Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2013-B-127 Vedolizumab (Colitis ulcerosa)

Stand: Januar 2014

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Vedolizumab [Erwachsene Patienten mit Colitis ulcerosa]	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*siehe Übersicht II* Zugelassene Arzneimittel im Anwendungsgebiet:
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Patientenindividuell Operation
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Escherichia coli ausgenommen vom Verordnungsausschluss nach AM-RL; Anlage III; Nr. 22: Escherichia coli Stamm Nissle 1917 nur zur Behandlung der Colitis ulcerosa in der Remissionsphase bei Unverträglichkeit von Mesalazin
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*
[…] vorzugsweise eine Therapie, […] die sich in der praktischen Anwendung bewährt hat.	Marktverfügbarkeit

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Vedolizumab ATC-Code Entyvio®	Geplantes Anwendungsgebiet laut Beratungsanforderung: Vedolizumab ist zugelassen für die Behandlung der mittelschweren bis schweren aktiven Colitis Ulcerosa bei erwachsenen Patienten, die auf eine konventionelle Therapie oder einen Tumor-Nekrose-Faktor alpha (TNF-α) Inhibitor unzureichend, nicht oder nicht mehr ansprechen oder bei denen eine Unverträglichkeit oder Kontraindikation vorliegt
Tumornekrosefaktor alpha (TNF-alpha)-Inhibitoren	
Infliximab L04AB02 Remicade®	[…] Colitis ulcerosa Remicade ist indiziert zur Behandlung der mittelschweren bis schweren aktiven Colitis ulcerosa bei erwachsenen Patienten, die auf eine konventionelle Therapie, einschließlich Kortikosteroide und 6-Mercaptopurin (6-MP) oder Azathioprin (AZA), unzureichend angesprochen haben oder die eine Unverträglichkeit oder Kontraindikation für solche Therapien haben.
Adalimumab L04AB04 Humira®	[…] Colitis ulcerosa Humira ist indiziert zur Behandlung der mittelschweren bis schweren aktiven Colitis ulcerosa bei erwachsenen Patienten, die auf die konventionelle Therapie, einschließlich Glukokortikoide und 6-Mercaptopurin (6-MP) oder Azathioprin (AZA), unzureichend angesprochen haben oder die eine Unverträglichkeit gegenüber einer solchen Therapie haben oder bei denen eine solche Therapie kontraindiziert ist.
Golimumab L04AB6 Simponi®	[…] Simponi ist indiziert zur Behandlung der mittelschweren bis schweren aktiven Colitis ulcerosa bei erwachsenen Patienten, die auf eine konventionelle Therapie, einschließlich Kortikosteroide und 6-Mercaptopurin (6-MP) oder Azathioprin (AZA), unzureichend angesprochen haben oder die eine Unverträglichkeit oder Kontraindikation für solche Therapien haben.
Aminosalicylsäuren	
Mesalazin A07EC02 generisch	Akutbehandlung der Colitis ulcerosa und Rezidivprophylaxe […]
Sulfasalazin A07EC01 Generisch (oral und topisch)	Akutbehandlung und Rezidivprophylaxe der Colitis ulcerosa […]
Olsalazin	Leichte und mittelschwere Schübe der akuten Colitis ulcerosa.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
A07EC03 Dipentum®	Rezidivprophylaxe der Colitis ulcerosa.
sonstige	
Escherichia coli	Colitis ulcerosa in der Remissionsphase […]

Quellen: Fachinformationen

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Indikation für die Recherche von Vedolizumab:

Vedolizumab ist zugelassen für die Behandlung der mittelschweren bis schweren aktiven Colitis ulcerosa bei erwachsenen Patienten, die auf eine konventionelle Therapie oder einen Tumor-Nekrose-Faktor alpha (TNF-α) Inhibitor unzureichend, nicht oder nicht mehr ansprechen oder bei denen eine Unverträglichkeit oder Kontraindikation vorliegt.

Berücksichtigte Wirkstoffe/Therapien:

Für das Anwendungsgebiet zugelassenen Arzneimittel, s. Unterlage zur Beratung in AG: „Übersicht zVT, Tabelle II. Zugelassene Arzneimittel im Anwendungsgebiet“

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation ***„Colitis ulcerosa“*** durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre *(ggf. anpassen)* eingeschränkt und die Recherche am 21.01.2014 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (einschl. NHS CRD-Datenbanken), MEDLINE (PubMed), Leitlinien.de (ÄZQ), AWMF, GIN, NGC, TRIP, DAHTA, NIHR HSC. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 259 Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Nach zwei Auswahlschritten – Titel-Abstrakt-Sichtung und Volltextprüfung – wurden insgesamt 27 Quellen in diese synoptische Evidenz-Übersicht aufgenommen.

Abkürzungen

ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
AZA	Azathioprine
5-ASA	5-aminosalicylic acid
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CD	Crohn ’ s disease
DAHTA	Deutsche Agentur für Health Technology Assessment
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IBD	Infl ammatory bowel disease
LMWH	Low molecular weight heparins
MP	Mercaptopurine
MLN-2	Recombinant humanized IgG1 monoclonal antibody
NHS CRD	National Health Services Center for Reviews and Dissemination
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
NIHR HSC	National Institute for Health Research Horizon Scanning Centre
TRIP	Turn Research into Practice Database
UFH	Unfractionated heparin
UC	Ulcerative colitis

Behm 2009: Humanized antibody to the alpha4beta7 integrin for induction of remission in ulcerative colitis (Review).	1. Fragestellung To determine the efficacy and safety of MLN-02 for induction of remission in ulcerative colitis.
	2. Methodik Population: Patients >18 years of age with moderately severe ulcerative colitis as defined by conventional clinical and/or endoscopic criteria. Intervention: MLN-02 Komparator: placebo or controlmedication Endpunkte: primär: clinical remission; sekundär: clinical response; endoscopic remission rates; disease-specific quality of life; incidence and type of adverse events. Suchzeitraum (Aktualität der Recherche): 1966-01/2008 Anzahl eingeschlossene Studien/Patienten (Gesamt): 1 study (n=181)
	3. Ergebnisdarstellung *Clinical remission and clinical response:* • MLN-02 was found to be effective for induction of clinical response (RR = 1.78, 95%CI 1.22 to 2.60) and remission (RR = 2.25, 95%CI 1.17 to 4.36) in patients with moderately severe ulcerative colitis. *Disease-specific quality of life:* • Patients receiving MLN-02 had higher IBDQ scores than patients receiving placebo. *Endoscopic remission rates:* • There was a trend toward increased endoscopic remission with MLN-02 relative to placebo, although this difference was not statistically significant (total MLN-02 20%versus placebo 8%; P = 0.05; RR = 2.46, 95% CI 0.98 to 6.15). *Adverse events:* • Adverse events occurred in a similar proportion of patients treated with MLN-02 compared to placebo (RR = 1.60, 95% CI 0.67 to 3.83). Neutralizing antibodies were found in a significant proportion of patients receiving MLN-02, and in the group of patients with high antibody titers clinical remission rates were no different than placebo. • No opportunistic infections were reported.
	4. Anmerkungen/Fazit der Autoren Data from one trial suggests thatMLN-02 may be effective for induction of clinical response and remission in patients with moderately severe ulcerative colitis. Adverse events appear to be similar to placebo, although immunogenicity may be an issue. Further trials are needed to confirm the results of this study and to define the optimal dose and

	frequency of administration of MLN-02. 5. Hinweise durch GS Ergebnisse beruhen auf nur einer Studie (N=181 Patienten)
Chande 2011: Unfractionated or Low Molecular Weight Heparin for Induction of Remission in Ulcerative Colitis: A Cochrane Inflammatory Bowel Disease and Functional Bowel Disorders Systematic Review of Randomized Trials.	1. Fragestellung We aimed to systematically review the efficacy of unfractionated heparin (UFH) or low molecular weight heparins (LMWH) for remission induction in patients with ulcerative colitis (UC).
	2. Methodik Population: Adult patients with UC Intervention: low molecular weight heparins (LMWH) or unfractionated heparin (UFH) Komparator: placebo or corticosteroids Endpunkte: Clinical remission; clinical-, endoscopic-, or histological improvement Suchzeitraum (Aktualität der Recherche): bis 04/2011 Anzahl eingeschlossene Studien/Patienten (Gesamt): 8 (n=k.A.)
	3. Ergebnisdarstellung *LMWH vs. placebo:* • LMWH administered subcutaneously showed no benefit over placebo for any outcome, including clinical remission, and clinical, endoscopic, or histological improvement. • High-dose LMWH administered via an extended colon-release tablet demonstrated benefit over placebo for: - clinical remission (odds ratio [OR] 2.73; 95% confidence interval [CI] 1.32–5.67; P = 0.007), - clinical improvement (OR 2.99; 95% CI 1.30–6.87; P = 0.01) - endoscopic improvement (OR 2.25; 95% CI 1.01–5.01; P = 0.05) - but not endoscopic remission or histologic improvement - LMWH was not beneficial when added to standard therapy for clinical remission, clinical improvement, endoscopic remission, or endoscopic improvement. *Unfractionated heparin vs. corticosteroids:* • One study examining unfractionated heparin (UFH) versus corticosteroids for the treatment of severe UC demonstrated the inferiority of UFH for clinical improvement. • More patients assigned to UFH had rectal hemorrhage as an adverse event.
	4. Anmerkungen/Fazit der Autoren

	LMWH administered by extended colon-release tablets may be effective for the treatment of active UC. This benefit needs to be confirmed by further randomized controlled studies. The same benefits were not seen when LMWH was administered subcutaneously at lower doses. There is no evidence to support the use of UFH for the treatment of active UC.
Sherlock 2010: Oral budesonide for induction of remission in ulcerative colitis (Review).	1. Fragestellung To systematically review the safety and efficacy of oral budesonide for induction of remission in ulcerative colitis. **Keine Zulassung für Budesonid im Anwendungsgebiet!**
	2. Methodik Population: Participants of all ages with a confirmed diagnosis of moderate to severe UC Intervention: oral budesonide Komparator: placebo or an active agent (corticosteroid or 5-ASA product) Endpunkte: primär: induction of clinical remission; sekundär: clinical, histologic and endoscopic improvement, endoscopic mucosal healing, change in disease activity index scores, adverse events and study withdrawals Suchzeitraum (Aktualität der Recherche): 1950-11/2009 Anzahl eingeschlossene Studien/Patienten (Gesamt): 3 (n=k.A. Patientenanzahl nur für die Einzelstudien angegeben)
	3. Ergebnisdarstellung *Oral Budesonide vs. prednisolone:* • A small pilot study reported no statistically significant difference in endoscopic remission between budesonide and prednisolone (RR 0.75, 95% CI 0.23 to 2.42). • The study was small and not powered to evaluate the impact of budesonide on clinical remission. Suppression of plasma cortisol was significantly more common in prednisolone treated patients (RR 0.02, 95% CI 0.0 to 0.33) *Oral Budesonide vs. mesalamine:* Induction of Clinical Remission: • Oral budesonide was significantly less likely to induce clinical remission than oral mesalamine after 8 weeks of therapy (RR 0.72, 95% CI 0.57 to 0.91). *Oral Budesonide vs. placebo:* • no significant benefit of oral budesonide in comparison to placebo for inducing clinical remission after 4 weeks of treatment (RR 1.41, 95% CI 0.59 to 3.39).

	4. Anmerkungen/Fazit der Autoren At present, there is no evidence to recommend the clinical use of oral budesonide for the induction of remission in active ulcerative colitis. Mesalamine is superior to budesonide for the treatment of active ulcerative colitis. Hinweise GS Budesonid hat keine Zulassung für das Anwendungsgebiet Colitis ulcerosa.
Timmer 2012: Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis.	1. Fragestellung To assess the effectiveness and safety of azathioprine and 6-mercaptopurine for maintaining remission of ulcerative colitis.
	2. Methodik Population: Patients with idiopathic ulcerative colitis Vergleich: Azathioprine vs. Placebo; Azathioprine or 6-Mercaptopurine vs. 5-Aminosalicylate or Sulfasalazine; 6-Mercaptopurine versus Methotrexate Endpunkte: primär: failure tomaintain clinical or endoscopic remission at 12 months, sekundär: adverse event (particularly opportunistic infection, pancreatitis, bone marrow failure, neoplasia and death) and withdrawal due to adverse events Suchzeitraum (Aktualität der Recherche): Von Beginn der jeweiligen DB bis 06/2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 6 (n=286)
	3. Ergebnisdarstellung *Azathioprine versus Placebo (4 Studien, N=232 Patienten):* • azathioprine was significantly superior to placebo for maintenance of remission. • Forty-four per cent (51/115) of patients in the azathioprine group failed to maintain remission compared to 65%(76/117) of patients receiving placebo (RR0.68, 95% CI 0.54 to 0.86). *Azathioprine or 6-Mercaptopurine versus 5-Aminosalicylate or Sulfasalazine (2 studies):* • Two trials that compared 6-mercaptopurine to mesalazine, or azathioprine to sulfasalazine showed significant heterogeneity -> not pooled. • Fifty per cent (7/14) of 6-mercaptopurine patients failed to maintain remission compared to 100% (8/8) of mesalamine patients (1 study, 22 patients; RR 0.53, 95% CI 0.31 to 0.90). • Fifty-eight per cent (7/12) of azathioprine patients failed to maintain remission compared to 38% (5/13) of sulfasalazine patients (1 study, 25 patients; RR 1.52, 95% CI 0.66 to 3.50).

	6-Mercaptopurine versus Methotrexate (1 study): • One small study found that 6-mercaptopurine was superior to methotrexate for maintenance of remission. • In the study, 50% (7/14) of 6-mercaptopurine patients and 92% (11/12) of methotrexate patients failed to maintain remission (1 study, 26 patients; RR 0.55, 95% CI 0.31 to 0.95) *Adverse Events Across All Trials:* • no statistically significant difference between azathioprine and control in the incidence of adverse events (placebo vs. active comparator studies) • Nine per cent (11/127) of azathioprine patients experienced at least one adverse event compared to 2% (3/130) of placebo patients (5 studies, 257 patients; RR 2.82, 95% CI 0.99 to 8.01). • Patients receiving azathioprine were at significantly increased risk of withdrawing due to adverse events. • Eight per cent (8/101) of azathioprine patients withdrew due to adverse events compared to 0% (0/98) of control patients (5 studies, 199 patients; RR 5.43, 95% CI 1.02 to 28.75). • Adverse events related to study medication included acute pancreatitis (3 cases) and significant bone marrow suppression (5 cases). • Deaths, opportunistic infection or neoplasia were not reported.
	4. Anmerkungen/Fazit der Autoren Azathioprine therapy appears to be more effective than placebo for maintenance of remission in ulcerative colitis. Azathioprine or 6-mercaptopurine may be effective as maintenance therapy for patients who have failed or cannot tolerate mesalazine or sulfasalazine and for patients who require repeated courses of steroids. More research is needed to evaluate superiority over standard maintenance therapy, especially in the light of a potential for adverse events from azathioprine.

Systematische Reviews

Assasi 2009: Anti-TNF-α Drugs for Refractory Inflammatory Bowel Disease: Clinical- and Cost-Effectiveness Analyses.	1. Fragestellung (Systematischer Review zu Anti-TNF- α) The aims of this HTA are to evaluate the comparative clinical-effectiveness of anti-TNF-α drugs in patients with CD or UC who have an inadequate response to conventional therapy (including 5-ASA derivatives, immunosuppressant drugs [azathioprine, cyclosporine, mercaptopurine, and methotrexate] and corticosteroids) and to determine their economic value compared with that of conventional therapy and surgical interventions.
	2. Methodik Population: Adults who are aged 18 years and older with luminal or fistulizing UC who are not responding to conventional treatment. Intervention: Infliximab, Adalimumab, Etanercept Komparator: • Intra-class comparison of placebo, infliximab, adalimumab, and etanercept; • Inter-class comparison of conventional therapy (including 5-ASA derivatives [5-ASA, olsalazine, sulfasalazine], immunosuppressant drugs [azathioprine, cyclosporine, mercaptopurine, methotrexate] and corticosteroids) • Surgical interventions, particularly colectomy for UC Endpunkte: Clinical response in UC: A decrease in Disease Activity Index (or Mayo score) of three points or more from the baseline, which should be at least 30% of the baseline score; and a decrease in the subscore for rectal bleeding of one point or more, or an absolute subscore for rectal bleeding of 0 or 1 Suchzeitraum: Beginn der jeweiligen DB bis 11/2008 Anzahl eingeschlossene Studien/Patienten (Gesamt): 20 RCTs und 17 Beobachtungsstudien oder single-arm Studien/Patientenanzahl nur für jede einzelne Studie berichtet (range n=11 to 384)
	3. Ergebnisdarstellung • No head-to-head trials comparing the effectiveness of infliximab with adalimumab or etanercept in UC were found. • No publications of randomized studies were identified on which to base an assessment of the effectiveness of adalimumab and etanercept in the treatment of refractory UC.
	4. Anmerkungen/Fazit der Autoren Although infliximab and adalimumab have been shown to provide clinical benefit, the costs associated with these treatments could be perceived as high. Based on the incremental cost-utility findings from our primary economic evaluations, adalimumab and infliximab for the treatment of IBD may not be perceived to be a cost-effective use of health care resources.
Bultman 2010:	1. Fragestellung

Systematic review: steroid withdrawal in anti-TNF-treated patients with inflammatory bowel disease.	To conduct a systematic review to establish figures for steroid withdrawal in anti-TNF treated inflammatory bowel disease-patients.
	2. Methodik (Systematischer Review zu Anti-TNF-α) Population: IBD patients (In den 2 Studien zu UC wurden Patienten mit mittelschwerer bis schwerer akiver Colitis ulcerosa eingeschlossen) Intervention: Anti-TNF-α Komparator: placebo or conventional medication Endpunkte: Steroid withdrawal during anti-TNF-treatment Suchzeitraum: Bis 01/2009 Anzahl eingeschlossene Studien/Patienten (Gesamt): 5 Studien (3 Studien für CD; 2 Studien für UC) / Angabe nur für jede einzelne Studie (range 241-243 Patienten)
	3. Ergebnisdarstellung b. basierend auf 5 Studien zu Infliximab und eine Studie zu Adalimumab) c. • Overall, in the adult population, up to 38% of the patients were able to withdraw corticosteroids during infliximab therapy. • In the paediatric population, up to 75% of the patients were able to withdraw corticosteroids during infliximab therapy.
	4. Anmerkungen/Fazit der Autoren Although a consensus on the definition of steroid-sparing is lacking, approximately two-thirds of the inflammatory bowel disease-patients are unable to withdraw corticosteroid treatment during anti-TNF therapy.
Chang 2013: Infliximab versus cyclosporine as rescue therapy in acute severe steroid-refractory ulcerative colitis: a systematic review and meta-analysis.	1. Fragestellung This study aims to systematically review published studics directly comparing cyclosparine and infliximab in acute severe steroid-refectory UC and to perfom meta-analyses of the relevant evidence.
	2. Methodik Population: Patients with acute severe steroid-refractory ulcerative colitis Vergleich: Infliximab vs. Cyclosporin Endpunkte: 3-month colectomy rate; 12-month colectomy rate; Adverse drug reactions; postoperative complications Suchzeitraum: Bis 05/2012 Anzahl eingeschlossene Studien/Patienten (Gesamt): 6 studies/321 Patienten (N=179 in the infliximab arm and N=142 in the cyclosporine arm)
	3. Ergebnisdarstellung a. 6 der eingeschlossenen Studien relevant

	b. *3-month colectomy rate:* • no significant differences between infliximab and cyclosporine in the 3-month colectomy rate (31.8% in the infliximab arm versus 30.3% in thc cyclosporine arm: OR=0.86 95% CI=0.31 to 2.41, p=0.775 *12-month colectomy rate:* • no significant difference in the rate of colectomy on follow-up at 12 months after using infliximab (41.7 %) or cyclosporine (44.9 %) as a rescue therapy during initial acute severe exacerbations (0R=0.60, 95% Cl=0.I9-1.89, p=0.381 *Adverse drug reactions:* • no significant difference in the rate of adverse drug reactions when using infliximab (21.8 %) or cyclosporine (23.9 %) as a rescue therapy (0R=0.76, 95% CI=0.34- 1.70 ,p=0.508) *Postoperative complications:* • no significant difference in the postoperative complication rate after colectomy (2.8% in the inlliximab arm versus 0.7% in the cyclosporine arm; OR=1.66, 95% CI=0.26-10.50, p=0.591
	4. Anmerkungen/Fazit der Autoren Infliximab and cyclosporine are comparable when used as rescue therapy in acute severe steroid refractory UC. Randomized trials are required to further cvaluate these agents.
Feagan 2013: Are There Any Differences in the Efficacy and Safety of Different Formulations of Oral 5-ASA Used for Induction and Maintenance of Remission in Ulcerative Colitis? Evidence from Cochrane Reviews.	1. Fragestellung The main objective of this review was to determine if there are any differences in efficacy or safety among the oral 5-ASA drugs.
	2. Methodik Population: Patienten mit mittelschwerer bis schwerer Colitis ulcerosa Intervention: oral 5-ASA Komparator: formulations of 5-ASA (including Asacol, Claversal, Salofalk, and Pentasa) Endpunkte: primary: failure to induce global or clinical remission; failure to induce global/clinical remission or improvement; and failure to maintain global/clinical remission (relapse); secondary: failure to adhere to the medication regimen and adverse events including the proportion of patients who experienced at least one adverse event, a serious adverse event, and withdrawal from therapy due to an adverse event Suchzeitraum (Aktualität der Recherche): Beginn der jeweiligen DB bis 02/2013

	Anzahl eingeschlossene Studien/Patienten (Gesamt): 17 studies (n=2925)
	3. Ergebnisdarstellung ***Oral 5-ASA versus Comparator 5-ASA*** *Failure to Induce Global/Clinical Remission (11 studies; n=1968):* • no statistically significant difference in failure to enter global or clinical remission between various formulations of 5-ASA (including balsalazide, Pentasa, olsalazine, MMX mesalazine, Ipocol, and 5-ASA micropellets) and comparator formulations of 5-ASA (including Asacol, Claversal, and Salofalk) *Failure to Induce Global/Clinical Remission or Improvement (8 studies; n=1647):* • no statistically significant difference in failure to improve clinically between various formulations of 5-ASA (including balsalazide, Pentasa, olsalazine, MMX mesalazine, and 5-ASA micropellets) and comparator formulations of 5-ASA (including Asacol, Claversal, Salofalk, and Pentasa) *Failure to Maintain Global/Clinical Remission at 12 Months (5 studies; n=457):* • no statistically significant difference in relapse between various formulations of 5-ASA (including balsalazide, Pentasa, and olsalazine) and comparator formulations of 5-ASA (including Asacol and Salofalk) *Adverse events (13 studies; n=1933):* • no statistically significant difference in the incidence of adverse events between various formulations of 5-ASA (including balsalazide, Pentasa, olsalazine, MMX mesalazine, Ipocol, and 5-ASA micropellets) and comparator formulations of 5-ASA (including Asacol, Claversal, and Salofalk)
	4. Anmerkungen/Fazit der Autoren There does not seem to be any difference in efficacy or safety among the various formulations of oral 5-ASA. Oral mesalamine is an effective and safe treatment of mild-to-moderate or quiescent ulcerative colitis regardless of the chosen formulation.
Ford 2011: Efficacy of Biological Therapies in	1. Fragestellung To assess the evidence for treatment of the condition with biological therapies.

Inflammatory Bowel Disease: Systematic Review and Meta-Analysis.	2. Methodik Population: Patienten mit mittelschwerer bis schwerer Colitis ulcerosa Intervention: biological therapies Komparator: placebo Endpunkte: primary: failure to achieve remission and preventing relapse; secondary: adverse events Suchzeitraum (Aktualität der Recherche): 1966 bis 12/2010 Anzahl eingeschlossene Studien/Patienten (Gesamt): 27 studies (n=k.A.)
	3. Ergebnisdarstellung a. 5 der eingeschlossenen Studien sind für die Fragestellung relevant, Anzahl der Patienten (range: 11-364) *Induction of remission:* • There were 5 RCTs (n=827), that reported efficacy of biological therapies in inducing remission in patients with moderately to severely active UC who had failed, or were receiving, therapy with corticosteroids • Remission was not achieved in 231(42.9%) of 539 patients randomized to infliximab at 6 weeks to 3 months, compared with 201 (69.8 %) of 288 assigned to placebo • There was a statistically significant benefit of infliximab over placebo, with a RR of remission not being achieved of 0.72 (95 % CI 0.57 – 0.91) *Preventing relapse:* • There were no RCTs examining this issue
	4. Anmerkungen/Fazit der Autoren Biological therapies were superior to placebo in inducing remission of active CD and UC, and in preventing relapse of quiescent CD.
Ford et al. 2013: Opportunistic Infections With Anti-Tumor Necrosis Factor- α Therapy in Inflammatory Bowel Disease: Meta-Analysis of Randomized Controlled Trials.	1. Fragestellung Several anti-tumor necrosis factor- α (TNF α) antibodies have demonstrated efficacy in Crohn's disease (CD) and ulcerative colitis (UC). These drugs carry the theoretical risk of opportunistic infection, but no systematic review and meta-analysis has examined this issue specifically.
	2. Methodik Population: Patienten mit mittelschwerer bis schwerer Colitis ulcerosa Intervention: anti-TNF α (adalimumab, certolizumab, golimumab, or infliximab) Komparator: plazebo Endpunkte: Opportunistic infections (*Mycobacterium tuberculosis* , oral or esophageal candidiasis, varicella-zoster virus infection, herpes zoster infection, Epstein-Barr virus or cytomegalovirus infection,

	Nocardia infection, *Pneumocytsis jirovecii* infection, *ycobacterium avium complex* infection, herpes simplex infection, or other unspecified opportunistic infections) Suchzeitraum (Aktualität der Recherche): 1946 bis 11/2011 Anzahl eingeschlossene Studien/Patienten (Gesamt): 22 studies (n=4,135 patients)
	3. Ergebnisdarstellung a. 7 der eingeschlossenen Studien relevant für Fragestellung, Anzahl der Patienten (n=2,488) • **Subgroup analyses of RR of opportunistic infection with anti-TNF therapies vs. placebo in UC:** 1.78; 95% CI 0.72 – 4.42 Overall risk of opportunistic infections with anti-TNF a therapy vs. placebo: • The RR of developing an opportunistic infection was significantly higher with anti-TNF α therapy (2.05; 95 % CI 1.10 – 3.85, NNH = 500; 95 % CI 200 – 1,567). • The RR of tuberculosis infection was 2.52 (95 % CI 0.62 – 10.21).
	4. Anmerkungen/Fazit der Autoren Anti-TNF therapy doubles the risk of opportunistic infections in inflammatory bowel disease patients. This underlines the importance of adherence to guidelines for their prevention and management.
Gisbert 2009: Meta-analysis: the efficacy of azathioprine and mercaptopurine in ulcerative colitis.	1. Fragestellung To review systematically the efficacy of azathioprine (AZA) and mercaptopurine (MP) in UC, and to conduct a meta-analysis of randomized clinical trials evaluating the efficacy of AZA/MP for the induction or maintenance of UC clinical remission.
	2. Methodik Population: Patienten mit UC (unterschiedliche Schweregrade) Intervention: Azathioprine (AZA) und Mercaptopurin Komparator: Placebo, Mesalazin, Sulfalazin, Aminosalicylates Endpunkte: “success of treatment”, defined as the induction or the maintenance of clinical remission Suchzeitraum (Aktualität der Recherche): Von Beginn der jeweiligen DB bis 05/2008 Anzahl eingeschlossene Studien/Patienten (Gesamt): 30 Studien (davon 7 kontrollierte Studien, die in die MA eingeschlossen) wurden/ (n=1632 Patienten)
	3. Ergebnisdarstellung a. 7 der eingeschlossenen Studien relevant für Fragestellung • Mean efficacy of AZA/MP was 65% for induction and 76% for

	maintenance of the remission. *Induction of remission:* • four studies (89 AZA/MP-treated patients) showed mean efficacy of 73% vs. 64% in controls (OR = 1.59; 95% CI = 0.59–4.29). *Maintenance of remission:* • six studies (124 AZA/MP-treated patients) showed mean efficacy of 60% vs. 37% in controls (OR = 2.56; 95% CI = 1.51–4.34). • When only studies comparing AZA/MP vs. placebo were considered, OR was 2.59 (95% CI = 1.26–5.3), absolute risk reduction was 23% and number needed-to-treat (NNT) to prevent one recurrence was 5
	4. Anmerkungen/Fazit der Autoren Thiopurine drugs (AZA/MP) are more effective than placebo for the prevention of relapse in UC, with an NNT of 5 and an absolute risk reduction of 23%. (5.Hinweise durch GS) Patienten mit unterschiedlichen Schweregraden eingeschlossen. Aufgrund der Therapie vermehrt Patienten mit mittelschwerer bis schwerer UC eingeschlossen.
Huang 2011: A meta-analysis of the therapeutic effects of tumor necrosis factor-α blockers on ulcerative colitis.	1. Fragestellung To evaluate the therapeutic effects of TNF-α blockers on ulcerative colitis (UC) and their safety.
	2. Methodik Population: Patienten mit mittelschwerer bis schwerer Colitis ulcerosa Intervention: TNF-α blockers Komparator: placebo or other drugs as control Endpunkte: Clinical response and clinical relief; Colectomy; Mucosal healing, Quality of life, Side effects Suchzeitraum (Aktualität der Recherche): Bis 2010 Anzahl eingeschlossene Studien/Patienten (Gesamt): 9 studies (n=1,226 patients)
	3. Ergebnisdarstellung a. 9 der eingeschlossenen Studien relevant für die Fragestellung b. Infliximab was used in eight papers and adalimumab in one paper.

	Placebo was used in seven papers and hormones in two papers. *Clinical response and clinical relief:* • Short-term response, short-term relief, long-term response, and long-term relief were better in the TNF-α blocker group than in the control group (P< 0.05). *Colectomy:* • TNF-α blockers decreased the colectomy rate (P< 0.05). *Mucosal healing and quality of life:* • There were no significant differences in mucosal healing and quality of life between the two groups (P> 0.05). *Side effects:* • The rates of adverse reactions were similar in the two groups (P>0.05), but the rate of severe adverse reactions was significantly lower in the TNF-α blocker group than in the control group (P<0.05).
	4. Anmerkungen/Fazit der Autoren TNF-α blockers have better therapeutic effects on moderate or severe UC, which shows little response to conventional therapy. TNF-α blockers can induce short-term response, maintain long-term clinical response and clinical relief, and decrease the colectomy rate and the severe adverse reaction rate, but they fail to improve quality of life and mucosal healing.
Khan 2011: Efficacy of Immunosuppressive Therapy for Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis.	1. Fragestellung We performed an updated systematic review of the literature to clarify the efficacy of immunosuppressive therapy at inducing remission and preventing relapse in ulcerative colitis (UC) and Crohn's disease (CD).
	2. Methodik Population: Adults (> 90 % of patients aged > 16 years) with inflammatory bowel disease Intervention: AZA, 6-MP, MTX, cyclosporine or tacrolimus Komparator: placebo or no intervention Endpunkte: failure of remission, relapse by endoscopic evidence Suchzeitraum (Aktualität der Recherche): 1966 bis 12/2010 Anzahl eingeschlossene Studien/Patienten (Gesamt): 2 studies (n=130 patients)
	3. Ergebnisdarstellung *a. 2 der eingeschlossenen studien relevant; 130 Patienten* **Immunosuppressive therapy in active UC:** ***AZA vs. placebo (2 studies; n=130):*** • There was a trend to benefit of AZA compared with placebo but this

	did not achieve statistical significance (RR = 0.85; 95 % CI = 0.71 – 1.01; *P* = 0.07) ***MTX vs. placebo (1 study; n=67):*** • no statistically significant benefit of MTX over placebo (RR = 1.29; 95 % CI = 0.95 – 1.75) ***Cyclosporine vs. placebo (1 study; n=20):*** • a statistically significant benefit of active therapy (RR = 0.84; 95 % CI = 0.65 – 1.07)
	4. Anmerkungen/Fazit der Autoren Most evidence relates to AZA / 6-MP where there is no statistically significant benefi t at inducing remission in active CD and UC. Thiopurine analogs may prevent relapse in quiescent UC and CD. However, there is a paucity of data for immunosuppressive therapy in IBD and more research is needed. 5. Hinweise durch GS: • Nur die Ergebnisse für UC dargestellt • Patienten mit unterschiedlichen Schweregraden eingeschlossen. • Aufgrund der Therapie vermehrt Patienten mit mittelschwerer bis schwerer UC eingeschlossen.
Leung et al. 2008: Exposing the Weaknesses: A Systematic Review of Azathioprine Efficacy in Ulcerative Colitis.	1. Fragestellung We performed a systematic review and meta-analysis to evaluate the clinical efficacy of 6-thioguanine anti-metabolites for the maintenance of clinical remission after standard induction with corticosteroids.
	2.Methodik Population: Patienten mit mittelschwerer bis schwerer Colitis ulcerosa Intervention: AZA Komparator: 5-ASA and/ or placebo Endpunkte: sucess of treatment Suchzeitraum (Aktualität der Recherche): 1966 bis 06/2006 Anzahl eingeschlossene Studien/Patienten (Gesamt): 5 studies (n=k.A.)
	3. Ergebnisdarstellung • The pooled relative risk estimate for ‘‘success of treatment’’ with azathioprine (AZA) compared to 5-aminosalicylic acid or placebo was 1.42 [95% confidence interval (CI): 0.93–2.17, p = 0.109]; • Using only trials of a higher quality: a pooled relative risk estimate

	of 2.05 (95% CI: 1.30–3.23, p = 0.002) was obtained.
	4. Anmerkungen/Fazit der Autoren Pooled results demonstrated a modest efficacy of AZA for the treatment of ulcerative colitis. However, the use of AZA for the management of UC is not based on high-quality evidence.
Nikfar et al. 2011: A Systematic Review and Meta-analysis of the Efficacy and Adverse Events of Infliximab in Comparison to Corticosteroids and Placebo in Active Ulcerative Colitis.	1. Fragestellung The present meta-analysis was performed to collect and review all the clinical trials tlmt investigated the efficacy and tolerability of infliximab in order to determine whether infliximab is more effective than placebo or corticosteroids in inducing response and remission in UC.
	3. Methodik Population: Patienten mit schwerer Colitis ulcerosa Vergleiche: infliximab vs. placebo; infliximab vs. corticosteroids Endpunkte: clinical remission, adverse events, serious adverse events Suchzeitraum (Aktualität der Recherche): 1966 bis 09/2010 Anzahl eingeschlossene Studien/Patienten (Gesamt): 8 studies (n=884 patients)
	4. Ergebnisdarstellung *Infliximab vs. placebo (5 Studien, 827 Patienten):* Clinical remission: • Relative Risk (RR) for clinical remission was 1.93 with a 95% Confidence Interval (CI) of 1.62-2.3 and a significant RR (p<0.0001) Adverse events: • RR was 1.07 with a 95% CI of 0.99-1.14, a non-significant RR (p =0.0725) Serious adverse events: • RR was 0.83 with a 95% CI of 0.44-1.54 as a non-significant RR (p = 0.5472). *Infliximab vs. corticosteroids (3 Studien, 57 Patienten):* Clinical remission: • RR was 1.07 with a 95% CI of 0.87-1.31 as a non-significant RR (p = 0.5353)
	5. Anmerkungen/Fazit der Autoren: The present meta-analysis fmmd tlmt patients receiving infliximab were 1.93 tim es more likely to go to the remission as compared to those receiving placebo while the risk of adverse events in the patients receiving infliximab was just 1.07 tim es as compared to the placebo group. Among these adverse events, the risk of serious ones was 0.83

	times in the infliximab group in comparison to placebo. Also it was sho\Vll tlmt patients receiving infliximab were 1.07 times more likely to go to the remission compared to those receiving corticosteroids. Comparison of remission in infliximab group and that of placebo was statistically significant but other Relative Risks (RR) were not significant.
Vogelaar 2009: The impact of biologics on health-related quality of life in patients with inflammatory bowel disease.	1. Fragestellung To review and evaluate the current literature on the effect of biologics on HRQoL of IBD patients.
	2.Methodik Population: Patienten mit mittelschwerer bis schwerer CU oder CD Intervention: infliximab, adalimumab, certolizumab, and natalizumab Komparator: placebo Endpunkte: health-related quality of life (HRQoL) Suchzeitraum (Aktualität der Recherche): 1980-2009 Anzahl eingeschlossene Studien/Patienten (Gesamt): 8 studies; (Anzahl der Patienten je Studie angegeben, range:79-728)
	3. Ergebnisdarstellung *Infliximab vs. placebo (2 RCTs):* • significant improvement of HRQoL compared to placebo which was sustained over the long term. *Adalimubab vs. placebo (1 RCT):* • significant and sustained improvement of HRQoL compared to placebo. • This study showed also significant decrease of fatigue in the adalimumab treated patients. *Certolizumab vs. placebo (3RCTs):* • significant improvement of HRQoL in the intervention group compared to placebo. *Natalizumab vs. placebo (2 RCTs):* • One study showed significant and sustained improvement compared to placebo, and also scores of HRQoL comparable to that in the general population, but in the other no significant results were found.
	4. Anmerkungen/Fazit der Autoren: The biologics infliximab, adalimumab, certolizumab, and natalizumab demonstrated significant improvement of HRQoL of IBD patients compared with placebo. However, we found differences in improvement of HRQoL between the different biologics.

	5. Hinweise durch GS: Einschluss von Patienten Colitis ulcerosa oder mit Crohn's disease.
Wang et al. 2012: Meta-analysis of broad-spectrum antibiotic therapy in patients with active inflammatory bowel disease.	1. Fragestellung The objective of this meta-analysis was to perform a systematic review and meta-analysis of randomized, placebo-controlled clinical trials to assess the effectiveness of antibiotic therapy in patients with CD and UC.
	2. Methodik Population: patients with active inflammatory bowel disease Intervention: antibiotics (ciprofloxacin, amoxicillin plus tetracycline plus metronidazole, tobramycin, metronidazole) Komparator: placebo Endpunkte: Remission Suchzeitraum (Aktualität der Recherche): 1970 bis 2010 Anzahl eingeschlossene Studien/Patienten (Gesamt): 9 studies (n=626 patients)
	3. Ergebnisdarstellung *Remission (Antibiotika: N=310 Patienten; Placebo: N=316 Patienten):* • Remission was induced in 64.2% of the patients treated with antibiotics, compared with 47.5% of the placebo group • The pooling of these trials yielded an OR of 2.17 (95% CI, 1.54-3.05) in favor of antibiotic therapy
	4. Anmerkungen/Fazit der Autoren These results suggest that antibiotics improve clinical outcomes in patients with IBD. 5. Hinweise durch GS: Nur die Ergebnisse für UC dargestellt
	6. Anmerkungen/Fazit der Autoren Preoperative infliximab use does not increase the risk of early postoperative complications in patients with ulcerative colitis undergoing abdominal surgery.

Leitlinien

Dignass 2011: Aktualisierte Leitlinie zur Diagnostik und Therapie der Colitis ulcerosa 2011 – Ergebnisse einer Evidenzbasierten konsensus-konferenz.	S3-Leitlinie

Methodik

Grundlage der Leitlinie: Überarbeitete Leitlinie, die im Wesentlichen auf der Leitlinie der Deutschen Gesellschaft für Verdauungs- und Stoffwechselkrankheiten (DGVS) aus dem Jahr 2004 sowie der Leitlinie der European Crohn's and Colitis Organization (ECCO) von 2008 basiert.
Die Struktur der Leitlinie orientiert sich am Deutschen Instrument zur methodischen Leitlinien-Bewertung (DELBI) und entspricht den Anforderungen der AWMF an eine S3-Leitlinie. Details zur Methodik sind in einem separaten Methodenreport dargestellt.

Suchzeitraum: bis 05/2009

Die Gültigkeit dieser überarbeiteten Leitlinie wird auf 5 Jahre geschätzt, sodass die Revision für 2016 geplant ist.

Evidenzgrade:

A	Direkt anwendbare Studien der Evidenzklasse 1
B	Studien der Evidenzklasse 2 oder 3 oder indirekte Anwendbarkeit[1] von Studien der Evidenzklasse 1
C	Studien der Evidenzklasse 4 oder indirekte Anwendbarkeit[1] von Studien der Evidenzklasse 2 oder 3
D	Studien der Evidenzklasse 5 oder indirekte Anwendbarkeit[1] von Studien der Evidenzklasse 4 oder beunruhigend uneinheitliche oder nicht aussagekräftige Studien irgendeiner Evidenzklasse

Empfehlungsstärken:

Empfehlungsstärke	Formulierung	Bedeutung für Ärzte	Bedeutung für Patienten
stark positiv	„soll"	Die meisten Patienten sollen die empfohlene Intervention erhalten „Definitely do it!"	Die meisten Patienten würden sich für die empfohlene Intervention entscheiden und nur eine kleine Zahl dagegen
abgeschwächt positiv	„sollte" oder „kann"	Unterschiedliche Entscheidungen sind bei verschiedenen Patienten angemessen, die von der Situation des Patienten abhängen, aber auch von seinen persönlichen Vorstellungen und Präferenzen „Probably do it!"	Die Mehrzahl der Patienten würde sich für die Intervention entscheiden, aber viele nicht
abgeschwächt negativ	„sollte eher nicht"	„Probably don't do it!"	Die Mehrzahl der Patienten würde sich gegen die Intervention entscheiden, aber viele auch dafür
stark negativ	„soll nicht"	„Definitely don't do it!"	Die meisten Patienten würden sich gegen die empfohlene Intervention entscheiden und nur eine kleine Zahl dafür
unklar	„Eine generelle Empfehlung bezüglich … kann aufgrund der unzureichenden Datenlage nicht gegeben werden."		

Konsensusstärken:

starker Konsens	Zustimmung von > 95 % der Teilnehmer
Konsens	Zustimmung von > 75 – 95 % der Teilnehmer
mehrheitliche Zustimmung	Zustimmung von > 50 – 75 % der Teilnehmer
kein Konsens	Zustimmung von weniger als 50 % der Teilnehmer

Empfehlungen:

- Die Behandlung einer schweren, aktiven CU mit Zeichen einer systemischen Beteiligung sollte unter stationären Bedingungen erfolgen. [Evidenzgrad: D, Konsensusstärke: Konsens, Empfehlungsstärke: ↑]
- Ein schwer verlaufender Schub einer CU mit Zeichen einer systemischen Beteiligung soll mit einer intravenösen Steroidtherapie (z. B. 1mg/kg Körpergewicht Prednisolonäquivalent pro Tag) behandelt werden. [Evidenzgrad: B, Konsensusstärke: sehr stark, Empfehlungsstärke: ↑↑]
- Sollte eine Steroidtherapie aufgrund einer Kontraindikation oder Intoleranz nicht infrage kommen, so kann alternativ eine Therapie mit Ciclosporin A (B), Infliximab (B) oder Tacrolimus (C) zum Einsatz kommen. [Evidenzgrad: siehe Empfehlungstext, Konsensusstärke: Konsens, Empfehlungsstärke: ↑]
- Diese Patienten sollen intensiv überwacht und, insbesondere jene mit toxischem Verlauf, in enger Zusammenarbeit von Gastroenterologen/ Kindergastroenterologen und Chirurgen betreut werden. [Evidenzgrad: D, Konsensusstärke: starker Konsens, Empfehlungsstärke: ↑↑]

Colitis ulcerosa refraktär auf systemische Steroidtherapie:

- Zur Beurteilung des Ansprechens der systemischen Steroidtherapie sollen das klinische Bild und objektivierbare Parameter (z. B. Stuhlfrequenz, Blutbeimengungen im Stuhl, Hb-Wert, Ultraschallbefund, Endoskopiebefund) herangezogen werden. [Evidenzgrad: D, Konsensusstärke: starker Konsens, Empfehlungsstärke: ↑↑]
- Bei nicht ausreichendem Ansprechen auf eine systemische Steroidtherapie soll Ciclosporin A (A), Infliximab (A) oder Tacrolimus (B) eingesetzt werden. Bei der Therapieentscheidung soll immer auch eine chirurgische Therapiealternative in Betracht gezogen werden (B). [Evidenzgrad: siehe Empfehlungstext, Konsensusstärke: Konsens, Empfehlungsstärke: ↑↑]
- Nach Ansprechen auf eine Therapie kann eine Azathioprin- oder eine 6-Mercaptopurin-Therapie eingeleitet werden. [Evidenzgrad: B, Konsensusstärke: Konsens, Empfehlungsstärke: ↑]
- Tritt unter oben genannter Therapie eine klinische Zustandsverschlechterung ein, soll eine chirurgische Therapie durchgeführt werden. Die chirurgische Therapie kann ebenso indiziert sein, wenn nach 4 – 7 Tagen keine Verbesserung des klinischen

	Zustands eintritt. [Evidenzgrad: D, Konsensusstärke: starker Konsens, Empfehlungsstärke: ↑↑]
Dignass 2013: Second European evidence-based Consensus on the diagnosis and management of ulcerative colitis: Current management.	Leitlinie *der* European Crohn's and Colitis Organisation (ECCO)
	Methodik Grundlage der Leitlinie: Systematisches Vorgehen bei der Literaturrecherche in Medline und Cochrane Database angegeben, aber keine weiteren Details (z.B. Suchzeitraum) beschrieben. Konsensuskonferenz wurde abgehalten.
	Empfehlungen: **Severe ulcerative colitis of any extent:** *ECCO Statement 5D* • Patients with bloody diarrhoea ≥6/day and any signs of systemic toxicity (tachycardia N90 bpm, fever N37.8 °C, Hb b10.5 g/dL, or an ESR N30 mm/h) have severe colitis and should be admitted to hospital for intensive treatment [EL5, RG D]. **Intravenous-steroid refractory ulcerative colitis of any extent:** *ECCO Statement 5F* • The response to intravenous steroids is best assessed objectively around the third day [EL2b, RGB]. Treatment options including colectomy should be discussed with patients with severely active UC not responding to intravenous steroids. Second line therapy with either ciclosporin [EL1b, RG B], or infliximab [EL1b, RG B] or tacrolimus [EL4, RG C] may be appropriate. If there is no improvement within 4–7 days of salvage therapy, colectomy is recommended [EL4, RG C]. Third line medical therapy may be considered at a specialist centre [EL4, RG C]. **'Steroid-dependent', active ulcerative colitis**: *ECCO Statement 5F* • Patients with steroid-dependent disease should be treated with azathioprine/mercaptopurine [EL1b, RG B]. **Oral steroid-refractory ulcerative colitis:** Statement 5H • Outpatients with moderately active steroid refractory disease should be treated with anti TNF therapy [EL1b, RG B] or tacrolimus [EL2b, RG C], although surgical options or admission for parenteral steroid therapy could also be considered [EL5 RG D] **Immunomodulator-refractory ulcerative colitis:** ECCO Statement 5I • Patients with moderately active ulcerative colitis refractory to

	thiopurines should be treated with anti TNF therapy [EL1b, RG B] or tacrolimus [EL4, RG C] although colectomy should also be considered. Continued medical therapy that does not achieve a clear clinical benefit is not recommended [EL5, RG D]. **Maintenance of remission** *ECCO Statement 6A* • The goal of maintenance therapy in UC is to maintain steroid-free remission, clinically [EL1, RG A] and endoscopically defined [EL2, RG B] ECCO Statement 6F Choice of maintenance treatment in UC is determined by disease extent [EL1b, RG B], disease course (frequency of flares) [EL5, RG D], failure of previous maintenance treatment [EL5, RG D], severity of the most recent flare [EL5, RG D], treatment used for inducing remission during the most recent flare [EL5, RG D], safety of maintenance treatment [EL1b, RG B], and cancer prevention [EL2a, RG B]
NICE 2013: Ulcerative colitis Management in adults, children and young people.	NICE Leitline
	Methodik Grundlage der Leitlinie: The methods and processes for developing NICE clinical guidelines are described in The guidelines manual. Suchzeitraum: Interventions that must (or must not) be used: We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening. Interventions that should (or should not) be used – a 'strong' recommendation: We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that an intervention will not be of benefit for most patients. Interventions that could be used: We use 'consider' when we are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the

	healthcare professional should spend more time considering and discussing the options with the patient.
	Empfehlungen: ***Step 1 therapy*** • For people admitted to hospital with acute severe ulcerative colitis (either a first presentation or an inflammatory exacerbation): - offer intravenous corticosteroids to induce remission **and** - assess the likelihood that the person will need surgery (see recommendation) • Consider intravenous ciclosporin or surgery for people: - who cannot tolerate or who decline intravenous corticosteroids **or** - for whom treatment with intravenous corticosteroids is contraindicated. Take into account the person's preferences when choosing treatment. ***Step 2 therapy*** • Consider adding intravenous ciclosporin to intravenous corticosteroids or consider surgery for people: - who have little or no improvement within 72 hours of starting intravenous corticosteroids **or** - whose symptoms worsen at any time despite corticosteroid treatment. Take into account the person's preferences when choosing treatment. For guidance on infliximab for treating acute severe ulcerative colitis (all extents of disease) in people for whom ciclosporin is contraindicated or clinically inappropriate, refer to Infliximab for acute exacerbations of ulcerative colitis (NICE technology appraisal guidance 163).
Sowerby Centre for Health Informatics at Newcastle (SCHIN) 2010: Ulcerative colitis (Prodigy).	Prodigy Leitlinie
	Methodik Grundlage der Leitlinie: A literature search was conducted for guidelines, systematic reviews and randomized controlled trials on primary care management of ulcerative colitis. http://prodigy.clarity.co.uk/about/how_we_produce_prodigy_topics#-475152 Suchzeitraum: Date unrestricted bis 02/2010 LoE und GoR: k.A.
	Empfehlungen: **The most commonly prescribed drugs are:** • Corticosteroids — topical corticosteroids are preferred to systemic steroids; they are used only for the induction of remission.

	• Thiopurines (azathioprine and mercaptopurine) — although neither drug is licensed for ulcerative colitis. • Aminosalicylates (ASAs) — including balsalazide, mesalazine, olsalazine, and sulfasalazine. • **Ciclosporin may be used if the person has severe acute ulcerative colitis that is refractory to corticosteroid treatment.** o Infliximab may be used when treatment with ciclosporin is inappropriate or contraindicated. Ist management is likely to be carried out entirely in secondary care. **Basis for recommendation** *Aminosalicylates:* • PRODIGY found evidence from systematic reviews of randomized controlled trials that aminosalicylates are effective for inducing and maintaining remission in ulcerative colitis. *Corticosteroids:* • PRODIGY found evidence from uncontrolled trials that rectal and intravenous corticosteroids are effective for inducing remission in people with ulcerative colitis. • Because they have significant adverse effects with prolonged use, corticosteroids are not used to maintain remission [BNF 59, 2010]. *Infliximab* (a cytokine modulator): • PRODIGY found evidence from systematic reviews of randomized placebo-controlled trials that infliximab is effective for both inducing and maintaining remission in people with moderately-severe ulcerative colitis. *Thiopurines (azothioprine and mercaptopurine):* PRODIGY found evidence from systematic reviews of randomized controlled trials that the thiopurines (azathioprine and mercaptopurine) are not effective for inducing remission. However, there is moderate evidence that thiopurines are effective for maintaining remission.
Kornbluth 2010: Erratum: Ulcerative Colitis Practice Guidelines in Adults: American College of Gastroenterology, Practice Parameters Committee.	*Leitlinie des* American College of Gastroenterology
	Methodik Grundlage der Leitlinie: Leitlinie nach dem GRADE approach. Double-blind placebo controlled studies are preferable, but compassionate-use reports and expert review articles are used in a thorough review of the literature conducted through Medline with the National Library of Medicine. Suchzeitraum: k.A. LoE und GoR: • Grade A recommendations imply that there is consistent level 1 evidence (randomized controlled trials),

	• Grade B indicates that the evidence would be level 2 or 3, which are cohort studies or case – control studies, • Grade C recommendations are based on level 4 studies, meaning case series or poor-quality cohort studies, • Grade D recommendations are based on level 5 evidence, meaning expert opinion.
	Empfehlungen: *RECOMMENDATIONS FOR MANAGEMENT OF SEVERE COLITIS* • The patient with severe colitis refractory to maximal oral treatment with prednisone, oral aminosalicylate drugs, and topical medications may be treated with infliximab 5 mg / kg if urgent hospitalization is not necessary (Evidence A). • The patient who presents with toxicity should be admitted to hospital for a course of intravenous steroids (Evidence C). • Failure to show significant improvement within 3 – 5 days is an indication for either colectomy (Evidence B) or treatment with intravenous cyclosporine (CSA; Evidence A) in the patient with severe colitis. • Long-term remission in these patients is significantly enhanced with the addition of maintenance 6-MP (Evidence B). • Infliximab may also be effective in avoiding colectomy in patients failing intravenous steroids but its long-term efficacy is unknown in this setting (Evidence A).
Bitton 2012: Treatment of Hospitalized Adult Patients With Severe U lcerative Co I itis: Toronto Consensus Statements.	Leitlinie der Canadian Association of Gastroenterology consensus group
	Methodik Grundlage der Leitlinie: The modified GRADE {Grading of Recommendations Assessment, Development, and Evaluation) criteria were used to rate the strength of recommendations and the quality of evidence. Suchzeitraum: ab 2005 Summary of categories used in the voting and evidence grading processes *Voting options: Ievei of agreement* Agree strongly (A+) Agree with minor reservation (A) Agree with major reservatian (A-) Disagree with minor reservatian (D) Disagree w1th major reservatian (D-) Disagree strongly (D +) *Grade of recommendation* 1A: Strang recommendatian, high-quality evidence 1B: Strang recammendatian, maderate-quality evidence 1C: Strang recammendatian, law-quality ar very law-quali(y evidence

	2A: Weak recommendation, high-quality evidence 2B: Weak recommendatian, maderate-quality evidence 2C: Weak recammendation, law-quality or very law-quality evidence *Voting options: Ievei of agreement:* Agree strongly (A+); Agree with minor reservation (A); Agree with major reservatian (A-); Disagree with minor reservatian (D); Disagree w1th major reservatian (D-); Disagree strongly (D +)
	Empfehlungen: - Routine use of antibiotics is not recommended. Vote: A + = 67%, A = 33%; Grade of recommendation: **1B** *Steroid use and predictors of steroid failure* - First-line medical therapy for patients should be intravenous corticosteroids. Vote: A + = 86%, A = 14%; Grade of recommendation: **1A** - Patients who fail to improve on intravenous corticosteroids within 72 h, as determined by clinical, radiological, and laboratory parameters, have poor outcomes and should be considered for either surgery or second-line medical therapy. Vote: A + = 81%, A = 19%; Grade of recommendation: **1B** *Cyclosporine and infliximab* - Either intravenous cyclosporine or infliximab is an appropriate choice for selected patients who have failed intravenous corticosteroid therapy. Vote: A + =48%, A= 48%, A-=4%; Grade of recommendation: **1A** - A decision regarding response to infliximab or cyclosporine should be made within 5-7 days after initiation of such therapy. Vote: A+ =81%, A= 19%; Grade ofrecommendation: **1C** - Cyclosporine and infliximab should be utilized at centers with appropriate experience and support in their use. Vote: A+ =67%,A=29%; A-=4%; Gradeofrecommendation: **1C** - Patients who respond to intravenous cydosporine should be switched to oral cydosporine; subsequently azathioprine or 6-MP (6-mercaptopurine) should be initiated. Vote: A + = 67%, A = 33%; Grade of recommendation: **1C** - Patients who respond to a single infusion of infliximab should be given two additional induction doses at 2 and 6 weeks, followed by maintenance infliximab therapy. Vote: A + =57%, A = 38%, A- = 0%, D- = 5%; Grade of recommendation: **1B** - Sequential rescue therapy with cyclosporine and infliximab should be avoided. Vote: A + = 85%, A = 10%, A- = 5%; Grade of recommendation: **1B**

	Surgical issues - Urgent surgical consultation should be obtained for all patients with systemic toxicity or megacolon. Vote: A + = 100%; Grade of recommendation: **1B** - Patients who have failed primary therapy and are being considered for infliximab or cyclosporine therapy should have a concomitant surgical consult. Vote: A+ =81%,A=14%,A- =5%; Grade of recommendation: **1C** - Patients who fail to respond to infliximab or cyclosporine within 5-7 days have a poor outcome and surgery is advisable. Vote: A + = 81%, A = 19%; Grade of recommendation: **1B** *Key recommendations:* ➢ for the treatment of hospitalized patients with severe UC include early escalation to second-line medical therapy with either infliximab or cyclosporine in individuals in whom parenteral steroids have failed after 72 h. ➢ These agents should be used in experienced centers where appropriate support is available. Sequential therapy with cyclosporine and infliximab is not recommended. ➢ Surgery is an option when first-line steroid therapy fails, and is indicated when second-line medical therapy fails and/or when complications arise during the hospitalization.
Orlando et al. 2011: The Italian Society of Gastroenterology (SIGE) and the Italian Group for the study of Inflammatory Bowel Disease (IG-IBD) Clinical	*Leitlinie der* Italian Society of Gastroenterology (SIGE) and the Italian Group for the study of Inflammatory Bowel Disease (IG-IBD)
	Methodik Grundlage der Leitlinie: The Oxford methodology was used to establish levels of evidence and degree of recommendations. A complete research thorough Pub Med, Embase, Cochrane database was done by each expert in order to formulate recommendations. Suchzeitraum: k.A. LoE und GoR:

Practice Guidelines: The use of tumor necrosis factor-alpha antagonist therapy in Inflammatory Bowel Disease.	Levels of evidence and grades of recommendation based on the Oxford Centre for Evidence Based Medicine [8]. **Levels of evidence** 1a – Systematic review (SR) with homogeneity of Level 1 diagnostic studies – Systematic review (SR) with homogeneity of randomised controlled trials (RCTs) 1b – Validating cohort study with good reference standards – Individual RCT (with narrow Confidence interval) 1c – Specificity is so high that a positive result rules in the diagnosis ("SpPin") or sensitivity is so high that a negative result rules out the diagnosis ("SnNout") – All or none 2a – SR with homogeneity of level> 2 diagnostic studies – SR (with homogeneity) of cohort studies 2b – Exploratory cohort study with good reference standards – Individual cohort study (including low quality RCT; e.g., <80% follow-up) 2c – "Outcomes" research; ecological studies 3a – SR with homogeneity of 3b and better studies – SR with homogeneity of case–control studies 3b – Non-consecutive study; or without consistently applied reference standards – Individual case–control study 4 – Case–control study, poor or non-independent reference standard – Case-series (and poor quality cohort and case–control studies) 5 – Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" – Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" **Grades of recommendation** A – Consistent level 1 studies B – Consistent level 2 or 3 studies or extrapolations from level 1 studies C – Level 4 studies or extrapolation from level 2 or 3 studies D – Level 5 evidence or troublingly inconsistent or inconclusive studies of any level Empfehlungen: *Induction and maintenance of response/remission in moderate-to-severe steroid-refractory or steroid-dependent Ulcerative Colitis* • Infliximab induction regimen can be used in patients with moderate-to-severe UC who are refractory to systemic corticosteroids [EL 1b, RG A] and in corticosteroid-dependent patients who are intolerant/refractory to thiopurines **[EL 2b, RG C]** • One year scheduled treatment with Infliximab can be used in patients who have responded to infliximab induction [EL 1b, RG A]. In patients who are thiopurine-naïve, maintenance therapy with thiopurines alone is a valuable option **[EL 5, RG D]** • The duration of the therapy over 1 year should be carefully evaluated on a case-by-case basis **[EL 4, RG C]** • Maintenance therapy with infliximab that achieves only response should be carefully evaluated in the face of a colectomy **[EL 5, RG D]**

	Induction and maintenance of response/remission in severe steroids refractory Ulcerative Colitis • Infliximab reduces colectomy rate within 3 months in steroid-refractory severe UC **[EL 1b, RG A]** • A colectomy is recommended if there is no improvement within 5 days **[EL 5, RG D]** • Infliximab should be avoided in patients with a complicated disease **[EL 5, RG D]** • Re-infusions seem more effective than one single infusion to prevent early colectomy **[EL 4, RG C]**, but there is insufficient evidence to provide recommendations on the ideal dosing schedule. Antibiotic prophylaxis against opportunistic infections is suggested **[EL 5, RG D]** **Anti-TNF_ and malignancies** • Recommendations reported for anti-TNFa agents and malignancies in CD, are also suggested for UC, although the number and follow-up of treated patients are significantly lower than for CD **[EL 4, RG C]** *Infections* • The risk of infections is increased in patients treated with anti-TNFa agents **[EL 1]** • It is not clear whether this risk is related to biologics or to steroids use, severity of disease and narcotic drugs **[EL 3b]** • The risk of severe infections is not usually increased **[EL 1]** but it seems higher in elderly patients **[EL 3]** • Biologics should not be started during infections **[EL 5, RG D]** *Bacterial and fungal infections* • Anti-TNFa therapy should be temporarily stopped until the resolution of the active bacterial infection **[EL 5,RG D]** • *Clostridium difficile* infection must be ruled out before starting anti-TNF a therapy **[EL 2, RG B]** • Patients on immunomodulator therapy have a higher risk of pneumococcal infection **[EL 4]** • Pneumococcal vaccination is recommended in elderly patients, whereas it is a valuable option in the other age groups on anti-TNF_ therapy **[EL 5, RG D]** • Consider *Pneumocystis jiroveci* (*P. carinii*) pneumonia prophylaxis in patients treated with anti-TNF_ agents who are also receiving other immunosuppressive medications, particularly high-doses of glucocorticoids **[EL 4, RG D]**
Brazilian Study Group of Inflammatory Bowel Diseases 2010: CONSENSUS	*Leitlinie der* **Brazilian Study Group of Inflammatory Bowel Diseases**
	Methodik Grundlage der Leitlinie: Leitlinie nach dem Grade approch (The grades standardized by the American Gastroenterological Association (AGA) were adopted by the present consensus guidelines)

GUIDELINES FOR THE MANAGEMENT OF INFLAMMATORY BOWEL DISEASE.	Suchzeitraum:k.A. The grades standardized by the American Gastroenterological Association (AGA) were adopted by the present consensus guidelines as follows: **Grade A** - consistent evidences from well-designed controlled randomized trials with an adequate number of patients. **Grade B –** evidences from at least a well-designed trial with or without randomization or from meta-analyses. **Grade C -** evidences based on clinical experience
	Empfehlungen: *Severe and fulminant UC* • These patients face a real risk of death and should be admitted to hospital to undergo intensive treatment. • The choice treatment is parenteral corticosteroids (e.g., hydrocortisone, 100 mg IV, 3-4 times/day). • Corticosteroid response assessment must be done between 3 and 7 days and rescue or surgical treatment is indicated in case of therapeutic failure ➢ **Grade B** ➢ Besides corticosteroid treatment it is important to: a) correct hydroelectrolytic disturbances, specially potassium and magnesium b) research *C. difficile* toxin c) institute enteral diet d) suspend any anti-inflammatory, anticholinergic, antidiarrheic or opiate drug that the patient might be taking e) carry out blood transfusion if hemoglobin is lower than 10 g/dL; f) start prophylactic subcutaneous heparin **Grade B** • Fulminat cases with or without toxic megacolon must be clinically and radiologically evaluated and be supervised by a coloproctologist. • In such cases, rescue therapy must be carried out with cyclosporine IV, or infliximab ➢ **Grade A** • All patients undergoing successful rescue treatment must receive an oral aminosalicylate (SSZ or mesalazine) besides an immunosuppressor and/or infliximab. • However, the long-term possibility to preserve the colon is not promising ➢ **Grade C** *Corticosteroid-refractory IBD patients* • For the therapeutic approach of corticosteroid-refractory patients, the

<table>
<tr><td></td><td>severity of disease must be considered.
• Also it is important to bear in mind that immunosuppressor's time of action is longer (3-4 months).
• On the other hand, anti-TNF acts more quickly and is the choice treatment for these patients.
• Patients already using an immunosuppressor must take anti-TNF as well and in case of UC surgery must be considered.
• Many patients benefit from adjuvant nutritional therapy preferably via an enteral feeding tube
➢ Grade C</td></tr>
<tr><td rowspan="3">Mowat 2011: Guidelines for the management of inflammatory bowel disease in adults.</td><td>These guidelines have been commissioned by the Clinical Services and Standards Committee of the
British Society of Gastroenterology (BSG)</td></tr>
<tr><td>Methodik

Grundlage der Leitlinie: The guidelines were drafted shortly after the ECCO consensus
was published in the knowledge of the extremely rigorous nature and literature review accompanying that process; throughout the current document, reference is made to the ECCO consensus statements.

Suchzeitraum:

LoE und GoR (adapted from the Oxford Centre for Evidence Based Medicine):

<table>
<tr><th>EL</th><th>Individual study</th><th>Technique</th></tr>
<tr><td>1a</td><td>Systematic review (SR) with homogeneity of level 1 diagnostic studies</td><td>Systematic review (SR) with homogeneity of randomised controlled trials (RCTs)</td></tr>
<tr><td>1b</td><td>Validating cohort studies with good reference standards</td><td>Individual RCT (with narrow CI)</td></tr>
<tr><td>1c</td><td>Specificity is so high that a positive result rules in the diagnosis (SpPIn) or sensitivity is so high that a negative result rules out the diagnosis (SnNout)</td><td>All or none</td></tr>
<tr><td>2a</td><td>SR with homogeneity of >level 2 diagnostic studies</td><td>SR (with homogeneity) of cohort studies</td></tr>
<tr><td>2b</td><td>Exploratory cohort study with good reference standards</td><td>Individual cohort study (including low quality RCT; eg, <80% follow-up)</td></tr>
<tr><td>2c</td><td></td><td>'Outcomes' research; ecological studies</td></tr>
<tr><td>3a</td><td>SR with homogeneity of 3b and better studies</td><td>SR with homogeneity of case-control studies</td></tr>
<tr><td>3b</td><td>Non-consecutive study; or without consistently applied reference standards</td><td>Individual case–control study</td></tr>
<tr><td>4</td><td>Case–control study, poor or non-independent reference standard</td><td>Case series (and poor quality cohort and case–control studies)</td></tr>
<tr><td>5</td><td>Expert opinion without explicit critical appraisal, or based on physiology, 'bench research' or 'first principles'</td><td>Expert opinion without explicit critical appraisal, or based on physiology, 'bench research' or 'first principles'</td></tr>
<tr><td>RG</td><td>GRADES OF EVIDENCE</td><td></td></tr>
<tr><td>A</td><td>Consistent level 1 studies</td><td></td></tr>
<tr><td>B</td><td>Consistent level 2 or 3 studies or extrapolation from level 1 studies</td><td></td></tr>
<tr><td>C</td><td>Level 4 studies or extrapolation from level 2 or 3 studies</td><td></td></tr>
<tr><td>D</td><td>Level 5 evidence or troublingly inconsistent or inconclusive studies of any level</td><td></td></tr>
</table>
</td></tr>
<tr><td>Empfehlungen:

Recommendations for the treatment of Acute severe ulcerative colitis:
Intravenous corticosteroids:
• Either hydrocortisone 100 mg four times a day or methylprednisolone 60 mg/day (EL1b, RGB)
• Higher doses of steroids offer no greater benefit, but lower doses are less effective.
• Consideration of colectomy or rescue therapy with either intravenous ciclosporin (CsA) 2 mg/kg/day OR infliximab (IFX) if there is no improvement by day 3 or there is subsequent deterioration (EL1b, RG</td></tr>
</table>

	B) • For patients already on immunosuppressive therapy such as AZA/MP at the time of presentation, surgery should be considered as the first option **(EL4, grade D)** *Rescue with intravenous CsA:* • 2 mg/kg/day is as effective as 4 mg/kg/day with decreased toxicity • Magnesium, cholesterol and creatinine should be measured within 48 h of starting CsA • Beware contraindications ($Mg2^{+}$<0.5 mM or cholesterol <3.0 mM) and be vigilant for toxicity • Following induction of remission, oral CsA for 3-6 months is appropriate **(EL 1b, RG B)** • Intravenous CsA alone may be as effective as methylprednisolone, but potential side effects mean that it is rarely an appropriate single first line therapy **(EL1b, RG C)** *Rescue with IFX:* • dose induction of 5 mg/kg (0, 2 and 6 weeks). The side effects of IFX, including therapy associated risk of mortality, should be discussed fully prior to its initiation **(EL2, grade C)** • IFX maintenance therapy in ulcerative colitis is not recommended because of the low corticosteroid-free remission rates after 1 year, and the limited data on subsequent need for colectomy **(EL1b, grade C)** • IFX should be given as a 'bridge' to longer term immunosuppressive therapy such as AZA/MP. • If no response to rescue therapy is seen within 4-7 days, colectomy is recommended **(EL5, RG D)**. Specifically, we do not recommend CsA after IFX or vice versa **(EL5, RG B)** *Other factors to consider:* • The long-term follow-up of patients following an attack of acute severe ulcerative colitis reveals 50% of those who do not enter complete remission with steroids will require colectomy within 1 year • Patients who avoid surgery should be considered for maintenance therapy with a thiopurine. • On discharge, oral steroids should be tapered over 8 weeks. Supplementation with calcium and vitamin D is recommended.

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library am 21.01.2014

Schritt	Suchfrage
1	MeSH descriptor: [Colitis, Ulcerative] explode all trees
2	MeSH descriptor: [Inflammatory Bowel Diseases] explode all trees
3	ulcerative colitis:ti
4	ulcerative colitis:ab
5	#1 or #2 or #3 or #4
6	#5 from 2009 to 2014
7	#5 from 2013 to 2014

MEDLINE (PubMed) am 21.01.2014

Schritt	Suchfrage
#1	Search “colitis, ulcerative"[MeSH Terms]
#2	Search "ulcerative colitis"[Title/Abstract]
#3	Search inflammatory bowel diseases [mh:noexp]
#4	Search ((#1) OR #2) OR #3
#5	Search (((((activi*[Title/Abstract]) OR active*[Title/Abstract]) OR activa*[Title/Abstract]) OR acute[Title/Abstract]) OR severe[Title/Abstract]) OR mild[Title/Abstract]
#6	Search (#4) AND #5
#7	Search #6 Filters: Systematic Reviews; Meta-Analysis
#8	Search ((((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
#9	Search (#6) AND #8
#10	Search #7 OR #9 Filters: published in the last 5 years
#11	Search (#7) OR #9 Publication date from 2013/07/01 to 2014/12/31

MEDLINE (PubMed) nach Leitlinien am 21.01.2014

Schritt	Suchfrage
#1	Search “colitis, ulcerative"[MeSH Terms]
#2	Search "ulcerative colitis"[Title/Abstract]
#3	Search inflammatory bowel diseases [mh:noexp]
#4	Search ((#1) OR #2) OR #3
#5	Search (((((activi*[Title/Abstract]) OR active*[Title/Abstract]) OR activa*[Title/Abstract]) OR acute[Title/Abstract]) OR severe[Title/Abstract]) OR mild[Title/Abstract]
#6	Search ((#4) AND #5 Filters: Guideline; Practice Guideline
#7	Search guideline*[Title] AND #7
#8	Search #7 OR #6 Filters: published in the last 5 years
#9	Search #7 OR #6 Filters: Publication date from 2013/07/01 to 2014/12/31

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Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2013-B-126 Vedolizumab (Morbus Crohn)

Stand: Januar 2014

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Vedolizumab [Erwachsene Patienten mit Morbus Crohn]	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*siehe Übersicht II* Zugelassene Arzneimittel im Anwendungsgebiet:
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Patientenindividuell Operation
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Therapiehinweis zu Infliximab bei Morbus Crohn (Beschluss vom 16.10.2000)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*
[…] vorzugsweise eine Therapie, […] die sich in der praktischen Anwendung bewährt hat.	„nicht angezeigt“

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Vedolizumab ATC-Code Entyvio®	Geplantes Anwendungsgebiet laut Beratungsanforderung: Vedolizumab ist zugelassen für die Behandlung der mittelschweren bis schweren aktiven Morbus Crohn bei erwachsenen Patienten, die auf eine konventionelle Therapie oder einen Tumor-Nekrose-Faktor alpha (TNF-α) Inhibitor unzureichend, nicht oder nicht mehr ansprechen oder bei denen eine Unverträglichkeit oder Kontraindikation vorliegt
Tumornekrosefaktor alpha (TNF-alpha)-Inhibitoren	
Infliximab L01XC11 Remicade®	Remicade ist indiziert zur: · Behandlung eines mäßig- bis schwergradig aktiven Morbus Crohn bei erwachsenen Patienten, die trotz eines vollständigen und adäquaten Therapiezyklus mit einem Kortikosteroid und/oder einem Immunsuppressivum nicht angesprochen haben oder die eine Unverträglichkeit oder Kontraindikationen für solche Therapien haben. · Behandlung von aktivem Morbus Crohn mit Fistelbildung bei erwachsenen Patienten, die trotz eines vollständigen und adäquaten Therapiezyklus mit einer konventionellen Behandlung (einschließlich Antibiotika, Drainage und immunsuppressiver Therapie) nicht angesprochen haben.
Adalimumab L01XC04 Humira®	Humira ist indiziert zur Behandlung des mittelschweren bis schweren, aktiven Morbus Crohn bei erwachsenen Patienten, die trotz einer vollständigen und adäquaten Therapie mit einem Glukokortikoid und/oder einem Immunsuppressivum nicht ausreichend angesprochen haben oder die eine Unverträglichkeit gegenüber einer solchen Therapie haben oder bei denen eine solche Therapie kontraindiziert ist.
Aminosalicylsäuren	
Mesalazin A07EC02 Salofalk® (Tab)	Morbus Crohn: zur Behandlung des akuten Schubs
Sulfasalazin A07EC01 Azulfidine®	Akutbehandlung des milden bis moderaten Morbus Crohn bei Befall des Kolons.

Quellen: Fachinformationen

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Indikation für die Recherche bei Vedolizumab:
Vedolizumab ist zugelassen für die Behandlung der mittelschweren bis schweren aktiven Morbus Crohn bei erwachsenen Patienten, die auf eine konventionelle Therapie oder einen Tumor-Nekrose-Faktor alpha (TNF-α) Inhibitor unzureichend, nicht oder nicht mehr ansprechen oder bei denen eine Unverträglichkeit oder Kontraindikation vorliegt.

Berücksichtigte Wirkstoffe/Therapien:
TNF-alpha-Blocker: Infliximab, Adalimumab; **Kortikosteroide:** Prednisolon; **Immunsuppressiva:** Azathioprin; **Weitere:** Budesonid, Mesalazin, Sulfasalazin

Systematische Recherche:
Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation ***„Morbus Crohn“*** durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am ***14.01.2014*** abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (einschl. NHS CRD-Datenbanken), MEDLINE (PubMed), Leitlinien.de (ÄZQ), AWMF, NGC, TRIP, DAHTA, NIHR HSC. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.
Die Recherche ergab ***421*** Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Davon wurden **113** Quellen eingeschlossen. Insgesamt ergab dies **21** Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Abkürzungen

5-ASA	5-Aminosalicylsäure
6-MP	6-mercaptopurine
AE	Adverse event
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
AZA	Azathioprine
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
CD	Crohn’s disease
CDAI	Crohn's Disease Activity Index
CR	Clinical response
DAHTA	Deutsche Agentur für Health Technology Assessment
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of recommendation
HBI	Harvey-Bradshaw Index
IBD	Inflammatory bowel disease
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LoE	Level of evidence
MD	Mean difference
MTX	Methotrexat
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
NIHR HSC	National Institute for Health Research Horizon Scanning Centre
NNT	Number needed to treat
OR	Odds ratio
RCT	Randomized controlled trial
RR	Relative risk
SR	Systematic review
TNF	Tumornekrosefaktor
TRIP	Turn Research into Practice Database
UC	Ulcerative colitis

Doherty et al. (2009). Interventions for prevention of post-operative recurrence of Crohn's disease. Cochrane Database Syst Rev 2009; (4): CD006873.	1. Fragestellung To undertake a systematic review of the use of medical therapies for the prevention of post-operative recurrence of Crohn's disease
	2. Methodik **Population**: Patients with Crohn's disease who have undergone surgical resection (ileal resection, ileo-colonic resection, colonic resection) and were subsequently commenced on medical therapy to prevent recurrence of the disease. Cases where surgery was performed with resection of diseased segments and anastomosis of non-involved intestines were considered "surgical resection". **Intervention**: Mesalamine (mesalazine), 5-aminosalicyclate, sulfasalazine (sulphasalazine), metronidazole, ornidazole, azathioprine, 6-mercaptopurine (6-MP), methotrexate, probiotics, enteral nutrition, infliximab, adalimumab, certolizumab, and natalizumab. **Komparator**: placebo, or other medical therapies **Endpunkt**: clinical recurrence within 12 month **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: 1966-2009 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 23 trials
	3. Ergebnisdarstellung **5-ASA vs. Placebo (4 trials, n=652)**: statistically significant difference in favor of 5-ASA, RR 0.76 (0.62-0.94), I^2=0%. NNT=12 **Immunosuppressives vs. 5-ASA (4 trials, n=349)**: no statistically significant difference **Immunosuppressives vs. Placebo (2 trials, n=167)**: statistically significant difference in favor of immunosuppressives, (RR 0.59; 95% CI 0.38 to 0.92, NNT = 7)
	4. Anmerkungen/Fazit der Autoren Our current approach is to recommend short term use of antibiotic therapy in the immediate post-operative period to patients with risk factors for early recurrence (and where tolerated). This may then be followed by endoscopic re-assessment (by colonoscopy at 3 to 6 months post surgery) with discussion of the risks and benefits of 5-ASA versus immunosuppressive or anti-TNF therapy with patients in the context of the degree of endoscopic recurrence observed.
Benchimol et al. (2009). Budesonide for maintenance of remission in Crohn's	1. Fragestellung The primary objective was to assess the efficacy of budesonide therapy for maintenance of remission in Crohn's disease.

disease. Cochrane Database of Systematic Reviews 2009; (1)	2. Methodik **Population**: patients of any age with CD **Intervention**: Oral budesonide **Komparator**: k.A. **Endpunkt**: Maintenance of remission **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: up to 2008 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 11 trials
	3. Ergebnisdarstellung <u>Maintenance of Clinical Remission</u> **Budesonide 6 mg vs placebo**: no statistically significant difference **Budesonide 3 mg vs placebo**, 3 month (4 trials, n=263): significant difference in favor of budesonide, RR 1.31 [1.03, 1.67], I^2=0%. no statistically significant difference after 6 and 12 month <u>Time to Relapse</u> **Budesonide 6 mg vs placebo** (4 trials, n=171): statistically significant difference in favor of budesonide, MD 59.93 [19.02, 100.84], I^2=58% **Budesonide 3 mg vs placebo** (5 trials, n=340): statistically significant difference in favor of budesonide, MD 30.59 [9.10, 52.09], I^2=2% <u>Proportion of Patients with Treatment-Related Adverse Events at 12 Months</u> **Budesonide 6 mg vs placebo** (5 trials, n=419): statistically significant difference in favor of placebo RR 1.49 [1.01, 2.19], I^2=34% **Budesonide 3 mg vs placebo** (5 trials, n=440): no statistically significant difference
	4. Anmerkungen/Fazit der Autoren The existing data suggest that budesonide is not effective for maintenance of remission in CD, particularly when used beyond 3 months following induction of remission. Budesonide may confer benefit in terms of a lower mean CDAI score and a longer time to relapse of disease. However these mild benefits are outweighed by the risk of adrenocorticoid suppression when using budesonide for extended periods of time. Patients receiving 6 mg daily of budesonide for extended periods of time experienced a higher rate of treatment-related adverse events, although these events did not result in study withdrawal and therefore may have been relatively mild. In light of these results, budesonide cannot be recommended for maintenance therapy in quiescent Crohn's disease.
McDonald et al. (2012). Methotrexate for induction of remission in refractory Crohn's	1. Fragestellung The primary objective was to assess the efficacy and safety of methotrexate used for the treatment of active refractory Crohn's disease.
	2. Methodik **Population**: Patients greater than 17 years of age with refractory Crohn's disease

disease. Cochrane Database Syst Rev 2012; 12 CD003459.	**Intervention**: oral or parenteral methotrexate **Komparator**: placebo or a control medication **Endpunkt**: clinical remission, adverse events **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: up to 2012 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 7 trials
	3. Ergebnisdarstellung The seven included studies differed with respect to participants, intervention, and outcomes to the extent that it was considered to be inappropriate to pool the data for meta-analysis. <u>Induction of remission</u> • Two studies which employed low doses of oral methotrexate showed no statistically significant difference for induction of remission between methotrexate and placebo treated patients. • no statistically significant difference for induction of remission between oral methotrexate and oral 6-mercaptopurine • Maté-Jiménez 2000 did find a statistically significant difference in efficacy between oral methotrexate and oral 5-ASA. Twenty per cent (3/15) of patients administered methotrexate and 86% (6/7) of patients administered 5-ASA failed to enter remission (RR 0.23, 95%CI 0.08 to 0.67). • no advantage for induction of remission with the combination of intravenous and oral methotrexate with infliximab compared to infliximab alone • The Feagan 1995 study which employed a higher dose of intramuscularly administered methotrexate showed a statistically significant benefit relative to placebo. <u>Adverse events</u> • Two studies reported the proportion of patients who experienced at least one adverse event (Ardizzone 2003; Schröder 2006).The proportion of patients who experienced at least one adverse event was significantly higher in methotrexate patients compared to azathioprine. • Schröder 2006 reported no significant difference in adverse events between the combination of methotrexate and infliximab compared to infliximab monotherapy. •
	4. Anmerkungen/Fazit der Autoren There is evidence from a single large randomized trial which suggests that intramuscular methotrexate (25 mg/week) provides a benefit for induction of remission and complete withdrawal from steroids in patients with refractory Crohn's disease. Lower dose oral methotrexate does not appear to provide any benefit relative to relative to placebo or active comparator (e.g. azathioprine or 6-mercaptopurine). The addition of methotrexate to infliximab therapy does not appear to provide any additional benefit over infiximab monotherapy.

Patel et al. (2009). Methotrexate for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2009; (4): CD006884.	1. Fragestellung To conduct a systematic review of randomized trials examining the efficacy and safety of methotrexate for maintenance of remission in patients with Crohn's disease.
	2. Methodik **Population**: Adult patients (> 18 years of age) with chronic active Crohn's disease **Intervention**: methotrexate **Komparator**: placebo or an active comparator **Endpunkt**: maintaining clinical remission, relapse, adverse events **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: 1980-2009 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 3 trials
	3. Ergebnisdarstellung <u>maintaining clinical remission</u> **Methotrexate versus placebo** (2 trials, n=98): statistically significant difference in favor of methotrexate, OR 3.11 (95% CI 1.31 to 7.41; P = 0.01, I^2=0% **Methotrexate versus 6-mercaptopurine**: no statistically significant difference
	4. Anmerkungen/Fazit der Autoren There is evidence from a single, well-designed randomized trial that methotrexate 15mg intramuscularly weekly can be safely used for maintenance of remission in Crohn's disease. Intramuscular and subcutaneous routes have similar pharmacokinetics; however, self-injecting via a subcutaneous route is easier and better tolerated by patients (Balis 1988; Egan 1999b; Arthur 2002). Accordingly, methotrexate is usually administered subcutaneously in practice.
Prefontaine et al (2009). Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2009; (1)	1. Fragestellung We performed a meta-analysis of all published randomized, double-blind, placebo-controlled trials of azathioprine or 6-mercaptopurine therapy in patients with quiescent Crohn's disease.
	2. Methodik **Population**: Patients greater than 18 years of age with quiescent Crohn's disease **Intervention**: azathioprine or 6-mercaptopurine **Komparator**: k.A. **Endpunkt**: maintenance of remission **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: upt to 2008 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 8 trials

	3. Ergebnisdarstellung Maintenance of remission **Azathioprine** (8 trials, n=463): statistically significant difference in favor of azathioprine OR 2.32 [1.55, 3.49], I^2=10% **6-MP** (1 trial, n=87): statistically significant difference in favor of 6-MP, OR 3.32 [1.40, 7.87]. Withdrawals due to adverse events **Azathioprine** (6 trials, n=530): statistically significant difference in favor of placebo (OR 3.74; 95% CI 1.48 to 9.45, I^2=61%)
	4. Anmerkungen/Fazit der Autoren Among patients in remission, azathioprine has a benefit for maintaining remission (Peto OR 2.32; 95% CI 1.55 to 3.49). There is weak evidence for a steroid sparing effect with azathioprine treatment. 6-Mercaptopurine may provide benefit for maintenance of remission. The trials were of relatively short duration, so the long term effectiveness of azathioprine and 6-mercaptopurine is unclear. Although azathioprine and 6-mercaptopurine may be effective for maintenance of remission in Crohn's disease their use is limited by serious adverse events which lead to cessation of therapy in 9 to 25% of patients.
Prefontaine et al. (2010). Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Cochrane Database Syst Rev 2010; (6): CD000545.	1. Fragestellung To determine the effectiveness of azathioprine and 6-mercaptopurine for induction of remission in active Crohn's disease.
	2. Methodik **Population**: Adult patients (age > 18 years) with Crohn's disease **Intervention**: Oral azathioprine (2.0 to 3.0 mg/kg/d) or 6-mercaptopurine (50 mg/d or 1.5 mg/kg/d) **Komparator**: placebo **Endpunkt**: induction of remission **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: up to 2009 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 8 trials
	3. Ergebnisdarstellung Induction of remission **azathioprine, 6-Mercaptopurine, combined azathioprine and 6-mercaptopurine** (8 trials, n=425): statistically significant difference in favor of intervention OR 2.43 [1.62, 3.64], I^2=73% **6-Mercaptopurine vs. Methotrexate**: no statistically significant difference Adverse effects: statistically significant difference in favor of placebo, OR 3.44 [1.52, 7.77], I^2=39%

	4. Anmerkungen/Fazit der Autoren Azathioprine and 6-mercaptopurine are effective therapy for inducing remission in active Crohn's disease. Adverse events were more common among patients on active therapy.
Lim et al. (2010). Aminosalicylates for induction of remission or response in Crohn's disease. Cochrane Database Syst Rev 2010; (12): CD008870.	1. Fragestellung To critically examine current available data on the efficacy of sulfasalazine and mesalamine for inducing remission or clinical response in patients with mildly to moderately active Crohn's disease.
	2. Methodik **Population**: Adults with mildly to moderately active Crohn's disease. **Intervention**: oral sulfasalazine or mesalamine alone **Komparator**: placebo, corticosteroids, and other aminosalicylates (alone or in combination with corticosteroids) **Endpunkt**: Induction of remission, Response to treatment **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: 1966-2010 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 19 trials
	3. Ergebnisdarstellung <u>Sulfasalazine versus placebo (3 trials)</u> **Induction of remission (CDAI <150), therapeutic response (VHI decrease >=25%) or clinical improvement**: no statistically significant difference (RR 1.51 [0.97, 2.35]) **Induction of remission (CDAI <150):** statistically significant difference in favor of Sulfasalazine RR 1.38 [1.02, 1.87], I^2=0% <u>Sulfasalazine versus corticosteroids (2 trials)</u> **Induction of remission (CDAI <150):** statistically significant difference in favor of corticosteroids RR 0.66 [0.53, 0.81], I^2=0% <u>Sulfasalazine versus combination therapy with sulfasalazine and corticosteroids (1 trial)</u> **Induction of remission:** statistically significant difference in favor of sulfasalazine and corticosteroids RR 0.64 [0.47, 0.86] <u>Mesalamine versus placebo (8 trials)</u> Controlled-release mesalamine **Decrease in CDAI >=50, HBI >=2 or improvement/remission**: no statistically significant difference **Induction of remission (CDAI <=150 + decrease of >=50:** no statistically significant difference Delayed-release mesalamine **Induction of remission or clinical improvement**: statistically significant difference in favor of Placebo compared to olsalazine (2 g/day), RR 0.36 [0.18, 0.71], 1 trial. Statistically significant difference in favor of Asacol (3.2 g/day) compared to placebo, RR 2.70 [1.06, 6.88], 1 trial. <u>Mesalamine versus corticosteroids (4 trials conventional corticosteroids, 1 trial</u>

	budesonid) **Induction of remission (CDAI < or =150 with or without decrease of at least 60 points)**: no statistically significant difference compared to corticosteroids. **Induction of remission (CDAI < or = 150)**: statistically significant difference in favor of budesonide RR 0.56 [0.40, 0.78] Mesalamine versus sulfasalazine alone or in combination with corticosteroids (2 trials) **Induction of remission (CDAI < 150) or clinical improvement**: no statistically significant difference
	4. Anmerkungen/Fazit der Autoren 1. Sulfasalazine at 3 to 6 g/day was only modestly superior to placebo, with benefit confined to those with colitis. 2. Sulfasalazine was inferior and not a useful adjunct to corticosteroid therapy. 3. Olsalazine and mesalamine at 1 to 2 g/day were ineffective and not superior to placebo. 4. Higher doses of mesalamine at 3 to 4.5 g/day: a. Have resulted in statistically significant but clinically insignificant changes in CDAI scores but have not been consistently shown to be effective for induction of remission in mild to moderately active Crohn's disease. b. Are inferior to budesonide. Although the superiority of conventional steroids has not been consistently demonstrated, in the absence of a sufficiently powered formal equivalence or non-inferiority study, it is likely that mesalamine would be inferior to conventional steroids. 5. There was a lack of good quality clinical trials comparing sulfasalazine with other mesalamine formulations. To date, while a body of evidence suggests a small benefit of aminosalicylates on clinical indices used to assess Crohn's disease activity, there is insufficient evidence to indicate that they are effective for induction of remission or mucosal healing.
Gordon et al. (2011). Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease. Cochrane Database of Systematic Reviews 2011;	1. Fragestellung The primary objective was to evaluate the efficacy of 5-ASA agents for the maintenance of surgically-induced remission in Crohn's disease. The secondary objective was to determine the frequency of adverse events associated with the use of 5-ASA agents for the maintenance of remission in Crohn's disease.
	2. Methodik **Population**: Patients of any age with Crohn's disease who were in remission following surgery, defined by a recognized Crohn's disease activity index or endoscopy, or who have undergone a curative surgical resection, as defined by the authors were considered for inclusion. **Intervention**: 5-ASA **Komparator**: Placebo, other intervention **Endpunkt**: clinical relapse, endoscopic recurrence

(1).	**Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: 1966-2010 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 9 trials
	3. Ergebnisdarstellung <u>5-ASAs vs. Placebo</u> **Relapse (8 trials, n=1,061)**: statistically significant difference in favor of 5-ASA, OR 0.71 [0.54, 0.94], I^2=0% **Safety (4 trials, n=664)**: no statistically significant difference <u>5-ASA vs. Immunosuppressives</u> **Relapse (2 trials, n=233)**: no statistically significant difference **Safety (2 trials, n=233)**: statistically significant difference in favor of 5-ASA, OR 0.46 [0.22, 0.97], I^2=0%
	4. Anmerkungen/Fazit der Autoren The results of the pooled analyses suggest that 5-ASA preparations may be marginally superior to placebo for the maintenance of surgically induced remission in patients with Crohn's disease. The results of the pooled analyses should be interpreted with caution due to methodological and statistical issues as well as possible publication bias. The potential benefit provided by 5-ASA drugs is modest with a number needed to treat of approximately 16 to 19 patients to avoid one relapse which raises issues about the cost-effectiveness of this therapy. However, 5-ASA drugs are safe and well tolerated. The incidence of adverse events did not appear to be different in patients receiving 5-ASA compared with those receiving placebo. We found no evidence in this review to suggest that 5-ASA preparations differ in efficacy to purine antimetabolites

Systematische Reviews

Mills et al. (2011). Crohn's disease. http://clinicalevidence.bmj.com/x/systematic-review/0416/overview.html, Zugriff am 16.01.2014.	1. Fragestellung What are the effects of medical treatments to induce remission in adults with Crohn's disease? What are the effects of medical interventions to maintain remission in adults with Crohn's disease; and to maintain remission following surgery?
	2. Methodik **Population**: adults with Crohn's disease **Intervention:** aminosalicylates, antibiotics, zathioprine/mercaptopurine, ciclosporin, corticosteroids (oral), enteral nutrition, fish oil, infliximab, methotrexate, probiotics, resection, segmental colectomy, smoking cessation, and strictureplasty **Komparator**: Placebo, another intervention **Endpunkt**: k.A. **Methode**: systematic review of systematic reviews of RCTs, RCTs, observational studies **Suchzeitraum**: 1966-2009 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 93 systematic reviews, RCTs and observational studies
	3. Ergebnisdarstellung What are the effects of medical treatments to induce remission in adults with Crohn's disease? **Oral corticosteroids:** • Methylprednisolone or prednisolone compared with placebo Methylprednisolone and prednisolone (combined analysis) are more effective at increasing remission rates at 15 weeks and longer in people with Crohn's disease (high quality evidence). • Budesonide compared with placebo Budesonide is more effective at increasing the rate of clinical remission at 12, 24, and 38 weeks in people with ileocolonic Crohn's disease not extending beyond the hepatic flexure (high-quality evidence). • Budesonide compared with methylprednisolone or prednisolone Budesonide and methylprednisolone or prednisolone seem equally effective at increasing remission rates in the shorter term (12 weeks) in people with Crohn's disease, but budesonide seems less effective at increasing remission rates in the longer term (24–28 weeks) in people with • Crohn's disease (high-quality evidence). **Aminosalicylates**: • Mesalazine compared with placebo (3 SRs, 1 RCT): Mesalazine seems more effective at reducing Crohn's Disease Activity Index scores at 3 months, but not at increasing remission at 6 weeks or 4 months, in people with Crohn's disease (moderate-quality evidence) • Olsalazine compared with placebo (1 RCT): Olsalazine seems less effective at increasing remission rates in people with Crohn's disease (moderate-quality evidence).

	• Sulfasalazine compared with placebo (1 RCT): Sulfasalazine seems more effective at increasing remission rates at 17 weeks in people with Crohn's disease (moderate-quality evidence). **Azathioprine or mercaptopurine (1 RCT)**: • Compared with placebo: Azathioprine or mercaptopurine seem more effective at increasing remission rates at 17 weeks in people with Crohn's disease (moderate-quality evidence). **Infliximab (2 SRs):** • Compared with placebo: Infliximab seems more effective at increasing remission rates at 4 weeks in people with moderate to severe Crohn's disease (moderate-quality evidence). <u>What are the effects of medical interventions to maintain remission in adults with Crohn's disease?</u> **Aminosalicylates:** • Compared with placebo (1 SR): Aminosalicylates (mesalazine or olsalazine) seem no more effective at reducing recurrence in people with Crohn's disease in medically induced remission (moderate-quality evidence). • Mesalazine compared with placebo (1 SR): Mesalazine is more effective at maintaining medically induced remission in people with Crohn's disease. pH7-dependent mesalazine is more effective at maintaining remission in people with medically induced remission, but pH6-dependent and controlled-release mesalazine are no more effective at maintaining medically induced remission in people with Crohn's disease (high-quality evidence). **Azathioprine** • Compared with placebo (1 SR): Azathioprine is more effective at maintaining remission in people with Crohn's disease at 6 to 24 months (high-quality evidence). • Compared with budesonide (1 RCT): Azathioprine and budesonide seem equally effective at maintaining remission at 12 months in people with Crohn's disease (moderate-quality evidence). **Methotrexate** • Compared with placebo (1 SR): Methotrexate seems more effective at maintaining clinical remission in people with Crohn's disease (moderate-quality evidence). **Infliximab** • Compared with placebo (3 SRs): Infliximab is more effective at maintaining clinical remission in people with Crohn's disease at 44 to 54 weeks (high-quality evidence). • Compared with placebo Infliximab may be more effective at improving quality of life (assessed using IBDQ and SF-36 questionnaire) at 54 weeks in people with Crohn's disease (low-quality evidence). • The most recent review (search date 2007, 3 RCTs) found that infliximab (5 mg or 10 mg every 8 weeks) significantly increased the proportion of

	people who maintained clinical remission at 44 to 54 weeks (2 RCTs, 404 people, Crohn's Disease Activity Index [CDAI] <150 after induction of remission with infliximab: 93/259 [36%] with infliximab v 22/145 [15%] with placebo; RR 2.50, 95% CI 1.64 to 3.80; P = 0.00001).
	4. Anmerkungen/Fazit der Autoren Aminosalicylates may be used for induction of remission in ambulatory people with mild to moderate disease who can tolerate oral intake. However, evidence suggests that benefit over placebo is marginal, and previous response to aminosalicylates should be taken into account when deciding whether to prescribe these drugs. Treatment decisions are often based on the site of disease and whether it is active, but there are not enough participant numbers in the RCTs to confirm this approach. Although previously published reviews found no benefit for aminosalicylates in maintenance of remission, the possibility of a minor beneficial effect in maintaining remission, combined with the relative safety of this drug and the suggestion that mesalazine may have a role in reducing cancer risk in inflammatory bowel disease, means that in practice many people have remained on aminosalicylates in the long term. There is good evidence to support the use of infliximab to maintain remission in people with Crohn's disease that is refractory to corticosteroids or conventional immunosuppressants (azathioprine, mercaptopurine, and methotrexate).
Ford et al. (2011). 5-aminosalicylates prevent relapse of Crohn's disease after surgically induced remission: systematic review and meta-analysis. *eingeschlossen*. Am J Gastroenterol. 106(3), 413-420. 2011.	1. Fragestellung Evidence from randomized controlled trials (RCTs) for the use of 5-aminosalicylic acid (5-ASA) drugs in Crohn's disease (CD) in remission after a surgical resection is conflicting. We conducted a systematic review and meta-analysis of RCTs to examine this issue.
	2. Methodik **Population**: Adults (> 90 % of patients aged > 16 years) with luminal Crohn's disease who were in remission after an intestinal resection **Intervention**: 5-ASA (Sulfasalazine, mesalamine, balsalazide, or olsalazine) **Komparator**: placebo or no therapy **Endpunkt**: relapse of disease activity **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: 1966-2010 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 11 (n=1,282)
	3. Ergebnisdarstellung All trials used either sulfasalazine or mesalamine Relapse of disease activity: **5-ASA vs. placebo or no therapy (11 trials, n=1,282)**: statistically significant difference in favor of 5-ASA, (RR = 0.86; 95 % CI = 0.74 – 0.99, I^2=35%) **Sulfasalazine vs. placebo or no therapy (5 trials, n=448)**: no statistically significant difference

	Mesalamine vs. placebo or no therapy (6 trials, n=834): statistically significant difference in favor of 5-ASA, (RR = 0.80; 95 % CI = 0.70 – 0.92, I^2=0%) **Safety (3 trials)**: No statistically significant difference in the incidence of adverse events
	4. Anmerkungen/Fazit der Autoren This systematic review and meta-analysis has demonstrated that 5-ASA drugs are more effective than placebo or no treatment in preventing relapse of luminal CD after a surgically induced remission, with an NNT to prevent one patient experiencing a relapse of disease activity of 13. This modest beneficial effect appeared to be limited to mesalamine, with sulfasalazine demonstrating no superiority over control therapy in five trials containing over 400 patients.
Kawalec et al. (2013). Tumor necrosis factor-alpha antibodies (infliximab, adalimumab and certolizumab) in Crohn's disease: systematic review and meta-analysis. Arch Med Sci 9(5), 765-779.	1. Fragestellung This meta-analysis compares the effectiveness and safety of tumor necrosis factor α (TNF-α) antibodies (infliximab, adalimumab and certolizumab) with either a placebo or each of them in the treatment of Crohn's disease (CD).
	2. Methodik **Population**: adults (≥ 18 years old) with moderate to severe, as well as fistulizing, active CD. **Intervention**: infliximab, adalimumab and certolizumab **Komparator**: infliximab, adalimumab and certolizumab or placebo **Endpunkt**: clinical response (a reduction of ≥ 70 points (CR-70) or of ≥ 100 points (CR-100) from the baseline in the CDAI score), clinical remission (a decrease in the CDAI score of ≤ 150 points from baseline), safety **Methode**: systematic review and meta-analysis of randomized studies. The studies included had to be performed with a control group but not necessarily with random allocation and/or blinding. **Suchzeitraum**: up to Nov. 2012 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 19 trials (18 RCTs, 1 CCT)
	3. Ergebnisdarstellung <u>TNF-α antibodies vs. placebo</u> **Induction of remission** at week 4 (8 trials, n=2277): statistically significant difference in favor of TNF-α antibodies (RR = 1.90, 95% CI: 1.55–2.33, p < 0.00001, I^2=0%). **Maintenance of remission** at weeks 48-56 (6 trials, n=1141): statistically significant difference in favor of TNF-α antibodies (RR = 1.86, 95% CI: 1.61–2.15, p < 0.00001, I^2=2%) **Safety**: In the overall analysis, there was no significant difference in the frequency of any AEs between anti-TNF therapy and the placebo (RR = 1.00, 95% CI: 0.90–1.12, p = 0.97) in the short-term induction treatment (range: 4–

	12 weeks). Infliximab vs. placebo **Induction of remission** at week 4 (1 trial, n=98): no statistically significant difference, RR 4.88 (0.72, 33.24), p=0,11 **Maintenance of remission** at weeks 48-56 (2 trials, n=408): statistically significant difference in favor of infliximab, RR 2.28 (1.48, 3.50), p=0,0002, I^2=0% Adalimumab vs. placebo **Induction of remission** at week 4 (3 trials, n=714): statistically significant difference in favor of adalimumab, RR 2.42 (1.60, 3.63), p<0,0001, I^2=0% **Maintenance of remission** at weeks 48-56 (4 trials, n=733): statistically significant difference in favor of adalimumab, RR 3.03 (2.21, 4.16), p<0,0001, I^2=27%
	4. Anmerkungen/Fazit der Autoren The results of the meta-analysis demonstrated that anti-TNF therapy has a beneficial effect on induction and maintenance of clinical remission and response, as well as fistula healing, when compared with placebo. Based on a safety analysis, there was no evidence for an increase in the incidence of any adverse events related to anti-TNF when compared with placebo. In conclusion, the risk-benefit ratio of therapy with infliximab, adalimumab or certolizumab in CD is therefore in favor of these agents.
Ford et al. (2011). Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol 2011; 106 (4): 644-59.	1. Fragestellung Systematic review and meta-analysis of RCTs to estimate the efficacy and safety of TNF-alpha drugs in IBD.
	2. Methodik **Population**: adult patients (> 90 % of participants over the age of 16 years) with active or quiescent IBD **Intervention**: infliximab, adalimumab, certolizumab, natalizumab **Komparator**: placebo **Endpunkt**: failure of remission, relapse of disease activity **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: 1966-2010 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 27 trials
	3. Ergebnisdarstellung Remissionsinduktion **TNF-alpha Antikörper** (10 trials, n=2756): statistically significant difference in favor of TNF-alpha antibodies vs. placebo, RR 0.87 (0.80, 0.94), I^2=68%. **Infliximab** (3 trials, n=562): statistically significant difference in favor of Infliximab (RR 0.68; 95%CI 0.52, 0.90, I^2=78%) **Adalimumab** (3 trials, n=714): statistically significant difference in favor of Adalimumab (RR 0.85; 95%CI 0.79, 0.91, I^2=0%) Remissionserhaltung:

	TNF-alpha Antikörper (5 trials, n=1390): statistically significant difference in favor of TNF-alpha antibodies vs. placebo, RR 0.71 (0.65, 0.76), I^2=5%. **Infliximab** (2 trials, n=408): statistically significant difference in favor of Infliximab (RR 0.72; 95%CI 0.63, 0.83, I^2=0%) **Adalimumab** (2 trials, n=554): no statistically significant difference
	4. Anmerkungen/Fazit der Autoren Infliximab and adalimumab were superior to placebo in inducing remission of active luminal CD, while there was no statistically significant difference detected between certolizumab and placebo. However, when the SONIC study was excluded from the analysis, there was no statistically significant difference detected between infliximab and placebo. In preventing relapse of quiescent luminal CD, once remission or response to therapy had been achieved, both infliximab and certolizumab appeared more effective than placebo, although the latter was studied in only one trial.
Costa et al. (2013). Infliximab reduces hospitalizations and surgery interventions in patients with inflammatory bowel disease: a systematic review and meta-analysis. Inflamm Bowel Dis 19(10), 2098-2110.	1. Fragestellung We systematically reviewed infliximab benefit in reducing hospitalizations and/or major surgery rates in patients with inflammatory bowel disease (IBD) .
	2. Methodik **Population**: All types of study participants were allowed irrespective of IBD severity, baseline diseases, and risk factors. Only studies evaluating adult patients (aged 18 years or older) were considered. **Intervention**: infliximab **Komparator**: placebo **Endpunkt**: hospitalization, major surgery rate **Methode**: systematic review and meta-analysis of RCTs and observational studies **Suchzeitraum**: up to 2012 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 9 RCTs, 18 observational studies (n=1912)
	3. Ergebnisdarstellung **Hospitalization** (3 RCTs): statistically significant difference in favor of Infliximab (OR, 0.51; 95% CI, 0.40–0.65; I^2=0%) **Major surgery rate** (3 RCTs): statistically significant difference in favor of Infliximab (OR, 0.31; 95% CI, 0.15–0.64; I^2=0%)
	4. Anmerkungen/Fazit der Autoren Taken together, our results suggest an important role of infliximab treatment in hospitalization and surgery (at least for patients with CD) risk reduction. This impact is clinically and economically relevant because hospitalization and surgery are considered to be markers of disease severity and significantly contribute to the total direct costs associated with IBD falling on the health care system. Specific designed prospective long-term effectiveness studies are

	required to establish definite conclusions and to better estimate the true magnitude of this impact. 5. Hinweise durch GS Obwohl auch Ergebnisse von Beobachtungsstudien berichtet werden, werden in der vorliegenden Synopse nur Ergebnisse der gepoolten RCTs dargestellt
Lin et al. (2011). Meta-analysis: efficacy and safety of combination therapy of infliximab and immunosuppressives for Crohn's disease. Eur J Gastroenterol. Hepatol. 23(12), 1100-1110.	1. Fragestellung To compare the combination therapy with the monotherapy in induction and maintenance remission by comparing studies with similar designs.
	2. Methodik **Population**: diagnosis of CD, patients > 18 **Intervention**: infliximab and immunosuppressives **Komparator**: monotherapy **Endpunkt**: steroid-free clinical remission, safety **Methode**: systematic review and meta-analysis of RCTs and cohort studies **Suchzeitraum**: up to 2010 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 5 (n=1026)
	3. Ergebnisdarstellung <u>Induction of remission</u> **Combination therapy vs. infliximab** (2 trials, n=353): no statistically significant difference **Combination therapy vs. immunosuppressives** (2 trials, n=450): statistically significant difference in favor of combination therapy, OR 3.10 [2.07–4.62], I^2=0% **Combination therapy vs. monotherapy** (4 trials, n=803): statistically significant difference in favor of combination therapy OR 2.50 [1.46–4.30], I^2=60,5% <u>Maintenance of remission</u> **Combination therapy vs. infliximab** (2 trials, n=353): statistically significant difference in favor of combination therapy OR 1.64 [1.07–2.49], I^2=0% **Combination therapy vs. immunosuppressives** (2 trials, n=450): statistically significant difference in favor of combination therapy, OR 3.13 [2.12–4.62], I^2=0% **Combination therapy vs. monotherapy** (4 trials, n=803): statistically significant difference in favor of combination therapy OR 2.32 [1.75–3.08], I^2=39,5% **Safety**: In overall analysis, there was no significant difference in the frequency of total adverse events between combination therapy and monotherapy (OR=1.07; 95% CI= 0.72–1.59; P=0.75).
	4. Anmerkungen/Fazit der Autoren Overall, the results of our meta-analysis demonstrated that combination

	therapy of infliximab and immunosuppressives is safe and more effective compared with monotherapy in patients with CD refractory to first-line therapy. 5. Hinweise durch GS 3 der 5 eingeschlossenen Studien sind RCTs. Anhand der Beschreibung der Studien in der Meta-Analyse ist zu vermuten, dass die zwei weiteren Studien auch RCTs sind, dies ist aber der Meta-Analyse nicht eindeutig zu entnehmen.
Ford et al (2011). Glucocorticosteroid therapy in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol. 106(4), 590-599.	1. Fragestellung The use of glucocorticosteroids to treat both Crohn's disease (CD) and ulcerative colitis (UC) is widespread, but no systematic review and meta-analysis has examined the issue of efficacy of these agents in its entirety.
	2. Methodik **Population**: Adults (> 90 % of patients aged > 16 years) with inflammatory bowel disease **Intervention**: Standard glucocorticosteroids, budesonide **Komparator**: placebo **Endpunkt**: remission, prevention of relapse **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: up to 2010 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 20 (15 for CD)
	3. Ergebnisdarstellung <u>Induction of remission</u> standard glucocorticosteroids vs. placebo (2 trials, n=267): no statistically significant difference budesonide vs. placebo (2 trials, n=458): statistically significant difference in favor of budesonide (RR of failure to achieve remission = 0.73; 95 % CI 0.63 – 0.84, I^2 = 0 % , P = 0.82) standard glucocorticosteroids vs. budesonide (6 trials, n=669): statistically significant difference in favor of standard oral glucocorticosteroids (RR of failure to achieve remission = 0.82; 95 % CI 0.68 – 0.98, I^2=0%) <u>Maintenance of remission</u> budesonide vs. placebo (5 trials, n=559): no statistically significant difference
	4. Anmerkungen/Fazit der Autoren There were only two placebo-controlled trials that evaluated standard glucocorticosteroids in active CD, and there was no statistically significant benefit in our primary analysis. This is likely to be a reflection of the modest amount of data available, as both trials reported a definite benefit of active therapy, and other approaches to the analysis also suggested a significant benefit with the NNT of 3. Budesonide appeared superior to placebo for inducing remission in active CD, but was inferior to standard glucocorticosteroids, again suggesting that the latter are indeed effective for the treatment of active CD.

Khan et al. (2011)..Efficacy of immunosuppressive therapy for inflammatory bowel disease: a systematic review and meta-analysis. Am J Gastroenterol 2011; 106 (4): 630-42.	1. Fragestellung To clarify the efficacy of immunosuppressive therapy at inducing remission and preventing relapse in ulcerative colitis (UC) and Crohn's disease (CD).
	2. Methodik **Population**: adult patients (> 90 % over 16 years) with IBD (either CD or UC) **Intervention**: 6-MP, AZA, MTX, cyclosporine, and tacrolimus **Komparator**: placebo, no intervention **Endpunkt**: remission, relapse **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: up to 2010 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 20
	3. Ergebnisdarstellung <u>Induction of remission</u> **AZA or 6-MP vs. placebo** (5 trials, n=380): no statistically significant difference **MTX vs. placebo** (2 trials, n=193): no statistically significant difference **Overall data for immunosuppressive therapy vs. placebo**: statistically significant difference in favor of immunosuppressant therapy, (RR = 0.84; 95 % CI = 0.76 – 0.94, I^2=0%) **Safety**: no statistically significant difference <u>Maintenance of remission</u> **AZA or 6-MP vs. placebo** (2 trials, n=198): no statistically significant difference **MTX vs. placebo** (1 trials, n=76): statistically significant difference in favor of MTX (RR = 0.57; 95% CI = 0.35 – 0.94). Study had a high risk of bias. **Overall data for immunosuppressive therapy vs. placebo**: no statistically significant difference **Safety**: no statistically significant difference
	4. Anmerkungen/Fazit der Autoren Overall, the quality of trials that evaluate these interventions is poor with only two having a low risk of bias. A Cochrane systematic review suggests AZA / 6-MP is effective at inducing remission in active CD. Our systematic review, however, suggests that there is insufficient evidence that AZA / 6-MP is effective at inducing remission in CD. When high quality systematic reviews come to divergent conclusions it is important to establish the reason for the discrepancy. The Cochrane systematic review included improvement of symptoms as a primary outcome as well as induction of remission. Furthermore, they included one trial that measured improvement in symptoms at 1 year whereas our review excluded induction trials that evaluated patients > 17 weeks. Even if this trial were included, the results would not be statistically significant using RR as a summary statistic. The Cochrane review used the Peto OR as a summary statistic.

Leitlinien

<table>
<tr><td rowspan="3">Hofmann et al. (2008). S3-Leitlinie „Diagnostik und Therapie des Morbus Crohn“ Ergebnisse einer Evidenz-basierten Konsensuskonferenz der Deutschen Gesellschaft für Verdauungs- und Stoffwechselkrankheiten zusammen mit dem Kompetenznetz Chronisch entzündliche Darmerkrankungen. Z Gastroenterol 2008; 46: 1094 – 1146.</td><td>Leitlinie getragen von: Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie, Deutsche Gesellschaft für Chirurgie, Deutsche Gesellschaft für Ernährungsmedizin, Deutsche Gesellschaft für Innere Medizin, Deutsches Kollegium für Psychosomatische Medizin, Deutsche Gesellschaft für Koloproktologie, Gesellschaft für Pädiatrische Gastroenterologie und Ernährung, Deutsche Gesellschaft für Pathologie.</td></tr>
<tr><td>Methodik
Grundlage der Leitlinie: Systematische Literaturrecherche nach Systematischen Reviews und Primärstudien. Alle Empfehlungen sind mit Literaturstellen belegt.
Suchzeitraum: 2001-2007
Gültigkeit der Leitlinie ist seit dem 1.6.2013 ausgelaufen
LoE und GoR
<table>
<tr><th>Empfehlungs-grad</th><th>Definition</th></tr>
<tr><td>A</td><td>Direkt anwendbare Studien der Evidenzklasse 1</td></tr>
<tr><td>B</td><td>Studien der Evidenzklasse 2 oder 3;
oder Extrapolationen von Studien der Evidenzklasse 1
oder Studien der Evidenzklasse 1 mit Mehrheitsent-scheidung</td></tr>
<tr><td>C</td><td>Studien der Evidenzklasse 4;
oder Extrapolationen von Studien der Evidenzklasse 2 oder 3
oder Empfehlungsgrad B mit Mehrheitsentscheidung</td></tr>
<tr><td>D</td><td>Studien der Evidenzklasse 5;
oder Extrapolationen von Studien der Evidenzklasse 4
oder Empfehlungsgrad C mit Mehrheitsentscheidung
oder auffällig inhomogene oder nicht aussagekräfti-ge Studien irgendeiner Evidenzklasse</td></tr>
</table></td></tr>
<tr><td>Empfehlungen

Morbus Crohn mit Ileozökalbefall
<u>Mäßige Entzündungsaktivität</u>
• Patienten mit Ileozökalbefall und mäßiger Entzündungsaktivität sollten vorzugsweise mit Budesonid oder systemisch wirkenden Glukokortikoiden behandelt werden (A). Die enterale Ernährungstherapie ist ebenfalls effektiv und kann bei ausgewählten Patienten angewandt werden (A).
• Antibiotika sollten bei Verdacht auf infektiöse Komplikationen im Rahmen der Grunderkrankung zusätzlich verabreicht werden (GoR D).
• Neben Budesonid oder systemisch wirkenden Glukokortikoiden ist die enterale Ernährungstherapie ebenfalls effektiv und kann bei ausgewählten Patienten (Pateinten mit guter Therapietreue und deutlich erniedrigtem Körpergewicht) angewandt werden (GoR A).</td></tr>
</table>

	Hohe Entzündungsaktivität • Morbus Crohn Patienten mit Ileozökalbefall und hoher Entzündungsaktivität sollten initial mit systemisch wirkenden Glukokortikoiden behandelt werden (A). • Bei inkomplettem Ansprechen auf systemisch wirkende Glukokortikoide sollten zusätzlich zu systemisch wirkenden Glukokortikoiden Azathioprin bzw. 6-MP als Immunsuppressiva (oder, falls Unverträglichkeiten bestehen bzw. Nebenwirkungen auftreten, Methotrexat) eingesetzt werden (GoR A). Die Behandlung mit Antikörpern gegen TNF-alpha sollte bei Nichtansprechen auf Glukokortikoide und Immunsuppressiva bzw. bei Nebenwirkungen dieser Therapieformen – nach Ausschluss chirurgischer Therapieoptionen – durchgeführt werden (GoR A). Im Einzelfall können bei Persistenz der hohen Krankheitsaktivität trotz adäquater Steroiddosis oder Kontraindikation für Glukokortikoide anti-TNF-alpha-Antikörper vor Immunsuppressiva eingesetzt werden (GoR A). **Colitis Crohn** Mäßige Entzündungsaktivität • Patienten mit Crohn-Kolitis mit leichter bis mäßiger Aktivität sollten entweder mit Sulfasalazin oder systemisch wirksamen Glukokortikoiden behandelt werden (GoR A). Hohe Entzündungsaktivität • Für Patienten mit hoher Krankheitsaktivität gelten dieselben Therapieprinzipien wie für Patienten mit Ileozökalbefall (GoR A). • Bei Patienten mit Frührezidiv sollte Azathioprin bzw. 6-Mercaptopurin zusätzlich (oder, falls Unverträglichkeiten bestehen bzw. Nebenwirkungen auftreten, Methotrexat) eingesetzt werden (B). **Ausgedehnter Dünndarmbefall** Mäßige bis hohe Entzündungsaktivität • Ein Morbus Crohn mit ausgedehntem Dünndarmbefall sollte mit systemisch wirkenden Glukokortikoiden behandelt werden (B). • Bei mäßiger bis schwerer Krankheitsaktivität sollte diese Therapie frühzeitig durch eine immunsuppressive Therapie mit Azathioprin bzw. 6-MP (oder, falls Unverträglichkeiten bestehen, Methotrexat) ergänzt werden (C). • Die Behandlung mit TNF-alpha-Hemmern sollte bei Nichtansprechen auf Glukokortikoide und Immunsuppressiva nach Ausschluss chirurgischer Therapieoptionen durchgeführt werden (GoR nicht angegeben). • Da bei Patienten mit Dünndarmbefall eine Mangelernährung droht, sollte eine enterale Ernährungstherapie frühzeitig in Betracht gezogen werden (GoR C).

	Steroidrefraktärer Verlauf • Der steroidrefraktäre Morbus Crohn sollte mit Azathioprin/6-MP (oder, falls Unverträglichkeiten bestehen, Methotrexat) behandelt werden (GoR A). • Wenn keine infektiösen Komplikationen vorhanden sind, wenn kein Ansprechen auf die immunsuppressive Therapie erfolgt, wenn Kontraindikationen für diese bestehen oder wenn ein schnelles Ansprechen notwendig ist, ist eine zusätzliche Therapie mit TNF-alpha-Hemmern indiziert. Chirurgische Therapieoptionen sollten vorher erwogen und in die Diskussion miteinbezogen werden (GoR A). (Anmerkung der Autoren: In den großen kontrollierten Studien, die die Wirkung von TNF-alpha-Hemmern bei Patienten mit therapierefraktärem Verlauf überprüfen, ist nur ein Teil der Patienten mit Glukokortikoiden vorbehandelt. Die Ergebnisse dieser Studien können also nur eingeschränkt auf Patienten übertragen werden, die auf eine hoch dosierte Steroidmedikation (1mg/kg KG) nicht ansprechen. Man kann davon ausgehen, dass bei Patienten, bei denen durch die Behandlung mit systemisch wirkenden Steroiden innerhalb eines adäquaten Zeitraums (der auch durch die Krankheitsaktivität bestimmt wird) keine Remission erreicht werden kann, die Behandlung mit TNF-alpha-Hemmern (Infliximab, Adalimumab) zu einem Therapieerfolg in bis zu 70% der Patienten führt. **Rezidiv nach steroidabhängigem Verlauf** • Kommt es in dieser Situation zu einem akuten Schub, scheint eine erneute Stoßtherapie mit systemisch wirkenden Glukokortikoiden weniger effektiv als eine Induktionstherapie mit TNF-alpha-Hemmern (GoR D). • Vor dem Hintergrund der potenziellen Nebenwirkungen ist eine sorgfältige Abwägung beider Therapieoptionen sowie chirurgischer Therapieoptionen notwendig (GoR D). **Remissionserhaltende Therapie** • Steroide sind für die remissionserhaltende Therapie ungeeignet (A). • Bei Patienten mit komplexem Krankheitsverlauf sollte Azathioprin/ 6-Mercaptopurin als remissionserhaltende Therapie verabreicht werden (A). • Bei Patienten, bei denen eine Azathioprin- oder 6-Mercaptopurin-Behandlung zur Remissionserhaltung durchgeführt wird und die einen Schub erleiden, sollten Dosis und Zuverlässigkeit der Medikamenteneinnahme überprüft werden (GoR B). • Bei Azathioprin/ 6-Mercaptopurin-Versagen: Es können Methotrexat (GoR C) oder TNF-alpha-Hemmer (GoR A) eingesetzt werden allein oder in Kombination (GoR A) eingesetzt werden. Eine Operation muss insbesondere bei lokalisiertem Befall als Option mitbedacht werden (GoR B). Für Infliximab ist eine Erhaltungstherapie einer einmaligen

	Induktionstherapie bzw. einer an der Krankheitsaktivität orientierten Wiederholungstherapie überlegen (GoR nicht angegeben). • Remission nach Anti-TNF-alpha Therapie: Wenn eine Remission durch anti-TNF-alpha-Hemmer induziert werden konnte, sind Azathioprin, 6-Mercaptopurin, Methotrexat oder TNF-alpha-Hemmer für die remissionserhaltende Therapie geeignet (GoR A). Eine Operation muss insbesondere bei lokalisiertem Befall als Option mitbedacht werden (GoR C). • Postoperative Remissionserhaltung: Mesalazin hat in der postoperativen Remissionserhaltung eine geringe Wirkung und kann eingesetzt werden (GoR A). Antibiotika der Imidazol-Gruppe sollten wegen der hohen Nebenwirkungsrate zur Remissionserhaltung nicht eingesetzt werden (GoR A). Eine generelle Indikation zur postoperativen medikamentösen Therapie gibt es nicht (GoR A).
Dignass et al. (2010). European Crohns and Colitis Organization (**ECCO**) The second European evidence-based consensus on the diagnosis and management of Crohn's disease: Current management. Journal of Crohn's and Colitis 2010; 4 28-62.	Leitlinie der European Crohn's and Colitis Organisation **Methodik** Grundlage der Leitlinie: Systematisches Vorgehen bei der Literaturrecherche in Medline und Cochrane Database angegeben, aber keine weiteren Details (z.B. Suchzeitraum) beschrieben. Konsensuskonferenz wurde abgehalten. LoE, GoR:

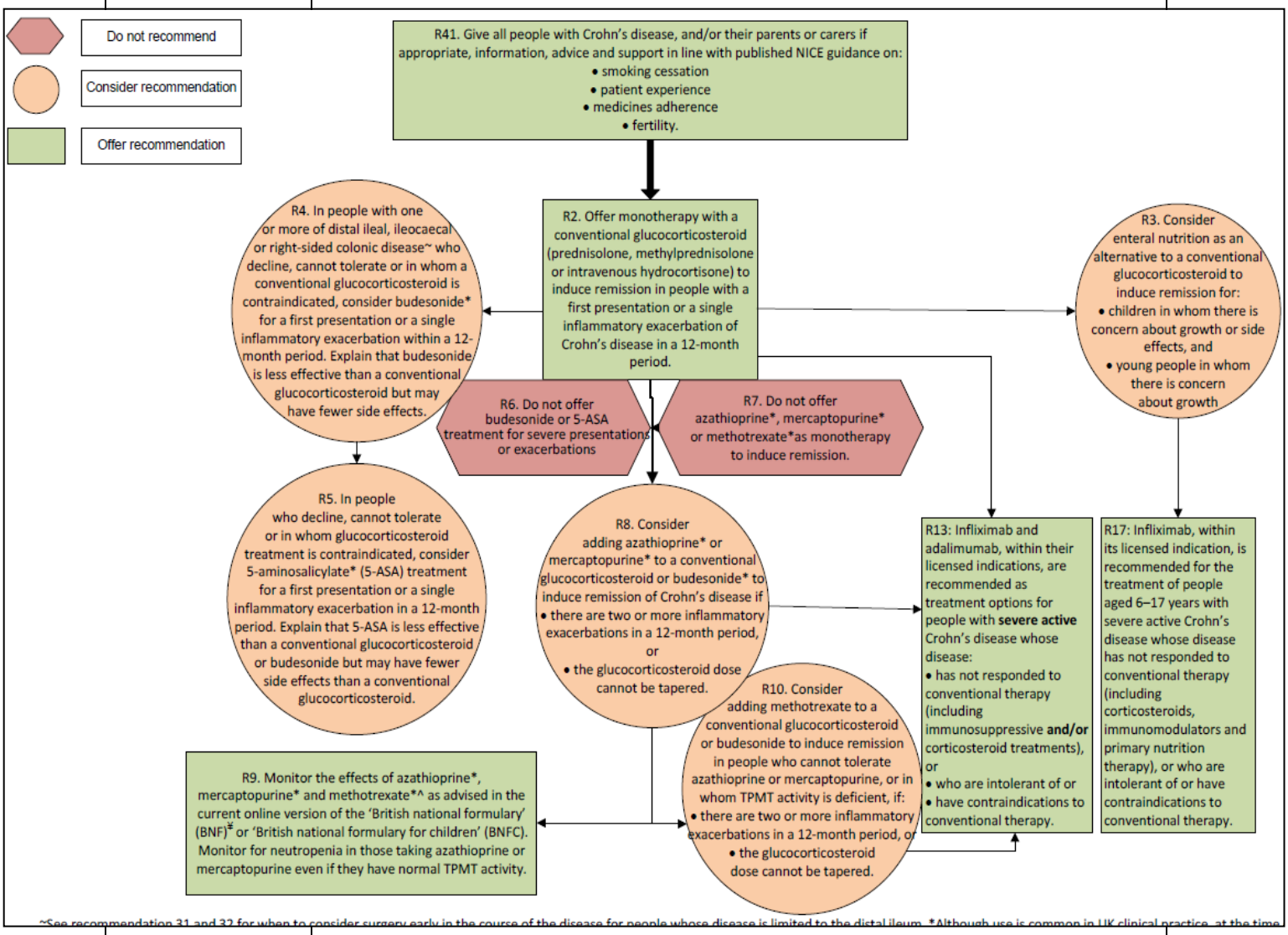
Level	Individual study	Technique
1a	Systematic review (SR) with homogeneity of Level 1 diagnostic studies	Systematic review (SR) with homogeneity of randomised controlled trials (RCTs)
1b	Validating cohort study with good reference standards	Individual RCT (with narrow Confidence Interval)
1c	Specificity is so high that a positive result rules in the diagnosis ("SpPin") or sensitivity is so high that a negative result rules out the diagnosis ("SnNout")	All or none
2a	SR with homogeneity of level >2 diagnostic studies	SR (with homogeneity) of cohort studies
2b	Exploratory cohort study with good reference standards	Individual cohort study (including low quality RCT; e.g., <80% follow up)
2c		"Outcomes" research; ecological studies
3a	SR with homogeneity of 3b and better studies	SR with homogeneity of case–control studies
3b	Non-consecutive study; or without consistently applied reference standards	Individual case–control study
4	Case–control study, poor or non-independent reference standard	Case-series (and poor quality cohort and case–control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Grades of recommendation	
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies or extrapolations from level 1 studies
C	Level 4 studies or extrapolations from level 2 or 3 studies
D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level

	Empfehlungen **Morbus Crohn mit Ileozökalbefall** <u>Mäßige Entzündungsaktivität</u> • bei aktivem, steroidrefraktärem Krankheitsverlauf sollte die Therapie mit TNF-alpha-Hemmern in Betracht gezogen werden (LoE 1b, GOR B). <u>Hohe Entzündungsaktivität</u> • TNF-alpha-Hemmer sollten bei Patienten mit nachweisbarem aktivem Krankheitsverlauf eingesetzt werden, wenn der Patient ein Rezidiv aufweist (LoE 1a, GOR B für Infliximab).

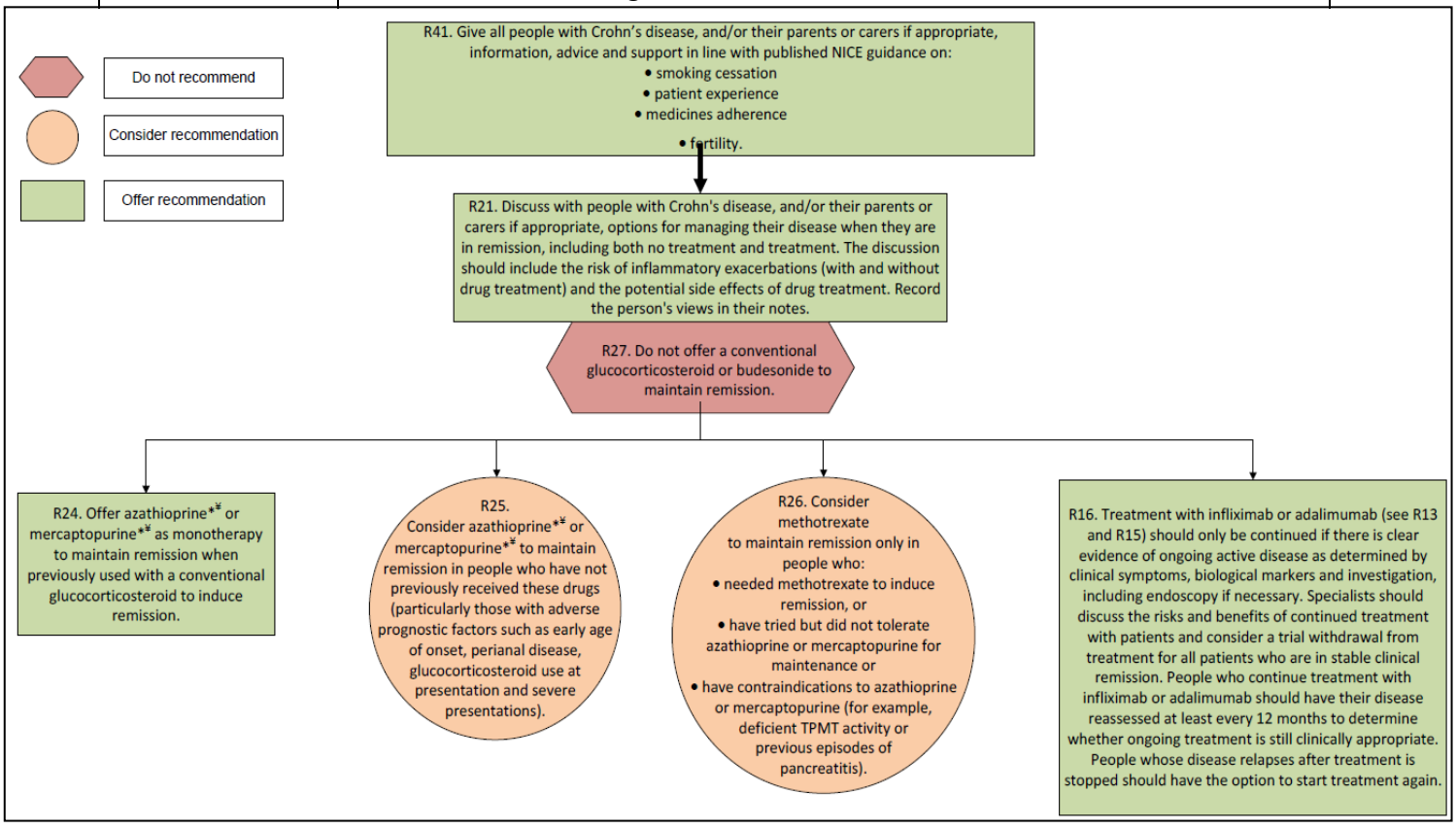
	• Chirurgische Optionen sind eine Alternative und sollten in Betracht gezogen werden (LoE 5, GOR D). <u>Colitis Crohn</u> • Bei vorkommen eines Rezidiv sollte Anti-TNF-alpha Therapie in Betracht gezogen werden (LoE 1a, GOR B für Infliximab). • Chirurgische Optionen sind eine Alternative und sollten vor Behandlung mit TNF-alpha-Hemmern in Betracht gezogen werden (LoE 5, GOR D). <u>Ausgedehnter Dünndarmbefall</u> • Nach Remissionsinduktion mit Steroiden und Immunsuppressiva, bei vorkommen eines Rezidiv Anti-TNF-alpha Therapie in Betracht ziehen, wenn ein Nachweis eines moderaten bis schweren aktiven Krankheitsgeschehens vorliegt (LoE 5, GOR D). • Zusätzliche Ernährungstherapie ist angebracht (LoE 4, GOR C). <u>Befall des Ösophagus und Magens</u> • Behandlung mit Protonenpumpenhemmern mit oder ohne Steroide ist angezeigt (LoE 5, GOR D). • Die Therapie mit Antikörpern gegen TNF-alpha ist eine Option bei schwerem oder therapierefraktärem Verlauf (LoE 4, GOR D). <u>Steroidrefraktärer Verlauf</u> • Bei nachweisbar aktivem Krankheitsverlauf sollten steroidrefraktäre Patienten mit TNF-alpha-Hemmern mit oder ohne Immunsuppressiva (Methotrexat oder Thiopurin) behandelt werden (LoE 1a, GOR B für Infliximab). • Steroidabhängige Patienten sollten mit Thiopurin oder Methotrexat mit oder ohne TNF-alpha Hemmern behandelt werden (LoE 1a, GOR A für Thiopurin und Methotrexat, LoE 1a, GOR B für Infliximab und Adalimumab).
NICE (2012). Crohn's disease: Management in adults, Children and young people (CG152), Stand: 10/2012. London (UK).	Leitlinie des National institute for health and care excellence **Methodik** Grundlage der Leitlinie: Systematische Literatursuche nach RCTs (und, wenn keine RCTs vorlagen, Primärstudien auf niedrigerem Evidenzniveau). Qualität der eingeschlossenen Studien mit GRADE bewertet. Validierungsprozess mit öffentlicher Konsultation. Suchzeitraum: bis 13 März 2012 **Overall quality of outcome evidence in GRADE** **Level** / **Description** High: Further research is very unlikely to change our confidence in the estimate of effect Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate Very low: Any estimate of effect is very uncertain

Empfehlungen
Remissionsinduktion



~See recommendation 31 and 32 for when to consider surgery early in the course of the disease for people whose disease is limited to the distal ileum. *Although use is common in UK clinical practice, at the time

Remissionserhaltung



	Kontraindikationen bestehen oder die intolerant auf die Behandlung reagieren. • 5-ASA kann gegeben werden, wenn Kortikosteroide nicht in Frage kommen. • 5-ASA nicht bei schwerer Krankheitsaktivität empfohlen. • Immunsuppressiva nicht generell als Monotherapie empfohlen (nur add-on zu Steroiden). In a meta-analysis of six RCTs (n = 718) (follow-up 6 to 18 weeks) 5-ASA treatment was more effective for induction of remission in adults than placebo (RR1.51 [95% CI 1.2 to 1.92]). [VERY LOW QUALITY] In a meta-analysis of three RCTs (n = 256) (follow-up 16 weeks) there was no significant difference in adverse events between 5-ASAs and placebo (RR 1.04 [0.8 to 1.36]). [VERY LOW QUALITY] In a meta-analysis of two RCTs (n = 156) (follow-up 16 to 30 weeks) there was no significant difference in remission between 5-ASA treatment and AZA/MP (RR 0.81 [0.52 to 1.24] fixed effect; RR 0.48 [0.68 to 1.67] random effects). [VERY LOW QUALITY] **Remissionserhaltung** • Infliximab und Adalimumab Therapie nur fortsetzen, wenn eindeutige Hinweise auf aktives Krankheitsgeschehen vorliegen. • Remissionserhaltung nach OP: 5-ASA Behandlung kann in Betracht gezogen werden. Enterale Ernährung nicht empfohlen. In a meta-analysis of six RCTs (n = 1112) comparing 5-ASA to placebo for relapse (not including withdrawals) for a 12-month trial duration, patients taking 5-ASA were significantly less likely to relapse than those taking placebo (RR 0.76 [0.64 to 0.90]).[MODERATE QUALITY] In a meta-analysis of six RCTs (n = 1112) comparing 5-ASA to placebo for relapse (including all withdrawals) for a 12-month trial duration, there was no significant difference in relapse between patients taking 5-ASA or placebo. (RR 1.01 [0.91 to 1.12] [fixed effect]; RR 0.96 [0.80 to 1.15] [random effects]).[MODERATE QUALITY] In one RCT (n = 161) comparing 5-ASA to placebo for maintenance of remission for a two-year trial duration, there was no significant difference in relapse between patients taking 5-ASA vs. placebo (RR 0.84 [0.58 to 1.23]).[LOW QUALITY] In one RCT (n = 159) there was no significant difference in maintenance of remission at one year or two years between patients taking sulfasalazine vs. placebo. (RR 0.96 [0.75 to 1.24] and RR 0.76 [0.43 to 1.34] respectively).[HIGH-LOW QUALITY] In a meta-analysis of two RCTs comparing azathioprine vs. placebo for maintenance of remission (n = 134) azathioprine therapy was significantly more effective than placebo for relapses at 12 months (RR 0.21 [0.06 to 0.68]).[MODERATE QUALITY]

Orlando et al. (2011). The Italian Society of Gastroenterology (SIGE) and the Italian Group for the study of Inflammatory Bowel Disease (IG-IBD) Clinical Practice Guidelines: The use of tumor necrosis factor-alpha antagonist therapy in inflammatory bowel disease. Dig Liver Dis; 43 (1): 1-20.	Leitlinie der Italian Society of Gastroenterology zu TNF-alpha Hemmern bei Morbus Crohn
	Methodik Grundlage der Leitlinie: Systematisches Vorgehen bei der Literaturrecherche in Medline, Embase und Cochrane Database angegeben, aber keine weiteren Details (z.B. Suchzeitraum) beschrieben. Konsensuskonferenzen wurden abgehalten. LoE, GoR:

1a	Systematic review (SR) with homogeneity of Level 1 diagnostic studies	Systematic review (SR) with homogeneity of randomised controlled trials (RCTs)
1b	Validating cohort study with good reference standards	Individual RCT (with narrow Confidence interval)
1c	Specificity is so high that a positive result rules in the diagnosis ("SpPin") or sensitivity is so high that a negative result rules out the diagnosis ("SnNout")	All or none
2a	SR with homogeneity of level > 2 diagnostic studies	SR (with homogeneity) of cohort studies
2b	Exploratory cohort study with good reference standards	Individual cohort study (including low quality RCT; e.g., <80% follow-up)
2c		"Outcomes" research; ecological studies
3a	SR with homogeneity of 3b and better studies	SR with homogeneity of case–control studies
3b	Non-consecutive study; or without consistently applied reference standards	Individual case–control study
4	Case–control study, poor or non-independent reference standard	Case-series (and poor quality cohort and case–control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Grades of recommendation

A	Consistent level 1 studies
B	Consistent level 2 or 3 studies or extrapolations from level 1 studies
C	Level 4 studies or extrapolation from level 2 or 3 studies
D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level

Empfehlungen

- TNF-alpha-Hemmer sind eine effektive Option bei moderatem bis schwerem steroidrefraktärem MC (Infliximab: LoE 1b, GoR A; Adalimumab: LoE 1b, GoR B). Immunsuppressiva können bei Therapienaiven Pateinten zusätzlich gegeben werden (LoE 1b, GoR B)
- Adalimumab als Zweitlinientherapie für Patienten mit primärem Therapieversagen bei Infliximab (LoE 4, GoR C) oder mit Verlust des Ansprechens oder Unverträglichkeit gegenüber Infliximab (LoE 1b, GoR

	B). • TNF-alpha-Hemmer (Infliximab, Adalimumab) sind effektiv für Remissionserhaltung bis zu einem Jahr wenn der Patient auf die Induktionstherapie angesprochen hat (LoE 1a, GoR A). • TNF-alpha-Hemmer (Infliximab, Adalimumab) sollten die Therapie der Wahl sein, wenn Remissionserhaltung mit Immunsuppressiva fehlgeschlagen ist (LoE 1b, GoR B).
Sadowski et al. (2009). Canadian Association of Gastroenterology Clinical Practice Guidelines: The use of tumour necrosis factor-alpha antagonist therapy in Crohn's disease. Can J Gastroenterol 2009; 23 (3): 185-202.	Leitlinie der Canadian Association of Gastroenterology zu TNF-alpha Hemmern bei Morbus Crohn
	Methodik Grundlage der Leitlinie: Systematische Literaturrecherche in Embase, Medline und CINAHL. Bewertung der Studienqualität mit GRADE. Die Konsensgruppe, bestehend aus 25 Mitgliedern, bewertete die aus der Literatur extrahierten und gegradeden Aussagen. Suchzeitraum: 2004-2008 **Schemata for voting and grading the evidence in the literature** **Voting options for the Consensus Committee** A Agree strongly B Agree with minor reservation C Agree with major reservation D Disagree with minor reservation E Disagree with major reservation F Disagree strongly **Levels of evidence using the GRADE approach** High: Additional research is unlikely to change the Committee's confidence in the estimate of the effect Moderate: Additional research is likely to add important information thereby impacting the Committee's confidence in the estimate of the effect. In turn, this may lead to a change in the estimate of the effect Low: Additional research is likely to impact both the Committee's confidence in the estimate of the effect and change their estimate of the effect Very Low: Any estimate of the effect is uncertain *GRADE Grading of Recommendations, Assessment, Development and Evaluation*
	Empfehlungen **Remissionsinduktion** • Therapie mit Infliximab, Adalimumab oder Certolizumab ist klinisch wirksam zur Remissionsinduktion bei Patienten die auf konventionelle Therapie (Immunsuppressiva (Purin Antimetaboliten / Methotrexat) und / oder Kortikosteroide) nicht ansprechen. (GRADE: High; Vote: A 96%, B 4%).

	Remissionserhaltung • Für Patienten, die auf eine Remissionsinduktion angesprochen haben, sind Infliximab (5 mg / kg alle 8 Wochen), Adalimumab (40 mg subkutan alle zwei Wochen) oder Certolizumab (400 mg subkutan alle vier Wochen) effektiv zur Remissionserhaltung. (GRADE: High; Vote: A 72%, B 28%). • Für Patienten die suboptimal auf TNF-alpha Hemmer ansprechen kann die Erhaltungstherapie mit einem anderen TNF-alpha Hemmer fortgesetzt werden. (GRADE: Low; Vote: A 28%, B 64%, C 4%, D 4%.) Previous exposure to a TNF antagonist agent is associated with a reduced response to a new TNF antagonist drug compared with those who are TNF antagonist naive. However, in a group of patients specifically selected for loss of response to infliximab maintenance therapy, switching to adalimuab resulted in a 14% increase in the remission rate at week 4 compared with placebo (21% versus 7%; P<0.001). This trend was also observed in two earlier small pilot studies as well as an open-label trial.

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library am 13.01.2014

#	Suchfrage
1	MeSH descriptor: [Crohn Disease] explode all trees
2	MeSH descriptor: [Inflammatory Bowel Diseases] explode all trees
3	Crohn or crohn's or inflammatory bowel diseases:ti,ab,kw
4	#1 or #2 or #3
5	#1 or #2 or #3 from 2009 to 2014

SR, HTAs in PubMed (Medline) am 13.01.2014

#	Suchfrage
1	"Crohn Disease"[Mesh]
2	"inflammatory bowel diseases/drug therapy"[MeSH Terms]
3	((Crohn[Title/Abstract]) OR crohn's[Title/Abstract]) OR „inflammatory bowel diseases”[Title/Abstract]
4	((#1) OR #2) OR #3
5	((((((activi*[Title/Abstract]) OR active*[Title/Abstract]) OR activa*[Title/Abstract]) OR flare[Title/Abstract]) OR acute[Title/Abstract]) OR severe[Title/Abstract]) OR mild[Title/Abstract]
6	(#4) AND #5
	(((((drug[Title/Abstract]) OR (drug therap*)[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR treat[Title/Abstract]) OR treatment*[Title/Abstract]
7	(#6) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
8	(#6) AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
9	#7 OR #8
10	(#9) AND ("2009/01/01"[PDAT] : "2014/01/13"[PDAT])

Leitlinien in PubMed (Medline) am 13.01.2014

#	Suchfrage
1	"Crohn Disease"[Mesh]
2	"inflammatory bowel diseases/drug therapy"[MeSH Terms]
3	((Crohn[Title/Abstract]) OR crohn's[Title/Abstract]) OR „inflammatory bowel diseases”[Title/Abstract]
4	((#1) OR #2) OR #3
5	((((((activi*[Title/Abstract]) OR active*[Title/Abstract]) OR activa*[Title/Abstract]) OR flare[Title/Abstract]) OR acute[Title/Abstract]) OR severe[Title/Abstract]) OR mild[Title/Abstract]
6	(#4) AND #5
12	(#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title])
13	(#12) AND ("2009/01/01"[PDAT] : "2014/01/13"[PDAT])

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