Treatment algorithm for Crohn's Disease

Swiss expert recommendation – Based on ECCO guidelines 2010[1,2] 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.

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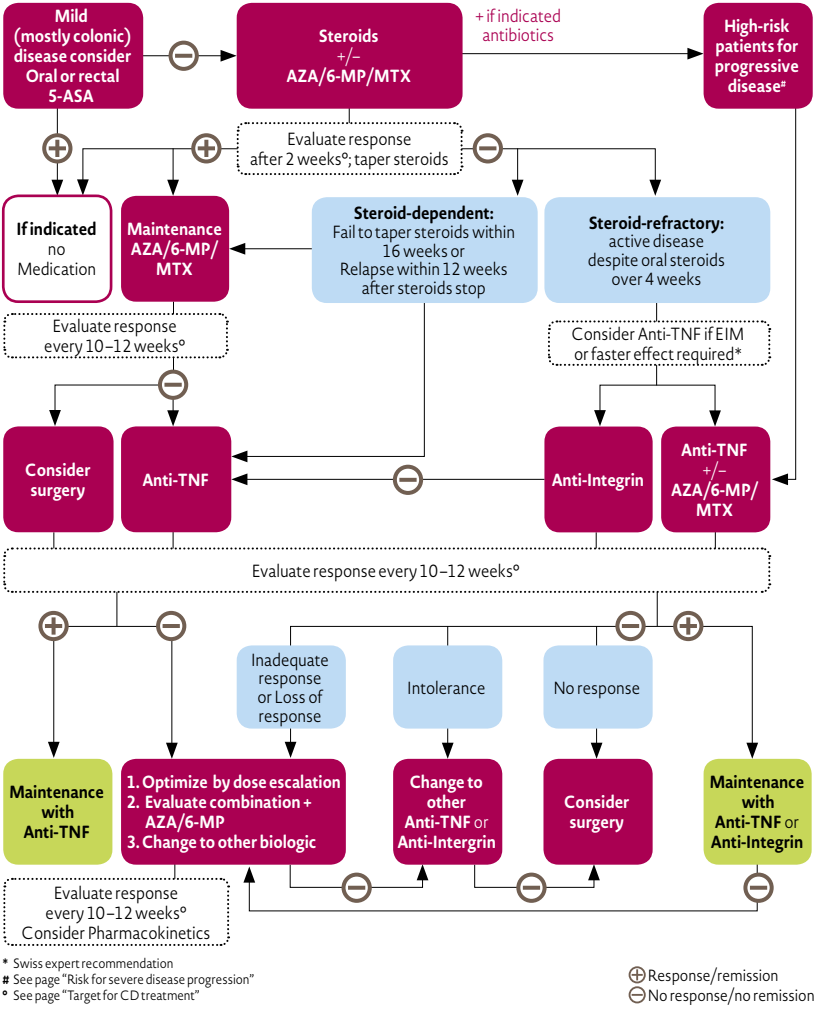
Dosing of therapies[4]

	Substance	Dosage
5-ASA	Mesalazine	3–4.8 g/d
Corticosteroids	Budesonide	9 mg/d
	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
	Methotrexate (MTX)	10–25 mg pro week + 5 mg folic accid
Antibiotics	Metronidazole	1000–1500 mg/d
	Ciprofloxacine	1000 mg/d
Biologics	Adalimumab (Humira®)	Subcutaneous Week 0: 160 mg Week 2: 80 mg Week 4: 40 mg Then every 2 weeks: 40 mg
	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
	Certolizumab Pegol (Cimzia®)	Subcutaneous Week 0: 400 mg Week 2: 400 mg Week 4: 400 mg Then every 4 weeks: 400 mg
	Vedolizumab (Entyvio®)	Infusion over 30 min Week 0: 300 mg Week 2: 300 mg Week 6: 300 mg Then every 8 weeks: 300 mg

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

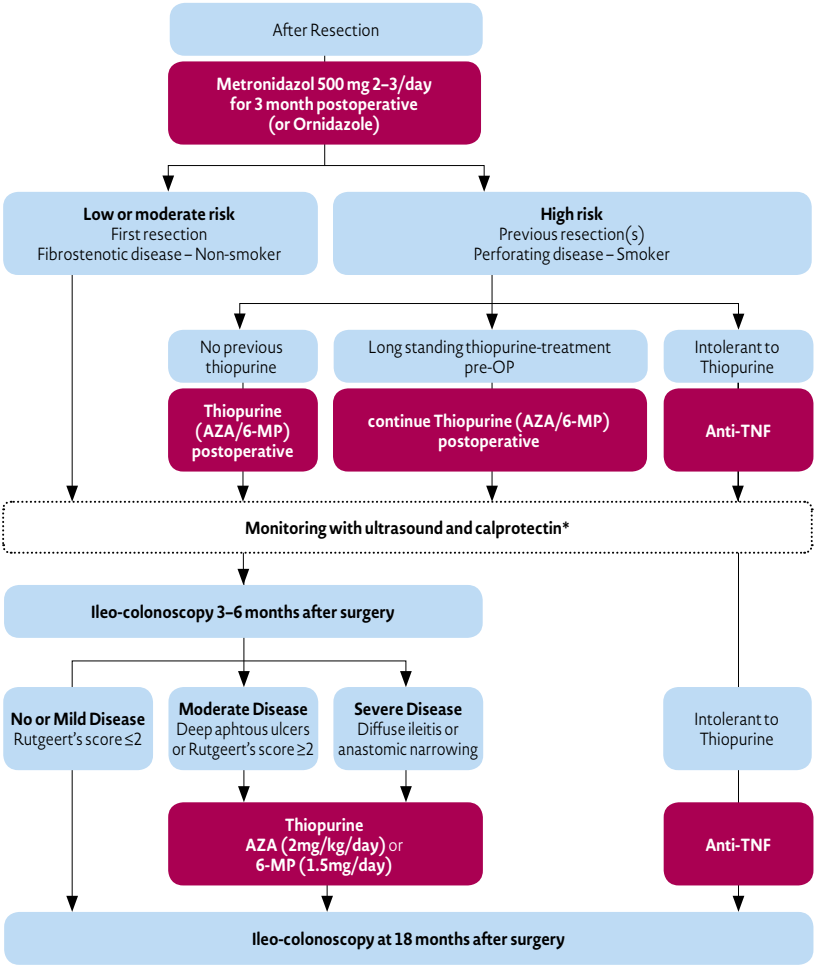
Luminal Crohn's Disease (without Fistula)[1-3,14,15]



* Swiss expert recommendation
# See page "Risk for severe disease progression"
° See page "Target for CD treatment"

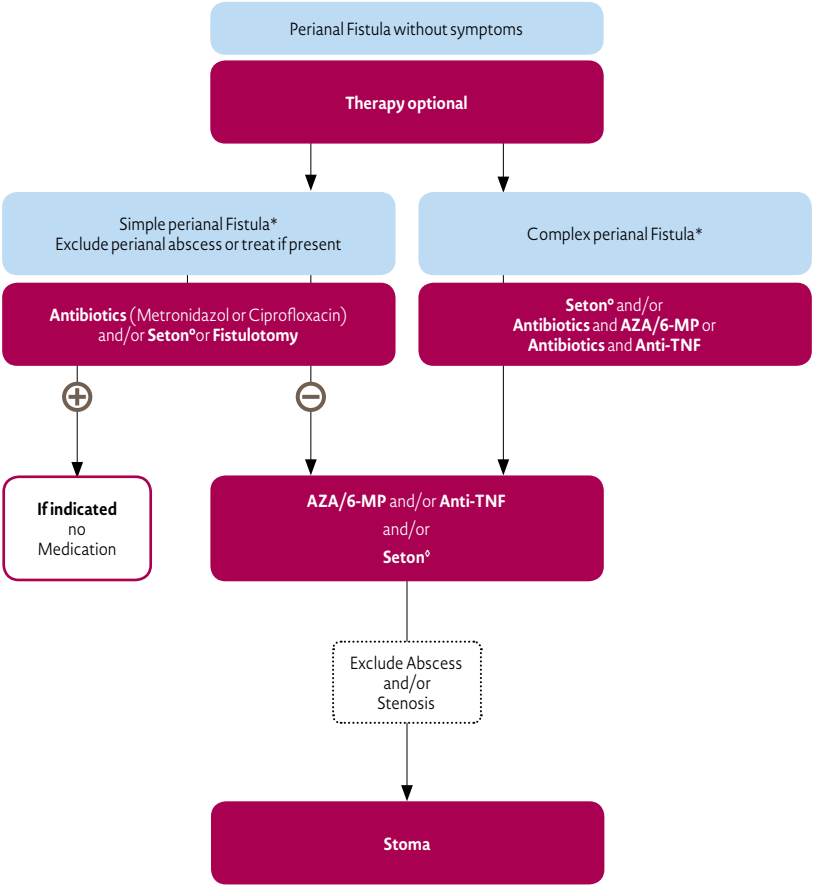
⊕ Response/remission
⊖ No response/no remission

Postoperative Crohn's disease[1-3,16,28,29]



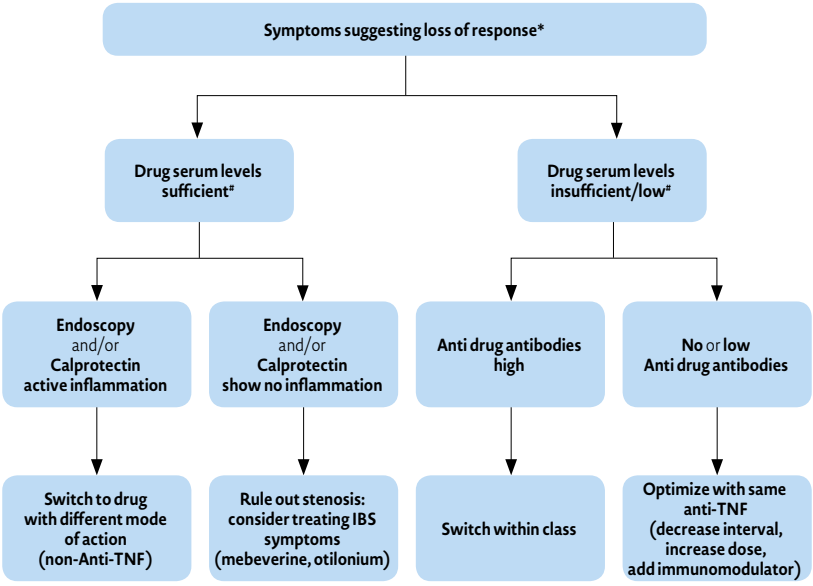
* Swiss expert recommendation

Fistulating disease[1-3]



* **Simple fistulas :** perianal fistula without branching; **complex fistulas :** Perianal branched fistula.
◊ Seton: Non-cutting Seton.

Pharmacokinetics under Biologic treatment[17,18]



* Loss of response
  - Low serum Drug serum levels (just before next infusion / injection)
  - Immunogenicity by neutralizing antibody formation
  - Fibrostentic structures

Range can vary according to used test

Risk for severe disease progression[19]

Prognostic factor	Impact
Young age at diagnosis	• Disabling CD[a] (< 40 years) • Need for surgery • More frequent L4 disease (paediatric patients) • More frequent extensive disease (paediatric patients) • Intestinal failure
Requirement for steroids at diagnosis Complicated behaviour (B2 abd/or B3)[c]	• Disabling CD[a] • Surgery • Hospitalization
Ileal disease (L1)[c] and ileocolonic disease (L3)[c]	• Surgery • Disabling CD[a] • Complicated behaviour • Disease behaviour progression[b] • Time to hospitalization
Colonic CD	• Inflammatory phenotype • Milder course (protective from hospitalization and surgery) • Permanent stoma (distal disease, severe rectal disease, rectal resection)
Upper GI extent (L4)[c]	• Complicated behaviour • Hospitalization • Multiple surgeries
Perianal disease	• Disabling CD[a] • Permanent stoma (refractory perianal disease, anal canal stricture, complex fistulizing disease)
Deep ulcerations at index colonoscopy	• Surgery • Penetrating complications
Smoking	• Complicated CD (disease progression) • Higher therapeutic requirements • Risk for first surgery (conflicting evidence)
Positive antimicrobial markers	• Risk of complicated phenotype and surgery (increasing with higher number of positive antibodies and higher titres)
NOD2 mutations	• Ileal disease • Risk for surgery

Target for CD treatment[20]

- Clinical/ PRO remission, defined as resolution of abdominal pain and diarrhea/altered bowel habit.
- Endoscopic remission, defined as resolution of ulceration at ileocolonoscopy
- Resolution of findings of inflammation on cross-sectional imaging in patients who cannort be adequately assessed with ileocolonoscopy.
- Biomarker remission (normal CRP and Caloprotectin) – optional

a As defined by Beaugerie[21]; **b** B2 and/or B3; **c** According to Vienna and Montreal classifications: location, ileal (L1); colonic (L2); ileocolonic (L3); isolated upper gastrointestinal tract (L4) and behaviour, non-stricturing, non-penetrating (B1); stricturing (B2); penetrating (B3).
PRO = Patient reported outcomes

Screening before Anti-TNF-therapy[5]

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[6]: a. *Clostridium difficile* toxin positive in stools b. CMV infection proven by biopsies c. Parasites in stool d. stool culture to excluce 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)[9]	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[6] 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[8]
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

Monitoring efficacy and safety[7]

	Diagnosis	Monitoring: Symptomatic Disease
Symptoms	• Symptom assessment • HBI/CDAI/IBDQ (establish baseline)	**Each visit:** • Symptom assessment • HBI/CDAI/IBDQ
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	• Ileocolonoscopy with segmental biopsies • Oesophagogastroduodenoscopy • If results inconclusive: Small-bowel capsule endoscopy	• Patients with unclear clinical presentation: • Ileocolonoscopy (confirm disease activity) • If results inconclusive: Small-bowel capsule endoscopy
Imaging	• Ultrasonography • MRI (evaluate involvement of small bowels, detect suspected extraintestinal complications)	• MRI (monitor disease activity) • CT for the detection of suspected complications (bowel obstruction, perforation, toxic colon distention)

	Monitoring: Asymptomatic Disease	Monitoring: Post-Surgery
Symptoms	**Each visit:** • Symptom assessment • HBI/CDAI/IBDQ (verify remission)	**Every 3 months in 1st year, then every 6–12 months:** • Symptom assessment • HBI/CDAI/IBDQ
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)	**Every 3–6 months:** • Routine lab and inflammatory markers • CRP • Faecal calprotectin If needed: Biologic drug serum levels
Endoscopy	**In case of suspected disease progression or 6 months after start of biologics therapy:** • Ileocolonoscopy	**3–6 months after surgery:** • Ileocolonoscopy (detect recurrence) • Further endoscopy dependent on ileocolonoscopy findings
Imaging	**In case of suspected disease progression:** • Ultrasonography • MRI (evaluate involvement of small bowels)	• Ultrasonography (detect recurrence) • 3 months after small bowel resection • Regularly in patients with high risk of recurrence

CDAI = Crohn's Disease Activity Index; **CRP** = C-reactive protein; **CT** = Computer tomography; **HBI** = Harvey-Bradshaw Index; **IBDQ** = Inflammatory Bowel Disease Questionnaire; **MRI** = Magnetic Resonance Imaging

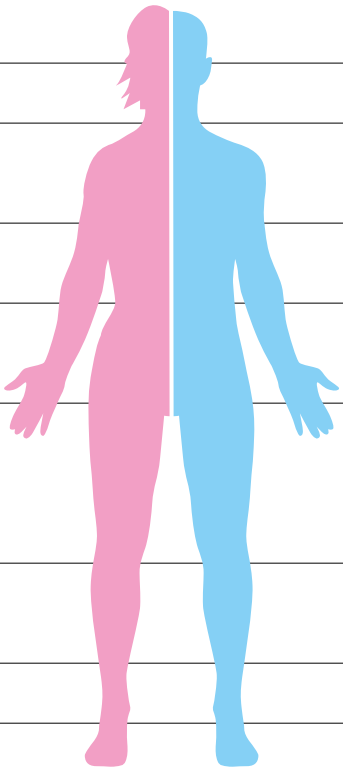
Treatments during pregnancy[13,22-24,30]

Class	Substance	FDA pregnancy category	Use during pregnancy	Use during breast feeding
Cortico-steroids	Budesonide	B	Low risk, likely compatible	Compatible; clinically insignificant concentration found in 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.	Compatible; clinically insignificant concentration found in breast milk Low risk, breastfeeding after 4 h
Antibiotics	Amoxicillin with clavulanic acid	B	Low risk, preferred antibiotic during pregnancy	Compatible, enters breast milk
	Ciprofloxacine	C	Low risk, affinity for cartilage	Compatible, enters breast milk
	Metronidazole	B	Low risk, avoid 1st trimester due to possible risk of orofacial clefts	Contraindicated; enters breat milk
5-ASA	Mesalazine	B	Low risk	Low risk
	Asacol	C	Low risk but contains DBP	Low risk
Immunosuppressives	Azathioprine 6-Mercapto-purine	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.
	Methotrexate	X	Contraindicated: teratogenic, abortifacient Supplement with folic acid. Discontinue 3–6 mo before conception	Contraindicated, enters breast milk
	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.	High molecular weight and low oral availability; absorption by the newborn unlikely. No clinical abnormalities in case reports.
	Certolizumab (Cimzia®)	B	Low risk Does not actively cross placenta	Compatible; clinically insignificant concentration found in breast milk
	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)

Extra-intestinal Manifestations[25-27]

20-40% of patients with Crohn's disease will develop extra-intestinal manifestations[25-27]



Crohn's disease		Ulcerative Colitis
Uveitis	15,7%	10,5%
	23,4%	18,1% Stomatitis / oral ulcer
Psoriasis	2,8%	2,9%
	18,3%	13,3% Ankylosing spondylitis
Primary sclerosing cholangitis	2,0%	18,1%
	74,2%	59,1% Arthritis
Pyoderma gangra enosum	3,6%	8,6%
	12,5%	12,4% Erythema nodosum

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

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