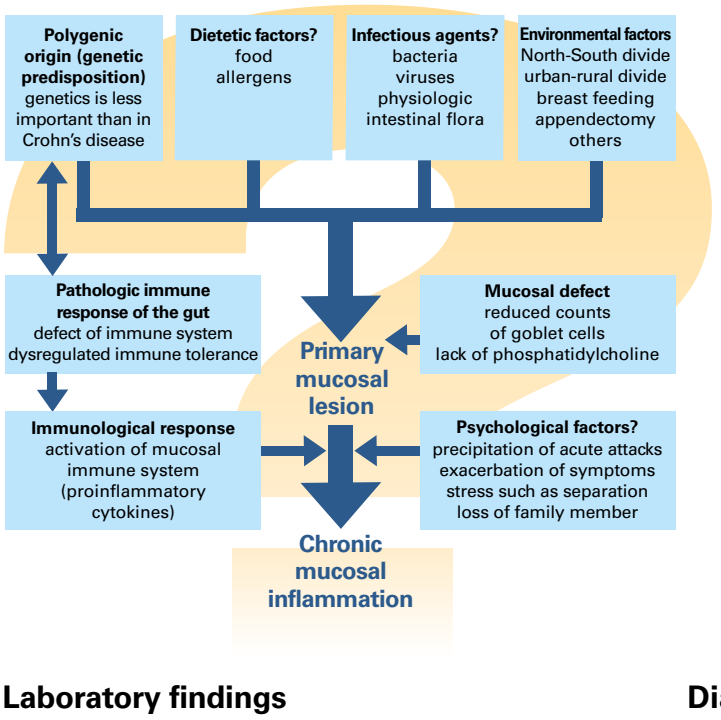
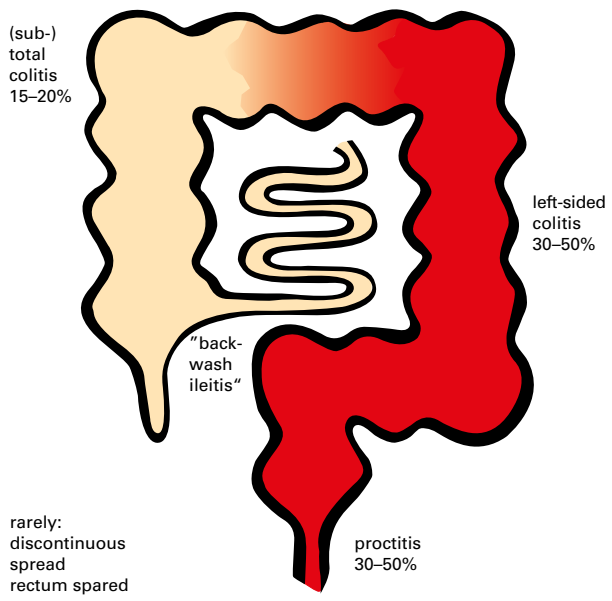
Ulcerative Colitis

Epidemiology – Etiopathology – Clinical features – Diagnosis – Therapy

Aspects of etiopathology



Localization of ulcerative colitis at time of diagnosis



Epidemiology (Europe)

Incidence (new cases):
up to 24 cases/100,000 inhabitants per year

Prevalence (patients):
up to 500 cases/100,000 inhabitants

Clinical features

Acute attacks alternate with asymptomatic intervals;
chronically active course (> 2 relapses/year,
incomplete remission despite adequate treatment)

1. Intestinal symptoms:
diarrhea with macroscopic visible blood and mucus
abdominal pain, possibly tenesmus
tenderness, abdominal pain caused by palpation, most often in the left lower abdomen

2. Extraintestinal symptoms:
anemia, fever
weight loss, feeling of illness
arthritis, sacroiliitis
erythema nodosum, pyoderma gangraenosum
eye symptoms

3. Concomitant diseases:
primary sclerosing cholangitis
amyloidosis, liver diseases
association with ankylosing spondylitis
osteoporosis (rare)

Laboratory findings

1. Disease activity:
ESR after Westergren ↑
leukocytes ↑
hemoglobin ↓
total protein ↓, electrophoresis
acute-phase proteins ↑
C-reactive protein ↑
calprotectin in stool ↑

2. Deficiencies:
albumin ↓
hemoglobin ↓, reticulocytes
iron ↓, ferritin ↓, (transferrin ↑)
electrolytes

3. Exclusion of infectious causes:
direct verification of pathogens in stool, including parasites

fecal verification of Clostridium difficile as well as Clostridium toxins A + B

exclusion of cytomegalovirus (smear test, mucosal biopsy)
by antigen analysis or PCR

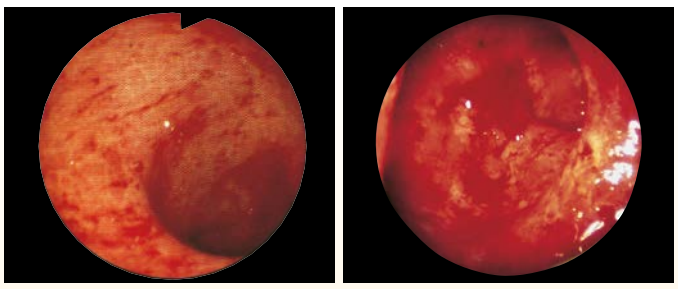
serologic pathogen verification

4. Detection of pANCA in the absence of ASCA to differentiate from Crohn's disease

Differential diagnosis

- colitis caused by infectious agents: Salmonella, Shigella, Campylobacter jejuni/coli, Yersinia, Amoeba, Chlamydia
- pseudomembranous colitis (Clostridium difficile)
- **Crohn's disease of the colon**
- ischemic colitis, radiation colitis, microscopic colitis
- drug-induced colitis/proctitis
- colon carcinoma
- eosinophilic colitis
- diverticulitis

Diagnosis

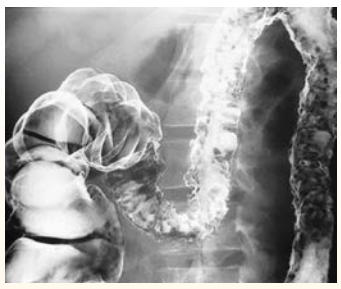


Endoscopy combined with stepped biopsies (determination of extent, exclusion of "microscopic colitis", correlation with disease activity)

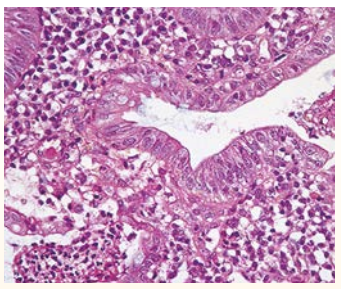
active stage
- reddening
- loss of mucosal vascularity
- mucosal granularity
- contact susceptibility, petechiae, hemorrhage, mucus, pus
- flat, confluent, shallow mucosal ulcers
- pseudopolyps (inflammatory, non-neoplastic)
- most common continuous circumferential involvement, spread extending proximally, occasionally discontinuous extent with or without affecting the rectum, "back-wash ileitis"

inactive stage
- pale, atrophic mucosa with sporadic pseudopolyps
- endoscopic surveillance with stepped biopsies

Sonography
- extent of disease
- detection of complications
- follow up



Radiology (not for routine examination, but to answer defined questions: acute abdomen?, stenosis of the colon?)
- granulated mucosa, spiculae
- ulcers, collar-button ulcers
- pseudopolyps
- loss of haustral pattern
- massive distention of the colon (toxic megacolon)
- ERC, MRC (bile ducts?)
- CT-, MR-colonography

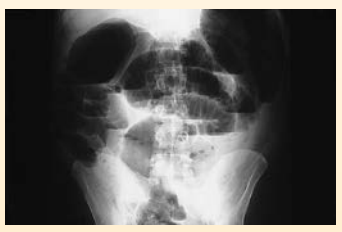


Histology
- continuous polymorphonuclear infiltration, limited to mucosa
- crypt abscesses
- reduction of goblet cells

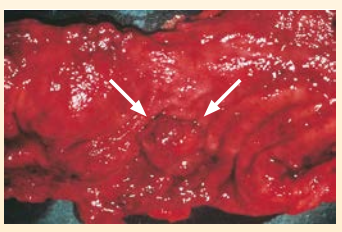
Severity of the attack

Truelove-Witts classification and endoscopic image:

Mild attack	≤ 4 diarrhea/day, small amounts of blood and mucus, no fever, no tachycardia, anemia not severe, little feeling of illness
Moderate attack	5–8 bloody, mucous diarrhea/day, fever (< 38°C, 100°F), feeling of illness
Severe attack (fulminant attack)	> 8 bloody diarrhea/day, fever (> 38°C, 100°F), tachycardia, anemia (hemoglobin < 10.5 g %), patient is in a very bad condition



Complication
Toxic megacolon
in ulcerative pancolitis



Complication
Resected specimen
of a colitis carcinoma

Medical therapy for induction of remission

Mild attack:
mesalazine (5-ASA) 3 g/day (as colon-release formulation, combined pH-dependent coating and sustained release from core matrix) **or**
olsalazine 3–4 x 0.5 g/day **or**
sulfasalazine 3–4 x 1 g/day

If treatment with mesalazine is not sufficient: Budesonide MMX 9 mg/day
Alternative and/or combined local therapy if affecting the rectum, distal colon or pancolitis:
Proctitis: mesalazine (5-ASA) or sulfasalazine suppositories or mesalazine and/or corticosteroid rectal foam
Left-sided colitis: mesalazine (5-ASA) or sulfasalazine enemas and/or budesonide rectal foam (2 mg) or corticosteroid enemas

Moderate attack:
Treatment: see mild attack, plus
oral **prednisone** 40–60 mg daily, with weekly reduction of the daily dose for 10 mg and later on for 5 mg according to clinical improvement
(without budesonide or steroid enemas and rectal foam)

Severe attack:
prednisone 100 mg/day initially or higher dosage, possibly at night, if necessary intravenously; dosage dependent on clinical features and response
(mesalazine or olsalazine or sulfasalazine orally if oral uptake of granules or tablets is possible)

Moderate to severe attack with steroid-dependent or therapy-refractory course:
TNF-α-antibodies: infliximab 5 mg/kg body weight, i.v. at weeks 0, 2, and 6, for maintenance of remission 5 mg/kg body weight i.v. every 8 weeks
(infliximab biosimilars accordingly) **or**
adalimumab 160 mg s.c. at week 0, 80 mg s.c. at week 2, for maintenance of remission 40 mg s.c. every 2 weeks **or**
golimumab 200 mg s.c. at week 0, 100 mg s.c. at week 2, for maintenance of remission 50 mg (≥ 80 kg body weight: 100 mg) s.c. every 4 weeks **or**

$\alpha_4\beta_7$-integrin-antibodies: vedolizumab 300 mg i.v. at weeks 0, 2 and 6, for maintenance of remission 300 mg i.v. every 8 weeks

Cave: Possible long-term risks not yet fully known! Before initiation of therapy with biologics: exclusion of TBC / latent TBC (chest x-ray, Interferon-gamma release assay); Hepatitis B, C; HIV, EBV; severe infections, abscesses, severe heart failure, neurological disorders

cyclosporine A 2–4 mg/kg body weight/day, continuous infusion for 24 h during 1 week or orally **or**

tacrolimus 0.01 mg/kg body weight/day, i.v. or 0.1–0.2 mg/kg body weight/day orally

Cave: monitoring of serum levels during therapy with cyclosporine or tacrolimus

Prior starting immunosuppressive therapy with biologics/antibodies or cyclosporine, reconsider the possibility of surgical intervention in ulcerative colitis (curative colectomy and ileo-anal pouch anastomosis) to avoid drug side-effects

Supplementation of electrolytes, albumin, blood transfusions, coagulation factors, intensive care, (total parenteral nutrition)

In septic-toxic situations, if necessary antibiotics with special regard to anaerobes, i.e. ciprofloxacin, imipenem, and others

Chronically active ulcerative colitis and maintenance of remission:
azathioprine 1.5–2.5 mg/kg body weight/day (effective after 3–6 months, first in combination with acute-phase therapy, check EBV serostatus before starting treatment)
- in "steroid-dependent" or "steroid-refractory" course of disease
- in severe courses
- follow-up after cyclosporine, tacrolimus or anti-TNF-α–antibody treatment

In case of gastrointestinal intolerance, alternatively **6-mercaptopurine** 1–1.5 mg/kg body weight/day may be used

TNF-α-antibodies and $\alpha_4\beta_7$-integrin-antibodies: In the respective dosage for maintenance of remission (see above)

Therapy during remission

- mesalazine (5-ASA, 1.5–2 g/day orally) as colon-release formulation or olsalazine 2 x 0.5 g/day or sulfasalazine 2 x 1–1.5 g/day (suppositories, foam, and enemas also effective in proctitis/left-sided colitis)
- prophylaxis of carcinoma with salicylates (1–1.5 g/day)
- biologics: see induction therapy
- probiotics, i.e. non-pathogenic E. coli Nissle
- fiber-rich, wholesome diet
- supplementing of deficiencies, most of all iron
- antidiarrheal agents (codeine, lomotil, loperamide)

Complications in the course of ulcerative colitis:
perforation
toxic megacolon (2–13%), sometimes with perforation
massive bleeding from the colon

resistance to drug treatment with
- severe impairment of the patient
- septic-toxic situation
- severe extraintestinal symptoms

development of colon carcinoma, risk factors:
- ulcerative colitis > 10 years
- extensive involvement of the colon
- proof of dysplasia (intraepithelial neoplasia)
- primary sclerosing cholangitis
- younger than 18 years of age at first diagnosis

Annual surveillance colonoscopy with stepped biopsies for patients with these risk factors

Surgical therapy (interdisciplinary cooperation)

Proctocolectomy with rectal mucosectomy, ileoanal anastomosis and construction of a pelvic enteric pouch

For particular situations: proctocolectomy with permanent ileostomy
if possible, continent ileostomy with ileal loop reservoir (Kock)
colectomy and deep ileo-rectal anastomosis –
need for lifelong endoscopic surveillance (carcinoma)

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