Case scenario

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History

- 19 years old, female patient
- Non-smoker, without past medical history
- Admission in another medical unit (sept 2012):
  - Chronic diarrhea (since 2 months) with 6 loose stools /24 h, with blood and mucus and nocturnal daefecation
  - Moderate pain over the left iliac fossa and left abdominal flank
  - Weight loss (5 kg)
  - Without signs of systemic toxicity (no tachycardia, no fever)
- Diagnosis : moderate flare of ulcerative colitis, without mentioning the extension (proctoscopic examination)

What is ECCO guideline recommendation in this case?

ECCO Statement 5C

Extensive ulcerative colitis of mild–moderate severity should initially be treated with oral 5-ASA >2 g/day [EL1a, RG A], which should be combined with topical mesalazine to increase remission rates if tolerated [EL1b, RG A]. Once daily dosing with 5ASA is as effective as divided doses [EL1b, RG A]. Systemic corticosteroids are appropriate if symptoms of active colitis do not respond to mesalazine [EL1b, RG C]. Severe extensive colitis is an indication for hospital admission for intensive treatment [EL1b, RG B]

History

- Treatment (sept 2012-oct 2012):
  - **5-ASA per os 3 g/day**
  - **Antibiotics – 3rd generation cephalosporin (Ceftriaxonum)**
    Hemostatics

- Short-term evolution:
  - Reduced abdominal pain
  - 3-4 BM/ day, cvasinormal consistency, without blood
  - Treatment efficacy wasn`t evaluated endoscopically

Admission to Fundeni Clinical Institute
15th october 2012

Flare of symptoms:

- Clinical presentation:
  - 8-10 watery stools/ day, with blood and mucus
  - Crampy abdominal pain– left abdominal flank
  - Painfull abdominal distension
- Physical examination:
  - Underweight patient (W=48,3 kg, H=165 cm, BMI=17,6)
  - Paleness
  - Tachycardia
  - Subfebrile (T= 37,6-37,9)
  - Non-tender, mild-distended abdomen, painfull palpation of the left flank and iliac region.

Laboratory findings

-moderate anemia with low MCV ,MCH (Hb 9.2g/dl)

-leucocytosis (L 15160/mm3)

-inflammatory syndrome (Fibrynogen474mg/dl, ESR=38mm/h, CRP=20)

- mild hypoalbuminemia (Alb= 3,2 g/dl)

-hyposideremia (Iron= 25 mcg/dl)

- negative viral markers for HIV or hepatitis

Coprologic tests

- Macroscopic description: bloody, mucous stool
- Culture: absence of Salmonella,Shigella,Yersinia ; dysbiosis with Enteroccocus sp.
- Antibiogram
  - S: Linezolid, Teicoplanin, Vancomycin
  - R: Ofloxacin, Penicilin, Tetracycline,Nitrofurantoin,Norfloxacin

Plain abdominal X-ray:

-few small-bowel hydroaeric levels – pelvis and right iliac fossa , without pathological significance

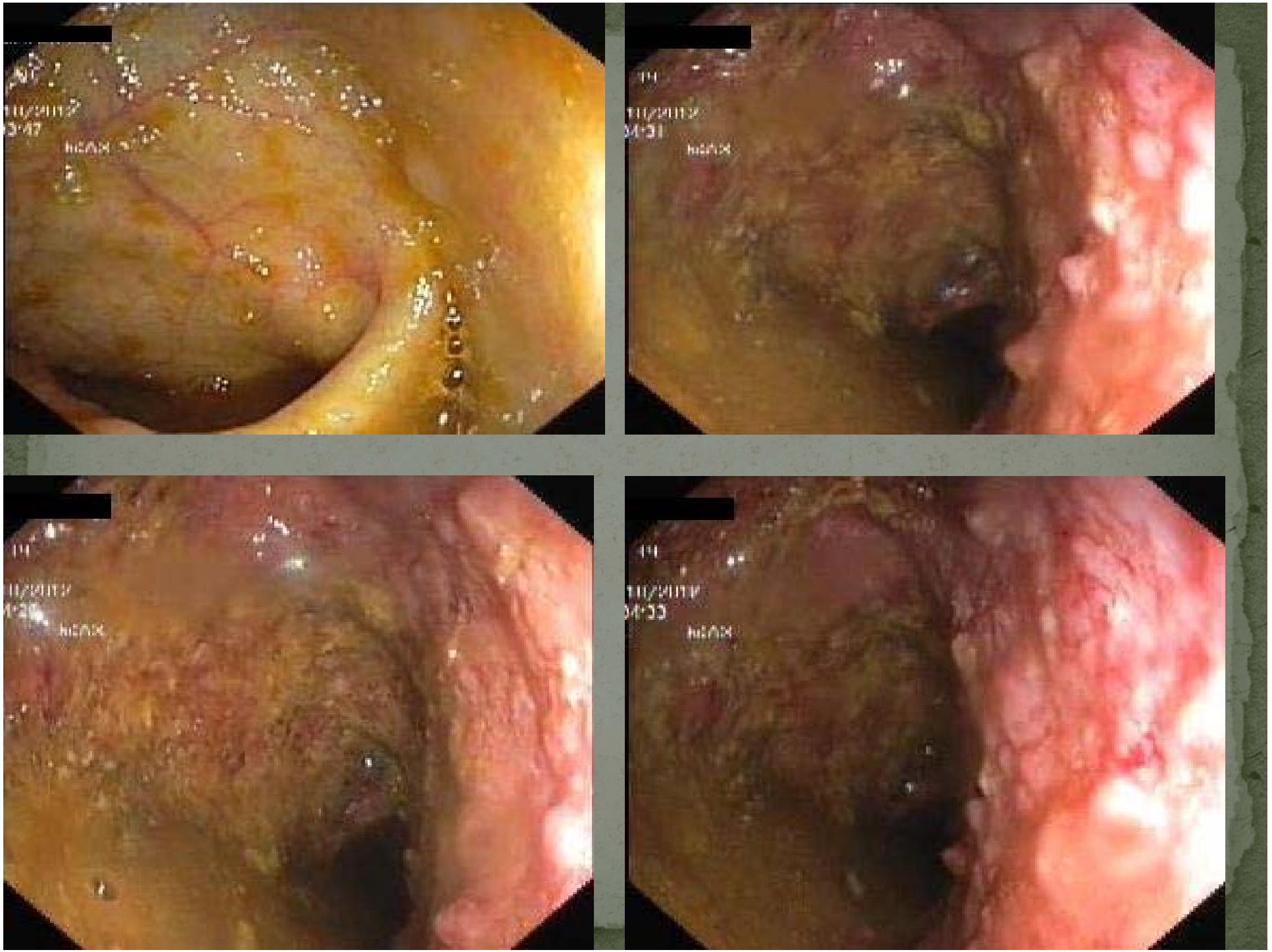
-moderate aeric distension

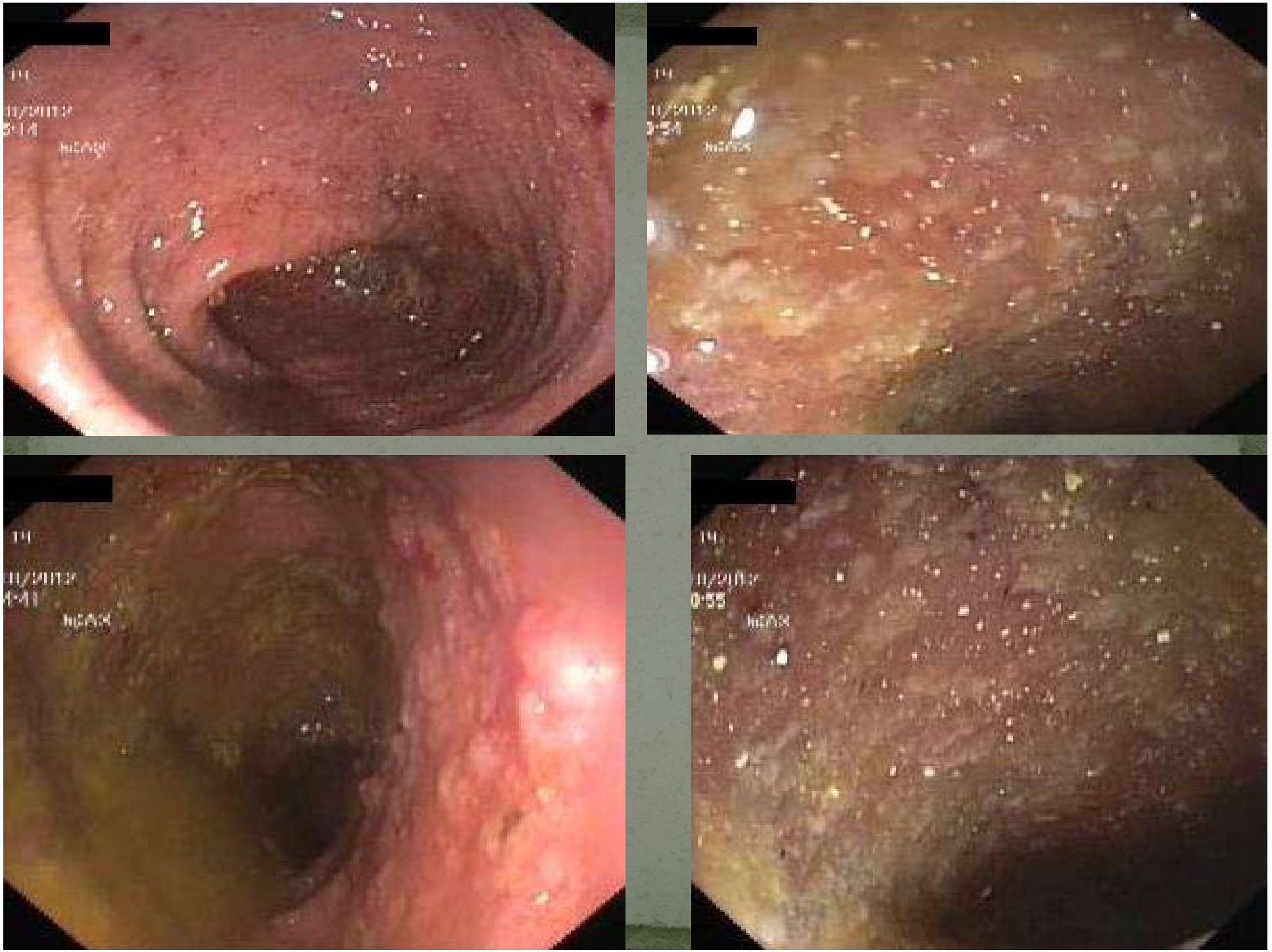
-no colonic dilatation

-without pneumoperitoneum

Colonoscopy

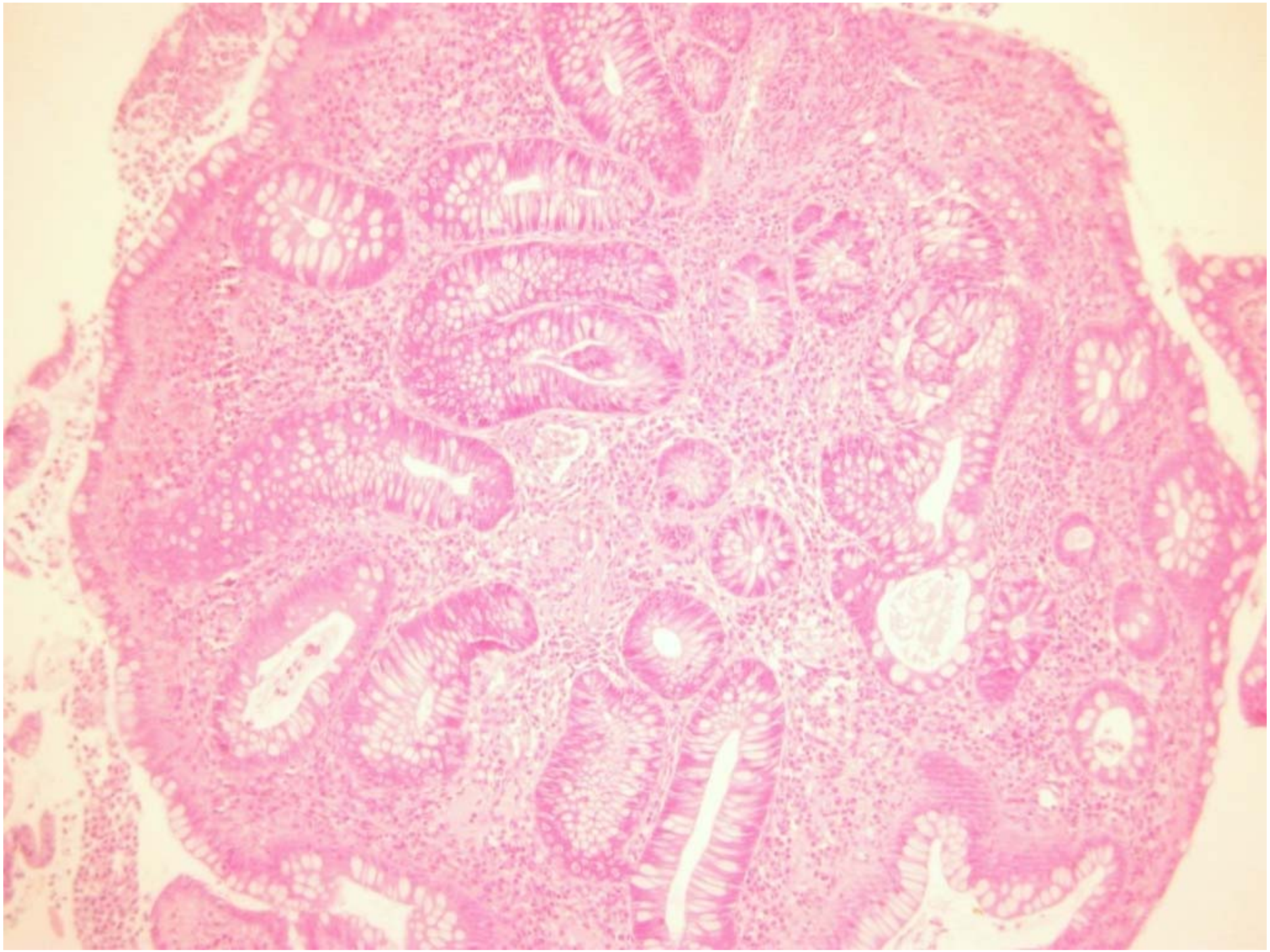
- Continous lesions ,without normal mucosal areas interposed - > ulcerations, edema, spontaneous and on-touch bleeding
- Extension: ascending colon
- Caecum and terminal ileum (15 cm): normal aspect

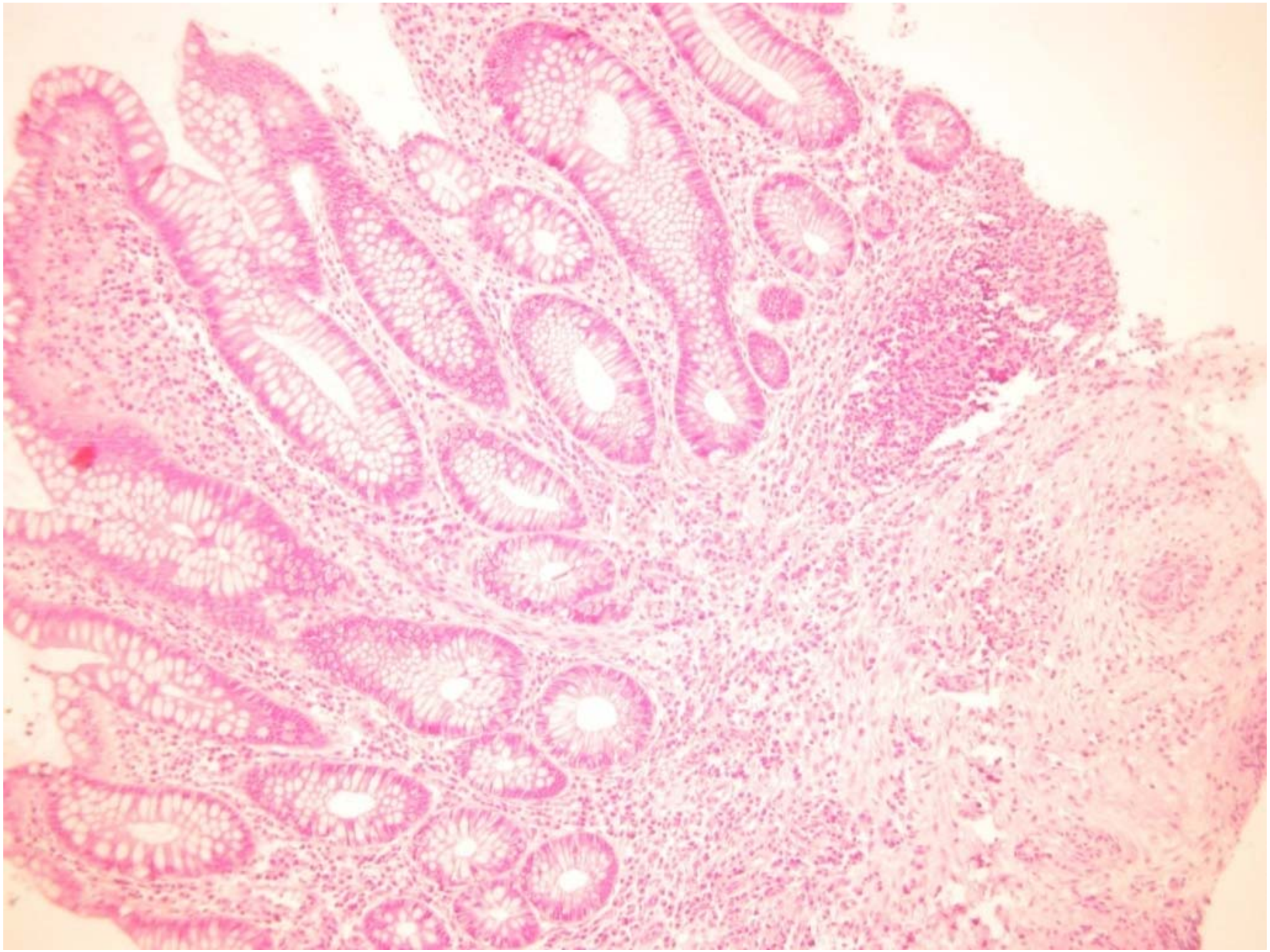


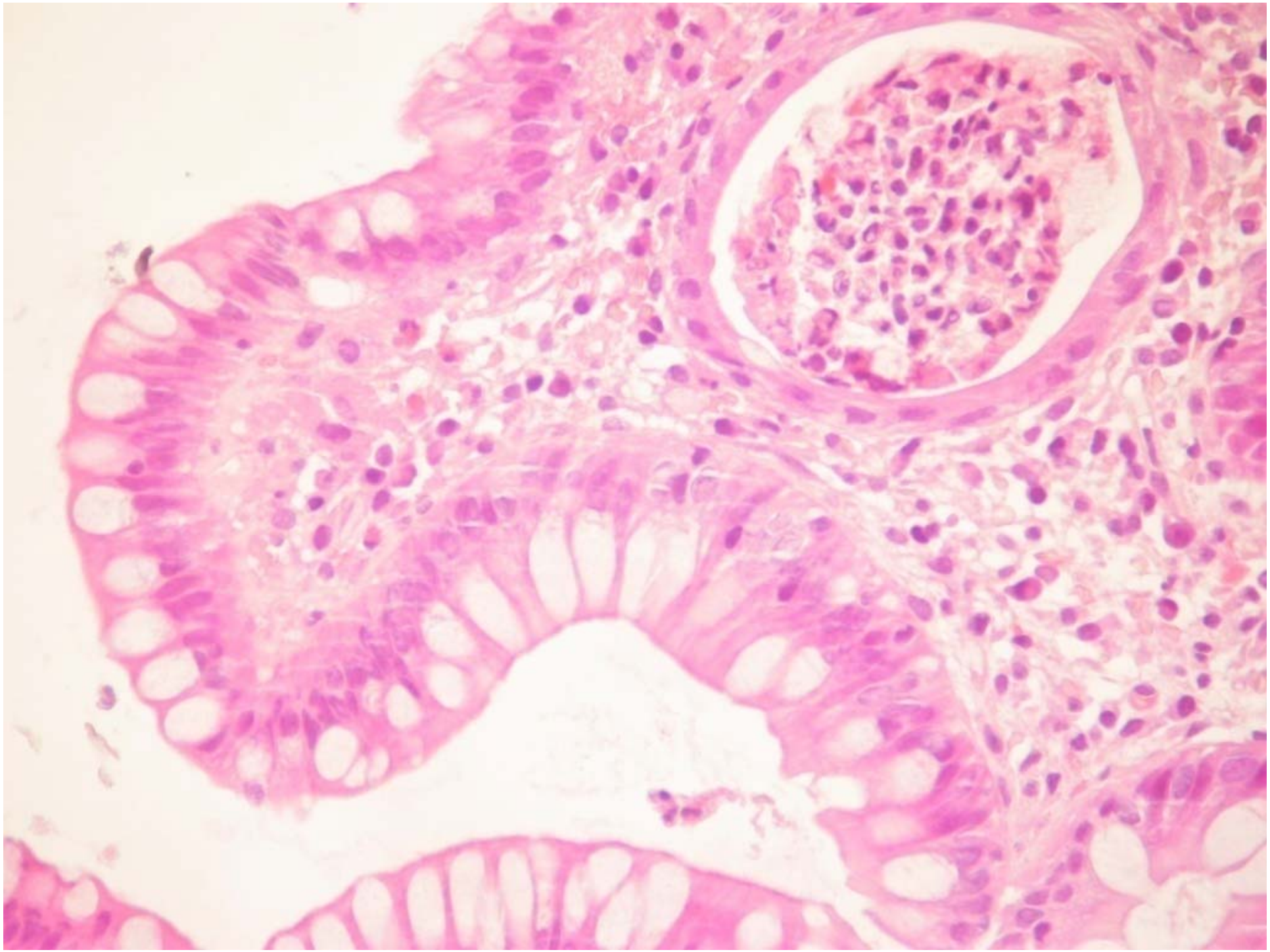


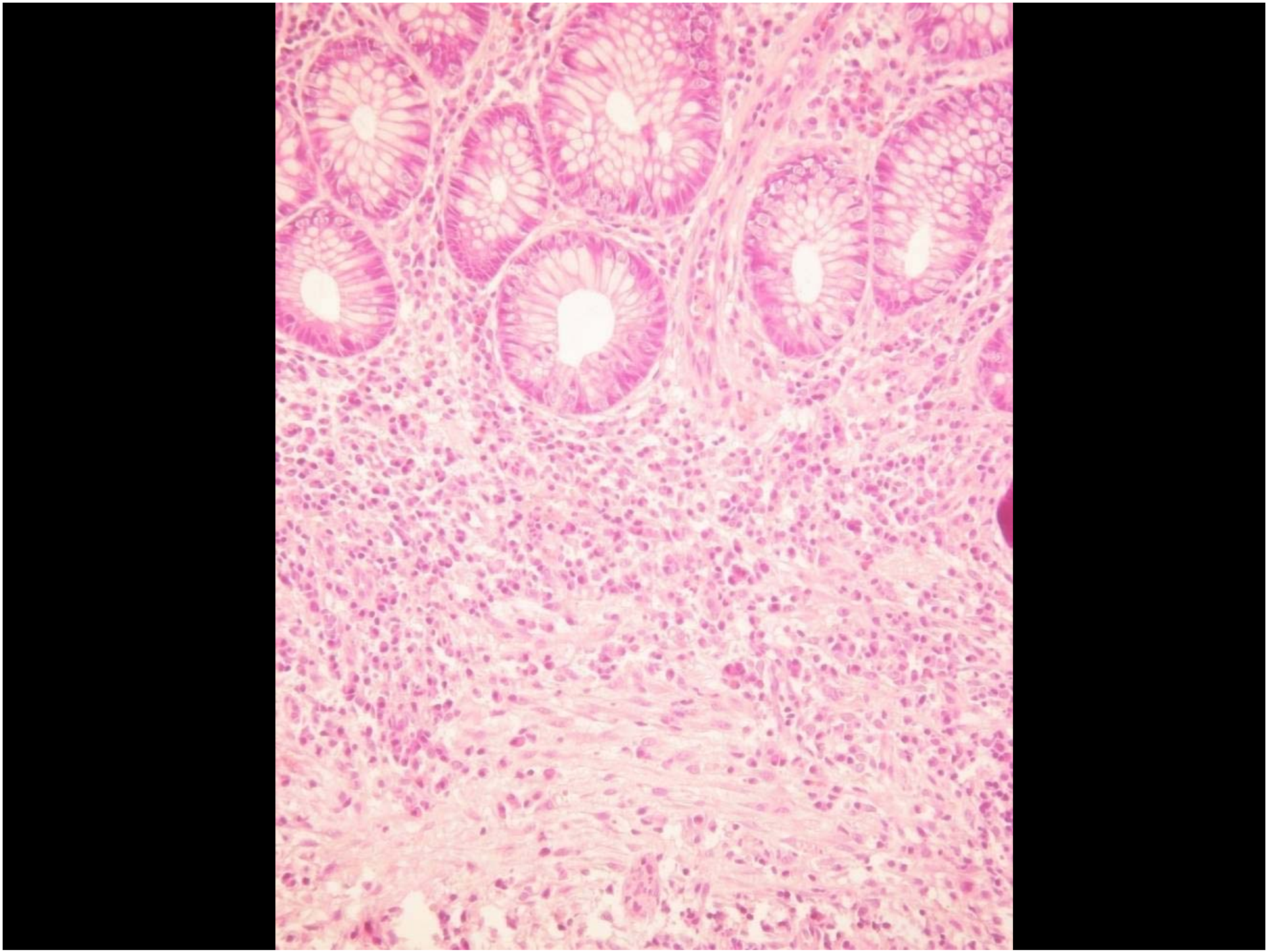
Histologic exam: ulcerative colitis

- active chronic inflammation
- without infiltration of the muscularis mucosae
- basal plasmocytosis
- distortion of crypt architecture
- normal aspect of the terminal ileum









Truelove & Witts severity index

Table 1. Measuring Disease Activity in UC: The Truelove and Witts Severity Index

	Mild	Moderate	Severe	Fulminant
Stool frequency	<4 stools daily (no blood)	>4 stools daily	>6 stools daily (with blood)	>10 stools daily (with continuous bleeding)
Toxicity	No signs of toxicity (heart rate >90, temperature >37.8°C, hemoglobin <10.5, ESR >30)	No/minimal signs of toxicity (heart rate >90, temperature >37.8°C, hemoglobin <10.5, ESR >30)	At least 1 sign of toxicity (heart rate >90, temperature >37.8°C, hemoglobin <10.5, ESR >30)	Abdominal tenderness
Imaging	No colonic dilatation	No colonic dilatation	No colonic dilatation	Colonic dilatation

Lichtiger severity index

Supplementary Table 1. Lichtiger Index

Score	0	1	2	3	4	5
Diarrheal, number of stools	0–2	3–4	5–6	7–9	≥10	
Nocturnal diarrhea	No	Yes				
Visible blood in stool	0%	<50%	≥50%	100%		
Abdominal tenderness	None	Mild and localized	Mild to moderate and diffuse	Severe or rebound		
Abdominal pain/cramping	None	Mild	Moderate	Severe		
Need for antidiarrheals	No	Yes				
General well-being	Perfect	Very good	Good	Average	Poor	Terrible
Fecal incontinence	No	Yes				

NOTE. Also known as the Modified Truelove Witts Severity Index. Severe ulcerative colitis was defined as a score of 12 or greater.[45]

DIAGNOSIS – ULCERATIVE COLITIS

- Extension: E3
- Severe flare (Truelove & Witts, Lichtiger Score)

Initial Treatment

- **Methylprednisolone iv** 60 mg/day without clinical improvement after 3 days of treatment – patient still having 10 stools/day.

- **Intravenous steroid refractory severe disease ->**

  - **Rapid test for Cl.Difficile Toxins A/B – POSITIVE**
  - **CMV IgG and IgM negative**

Supplementary Table 2. Suggestions for Diagnosis and Treatment of *C difficile* and CMV Infections In Inpatients With Ulcerative Colitis

C difficile	
Diagnosis	Toxin assays: enzyme-linked immunosorbent assay daily vs PCR (frequency unknown, possibly less frequently)
	Endoscopy: typical endoscopic features of *C difficile* infection may not be present
	Histology: typical histologic features of *C difficile* infection may not be present
Management	Initial therapy:
	If mild and uncomplicated: oral metronidazole or oral vancomycin
	If severe or complicated: oral vancomycin
	Recurrence: prolonged, high-dose, and/or tapering doses of oral vancomycin
CMV	
Diagnosis	Serum testing: CMV IgM and IgG, which together have a strong negative predictive value
	Endoscopy: deep ulcerations, patchy erythema, exudates, microerosions, diffuse edema, pseudotumors. Of note, CMV can affect the right colon alone in 30% of cases
	Histology (required for diagnosis): cytomegalic cells with large eosinophilic Cowdry type A intranuclear inclusions occasionally surrounded by a clear halo and smaller cytoplasmic inclusions Immunohistochemistry increases the sensitivity for detecting CMV to 93%
Management	Consider reducing immunosuppression
	Intravenous ganciclovir

Indication (Reference)	Definition (Based on Clinical Opinion)[a18]	Treatment (Strength and Quality of Evidence)[b]	Dosage
Initial episode, mild to moderate[88]	WBC ≤ 15,000 cells/mL and creatinine less than 1.5 baseline	-Discontinue nonessential antibiotics (A-II) -Consider holding immunosuppression[b] (C-II) -Metronidazole[d] (A-I)	-Metronidazole: 500 mg PO TID or 250 PO QID for 10-14 days
Initial episode, moderate to severe[18,88,89]	WBC > 15,000 cells/mL, creatinine >1.5 baseline	-Consider empiric antibiotics if high clinical suspicion (C-III) -if EIA for toxin only is negative, consider alternate testing (B-II) -Consider holding immunosuppression (C-II) -Vancomycin[e] (B-I)	-Vancomycin: 125 PO QID for 14 day
		-Fidaxomicin is an alternative to vancomycin but limited or no data in IBD patients (B-I)[f]	-Fidaxomicin: 200 mg PO BID × 10 days
Initial episode, severe, complicated[90–93]	Hypotension, shock, ileus, megacolon, organ failure	-Vancomycin (C-III) plus -Metronidazole IV (C-III)	-Vancomycin PO/NG: 500 mg QID -Vancomycin enema: 500 mg in 100 mL NS per rectum QID
		-If ileus, consider adding rectal vancomycin (C-III)	-Metronidazole 500 MG IV TID
		-Surgical consultation and low threshold for colectomy with rising lactate >5 or WBC > 50K (B-II)	

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Treatment

- **Metronidazole** 500mg TID iv + **Vancomycin** per os 500 mg QID – 14 days, with ondulant evolution
- Methyprednisolone iv continued for 7 days, then switch to oral corticoid .

- Associated : gas tube,pain relievers,antispastic agents ,fluid and electrolyte replacement,parenteral nutrition, anticoagulants (LMWH-enoxaparine)
- Control abdominal X-Ray: obvious reduction of abdominal distension, no hydroaeric levels

Clinical status at the end of ABT

- Altered general status
- 10-15 loose stools /day,with blood and mucus
- Fever (T=38,5)
- Shivers

Paraclinic data at the end of ABT

- Hb=11,4 g/dl
- WBC 30000/mmc
- Tr 416.000/mmc
- Fibrynogen 537 mg/dl
- Albumin 2,6
- CRP 40 mg/l
- PCT=0,224
- Negative stool test for CDI

ECCO Statement 5E

The response to intravenous steroids is best assessed objectively around the third day [EL2b, RGB]. Treatment options including colectomy should be discussed with patients with severely active UC not responding to intravenous steroids. Second line therapy with *either* ciclosporin [EL1b, RG B], *or* infliximab [EL1b, RG B] *or* tacrolimus [EL4, RG C] may be appropriate. If there is no improvement within 4–7 days of salvage therapy, colectomy is recommended [EL4, RG C]. Third line medical therapy may be considered at a specialist centre [EL4, RG C]

Ciclosporin

- Efficacy in severe UC in patients who have failed iv corticosteroids
- Standard dose: 2mg/kg/day
- Median time response: 4 days (allows timely colectomy in non responders)
- Limited acceptability (narrow therapeutic index and its side-effect profile)
- Low ability to prevent colectomy in the longer term, but switching to oral thiopurine may reduce this risk

-> patients refractory to thiopurine are not being considered for Ciclosporine rescue therapy

Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial

David Laharie, Arnaud Bourreille, Julien Branche, Matthieu Allez, Yoram Bouhnik, Jerome Filippi, Frank Zerbib, Guillaume Savoye, Maria Nachury, Jacques Moreau, Jean-Charles Delchier, Jacques Cosnes, Elena Ricart, Olivier Dewit, Antonio Lopez-Sanroman, Jean-Louis Dupas, Franck Carbonnel, Gilles Bommelaer, Benoit Coffin, Xavier Roblin, Gert Van Assche, Maria Esteve, Martti Färkkilä, Javier P Gisbert, Philippe Marteau, Stephane Nahon, Martine de Vos, Denis Franchimont, Jean-Yves Mary, Jean-Frederic Colombel, Marc Lémann*†, for the Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives*

Summary

Background Ciclosporin and infliximab are potential rescue treatments to avoid colectomy in patients with acute severe ulcerative colitis refractory to intravenous corticosteroids. We compared the efficacy and safety of these drugs for this indication.

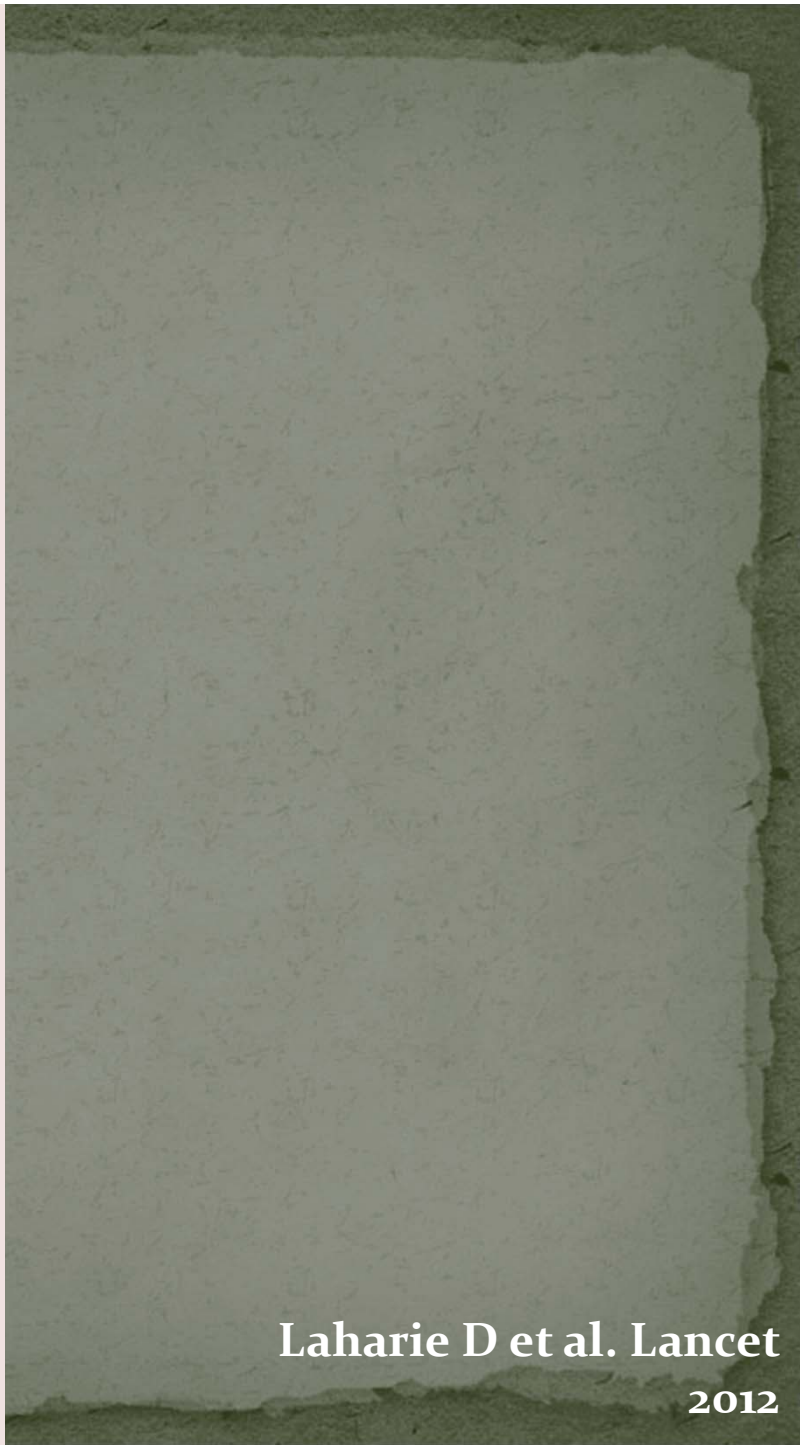
Lancet 2012; 380: 1909–15
Published Online
October 10, 2012

Laharie D et al. Lancet 2012

	Ciclosporin (n=58)	Infliximab (n=57)
Death	0*	0
Cardiovascular event	1*	1†
Severe infections	5	4
Cytomegalovirus colitis	2	1
Septicaemia	2‡	0
Urinary tract infection	0	1
Anal abscess	0	1
Fever of unknown origin	1	1
Renal event	0	0
Hepatic event	0	4§
Pulmonary event	1¶	0
Worsening of ulcerative colitis	3	7
Degenerative arthrosis	0	1
Total events	10	17
Total patients (%)	9 (16%)	14 (25%)

*A 66-year-old man developed myocardial ischaemia during the study and died during follow-up (day 137) from a myocardial infarction. †Venous thromboembolism. ‡Central-venous-catheter-related septicaemia with non-*aureus Staphylococcus*. §Increased aminotransferases leading to treatment withdrawal (at least two cases related to azathioprine). ¶Suspected pneumonia (unconfirmed).

***Table 3*: Severe adverse events during the study period according to treatment received**



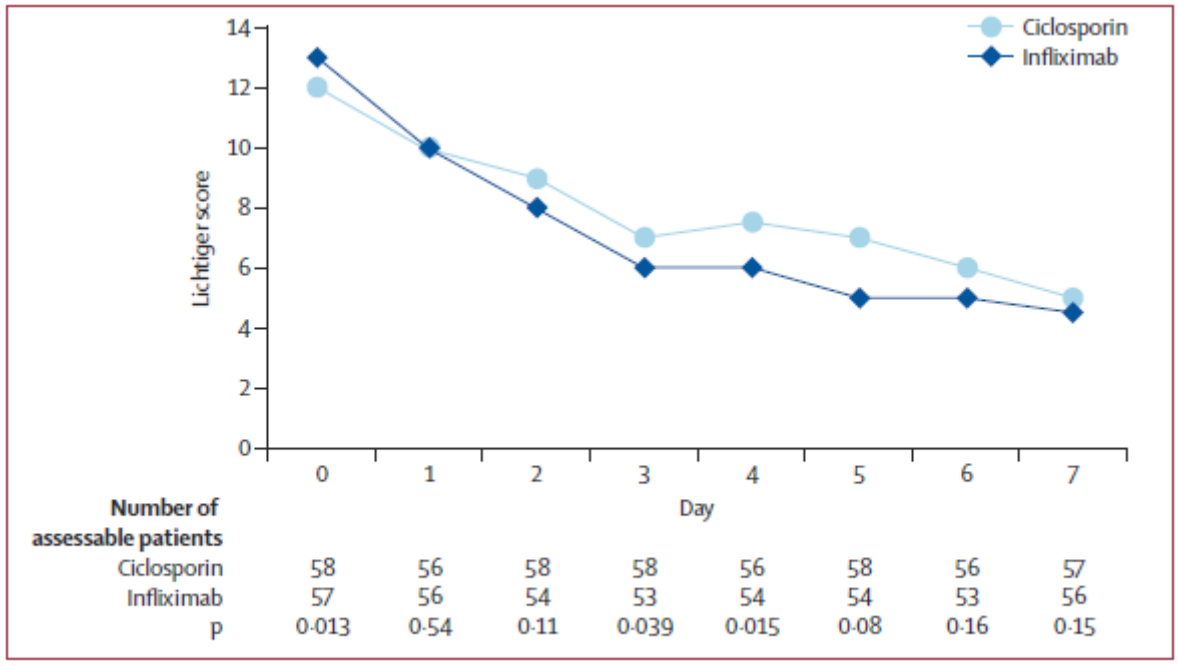


Figure 2: Lichtiger scores from day 0 to day 7, by treatment

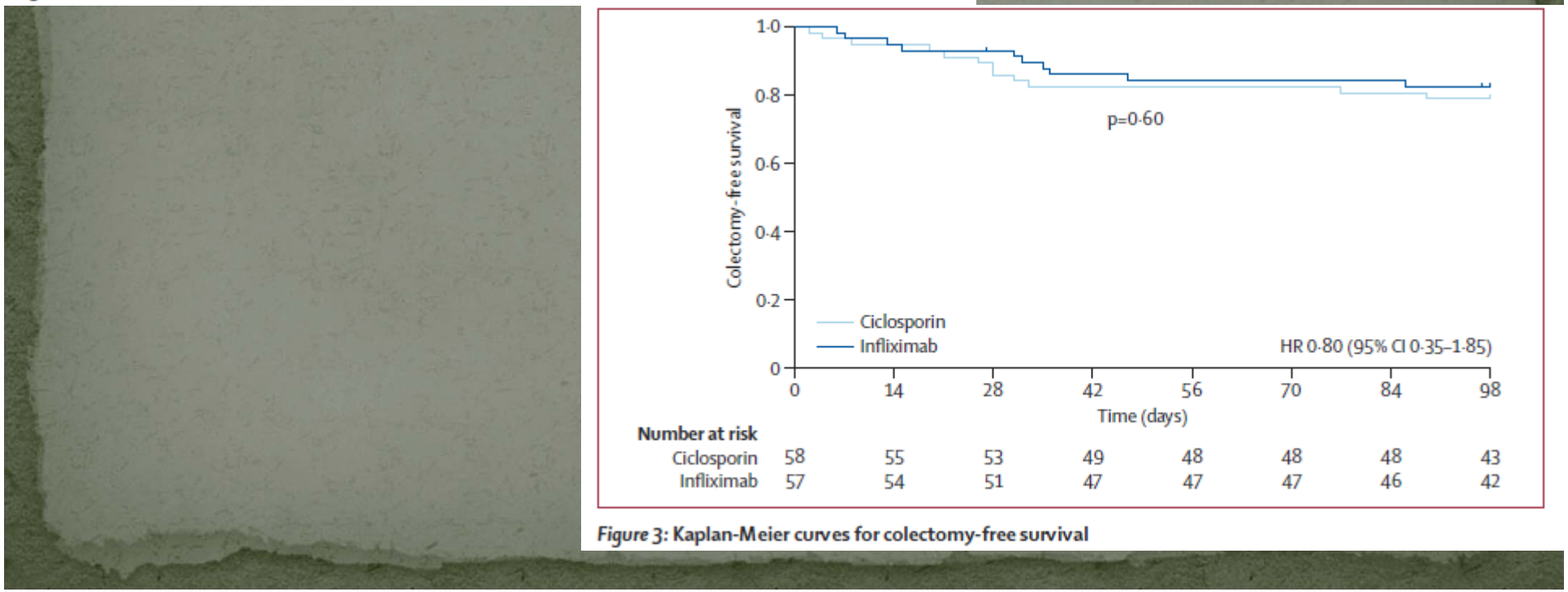


Figure 3: Kaplan-Meier curves for colectomy-free survival

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2007;5:345–351

Impact of *Clostridium difficile* on Inflammatory Bowel Disease

MAZEN ISSA,* ARAVIND VIJAYAPAL,* MARY BETH GRAHAM,‡ DAWN B. BEAULIEU,* MARY F. OTTERSON,§ SARAH LUNDEEN,§ SUSAN SKAROS,* LYDIA R. WEBER,* RICHARD A. KOMOROWSKI,‖ JOSH F. KNOX,* JEANNE EMMONS,* JASMOHAN S. BAJAJ,* and DAVID G. BINION*

**Division of Gastroenterology and Hepatology, ‡Division of Infectious Diseases, §Department of Surgery, and ‖Department of Pathology, Medical College of Wisconsin, Milwaukee, Wisconsin*

Table 1. IBD Patient Demographic and Disease Characteristics in 2005

	C difficile positive (n = 46)	*C difficile* negative (n = 953)	*P* value
Age (*y*)	38.8 ± 14.6	43.2 ± 14.6	NS
Female	25	535	NS
Male	21	418	
Crohn's disease	30 (65%)	707 (74%)	NS
Ulcerative colitis	16 (35%)	246 (26%)	
Duration of IBD (mean ± standard deviation, *y*)	7.5 ± 8.0	13.9 ± 11.8	.004
Colonic IBD involvement	42 (91%)	675 (71%)	.002
Immunomodulator maintenance	34 (74%)	535 (56%)	.02
Biologic therapy	13 (28%)	208 (22%)	NS
Current tobacco use	10 (27%)	153 (16%)	NS

NOTE. Immunomodulator maintenance included azathioprine, 6-mercaptopurine, and methotrexate. Biologic therapy included infliximab and adalimumab.

Salvage therapy with Infliximab

- Biologic therapy initiated on 31st oct 2012
- Infliximab 5mg/kg at 0,2,6 weeks
- 50 % of pacients with Infliximab as rescue therapy respond to treatment and do not need colectomy

Long MD & Plevy SE. Clin Gastroenterol Hepatol 2009

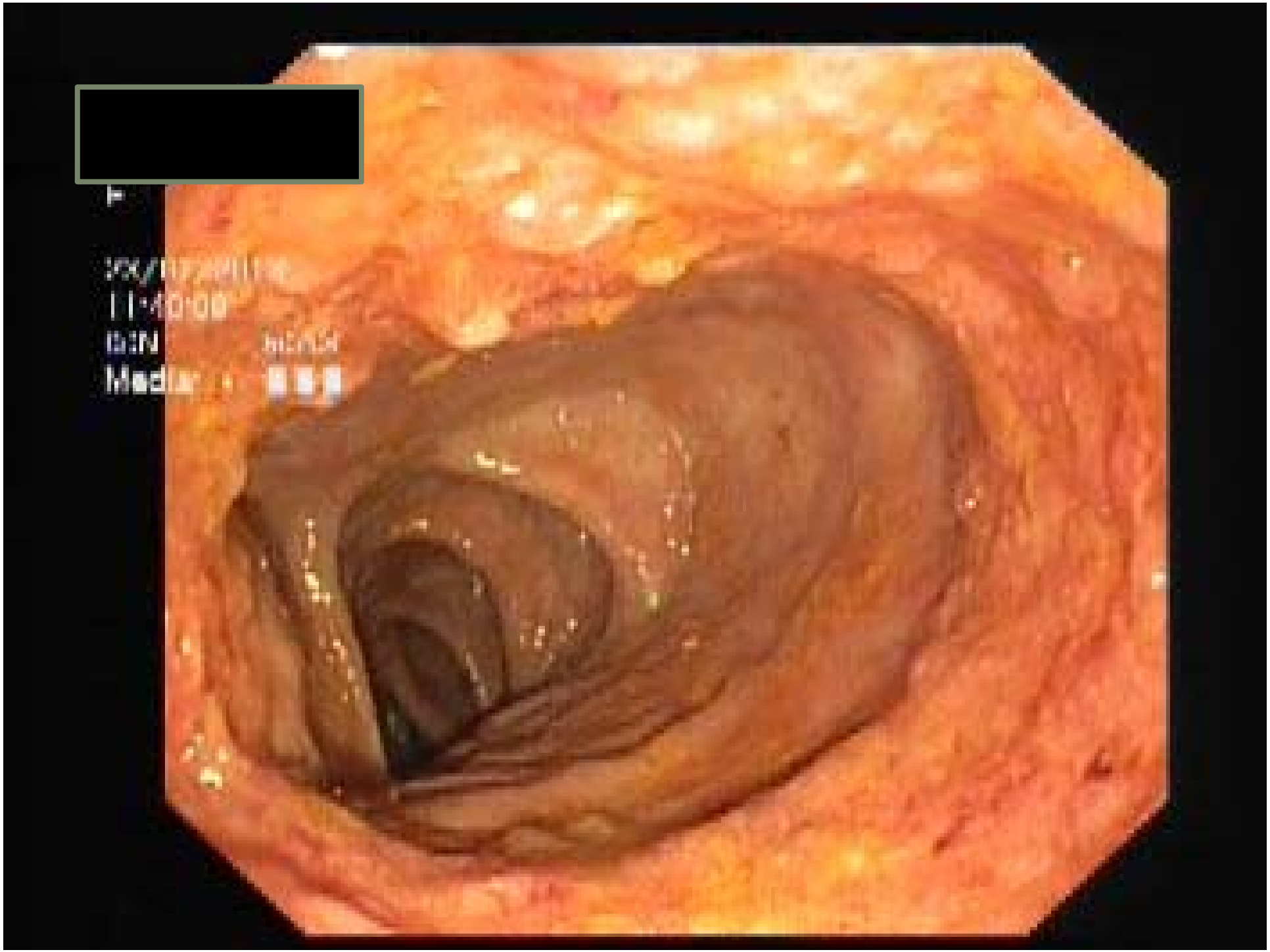
Follow-up

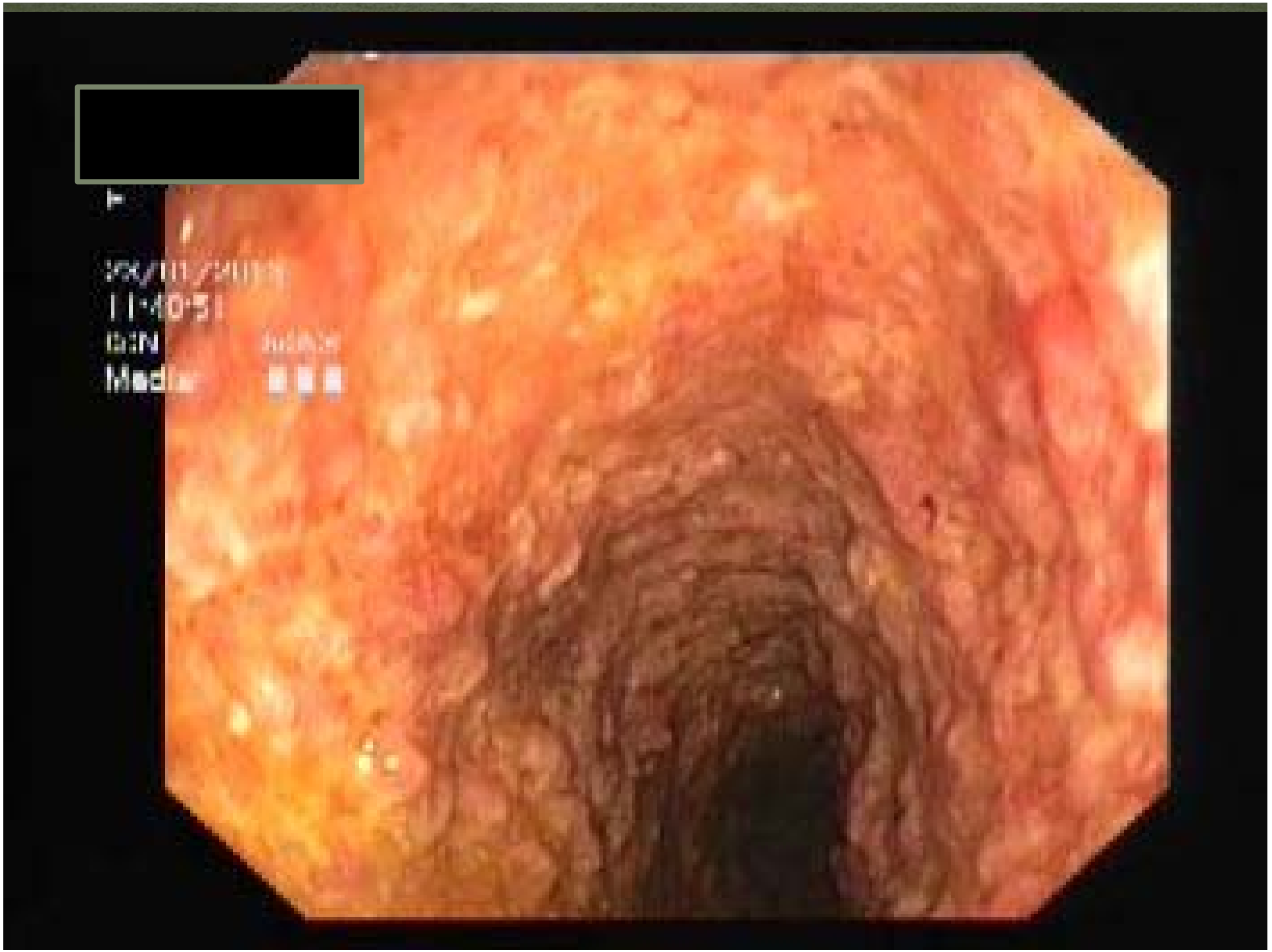
- **Biological improvement (5th nov -5 days after the 1st administration)**
  - **Hb 10.1g/dl**
  - **WBC 10.420/mm3**
  - **Tr 415.000/mm3**
  - **CRP 10.32mg/l**
  - **Albumin 3.1 g/dl**
- **Clinical improvement**
  - **2w** : 3-4 stools/day, without pathological products
- **Treatment: 5-ASA per os 4 g/day**

Follow-up

- 6 weeks application (12 dec 2012):
  - 1 stool/day, without blood or mucus
  - No abdominal pain
  - Laboratory :
    - CRP: 0,552 mg/l
    - Fibrynogen: 365,9 mg/dl
    - WBC: 9850/mmc
    - Hb=9,4 g/dl

- Relapse (22 jan 2013)
  - 5-8 loose stools/day, with blood and mucus
  - Crampy abdominal pain
  - Colonoscopy: continous lesions extending to the right colon
  - Laboratory : CRP-14,7 mg/l; fibrynogen – 496 mg/dl, WBC=8460/mmc,Hb-9,5 g/dl; negative toxins for CDI
  - Responded to treatment –
    - corticosteroids (5 days iv, followed by oral administration)
    - **AZA 2 mg/kg**



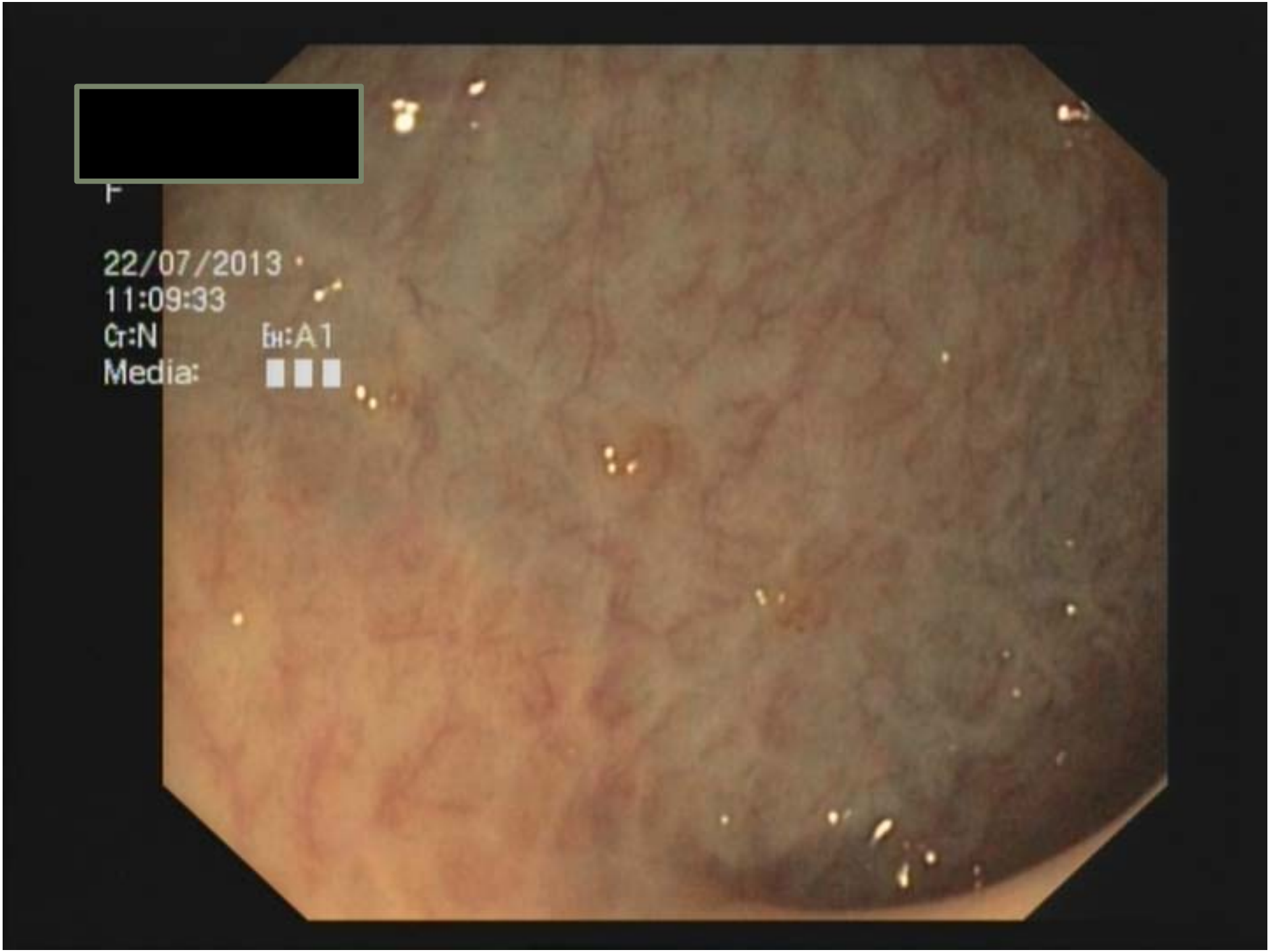


Follow-up

- 6 feb 2012 (4th application of Infliximab)
  - 2-3 stools/day, normal consistence, without blood or mucus
  - Without abdominal pain
  - Laboratory:
    - CRP- 4,89 mg/l
    - Fibrynogen – 440,3 mg/dl
    - WBC-14910/mmc
    - Hb- 9,7 g/dl

1 year follow- up ->nov 2013

- Without other flares of disease during 10 months
- Continued treatment with IFX 5mg/kgc at 8 w (8 aplications)+AZA 2 mg/kgc
- Clinical : 1 stool/day, normal consistency, no blood or mucus, no abdominal pain
- Biological: no imflammatory syndrome, no anemia
- Colonoscopy (july 2013) : endoscopic remission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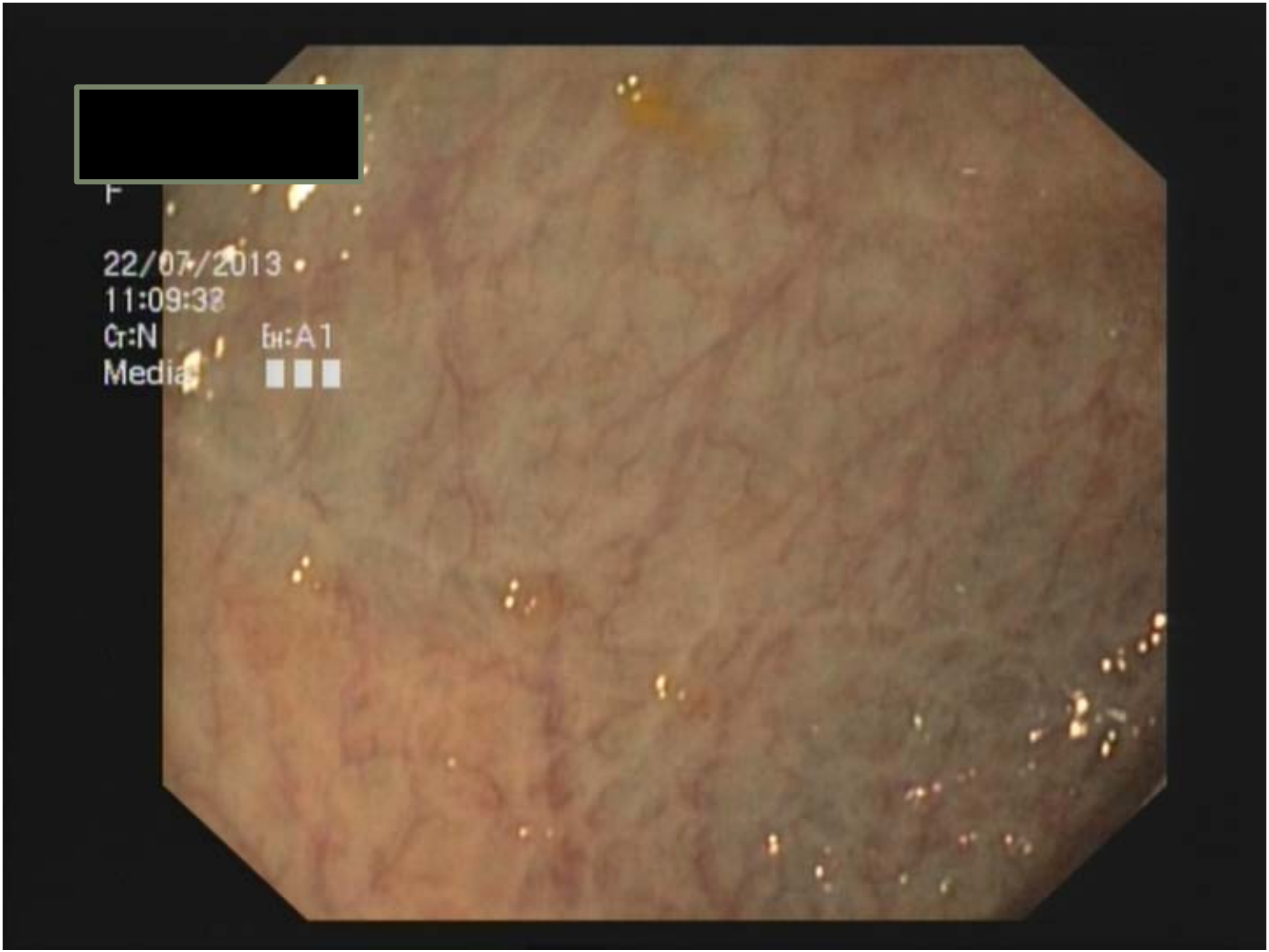
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CDI in IBD patients

- Epidemiology:
  - One population-based study by Ngueyn: prevalence of CDI in IBD patients > 8x than in non-IBD patients (37.3 cases vs 4.8 cases per 1000 discharges)
  - Ricciardi , Anathankrishan (1998-2005): CDI-UC (2.4 % -> 3.9 %), CDI-CD (0.8% -> 1.2%)
  - Rodemann (1998-2004): doubling of CDI in CD and tripling in UC.
- Asymptomatic carriers :
  - 8.2 % in IBD patients (higher in UC patients – 9.4 % vs CD-patients – 6.9 %) vs 1-2 % in general population :
    - Altered gut microbiome
    - Inability to form an appropiate antibody response
    - Epitelial disfunction and enhanced mucosal permeability
- Colectomy : 20 % colectomy rate in IBD-infected individuals compared to 1 % in non IBD infected patients

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CDI in IBD patients

- CDI in IBD patients characteristics:
  - Young age
  - Community aquired (76 %)
  - Antibiotics do not play a critical role
- CDI + IBD mortality :
  - >4.6 x then in IBD patients without CDI
  - >2x then in patients with Cdi , without IBD
- Atypical clinical, endoscopical and histological features

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Conclusions and case particularity

- Infliximab 5 mg/kg is an effective and safe rescue therapy in patients experiencing a severe attack of ulcerative colitis not responding to conventional treatment, avoiding colectomy in 50% of cases
- CDI maximally treated with antibiotics (Metronidazol + Vancomycin) is not considered a contraindication to biological treatment

Thank you!