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# *Case based discussion:*

## *The patient with bloody diarrhoea – differential diagnosis and initial diagnostic work-up*

Marjolijn Duijvestein, Amsterdam, the Netherlands
Axel Dignass, Frankfurt am Main, Germany

Barcelona, February 15, 2012

# 24 year-old woman:

*Blood in stools and faecal urgency*

- 24yr old woman presents with blood in stools and faecal urgency for 3 weeks
- 3 bowel movements/day
- Blood and mucus
- Generally well
- Temp 37.2°C

**The following diseases represent relevant differential diagnoses of IBD.**

*Which answer is not correct?*

1. Clostr. difficile colitis
2. CMV Colitis
3. Ischemic colitis
4. NSAID colitis
5. Gastroesophageal reflux disease (GERD)

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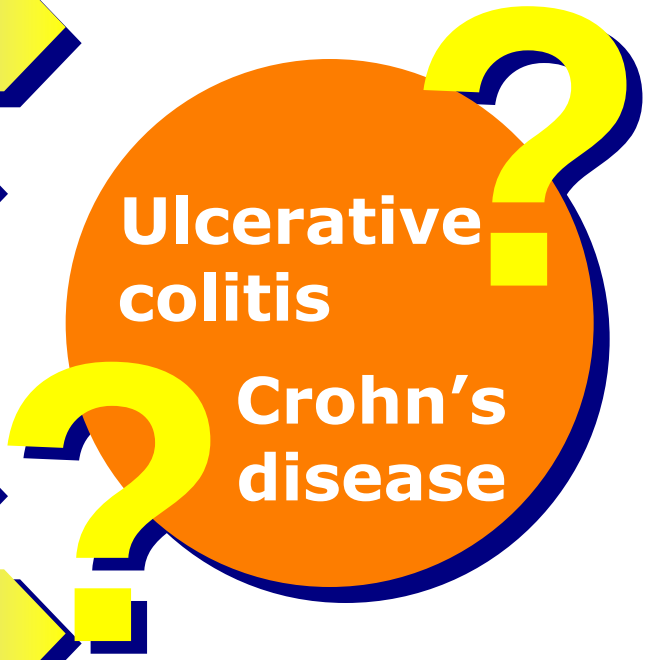
# Suspicion of an inflammatory bowel disease

- Diarrhea for > 4 weeks
- > 2 bowel movements per day
- Liquid or porridge-like stools
- Abdominal pain
- Blood in the stool



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# Characteristics of IBD

| | Crohn's disease | Ulcerative Colitis |
|---|---|---|
| **Rectal Bleeding** | ~20% | >90% |
| **Diarrhoea** | ~75% | ~50% |
| **Abdominal pain** | ~80% | ~50% |
| **Fistula** | ~20% | 0 |
| **Localization** | Skip lesions | Continuous |
| | Complete GI tract | Colon (>90% rectum) |
| **Histology** | Epitheloid granuloma | Crypt abscess |

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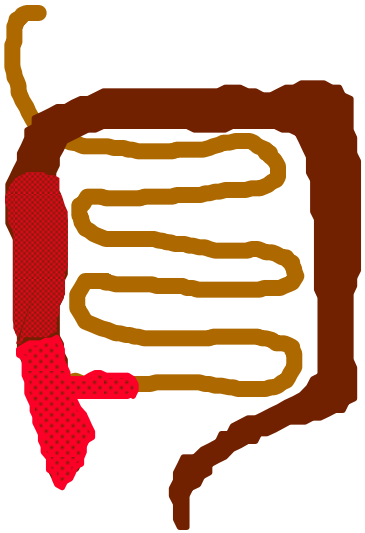
# Localisation of IBD

## CD



| | |
|---|---|
| Small bowel: | 30-40% |
| Ileocecal region: | 30-45% |
| Colon: | 20-30% |

## UC

| | |
|---|---|
| Rectum: | 95% |
| Leftsided-colitis: | 75% |
| Pancolitis: | 15-25% |

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# Medical history

*ECCO Statement:*

A full medical history should include detailed questioning about **the onset of symptoms, particularly recurrent episodes of rectal bleeding or bloody diarrhoea, urgency, tenesmus, abdominal pain, incontinence, nocturnal diarrhoea, and features of extra-intestinal manifestations.**

**Recent travel, food intolerances, contact with enteric infectious illnesses, medication (including antibiotics and non-steroidal anti-inflammatory drugs), smoking habit, sexual practice, family history of IBD and previous appendicectomy** should be explored [EL5, RG D)

# 24 year-old woman:

*Blood in stools and faecal urgency*

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- 3 bowel movements/day
- Blood and mucus
- Generally well
- Temp 37.2°C

- No past history, no recent travel, no antibiotics, no NSAIDs….

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# Examination

*ECCO Statement:*

In patients with UC physical examination should include general well-being, pulse rate, body temperature, blood pressure, body weight and height, abdominal examination for distention and tenderness, perineal inspection, digital rectal examination, oral inspection, and check for eye, skin and/or joint involvement.

**Physical examination may be unremarkable in patients with mild or even moderate disease** [EL5, RG D]

# Lab tests

- ESR, Leucocytes, Thrombos, CRP --> Inflammatory activity
- Hb, Albumine --> Severity
- Iron, Ferritin, Calcium, Vitamin B12, Folic Acid --> malnutrition
- AP, GGT, Amylase, Lipase --> Extraintestinal complications
- Repeated stool analysis: Bacteria, Parasites and Clostridium-Toxin, Calprotectin --> Infectious diarrhoea
- Special tests (pANCA, ASCA, NOD-2)

# 24 year-old woman:

*Blood in stools and faecal urgency*

- 24yr old woman presents with blood in stools and faecal urgency for 3 weeks
- 3 bowel movements/day
- Blood and mucus
- Generally well
- Temp 37.2°C

- No past history, no recent travel, no antibiotics, no NSAIDs….
- No bacteria, no parasites in stools.

# Initial management?

1. Antibiotics (ciprofloxacin or metronidazole)
2. 5-ASA orally 4 g/d
3. 5-ASA suppositories
4. 5-ASA enema
5. Combination of oral and topical 5-ASA
6. Steroid enema
7. Oral steroids
8. Perform colonoscopy
9. Other

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# Diagnosis

| | Ulcerative colitis | Crohn's disease |
|---|---|---|
| **First diagnosis and flare** | Colonoscopy<br>Small bowel radiology | Colonoscopy<br>Gastroscopy<br>Small bowel radiology |
| | ESR, WBC, CRP, $K^+$, $Ca^{++}$, $Mg^{++}$, AP, γ-GT, AST, ALT, platelets, vitamin A, vitamin $B_{12}$ and stool: pathogenic microbes | |
| **Follow-up** | Sigmoidoscopy<br>(Colonoscopy)<br>(Ultrasound, CT) | Ultrasound<br>(CT) |
| | ESR, WBC, CRP | |

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# Distribution of ulcerative colitis

*Montreal classification*

| Term | Distribution | Description |
|---|---|---|
| E1 | Proctitis | Involvement limited to the rectum (i.e. proximal extent of inflammation is distal to the rectosigmoid junction) |
| E2 | Left-sided | Involvement limited to the proportion of the colon distal to the splenic flexure (analogous to 'distal' colitis) |
| E3 | Extensive | Involvement extends proximal to the splenic flexure, including pancolitis |

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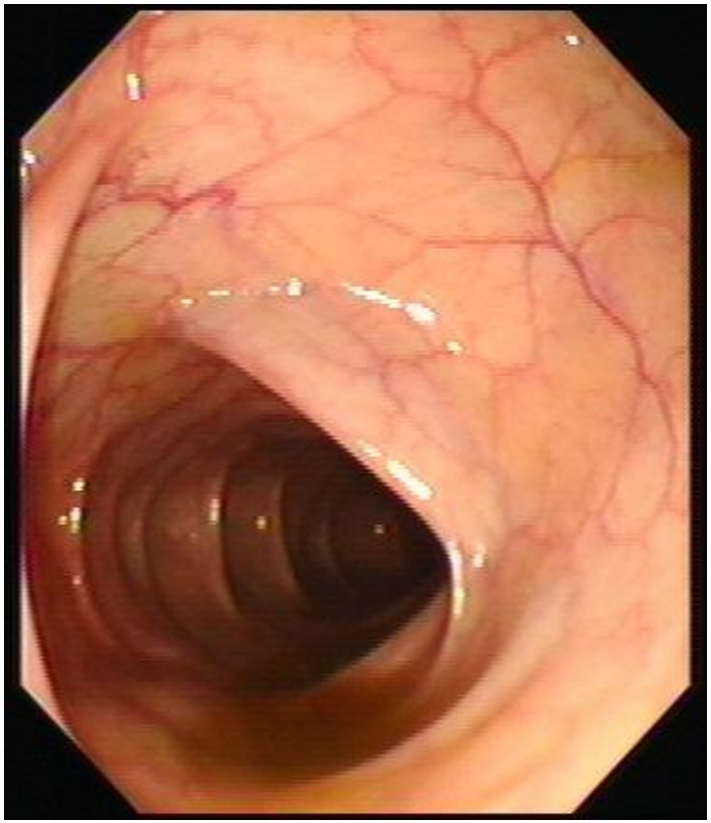
# Endoscopy of a normal colon



descending colon

rectum

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# UC

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# Chronic active UC

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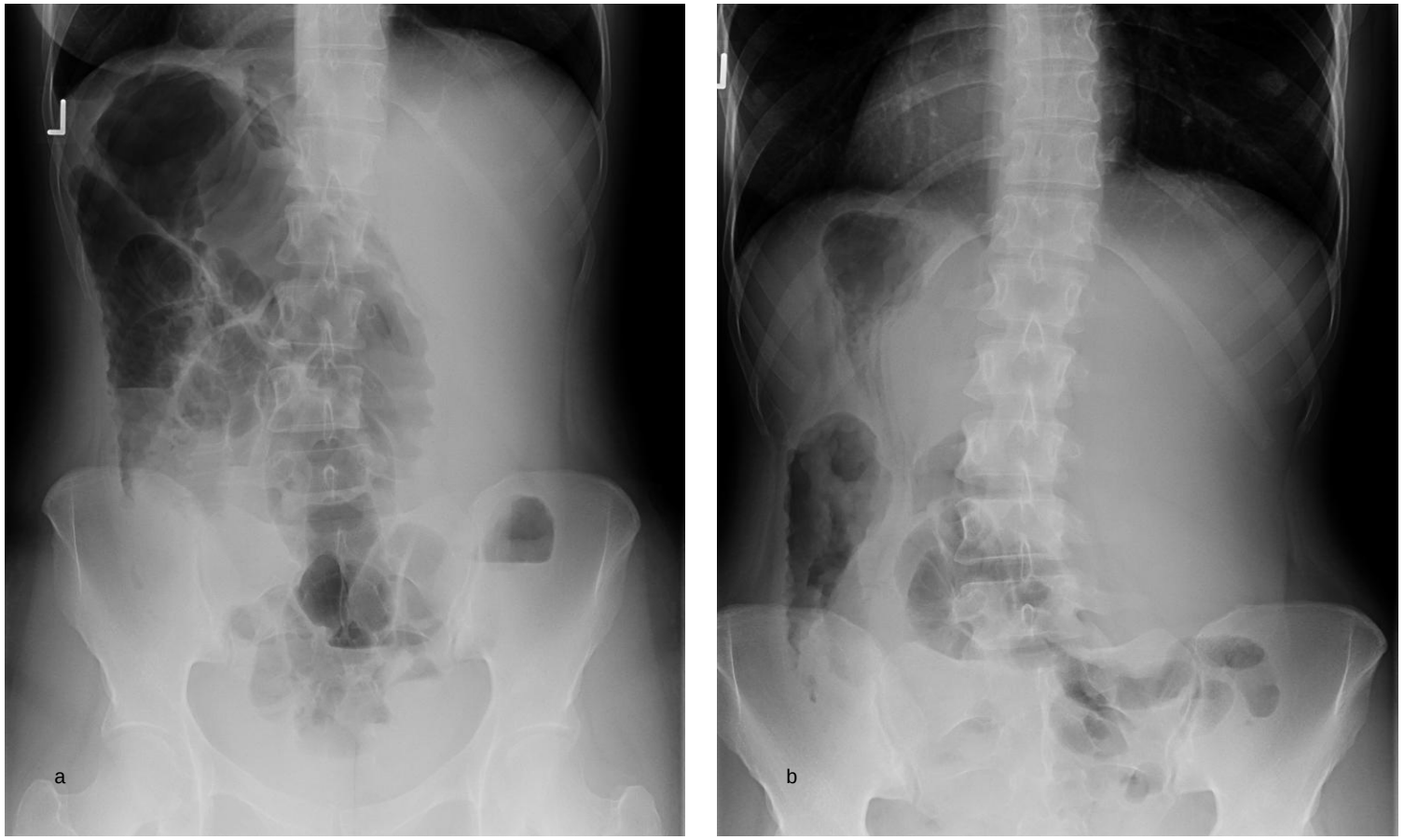
# Plain Abdominal X-Ray

*Toxic megacolon*



# Which diagnostic test has the greatest diagnostic power to diagnose IBD?

1. Blood count and CRP
2. TNFa-polymorphisms
3. Ileocolonoscopy with biopsies
4. Stool culture
5. Abdominal MRI

**Which diagnostic test does not provide additional benefit in differentiating between Crohn's disease and ulcerative colitis?**

1. Abdominal ultrasound
2. Enteroscopy
3. Ileocolonoscopy with biopsies
4. Calprotectin in stool
5. Abdominal MRI

# 24 year-old woman:

*Blood in stools and faecal urgency*

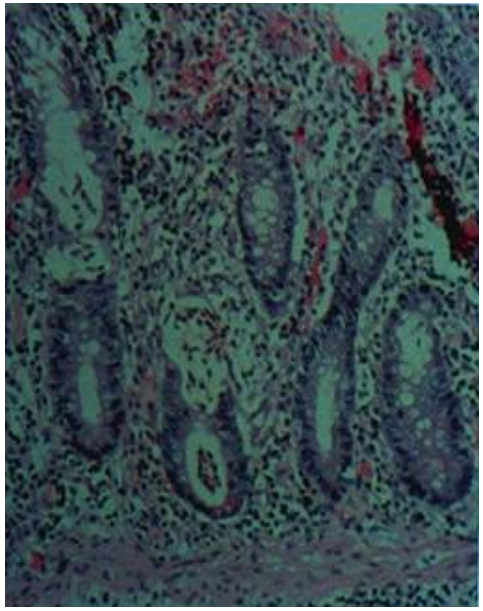
Colonoscopy:

- left sided ulcerative colitis
- friability and superficial ulceration till the left colon
- no deep ulceration
- no skip lesions

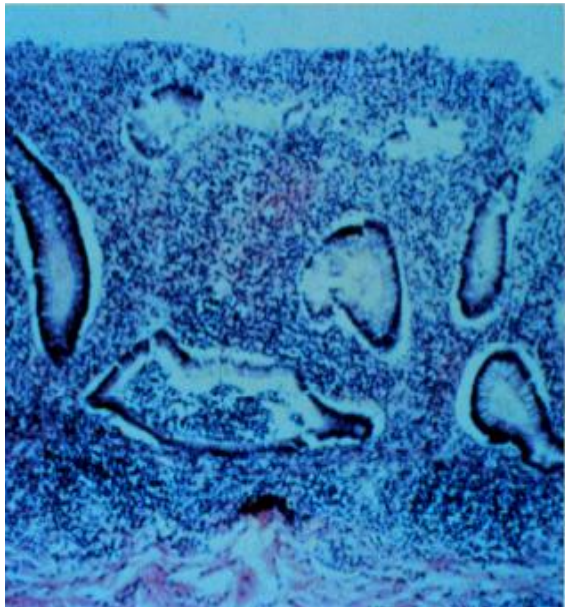
# Histology

*UC*

**mild**



**severe**



# Management?

1. Antibiotics (ciprofloxacin or metronidazole)
2. 5-ASA orally 4 g/d
3. 5-ASA as suppositories
4. 5-ASA enema
5. Combination of oral and topical 5-ASA
6. Steroid enema
7. Oral steroids 20 mg/d
8. Oral steroids 40 mg/d
9. Other

# ECCO Guidelines on CD and UC

**Crohn‘s Disease**

Dignass A et al., JCC 2010; 4:7-101

**Ulcerative Colitis**

Travis S et al., JCC 2008, 2:1-94, update 2012

**www.ecco-ibd.eu**

# Conventional therapy of IBD

## 5-ASA-Derivatives
Mesalazine
Sulfasalazine
Olsalazine
Balsalazide
MMX-Mesalazine

## Supportive therapy
Loperamide
Cholestyramine
Spasmolytics
Pain medication
Vitamins

## Steroids
Hydrocortisone
Prednisone
Methylprednisone
Beclomethasone
Budesonide
other

## Nutrition therapy
parenteral
enteral

## Immunmodulator & Biologics
Azathioprine/6-MP
MTX
Infliximab/Adalimumab/Certolizumab
Cyclosporine/Tacrolimus

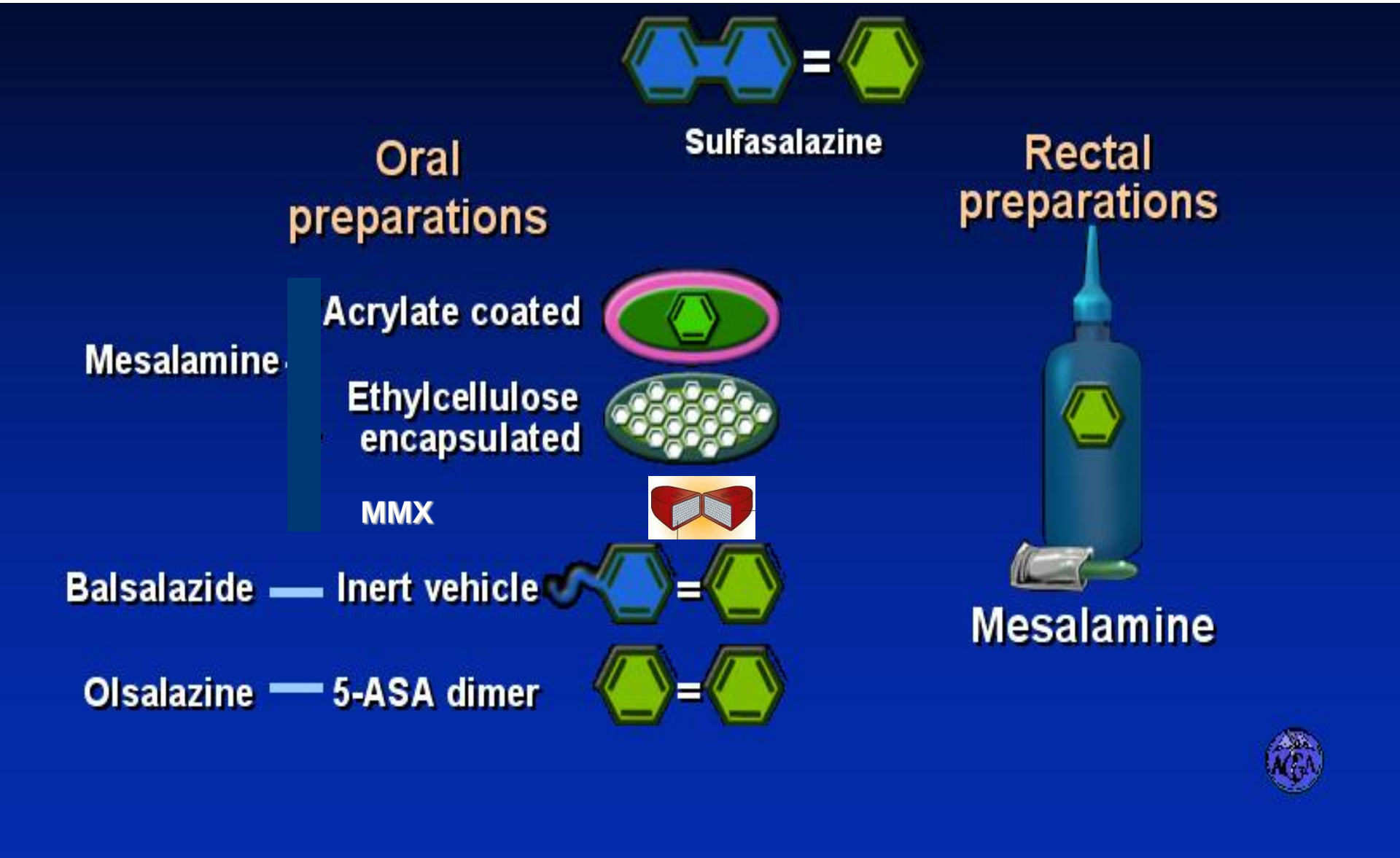
## Antibiotics/ Probiotics
Ciprofloxacin
Metronidazole
ECN/VSL
other

## Surgery
Strictures, neoplasia, refractory disease, therapy-associated side effects

ECCO Guidelines on CD & UC: Dignass et al. JCC 2010; Travis et al. JCC 2008

ECCO

# Galenic Formulations of 5-ASA



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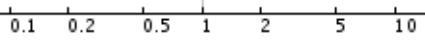
# Mesalazine in acute, mild to moderate flares of ulcerative colitis

Review: Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis
Comparison: 1 5-ASA vs. placebo
Outcome: 1 Failure to Induce Global/Clinical Remission

| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Peto,Fixed,95% CI | Weight | Peto Odds Ratio Peto,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Dose of 5-ASA: < 2 g | | | | | |
| Hanauer 1993 | 73/92 | 26/30 | | 14.1 % | 0.62 [ 0.22, 1.78 ] |
| Schroeder 1987 | 10/11 | 18/19 | | 1.8 % | 0.55 [ 0.03, 10.30 ] |
| Sninsky 1991 | 47/53 | 25/26 | | 5.8 % | 0.40 [ 0.08, 2.07 ] |
| **Subtotal (95% CI)** | **156** | **75** | | **21.7 %** | **0.55 [ 0.24, 1.28 ]** |
| Total events: 130 (Treatment), 69 (Control) | | | | | |
| Heterogeneity: Chi² = 0.20, df = 2 (P = 0.91); I² =0.0% | | | | | |
| Test for overall effect: Z = 1.39 (P = 0.16) | | | | | |
| 2 Dose of 5-ASA: 2 - 2.9 g | | | | | |
| Hanauer 1993 | 69/97 | 26/30 | | 17.6 % | 0.44 [ 0.17, 1.13 ] |
| Hanauer 1996 | 81/92 | 39/45 | | 13.4 % | 1.13 [ 0.39, 3.33 ] |
| Sninsky 1991 | 47/53 | 25/26 | | 5.8 % | 0.40 [ 0.08, 2.07 ] |
| **Subtotal (95% CI)** | **242** | **101** | | **36.8 %** | **0.61 [ 0.32, 1.17 ]** |
| Total events: 197 (Treatment), 90 (Control) | | | | | |
| Heterogeneity: Chi² = 1.98, df = 2 (P = 0.37); I² =0.0% | | | | | |
| Test for overall effect: Z = 1.48 (P = 0.14) | | | | | |
| 3 Dose of 5-ASA: >or=3 g | | | | | |
| Hanauer 1993 | 67/95 | 27/30 | | 17.3 % | 0.35 [ 0.14, 0.91 ] |
| Hanauer 1996 | 75/91 | 39/45 | | 16.6 % | 0.73 [ 0.28, 1.93 ] |
| Schroeder 1987 | 29/38 | 18/19 | | 7.5 % | 0.29 [ 0.07, 1.20 ] |
| **Subtotal (95% CI)** | **224** | **94** | | **41.5 %** | **0.46 [ 0.25, 0.84 ]** |
| Total events: 171 (Treatment), 84 (Control) | | | | | |
| Heterogeneity: Chi² = 1.60, df = 2 (P = 0.45); I² =0.0% | | | | | |
| Test for overall effect: Z = 2.51 (P = 0.012) | | | | | |
| **Total (95% CI)** | **622** | **270** | | **100.0 %** | **0.53 [ 0.36, 0.79 ]** |
| Total events: 498 (Treatment), 243 (Control) | | | | | |
| Heterogeneity: Chi² = 4.20, df = 8 (P = 0.84); I² =0.0% | | | | | |
| Test for overall effect: Z = 3.16 (P = 0.0016) | | | | | |
| Test for subgroup differences: Chi² = 0.43, df = 2 (P = 0.81), I² =0.0% | | | | | |




Sutherland & Macdonald, Cochrane Database Syst Rev, Update 2009

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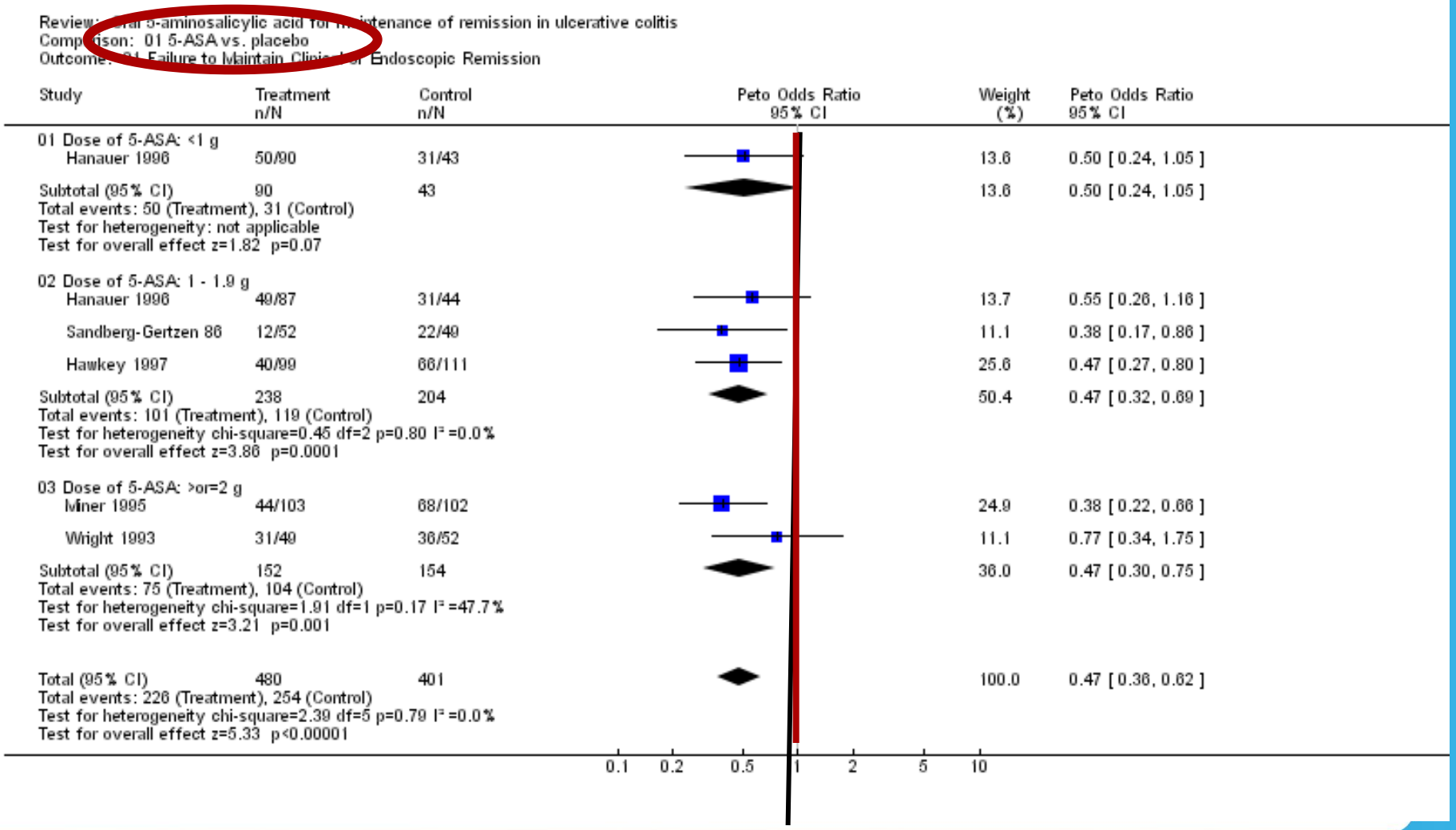
# Mesalazine for maintenance of remission in ulcerative colitis




Sutherland & Macdonald, Cochrane Database Syst Rev, Update 2009

# 5-ASA for distal active UC

- Mild or moderate activity
- Topical 5-ASA is more rapidly effective than oral 5-ASA
- Topical 5-ASA is more effective than topical steroids
- No dose-response effect for topical 5-ASA
- 1 g/d
- 50 % clinical response at 2 weeks
  70 % clinical response at 4 weeks

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# Active disease

*ECCO Statement: Left-sided UC*

- **Left-sided active UC of mild-moderate severity should initially be treated with topical aminosalicylates** [EL1b, RG B] **combined with oral mesalazine >2g/day** [EL1a, RG A].

- **Topical steroids or mesalazine alone are also effective, but less effective than combination therapy** [EL1b, RG B].

- **Topical mesalazine is more effective than topical steroid** [EL1a, RG A].

# Active disease

*ECCO Statement: Left-sided UC*

- **Oral aminosalicylates alone are less effective** [EL1a, RG A].
- **Systemic corticosteroids are appropriate if symptoms of active colitis do not respond rapidly to mesalazine** [EL1b, RG C].
- **Severe left-sided colitis is usually an indication for hospital admission for intensive treatment with systemic therapy** [EL1b, RG B]

# Reality of IBD care is suboptimal

| | Patients | (%) |
|---|---|---|
| Suboptimal dosing of 5-ASA | 21/33 | (64) |
| No topical 5-ASA-therapy | 9/12 | (75) |
| Treatment with steroids >3 months | 27/35 | (77) |
| No immunosuppressant despite indication | 16/27 | (59) |
| Suboptimal dosing of immunosuppressant | 9/11 | (82) |

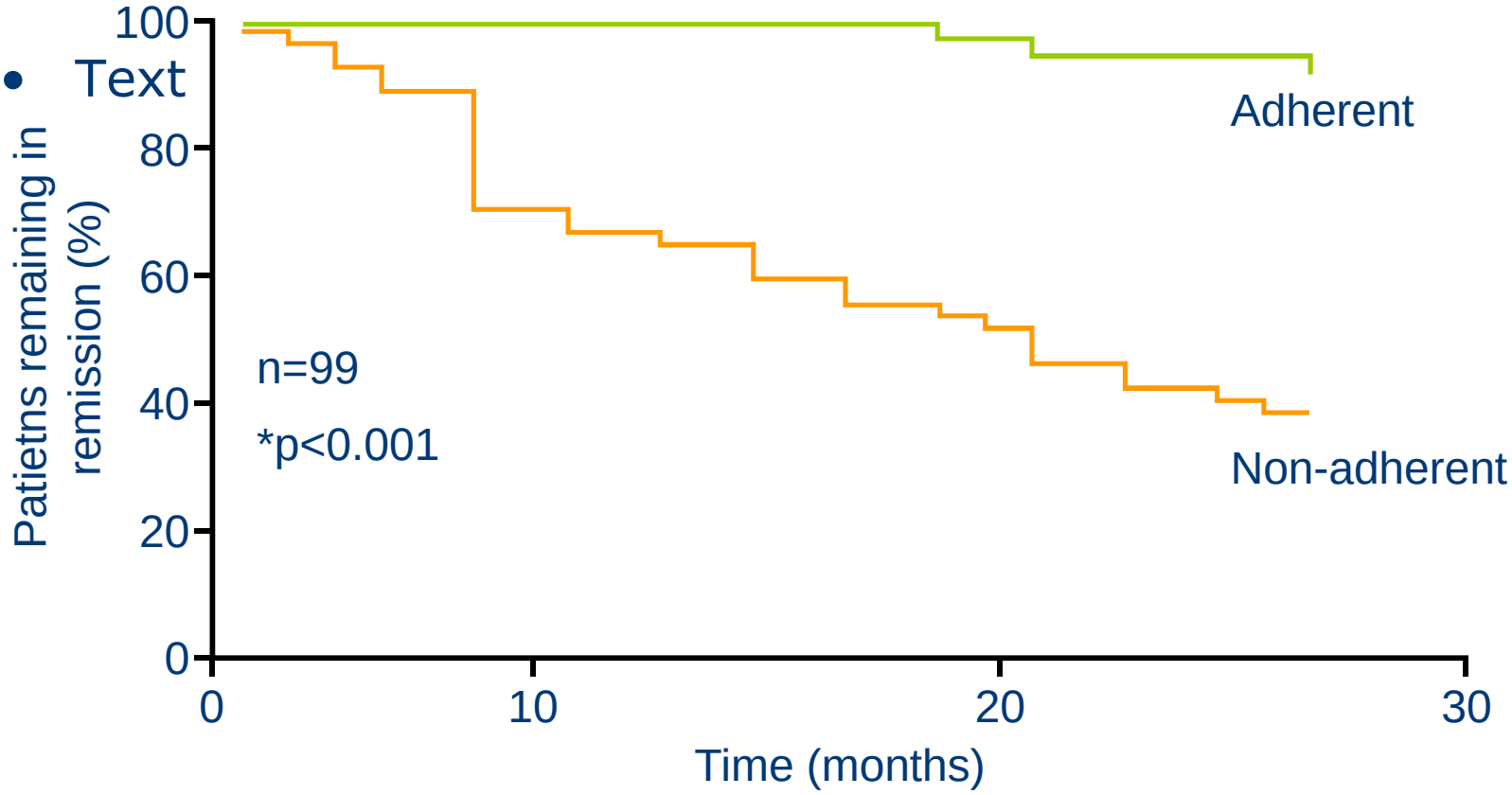
According to Reddy SI, et al. *Am J Gastroenterol* 2005

# How can 5-ASAs be used best in IBD?

- Improvement of adherence/ compliance
- Use of optimal preparation for disease location
  - Topical, oral, combined
  - foam vs. enema vs. suppository vs. oral
  - New formulations (granules, Eudragit-coated, ethylcellulose-coated, MMX)
- Use of combinations with other drugs
  - 5-ASA + other drug, e.g. immunomodulator, probiotics, antibiotics
- Use of optimal dose
- Individual dose adaptation (Patient guided)

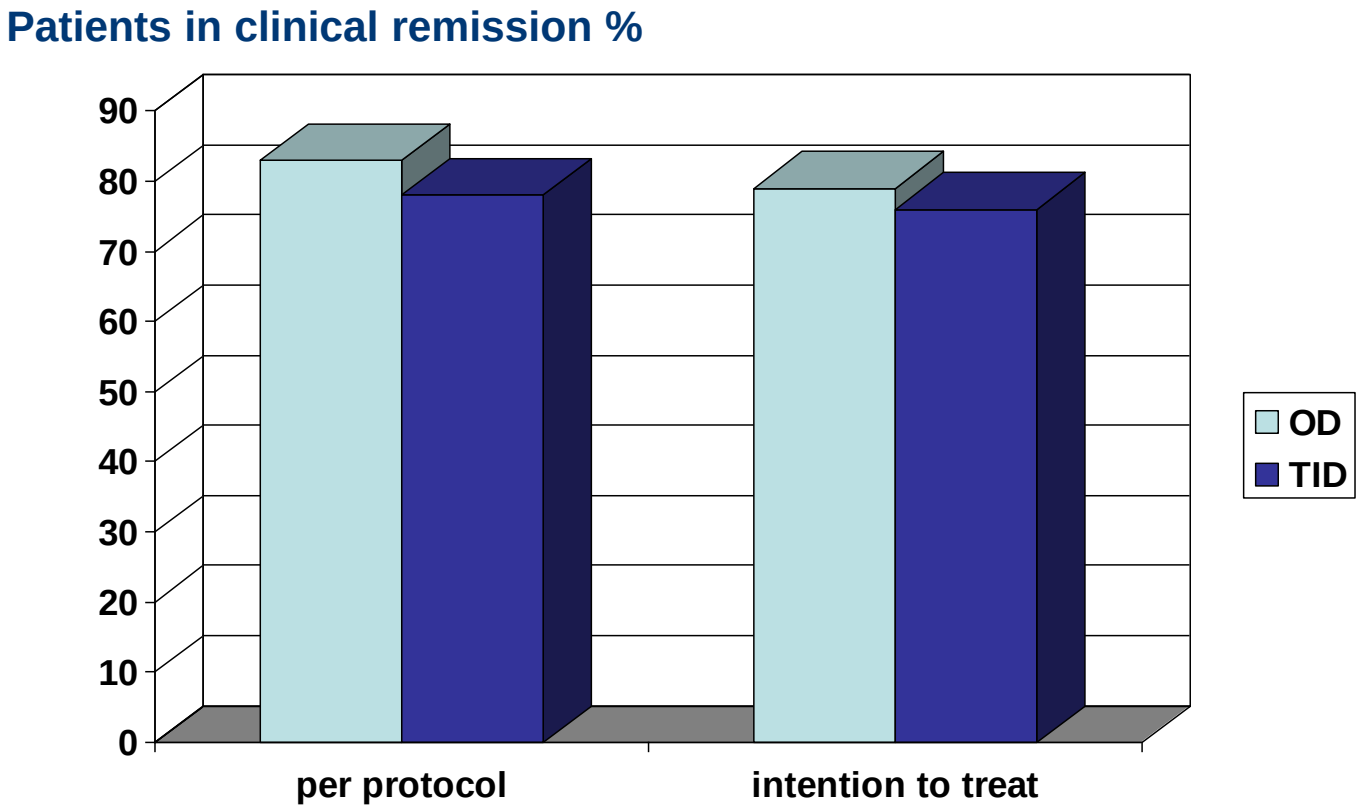
# Increased risk of relapse in patients non-adherent to mesalazine

- Text




Kane S, Am J Med 2003

# Once Daily Mesalazine Granules are non-inferior to three times daily tratment in mild to moderate active UC



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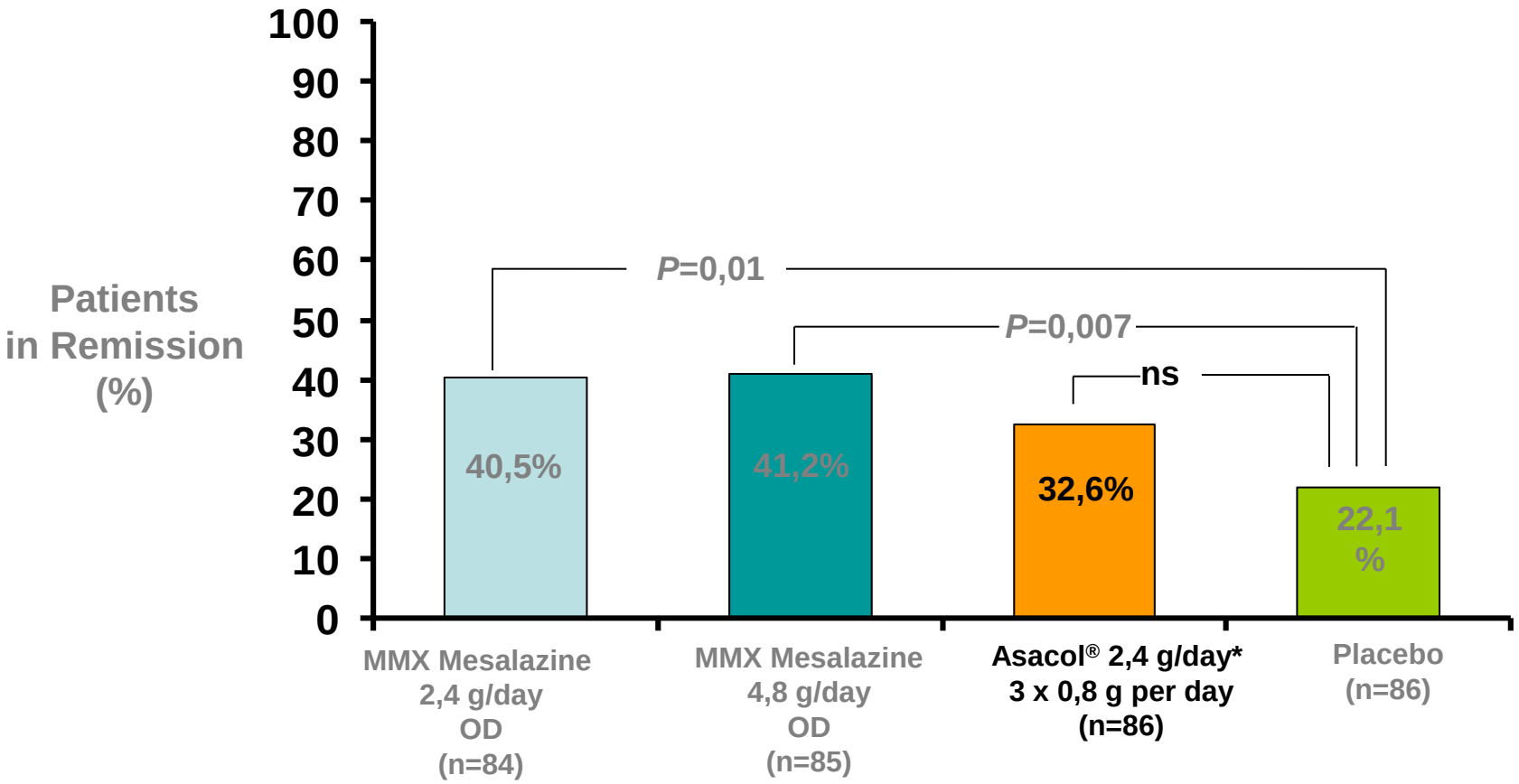
# Once Daily MMX Mesalazine is non-inferior to repeated dosing of Mesalazine in active UC




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

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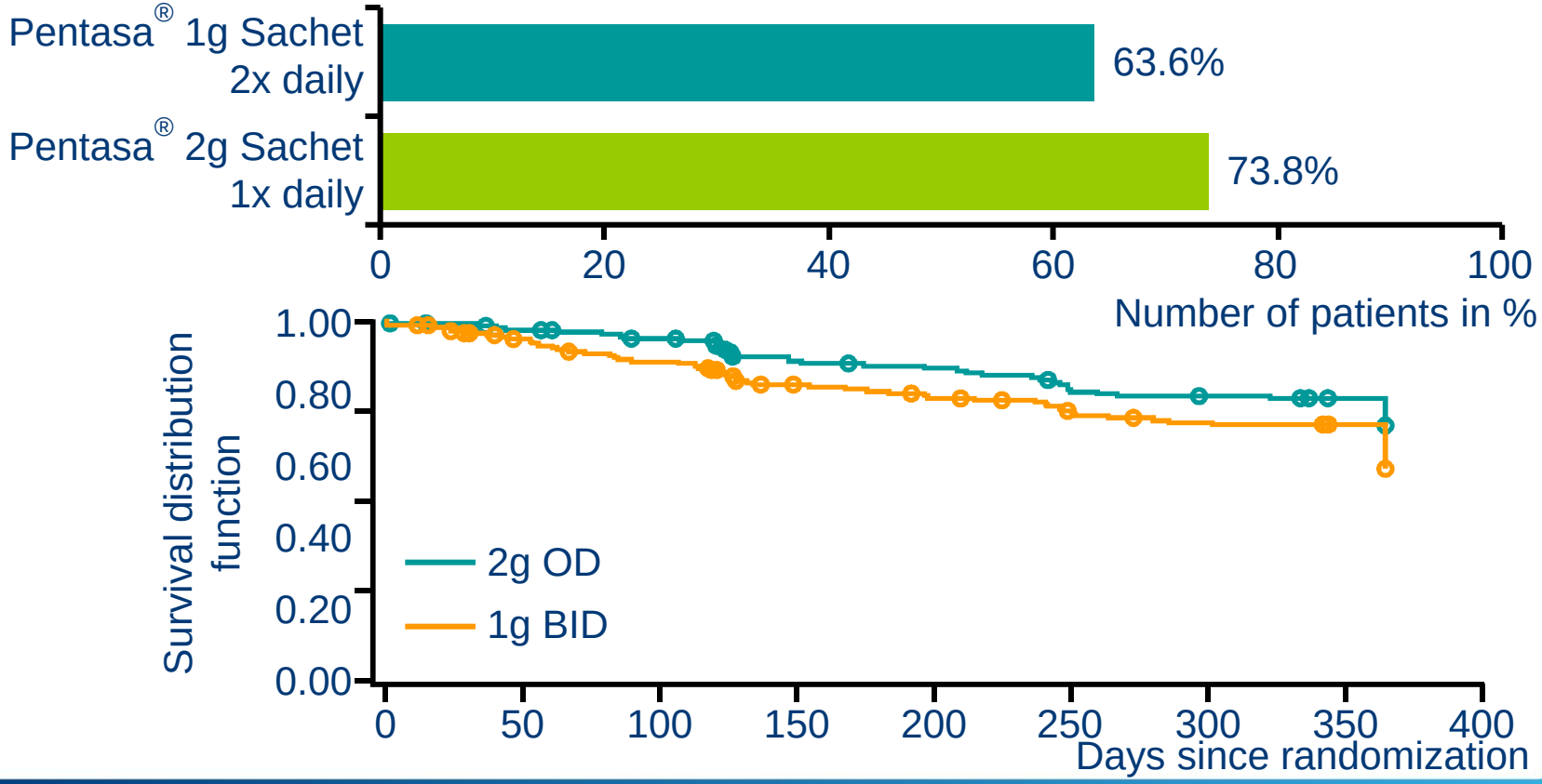
# OD is more efficacious than BID mesalazine as maintenance therapy in mild to moderate UC

PODIUM study

## Patients in clinical and endoscopical remission after 12 months




Dignass et al., CGH 2009

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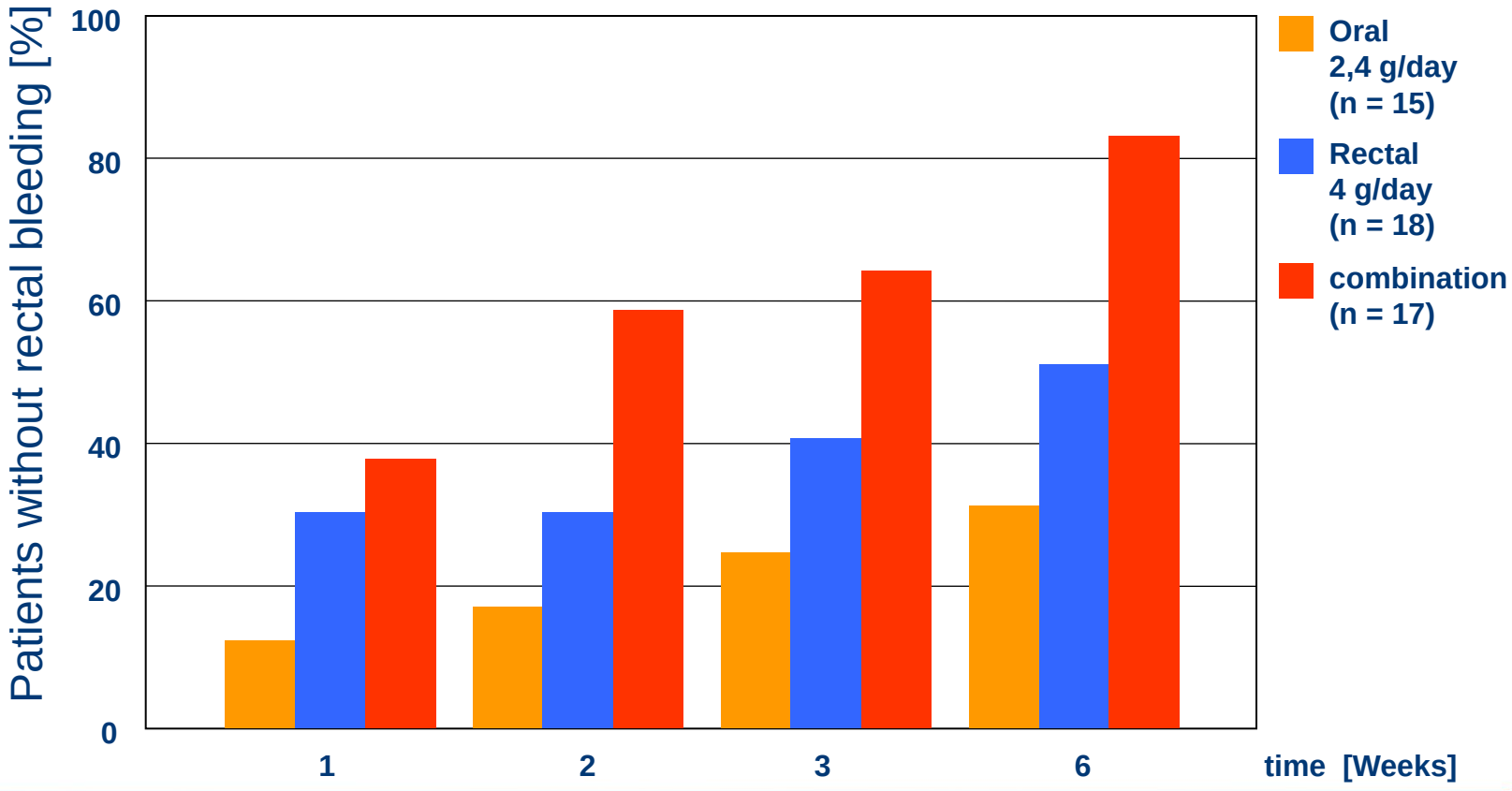
  - New formulations (granules, Eudragit-coated, ethylcellulose-coated, MMX)
- Use of combinations with other drugs
  - 5-ASA + other drug, e.g. immunomodulator, probiotics, antibiotics
- Use of optimal dose
- Individual dose adaptation (Patient guided)

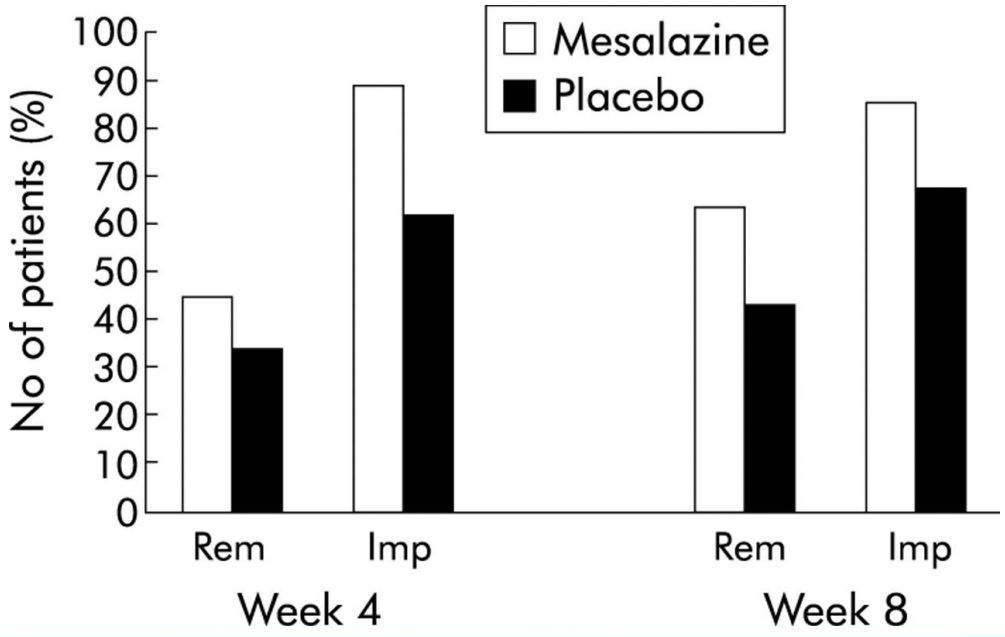
# A combined treatment with oral and rectal Mesalazine induces a more efficacious in distal active UC




Safdi et al. (1997)

# A combined treatment with oral and rectal Mesalazine induces a more rapid improvement in extensive active UC

*Remission and improvement rates. Percentage of patients achieving remission (ulcerative colitis disease activity index (UCDAI) of 0 or 1) or improvement (decrease in UCDAI >2 points)*




Marteau, P et al. Gut 2005;54:960-965

# Active disease

*ECCO Statement: steroids*

- There is a transatlantic divide on the threshold for using steroids. The European perspective is to introduce oral steroids at an early stage, because aminosalicylates cannot match the speed of response for patients suffering miserable symptoms. The US concern about steroid-induced side-effects is shared by patients, but may also be self-fulfilling. Late introduction of steroids may select a more refractory population.

# How does colitis extension impact the approach to mild to moderate colitis?

1. In left-sided colitis topical treatment with mesalazine alone usually suffices.
2. Extensive colitis affords higher doses of oral mesalazine.
3. Extensive colitis is primarily treated with oral steroids.
4. Only in extensive colitis a combination of oral and topical mesalazine is indicated.
5. In extensive colitis a lower threshold for the decision to treat with systemic steroids is recommended.

**Which of the following statements pertaining to the treatment of mild to moderate ulcerative colitis is correct?**

1. Meta-analysis has revealed a clear dose-remission relationship for oral mesalazine.
2. Response to oral mesalazine should be evaluated after 3 months.
3. A colitis flaring under appropriate maintenance therapy with mesalazine >2 g/day or immunomodulators is still to be considered mild.
4. Mesalazine is significantly better than sulphasalazine to induce remission.
5. A once daily application of oral mesalazine is more efficacious than divided doses correct

# Steroid dependant and refractory UC

- Patients with steroid-dependant disease should be treated with azathioprine/ mercaptopurine
- Outpatients with moderately active steroid refractory disease should be treated with anti TNF therapy or tacrolimus, although colectomy or admission for parenteral steroid therapy could also be considered

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# Azathioprine/ 6-MP

- Indicated in chronic active steroid refractory or –dependent IBD
- peroral dose of 2-2,5 mg/kg bw
- therapeutic effect in 12-26 weeks
- Steroid sparing
- Longterm therapy

Pearson DC et al., Ann Intern Med 1995; Present et al., NEJM 1980; Bouhnik Y et al., Lancet 1996, Lemann et al. Gastro 2005; Theodor et al., Am J Gastro 1981; Hawthorne et al., BMJ 1992; George J et al., Am J Gastro 1996

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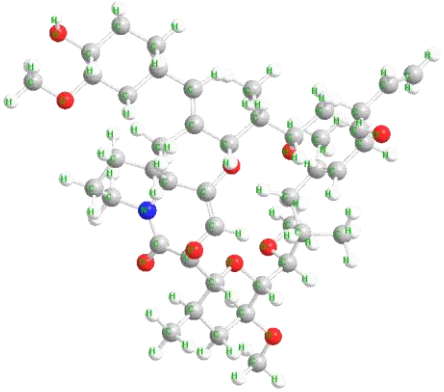
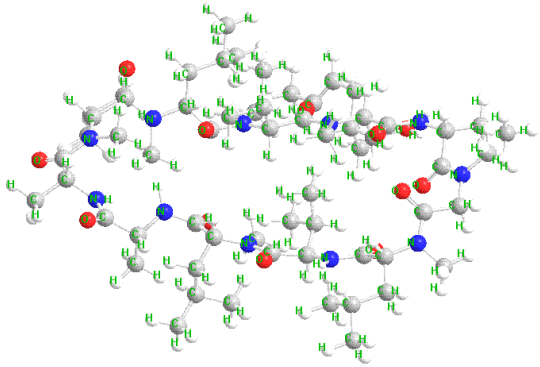
# Tacrolimus/ Cyclosporine





- modulation of T- and B-Lymphocytes
- inhibition of cytokine production (IL-2, IL-4, IFN$\gamma$)
- therapy with oral, intravenous or enema formulation
- rapid onset of action

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# TNFα-Inhibitors

**Infliximab**

Chimeric

CD
UC
RA

**Adalimumab**

humanized

CD
UC
RA

**Etanercept**

humanized
Receptor/ Fc
Fusion protein

RA

**Certolizumab**

humanized
Fab' Fragment

CD (US, CH)

RA