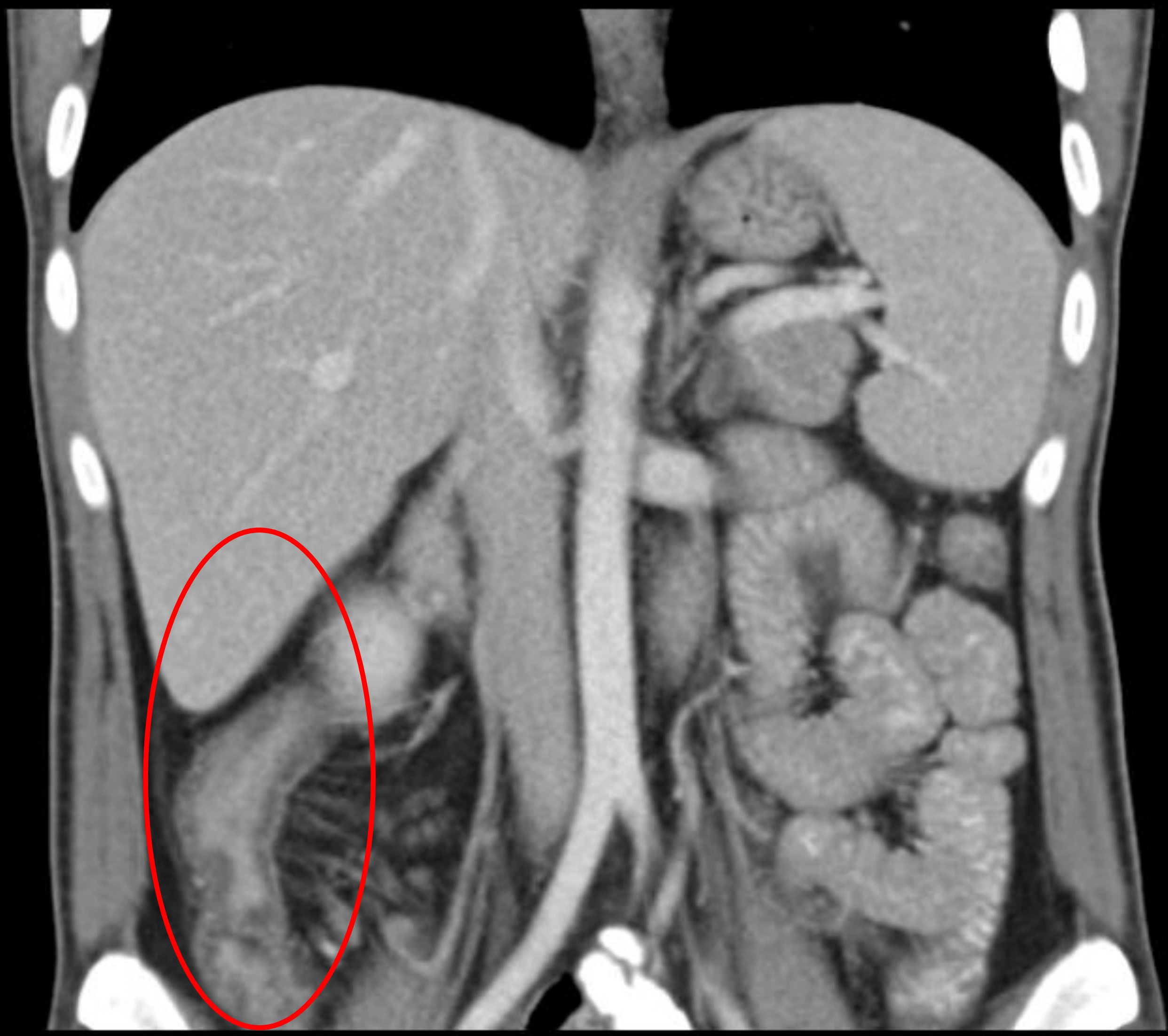
Plan

Autoantibodies, ANCA

Lupus Screen

Porphyria Screen

Whole Body CT



Case 2 : Gastro clinic Oct 2013

Further weight loss (65 to 47kg)

Loose bowel motions, occasional blood

Pain both loins and hips – difficulty walking and getting up in morning

Rash both hands and elbows

O/E

BMI 17.4

Generally unwell, no lymphadenopathy

Abdo exam unremarkable

Antalgic gait, limited ROM both hips

CRP 121

Mild anaemia

Thrombocytosis

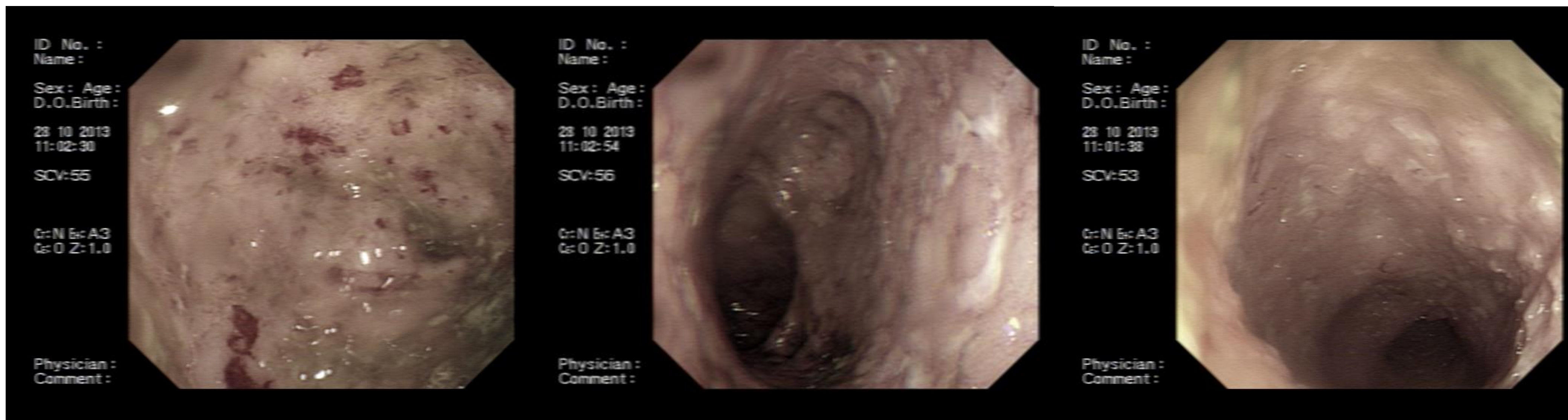
Albumin 32

<u>Plan</u>

Colonoscopy

Rheumatology review for likely sacroiliitis

Case 2: Colonoscopy



Case 2 : Diagnosis

- Ileo-colitis
- Some distal sparing, ‘skip lesions’
- Proximal cobblestone appearance

- Crohn’s Disease
  - Diff Diagnosis- TB

- IGRA Negative
- Histology supportive of Crohn’s

<u>Diagnosis</u>

Crohn’s Disease

<u>Treatment</u>

Oral Steroids

Case 2 : Review – Nov 2013

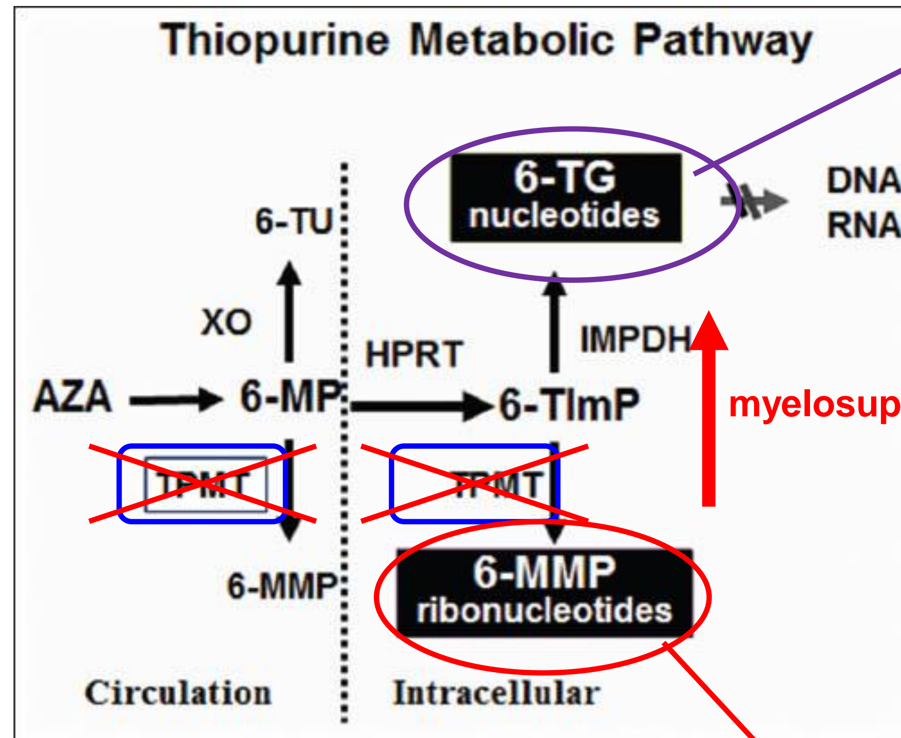
- Bowels improving
- 3kg weight gain

- MRI Small Bowel – Normal
- Ongoing back/hip pain

- Good response to Steroids

- Plan to start Azathioprine…

Azathioprine



Inhibition Lymphocyte proliferation
T cell apoptosis

myelosuppression

Hepatoxicity

Short arm chromo 6
Variant alleles

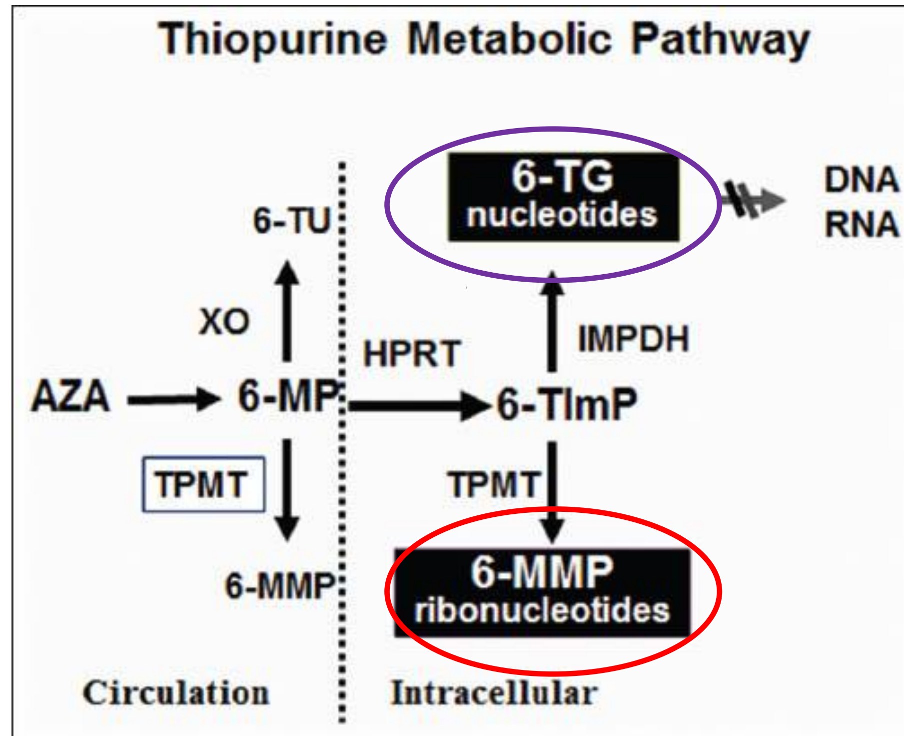
Homozygous (0.3%)	absent activity
Heterozygous (11%)	intermediate activity
No mutation (89%)	normal activity

Case 2 : Review – Dec 2013

- Normal TPMT, Azathioprine commenced 1.5.mg/kg
- Bowel symptoms resolved
- Weight gain, CRP 10

- Continue? Optimise treatments

Case 2 : Azathioprine Metabolites



Optimise Efficacy

Minimise Hepatoxicity

Case 2 : Review – Dec 2013

6-TGN	137	(low)
6MMP	553	(normal)

Azathioprine dose increased

Bowel symptoms resolved

Weight gain

CRP 10

He’s well…..

Case 2 : Treatment aims

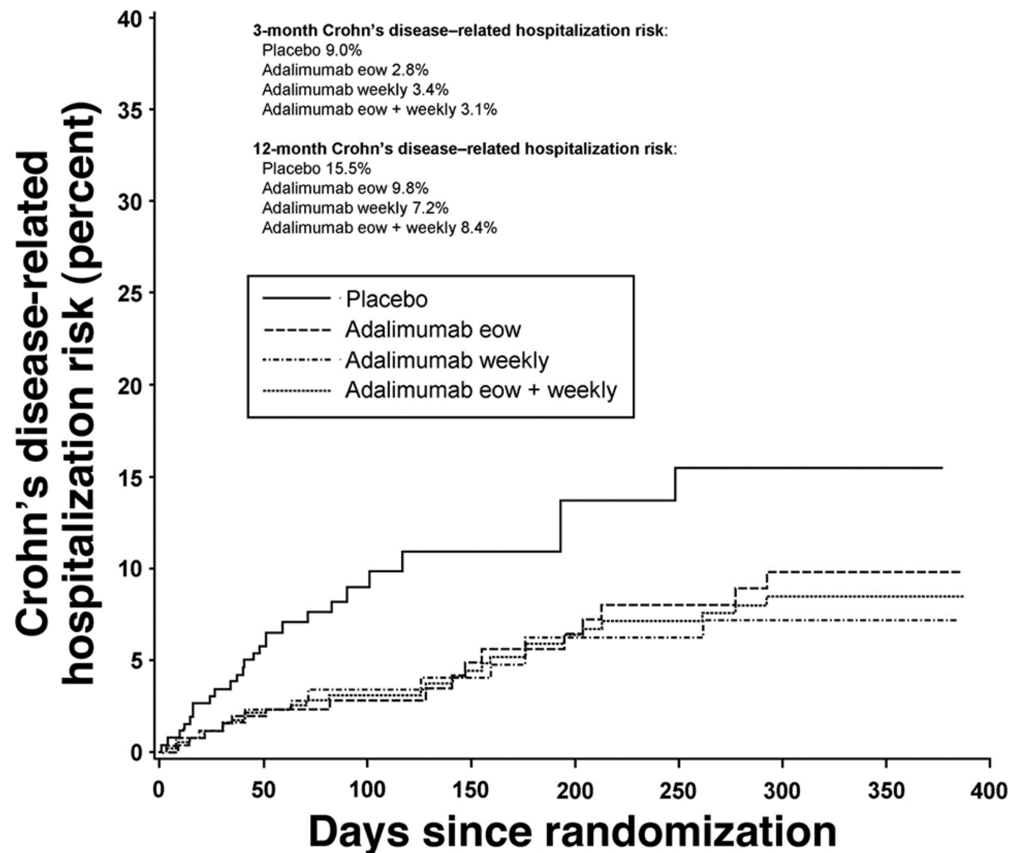
Treatment Target- **Mucosal Healing** (not just symptom resolution)

Aim to prevent complications, reduce need for surgery and improve QoL

Risk of over treating, exposing patient to risks of treatments

- High risk features:
- Young age
- Extra intestinal manifestations
- Smoking
- Extensive disease
- Steroid use

Case 2 : Mucosal Healing



Charm Study

Adalimumab Use

Decrease risk of hospitalisations.

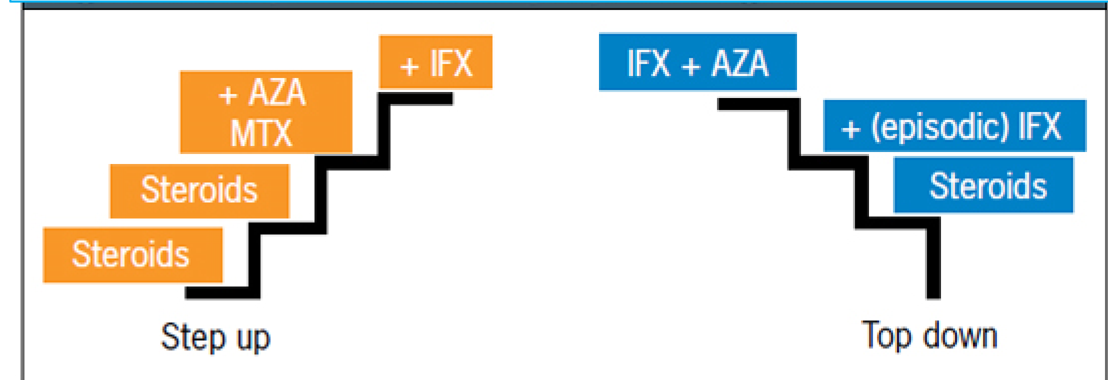
Epidemiological studies have shown decrease early surgical rates but not on longer term follow-up

Feagan B et al Gastroenterology 135;5; 1493-1499; 2008

Case 2 : MDT Discussion 9/2014

- Faecal Calprotectin 470 elevated despite Aza optimisation
- Adalimumab 40mg SC alt weeks commenced
- Review after 1 year treatment to assess response

Rapid step up Vs top down Approach



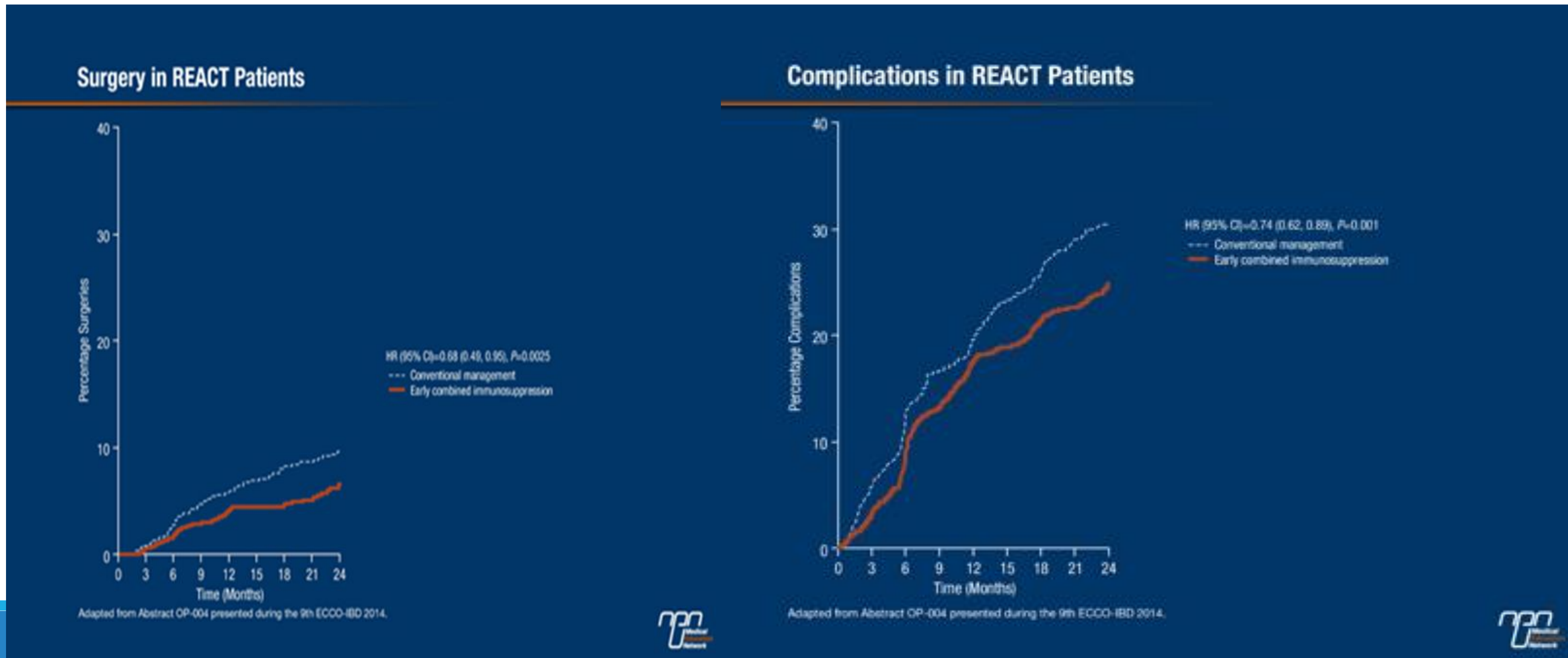
Case 2 : ‘Rapid Step Up’ REACT STUDY

- Early Combined immunosuppressant Vs Conventional treatment
- 1:1 randomisation
- 41 were randomly assigned to either ECI (n=22) or conventional management (n=19)
- Canada and Belgium and included ‘community hospital’
- 921 (85%) of the 1084 patients at ECI practices and 806 (90%) of 898 patients at conventional management practices completed 12 months follow-up and were included in an intention-to-treat analysis.

Khanna et al Lancet 2015 Sep 2. pii: S0140-6736(15)00068-9

Case 2 : 'Rapid Step up'

- Statistically significant and clinically important reductions with accelerated treatment were seen in time to first surgery (32%) and time to first complications (26%)

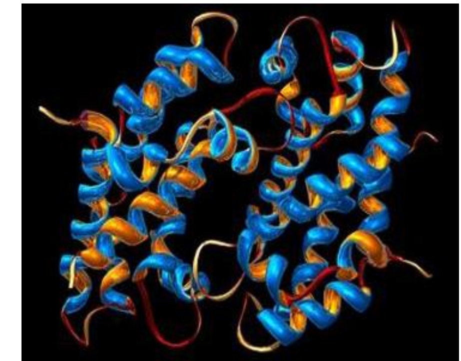


Case 2 : Faecal Calprotectin

- Protein released from Polymorphic nucleated cells and monocytes upon cellular activation (or death) at sites of active inflammation

- Highly stable in faecal samples (up to 7 days in stool samples kept at room temp).
- Decreases the need for endoscopy
- Sens 90%, Spec 83% for detecting ongoing inflammation

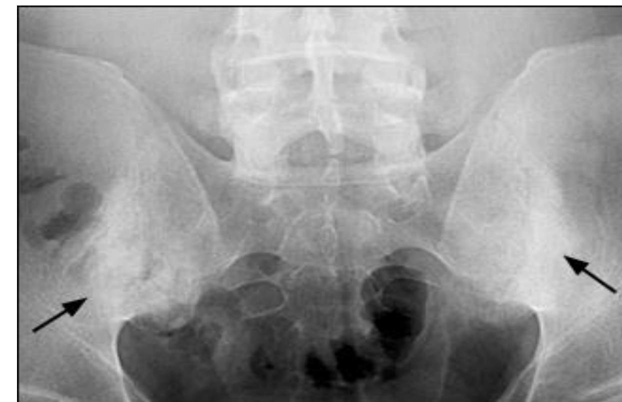
- IBD in remission: High FC 90% relapse at one year
  Low FC 10% relapse at one year



- IBD and IBS can co-exist!

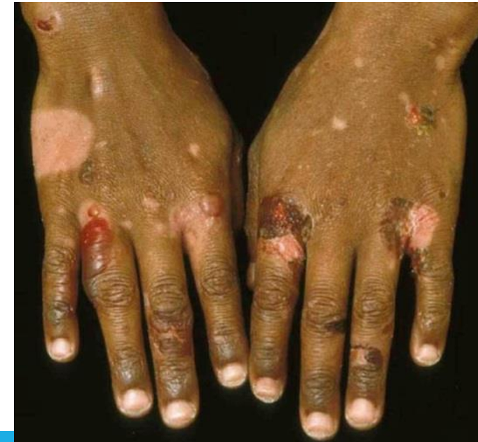
Case 2 : Rheumatology Review

- Sacroileitis – improved with immunomodulator therapy
- Chronic changes both hips – unlikely to improve
- Symptoms worsen off steroids – required further high doses
- May require joint replacement in long term



Case 2 : Dermatology Review

- Skin biopsy – Epidermolysis Bullosa Acquisita
- Multiple systemic immunosupressive agents
- Topical treatment – Dermovate ,Doublebase



Case 2 : What if he loses response?

- Annual risk approx 15% -exclude stricture, IBS symptoms, infection
- Immunogenicity – Anti Drug Antibodies
  - Persistent treatment – antibodies develop against the FAB fragment of both chimeric and humanised agents, immune complexes eliminated by RES
- Occurs in 37-61%, lower if on immunomodulator therapy
- Results in lower serum drug levels

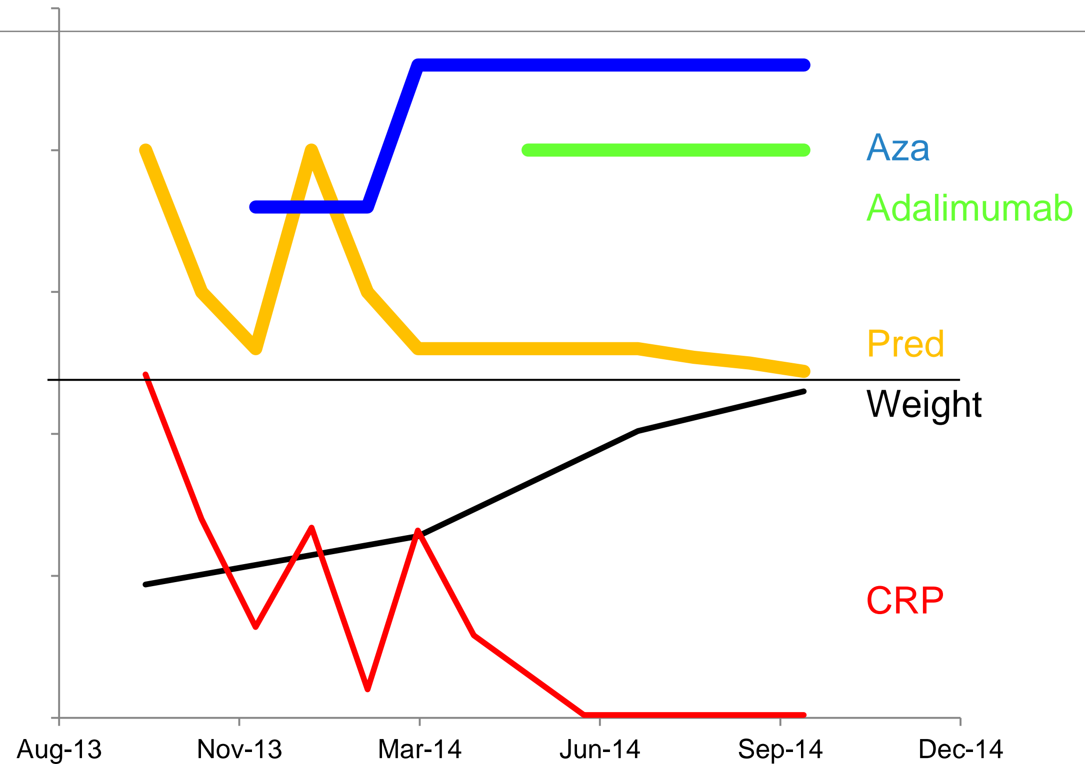
- Serum Drug Levels
  - Correlation between serum levels and clinical response (and endoscopic/biochemical response)
    - <1mcg/ml associated with loss of response
    - >12 mcg/ml associated with sustained clinical remission

Case 2 : Loss of response

	Anti Drug Antibodies Positive	Anti Drug Antibodies Negative
Optimal Drug Level	? Non neutralising antibodies ? False positive	Pharmacodynamic issue **Change target (not TNF)**
Low Drug Level	Immunogenicity **Switch to alternative anti TNF agent**	Bioavailability / Pharmacokinetics issue **Increase Dose** **Reduce administration interval**

Case 2 : Summary

- Effective Disease Control
- Optimised Immunomodulator Therapy
- Role of Faecal Calprotectin
- Improved Decision Making



Summary

- Management of UC
- Faecal Transplant
- Newer Drugs
- Crohn’s disease management
- Faecal calprotectin
- Drug monitoring

QUESTIONS?

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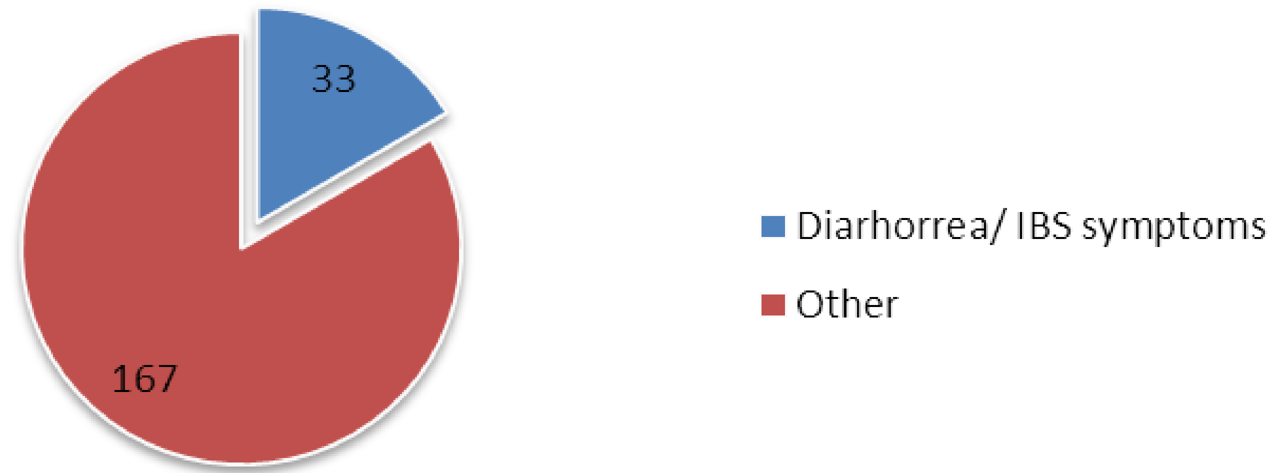
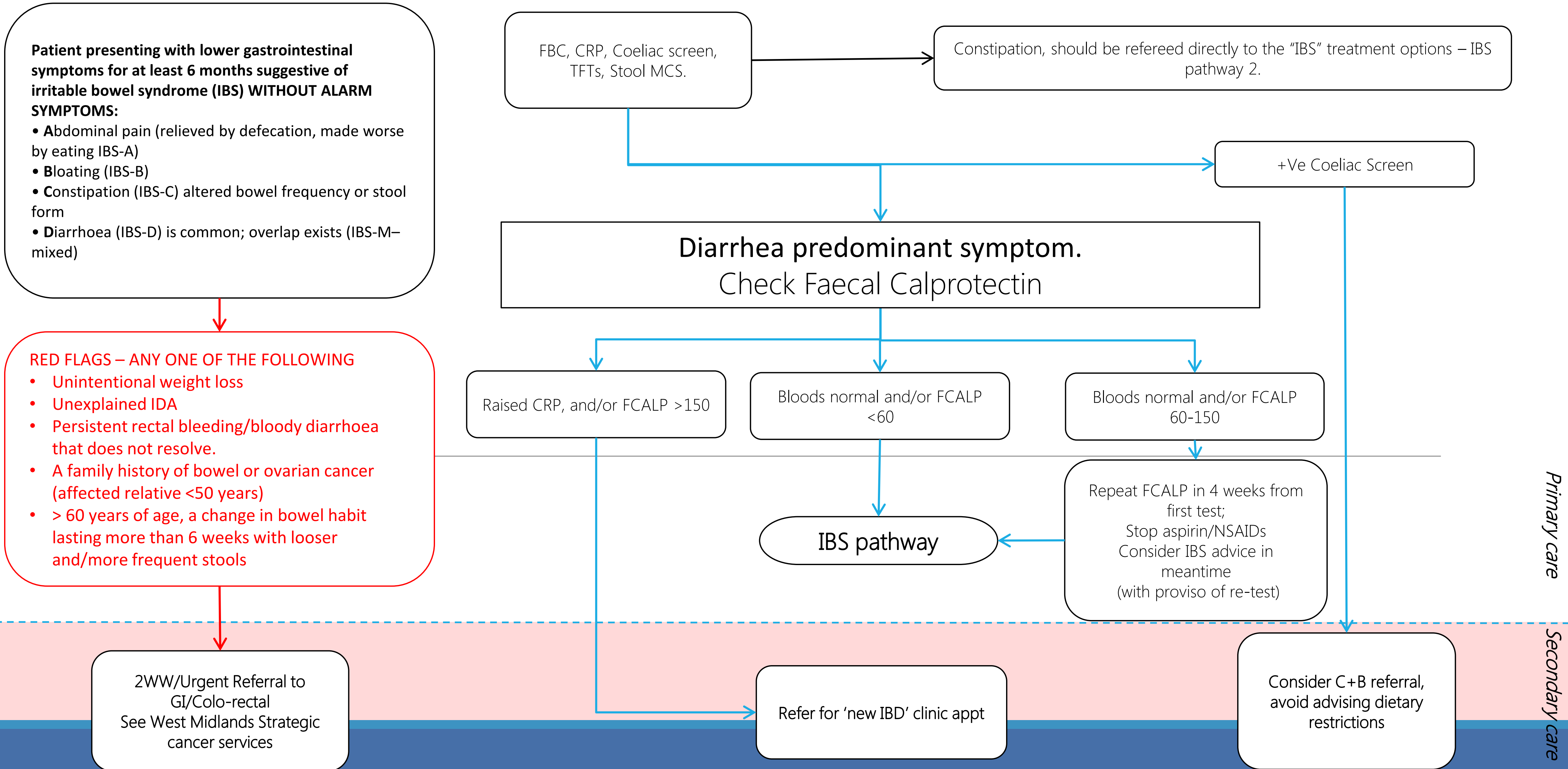

Indications for Flexible Sigmoidoscopy
(Nov' 14, Jun/Jul '15)
33
167
Diarhorrea/ IBS symptoms
Other

IBS pathway 1:
Presenting with IBS symptoms, baseline assessment.



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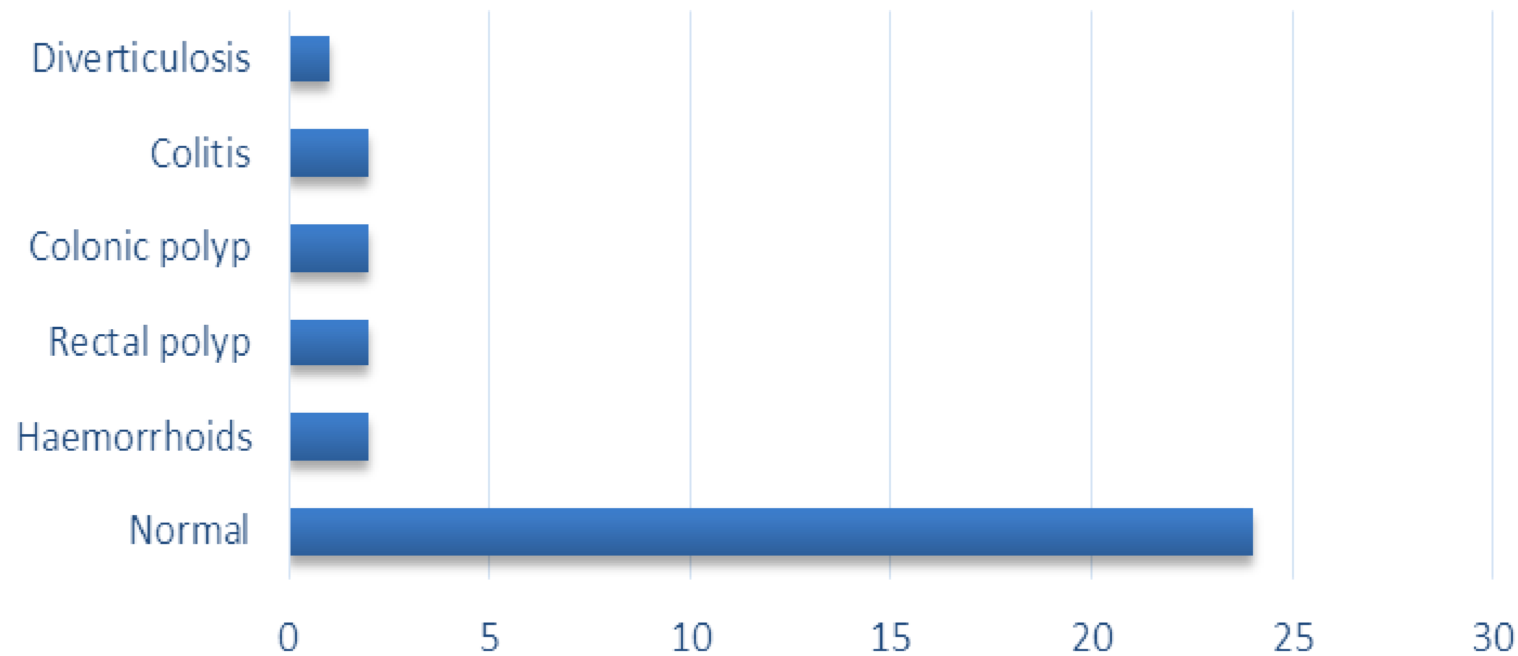
Flexible Sigmoidoscopy results for diarrhorrea/IBS symptoms in under <50's (Nov '14 + Jun/Jul '15)



Cost savings –local audit

- 31 unnecessary procedures
- Polyps detected were <5mm , solitary polyps. Bowel scope is offering sigmoidscopies to all 55 year olds.
- If even 80% of these were to avoid sigmoidoscopy this would save (24 x 344= £8,256 on sigmoidoscopies in 3/12) and in addition fewer clinic appointments (24 x 164= £ 3,936)
- Extrapolates to £12,192 /annum – cost of FC ((32 x 20) x 4 =£2560)= £9,632/annum saving

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IBD ASSESSMENT- use of FCP

- Escalating treatment to immunomodulators/biologics and assessing response
- Part of the annual review for IBD patients on biologics- can it stop?
- Use in post –operative assessment
- Use FCP to help differentiate between IBD flare and IBS overlap in known IBD patients.

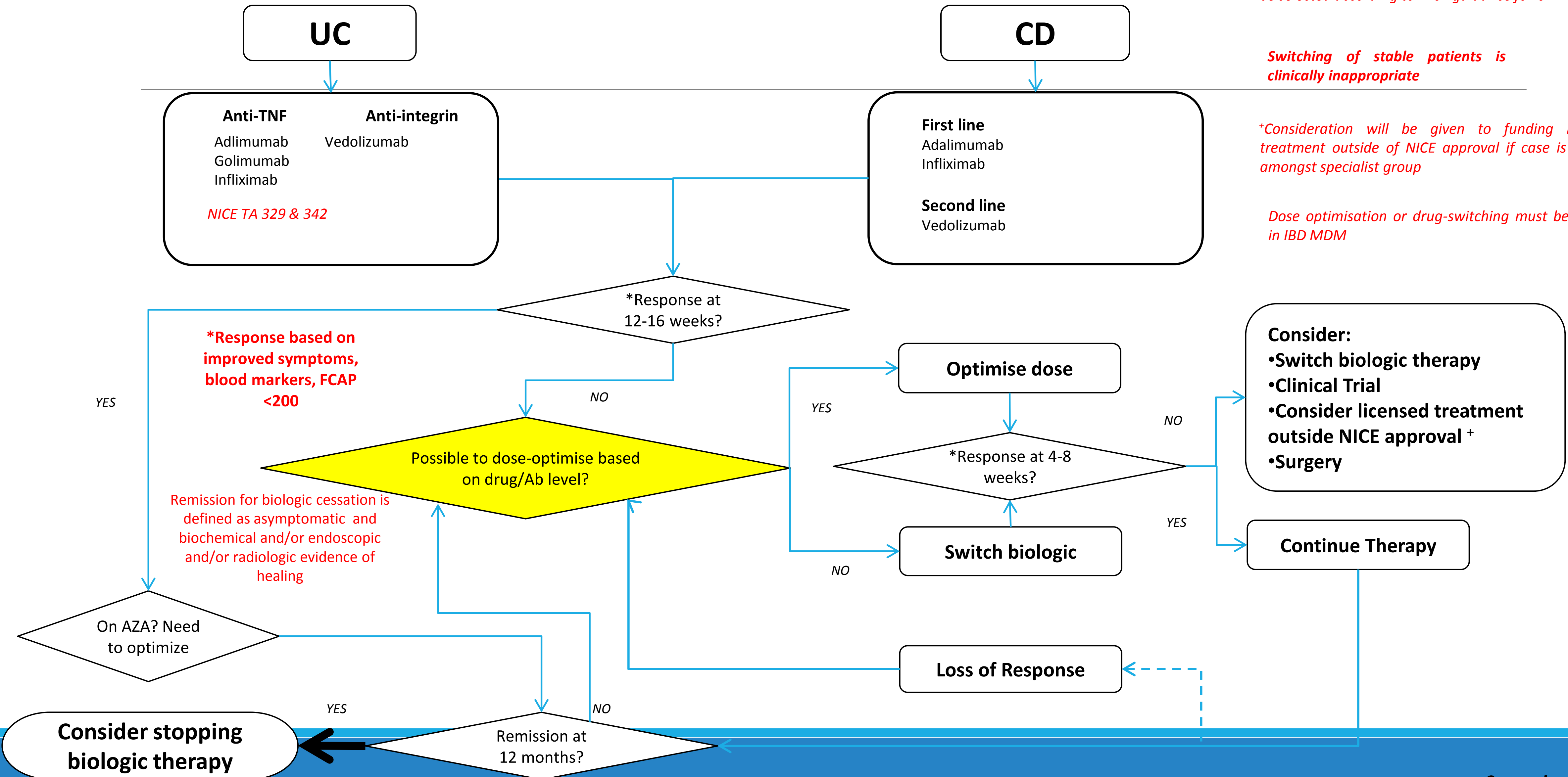
IBD pathway 3: BIOLOGIC THERAPY, links for pathway IBD 2

The most appropriate and cost-effective anti TNF will be selected according to NICE guidance for CD

Switching of stable patients is clinically inappropriate

+Consideration will be given to funding licensed treatment outside of NICE approval if case is agreed amongst specialist group

Dose optimisation or drug-switching must be discussed in IBD MDM



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IBD Assessment- when to stop anti-TNF

- -When to withdraw anti TNF-α therapy is important and driven by costs and concerns about long term safety. Faecal calprotectin levels may assist in this decision making.
- Louis et al demonstrated that relapse after IFX withdrawal was associated with various risk factors including a faecal calprotectin concentration of ≥ 300 μg/g.
  - Louis E, Mary JY,. Gastroenterology. 2012;142:63–70

- Local Audit – 32% of IBD audit having appropriate biologic annual review
- NICE have performed cost and technology appraisals, and have estimated annual costs of infliximab, adalimumab, golimumab at £12584, £9295 and £12208 respectively (for a patient weight of 73kg without vial sharing/procurement discounts).

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IBD assessment-post-op assessment

- Current recommended that all CD patients undergo full colonoscopy post TI resection where it is likely to affect treatment (ECCO 2013)
  - 174 post op CD patients POCER trial[1]
  - FC can be used to assess post-operative recurrence
- Lin, Chen et al (2014)[2]
  - 13 studies (744 patients with UC and 727 with CD) in the final analysis
  - FCP is a reliable marker for assessing IBD disease activity and may have greater ability to evaluate disease activity in UC than CD

1. Kham et al , Gastroenterology 2014
2. Lin, Chen et al (2014)Meta-analysis: Fecal calprotectin for assessment of inflammatory bowel disease activity. Inflammatory Bowel Diseases, vol./is. 20/8(1407-1415), 1078-0998;1536-4844

Summary

- A non-invasive sensitive and specific test
- Decreases secondary care referrals and endoscopy
- NICE recommended for differentiating IBD and IBS
- IBD Monitoring may help reduce drug cost and endoscopy cost
- Agreed pathways for its use across major Trusts in Birmingham

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Cost Implications

- Flexible sigmoidoscopy £344 (up to £805)
- Clinic appointments (£164)
- FCP test current cost £20

- Extrapolate numbers from GP from Cannock chase and Stafford and Surround CCG data- 534 tests/annum
- 214 patients currently on biologic drugs
- Circa 500 new cases/treatment changes/post op
- Ie total of 1248 tests/year- £24,960

Local context

Cannock Chase CCG

- 132,664 population
- 26 Member Practices
- Cannock Chase has been classified as a Manufacturing Town (Office of National Statistics cluster groupings).
- The health of the population is generally poor, healthy life expectancy is estimated to be 67 years for men and 70 years for women in Cannock Chase.

Stafford & Surrounds CCG

- 145,487 population
- 14 Member Practices
- Stafford and Surrounds is considered to be a Prospering Smaller Town (Office of National Statistics cluster groupings).
- The health of the population in Stafford is good. Men in Stafford have similar life expectancy to the national average.

Outcomes

- Since its full launch across both CCG's there have been 534 calprotectin tests carried out in primary care 12 months
- 300 of these had a negative result and as such were not referred to hospital (56%)
- 13 out of our 14 practices in Stafford are using the tests on a monthly basis
- 16 out of 27 practices in Cannock are using the test on a monthly basis

IBD assessment

- D'Haens, Ferrante et al (2012)[1] 126 IBD patients
- Median fecal calprotectin levels were:
  - 175 (44–938) µg/g in CD
  - 465 (61–1128) µg/g in UC
  - 54 (16–139) µg/g in IBS.
- Correlations were significant with endoscopic disease scores in both CD and in UC
- > 250 µg/g indicated the presence of large ulcers with a sensitivity of 60.4% and a specificity of 79.5% in CD.
- ≤250 µg/g predicted endoscopic remission (CDEIS ≤3) with 94.1% sensitivity and 62.2% specificity
- In UC FCP >250 µg/g gave a sensitivity of 71.0% and a specificity of 100.0% (PPV 100.0%, NPV 47.1%) for active mucosal disease activity (Mayo >0)

1. D'Haens, Ferrante et al (2012) Fecal calprotectin is a surrogate marker for endoscopic lesions in inflammatory bowel disease. **Inflammatory Bowel Diseases** Volume 18, Issue 12, pages 2218–2224.

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IBD assessment

- Bundhoo, Aravinthan et al (2014)
- 2 year period from 110 patients with IBD with regular out-patient assessment
- Normal (<50 µg/g), borderline (50–100 µg/g) and elevated (>100 µg/g)
- 44(40%) 5(4.5%) and 61(55.5%) patients had normal, borderline and ↑ FCP
- Three patients with normal FC (6.8%), compared to 29 (47.5%) with ↑ FCP required treatment escalation for symptom control
- FCP returned to normal levels in those selected for treatment escalation
- 104/110 **(94.5%)** of patients avoided investigative colonoscopy

1. Bundhoo, Aravinthan et al (2014) The Benefits Of Using Faecal Calprotectin As A Monitoring Tool To Assess Inflammatory Bowel Disease And Pre-emptively Upregulate Treatment In Asymptomatic Patient.**Gut** 63:A81-A82.

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IBD assessment

- Molander, Björkesten et al. (2012)
- 60 IBD patients (34 CD & 26 UC) treated with TNFα antagonists, either infliximab (*n* = 42) or adalimumab (*n* = 18)
- After induction, FCP was normalized (≤100 µg/g) in 31 patients (52%)
- At ≈12 months, 26/31 (84%, 18 CD, 8 UC) of the patients with normal FC after induction were in clinical remission
- Only 11/29 (38%, 9 CD, 2 UC) of those with an elevated (≥100 µg/g) postinduction FC were in clinical remission
- After induction therapy with TNFα antagonists, a cutoff concentration of 139 µg/g for FC had a sensitivity of 72% and a specificity of 80% to predict a risk of clinically active disease after 1 year.

1. Molander, Björkesten, et al. (2012), Fecal calprotectin concentration predicts outcome in inflammatory bowel disease after induction therapy with TNFα blocking agents. **Inflamm Bowel Dis,** 18: 2011–2017