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

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Disclaimer: The treatment algorithms are simplified recommendations, which can not represent each particular patient case. The authors are not liable for any treatment decision, which should always be based on adequate clinical evaluation by the attending physician.
## Dosing of therapies

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

bw = body weight; d = day
Mild to moderate Ulcerative Colitis

Acute flare with no evidence for infectious disease

- Proctitis
  - Rectal 5-ASA: 1 g suppository

- Left-sided colitis
  - Rectal 5-ASA: enema or foam ≥ 2 g

- Extensive colitis
  - Oral 5-ASA ≥ 2 g and rectal 5-ASA ≥ 2 g

Evaluate response after 2 weeks; remission after 4 – 8 weeks°

- Maintenance with rectal 5-ASAa,b
- Rectal steroids
- Maintenance with rectal and/or oral 5-ASAa,b
- Optimize oral 5-ASA dose (up to 4.8 g/d)
- Maintenance with oral +/– rectal 5-ASAa

Add on

- Oral 5-ASA (up to 4.8 g/d)
- Moderate active UC

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”
**Moderate to Severe Active Ulcerative Colitis**

**Predictors for Disease Progression**
- Performance status
- Age
- Number of hospitalizations
- Symptomatic bleeding
- Perforation
- Steroid-refractory UC: active disease despite oral steroids (up to 0.75 mg/kg/d prednisolone) over 4 weeks

**Oral and Topical 5-ASA**
- Maintenance treatment recommended for all patients
- On-demand treatment only possible for patients with mild disease
- E.coli Nissle may be used as alternative for maintenance treatment in case of intolerance to 5-ASA

**Response/Remission**
- No response/no remission
- Evaluate response after 2 weeks; remission after 4 – 8 weeks

**Predictors for Disease Progression**
- Oral steroids alone or consider Budesonide MMX
- Steroid-refractory UC: active disease despite oral steroids (up to 0.75 mg/kg/d prednisolone) over 4 weeks

**Oral Steroids**
- Evaluate response after 2 weeks; remission after 4 – 8 weeks

**Steroid-dependent UC:**
- Fail to taper steroids within 16 weeks
- Relapse within 12 weeks after steroids stop

**Anti-TNF**
- Consider anti-TNF if EIM or faster effect required
- Assess response after initiation

**Anti-Integrin**
- Assess response after 2 weeks; remission after 4 – 8 weeks

**Maintenance with Oral and/or Rectal 5-ASA**
- 1) Optimize by dose escalation
- 2) Evaluate combination + AZA/6-MP
- 3) Change to other biologic
- Re-Evaluate response every 12 weeks; Consider Pharmacokinetic

**AZA/6-MP**
- Assess response after 2 weeks; Remission after 4 – 8 weeks

**Maintenance with AZA/6-MP**
- Consider anti-TNF if EIM or faster effect required

**Response/Remission**
- Response/remission
- No response/no remission

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*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"
Consider drug level testing to guide dose increases or modifications

- Data for hospitalized patients only available for Infliximab.
- Exclude low Mg/Cholesterol.
- 3rd line immunosuppressive therapy restricted to specialized centers

bw = body weight; d = day

**Hospital admission in case of**: bloody diarrhea ≥ 6/day and one or more signs of systemic toxicity:
- tachycardia > 90 bpm
- fever > 37.8 °C
- Hb < 10.5 g/dl
- ESR > 30 mm/h
- CRP > 30 mg/l

Exclude infection

**i.v. corticosteroids**

Methylprednisolone 0.5 – 1 mg/kg bw/24 h

Assess response after 3 days
Discuss treatment options including colectomy

Switch to oral steroids and taper

AZA naive

Prior AZA failure

AZA/6-MP

Anti-TNF

Anti-TNF

Ciclosporine or Tacrolimus

Assess response after 4 – 7 days

Choice of specific 2nd line treatment depends on clinical setting

- AZA naive
- Prior AZA failure

AZA/6-MP

Anti-TNF

Anti-TNF

Ciclosporine or Tacrolimus

3rd line immunosuppressive therapy or colectomy

**Response/remission**

**No response/no remission**
Suspicious symptoms are increased stool frequency and consistency, cramping, tenesmus, incontinence and urgency
Bleeding, fever, and EIM are rarer presenting symptoms
Pouchitis more likely with:
- Extensive UC
- EIM especially PSC
- Non-smokers (smoking increases risk of Crohn's disease of the pouch)
- P-ANCA positivity
- NSAIDs
- Backwash ileitis
- Previous colonic dysplasia

Exclude infection

Ciprofloxacin 1 g/d for 2 weeks or Metronidazole 20 mg/kg/d for 2 weeks 2nd line therapy
Budesonide enemas (2 mg/100 ml)
VSL#3 (6 g/d)

Assess response after 4 weeks

If indicated
no Medication

Combination antibiotics or budesonide

Anti-TNF

Alternative agents

Response/remission
No response/no remission

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
## Risk for severe disease progression

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

### Target for UC treatment

- 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

## Diagnosis Monitoring: Symptomatic Disease

- **Symptom assessment**
- **Mayo score/IBDQ/CAI** (establish baseline)

### Laboratory
- Routine lab and inflammatory markers (blood count, liver profile, albumin, iron studies, renal function, Vitamins B12 + D, folic acid)
- **CRP**
- **Faecal calprotectin**

### Endoscopy
- Rectoscopy with segmental biopsies
- If inconclusive: Colonoscopy

### Imaging
- Ultrasonography

## Monitoring: Symptomatic Disease

### Each visit:
- **Symptom assessment**
- **Mayo score/IBDQ/CAI**

### Laboratory
- **CRP**
- **Faecal calprotectin**
- **Faecal cultures and rule out C. difficile toxins in stool**
- If needed: Biologic drug serum levels

### Endoscopy
- Patients with unclear clinical presentation:
  - Rectoscopy (confirm disease activity)
  - If inconclusive: Colonoscopy

### Imaging
- **CT** for the detection of suspected complications (bowel obstruction, perforation, toxic colon distention)

## Monitoring: Asymptomatic Disease

### Each visit:
- **Symptom assessment**
- **Mayo score/IBDQ/CAI** (verify remission)

### Laboratory
- **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

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CAI = Clinical Activity Index; CRP = C-reactive protein; CT = Computer tomography; IBDQ = Inflammatory Bowel Disease Questionnaire; MRI = Magnetic Resonance Imaging
## Contraindications or warnings for Anti-TNF-therapy with respect to findings during screening before treatment.

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>If yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Serious infection (incl. active TB) or sepsis&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Contraindicated&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
| 2. In case of flare<sup>8</sup>:  
  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)<sup>8</sup> | 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<sup>8</sup> |
| 7. HIV-positive, uncontrolled disease | Contraindicated |
| 8. Positive HBV serology<sup>9</sup>  
  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<sup>10</sup> |
| 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**

<table>
<thead>
<tr>
<th>Proctitis</th>
<th>Left-sided/extensive colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>No evidence of previous or current endoscopic and/or microscopic inflammation proximal to the rectum: surveillance nationally recommended colon cancer screening</td>
<td>Determine risk profile 6–8 years after first manifestation. Chromoendoscopy should be performed for surveillance if available (ECCO statement 13G)</td>
</tr>
</tbody>
</table>

- 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.\(^{20,23}\)

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

**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

**Symptoms suggesting loss of response**

- **Drug serum levels sufficient**
  - Endoscopy and/or calprotectin show active inflammation
  - Switch to drug with different mode of action (non-Anti-TNF)
- **Drug serum levels insufficient/low**
  - Endoscopy and/or calprotectin show no inflammation
  - Roule out stenosis: consider treating IBS symptoms (mebeverine, otilonium)
  - Anti drug antibodies high
  - No or low Anti drug antibodies

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

# Range can vary according to used test

**References:**
40. www.swissmedicinfo.ch.