REVIEW ARTICLE

The Diagnosis and Treatment of Crohn's Disease and Ulcerative Colitis

Daniel C. Baumgart

SUMMARY

Introduction: Crohn's disease and ulcerative colitis are chronic inflammatory diseases resulting from an inappropriate immune response, in genetically susceptible individuals, to microbial antigens of commensal microorganisms. This inappropriate response is promoted by certain environmental factors. Both diseases manifest themselves primarily in the gastrointestinal tract yet can, in principle, affect all of the organ systems of the body. The purpose of this review article is to heighten awareness of these diseases among physicians whose primary clinical activities lie outside gastroenterology.

Methods: This is not a systematic review nor a meta-analysis. It is mainly based on the guidelines of national (DGVS and DATED) and international (AGA, ACG, BSG, CCFA, ECCO) specialist societies and expert groups, as well as on important reviews and a limited number of pivotal randomized, double-blind, controlled, multicenter studies.

Results: More than 300 000 people in Germany suffer from chronic inflammatory bowel diseases. The incidence and prevalence of IBD have risen in the past 10 years, particularly for Crohn's disease. Every fifth IBD patient is a child or adolescent. A better understanding of key events in the inflammatory cascade, e.g., the activation and polarization of T cells by TNF-alpha, IFN-gamma and IL-12/18 through dendritic cells, has led in recent years to the development of many new immune-modulating and biological treatments. Advanced endoscopic techniques and contrast-enhanced tomographic imaging techniques have expanded diagnostic capabilities.

Conclusion: A cure is still not possible, yet the opportunities for diagnosis and treatment have improved significantly. Early diagnosis is important so that patients can be referred onward for further diagnostic evaluation and appropriate treatment without delay.

Dtsch Arztebl Int 2009; 106(8): 123–33
DOI: 10.3238/arztebl.2009.0123

Key words: Crohn's disease, ulcerative colitis, diagnosis, treatment, chronic disease

Crohn's disease and ulcerative colitis are the two main forms of chronic inflammatory bowel disease. The clinical features, diagnostic assessment, and treatment of these diseases are the topic of this review article (1, 2). Their complex epidemiology, pathogenesis, and pathophysiology are extensively discussed elsewhere (2, 3).

Very important factors in the epidemiology of these diseases include the following:

- Ethnic origin
- The presence of susceptibility regions on at least 12 chromosomes
- Geographical factors
- Lifestyle.

These factors can contribute singly or in combination to the occurrence of the disease. In summary, chronic inflammatory bowel diseases result from an inappropriate innate and acquired immune response to commensal microorganisms in genetically susceptible individuals.

Crohn's disease is a transmural inflammatory disease of the mucosa with episodic progression. It can affect every part of the gastrointestinal (GI) tract from the mouth to the anus. Typical manifestations include discontinuous involvement of different segments of the GI tract (L1–L4) and the development of complications such as strictures, abscesses, and fistulae (B1–B3p) (4–6). The Montreal classification also takes the age at initial diagnosis into account (A1–A3) (*box*).

Ulcerative colitis is a nontransmural inflammatory disease with episodic progression that is restricted to the colon. Depending on the part of the colon that is involved, it can be designated according to the Montreal classification as proctitis (E1), left colitis (sigmoid and descending colon) (E2), or extensive colitis (pancolitis) (E3). In a few patients, inflammation of the terminal ileum ("backwash ileitis") can also develop, making it difficult to distinguish this form of ulcerative colitis from Crohn's ileocolitis (5, 7, 8) (*box*).

Methods

This article is neither a systematic review nor a meta-analysis. Excellent meta-analyses are already available, e.g., in the library of the Cochrane Collaboration (www.cochrane.org/reviews/eu/topics/73.html). Rather, it is intended as a general, practice-oriented overview of the diagnosis and treatment of Crohn's disease and ulcerative colitis. The guidelines of national (DGVS,

Medizinische Klinik mit Schwerpunkt Gastroenterologie und Hepatologie, Charité, Campus Virchow Klinikum, Medizinische Fakultät der Humboldt Universität zu Berlin: PD Dr. med. Baumgart

BOX

Montreal classification of Crohn's disease and ulcerative colitis (5)

Crohn's disease

- A1 < 16 years old at diagnosis
- A2 17 to 40 years old at diagnosis
- A3 > 40 years old at diagnosis
- L1 terminal ileum
- L2 colon
- L3 ileocolon
- L4 upper GI tract
- L4+ lower GI tract and distal disease
- B1 without stricture formation, nonpenetrating
- B2 with stricture formation
- B3 internally penetrating
- B3p perianally penetrating

Ulcerative colitis

- E1 proctitis
- E2 left colitis
- E3 pancolitis

DACED) and international (AGA, ACG, BSG, CCFA, ECCO) specialist societies and expert groups are emphasized, and important review articles are cited, along with only a few pivotal randomized, double-blind, multicenter studies. Recent international guidelines are given priority over national consensus statements in order to give the reader the most up-to-date information possible.

Therapeutic recommendations are based mainly on the ECCO Consensus (ECCO = European Crohn's and Colitis Association) and the guidelines of the German Society for Digestive and Metabolic Diseases (Deutsche Gesellschaft für Verdauungs- und Stoffwechselkrankheiten, DGVS), which are discussed in the context of the author's own clinical experience and practice. The evidence levels (EL) and recommendation grades (RG) given here are based on the categories of the Oxford Centers for Evidence-Based Medicine (www.cebm.net/levels_of_evidence.asp#refs); thus, 1 is the highest level of evidence and A is the strongest recommendation grade. In the DGVS guidelines, the recommendation grade is given as A, B, C, or D.

Clinical features

The clinical features of the disease depend on its localization (*box*) and often include diarrhea, abdominal pain, fever, clinical signs of subileus or ileus, and/or the passage of blood and mucus per rectum. Patients with Crohn's disease often do not have bloody diarrhea, but rather abdominal pain or nonspecific abdominal symptoms. Patients with left colitis or ulcerative proctitis generally have a milder disease course (*box*, *table 1*).

Extra-intestinal manifestations

Patients with Crohn's disease and ulcerative colitis can develop extra-intestinal manifestations (*table 2*). The most common types affect the musculoskeletal system (*figure 1*), the skin (*figure 2*), the eyes, and the hepatobiliary system (9, 10). These extra-intestinal manifestations are to be distinguished from the so-called associated autoimmune diseases (*table 2*).

The occurrence and severity of extra-intestinal manifestations may be independent of the clinical course of the underlying illness, i.e., some patients may present with an extra-intestinal manifestation as their first symptom of the disease while they still have only mild gastrointestinal manifestations, or none at all. In such situations, the clinician should always look for evidence of Crohn's disease or ulcerative colitis. In case optimizing the pharmacological treatment of the underlying gastrointestinal disease fails to improve the extra-intestinal manifestations, these may need to be treated with expert consultation in the medical specialties dealing specifically with the affected organs.

Diagnosis and assessment of disease activity

The diagnoses of Crohn's disease and ulcerative colitis are made on clinical grounds supplemented with objective findings of radiological, endoscopic, and histological examination. In some cases, the diagnostic evaluation must be repeated after a certain period of time has passed. There is no gold standard for diagnosis (ECCO EL5, RG5, DGVS D) (4–7). When establishing the diagnosis, one must exclude other inflammatory, toxic, vascular, neoplastic, and infectious etiologies of enteritis and/or colitis (11) (*tables 1 and 3*).

Ulcerative colitis—According to the ECCO Consensus and the Montreal classification, the degree of activity of ulcerative colitis can be classified as follows (4):

- Mild (S1) (up to 4 stools per day, possibly bloody; pulse, temperature, hemoglobin concentration, and erythrocyte sedimentation rate [ESR] normal)
- Moderate (S2) (4 to 6 bloody stools daily and no signs of systemic involvement)
- Severe (S3) (more than 6 bloody stools daily and signs of systemic involvement, such as temperature above 37.5°C, heart rate above 90/min, hemoglobin concentration below 10.5 g/dL, or ESR above 30 mm/h).

A patient in clinical remission (S0) should have no more than 3 stools per day without any admixture of blood or increased urgency of defecation (5).

Crohn's disease—The degree of activity of Crohn's disease is classified as follows, according to the ECCO Consensus (4):

- Mild (the patient is able to walk and can tolerate oral nutrition; there are no signs of dehydration, systemic involvement, abdominal pain or mass, ileus, or loss of more than 10% of body weight; the C-reactive protein [CRP] is usually elevated)
- Moderate (the patient suffers from intermittent vomiting, loss of more than 10% of body weight, lack of response to drug therapy for mild Crohn's

TABLE 1

Differential diagnosis of ulcerative colitis and Crohn's disease (1)

	Ulcerative colitis	Crohn's disease
Epidemiology		
Sex ratio (M:F)	1:1	2:1
Nicotine	Can prevent disease*	Precipitates disease & episodes
Genetic components	Yes, but less than in Crohn's disease	Yes
Clinical manifestations		
Hematochezia	Common	Rare
Blood and mucus per rectum	Common	Rare
Small bowel involvement	No (except in "backwash ileitis")	Yes
Upper GI tract involvement	No	Yes
Abdominal mass	Rare	Sometimes in the right lower quadrant
Extra-intestinal manifestations	Common	Common
Small bowel ileus	Rare	Common
Colonic obstruction	Rare	Common
Perianal fistulae	No	Common
Biochemical findings		
ANCA-positive	Common	Rare
ASCA-positive	Rare	Common
Histopathology		
Transmural mucosal inflammation	No	Yes
Abnormal crypt architecture	Yes	Unusual
Cryptitis and crypt abscesses	Yes	Yes
Granulomata	No	Yes, but rare in mucosal biopsies of the bowel
Fissures or so-called skip lesions	Rare	Common

* But not in the pharmacological sense; therapeutic studies negative.
GI, gastrointestinal; ANCA, anti-neutrophilic cytoplasmic antibodies; ASCA, anti-Saccharomyces cerevisiae antibodies.

TABLE 2

Common extra-intestinal manifestations and associated autoimmune diseases (9, 10)

Extra-intestinal manifestations	Associated autoimmune diseases
Musculoskeletal manifestations	
– peripheral arthritis	Addison's disease
(type I: pauciarticular arthritis)	Autoimmune hemolytic anemia
(type II: polyarthritis)	Idiopathic thrombocytopenic purpura (ITP)
– axial arthropathies	Myasthenia gravis
(ankylosing spondylitis/Bekhterev's disease with sacroiliitis/enthesitis)	Multiple sclerosis
Dermatological manifestations	
– pyoderma gangrenosum	Systemic lupus erythematosus
– erythema nodosum	Psoriasis
Ocular manifestations	
– anterior/posterior uveitis	Celiac sprue
– episcleritis/scleritis	Polymyalgia rheumatica
Hepatobiliary manifestations	
– primary sclerosing cholangitis (PSC)	Asthma
– autoimmune hepatitis (AIH)	Thyroiditis
– overlap syndrome/autoimmune cholangitis	Autoimmune pancreatitis
	Pericarditis
	Nephritis
	Bronchitis
	Diabetes mellitus type I

Figure 1:

MRI of the pelvis: severe erosions of the sacroiliac joint in sacroiliitis as an extra-intestinal manifestation (axial arthropathy) in a patient with Crohn's disease

Figure 2: Pyoderma gangrenosum as an extraintestinal manifestation in a patient with ulcerative colitis

disease, or a painful mass; there is no ileus, and the CRP is elevated)

- Severe (the patient is cachectic with a body-mass index [BMI] under 18 or else has ileus, an abscess, or persistent symptoms despite intensive treatment; the CRP is elevated).

Clinical remission is said to be present if the patient is asymptomatic and has no sign of active inflammation. This includes patients who have responded to pharmacological or surgical treatment without any residual evidence of disease activity.

In clinical studies, the degree of activity of the disease can be quantified with the aid of a number of different indices, which, however, play no role in everyday clinical practice (DGVS B) (12, 13). As no index, taken alone, can provide a complete picture of the disease, data obtained in clinical studies are often difficult to interpret. A basic diagnostic algorithm derived from our own outpatient practice in a university medical center is summarized in *table 3*.

Treatment with pharmacological agents

Goals

The goals of treatment for both varieties of chronic inflammatory bowel disease are the rapid induction of a steroid-free remission and the prevention of complications of the disease itself and its treatment. As a rule, the treatment is chosen on the basis of the extent and degree of severity of the disease, its responsiveness to previous treatments, and the individual patient situation (*tables 4 and 5*).

Duration and choice of treatment

Long-term treatment to maintain the patient in a state of remission should be provided to all patients with Crohn's disease (no applicable ECCO Consensus statement) and ulcerative colitis (ECCO EL 1a, RG A).

With respect to the choice of drugs and the timing of their use, some of the professional societies favor a stratified approach. The usefulness of a "treatment pyramid" of this type is currently debated, because there is evidence from other specialties that the early administration of highly potent drugs such as anti-TNF biological agents may prevent late complications. On the other hand, treatment with immune modulators and biologics confers a cumulative risk of infections, lymphoma, and other types of malignancy, particularly in adolescents (14). It remains to be seen whether early, aggressive treatment can be applied successfully in this area of gastroenterology (15).

There is also a lack of consensus with respect to the optimal duration of treatment and to certain types of combination therapy. For the purine analogs, for example, some professional societies recommend temporary cessation of treatment under certain conditions after 2 years of remission and a total of 4 years of treatment (DGVS), while the author and other experts recommend continued treatment.

Still greater uncertainty besets the newer types of biological therapy, because scientific data are lacking to date. Most experts would agree that treatment with TNF-blockers should be continued only if the patient has shown a response after the first two doses (i.e., induction). It is also clear that episodic therapy—in distinction to regular, uninterrupted treatment—is associated with a less favorable disease course and a higher risk of adverse effects (immunization, allergic reactions). It remains unclear, however, when biological therapy should be stopped. Most clinical trials were performed for no more than 52 weeks and therefore are of no help in answering this question. At present, long-term data are being gathered in treatment registries, so that well-founded conclusions on this subject ought to be possible in the future.

Crohn's disease

All patients with Crohn's disease should be urged not to smoke, because smoking predisposes to exacerbations and complications (ECCO EL 1b, RG B, DGVS A).

TABLE 3

Basic diagnostic evaluation for patients with suspected ulcerative colitis or Crohn's disease as performed in the author's university hospital outpatient practice.* The evidence levels and recommendation grades given are those of the ECCO Consensus (4, 7).

Directed diagnostic technique	Ulcerative colitis	Evidence level and recommendation grade	Crohn's disease	Evidence level and recommendation grade
History Onset of manifestations, blood/mucus in stool, tenesmus, fecal incontinence, nocturnal diarrhea, travel and dietary history, bowel infections, use of NSAID, cigarette smoking, family history of CD or UC, appendectomy status	Yes	EL 5, RG D	Yes	EL 5, RG D
Current findings Pulse, BP, temperature, weight, height, BMI, abdomen, inspection of the perineum, digital rectal examination, examination for extra-intestinal manifestations (eyes, skin, joints, muscles)	Yes	EL 5, RG D	Yes	EL 5, RG D
Laboratory tests Electrolytes, urea, creatinine, complete blood count, ESR, liver enzymes, bilirubin, alkaline phosphatase, transferrin, ferritin, vitamin B12, folic acid, CRP, urinalysis	Yes	EL 5, RG D except for CRP and ESR	Yes	EL 5, RG D except for CRP, EL 2 RG B
Stool tests Stool testing for bacterial organisms and resistance, C. difficile, lactoferrin or calprotectin	Yes	C. diff. EL 4, RG C Calprotectin EL 2b, RG B	Yes	EL 5, RG D except for C. diff. EL 2, RG B
Endoscopy EGD with biopsies Colonoscopy with ileoscopy and stepwise biopsy	No Yes	 EL 5, RG D	Yes, if symptomatic Yes	EL 5, RG A EL 1b, RG A
Imaging studies Ultrasound of the abdomen and bowel Extended small bowel diagnostic testing (conventional or CT/MR-Sellink) Search for extra-intestinal complications (US, CT, MRI) Search for fistulae or abscesses (US, CT, MRI) Capsule endoscopy (WCE) Virtual colography MRCP ERC(P) with balloon dilatation	Yes No Yes, if suspected No No If PSC is suspected If PSC is present with dominant strictures	EL 3, RG C EL 2b, RG B EL 4, RG C	Yes Yes Yes, if suspected Yes, if suspected Yes, if terminal ileum normal or not visualizable, or if other imaging studies are negative No If PSC is suspected If PSC is present with dominant strictures	EL 1a, RG A EL 1b, RG A EL 1c, RG A EL 1c, RG A EL 2, RG B EL 2a, RG B
Consultation or collaborative treatment with other medical specialties Surgery, rheumatology, dermatology, ophthalmology, gynecology, urology	When indicated		When indicated	

*There is no gold standard for diagnostic testing (ECCO, EL 5, RG D). This list is intended as an orientation for the reader and no claim of completeness is made. For certain patterns of disease involvement, in the presence of complications, or before certain types of treatment, other diagnostic techniques can and should be used.

ECCO, European Crohn's and Colitis Organization; NSAID, non-steroidal anti-inflammatory drug;

CD, Crohn's disease; UC, ulcerative colitis; BP, blood pressure;

BMI, body-mass index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; C. diff., Clostridium difficile;

EGD, esophagogastroduodenoscopy; US, ultrasonography; CT, computerized tomography; MRI, magnetic resonance imaging;

WCE, wireless capsule endoscopy; MRCP, magnetic resonance cholangiopancreatography;

ERC(P), endoscopic retrograde cholangio(pancreatic)graphy; PSC, primary sclerosing cholangitis

Mild and moderate Crohn's disease restricted to the ileum and cecum

In mild Crohn's disease restricted to the ileum and cecum, induction therapy with budesonide can be started (ECCO EL 2a, RG B, DGVS A). Budesonide interferes with bone metabolism less than conventional steroids. Its protracted use, however, impairs the hypothalamic-pituitary regulation of glucocorticoid metabolism. This and the fact that budesonide was found to be unable to sustain remission for more than 6 months in controlled studies limit its utility to the induction of remission.

Most of the studies of mesalazine that have been performed with adequate scientific methodology have shown this agent to be ineffective for the induction of remissions (DGVS A). Because some controversy on this topic remains, the ECCO Consensus formulated a statement that it possesses "limited effectiveness" (ECCO EL 1a, RG B). The author and many other expert colleagues around the world no longer use mesalazine to treat Crohn's disease.

Moderate and severe cases of Crohn's disease can also be treated with systemic corticosteroids, given either by mouth or by the intravenous route (ECCO EL 1a, RG A, DGVS A). In parallel, remission maintenance therapy with azathioprine or 6-mercaptopurine should be begun (ECCO EL 1a, RG B; except for initial manifestations, DGVS A). These drugs have a long latency of effect and thus cannot be used to induce a remission in the acute phase. When the treatments mentioned fail or are contraindicated, infliximab (ECCO EL 1b, RG A, DGVS) or adalimumab (DGVS A) can also be used (*table 4*).

Involvement of the small intestine or the upper gastrointestinal tract

Patients with extensive small-bowel involvement with a moderate or severe course should be treated with systemic corticosteroids (ECCO EL 1a, RG B, DGVS A and B). In parallel, remission maintenance therapy with azathioprine/6-mercaptopurine should be started (ECCO EL 1a, RG B, DGVS A); in case of failure or intolerance, methotrexate can be used instead (ECCO EL 1b, RG B, DGVS A). The use of infliximab should be considered in cases of nonresponse to treatment (EL 1b, RG B, DGVS A). If the upper GI tract is affected, a proton pump blocker such as esomeprazole should also be given (EL 5 RG D, DGVS C). If the esophagus is affected, systemic glucocorticoids are the first line treatment (DGVS B) (*table 4*).

Crohn's ileocolitis

Mild Crohn's ileocolitis can be treated with sulfasalazine (ECCO EL 1b, RG A, DGVS A) or with systemic corticosteroids (ECCO EL 1a, RG A, DGVS A). Remission maintenance therapy with azathioprine, 6-mercaptopurine, or methotrexate should be begun in parallel (ECCO EL 1a, RG B, except for initial manifestations). If the above treatment fails or is contraindicated, infliximab (ECCO EL 1b, RG B) or adalimumab can also be used (*table 4*).

Fistulating Crohn's disease

Fistulating disease must be treated by gastroenterologists in collaboration with surgeons and, in some cases, with experts from other clinical disciplines such as gynecology and urology (DGVS D). Contrast-enhanced magnetic resonance imaging (MRI) of the pelvic floor is a particularly useful means of documenting the involvement of adjacent organs by complex fistulae (ECCO EL 2b, RG B). All patients with perianal fistulae should undergo proctoscopy (ECCO EL 2a, RG B, DGVS C). Abscesses must be adequately drained (DGVS B); this may require incision and the insertion of setons (ECCO EL 3, RG D). Perianal fistulae are easier to treat than internal fistulae, which often require major surgery. Internal fistulae penetrating into adjacent organs usually require complex treatment that is best provided by specialists.

Simple perianal fistulae are often initially treated with antibiotics, e.g., ciprofloxacin or metronidazole (ECCO EL 3, RG D). For complex perianal fistulae, azathioprine or 6-mercaptopurine should be given in parallel. Patients with perianal fistulae that respond inadequately to treatment with antibiotics, azathioprine, or 6-mercaptopurine can be treated with infliximab (ECCO EL 1b, RG B). Adalimumab is also effective in fistulating Crohn's disease but is not currently licensed for this indication in Germany (*table 4*).

Ulcerative colitis

Proctitis

Mild to moderate proctitis should be treated topically at first, e.g., with 1000 mg of mesalazine per rectum per day as induction therapy (ECCO EL 1b, RG B). If the response is inadequate or totally lacking, then a combination with oral mesalazine preparations or topical corticosteroids is more effective than monotherapy (ECCO EL 1b, RG B). The topically effective corticosteroids include hydrocortisone, budesonide, and beclomethasone. Effective remission maintenance therapy is usually achieved with topical mesalazine in a dose of, e.g., 3000 mg per week in 3 divided doses (ECCO EL 5, RG D) and/or oral mesalazine in a dose of at least 1000 mg daily (ECCO EL 1a, RG A) (*table 5*).

Left colitis

The treatment of choice for patients with mild to moderate left-sided ulcerative colitis consists of topical 5-aminosalicylic acid (ASA) derivatives (ECCO EL 1b, RG B, DGVS A) in combination with oral mesalazine preparations in a dose above 2000 mg daily (ECCO EL 1a, RG A). A dose of 1500 to 2400 mg 5-ASA po qd is effective for most patients. Patients who fail to respond adequately to oral 5-ASA preparations and/or topical treatment should be treated with systemic corticosteroids (ECCO EL 1b, RG C, DGVS B).

Severe left colitis must be treated in the hospital with systemic medications (ECCO EL 1b, RG B). The medical treatment can also include infliximab. Patients with a steroid-dependent (EL 1a, RG A) or steroid-refractory course (ECCO EL 1a, RG B) should be treated with azathioprine or 6-mercaptopurine for remission maintenance.

TABLE 4

Evidence-based treatment of Crohn's disease (1, 10, 23)

Medication	Dosage	Mild to moderate Crohn's disease		Severe Crohn's disease		Perianal fistulae		Postoperative remission maintenance
		Induction	Maintenance	Induction	Maintenance	Induction	Maintenance	
Sulfasalazine (oral)	Induction 3–6 g/d	Yes	No					No
Mesalazine (oral)		No* ¹	No* ¹					No* ¹
Prednisolone (oral)	Induction 0.25 mg/kg to 0.75 mg/kg	Yes	No	Yes	No			No
Methyl-prednisolone (oral)	Induction 48 mg/d	Yes	No	Yes	No			
Prednisolone (IV)	Induction 60 mg/d			Yes				
Budesonide (oral)	Induction 9 mg/d Maintenance 6 mg/d* ²	Yes	No* ²		Yes* ²			No
Metronidazole (oral)	Induction 10–20 mg/kg/d	No* ¹				Yes* ³		No* ⁴
Azathioprine (oral)	2–3 mg/kg/d	No* ⁵	No* ⁶	No* ⁵	Yes	No* ⁵	Yes	Yes
6-Mercaptopurine (oral)	Maintenance 1.5 mg/kg/d	No* ⁵	No* ⁶	No* ⁵	Yes	No* ⁵	Yes	Yes
Methotrexate (IM)	Induction 25 mg/week; maintenance 15–25 mg/week			Yes* ⁵	Yes			
Infliximab (IV)	Induction 5 or 10 mg/kg in weeks 0, 2, and 6; maintenance 5 or 10 mg/kg every 8 weeks			Yes	Yes	Yes	Yes	
Adalimumab (SC)	Induction 80 or 160 mg in week 0 and 40 or 80 mg in week 2; maintenance 40 mg every 2 weeks or weekly			Yes	Yes	Yes, in a subgroup analysis	Yes, in a subgroup analysis	

An empty square indicates that adequate evidence for or against the treatment in question is not available. For medicolegally binding recommendations regarding indications and dosages, see the Rote Liste ("Red List") and the corresponding information for physicians for the medication in question.

*¹, Recommended in current guidelines; the state of the evidence is inconsistent and does not unequivocally document efficacy.

*², Budesonide in a dosage of 6 mg/d prolongs the interval to the next relapse but does not meet the standard criteria for remission maintenance. It can also be used as a "steroid-sparing" medication for prednisolone-dependent patients.

*³, Recommended in some current guidelines; evidence-based in uncontrolled studies. No controlled studies have been performed to date.

*⁴, Studies have shown a short-term reduction in the occurrence of extensive endoscopic lesions, but no difference in clinical remission rates at 1 year.

*⁵, Slow onset of effect limits usefulness for inducing remissions.

*⁶, The toxicity profile of this drug makes it unsuitable for this indication.

TABLE 5

Evidence-based treatment of ulcerative colitis (1, 23, 24)

Medication	Dosage	Mild to moderate ulcerative colitis		Intractable ulcerative colitis	Severe ulcerative colitis	Remission maintenance	
		Distal	Extensive			Distal	Extensive
Sulfasalazine (oral)	Induction 2–6 g/d Maintenance 2–4 g/d	Yes	Yes	Yes ^{*1}	No ^{*2}	Yes	Yes
Mesalazine (suppositories)	Induction 0.5–1.5 g/d Maintenance 0.5–1 g/d	Yes	No	Yes ^{*1}	No ^{*2}	Yes	No
Mesalazine (enema)	Induction 1–4 g/d Maintenance 1–4 g/d	Yes	Yes (add-on therapy)	Yes ^{*1}	No ^{*2}	Yes	No
Mesalazine (oral)	Induction 1.6–4.8 g/d Maintenance 0.75–4 g/d	Yes	Yes	Yes ^{*1}	No ^{*2}	Yes	Yes
Olsalazine	Maintenance 1–2 g/d	No ^{*3}	No ^{*3}	No ^{*3}	No ^{*3}	Yes	Yes
Balsalazide	Induction 6.75 g/d (equivalent to Mesalazine 2.4 g/d) Maintenance 4 g/d (equivalent to Mesalazine 1.4 g/d)	Yes	Yes	Yes ^{*1}	No ^{*2}	Yes	Yes
Hydrocortisone (enema)	Induction 100 mg/d	Yes	No	Yes ^{*1}	Yes ^{*4}	No	No
Budesonide (enema)	Induction 2–8 mg/d	Yes	No	Yes ^{*1}	Yes ^{*4}	No	No
Corticosteroids (oral cortisone)	Induction 100 mg/d	Yes	Yes	Yes ^{*1}	No	No	No
Corticosteroids (oral prednisolone)	Induction 40–60 mg/d	Yes	Yes	Yes ^{*1}	No	No	No
Corticosteroids (prednisolone IV)	Induction 60 mg/d	No	No	Yes ^{*5}	Yes	No	No
Azathioprine (oral)	Maintenance 2–2.5 mg/kg/d	No	No	Yes	No	Yes	Yes
Ciclosporin (IV)	Induction 2–4 mg/kg/d	No	No	No	Yes	No	No
Tacrolimus (oral)	Induction Serum trough level (5–15 ng/mL) ^{*6}	No	No	No	Yes	No	No
Infliximab (IV)	Induction 5 or 10 mg/kg in weeks 0, 2, and 6; maintenance 5 or 10 mg/kg every 8 weeks	Yes	Yes	Yes	Yes	Yes	Yes

For medicolegally binding recommendations regarding indications and dosages, see the Rote Liste ("Red List") and the corresponding information for physicians for the medication in question.

^{*1}, Usually continued in mild and moderate colitis while other agents are gradually introduced in addition.

^{*2}, Usually discontinued because of the possibility of intolerance to sulfasalazine, mesalazine, or balsalazide.

^{*3}, Diarrhea often arises when this agent is given in high doses to patients with ulcerative colitis.

^{*4}, Treatment given in addition to intravenous corticosteroids.

^{*5}, Some patients who do not respond to oral steroids respond to intravenous steroids given as inpatient treatment.

^{*6}, Retrospective and uncontrolled studies show that trough levels of 4–8 ng/dL are also effective and are associated with fewer side effects.

TABLE 6

Safety and monitoring of medications commonly given to treat Crohn's disease and ulcerative colitis (9, 10, 25)

Substance	Side effects/ adverse events	Monitoring	Pregnancy and breast-feeding: FDA categories
Mesalazine	Rare PC	REN	B
Sulfasalazine	Rare PC	REN	B
Olsalazine	Rare PC	REN	C
Cortisone	INF, ENDO	GLU, BP	C
Prednisolone	INF, ENDO	GLU, BP	C
Hydrocortisone	INF, ENDO	GLU	C
Budesonide	INF	GLU	Not studied
Azathioprine	MAL, LY, INF	CBC, LFT	D
Methotrexate	MAL, LY, INF, P/LFIB	CBC, LFT	X
Tacrolimus	MAL, LY, INF	CBC, LFT, GLU, REN, NS	C
Ciclosporin	MAL, LY, INF	CBC, LFT, REN	C
Infliximab	MAL, LY, INF	TB, CHF, INF	B
Adalimumab	MAL, LY, INF	TB, CHF, INF	B

Extensive information on drug safety in relation to family planning can be found at the following website: <http://bbges.de>
Monitoring: CBC, complete blood count; LFT, liver function tests; GLU, glucose; REN, renal function tests; BP, blood pressure;
NS, neuropathy screening; TB, tuberculosis screening; CHF, exclusion of severe congestive heart failure;
INF, screening for active and, when indicated, opportunistic infection.
Important side effects: PC, pancreatitis; MAL, elevated risk of malignancy; LY, elevated risk of lymphoma;
INF, elevated risk of opportunistic infections; P/LFIB, elevated risk of pulmonary or hepatic fibrosis; ENDO, endocrine disturbances.
FDA categories (summarized): A, controlled studies show no risk; B, no evidence of risk in human beings;
C, risk cannot be ruled out—animal experiments show fetal effects;
D, demonstrated risk to human beings—the benefit should be carefully weighed against the known risk; X, contraindicated.

Patients who have required infliximab to induce a remission should receive continued, regular maintenance treatment with infliximab (ECCO EL 1b, RG A) (*table 5*).

Extensive ulcerative colitis—pancolitis

The initial treatment of extensive, mild to moderate ulcerative colitis consists of systemic mesalazine (in a dose above 2000 mg daily: ECCO EL 1a, RG A, DGVS A) as well as topical mesalazine (ECCO EL 1b, RG A). Patients who do not respond to such treatment, or who are already receiving effective remission maintenance therapy, should be treated with systemic corticosteroids (ECCO EL 1b, RG C, DGVS B). Severe left colitis must be treated in the hospital with systemic medications (ECCO EL 1b, RG B), including infliximab.

Patients with a steroid-dependent course (ECCO EL 1a, RG A) or a steroid-refractory course (ECCO EL 1a, RG B) should be treated with either azathioprine or 6-mercaptopurine for remission maintenance. Patients who have required infliximab to induce remission should receive regular maintenance therapy with infliximab (ECCO EL 1b, RG A) (*table 5*).

Severe ulcerative colitis

Patients with severe ulcerative colitis should be treated in the hospital (ECCO EL 5, RG D). Treatment with intravenous methylprednisolone at a dose of 60 mg

per day, or an equivalent dose of another steroid, should be initiated (ECCO EL 1b, RG B, DGVS A). Monotherapy with intravenous ciclosporin is reserved for patients who do not tolerate intravenous corticosteroids (ECCO EL 1b, RG C).

The response to intravenous steroids on the third day after the initiation of treatment is of critical importance for the course and should be evaluated objectively (ECCO EL 2b, RG B). Alternative treatment options thereafter include ciclosporin (ECCO EL 1b, RG B, DGVS A), tacrolimus (ECCO EL 1b, RG B, DGVS B), and infliximab (ECCO EL 1b, RG B).

Such treatments should be initiated and monitored in an experienced center. If drug therapy fails, proctocollectomy is indicated (DGVS C) (*table 5*).

Surgical treatment

Emergency surgery is indicated for patients with life-threatening complications, such as intestinal perforation, refractory bleeding, or toxic megacolon, that do not respond to pharmacotherapy (16). Elective surgery is indicated for patients with dysplasia or malignancy, a refractory disease course, or intolerance to long-term immunosuppression or other pharmacological therapies (17, 18). The most common surgical technique used to treat ulcerative colitis is total proctocolectomy with an ileal J-pouch anal anastomosis (IPAA). Specific

indications for surgery in Crohn's disease include the formation of fibrotic strictures causing partial or total intestinal obstruction, internal complicated fistulae, abdominal abscesses, and enterovesical, enterovaginal, and enterocutaneous fistulae (17).

Neoplastic complications and screening

Patients with ulcerative colitis and Crohn's ileocolitis have an elevated risk of developing colon cancer, while patients with Crohn's disease and enteritis have an elevated risk of developing small-bowel cancer (9, 18). Screening colonoscopy should be performed for the first time 8 to 10 years after the onset of the illness (ECCO EL 5, RG D). Patients with primary sclerosing cholangitis (PSC) have an even higher risk of carcinoma (ECCO EL 1a, RG A) and should undergo annual screening colonoscopy as soon as the diagnoses of chronic inflammatory bowel disease and PSC are established (ECCO EL 3, RG B) (19).

Safety and monitoring of pharmacotherapy

Many pharmacological treatments for chronic inflammatory bowel disease, especially corticosteroids, immune modulators, and immune suppressants, are associated with major adverse effects (20) (table 6). Biological agents should be used only after a careful weighing of their risks and benefits, as they confer an elevated risk of infection, lymphoma, and malignancy (21).

Furthermore, patients should be tested for the presence of an active infection (particularly tuberculosis, hep-

atitis, infectious enteritis or colitis (including *C. difficile* and cytomegalovirus [CMV]), especially before an immune-modulating or biological therapy is to be initiated. Opportunistic infections may arise later during the course of treatment, especially if multiple immune-modulating, immunosuppressive, or biological agents are used in combination (22). Complex therapies and refractory courses should be managed by appropriately trained and experienced clinicians. Special rules also apply to the vaccination of immunosuppressed patients.

Conflict of interest statement

The author has received unrestricted research grants from the Abbott, Astellas (Fujisawa), Biocodex, and Protein Design Labs companies. He has received honoraria for serving on Advisory Boards for the following companies: Abbott, Astra Zeneca, Berlex, Bristol Meyers Squibb, Centocor, Elan, Biogen, Essex, Medac, Ocera, Protein Design Labs, Schering, Schering Plough, UCB. He has organized continuing medical education events that were supported by the following companies: Abbott, Astra Zeneca, Dr. Falk, Ferring, Essex, Otsuka, Shire, UCB. All of his activities and contracts are in conformity with the "FSA-Kodex Fachkreise" (voluntary self-monitoring code for expert consultants to the pharmaceutical industry), have been checked by the Medicolegal Department of the Charité Hospital, Berlin, and have been approved by the directorate of the Faculty of Medicine.

Manuscript received on 7 May 2008; revised version accepted on 14 November 2008.

Translated from the original German by Ethan Taub, M.D.

REFERENCES

- Baumgart DC, Sandborn WJ: Inflammatory bowel disease: clinical aspects and established and evolving therapies. *Lancet* 2007; 369:1641–57.
- Baumgart DC, Carding SR: Inflammatory bowel disease: cause and immunobiology. *Lancet* 2007; 369: 1627–40.
- Xavier RJ, Podolsky DK: Unravelling the pathogenesis of inflammatory bowel disease. *Nature* 2007; 448: 427–34.
- Stange EF, Travis SP, Vermeire S, Beglinger C, Kupcinkas L, Geboes K, et al.: European evidence based consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. *Gut* 2006; 55 Suppl 1:i1–15.
- Silverberg MS, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR et al.: Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: Report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005; 19 Suppl A: 5–36.
- Hoffmann JC, Preiss JC, Autschbach F, Buhr HJ, Hauser W, Herrlinger K et al.: S3-Leitlinie „Diagnostik und Therapie des Morbus Crohn“. *Z Gastroenterol* 2008; 46: 1094–146.
- Stange EF, Travis SPL, Vermeire S, Reinisch W, Geboes K, Barakauskiene A et al.: European evidence-based Consensus on the diagnosis and management of ulcerative colitis: Definitions and diagnosis. *J Crohn's Colitis* 2008; 2: 1–23.
- Hoffmann JC, Zeitl M, Bischoff SC, Brambs HJ, Bruch HP, Buhr HJ et al.: Diagnostik und Therapie der Colitis ulcerosa: Ergebnisse einer evidenzbasierten Konsensuskonferenz der Deutschen Gesellschaft für Verdauungs- und Stoffwechselerkrankungen zusammen mit dem Kompetenznetz chronisch entzündliche Darmerkrankungen. *Leitlinien. Z Gastroenterol* 2004; 42: 979–83.
- Biancone L, Michetti P, Travis S, Escher JC, Moser G, Forbes A et al.: European evidence-based Consensus on the management of ulcerative colitis: Special situations. *J Crohn's Colitis* 2008; 2: 63–92.
- Caprilli R, Gassull MA, Escher JC, Moser G, Munkholm P, Forbes A et al.: European evidence based consensus on the diagnosis and management of Crohn's disease: special situations. *Gut* 2006; 55 Suppl 1: i36–i58.

Key messages

- Crohn's disease and ulcerative colitis result from an inappropriate innate and acquired immune response to commensal microorganisms in genetically susceptible individuals. These are systemic diseases of the immune system that manifest themselves primarily in the gastrointestinal tract. In principle, however, they can also affect all other organ systems, either with extra-intestinal manifestations or with so-called associated autoimmune diseases. Surgical treatment, therefore, is never curative.
- The clinical phenotype is highly heterogeneous, particularly in Crohn's disease. Not all patients present with bloody diarrhea. Thus, the diagnosis should always be considered when patients complain of abdominal pain or other types of abdominal distress as their main symptom. Some patients also present with extra-abdominal manifestations as their main initial symptoms.
- The introduction of biological therapies has significantly expanded the spectrum of treatments for Crohn's disease and ulcerative colitis. These therapies can markedly improve the quality of life of patients for whom they are suitable.
- The care of patients with these diseases requires the close interdisciplinary collaboration of pediatricians, internists/gastroenterologists, surgeons, and radiologists, as well as the treating primary care physicians.
- Modern therapies also present new risks and should therefore be ordered and monitored by appropriately trained and experienced clinicians.

11. Thielman NM, Guerrant RL: Clinical practice. Acute infectious diarrhea. *N Engl J Med* 2004; 350: 38–47.
12. Sandborn WJ, Feagan BG, Hanauer SB, Lochs H, Lofberg R, Modigliani R et al.: A review of activity indices and efficacy endpoints for clinical trials of medical therapy in adults with Crohn's disease. *Gastroenterology* 2002; 122: 512–30.
13. D'Haens G, Sandborn WJ, Feagan BG, Geboes K, Hanauer SB, Irvine EJ et al.: A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. *Gastroenterology* 2007; 132: 763–86.
14. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V: Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006; 295: 2275–85.
15. D'Haens G, Baert F, Van AG, Caenepeel P, Vergauwe P, Tuynman H et al.: Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet* 2008; 371: 660–7.
16. Berg DF, Bahadursingh AM, Kaminski DL, Longo WE: Acute surgical emergencies in inflammatory bowel disease. *Am J Surg* 2002; 184: 45–51.
17. Larson DW, Pemberton JH: Current concepts and controversies in surgery for IBD. *Gastroenterology* 2004; 126: 1611–9.
18. Itzkowitz SH, Present DH: Consensus conference: Colorectal cancer screening and surveillance in inflammatory bowel disease. *Inflamm Bowel Dis* 2005; 11: 314–21.
19. Loftus EV, Jr., Harewood GC, Loftus CG, Tremaine WJ, Harmsen WS, Zinsmeister AR et al.: PSC-IBD: a unique form of inflammatory bowel disease associated with primary sclerosing cholangitis. *Gut* 2005; 54: 91–6.
20. Lichtenstein GR, Abreu MT, Cohen R, Tremaine W: American Gastroenterological Association Institute technical review on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. *Gastroenterology* 2006; 130: 940–87.
21. Siegel CA, Hur C, Korzenik JR, Gazelle GS, Sands BE: Risks and benefits of infliximab for the treatment of Crohn's disease. *Clin Gastroenterol Hepatol* 2006; 4: 1017–24.
22. Toruner M, Loftus EV, Jr., Harmsen WS, Zinsmeister AR, Orenstein R, Sandborn WJ et al.: Risk factors for opportunistic infections in patients with inflammatory bowel disease. *Gastroenterology* 2008; 134: 929–36.
23. Travis SP, Stange EF, Lemann M, Oresland T, Chowers Y, Forbes A et al.: European evidence based consensus on the diagnosis and management of Crohn's disease: current management. *Gut* 2006; 55 Suppl 1: i16–i35.
24. Travis SPL, Stange EF, Lemann M, Öresland T, Bemelman WA, Chowers Y et al.: European evidence-based Consensus on the management of ulcerative colitis: Current management. *J Crohn's Colitis* 2008; 2: 24–62.
25. Mahadevan U, Kane S: American gastroenterological association institute technical review on the use of gastrointestinal medications in pregnancy. *Gastroenterology* 2006; 131: 283–311.

Corresponding author

PD Dr. med. Daniel C. Baumgart
 Charité – Campus Virchow Klinikum
 Medizinische Klinik mit Schwerpunkt
 Gastroenterologie und Hepatologie
 Augustenburger Platz 1
 13353 Berlin, Germany
 daniel.baumgart@charite.de
 www.danielbaumgart.de