Case Presentation

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Medical History

- Male patient , 29 years old
- Former smoker, up to 20 cigarettes/day
- No significant personal or familial medical history
- Presentation in september 2012 for:
  - chronic diarrhea since august 2012, 5-6 stools/day, blood and mucus
  - Weight loss 3-4 kg during last months
  - Temperature 37.5-37.7 C

Laboratory values

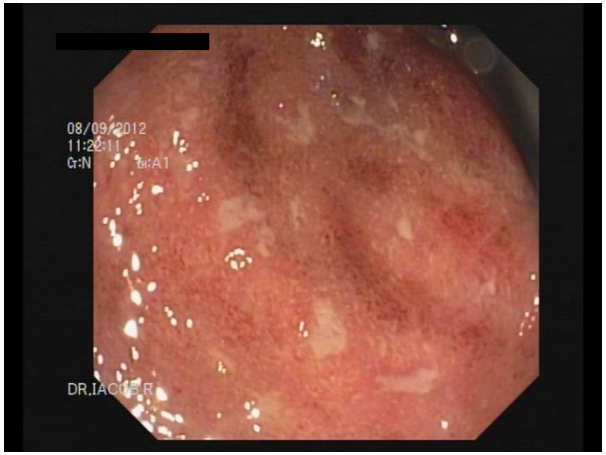
- WBC 11300/mm3, Neut 8090/mm3
- Hb 13.8 g/dl, Ht 39%
- Plt 356000/mm3
- Fbg 599 mg/dl
- Iron 14 ug/dl
- CRP 105 mg/l
- Stool culture, parasites - negative
- HIV negative
- ASCA, p-ANCA- negative

Colonoscopy - Sept 2012

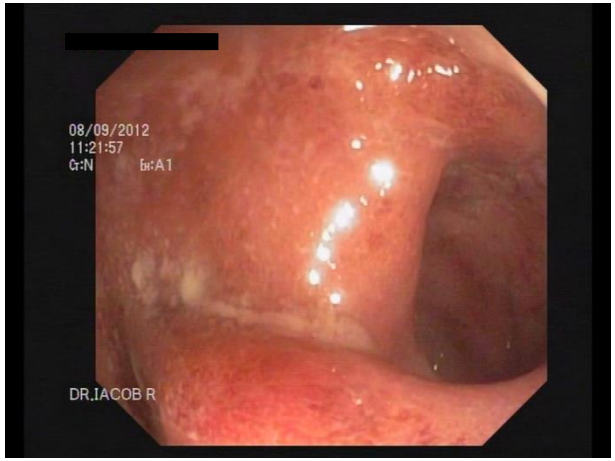
- Continuous inflammatory lesions of moderate severity starting from the rectum up to the ascending colon, with deeper ulcers at the level of the splenic flexure and distal transverse colon.
- Cecum and terminal ileum – no lesions
- Lesions distribution and endoscopic aspect - suggestive for ulcerative colitis

Colonoscopy - Sept 2012

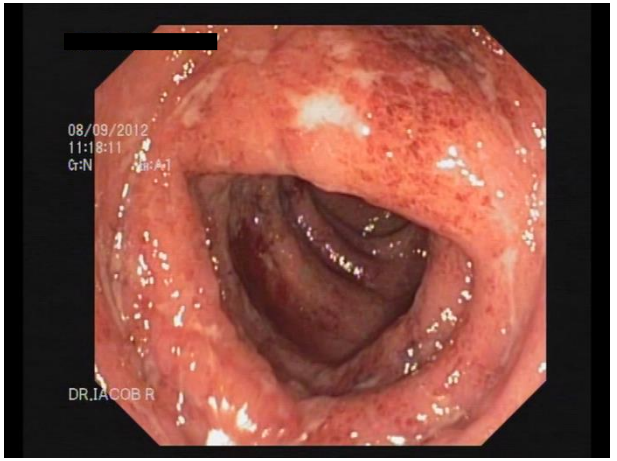
Rectum



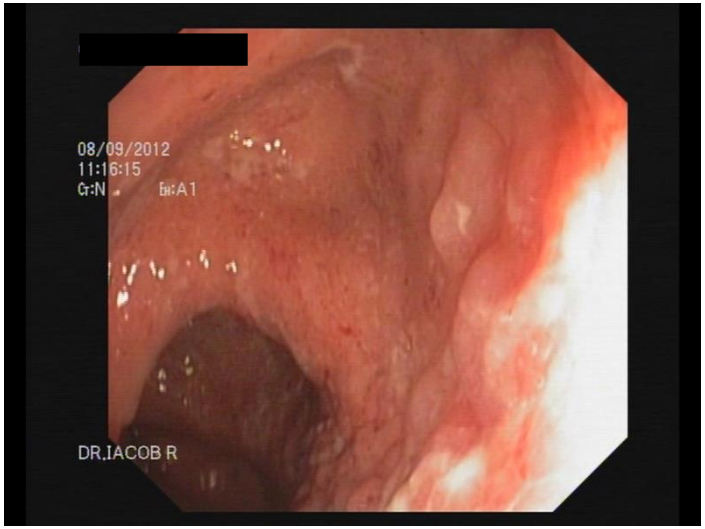
Sigmoid Colon



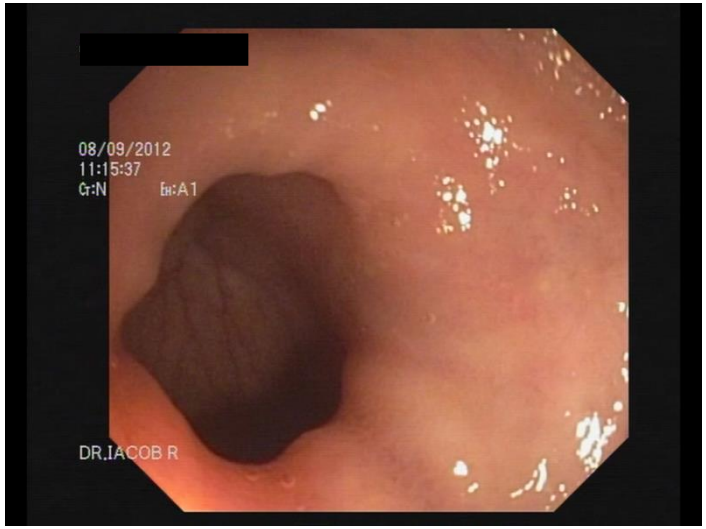
Transverse Colonc



Ascending Colon



Terminal Ileum



Follow-up

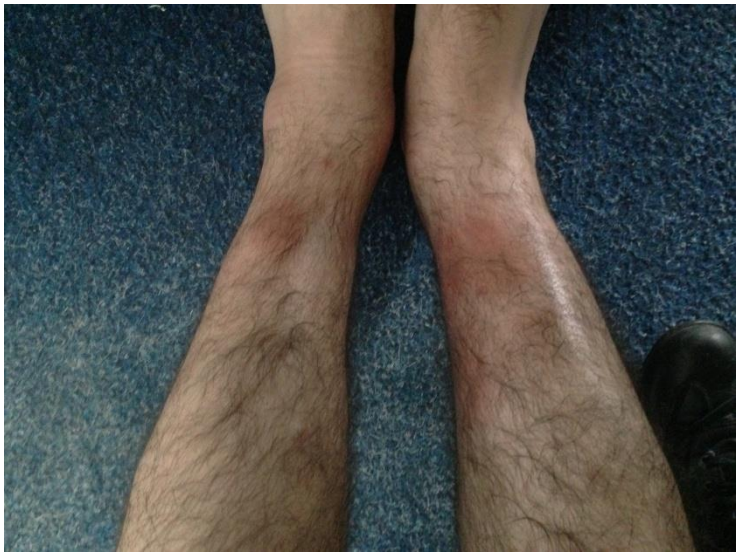
- Histopathology nonspecific chronic active inflammation ; no granulomas
- Diagnosis:
  - Ulcerative pancolitis -> moderate flare (Mayo score-9)
- Treatment
  - Induction of remission Oral steroids: 50 mg Prednisone -> rapid remission of symptoms

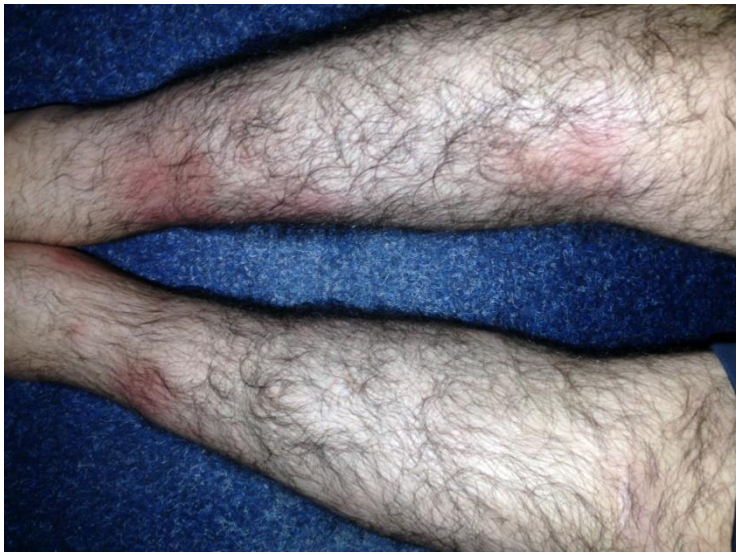
-Maintenance therapy: 5-ASA 3 g / day per os

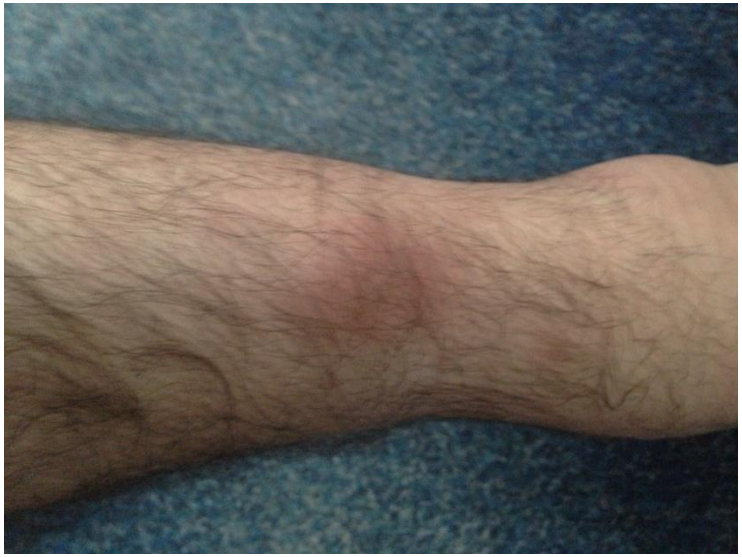
Medical History

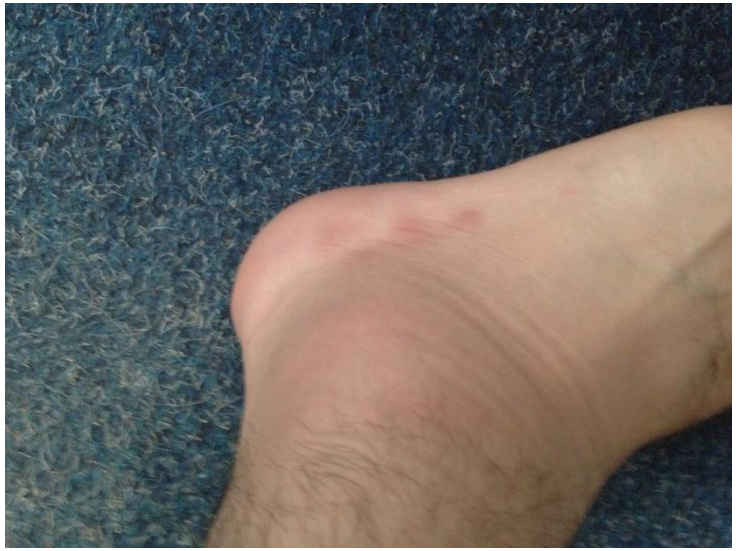
- December 2012 : the patient presents with violet, tender subcutaneous nodules affecting the anterior tibial areas , highly suggestive for erythema nodosum
- Lab values: WBC 10200/mm3, Neut 7120/mm3, Hb 14.1 g/dl, Ht 42.6%, IRN 20 ug/dl, CRP 69 mg/l, Fg 632 mg/dl
- Treatment: Potasium iodide 300 ug x3 + Dermovate (topical corticosteroid) – clinical improvement

Erythema Nodosum - Dec 2012









Medical History

- January 2013: new IBD flare
  - 6-8 bowel movements/day with blood and mucus
  - temperature - 37.8 C
- Lab values: WBC 15750/mm3, Neut 8670/mm3, Hb 12.4g/dl, Ht 38%, Fg 628 mg/dl, ESR 56 mm/h, CRP 87.7 mg/l

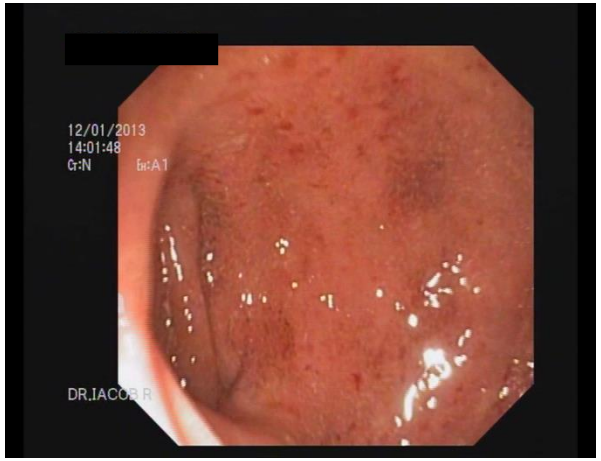
  -> severe flare (Truelove and Witts)

Colonoscopy - Jan 2013

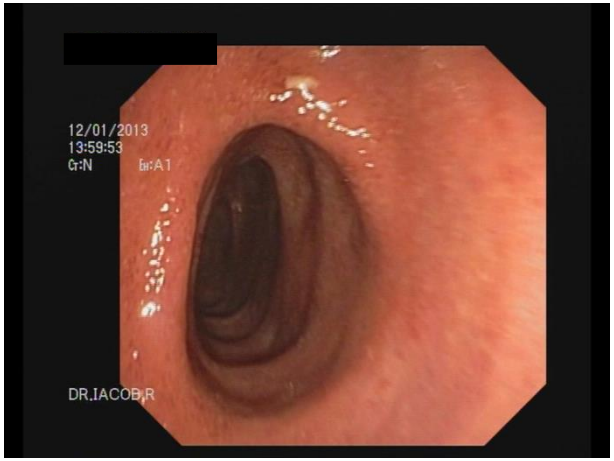
- Continuous inflammatory lesions of moderate severity starting from the rectum and extending proximally up to the transverse colon but with severe deep ulcers at the level of the splenic flexure and no lesions on the ascending colon.
- Lesions aspect and topography suggest more the diagnosis of IBD-U instead of UC. Differential diagnosis with colonic Crohn’s Disease.

Colonoscopy - Jan 2013

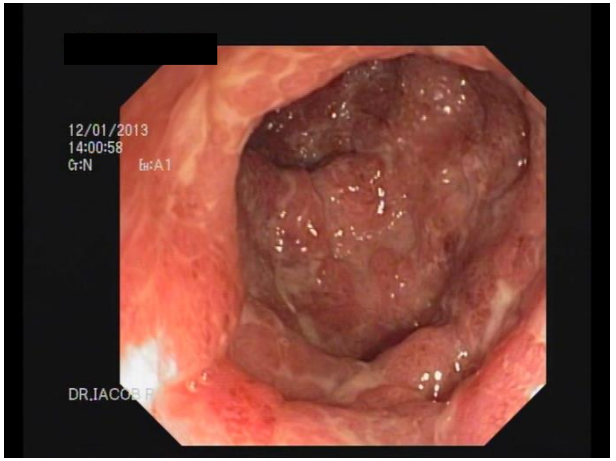
Rectum



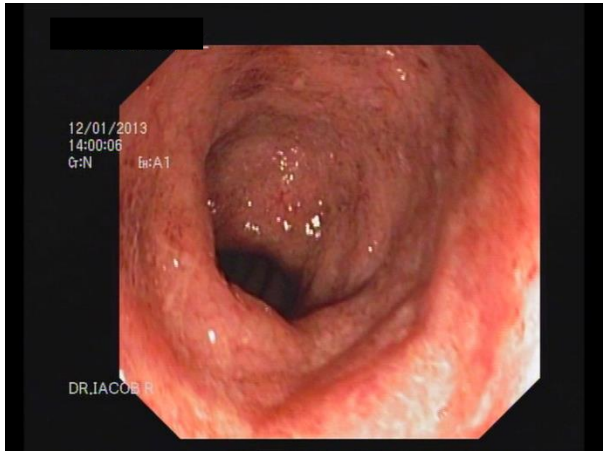
Sigmoid Colon

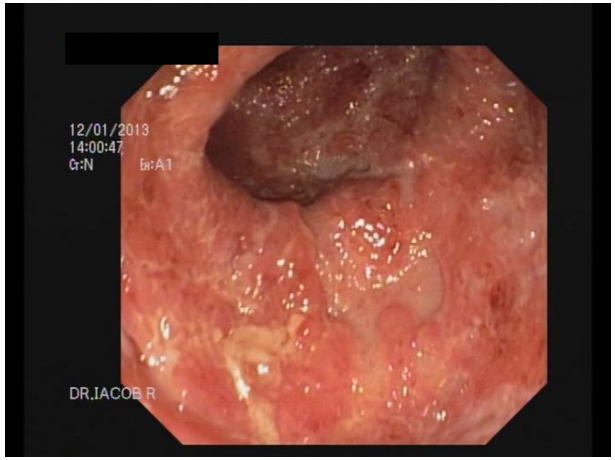


Splenic flexure

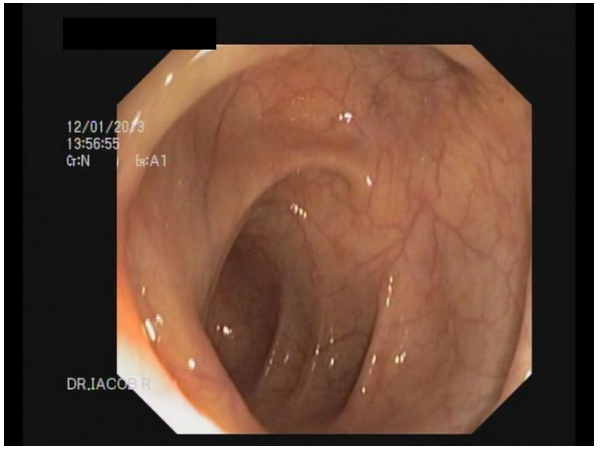


Distal transverse colon





Proximal transverse colon



Medical History

- Parenteral methyl-prednisolone 50 mg/day +Aza 150 mg/day
- No significant clinical improvement on iv steroids
- Re-check for causes of non-response: CMV IgM negative, Clostridium Difficile toxin A/B positive

Medical History

- Treatment:
  - Ab-Therapy: Metronidazole 500 mg x3/day + Vancomycine 500 mg x4/day per os
  - Stop Azathioprine
  - Maintain Metil-prednisolone iv 50 mg/day 7 days afterwards switch to oral corticosteroid

End of antibiotherapy

- Slight clinical improvement (5 bloody stools/day)
- Lab values: WBC 11120/mm3, Neut 8180/mm3, CRP 81.8, PCT 0.02 ng/ml, Quantiferon TB Gold negative.
- Start induction of remission with Adalimumab 160/80 mg at 0,2 w
- After the first application - rapid clinical improvement - 2 bowel movements/day, no blood in the stools
- Lab values: WBC 6820/mm3, CRP 19.3 mg/l

Medical history

- Before starting maintenance therapy with Adalimumab the patient presented with a new disease flare
- Lab values: 10100/mm3, CRP 145 mg/l, Fg 446 mg/l
- Again positive test for Cl. Difficile toxins

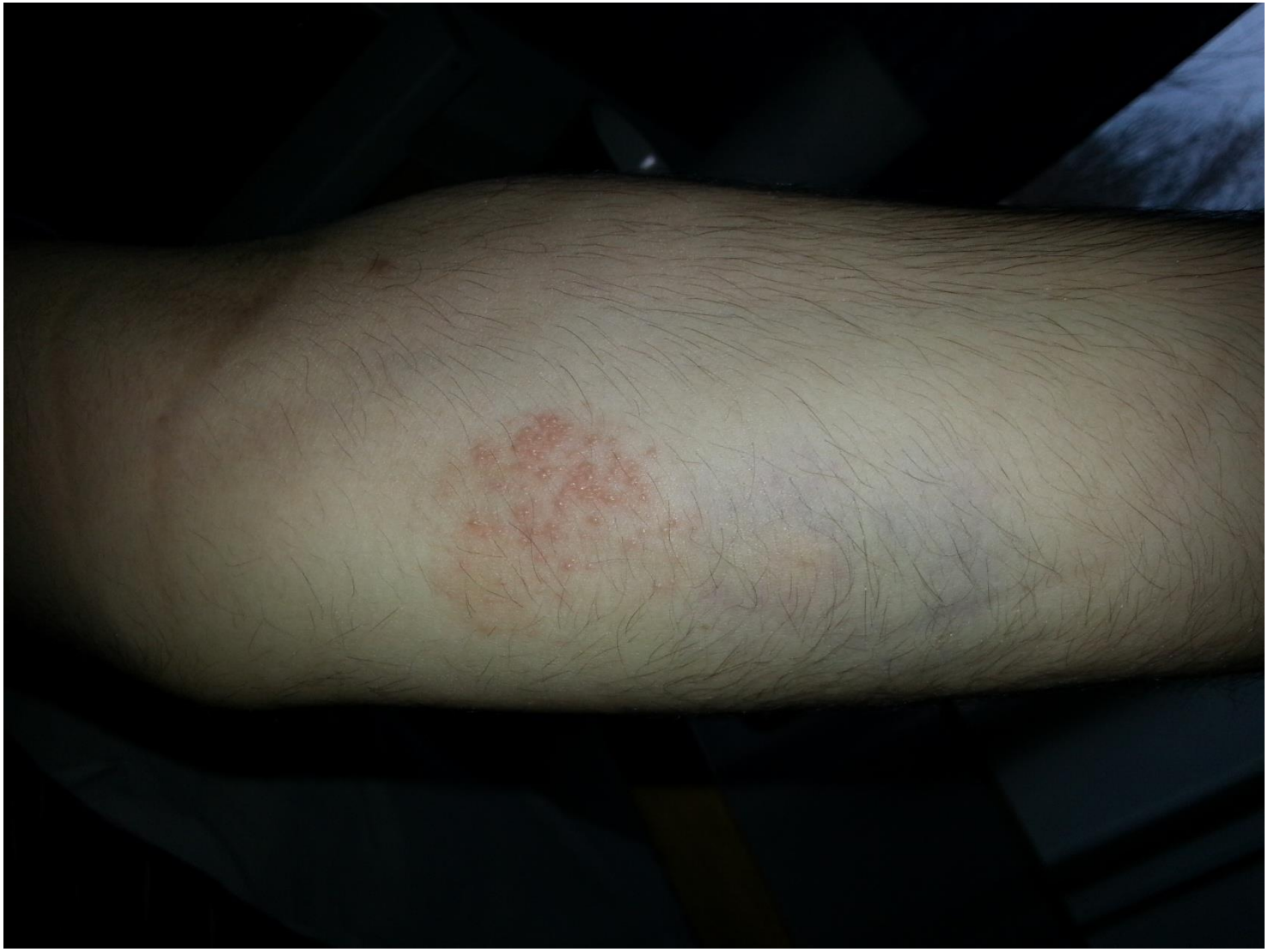
First reccurence of CDI

- Patients transferred to the Infectious Diseases Department for case isolation and treatment of recurrent Cl Diff infection
- Retreatment with
  - oral Vancomycine 500 mg x4/day +
  - Tigecycline 50 mg x2/day
  - Rifaximin 400 mg x3/day -14 days
- Stop Adalimumab
- Only oral Mesalasine 4g/day for IBD

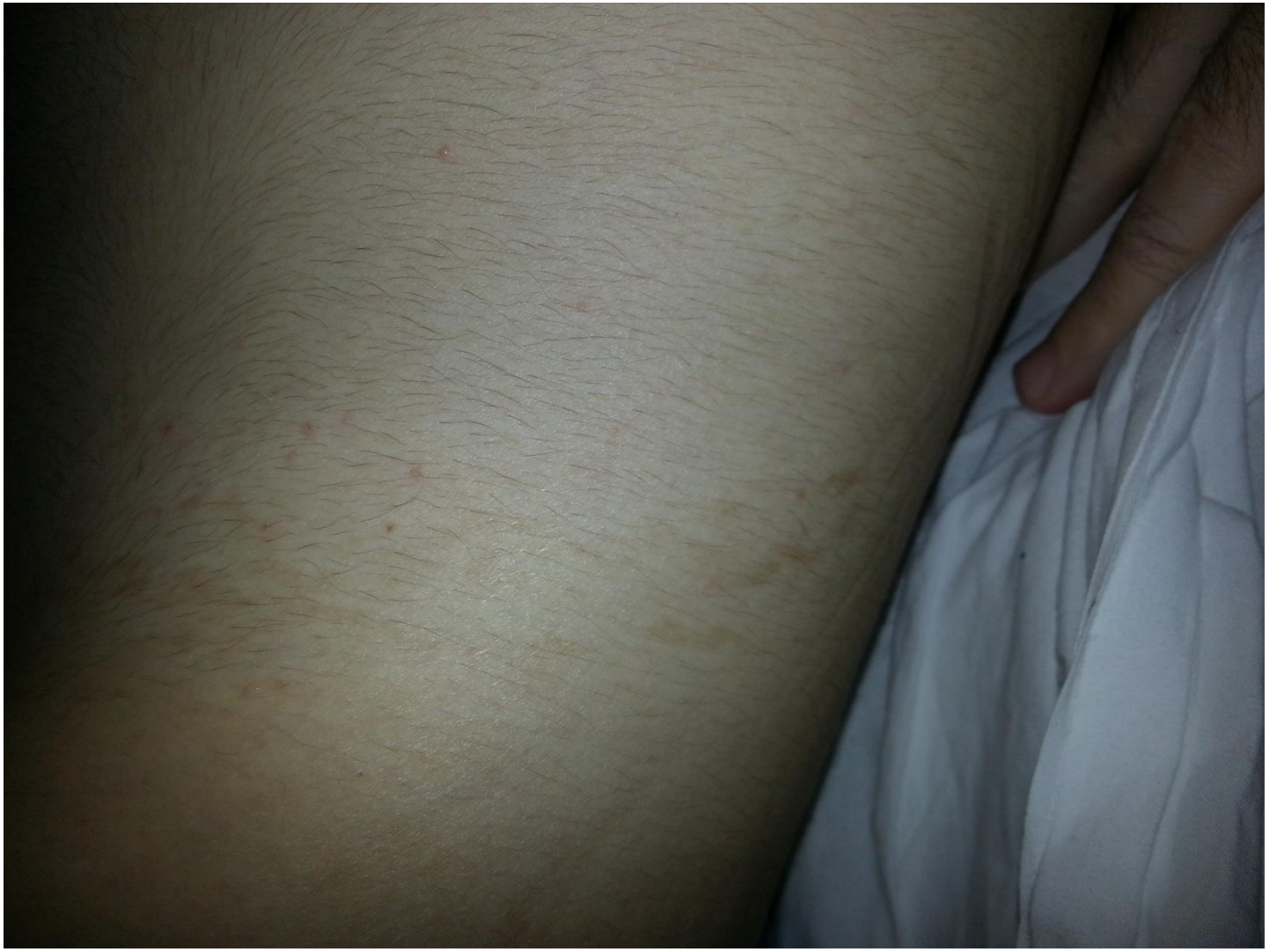
Medical History

- 07.03.2013: Patient re-transfered to Gastroenterology Ward for subsequent management of IBD
- Clinical: 4-8 bowel movements/day
- Lab values:WBC 11280/mm3, Neut 8590/mm3, Plt 643000/mm3, Hb 10.1 g/dl, ESR 50 mm/h, Fg 401 mg/dl, Alb 1.8 g/dl, TP 2.7 g/dl
- Cl Diff Toxin positive- 2nd reccurence
- Start Ab –therapy with Fidaxomycine 200 mg x2/day 10 days

11 Mar 2013 – Left Arm



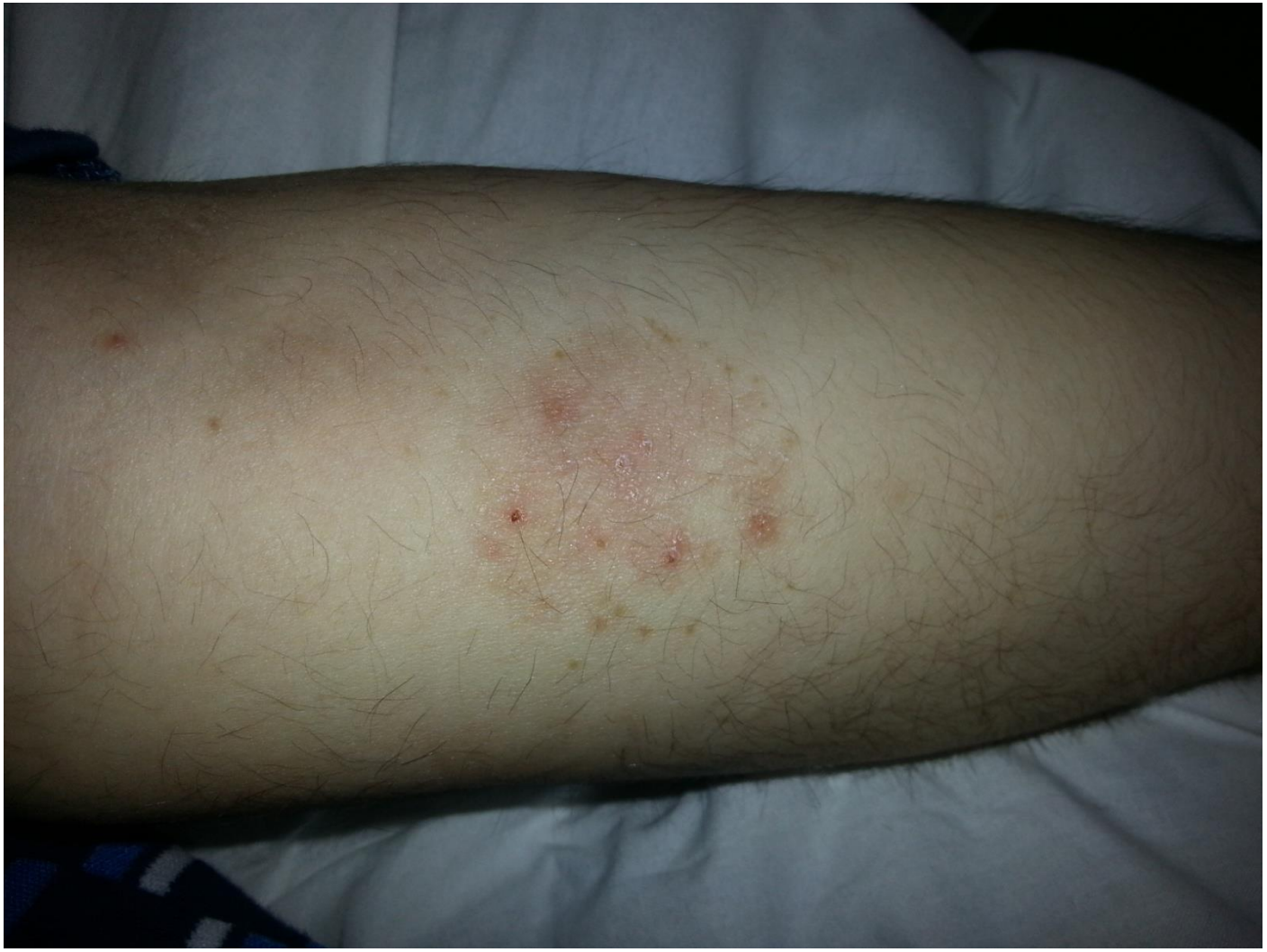
11 Mar 2013 – Left upper abdomen



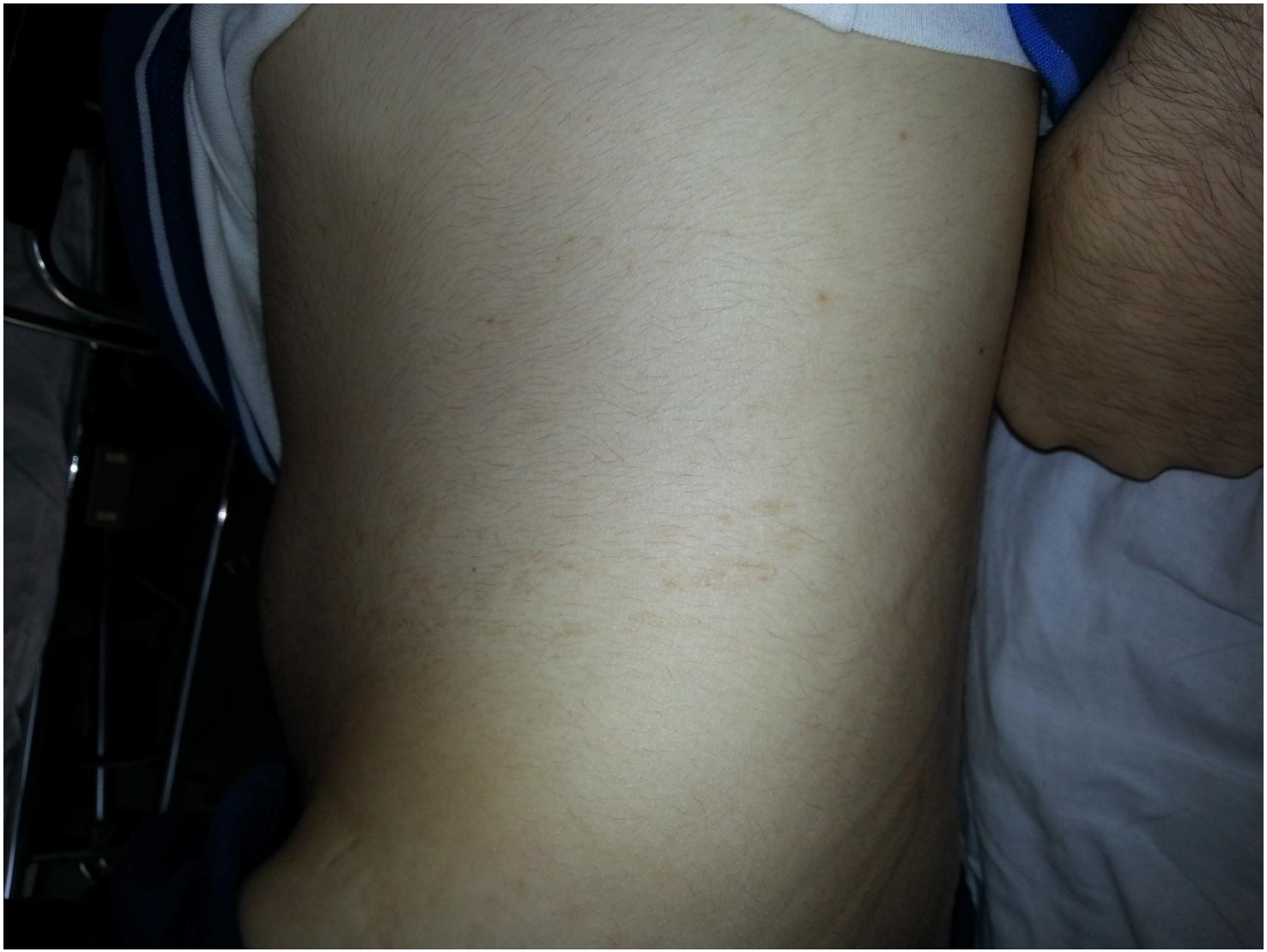
Medical History

- Diagnosis: Herpes Zoster
- Treatment: Acyclovir iv 10 mg/kg x3/day- 10 days
- Continue Fidaxomycine treatment up to 10 days
- IBD: Mesalasine 4g/day

18 Mar 2013 – Left arm



18 Mar 2013 - Left upper abdomen



Medical history

- CDI and HZ treated :
  - 7-10 bowel movements/day
  - No blood in stool
  - No fever
  - Lower limbs and scrotal edema
  - Pulse rate 95/min, BP 110/60 mmHg
- Lab values: WBC 6300/mm3, Hb 6,8 g/dl, Plt 671000/mm3, ESR 56, Alb 2.6 g/dl, TP 4.5 g/dl,PCR 149
- NB: possible adverse effects of Acyclovir treatment (?) as WBC decreased from 11000 to 6300/mm3 and Hb from 10 to 6.8 g/dl with no evident blood loss or signs of hemolysis, still high no. of bowel movements/day.

Clinical Question

- How should IBD be managed at this point:
  - New course of iv steroids? No, because previous experience showed resistance to corticoid therapy
  - Restart Anti TNF therapy? Yes, restart ADA 160/80 mg at 0,2 w -> clinical (3 BM/day without blood) and biological improvement (CRP 4 mg/l, WBC 5440/mmc ,Hb 11,8 g/dl)

Reccomended treatment on discharge

- Oral Vancomycine tapered as it follows: 125 mg QID 10 days, then 125mg BID 1 w, then 125 mg/d 1 w, then 125 mg / 2 days 3 weeks
- ADA maintainance therapy 40 mg/week

3rd recurrence of CDI

- June 2013 : 3rd reccurence of CDI
- Treatment proposed (Viena, Austria):

  Fecal Microbiota Transplantation

  - via ND tube and colonoscopy

  - donor: patient`s mother
- CDI resolved (negative toxin, negative stool culture) but still uncontrolled IBD activity under ADA 40 mg weekly + Oral corticosteroid (Prednisone 50 mg)+ AZA low dose 1mg/kg
- Capsule endoscopy – no small bowel lesions
- Colectomy was taken into consideration
- Therapeutic regimen proposed in Austria before colectomy:
  - IFX (Re-induction of remission 5 mg/kg S0-S2-S6 + maintenance 5 mg/kg at 8 weeks

Follow-up

- End of induction treatment:
  - Clinical remission (2 bm/day, without blood)
  - Biological remission (CRP =2,67 mg/l, fbg= 374,2 mg/dl, WBC=7720/mmc, Hb=13,6 mg/dl,alb=4,5 g/dl)
- Sept 2013 : AZA increased to 2,5 mg/kg/day
- Nov 2013: clinical and biological remission

Follow-up

- Last evaluation (dec 2013)- clinical and biological remission
- No signs of recurrence of CDI 6 months after FMT
- Current treatment:
  - IFX 5 mg/kg every 8 weeks
  - AZA 2,5 mg/kg/day
  - Oral corticosteroid 2.5 mg eod and should be stopped

Case particularity

- Severe chronic colitis (IBD-U) complicated with
  - Erythema nodosum
  - Herpes zoster
  - Recurrent infection with Clostridium difficile (3 recurrences) -> successfully treated with FMT administered via ND tube and colonoscopy

  - *Difficulty of the management of IBD in case of Zoster and C Diff infections in order to avoid colectomy*
  - *Spectacular response of CDI to FMT but no control of IBD disease activity*
  - *Ultimately control of IBD after resolution of CDI by combo-therapy*

Alternative therapies in CDI

- **Newer antibiotics:**
  - **Fusidic acid**
  - **Nitazoxanide** –noninferior to metronidazole or vancomycin
  - **Teicoplanin**- better bacteriologic cure and borderline superior symptomatic cure- compared to vancomycin (not available in US)
  - **Rifampin**
  - **Rifaximin**- decrease rate of recurrence (400 mg TID for 20 days after finishing a course of metrondiazole or vancomyicin: 21 % vs 49 %
  - **Bacitracin**
  - **Fidaxomicin** (FDA approved in may 2011) – macrocyclic **bactericid** antibiotic- lower recurrence (16,9 % vs 29,2 %) + higher efficacity in achieveing clinical cure (90 % vs 79.4 %) than vancomycin;
  - **Tygecycline** – broad-spectrum iv antibiotic with good fecal penetration, succesfull for treatment of severe or complicated CDI when prior therapy has failed; risk for superinfection with resistant organisms (Proteus mirabilis bacteriemia)

Alternative therapies in CDI

- **Probiotics**
  - Specifically Saccharomyces boulardii
  - Prevent the overgrowth of potentially pathogenic organisms
  - Stimulate the intestinal immune defense system
  - Adjuvant therapy, but no synergistic benefit in the setting of CDI
  - Not routinely recommended (recurrence not prevented, risk of fungemia in critically ill patients)

- **Immunotherapy (IVIG**)- high mortality rate (57%) in 21 patients treated with IVIG for severe infection -> useful for uncomplicated recurrent infection, with limited role in patients with end organ dysfunction

- **Fecal microbiota transplantation (FMT)**

Fecal microbiota transplantation (FMT)

- Recommended to patients with severe and recurrent *C. difficile infection who have failed multiple attempts at conventional antibiotic* therapy.
- Several routes have been used to administer fecal microbiota with cure rates ranging from **81 to 94 %** in patients with recurrent disease.
- Effectiveness varied by :
    - Route of instillation, Stool donor, Volume of FMT given, Treatments received before infusion
- Routes of administration:
  - Via the lower GI tract (enema or colonoscopy)
  - Via the upper GI tract (NG or ND tubes)
- A pooled analysis of 182 cases of recurrent CDI treated with FMT showed that colonoscopic FMT has a slightly higher cure rate than nasogastric FMT (93 versus 85 percent)

Fecal microbiota transplantation (FMT)

Donors

- Donor feces will be collected from healthy individuals , relative or friend may be a donor. However, donors should not share living quarters with the patient, as there is likelihood that they will share the same defective microbiota.
- Exclusion criteria for donors:

1. diarrhea (defined as 3 loose or watery stools per day for at least 2 consecutive days or 8 loose stools in 48 hours), history of IBD
2. use of antibiotics in the past 3 months.
3. HIV, HAV, HBV, HCV, active CMV, active EBV, Lues, HTLV
4. Presence of fecal bacterial pathogens (Salmonella, Shigella, Campylobacter, Yersinia) or pathogenic parasites
5. Positive *C. difficile stool toxin test (asymptomatic carriers)*
6. Risk factors for transmittable diseases, such as IV drug use, homosexuality or tattoos

Fecal microbiota transplantation (FMT)

- Protocol for lower GI tract administration:
  - oral vancomycin (500 mg twice daily for seven days) followed by a single oral lavage with 3 to 4 liters of polyethylene glycol with electrolytes purgative
  - 200 to 300 g of donor stool suspended in 200 to 300 mL of sterile normal saline (homogenized briefly in kitchen blender to a liquid consistency) administered via enema within 10 minutes of preparation, repeated daily for five days, encouraging patients to retain it for at least 5 h

Fecal microbiota transplantation (FMT)

- Protocol for upper GI tract administration:
  - in addition to antibiotics and preparation with a purgative, patients should receive a dose of a **PPI(eg, omeprazole 20 mg)** the evening before and the morning of the instillation.
  - the positioning is confirmed by x-ray and Gastrografin follow-through before proceeding with the infusion. It is recommended that **the tube remain in situ for a period of five days** to administer the infusion
  - A single instillation of 25 to 30 g of stool diluted in 50 mL of saline is typically sufficient in patients receiving the therapy via the upper GI tract.