Treatment algorithm for Ulcerative Colitis

Swiss expert recommendations – Based on ECCO guidelines for Ulcerative Colitis (2012)[1-3] and other published literature

Developed by:
Luc Biedermann, Stephan Brand, Emanuel Burri, Petr Hruz, Pascal Juillerat, Michael Manz, Michel Maillard, Gerhard Rogler, Bernhard Sauter, Alain Schoepfer, Frank Seibold, Stephan Vavricka.

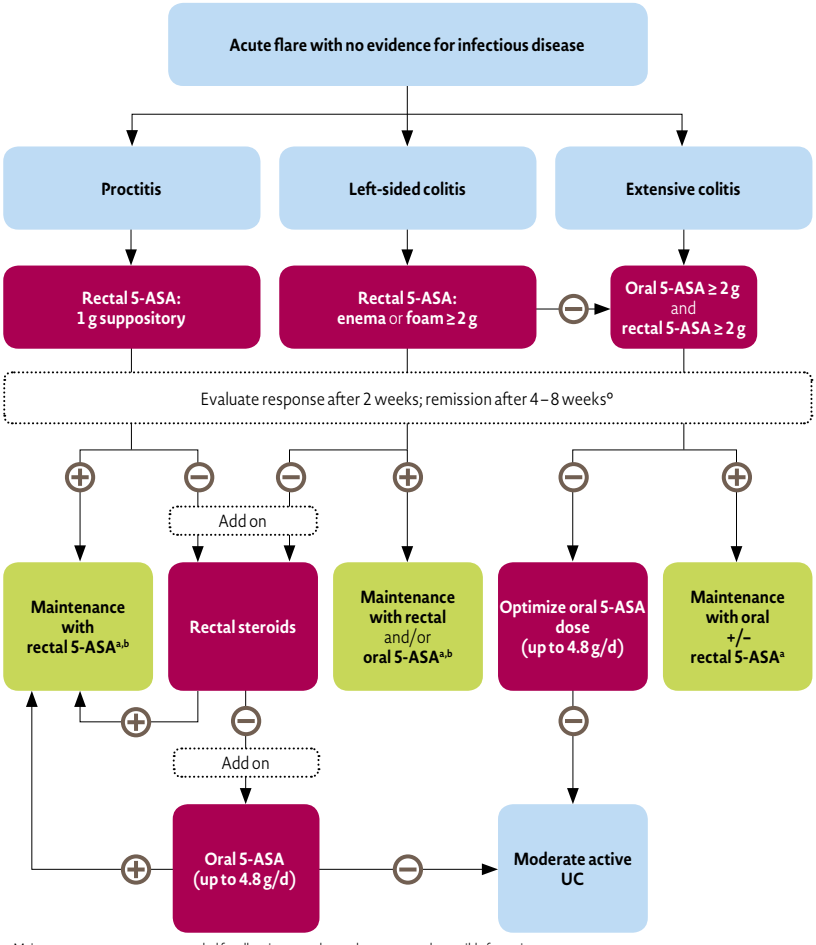
abbvie

Dosing of therapies[4]

	Substance	Dosage
5-ASA	Mesalazine	2–4.8 g/d (oral) 1–2 g/d (rectal) flare: 3 × 800 mg/d prophylaxis: 3 × 400 mg/d
Corticosteroids	Budesonide Budesonide MMX	2 mg/d (rectal) 9 mg/d (oral)
	Prednisone	0.75 – 1 mg/kg bw/d
Immunosuppressives	Azathioprine (AZA)	2 – 2.5 (max. 3) mg/kg bw/d
	6-Mercaptopurine (6-MP)	1 – 1.5 mg/kg bw/d
	Cyclosporine	2 mg/kg bw/24 hours i.v.
	Tacrolimus	0.1 mg/kg bw/d Serum concentration: 10 – 15 ng/ml
Biologics	Adalimumab (Humira®)	Subcutaneous Week 0: 160 mg Week 2: 80 mg Week 4: 40 mg Then every 2 weeks: 40 mg Dose escalation: every week 40 mg
	Golimumab (Simponi®)	Subcutaneous Week 0: 200 mg Week 2: 100 mg Week 4: 50 mg Then every 4 weeks: 50 mg (100 mg for patients > 80 kg)
	Infliximab (Remicade®)	Infusion over 30 – 90 min Week 0: 5 mg/kg Week 2: 5 mg/kg Week 6: 5 mg/kg Then every 8 weeks: 5 mg/kg
	Vedolizumab (Entyvio®)	Infusion over 30 min Week 0: 300 mg Week 2: 300 mg Week 6: 300 mg Then every 8 weeks: 300 mg Dose escalation: every 4 weeks 300 mg

bw = body weight; **d** = day

Mild to moderate Ulcerative Colitis[2,5]



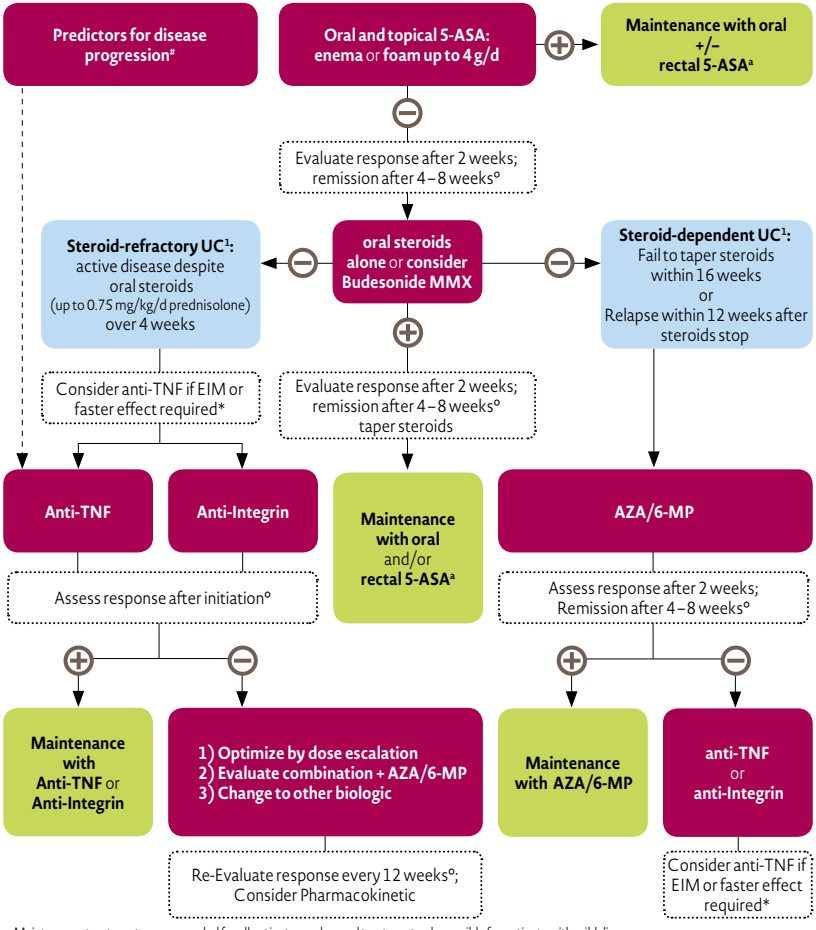
a Maintenance treatment recommended for all patients, on-demand treatment only possible for patients with mild disease

b In case of intolerance to 5-ASA, E.coli Nissle may be used as alternative for maintenance treatment

° See Page "Target for UC treatment"

⊕ Response/remission
⊖ No response/no remission

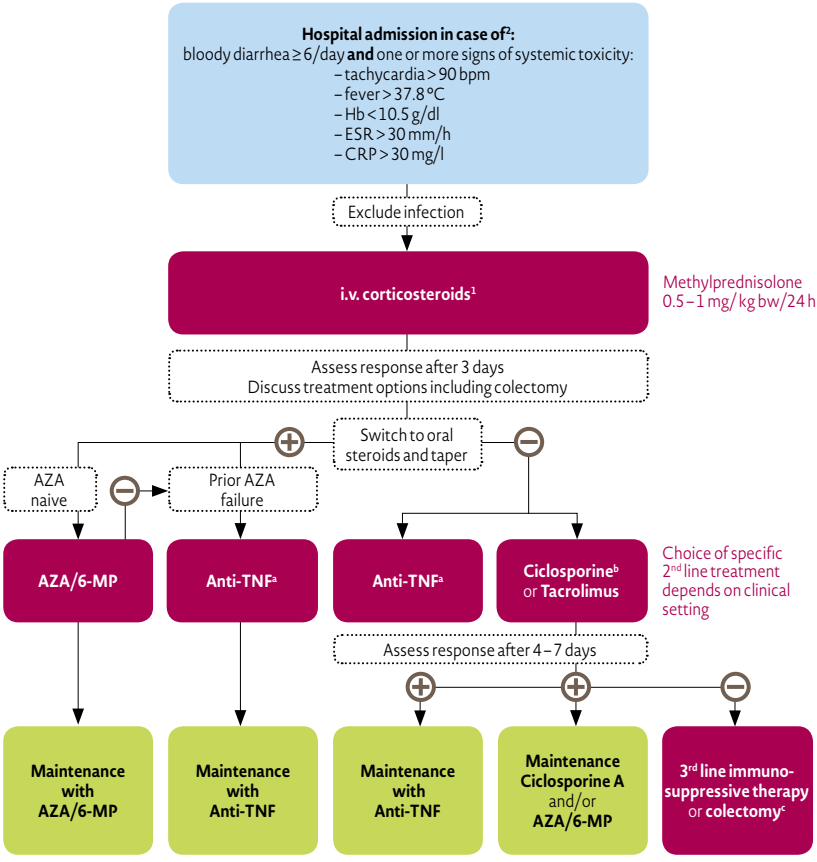
MODERATE TO SEVERE ACTIVE ULCERATIVE COLITIS[2,5,6]



a Maintenance treatment recommended for all patients, on-demand treatment only possible for patients with mild disease
b In case of intolerance to 5-ASA, E.coli Nissle may be used as alternative for maintenance treatment
* Swiss expert recommendation
# See page "Risk for severe disease progression"
° See Page "Target for UC treatment"

⊕ Response/remission
⊖ No response/no remission

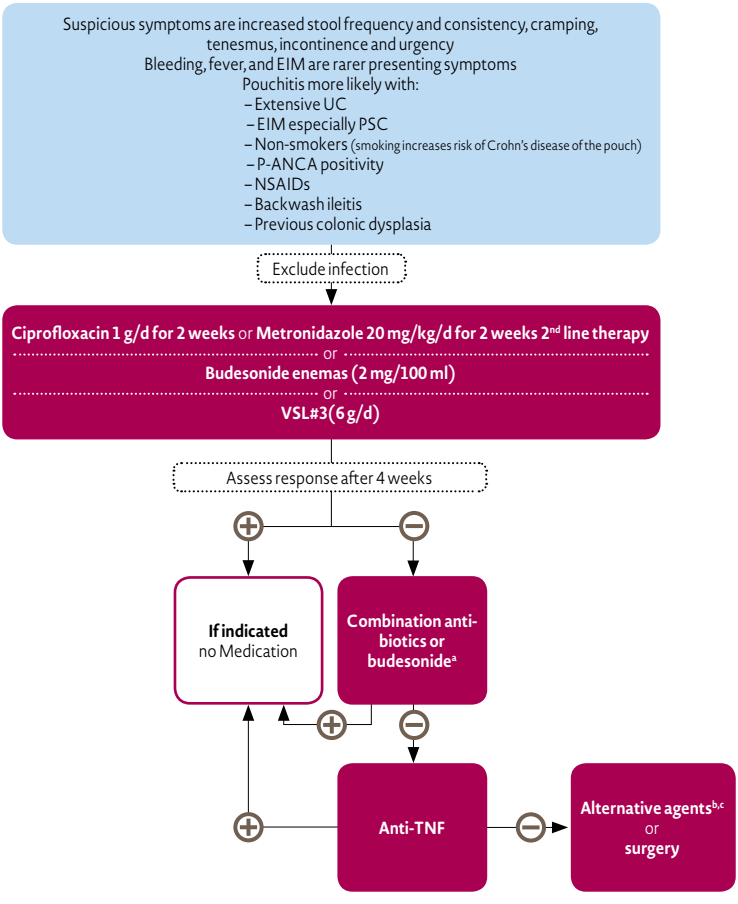
Severe Ulcerative Colitis[1,2,5]



Consider drug level testing to guide dose increases or modifications
a Data for hospitalized patients only available for Infliximab.
b Exclude low Mg/Cholesterol.
c 3rd line immunosuppressive therapy restricted to specialized centers
bw = body weight; **d** = day

⊕ Response/remission
⊖ No response/no remission

Pouchitis[11,24]



a Preferably combination antibiotic therapy, e.g. ciprofloxacin 1 g & tinidazole 1 g daily for 4 weeks. Remission in > 80%. Alternative treatment includes rifaximin 2 g daily or metronidazole 1 g daily for 4 weeks. Remission in > 80%.
b Ciclosporin enema; Azathioprine in those dependent on budesonide; Alicaforsen (anti-sense to ICAM-1) enema.
bw = body weight; **d** = day

⊕ Response/remission
⊖ No response/no remission

Risk for severe disease progression[25]

Prognostic factor	Impact
Young age at diagnosis	• More extensive disease (paediatric UC) • Colectomy • Proximal disease extension • Acute severe UC • Colorectal neoplasia
Family history	• Proximal disease extension (family history of IBD) • Colorectal neoplasia (family history of CRC)
Refractory proctitis (> 3 relapses per year)	• Proximal disease extension
Male sex	• Colectomy
Extensive colitis	• Colectomy • Acute severe UC • Hospitalization • Colorectal neoplasia
High histological inflammation score	• Colorectal neoplasia
Disease duration > 10 years	• Colorectal neoplasia • Colectomy
Steroid dependence/resistance	• Colectomy • Hospitalization
Smoking	• Less need for hospitalization • Proximal disease extension (protective) • Protective from colectomy
Concurrent infection (cytomegalovirus or Clostridium difficile)	• Flare and hospitalization
Primary sclerosing cholangitis	• Colectomy • Proximal disease extension • Colorectal cancer • Protective for hospitalization

Target for UC treatment[26]

- Clinical/ PRO remission, defined as resolution of rectal bleeding and diarrhea/altered bowel habit
- Endoscopic remission, defined as Mayo endoscopic subscore of 0–1
- Histological remission – optional

PRO = Patient reported outcomes

Monitoring efficacy and safety[7]

	Diagnosis	Monitoring: Symptomatic Disease
Symptoms	• Symptom assessment • Mayo score/IBDQ/CAI (establish baseline)	**Each visit:** • Symptom assessment • Mayo score/IBDQ/CAI
Laboratory	• Routine lab and inflammatory markers (blood count, liver profile, albumin, iron studies, renal function, Vitamins B12 + D, folic acid) • CRP • Faecal calprotectin	**Each visit:** • Frequency determined by severity and treatment • Routine lab and inflammatory markers • CRP • Faecal calprotectin • Faecal cultures and rule out C. difficile toxins in stool If needed: Biologic drug serum levels
Endoscopy	• Rectoscopy with segmental biopsies If inconclusive: Colonoscopy	• Patients with unclear clinical presentation: • Rectoscopy (confirm disease activity) if inconclusive: Colonoscopy
Imaging	• Ultrasonography	• CT for the detection of suspected complications (bowel obstruction, perforation, toxic colon distention)

	Monitoring: Asymptomatic Disease
Symptoms	**Each visit:** • Symptom assessment • Mayo score/IBDQ/CAI (verify remission)
Laboratory	**Each visit:** • CRP, Faecal calprotectin • Blood count **Every 3 – 12 months:** • Routine lab and inflammatory markers • Vitamins B12 + D If needed: Biologic drug serum levels (establish baseline)
Endoscopy	**In case of suspected disease progression or 6 months after start of biologics therapy:** • Rectoscopy if inconclusive: Colonoscopy
Imaging	**In case of suspected disease progression:** • Ultrasonography

CAI = Clinical Acitivity Index; **CRP** = C-reactive protein; **CT** = Computer tomography; **IBDQ** = Inflammatory Bowel Disease Questionnaire; **MRI** = Magnetic Resonance Imaging

Screening before Anti-TNF-therapy[12]

Contraindications or warnings for Anti-TNF-therapy with respect to findings during screening before treatment.

Evaluation	If yes
1. Serious infection (incl. active TB) or sepsis[4]	Contraindicated[4]
2. In case of flare[9]: a. *Clostridium difficile* toxin positive in stools b. CMV infection proven by biopsies c. Parasites in stool d. Stool culture to exclude infection	 Contraindicated Contraindicated Contraindicated Treat infection
3. Cardiac insufficiency NYHA III or IV	Contraindicated
4. Neurological disease	Consult neurologist
5. History of malignancy	Use with caution
6. Latent TB (i.e. positive IGRA test **or** abnormal x-ray suggestive of past TB not adequately treated **or** history of prior exposure to TB)[8]	Treatment with isoniazid 300 mg/d for 9 months or rifampicin 10 mg/kg daily for 4 months; TNF-therapy can be started after 1 month of preventive therapy[8]
7. HIV-positive, uncontrolled disease	Contraindicated
8. Positive HBV serology[9] a. HBsAg positive b. positive HBcAb and negative HBsAg	 Start anti-viral agents HBV DNA should be assessed every 2 – 3 months but antiviral therapy is not recommended unless HBV-DNA is detected
9. Chronic HCV infection	Use with caution[10]
10. Abnormal transaminase levels	Further evaluations
11. Women: last gynecological examination >1 year	Obtain exam

Vaccinations:
Check vaccination status prior to initiation of Anti-TNF-therapy, follow BAG recommendations on www.bag.admin.ch/impfungen
No live vaccination during Anti-TNF-therapy

Colon cancer screening[3]

Proctitis

No evidence of previous or current endoscopic and/or microscopic **inflammation proximal to the rectum: surveillance nationally recommanded colon cancer screening**

Left-sided/extensive colitis

Determine risk profile 6–8 years after first manifestation. Chromoendoscopy should be perforemd for surveillance if available (ECCO statement 13G)

High risk*: colonoscopy every 1–2 years from the 8th year after first manifestation

Low risk*: colonoscopy every 3–4 years from the 8th year after first manifestation

In case of concurrent PSC, surveillance colonoscopies should be carried out yearly from the point of PSC diagnosis irrespective of disease activity and extent.

Post-proctocolectomy:
Endoscopic surveillance is recommended for patients with dysplasia or cancer before or at the time of proctocolectomy.[20,23]

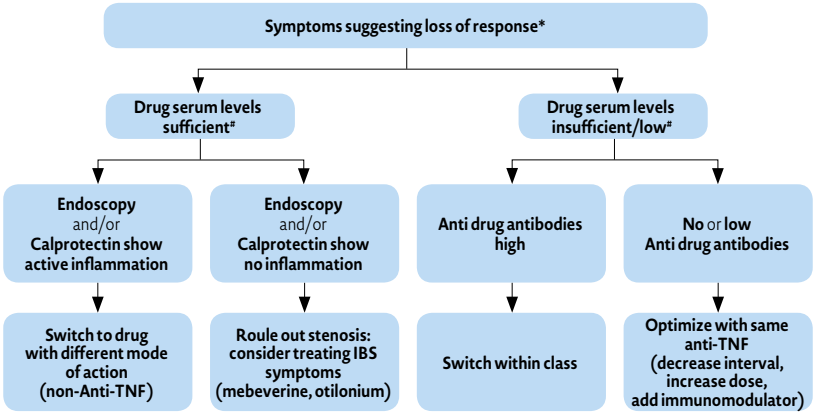
* Risk stratification mainly depends on extent of disease, severity of endoscopic and/or histological inflammation, pseudopolyps, concurrence of PSC, and family history of CRC.
PSC = Primary sclerosing cholangitis

Treatments during pregnancy[21,27-29,32]

Class	Substance	FDA pregnancy category	Use during pregnancy	Use during breast feeding
Antibiotics	Amoxicillin with clavulanic acid		Low risk, preferred antibiotic during pregnancy	Compatible, enters breast milk
	Ciprofloxacin	C	Low risk, affinity for cartilage Avoid 1st trimester	Avoid if possible, breastfeeding after 12–24 h, Compatible, enters breast milk
	Metronidazole	B	Low risk, avoid 1st trimester due to possible risk of orofacial clefts	Contraindicated; enters breat milk Avoid if possible, breastfeeding after 12–24 h
5-ASA	Mesalazine	B	Low risk	Low risk
	Asacol®	C	Low risk but contains DBP	Low risk
Corticosteroids	Budesonide	C	Low risk, likely compatible	Low risk Compatible; clinically insignificant concentration enters breast milk
	Systemic Steroids	C	Moderate risk; possible orofacial cleft (1st trimester exposure), adrenal insufficiency, gestational diabetes, premature rupture of membranes, preterm birth, infant infections. Risk of Low Birthweight	Compatible; clinically insignificant concentration enters breast milk Low risk, breastfeeding after 4 h
Immunosuppressives	Azathioprine 6-Mercaptopurine	D	1st trimester: no teratogenic risk in >1500 pregnant women treated orally. 2nd/3rd trimester: no evidence for fetotoxic risk.	In infants that are completely breastfed as a general rule no symptoms have been observed.
	Cyclosporine	C	Low risk Limited data: possible risk of complications, preterm birth, low birthweight	Contraindicated, enters breast milk
Biologics	Adalimumab (Humira®) Infliximab (Remicade®)	B	Low risk in monotherapy most likely safe, recommended to stop in 3rd trimester. 1st trimester: no teratogenic effect has been shown. 2nd/3rd trimester: active diaplacental transfer in case of more mature placenta. Theoretical concerns regarding development of immune system and reduced immunity of the newborn.	Low risk High molecular weight and low oral availability; absorption by the newborn unlikely. No clinical abnormalities in case reports.
	Golimumab (Simponi®)	B	Low risk in monotherapy Most likely safe, recommended to stop in 3rd trimester. Only case reports available[22]	Low risk No data published
	Vedolizumab (Entyvio®)	B	Limited human data, appears to be safe in animal studies	No human data, detected in milk of lactating monkeys

Category A: Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters). **Category B:** Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. **Category C:** Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. **Category D:** There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. **Category X:** Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits. (http://depts.washington.edu/druginfo/Formulary/Pregnancy.pdf)

Pharmacokinetics under Biologic treatment[30,31]



* Loss of response: a) Low serum Drug serum levels (just before next infusion /injection); b)Immunogenicity by neutralizing antibody formation; c)Fibrostentic structures

\# Range can vary according to used test

References:

1. Dignass A et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 1: Definitions and diagnosis. J Crohns Colitis. 2012 Dec;6(10):965-90. **2.** Dignass A et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 2: Current management. J Crohn's Colitis. 2012 Dec;6(10):991-1030. **3.** Van Assche G et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 3: Special situations. Journal of Crohn's and Colitis (2013) 7, 1–33. **4.** www.swissmedicinfo.ch. **5.** Frei P et al. Topical therapies in inflammatory bowel disease. Digestion. 2012;86 Suppl 1:36-44. **6.** Manz M et al. Treatment algorithm for moderate to severe ulcerative colitis. Swiss Med Wkly. 2011 Jun 27;141:w13235. **7.** Adapted from Sauter B et al. Monitoring disease activity and progression in Crohn,s disease. A Swiss perspective on the IBD ahead ‹optimised monitoring› recommendations; Digestion. 2014;89(4):299-309. doi: 10.1159/000360283. **8.** Beglinger C et al. Screening for tuberculosis infection before initiation of anti-TNF-a therapy. Swiss Med Wkly 2007;137:621–622. **9.** Rahier JF et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J Crohn's Colitis. 2014 Jun 1;8(6):443-68. **10.** Pompili M et al. Tumor necrosis factor-a inhibitors and chronic hepatitis C: a comprehensive literature review. World J Gastroenterol. 2013 Nov 28;19(44):7867-73. **11.** E-guide ECCO: http://www.e-guide.ecco-ibd.eu/algorithm/pouchitis. **12.** Pache I et al., TNF-a blockers in inflammatory bowel diseases: Practical consensus recommendations and a user's guide, Swiss Med Wkly. 2009; 139 (19–20): 278–287. **15.** Peyrin-Biroulet L et al. Results from the 2nd Scientific Workshop of the ECCO (1): Impact of mucosal healing on the course of inflammatory bowel disease. Journal of Crohn's and Colitis (2011) 5, 477–483. **16.** Schoepfer AM et al. Fecal calprotectin more accurately reflects endoscopic activity of ulcerative colitis than the Lichtiger Index, C-reactive protein, platelets, hemoglobin, and blood leukocytes. Inflamm Bowel Dis 2013;19:332–341. **17.** Burri E et al. The use of fecal calprotectin as a biomarker in gastrointestinal disease. Expert Rev Gastroenterol Hepatol. 2014 Feb;8(2):197-210. **18.** De Vos M et al. Fast and sharp decrease in calprotectin predicts remission by infliximab in anti-TNF naïve patients with ulcerative colitis. J. Crohn's Colitis 6(5), 557–562 (2012). **19.** Molander P et al. Fecal calprotectin concentration predicts outcome in inflammatory bowel disease after induction therapy with TNFa blocking agents. Inflamm Bowel Dis 2012;18:2011–2017. **20.** Scarpa M et al. Systematic review of dysplasia after restorative proctocolectomy for ulcerative colitis. Br J Surg. 2007 May;94(5):534-45. **21.** www.embryotox.de. **22.** Lau AG et al. Pregnancy Outcomes In Women Exposed To Golimumab. Arthritis & Rheumatism 65.Suppl. 10, Sp. Iss. Sl: S870-S871. (Oct 2013). **23.** Selvaggi F et al. Systematic review of cuff and pouch cancer in patients with ileal pelvic pouch for ulcerative colitis. Inflamm Bowel Dis. 2014 ul;20(7):1296-308. **24.** Greuter T et al. Alicaforsen, an antisense inhibitor of ICAM-1, as treatment for chronic refractory pouchitis after proctocolectomy: A case series. United European Gastroenterol J. 2016 Feb;4(1):97-104. doi: 10.1177/2050640615593681. Epub 2015 Jul 3. **25.** Torres J et al. Predicting Outcomes to Optimize Disease Management in Inflammatory Bowel Diseases; J Crohns Colitis. 2016 Jun 9. pii: jjw116. **26.** Peyrin-Biroulet L. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. Am J Gastroenterol. 2015 Sep;110(9):1324-38. doi: 10.1038/ajg.2015.233. Epub 2015 Aug 25. **27.** McConnell R A, Mahadevan U. Pregnancy and the Patient with Inflammatory Bowel Disease: Fertility, Treatment, Delivery, and Complications. Gastroenterol Clin North Am. 2016 Jun;45(2):285-301. doi: 10.1016/j.gtc.2016.02.006. **28.** Damas OM at al. Treating Inflammatory Bowel Disease in Pregnancy: The Issues We Face Today. J Crohns Colitis. 2015 Oct;9(10):928-36. doi: 10.1093/ecco-jcc/jjv118. Epub 2015 Jun 30. **29.** Van der Woude et al. ECCO Reproduction and pregnancy consensus (Edition 2015) CJ. J Crohn's Colitis. 2015;107-124. **30.** Vermeire S et al. Value of drug level testing and antibody assays in optimizing biological therapy; Front Gastr 2013; 4: 41-43. doi:10.1136/flgastro-2012-100241. **31.** Burri E et al. Diagnostischer Nutzen von Calprotectin im klinischen Alltag; Swiss Medical Forum - Schweizerisches Medizin-Forum 2016; 16(3): 68-73. **32.** Nguyen GC et al. The Toronto Consensus Statements for the Management of Inflammatory Bowel Disease in Pregnancy. Gastroenterology. 2016 Mar;150(3):734-757.e1. doi: 10.1053/j.gastro.2015.12.003. Epub 2015 Dec 11.

CHHUG160431_08/2016

AbbVie AG, Neuhofstrasse 23, 6341 Baar, Tel. 041 399 15 00, Fax 041 399 15 15

abbvie