Management of mild to moderate ulcerative colitis

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36-year old female with intermittent bloody diarrhea

- 36 y/o female
- Intermittent bloody diarrhea since 6 m ago
- 3-4 loose bloody stool
- Intermittent tenesmus
- Abdominal cramp
- No nocturnal ss

What is the next step?

- CBC ?
- ESR ?
- CRP ?
- S/E, OB, OVA ?
- Stool Calprotectin ?
- Colonoscopy, TI evaluation
- Rectosigmoidoscopy

What is the next step?

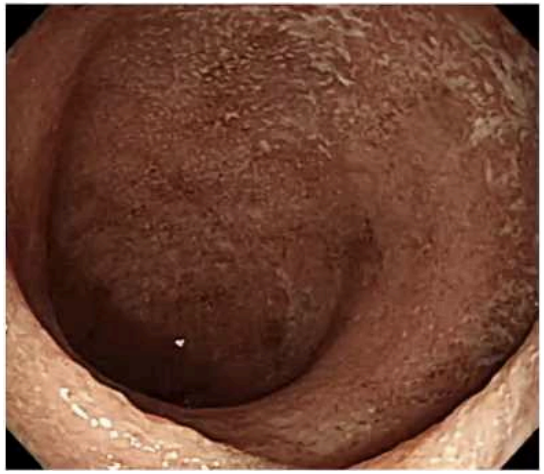
- CBC: Hb: 13.5, PLT: 469000, WBC: 9800
- ESR: 31
- CRP: 12
- S/E, OB, OVA : WBC: many RBC: many OVA: - OB: +++
- Stool Calprotectin: 870

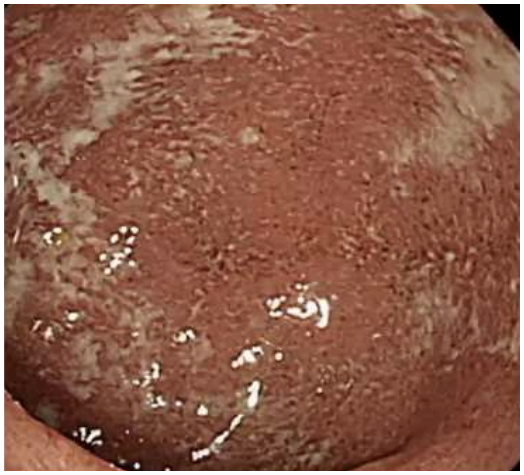
What is the next step?

- Colonoscopy, TI evaluation or Rectosigmoidoscopy ?
- Risks of colon preparation with PEG ?

Colonoscopy, TI evaluation, Biopsy

- Colonoscopy: loss of vascular pattern, friability in rectum, sigmoid, left and transverse colon. Normal right and TI.
- Patho: CCDC, Active phase, CMV -





Correct diagnosis?

- Differential diagnosis by history?
- Differential diagnosis by colonoscopy?
- Differential diagnosis by histology?
- Differential diagnosis by lab?

Which one of these tests would you recommend or not recommend in this stage?

- MR enterography
- S/E for WBC
- S/E for infections
- PANCA,CANCA
- Upper GI endoscopy

- If terminal ileum is normal, further evaluation of stomach and small bowel by upper endoscopy and cross-sectional imaging is not needed

- Unless other symptoms or findings suggest proximal GI involvement or diagnosis of Crohn's rather than UC

- stool testing to rule out Clostridioides difficile (C. diff) in patients suspected of having UC

- Not recommend serologic antibody testing to establish or rule out a diagnosis of UC

- Not recommend serologic antibody testing to determine the prognosis of UC

EGD

- **Routine upper endoscopic is not required in adults with new diagnosis of UC**

- **Should be restricted to those with symptoms of upper gastrointestinal disease**

- **Demonstration of fecal leukocytes alone is not sufficiently sensitive, nor specific for diagnosis or assessment of activity of UC.**

- **After excluding active infection in this patient, How would you manage this patient?**

- **What is your treatment plan?**

What to do at the initial step?

- Correct diagnosis
- Activity assessment
- Phenotyping
- prognostication
- Setting therapeutic goal
- Choice of initial therapy
- Patient education and engagement

Table 5. Mayo score for ulcerative colitis activity[a]

Parameter	Subscore (0–3)
Stool frequency	0 = normal number of stools
	1 = 1–2 stools more than normal
	2 = 3–4 stools more than normal
	3 = 5 or more stools more than normal
Rectal bleeding	0 = no blood seen
	1 = streaks of blood with stool less than one-half of the time
	2 = obvious blood with stool most of the time
	3 = blood alone passed without stool
Findings on endoscopy	0 = normal or inactive disease
	1 = mild disease (erythema, decreased vascular pattern, and mild friability)
	2 = moderate disease (marked erythema, lack of vascular pattern, friability, and erosions)
	3 = severe disease (spontaneous bleeding and ulcerations)
Physician's global assessment	0 = normal
	1 = mild disease
	2 = moderate disease
	3 = severe disease

New ACG UC Activity Index

	Remission	Mild	Moderate-Severe	Fulminant
Stools (#/day)	Formed stools	<4	>6	>10
Blood in stools	None	Intermittent	Frequent	Continuous
Urgency	None	Mild, occasional	Often	Continuous
Hemoglobin	Normal	Normal	<75% of normal	Transfusion required
ESR	<30	<30	>30	>30
CRP (mg/L)	Normal	Elevated	Elevated	Elevated
Fecal calprotectin (µg/g)	<150-200	>150-200	>150-200	>150-200
Endoscopy (Mayo subscore)	0-1	1	2-3	3
UCEIS	0-1	2-4	5-8	7-8

The Urgency of Urgency

Urgency Numeric Rating Scale (NRS)

- Patients report the severity of their bowel urgency symptom over the past 24 hours.
- Weekly average scores are calculated as mean score over a 7-day period.
- Higher scores indicate worse urgency severity (i.e., immediacy of need to have a bowel movement).

,

Urgency correlates the most with patient global rating of severity

COA	Sample Size	Pearson Correlation (95% CI)	Spearman Correlation (95% CI)
Average PGR-S score	41	0.802 (0.651, 0.888)	0.802 (0.651, 0.888)
Average number of daily stools	41	0.459 (0.171, 0.669)	0.516 (0.241, 0.707)

patient global rating of severity (PGR-S) scores

The Mayo endoscopic subscore

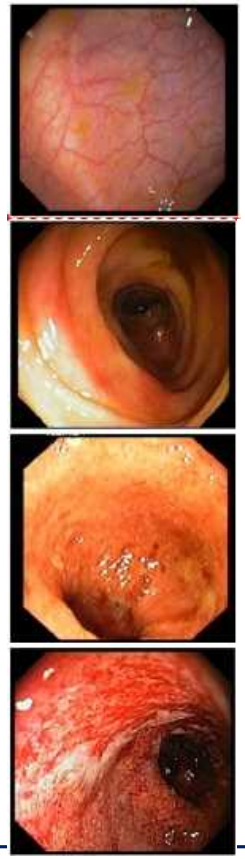
Findings of flexible proctosigmoidoscopy

0 = Normal or inactive disease

1 = Mild disease (erythema, decreased vascular pattern, mild friability)

2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)

3 = Severe disease (spontaneous bleeding, ulceration)



Schroeder KW et al. N Engl J Med
1987

What is the severity of this case?

What is difference between severity &activity

DISTINGUISH DISEASE ***ACTIVITY*** VS DISEASE ***SEVERITY***

Activity

Cross-sectional assessment of biologic inflammatory impact on symptoms, signs, endoscopy, histology, and biomarkers

Severity

Longitudinal (disease course) and historical factors that provide a picture of the prognosis and overall "burden" of disease

DISTINGUISH DISEASE ***ACTIVITY*** VS DISEASE ***SEVERITY***

Activity

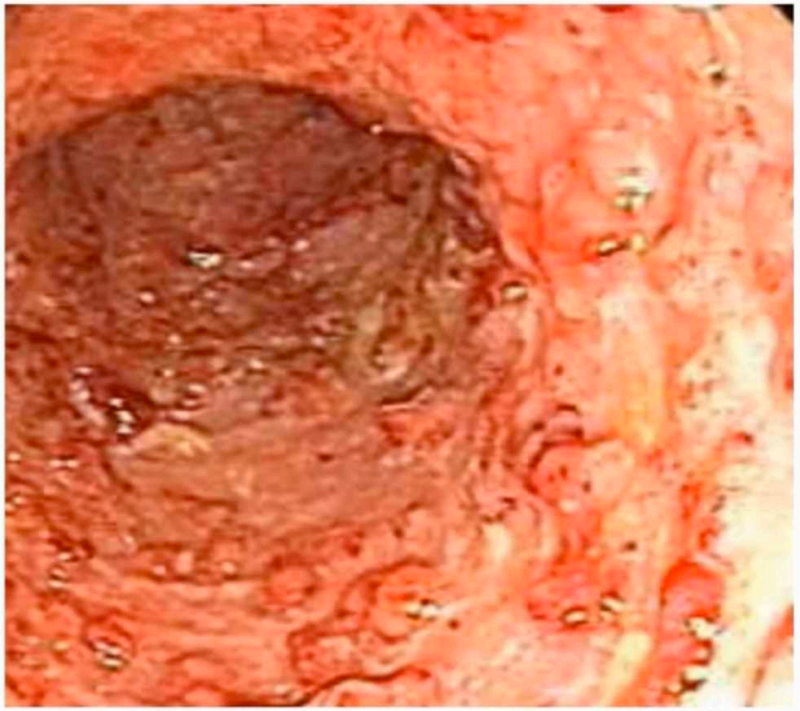
How is your patient TODAY?

Severity

What has your patient's disease course been over their history since diagnosis?

PROGNOSTIC FACTORS FOR SEVERE ULCERATIVE COLITIS

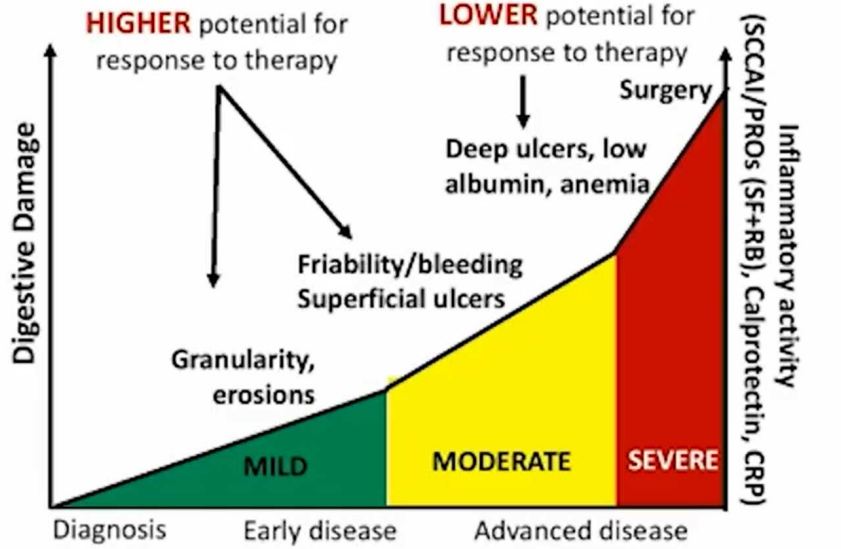
- Diagnosis age <40
- Extensive disease
- Severe endoscopic disease
- Hospitalization for colitis
- Elevated CRP
- Low serum albumin



Rubin T, et al. *Am J Gastroenterol.* 2019;114(3):385-413

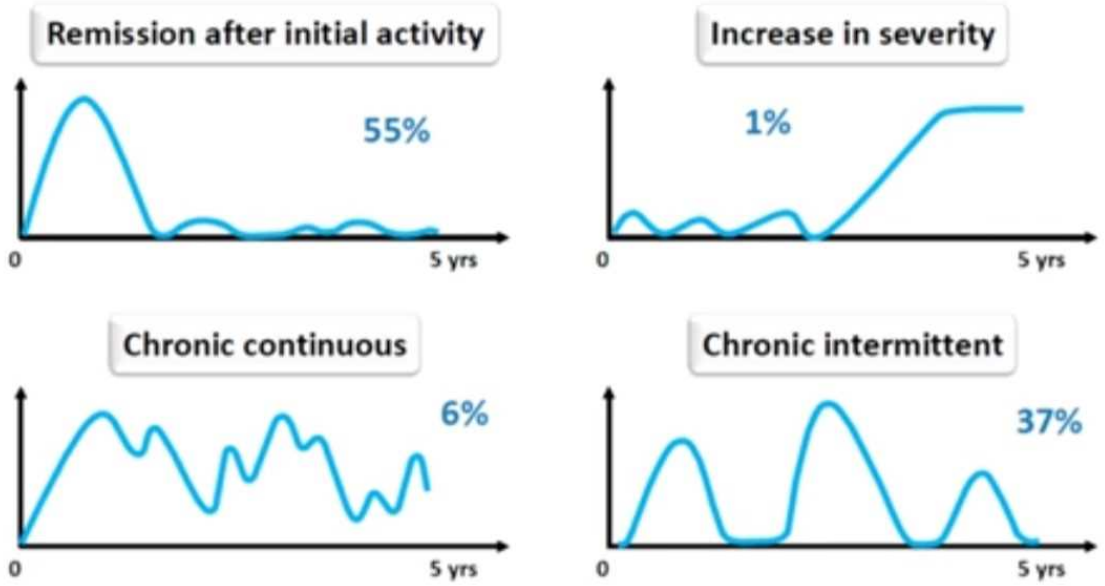
Defining UC disease **ACTIVITY** vs **SEVERITY**

Successful monitoring strategies begin with appropriate treatment selection at diagnosis



SCCAI: Simple Colitis Clinical Activity Index; PROs: patient reported outcomes, CRP: C-reactive protein

Disease course in UC



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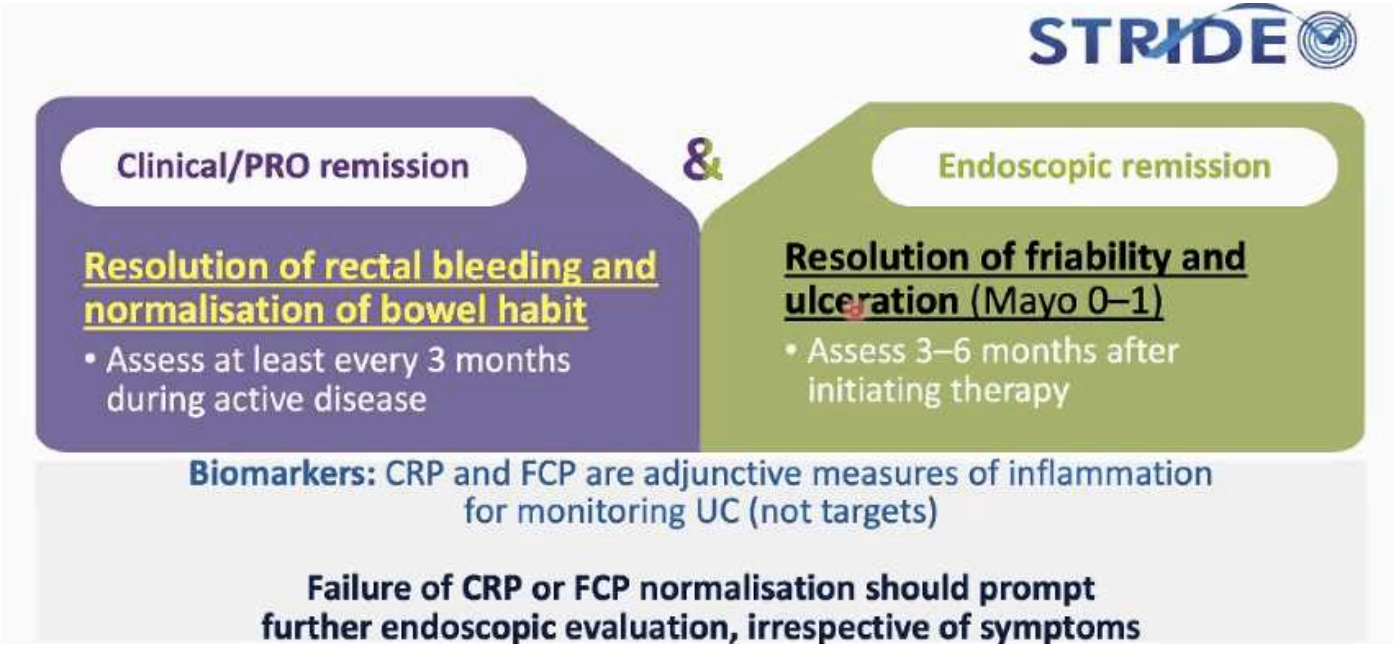
Solberg *et al.* 2009 Scand J Gastroenterol 44(4):431-40

Therapeutic target:

- Clinical remission ?
- Endoscopic remission ?
- Mucosal healing ?

Therapeutic target:

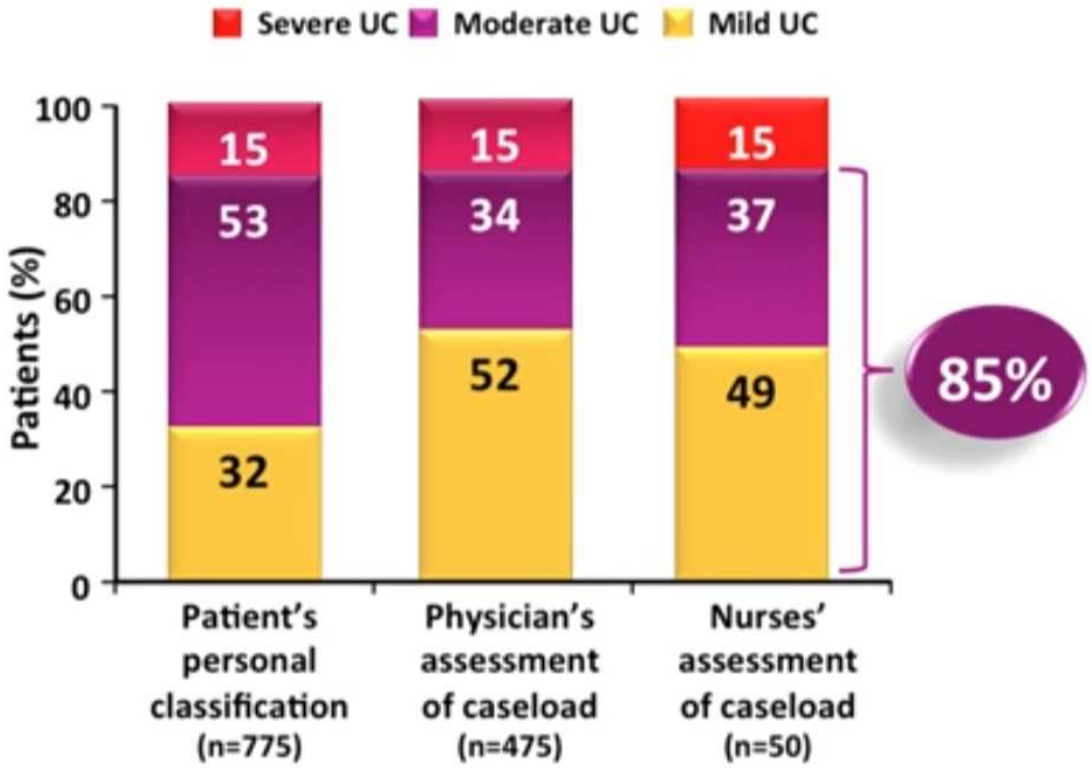
Clinical remission → & Endoscopic remission



CHOOSING IBD THERAPY

- Not every patient needs “top down” or “early intensive therapy”
- We need to determine who is at a high versus a low risk of disease complications
- We want to personalize a treatment plan
- And we need to be able to communicate this clearly to patients and providers

Majority of patients have mild to moderate UC



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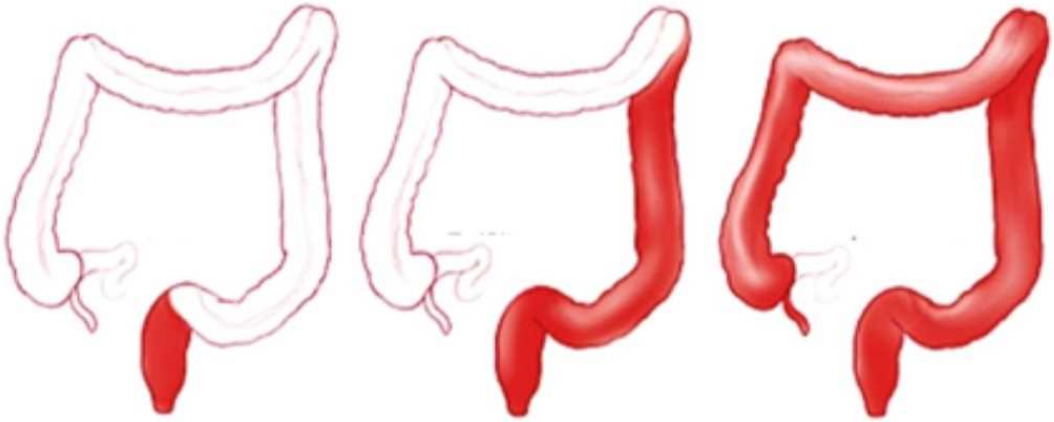
Schreiber S *et al. BMC Gastroenterol.* 2012;12(1):108

What groups of below drugs is your first choice?

- 5-Aminosalicylic acids
- Glucocorticoids
- Immunomodulators
- Biologics

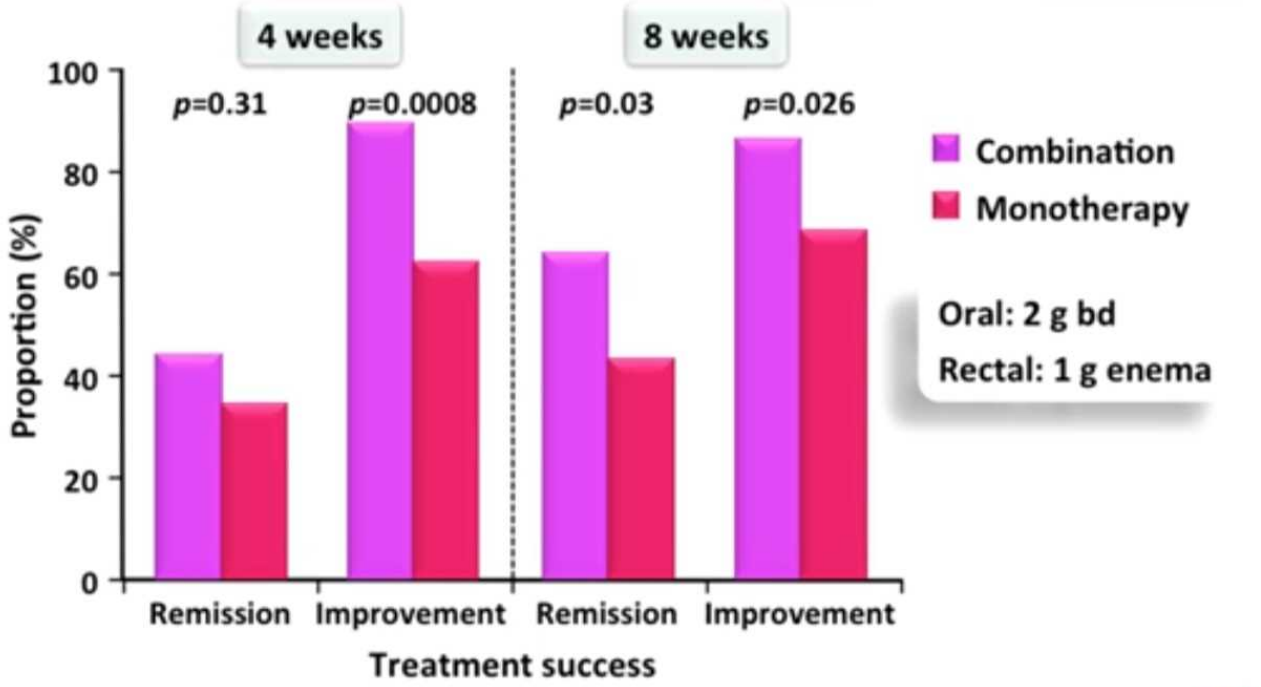
- **Do you prefer to choose oral, rectal or both in treatment of our patients?**

Consider extent of disease



Silverberg MS, *et al. Can J Gastroenterol* 2005; 19(Suppl A):5–36.

Combination oral and rectal 5-ASA versus oral 5-ASA therapy alone in pancolitis



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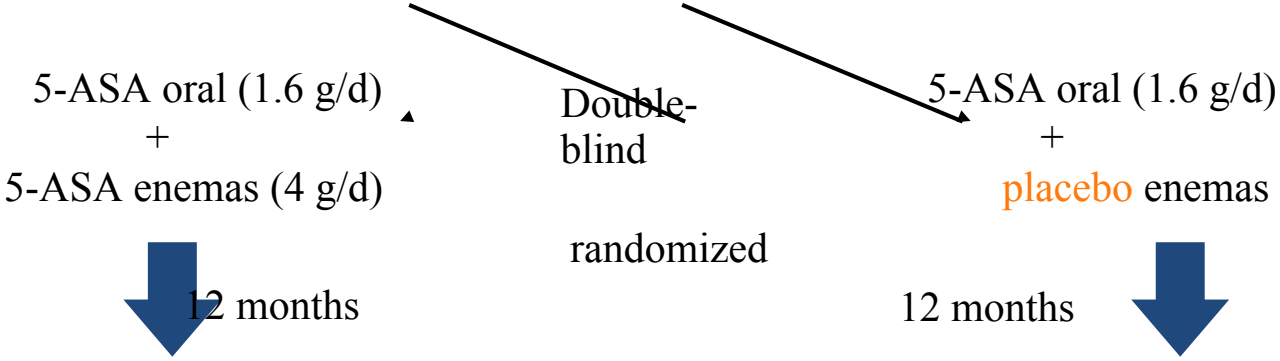
Marteau P *et al. Gut* 2005;54:960

Combination: 5-ASA oral + enema superior in maintenance of Left-sided UC

72 patients with UC (greater than proctitis) in remission x 1 month,
at least 2 relapses in past year



D'Albasio et al. Am J Gastroenterol 1997;92:1143-7.

What kind of rectal 5-ASA is better?

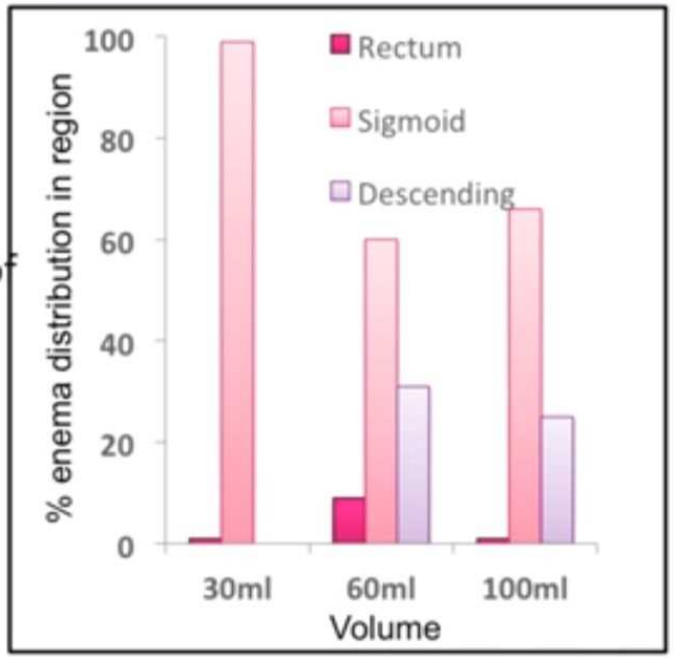
- Suppository
- Foam
- Enema
- Both of above forms

Enemas may not provide good 5ASA delivery to rectum

31 patients with UC

Scintigraphy after administration of enemas of different volume

Median delivery to different areas of interest



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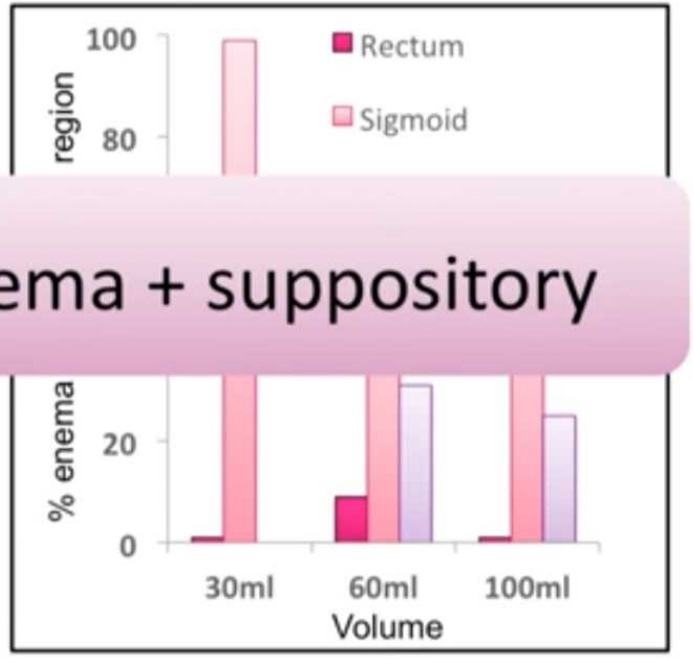
Van Bodegraven *et al* Aliment Pharmacol Ther. 1996; 10, 327-332

Enemas may not provide good 5ASA delivery to rectum

31 patients with UC



Consider enema + suppository

Median delivery to different areas of interest

Van Bodegraven *et al* Aliment Pharmacol Ther. 1996; 10, 327-332

Enema or Supp?

Supp:
- When?
- How?

Enema:
- When?
- How?

Enema or Supp?

ECCO statement 11A

A mesalamine 1-g suppository once daily is the preferred initial treatment for mild or moderately active proctitis [**EL1**]. Mesalamine foam or enemas are an alternative [**EL1**], but suppositories deliver the drug more effectively to the rectum and are better tolerated [EL3].

Harbord M. et al. *JCC* 2016

Enema or Supp?

ECCO statement 11C

Mild to moderately active left-sided ulcerative colitis should initially be treated with an aminosalicylate enema ≥ 1 g/day [EL1] combined with oral mesalamine ≥ 2.4 g/day [EL1], which is more effective than oral or topical aminosalicylates, or topical steroids alone [EL1].

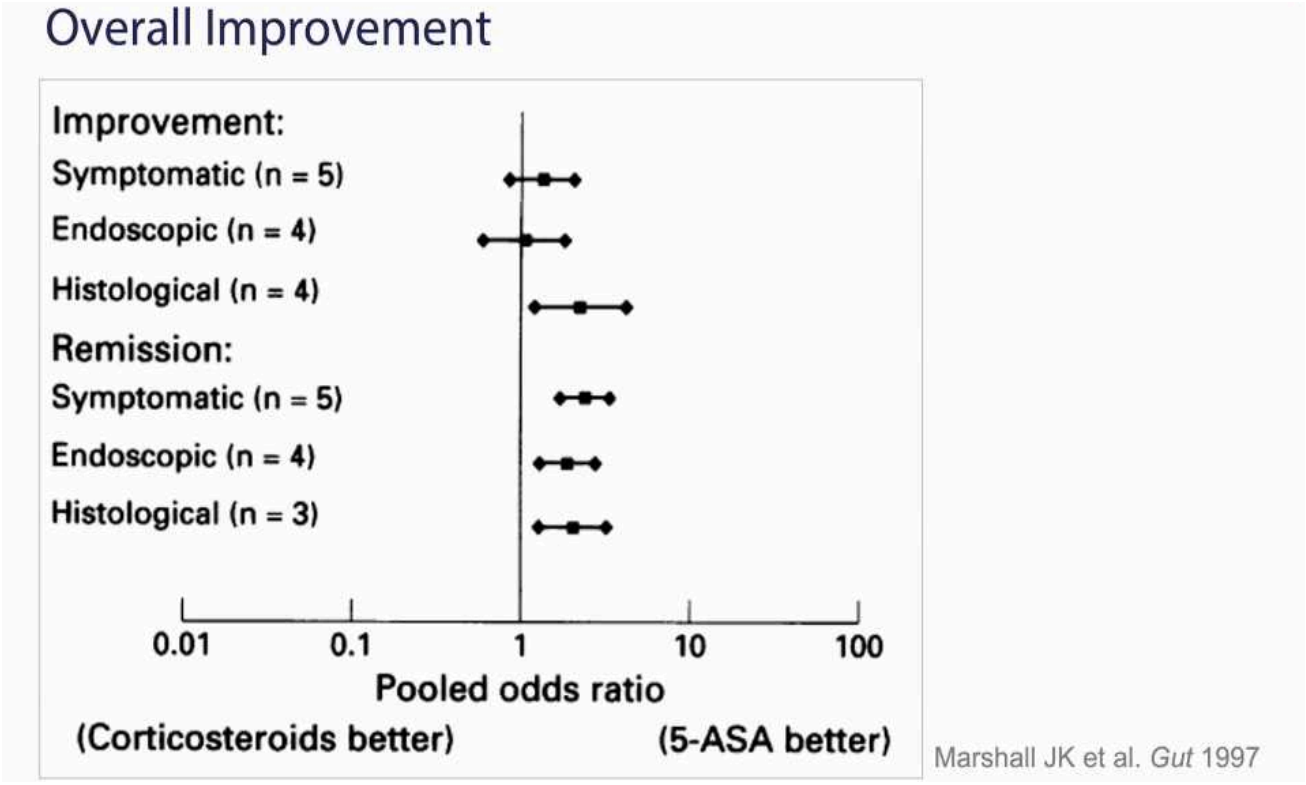
Harbord M. et al. *JCC* 2016

Topical Steroid?

Topical mesalamine is more effective than topical steroids [EL1].

Harbord M. et al. *JCC* 2016

Topical Steroid?



Marshall JK et al. *Gut* 1997

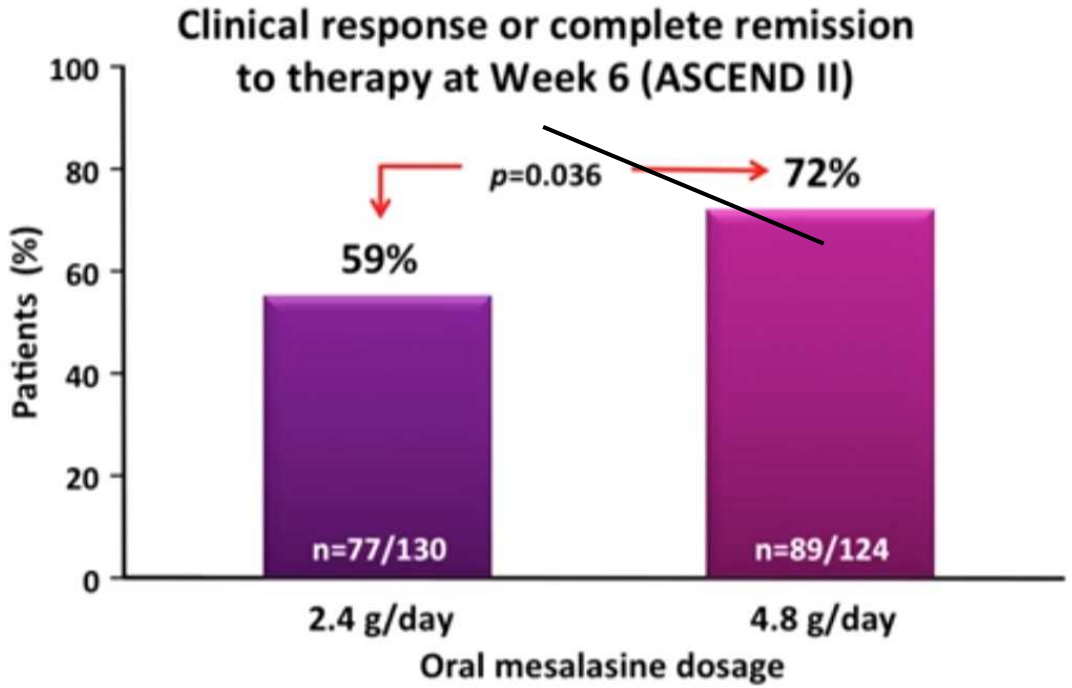
Pancolitis?

ECCO statement 11E

Mild to moderately active extensive ulcerative colitis should initially be treated with an aminosalicylate enema 1 g/day [**EL1**] combined with oral mesalamine ≥ 2.4 g/ day [**EL1**]. Once-daily dosing with mesalamine is as effective as divided doses [**EL1**]. ...

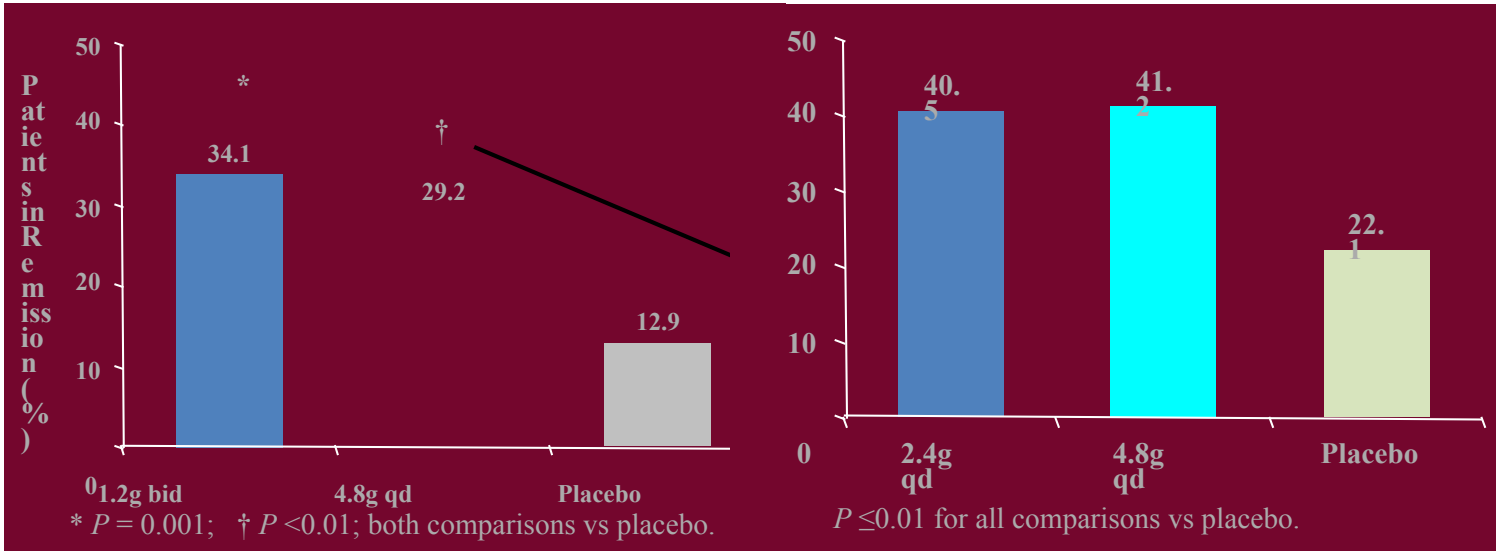
Harbord M. et al. *JCC* 2016

Optimise 5-ASA dose



Hanauer SB *et al*. Am J Gastroenterol. 2005 Nov;100(11):2478–85

Little Evidence of 5-ASA Dose Response in Active UC Beyond 2.4 g/Day

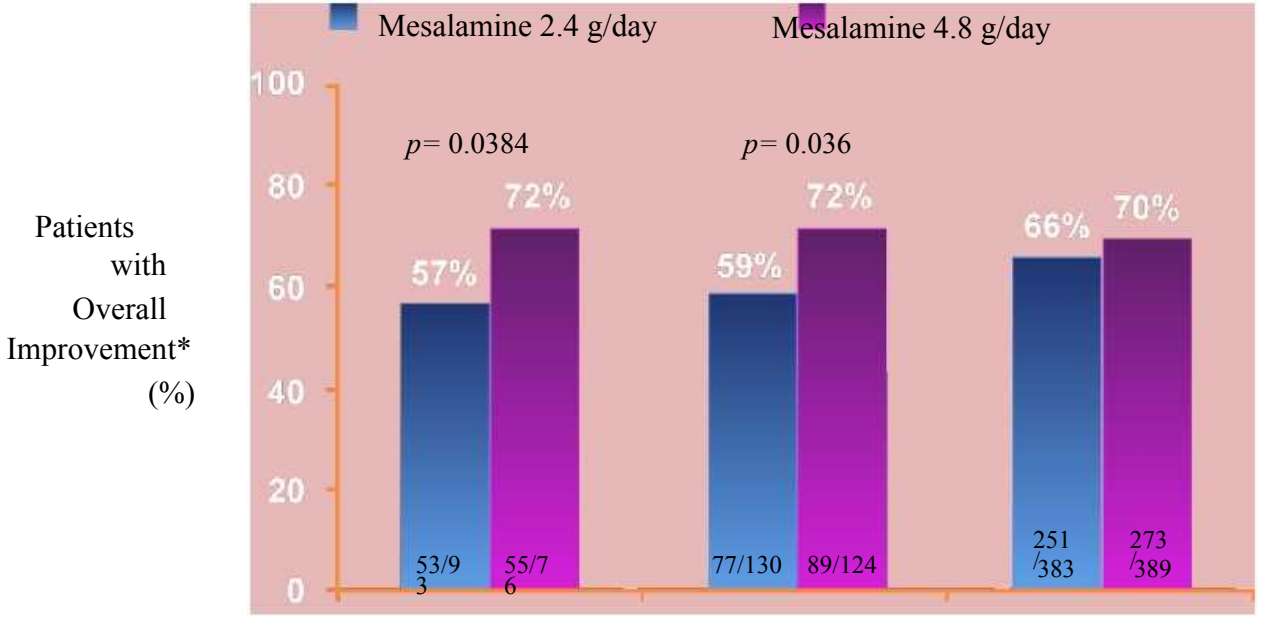


pH-Released Multimatrix Mesalamine Studies

Lichtenstein GR, et al. Clin Gastroenterol Hepatol. 2007; 5:95–102.

Kamm MA, et al. *Gastroenterology.* 2007;132:66–75.

Probable Dose Response >2.4 g/Day in **Moderately Severe** Active UC



1 HanauerSB et al. Can J Gastroenterol 2007;21:827-834. 2) Hanauer SB et al. Am J Gastrenterol 2005;100:2478-2485.
3) Sandborn WJ et al. Gastroenterology 2009;137(6):1934-43..

Which dose of 5-ASA do you recommend?

- **Low dose**
- **Standard dose**
- **High dose**

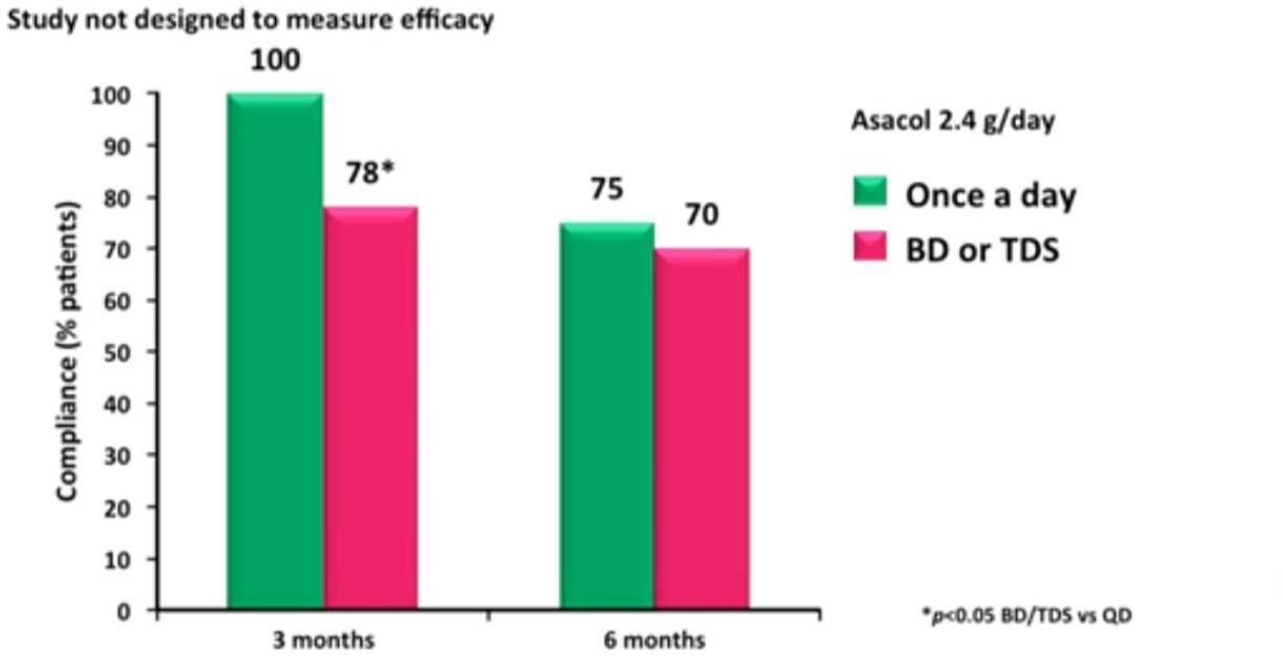
Recommendation 1. In patients with extensive mild–moderate UC, the AGA recommends using either standard-dose mesalamine (2–3 g/d) or diazo-bonded 5-ASA rather than low-dose mesalamine, sulfasalazine, or no treatment. *Strong recommendation, moderate quality evidence.*

Comment: Patients already on sulfasalazine in remission or patients with prominent arthritic symptoms may reasonably choose sulfasalazine 2–4 g/d if alternatives are cost-prohibitive, albeit with higher rate of intolerance.

Which is more effective and better?

- Single daily dose or divided dose of 5-ASA.

Once a day versus conventional dosing UC maintenance



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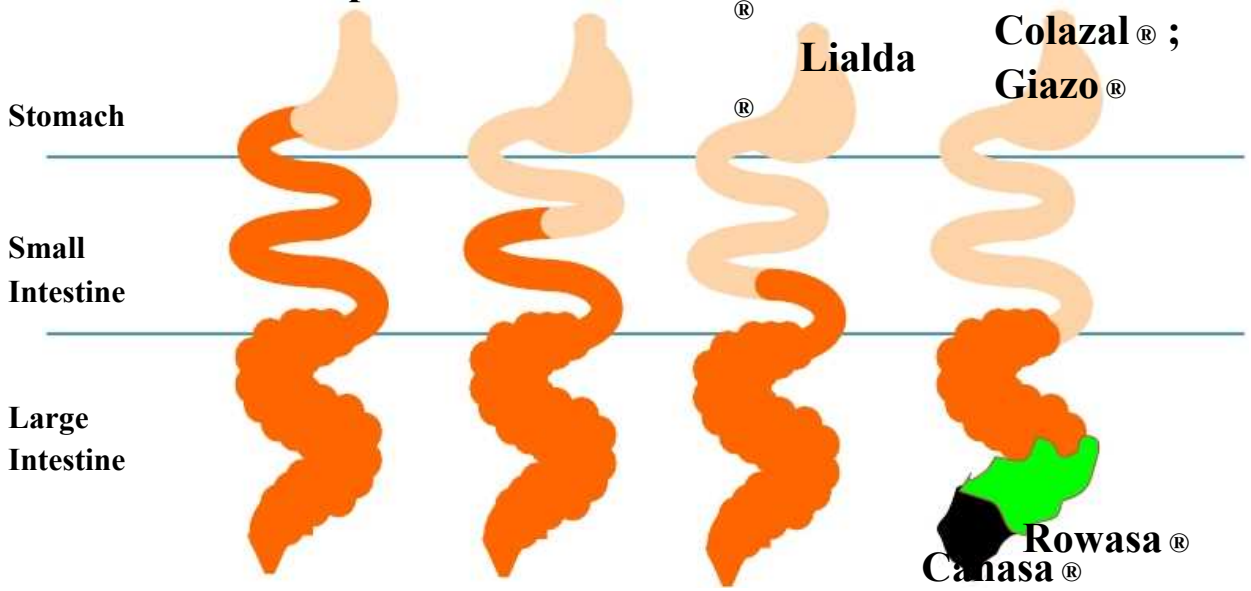
Kane S *et al.* Clin Gastro Hepatol 2003;1:170–3

Patient questions?

Are there any difference between Sulfasalazine /Pentasa/Asacol/Mesalazine?

Disposal of complete Asacol tablets

5-ASA Release Sites:



Mechanisms of Release	Moisture	pH ≥ 6; Moisture	pH ≥ 7; Moisture*	Azo-bond (orals) Directly applied (topicals)

: * Lialda utilizes both.

Sources: FDA package inserts / company websites.

5-Aminosalicylates: Side Effects

- Common: headache, hair loss
- Hypersensitivities
- Sulfa moiety in sulfasalazine is responsible for:
  - -hemolytic anemia
  - -reversible hypospermia
  - -allergic phenomena
  - -nausea
- Monitoring
  - Periodic BUN and creatinine given rare idiosyncratic cases of interstitial nephritis

Patient questions?

- Are there any concerns about infertility by Sulfasalazine/Mesalazine?

At FU:

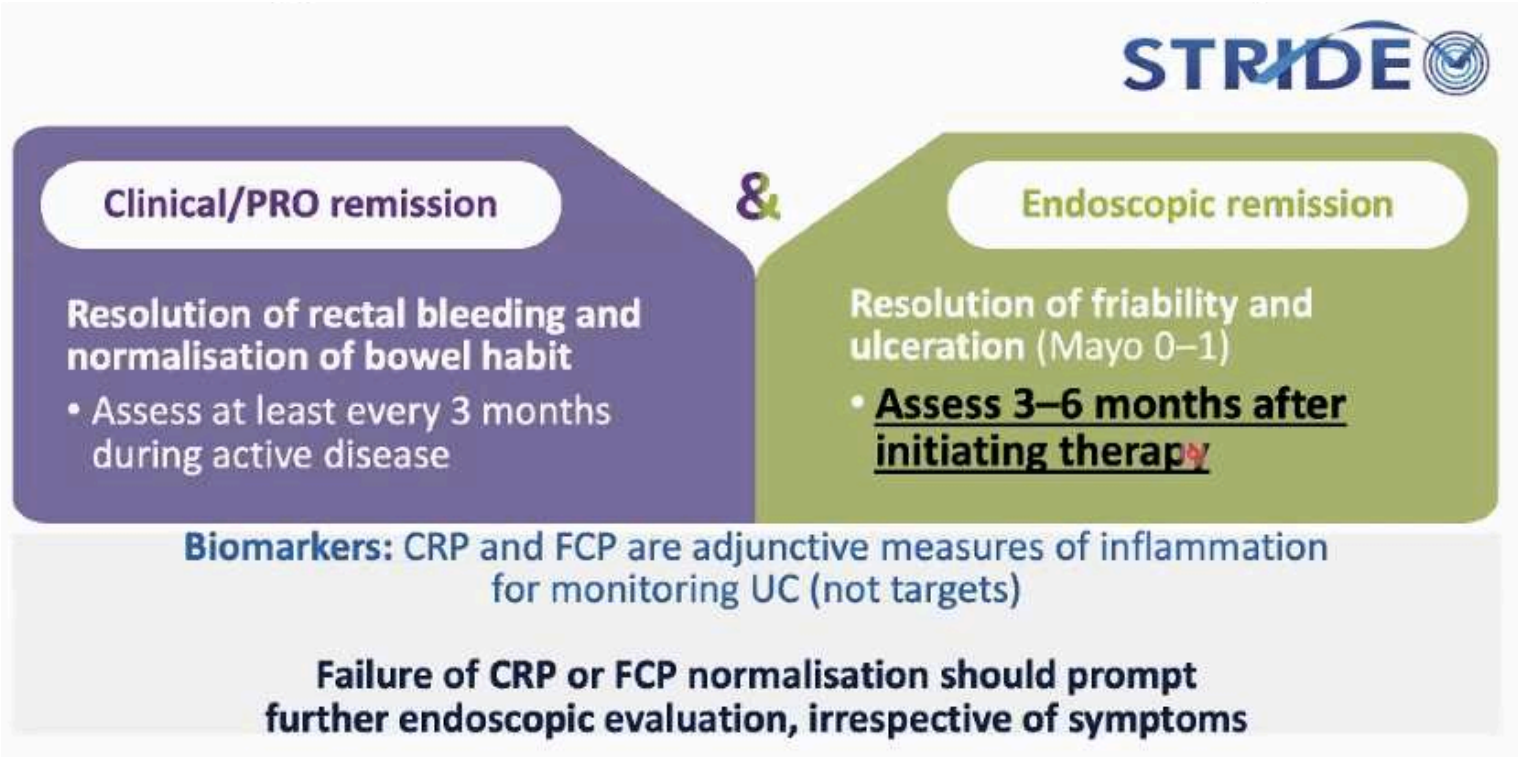
- After 8 w, she has 2-3 semiformed non-bloody stool without any nocturnal ss.

- WBC: 9700
- Hb: 14
- Plt: 332000
- ESR: 20
- CRP: 6

What is your next plan:

1. Keep Mesalamine 4 gr/d, stop Enema and Supp
2. Reduce Mesalamine 2 gr/d, stop Enema and supp
3. Reduce Mesalamine 1 gr/d, stop Enema and supp
4. Keep Mesalamine 4 gr/d, Enema qd and Supp qd till endoscopic evaluation at 3-6 m
5. Keep Mesalamine 4 gr/d, Enema qd and Supp qd till calprotectin test at 3-6 m

What is your next plan:



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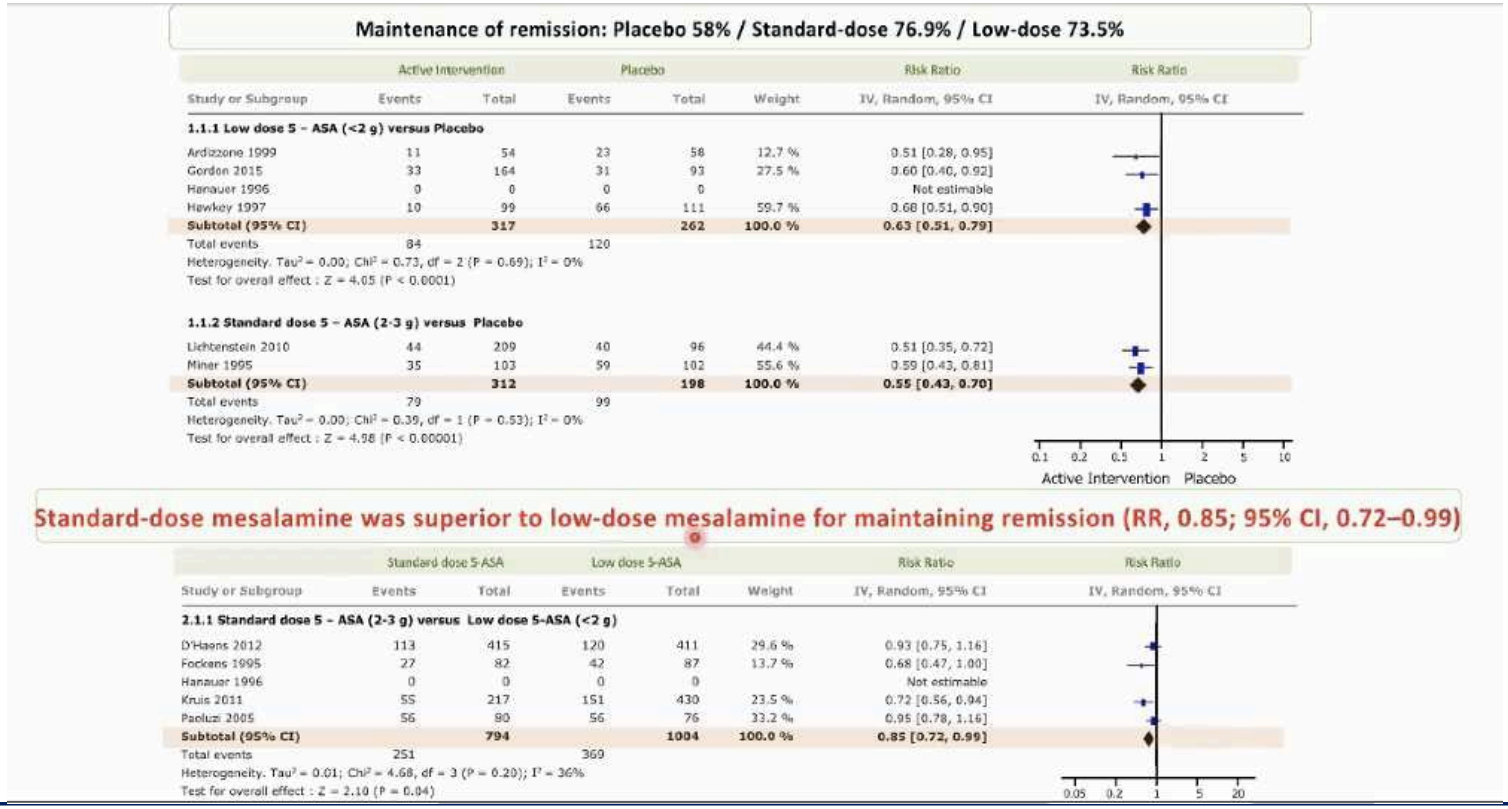


Maintenance of remission: Placebo 58% / Standard-dose 76.9% / Low-dose 73.5%

Study or Subgroup	Active Intervention Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.1.1 Low dose 5 – ASA (<2 g) versus Placebo						
Ardizzone 1999	11	54	23	58	12.7 %	0.51 [0.28, 0.95]
Gordon 2015	33	164	31	93	27.5 %	0.60 [0.40, 0.92]
Hanauer 1996	0	0	0	0		Not estimable
Hawkey 1997	10	99	66	111	59.7 %	0.68 [0.51, 0.90]
Subtotal (95% CI)		**317**		**262**	**100.0 %**	**0.63 [0.51, 0.79]**
Total events	84		120			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.73$, df = 2 (P = 0.69); $I^2 = 0\%$						
Test for overall effect: Z = 4.05 (P < 0.0001)						
1.1.2 Standard dose 5 – ASA (2-3 g) versus Placebo						
Lichtenstein 2010	44	209	40	96	44.4 %	0.51 [0.35, 0.72]
Miner 1995	35	103	59	102	55.6 %	0.59 [0.43, 0.81]
Subtotal (95% CI)		**312**		**198**	**100.0 %**	**0.55 [0.43, 0.70]**
Total events	79		99			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.39$, df = 1 (P = 0.53); $I^2 = 0\%$						
Test for overall effect: Z = 4.98 (P < 0.00001)						

Standard-dose mesalamine was superior to low-dose mesalamine for maintaining remission (RR, 0.85; 95% CI, 0.72–0.99)

Study or Subgroup	Standard dose 5-ASA Events	Total	Low dose 5-ASA Events	Total	Weight	Risk Ratio IV, Random, 95% CI
2.1.1 Standard dose 5 – ASA (2-3 g) versus Low dose 5-ASA (<2 g)						
D'Haens 2012	113	415	120	411	29.6 %	0.93 [0.75, 1.16]
Fockens 1995	27	82	42	87	13.7 %	0.68 [0.47, 1.00]
Hanauer 1996	0	0	0	0		Not estimable
Kruis 2011	55	217	151	430	23.5 %	0.72 [0.56, 0.94]
Paoluzi 2005	56	80	56	76	33.2 %	0.95 [0.78, 1.16]
Subtotal (95% CI)		**794**		**1004**	**100.0 %**	**0.85 [0.72, 0.99]**
Total events	251		369			
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 4.68$, df = 3 (P = 0.20); $I^2 = 36\%$						
Test for overall effect: Z = 2.10 (P = 0.04)						

Patient education?

- Control versus Cure
- Lifelong therapy
- Marriage
- Pregnancy
- Times between Colonoscopy
- Cost

Summary of tips about 5-ASA:

- Combination of oral and local therapy superior
- Consider dose-dependent effect of mesalazine
- Individual dose-adaption
- It might take some weeks until you see the response
- Consider adherence

For Mild-Moderate UC

Induction:

- Mild proctitis→ **rectal 5-ASA** recommended (1 g/day)[1,2,3,4,5]
- Left-sided mild UC→ **rectal 5-ASA** (≥1 g/day) in combination with **oral 5-ASA** (≥ 2.0 g/day)[1,2,3,4,5,6]
- Mild extensive UC→ **oral 5-ASA** (≥ 2.0 g daily)[1,5]
- Mild UC (any extent)→ use a low dose (2.0-2.4 g) of **5-ASA**[2], in comparison with a higher dose (4.8 g)[1]
- Mild-moderate UC not responding to **oral 5-ASA**→ +**budesonide MMX** 9 mg/day[1,2,3,5]

Maintenance:

- **Recommend against** systemic steroids[1,3,6]
- Mildly active proctitis→ **rectal 5-ASA** (1 g daily)[1,2,6]
- Mildly active left-sided or extensive UC→ **oral 5-ASA** therapy (≥ 2 g/day)[1,2,3,4]

- **You prescribe rectal enema in combination with 2.5 gr meselamin for her.**

- **When you evaluate treatment response**?

- **It is appropriate to evaluate tx response after 6 weeks**.

- **After 6 weeks you patient still have occasional abdominal pain and trace rectorrhagia**

Which of these should be considered:

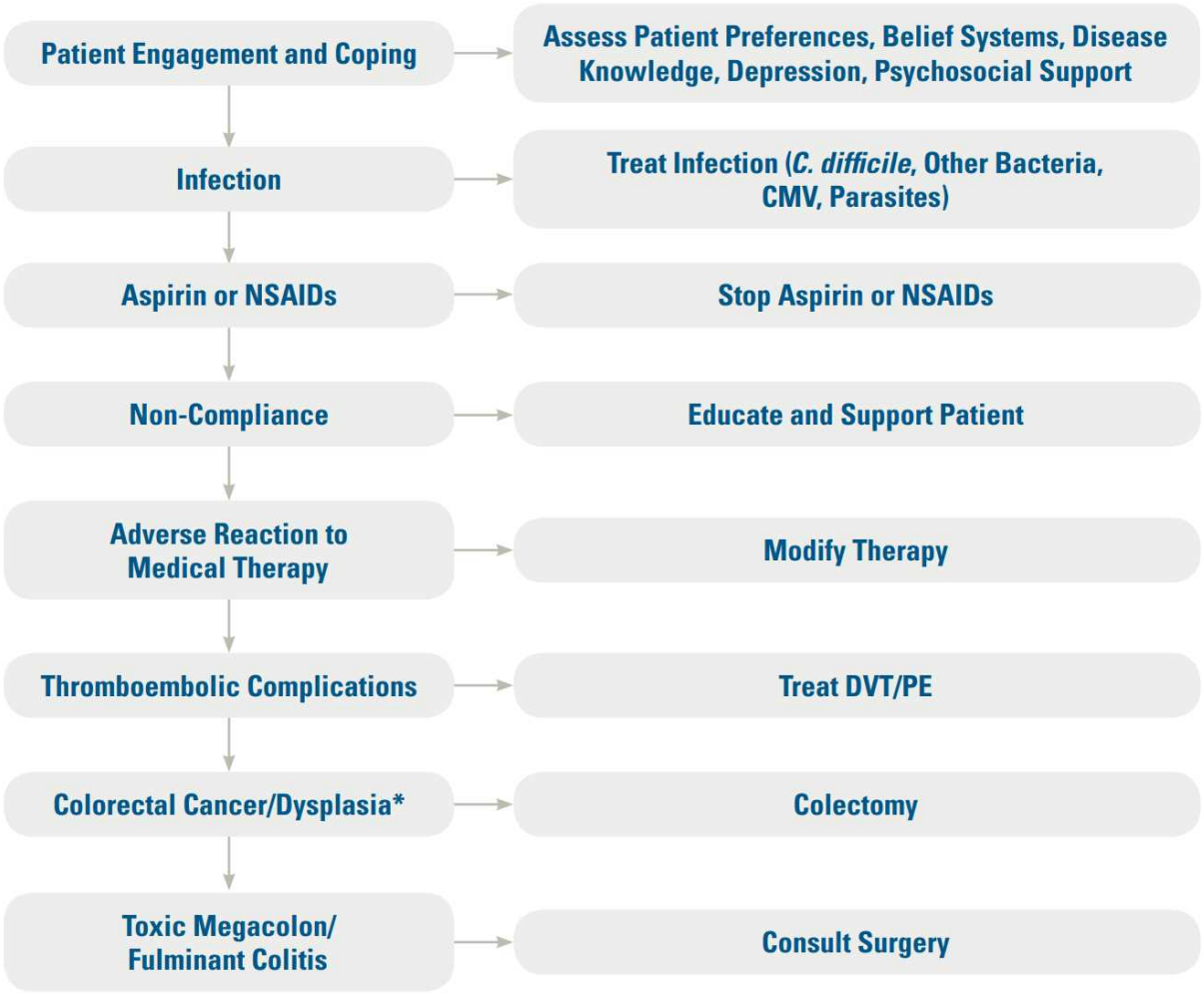
A. **Increasing 5-ASA dose**

B. **Changing 5 ASA brand**

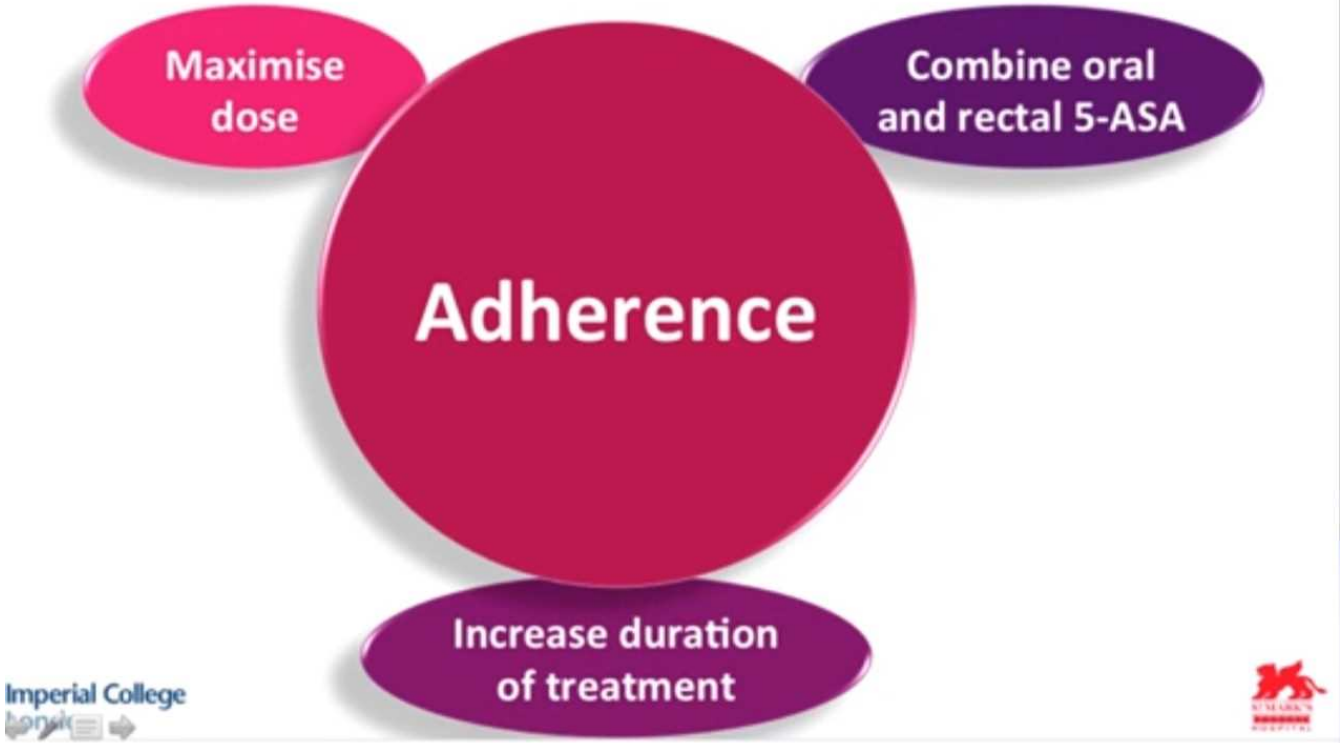
C. **Evaluating adherence**

D. **Evaluating other medication use**

ASSESS COMORBIDITIES AND DISEASE AND THERAPY-RELATED COMPLICATIONS (2)



How to optimise 5-ASA



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What is your decision in this step?

A. **Increasing 5ASA dose**
B. **Anti TNF**
C. **Oral prednisolone**
D. **Azaram**
E. **budesonide**

Induction of Remission: Moderate-Severe UC

- UC failing to respond to **5-ASA** therapy→ **oral systemic corticosteroids**[1,2,3,4]
- Moderate UC→ **oral budesonide MMX**[1]
- Moderate-severe UC of any extent→ **oral systemic corticosteroids**[1,3,4]
- **Anti-TNF** therapy using **adalimumab**, **golimumab** or **infliximab**[1,3]
- **Infliximab** in combination with a **thiopurine**[1,2,3,4]
- **Vedolizumab**[1,2,3]
- **Ustekinumab**[5]
- If failed **anti-TNF**→ **vedolizumab**[1,2,3,4] *or* **tofacitinib**[1] (or **ustekinumab**)[5]
- **Recommend against** monotherapy with **thiopurines** *or* **methotrexate**[1,3]

Budesonide in UC

- **90% first pass effect in liver**
- **Low systemic effect**
- **High topical anti inflammatory activity**
- **Generally fast acting drug(clinical response in7-10 days)**

Oral formulation:

- **Ileal release (both may be used in crohn)**
  - **PH and time dependent release**
  - **PH dependent release**

- **Colonic release (Disolced in PH>7,multimatrix,used in UC)**
- **Rectal formulation**

Which consideration is required

- Patient with cirrhosis
- Drug interaction(CYP3A inhibitor,ketoconazole,..)
- Grapefruit juice

Dosage recommendation

- Generally begin 9mg daily for 6-10 weeks.
- If symptoms improvd,reduce to 9mg every other day for 2 weeks
- Total :8-12 weeks

- If not responding in 10 weeks,change the drug
- Limit budesonide to a single course

- Limited effect on BMD
- Even better preservation of BMD in corton naïve
- Low risk in pregnancy
- Compatible with breast feeding


Thank you!!