Thieme

S3-Leitlinienreport – Colitis ulcerosa

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Autoren

Petra Lynen Jansen[1], Maria Kallenbach[1], Axel Dignass[3], Torsten Kucharzik[4]

Institute

1 Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten, Berlin, Germany
2 Clinical Guideline Services, Berlin, Germany
3 Medizinische Klinik I, Agaplesion Markus Krankenhaus, Frankfurt am Main, Germany
4 Klinik für Allgemeine Innere Medizin und Gastroenterologie, Klinikum Lüneburg, Lüneburg, Germany

Bibliografie

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Korrespondenzadresse

Prof. Dr. med. Torsten Kucharzik
Klinik für Allgemeine Innere Medizin und Gastroenterologie, Städtisches Klinikum Lüneburg, Bögelstr. 1, 21339 Lüneburg
torsten.kucharzik@klinikum-lueneburg.de

Prof. Dr. med. Axel Dignass
Medizinische Klinik I, Agaplesion Markus Krankenhaus, Wilhelm-Epstein-Str. 4, 60431 Frankfurt
axel.dignass@fdk.info

Geltungsbereich und Zweck

In Deutschland sind etwa 150 000 Einwohner an einer Colitis ulcerosa erkrankt. Für die meisten Patienten beginnt die Erkrankung während der Schulzeit oder der Berufsausbildung und dauert während des gesamten Lebens an. Neben dem persönlichen Leiden verursacht die Erkrankung beträchtliche Kosten für die Gesellschaft. Viele Patienten erhalten jedoch nach wie vor keine adäquate Therapie. Die Aktualisierung der zuletzt 2011 aktualisierten Leitlinie wird von den beteiligten Fachgesellschaften daher als besonders wichtig erachtet.

Zielorientierung der Leitlinie

Ziel der Leitlinie soll sein, in der hausärztlichen, internistischen, chirurgischen, pädiatrischen und gastroenterologischen Praxis einfach anwendbar zu sein. Die Behandlung besonders schwerer oder komplizierter Fälle, wie sie in Spezialambulanzen und spezialisierten Praxen erfolgt, kann durch diese Leitlinie nicht abgebildet werden.

Die Themen „Extraintestinale Manifestationen“ und „CED-assoziierte Erkrankungen“ sowie „Schmerzen“ wurden in der letzten Morbus-Crohn-Leitlinie von 2014 abgehandelt und sollten daher in der Colitis-ulcerosa-Leitlinie nicht erneut aufgegriffen werden. „Infektiologische Probleme“ sowie das Thema „Ernährung“ wurden in der letzten MC-Leitlinie nicht fokussiert und sollten daher in dieser Leitlinie gezielt aufgearbeitet werden.

Patientenzielgruppe sind Patienten mit Colitis ulcerosa jeden Alters.

Versorgungsbereich

Ambulant und stationär, hausärztlich, pädiatrisch, internistisch, chirurgisch und gastroenterologisch.

Anwenderzielgruppe/Adressaten

Die Leitlinie richtet sich an alle an der Diagnostik und Therapie beteiligten Berufsgruppen (Allgemeinmediziner, Internisten, Kinder- und Jugendmediziner, Chirurgen, Gastroenterologen, Pathologen, Fachassistenz CED) sowie Betroffene und Angehörige und Leistungserbringer (Krankenkassen, Rentenversicherungsträger).

Zusammensetzung der Leitliniengruppe: Beteiligung von Interessengruppen

Die Leitung der Leitlinienüberarbeitung erfolgte durch zwei Hauptkoordinatoren (Axel Dignass, Frankfurt, und Torsten Kucharzik, Lüneburg) in enger Abstimmung mit einer Steuergruppe (▶ **Tab. 1**).

Darüber hinaus wurden fünf Arbeitsgruppen (AGs) gebildet, die jeweils von zwei Leitern geleitet wurden (▶ **Tab. 2**). Aufgrund des Umfangs der zu bearbeitenden Themen wurde die AG Diagnostik von drei AG-Leitern geleitet. In den AGs wurden universitäre und nichtuniversitäre Ärzte, Klinikärzte und niedergelassene Ärzte in einem ausgewogenen Verhältnis eingesetzt. In den AGs

▶ **Tab. 1** Steuergruppe.

Name	Ort	Zuständigkeit
B. Bokemeyer	Minden	Vertreter der niedergelassenen Gastroenterologen, Kompetenznetz KN-CED
A. Dignass	Frankfurt	Koordinator, ALGK, DGVS
B. Kaltz	Berlin	DCCV
T. Kucharzik	Lüneburg	Koordinator, ALGK, ECCO
S. Schreiber	Kiel	Kompetenznetz KN-CED, universitäre Gastroenterologie
B. Siegmund	Berlin	ECCO, universitäre Gastroenterologie, DGVS

haben neben Gastroenterologen und Chirurgen Pädiater, Pathologen, Komplementärmediziner, Ernährungsmediziner, Fachassistenzen CED (FACED) und Patienten (DCCV) mitgearbeitet.

Aus jeder AG haben alle Mitglieder an der Onlinebefragung und fast alle Mitglieder an der Konsensuskonferenz teilgenommen.

Repräsentativität der Leitliniengruppe: Beteiligte Fachgesellschaften

DGVS (Deutsche Gesellschaft für Verdauungs- und Stoffwechselkrankheiten)
DGAV (Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie)
DGCH (Deutsche Gesellschaft für Chirurgie)
GPGE (Gesellschaft für pädiatrische Gastroenterologie und Ernährungsmedizin)
KN-CED (Kompetenznetz Darmerkrankungen)
DCCV (Deutsche Morbus Crohn/Colitis ulcerosa Vereinigung)
FACED (Fachangestellte für chronisch entzündliche Darmerkrankungen)
DGEM (Deutsche Gesellschaft für Ernährungsmedizin)
DGP (Deutsche Gesellschaft für Pathologie)
DGK (Deutsche Gesellschaft für Koloproktologie)
Die Deutschen Gesellschaft für Allgemeinmedizin und Familienmedizin (DEGAM) wurde zur Mitarbeit an der Leitlinie eingeladen, konnte das Leitlinienvorhaben aber aufgrund personeller Engpässe nicht unterstützen. Auch die Deutsche Gesellschaft für Innere Medizin e. V. (DGIM) wurde zur Mitarbeit an der Leitlinie eingeladen, hat sich aber nicht beteiligen können.

Repräsentativität der Leitliniengruppe: Beteiligung von Patienten

Direkte Mitarbeit von mehreren Vertretern der Deutschen Morbus Crohn/Colitis ulcerosa Vereinigung (DCCV) e. V.

Methodologische Exaktheit

Recherche, Auswahl und Bewertung wissenschaftlicher Belege (Evidenzbasierung)

Vorgängerversionen dieser Leitlinie sind die S3-Leitlinien Colitis ulcerosa von 2011 und 2008. Aufgrund neuer methodischer Anforderungen wurde vor Beginn der Überarbeitung die anzuwendende Methodik am 05.07.2016 im Rahmen einer Telefonkonferenz innerhalb der Steuergruppe diskutiert und anschließend konsentiert.

Die Suchstrategie der letzten Colitis-Leitlinie wurde von den Koordinatoren zusammen mit den AG-Leitern überarbeitet. Mit der systematischen Literaturrecherche dieser Aktualisierung wurde die clinical guideline services usergroup (CGS) beauftragt, die Literaturrecherche wurde von Frau Maria Kallenbach durchgeführt. Zunächst erfolgte eine systematische Suche nach Leitlinien, die nach dem Deutschen Instrument zur methodischen Leitlinienbewertung (DELBI) bewertet und deren Empfehlungen bei ausreichender methodischer Güte in einer Leitliniensynopse zusammengestellt wurden.

Für Themengebiete von besonderer klinischer Wichtigkeit, besonderer Strittigkeit oder besonders häufiger fehlerhafter Anwendung wurden von den AG-Leitern Schlüsselfragen definiert, eine systematische Literaturrechere de novo durchgeführt und Evidenztabellen erstellt. Die Literatur konnte bis zum Zeitpunkt der Konsensuskonferenz ergänzt werden. Empfehlungen, für die keine neue Evidenz vorlag, wurden unverändert aus der alten Leitlinie übernommen.

Die Aufgaben bei Literaturrecherche und Bewertung waren wie folgt verteilt (▶ **Tab. 3**).

Recherche nach evidenzbasierten Leitlinien

Zunächst wurde zentral eine Suche nach existierenden Leitlinien aus den letzten fünf Jahren (2011 – 2016) in

- MEDLINE,
- Google,
- Guidelines International Network,
- National Guideline Clearinghouse,
- CMA Infobase,
- der UK National Library of Health,
- SIGN und
- Der New Zealand Guidelines Group

▶ **Tab. 2** Mitglieder der Leitliniengruppe.

AG 1: Diagnostik	Leiter	R. Atreya, Erlangen (DGVS) B. Bokemeyer, Minden (KN-CED, DGVS) K. Herrlinger, Hamburg (DGVS)
	KK-Teilnehmer	D. Bettenworth, Münster (DGVS) M. Götz, Tübingen (DGVS) U. Helwig, Oldenburg (DGVS) L. Leifeld, Hildesheim (DGVS) G. Moog, Kassel (DGVS)[1] E. Rijcken, Münster (DGAV/DGK) F. Autschbach (DGP) G. Baretton, Dresden (DGP) I. Kanbach, Berlin (DCCV) S. Buderus, Bonn (GPGE)[1] P. Hartmann, Minden (FACED)
AG 2: Schub	Leiter	T. Kucharzik, Lüneburg (DGVS, KN-CED) B. Siegmund, Berlin (DGVS, KN-CED)1
	KK-Teilnehmer	J. Büning, Lübeck (DGVS) R. Ehehalt, Heidelberg (DGVS) W. Häuser, Saarbrücken (DGVS) F. Hartmann, Frankfurt (DGVS) K. Kannengiesser, Lüneburg (DGVS) K.-M. Keller, Wiesbaden (GPGE) A. Lügering, Münster (DGVS) S. In der Smitten, Berlin (DCCV) J. Zemke, Herne (FACED)
AG 3: Remissionserhaltung	Leiter	A. Dignaß, Frankfurt (DGVS) S. Schreiber, Kiel (KN-CED, DGVS)
	KK-Teilnehmer	C. Maaser, Lüneburg (DGVS) G. Rogler, Zürich (DGVS)[1] S. Koletzko, München (GPGE)[1] T. Kühbacher, Hamburg (DGVS) W. Kruis, Köln (DGVS) P. Esters, Frankfurt (DGVS)
AG 4: Therapie- und CED-Assoziierte Infektionen	Leiter	A. Stallmach, Jena (DGVS)[1] N. Teich, Leipzig (DGVS)[1]
	KK-Teilnehmer	M. Reinshagen, Braunschweig (DGVS) T. Andus, Stuttgart (DGVS) O. Bachmann, Hannover (DGVS) M. Bläker, Hamburg (DGVS) C. Veltkamp, Heidelberg (DGVS)
AG 5: Chirurgie/Pouchitis	Leiter	P. Kienle, Heidelberg (DGAV/DGK) A. Sturm, Berlin (DGVS)
	KK-Teilnehmer	S. Fichtner-Feigl, Freiburg (DGAV/DGCH/DGK)[1] K. Fellermann, Lübeck (DGVS) E. Stange, Stuttgart (DGVS) A. Kroesen, Köln (DGAV/DGCH/DGK) A. Pace, Neumünster (DGVS) B. Kaltz, Berlin (DCCV)
AG 6: Komplementärmedizin und Ernährung	Leiter	J. Langhorst, Essen (DGVS) J. Stein, Frankfurt (DGVS)
	KK-Teilnehmer	H. Matthes, Berlin (DGVS) D. C. Baumgart, Berlin (DGVS)[1] J. Ockenga, Bremen (DGEM, DGVS) J. Klaus, Ulm (DGVS) C. Gross, Berlin (DCCV)
Koordinatoren		A. Dignass, Frankfurt (DGVS) T. Kucharzik, Lüneburg (DGVS)

[1] entschuldigte Mitglieder.

▶ **Tab. 3** Ablauf der Literaturrecherche und Bewertung.

Teilpunkt	Verantwortlichkeit
Erstellen der Leitliniensynopse	CGS
Auswahl und Ergänzung der Schlüsselfragen unter Berücksichtigung der Leitliniensynopse und Übermittlung ans Leitlinienportal	Steuergruppe, AG-Leiter
Definition der Kriterien für die Literaturrecherche (Zeitraum, Studientyp, Sprache)	Steuergruppe, AG-Leiter
Systematische Literaturrecherche, Titel- und Abstractscreening	CGS
Screening klärungsbedürftiger Abstracts, ggf. Ergänzung von nicht gefundener Literatur	AG-Leiter oder von den AG-Leitern bestimmte Literaturverantwortliche
Screening Volltexte	CGS unter Einbezug der AG-Leiter oder von den AG-Leitern bestimmte Literaturverantwortliche
Bewertung nach Oxford, Erstellen der Evidenztabellen, Dokumentation der Suche	CGS

mit den Stichworten (Leitlinie OR guideline) AND ("Colitis ulcerosa" OR "ulcerative colitis") durchgeführt.

Dabei fanden sich neben der deutschen Leitlinie die Leitlinien der folgenden Organisationen: National Institute for Health and Clinical Excellence, UK (NICE), World Gastroenterology Organisation (WGO), Toronto Ulcerative Colitis Consensus Group (Toronto), European Crohn's and Colitis Organisation (ECCO), Französisches Expertengremium Inflammatory bowel disease (IBD), Sydney Organisation und New Zealand Society of Gastroenterology.

Bei Durchsicht der NICE-Leitlinie zeigte sich, dass diese eng definierte Fragestellungen abdeckt. Zudem ist die NICE-Leitlinie durch eine grundsätzlich andere Struktur als Clinical Pathway gestaltet, weshalb eine Gegenüberstellung mit den bisherigen Empfehlungen der DGVS-Leitlinie in der Leitliniensynopse nicht möglich war.

Zur Bewertung der methodologischen Qualität der identifizierten Leitlinien wurde die Domäne 3 „Methodologische Exaktheit der Leitlinien-Entwicklung" (Kriterien 8 – 14) des Deutschen Leitlinienbewertungsinstruments (DELBI) verwendet. Das Ergebnis der Bewertung ist in ▶ **Tab. 4** dargestellt.

Bei Durchsicht und Bewertung der identifizierten Leitlinien zeigte sich, dass die folgenden Leitlinien als zusätzliche Evidenzbasis für die Aktualisierung der Deutschen Leitlinie dienen können:

- The Toronto Consensus Group (2015): Clinical Practice Guidelines for the Medical Management of Nonhospitalized Ulcerative Colitis,
- ECCO (2012): Second European evidence-based consensus on the diagnosis and management of ulcerative colitis,
- NICE (2013): Ulcerative colitis: Management in adults, children and young people.

Die ECCO-Leitlinie, die Toronto-Leitlinie und die DGVS-Leitlinie wurden in einer Synopse gegenübergestellt (Anhang A), um Unterschiede sowie in der letzten DGVS-Leitlinie nicht behandelte Themen zu identifizieren.

Systematische Literaturrecherche

Die systematische Recherche nach Literatur wurde in der Zeit vom 06.12.2016 bis zum 07.01.2017 in der Medline-Datenbank über die PubMed-Suchoberfläche durchgeführt. Es wurden 4508 Suchtreffer aus Medline erzielt. Die Recherche in den Cochrane-Datenbanken erfolgte vom 07.12.2016 bis zum 12.01.2017, wobei 1339 Treffer erzielt wurden. Eine Auflistung der Suchtreffer für jede Recherche findet sich in ▶ **Tab. 5**.

Aus den gesamten Suchtreffern wurden 359 Dubletten entfernt, sodass 5488 Suchtreffer in der weiteren Literaturarbeit berücksichtigt wurden. Die Suchstrings und detaillierte Darstellungen der Recherchen sind im Anhang B zur jeweiligen Schlüsselfrage dargestellt.

Auswahl der Evidenz

Folgende Einschränkungen wurden in der Recherche und Auswahl der Evidenz vorgenommen:

- Deutsche und englische Veröffentlichungen,
- Systematische Reviews, Metaanalysen und randomisierte kontrollierte Studien,
- Probandenstudien (keine Tierversuche) und verfügbar im Volltext,
- Veröffentlichung ab Juni 2009 bis zum Recherchedatum.

Der Recherchezeitraum schließt damit bündig an den Recherchezeitraum der vorherigen Leitlinienversion (2003 – 06.2009) an. Weitere Ein- und Ausschlusskriterien ergaben sich aus dem jeweiligen PICO-Schema der Schlüsselfragen.

Die Auswahl der Evidenz erfolgte durch einen mehrstufigen Screeningprozess. Im Titel-Abstract-Screening wurden die Suchtreffer durch Methodiker*innen der CGS anhand der Ein- und Ausschlusskriterien auf potentielle Relevanz gescreent. Von den 5488 Suchtreffern wurden als 1255 als potenziell relevant eingeordnet. Sofern Literaturstellen für andere Schlüsselfragen als relevant eingeschätzt wurden und sie in den zugehörigen Sammlungen nicht enthalten waren, wurden sie diesen zugeordnet.

▶ **Tab. 4** Ergebnis der Leitlinienrecherche und -bewertung.

Organisation	Bewertung	Standardisierter Domänenwert (DELBI-Domäne 3)	Stand der Hintergrund-literatur
NICE 2013	Hochwertige Leitlinie zu eng definierten Fragestellungen	0,57	Recherche bis 15. November 2012 in Medline, Embase and Central, Cinahl
ECCO 2012	Evidenz- und konsensbasierte Leitlinie mit moderater Berichtsqualität	0,38	Recherche bis Juni 2012 in Medline und Central
Toronto 2015	Evidenz- und konsensbasierte Leitlinie mit moderater Berichtsqualität	0,48	Recherche bis Februar 2014 in Medline, Embase and Central
Frankreich 2016	„Expertenstatement", vergleichbar einer deutschen S1-Leitlinie		
WGO 2015	„Expertenstatement", vergleichbar einer deutschen S1-Leitlinie		
Sydney 2016	„Expertenstatement", vergleichbar einer deutschen S1-Leitlinie		
Neuseeland 2015	„Expertenstatement", vergleichbar einer deutschen S1-Leitlinie		

▶ **Tab. 5** Suchtreffer.

Literatursammlung	Medline	Cochrane Library	Duplikate	Ergebnis
AG 1 – Calprotectin Diagnostik	144	70	24	190
AG 1 – Eisenmangel Diagnostik	82	70	0	152
AG 1 – IEN	95	53	9	139
AG 1 – Überwachungskoloskopie	187	177	50	314
AG 2 – 1,2 Pankolitis, Linksseitskolitis, Proktitis	520	30	9	541
AG 2 – 3 steroid refraktärer Krankheitsverlauf	207	25	18	214
AG 2 – 4 steroid abhängiger Krankheitsverlauf	121	22	9	134
AG 2 – 5 Therapieversagen Anti-TNF	167	30	8	189
AG 3 – 1 Remissionserhaltung Aminosalicylate/Placebos	91	48	34	105
AG 3 – 2 Remissionserhaltung topische Aminosalicylate/ Glukokortikoide	20	18	3	35
AG 3 – 3 Remissionserhaltung E. Coli Mesalazin	10	3	1	12
AG 3 – 4 Remissionserhaltung bei Nichtansprechen auf Mesalazin	55	28	14	69
AG 3 – 5 Remissionserhaltung Infliximab/Biosimilars	21	2	1	22
AG 3 – 6 Remissionserhaltung bei Proktitis	103	42	12	133
AG 3 – 7 Therapieziel	98	68	8	158
AG 4 – Infektionen	971	214	60	1125
AG 5 – Chirurgie	94	73	0	167
AG 5 – postoperative Komplikationen	721	168	37	852
AG 6 – komplementäre Verfahren	801	198	62	937

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

* **Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

* * **As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".

Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

* *OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*

▶ **Abb. 1** CEBM Levels of Evidence 2011.

Zudem konnten Literaturstellen mit Klärungsbedarf markiert werden, wenn beispielsweise die thematische Relevanz für die Leitliniengruppe unklar war. Dies betraf 97 Literaturstellen, über deren Verbleib in der weiteren Literaturarbeit anschließend die Arbeitsgruppen der Leitlinie entscheiden konnten. Konnte in diesem Schritt der Klärungsbedarf nicht aufgehoben werden, wurde die Literaturstelle ausgeschlossen.

Zudem wurde das Rechercheergebnis durch die Leitliniengruppe auf Vollständigkeit überprüft und eventuell fehlende, relevante Studien wurden hinzugefügt. Die Literaturarbeit wurde über das Leitlinienportal der CGS Usergroup durchgeführt. Die Literatursammlungen waren der Leitliniengruppe zu jedem Zeitpunkt zur Einsicht verfügbar.

Im letzten Schritt des Screenings wurden die Volltexte der ausgewählten Publikationen auf die Erfüllung der o. g. Kriterien überprüft. Es wurden 173 relevante Literaturstellen identifiziert. Detaillierte Informationen können den PRISMA-Schemata im Anhang B entnommen werden.

Von AG 6 – Komplementäre Verfahren wurde parallel eine eigene Suche nach Literatur durchgeführt. Die Details der Suche sowie die Evidenztabellen der letztlich bewerteten Studien sind im Anhang D beigefügt.

Bewertung der Evidenz

Die Literaturbewertung wurde nach der Evidenzklassifizierung des Oxford Centre for Evidence-based Medicine 2011 (▶ **Abb. 1**) für Interventions- und diagnostische Studien durchgeführt. Studien mit methodischen Schwächen und/oder bedeutsamer Heterogenität wurden jeweils um ein Level herabgestuft. Abweichend von Oxford 2011 wurden Systematische Reviews, die ausschließlich auf Fallserien beruhten, mit Level 4 bewertet.

In der Literaturbewertung wurden systematische Übersichtsarbeiten und Metaanalysen priorisiert. Sofern RCT und Kohortenstudien in Systematischen Reviews guter Qualität enthalten waren, wurden diese nicht bewertet (im Schema mit Ausschlussgrund „In höherrangiger Veröffentlichung enthalten" geführt). Dies gilt analog für systematische Reviews zu gleichen Themen und Outcomes. Sofern sich mehr als die Hälfte der eingeschlossenen Studien überschnitt, wurde nur das Review der höchsten Qualität und mit jüngstem Veröffentlichungszeitpunkt berücksichtigt.

Die 173 im Volltext-Screening ausgewählten Literaturstellen wurden entsprechend dieser Systematik bewertet, wobei 37 Systematische Reviews sowie 17 RCT ausgeschlossen wurden. Ausschlussgründe für diese nicht weiter berücksichtigten Literaturstellen sind auf Anfrage im Leitlinienportal einsehbar.

Aus allen eingeschlossenen Literaturstellen wurden im nächsten Schritt Daten extrahiert und in Form von Evidenztabellen zusammengefasst. Neun Literaturstellen waren in mehr als einer

Literatursammlung enthalten, sodass diese nur einmal bewertet wurden.

Erstellung von Evidenztabellen

Aus allen eingeschlossenen Literaturstellen wurden im nächsten Schritt Daten extrahiert und in Form von Evidenztabellen im Leitlinienportal zusammengefasst. Diese sind im Anhang C zu den jeweiligen PICO-Schlüsselfragen dargestellt.

Insgesamt wurden Evidenztabellen für 90 systematische Reviews und 20 RCT erstellt.

Formulierung der Empfehlungen und strukturierte Konsensfindung

Auf der Grundlage von Recherche, Auswahl und Bewertung wurden die Empfehlungen und Hintergrundtexte durch die AGs erarbeitet und zunächst im E-Mail-Umlaufverfahren innerhalb der einzelnen AGs abgestimmt. Bei der Überführung der Evidenzstärke in die Empfehlungsstärke konnte der Empfehlungsgrad gegenüber dem Evidenzgrad aus den in ▶ **Abb. 2** angegebenen Gründen auf- oder abgewertet werden.

Die Graduierung der Empfehlungen erfolgte außerdem über die Formulierung soll, sollte, kann (▶ **Tab. 6**).

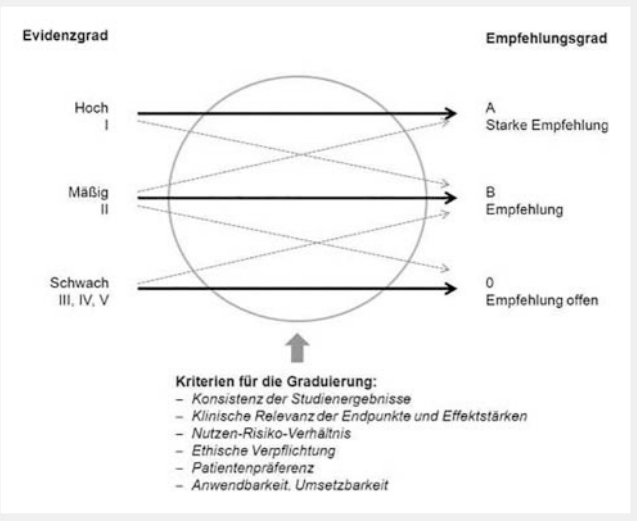
Konsensverfahren

Alle Empfehlungen wurden zunächst in einem Delphiverfahren von allen Leitlinienmitarbeitern mithilfe einer 5-stufigen Entscheidungsskala abgestimmt (ja, eher ja, unentschieden, eher nein, nein). Zu Empfehlungen, die nicht mit ja abgestimmt wurden, musste ein begründender Kommentar hinterlegt werden. Empfehlungen, die zu über 95 % mit ja/eher ja abgestimmt wurden, konnten bereits zu diesem Zeitpunkt verabschiedet werden.

Die Kommentare und Änderungsvorschläge der Delphirunde wurden von den AG-Leitern und den Koordinatoren gesichtet und die Empfehlungen überarbeitet. In einer strukturierten, Konsensuskonferenz unter unabhängiger Moderation von Frau Dr. Lynen stellten die AG-Leiter die Empfehlungen vor. Diese wurden, ggf. nach inhaltlichen Rückfragen und der Formulierung von Alternativvorschlägen, nach den Prinzipien der NIH-Konferenz diskutiert und mittels TED-System abgestimmt, bis eine Konsentierung erreicht wurde (> 75 %). Drei Empfehlungen (2.9, 4.9, 6.2.9) wurden mit mehrheitlicher Zustimmung (> 50 %) angenommen.

Diskutiert wurden:

- alle Empfehlungen, die in der Delphirunde weniger als 95 % Zustimmung erhalten hatten,
- Empfehlungen, die inhaltlich verändert wurden,
- Empfehlungen, die bereits in der Delphirunde verabschiedet worden waren, aber aufgrund von Dopplungen oder zur Verbesserung der inhaltlichen Stringenz der Leitlinie in den Kommentar verschoben wurden,
- neue Empfehlungen.



▶ **Abb. 2** Schema der Empfehlungsgraduierung.

▶ **Tab. 6** Schema zur Graduierung von Empfehlungen.

Empfehlungsgrad (nur S3)	Beschreibung	Syntax
A	starke Empfehlung	soll
B	Empfehlung	sollte
C	offen	kann

▶ **Tab. 7** Einteilung der Konsensstärke.

Konsens	% Zustimmung
starker Konsens	> 95
Konsens	> 75 – 95
mehrheitliche Zustimmung	> 50 – 75
kein Konsens	< 50

Empfehlungen, die in der Delphirunde nicht verabschiedet wurden und in den Kommentarteil verschoben wurden, wurden nicht erneut abgestimmt.

Die Konsensusstärke wurde gemäß ▶ **Tab. 7** festgelegt. Im Anschluss an die Konsensuskonferenz erfolgte die finale Überarbeitung der Kommentare durch die AG-Leiter und die redaktionelle Zusammenstellung der Leitlinie durch die Koordinatoren.

Statements

Als Statements werden Darlegungen oder Erläuterungen von spezifischen Sachverhalten oder Fragestellungen ohne unmittelbare Handlungsaufforderung bezeichnet. Sie werden entspre-

chend der Vorgehensweise bei den Empfehlungen im Rahmen eines formalen Konsensusverfahrens verabschiedet und können entweder auf Studienergebnissen oder auf Expertenmeinungen beruhen.

Expertenkonsens

Als Expertenkonsens werden Empfehlungen bezeichnet, zu denen keine systematische Recherche nach Literatur durchgeführt wurde. Teilweise wurde der Expertenkonsens auch angewandt, wenn nach ausführlicher Recherche keine Literatur vorlag. Diese Empfehlungen adressieren z. Bsp. Vorgehensweisen der guten klinischen Praxis, zu denen keine wissenschaftlichen Studien notwendig sind bzw. erwartet werden können. Für die Graduierung des Expertenkonsenses wurden keine Symbole verwendet; die Stärke der Empfehlung ergibt sich aus der verwendeten Formulierung (soll/sollte/kann) entsprechend der Abstufung in ▶ **Tab. 6**.

Externe Begutachtung und Verabschiedung

Verabschiedung durch die Vorstände der herausgebenden Fachgesellschaften/ Organisationen

Die Leitlinie wurde von allen beteiligten Fachgesellschaften begutachtet und konsentiert. Eine methodische Begutachtung und Freigabe erfolgte durch die AWMF.

Redaktionelle Unabhängigkeit und Finanzierung der Leitlinie:

Literaturrecherche, Konferenzen und Reisekosten wurden von der DGVS finanziert. Eine finanzielle Beteiligung Dritter erfolgte nicht. Mandatsträger und Experten arbeiteten ausschließlich ehrenamtlich.

Darlegung von und Umgang mit Interessenkonflikten

Im Einklang mit dem AWMF-Regelwerk zum Umgang mit Interessenkonflikten haben alle Teilnehmer Erklärungen auf dem entsprechenden AWMF-Formular vor Beginn der Konsensuskonferenz abgegeben (Anhang F). Die Interessenkonflikte wurden von den Koordinatoren der Leitlinie und Frau Lynen gesichtet und der Leitliniengruppe vor Beginn der Konsensuskonferenz präsentiert. Die Mandatsträger der Leitlinie gaben eine Vielzahl an Interessenkonflikten an. Nach Einschätzung der Leitliniengruppe stellen die interdisziplinäre Besetzung der Leitliniengruppe (einschließlich stimmberechtigter Patientenvertreter) und die systematische, extern durchgeführte Literaturrecherche und Bewertung eine wichtige Maßnahme zum Ausgleich dieser Interessenkonflikte dar. Mandatsträger mit personenbezogenen Zuwendungen (Zugehörigkeit zu Advisory Boards, Gutachter- und Vortragstätigkeit) wurden daher nach kritischer Bewertung durch die Leitliniengruppe nicht von den Abstimmungen ausgeschlossen, wenn die Art der Zuwendungen nicht einseitig (z. B. Zugehörigkeit zu mehreren Advisory Boards) und die wissenschaftliche Expertise nicht verzichtbar war. Finanzielle Zuwendungen, die ausschließlich wissenschaftlichen Institutionen zugeordnet werden konnten, führten nicht zu einer Stimmenthaltung (Drittmittel, Studienbeteiligung). Mandatsträger, deren Interessenkonflikte nicht vorlagen, oder Mandatsträger mit Eigentümerinteressen (z. B. Patente, Aktienbesitz, Firmenzugehörigkeit) erhielten kein Stimmrecht. Nach Überprüfung aller Interessenkonflikte wurden keine Mandatsträger ausgeschlossen.

▶ **Tab. 8** Zeitlicher Ablauf der Aktualisierung.

März 2016	Ausschreibung in der ZFG
Mai 2016	Beauftragung der Koordinatoren durch die DGVS
Juni 2017	Kick-off-Treffen Berlin
September 2016	Delphi-Verfahren
Juni 2017	Konsensuskonferenz Frankfurt

Verbreitung und Implementierung

Konzept zur Verbreitung und Implementierung

Die Leitlinie wird neben der Zeitschrift für Gastroenterologie im AWMF-Leitlinienportal (www.awmf.de) und auf der Homepage der DGVS (www.dgvs.de) veröffentlicht. Eine englische Übersetzung, ein Patientenleitfaden durch die Gastroliga sowie die DCCV (www.dccv.de) und ggfs. eine Kurzfassung sollen ebenfalls zur Verfügung gestellt werden.

Gültigkeitsdauer und Aktualisierungsverfahren

Der zeitliche Ablauf der Aktualisierung ist in ▶ **Tab. 8** dargestellt. Die letzte Überarbeitung dieser Leitlinienaktualisierung erfolgte im Mai 2018. Die Gültigkeit wird auf vier Jahre geschätzt. Die Überarbeitung wird durch den Leitlinienbeauftragten der DGVS initiiert werden.

Sollte es zwischenzeitlich wichtige Neuerungen in der Diagnostik und Therapie der Colitis ulcerosa geben, die eine kurzfristige Aktualisierung notwendig erscheinen lassen, entscheiden die Leitlinienkoordinatoren gemeinsam mit einer Aktualisierungsgruppe (B. Bokemeyer, P. Kienle, B. Siegmund, A. Stallmach) über die Notwendigkeit und die evtl. Inhalte einer Aktualisierung. Diese sollen dann online im Leitlinienportal der AWMF und auf der Homepage der DGVS veröffentlicht werden.

Anhänge

- Anhang A: Leitliniensynopse
- Anhang B: Literaturrecherche
- Anhang C: Evidenztabellen
- Anhang D: Literaturrecherche und Evidenztabellen AG 6
- Anhang E: Übersichtstabelle Evidenzgrundlage
- Anhang F: Interessenkonflikterklärungen

Anhang A: Leitliniensynopse

Kapitel nach DGVS-Leitlinie	DGVS (2011)	Evidenzgrad/ Empfehlungs-stärke	ECCO (2013)	Evidenzgrad/ Empfehlungs-stärkstärke	The Toronto Consensus Group (2015)	Evidenzgrad/ Empfehlungs-stärke
	EK: Level of Evidence (Oxford) (1 – 5) EG: Evidenzgrad (A-D) KKP: Klinischer Konsenspunkt (starke Empfehlung auf schwacher Evidenzgrundlage) Empfehlungsstärke: soll ++, sollte +, unklar + –, sollte nicht –, soll nicht ––		EL: Level of Evidence (Oxford) (1 – 5) RG: Grades of Recommendation (A-D)		H QE: High Quality Evidence M QE: Moderate QE L QE: Low QE Vl QE: Very low QE Grade: Strong recommendation ++ Weak recommendation +	
Klinische Diagnostik – Klassifikation *Empfehlungen 2.1 – 2.3*	Eine Klassifikation bez. der Ausdehnung der Erkrankung soll erfolgen.	D/KKP	*ECCO statement 2A* The extent of ulcerative colitis influences the patient's management. Disease extent influences the treatment modality and determines if oral and/or topical therapy is initiated [EL1b, RG B].	EL 1b RG B		
			Disease extent influences start and frequency of surveillance [EL2, RG B].	EL 2 RG B		
			Therefore, a classification according to extent of disease is recommended [EL5, RG D]	EL 5 RG D		
			ECCO statement 2B Classification of ulcerative colitis based on disease severity is useful for clinical practice and dictates the patient's management [EL1b, RG B].	EL 1b RG B		
			Disease severity influences the treatment modality and determines if no, oral, intravenous or surgical therapy is initiated. Indices of disease severity have not been adequately validated. Clinical, laboratory, imaging and endoscopic parameters, including histopathology assist physicians in patients' management [EL 2, RG B].	EL 2 RG B		
			There is no fully validated definition of remission. The best way of defining remission is a combination of clinical parameters (i. e. stool frequency ≤ 3/day with no bleed-ing) and a normal mucosa at endoscopy [EL5, RG D]. Absence of an acute inflammatory infiltrate at histology is helpful.	EL 5 RG D		

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	Es soll eine endoskopische Einteilung in die Proktitis (begrenzt auf das Rektum), die Linksseitenkolitis (Ausdehnung bis zur linken Flexur) und die ausgedehnte Kolitis erfolgen.	D/KKP	*ECCO statement 2A* The preferred classification is an endoscopic classification as outlined in the Montréal classification into ulcerative proctitis (limited to the rectum), left-sided colitis (up to the splenic flexure) and extensive colitis, and by maximal extent upon follow up [EL5, RG D].	EL 5 RG D		
			ECCO statement 2C A classification of UC according to age at onset is of value [EL2; RG B].	EL 2 RG B		
			Classification of UC according to the concomitant presence of PSC is important because it influences patients' management (surveillance) [EL2; RG C].	EL 2 RG C		
	Das gleichzeitige Vorliegen einer PSC soll dokumentiert werden, da dies die Überwachungsstrategie beeinflusst.	C/ ++	*ECCO statement 2 D* No evidence-based recommendation can be made to implement the routine clinical use of molecular markers (genetic, serologic) for the classification of UC patients [EL2, RG C].	EL 2 RG C		
Krankengeschichte *2.4 – 2.10*	Die Anamnese soll eine detaillierte Erfragung über Art und Beginn der Symptome, eine kürzliche Reiseanamnese, Nahrungsmittelunverträglichkeiten, Kontakte mit infektiösen Durchfallerkrankungen und die Medikamentenanamnese (insbesondere bez. Antibiotika und nicht steroidaler Antirheumatika) beeinhalten.	D/KKP	*ECCO statement 3A* Symptoms of ulcerative colitis are dependent upon extent and severity of disease, and most commonly include bloody diarrhoea, rectal bleeding, and/or rectal urgency. Nocturnal defaecation is also often reported. Systemic symptoms of malaise, anorexia, or fever are features of a severe attack [EL5, RG D].	EL 5 RG D		
			ECCO statement 3C A full medical history should include detailed questioning about the onset of symptoms, particularly recurrent episodes of rectal bleeding or bloody diarrhoea, urgency, tenesmus, abdominal pain, incontinence, nocturnal diarrhoea,	EL 5 RG D		

Kapitel nach DGVS-Leitlinie	DGVS (2011)	Evidenzgrad/ Empfehlungs-stärke	ECCO (2013)	Evidenzgrad/ Empfehlungs-stärkstärke	The Toronto Consensus Group (2015)	Evidenzgrad/ Empfehlungs-stärke
			and features of extra-intestinal manifestations. Recent travel, food intolerances, contact with enteric infectious illnesses, medication (including antibiotics and non-steroidal anti-inflammatory drugs), smoking habit, sexual practice, family history of IBD, family history of CRC and previous appendicectomy should be explored [EL5, RG D].			
			ECCO statement 3B Appendicectomy for histology proven appendicitis has been shown to provide some protection against sub-sequently developing UC and in reducing its severity if performed for 'true' appendicitis at a younger age [EL2b, RGB].	EL 2b RG B		
			The use of non-selective NSAIDs is associated with increased risk for exacerbating UC [EL2b, RGB].	EL2b RG B		
			Shortterm treatment with COX-2 inhibitors is probably safe [EL1b, RGB].	EL 1b RG B		
			A family history of CD or UC increases the risk for developing UC in another family member [EL2b, RG B].	EL 2b RG B		
	Bei etablierter Diagnose sollte die Anamnese weiterhin den Impfstatus, die Raucheranamnese, die Familien- und Sozialanamnese und die Frage nach einer evtl. vorliegenden Depression beinhalten.	D/+				
	Weiterhin soll die Anamnese Fragen bzgl. extraintestinaler Manifestationen (Mund, Haut, Augen und/oder Gelenke) sowie nach perianalen Abszessen, Fisteln und Analfissuren beinhalten.	D/KKP				
	Bei Erstdiagnose und beim Auftreten spezifischer Symptome soll eine komplette körperliche Untersuchung inkl. einer oralen und perianalen Inspektion, einer rektalen	D/KKP	*ECCO statement 3 D* In patients with UC physical examination should include general well-being, pulse rate, body temperature, blood pressure, body weight and height, abdominal	EL 5 RG D		

Kapitel nach DGVS-Leitlinie	DGVS (2011)	Evidenzgrad/ Empfehlungs-stärke	ECCO (2013)	Evidenzgrad/ Empfehlungs-stärkstärke	The Toronto Consensus Group (2015)	Evidenzgrad/ Empfehlungs-stärke
	Untersuchung und die Beachtung evtl. vorliegender extraintestinaler Manifestationen erfolgen.		examination for distention and tenderness, perianal inspection, digital rectal examination, oral inspection, and check for eye, skin and/or joint involvement. Physical examination may be unremarkable in patients with mild or even moderate disease [EL5, RG D]			
	Bei Kindern und Jugendlichen soll zusätzlich die Entwicklung von Gewicht, Länge und das Pubertätsstadium bei Erstdiagnose und regelmäßig im Krankheitsverlauf erfasst werden.	D/KKP				
	Die Diagnose einer Colitis ulcerosa soll auf dem Boden einer Kombination von Anamnese, klinischer Untersuchung und typischen laborchemischen, sonografischen, endoskopischen und histologischen Befunden gestellt werden.	D/KKP				
	Bei Zweifel bzgl. der Diagnose soll die Endoskopie inkl. Histologiegewinnung im Intervall wiederholt werden.	D/KKP	*ECCO statement 3E* A gold standard for the diagnosis of ulcerative colitis is not available. The diagnosis should be established by a combination of medical history, clinical evaluation, and typical endoscopic and histological findings. An infective cause should be excluded. Where there is doubt about the diagnosis, endoscopic and histological confirmation is necessary after an interval [EL5, RG D]	EL 5 RG D		
Diagnose *2.11 – 2.19*	Die initiale Labordiagnostik soll neben dem Blutbild mindestens folgende Parameter enthalten: Entzündungsstatus, Eisenhaushalt, Nierenfunktion, Transaminasen und Cholestaseparameter.	D/KKP	*ECCO statement 3F* Initial laboratory investigations should include a full blood count, serum urea, creatinine, electrolytes, liver enzymes, iron studies, and C-reactive protein (CRP) [EL5, RG D].	EL 5 RG D		
	Für die begleitende laborchemische Diagnostik eines Ansprechens auf die Therapie können CRP, BSG, Blutbild sowie fäkale Neutrophilenmarker herangezogen werden.	B/+	*ECCO statement 3F* Faecal calprotectin is an accurate marker of colonic inflammation. CRP and erythrocyte sedimentation rate (ESR) are useful markers tomonitor the response to treatment in severe colitis [EL2b, RGB].	EL 2b RG B		

Kapitel nach DGVS-Leitlinie	DGVS (2011)	Evidenzgrad/ Empfehlungs-stärke	ECCO (2013)	Evidenzgrad/ Empfehlungs-stärkstärke	The Toronto Consensus Group (2015)	Evidenzgrad/ Empfehlungs-stärke
	Eine intestinale Infektion soll ausgeschlossen werden.	D/KKP				
	Bei der Erstdiagnostik soll eine mikrobiologische Diagnostik auf bakterielle infektiöse Erreger inklusive Clostridium-difficile-Toxin erfolgen.	B/++	*ECCO statement 3F* Microbiological testing for infectious diarrhoea including Clostridium difficile toxin is recommended [EL2b, RG B].	EL 2b RG B		
	Bei Patienten mit entsprechender Reiseanamnese soll eine ergänzende Diagnostik bzgl. landestypischer Erreger durchgeführt werden.	D/KKP	*ECCO statement 3F* Additional stool tests may be necessary for patients who report a recent travel abroad [EL5, RG D].	EL 5 RG D		
	Bei etablierter Colitis ulcerosa soll bei schwerem Schub und bei therapierefraktärem Verlauf bzw. vor Intensivierung einer immunsuppressiven Therapie eine mikrobiologische Diagnostik inklusive Untersuchungen auf Clostridium-difficile-Toxin und Cytomegalievirus erfolgen.	B/++	*ECCO statement 3G* In patients with an established diagnosis of UC microbial testing is recommended in cases of severe or refractory relapse. This includes testing for C. difficile and Cytomegalovirus infection EL4, RG C].	EL 4 RG C		
	Die Diagnostik bzgl. Clostridium difficile soll mittels Toxinnachweis im Stuhl, bei therapierefraktärem Krankheitsverlauf und negativem Toxinnachweis zusätzlich durch Endoskopie mit Biopsie erfolgen.	C/++				
	Die CMV-Diagnostik soll eine CMV-PCR aus dem Blut oder die Histologie einschließlich einer Immunhistochemie aus der Darmbiopsie beinhalten.	D/KKP	3F: Patient's immunization status to various viral diseases and tuberculosis status should be assessed [EL5, RG D].	EL 5 RG D		
	Die quantitative Bestimmung von fäkalen Neutrophilenmarkern im Stuhl kann zur Abgrenzung nicht entzündlicher Ursachen der gastrointestinalen Beschwerden genutzt werden.	B/+				
Endoskopie *2.20 – 2.22*	Bei Verdacht auf Colitis ulcerosa soll eine Ileokoloskopie mit segmentalen Biopsien aus allen Darmabschnitten erfolgen, um die Diagnose zu stellen und die Ausdehnung der Erkrankung	D/KKP	*ECCO statement 3H* For suspected UC, colonoscopy, preferably with ileoscopy, and segmental biopsies including the rectum are the preferred procedures to establish the diagnosis and extent of disease [EL5, RGD].	EL 5 RG D		

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	festzustellen (siehe hierzu auch Kapitel 3).		Patients with a severe attack should have abdominal radiography and active disease confirmed by sigmoidoscopy as a first line procedure [EL5, RGD].	EL 5 RG D		
	Eine routinemäßige Koloskopie soll bei Patienten mit Colitis ulcerosa in der Remission bis zum Beginn der Karzinomüberwachung nicht erfolgen.	D/KKP	*ECCO statement 3 J* Findings at endoscopy for patients with UC in remission are predictive of outcome [EL2, RGB].	EL 3 RG B		
			Endoscopic reassessment is appropriate at a relapse, or for steroiddependent or –refractory UC or when considering colectomy [EL5, RGD].	EL 5 RG D		
	Eine endoskopische Evaluation mittels Endoskopie kann durchgeführt werden bei schwerem akutem Schub und bei therapierefraktären Verläufen zur Bestätigung der aktiven Erkrankung und zum Ausschluss von infektiösen Komplikationen.	D/+	*ECCO statement 3I* Instruments for measuring clinical and/or endoscopic disease activity in UC are available, but none has been subjected to an adequate validation process. In daily routine such indices are barely used. The incorporation of a simple clinical and/or endoscopic scoring system is desirable, intended to improve care of UC patients and torealise a standardised IT system for IBD. Immediate admission to hospital is warranted for all patients fulfilling Truelove and Witts' criteria for severe colitis to prevent delayed decision-making which may lead to increased perioperative morbidity and mortality [EL4, RGD].	EL 4 RG D		
Abgrenzung Crohn 2.23	Bei nicht eindeutig zu klassifizierender Colitis und zum Ausschluss eines Morbus Crohn sollte eine Diagnostik des oberen und mittleren Gastrointestinaltrakts mittels Ösophagogastroduodenoskopie (mit Biopsien) und mittels MRT des Dünndarms durchgeführt werden.	D/+				
Krankheitsaktivität 2.24	Die Anwendung klinischer und/oder endoskopischer Aktivitätsindizes kann hilfreich sein, um ein Therapieansprechen zu quantifizieren und Patientenverläufe zu objektivieren.	D/+				

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	Die hochauflösende abdominelle Sonografie soll Bestandteil der Diagnostik bei der Erstdiagnose sowie einem schweren akuten Schub zur Erfassung des Befallsmusters und insbesondere bei Verdacht auf Komplikationen sein.	B/++	*ECCO statement 3K* No endoscopic feature is specific for UC. The most useful endoscopic features of UC are considered to be continuous and confluent colonic involvement with clear demarcation of inflammation and rectal involvement [EL2b, RGB].	EL 2b RG B		
			Endoscopic severity of UC may be best reflected by the presence of mucosal friability, spontaneous bleeding and deep ulcerations [EL2b, RGB].	EL 2b RG B		
			ECCO statement 3 M Virtual colonography is an evolving technology. The limited data currently available do not demonstrate a diagnostic value for assessing the disease extent in patients with suspected or proven UC [EL4, RGC].	EL 4 RG C		
Kolonstenose *2.26 – 2.28*	Da das Vorliegen einer Kolonstenose bei Colitis ulcerosa malignitätsverdächtig ist, soll eine ausgiebige Biopsieentnahme aus dem Bereich der Stenose erfolgen.	D/KKP	*ECCO statement 3N* Each colonic stenosis in UC should raise the suspicion of colorectal carcinoma. Multiple biopsies should betaken and a surgical option should be sought. When endoscopic intubation of the colon is not possible, imaging procedures, such as double contrast barium enema, CT and/ or MRI colonography may be employed [EL5, RGD].	EL 5 RG D		
	Bei unklarer Dignität einer Kolonstenose soll die Entscheidung zur Operation großzügig gestellt werden.	D/KKP				
	Falls eine endoskopische Passage der Stenose unklarer Dignität nicht möglich ist, sollte eine weiterführende radiologische Diagnostik mittels Computertomografie oder Magnetresonanztomografie erfolgen.	D/+				
Pädiatrie *2.29 – 2.30*	Die Diagnose einer Colitis ulcerosa soll bei Kindern bei Vorliegen von chronischen (> 4 Wochen) oder rezidivierenden (> 2 Episoden innerhalb von 6 Monaten) blutigen Durchfällen	D/+				

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	nach Ausschluss einer infektiösen Genese in Betracht gezogen werden.					
	Die initiale Diagnostik bei Kindern und Jugendlichen mit Verdacht auf eine chronisch entzündliche Darm-erkrankung soll eine Ileokoloskopie mit Entnahme von Stufenbiopsien beinhalten. Im gleichen Untersu-chungsgang soll eine Ösophagogas-troduo-denoskopie mit Entnahme von Stufenbiopsien erfolgen.	D/KKP				
Histopathologie *3.1 – 3.7*	Die histologische Untersuchung von endoskopischen Mukosabiopsien stellt einen wichtigen Baustein zur Diagnose einer Colitis ulcerosa dar. Zur Erstdiagnose einer Colitis ulcerosa sollen multiple Biopsienent-nahmen aus dem terminalen Ileum und jedem Kolonsegment unter Einschluss des Rektums (Ein-sendung in getrennten Probengefäßen) untersucht werden.	B/++	*ECCO statement 4A* For a reliable diagnosis of ulcerative colitis multiple biopsies from five sites around the colon (including the rectum) and the ileum should be obtained. Mul-tiple implies a minimum of two samples [EL1b, RGB].	EL 1b RG B		
			ECCO statement 4B Biopsies should be accompanied by clini-cal information including the age of the patient, duration of disease and duration and type of treatment [EL1b, RGB].	EL 1b RG B		
			Biopsies from different regions should be handled in such a way that the region of origin can be identified [EL1c, RGA].	EL 1c RG A		
			This can be done by using different con-tainers, multiwall cassettes, or an aceta-te strip [EL5, RG D].	EL 5 RG D		
			All tissue samples should be fixed imme-diately by immersion in buffered forma-lin or an equivalent solution prior to transport. It is recommended that multi-ple sections from each sample are examined [EL5, RGD].	EL 5 RG D		

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	Histopathologische Kriterien, die bei der Beurteilung von Biopsien zur Diagnose einer Colitis ulcerosa herangezogen werden sollen, sind: diffuse panmuko-sale chronische Entzündung (Lymphozyten und Plasmazellen) in Kombination mit einer Störung der Kryptenarchitektur/ Kryptenatrophie, Plasmozytose im basalen Schleimhautstroma, Panethzell-Metaplasien distal der rechten Kolonflexur, Reduktion der Anzahl von Becherzellen bzw. des Muzingehalts der Einzel-zelle, kontinuierliche Verteilung der entzündlichen und strukturellen Schleimhautveränderungen, abnehmen-der Gradient von distal nach proximal.	D/KKP	*ECCO statement 4C* Basal plasmacytosis at the initial onset has a high predictive value for the diagnosis of IBD [EL 3, RG C].	EL 3 RG C		
			Repeat biopsies after an interval may help to solve differential diagnostic problems and establish a definitive diagnosis especially in adults, by showing additional features [EL 5, RG D].	EL 5 RG D		
			ECCO statement 4E A diagnosis of established ulcerative colitis is based upon the combination of: basal plasmacytosis (defined as presence of plasma cells around (deep part of the lamina propria) or below the crypts (subcryptal)), heavy, diffuse transmucosal lamina propria cell increase and widespread mucosal or crypt architectural distortion [EL 1a, RG A].	EL 1a RG A		
	Im Initialstadium einer Colitis ulcerosa (Dauer < 4 – 6 Wochen) kann eine Störung der Krytenarchitektur/ Kryptenatrophie fehlen. Der Nachweis einer basalen Plasmozytose kann in diesem Kontext als Frühzeichen einer potenziellen chronisch-entzündlichen Darmerkrankung gewertet werden.	B/+	*ECCO statement 4F* Widespread mucosal or crypt architectural distortion, mucosal atrophy and a villous or irregular mucosal surface appear later during the evolution of the disease (4 weeks ormore). They suggest a diagnosis of ulcerative colitis in established disease [EL 2, RG B].	EL 2 RG B		
			ECCO statement 4G Basal plasmacytosis is a good diagnostic feature in established ulcerative colitis [EL 2, RG B].	EL 2 RG B		
			A heavy, diffuse transmucosal lamina propria cell increase is a good diagnostic feature in established active disease [EL 2, RG B].	EL 2 RG B		
			Distribution of inflammation along the colon, with a decreasing gradient of inflammation from distal to proximal is in favour of a diagnosis of ulcerative colitis in an untreated patient [EL5 RG D].	EL 5 RG D		

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			ECCO statement 4H General or widespread crypt epithelial neutrophils (cryptitis and crypt abscesses) favour ulcerative colitis. However these lesions may occur in infections and other types of colitis [EL 2b, RG B].	EL 2b RG B		
			Lamina propria and intraepithelial neutrophils are absent in inactive or quiescent disease. [EL 2b, RG B].	EL 2b RG B		
	Abweichende morphologische Befundmuster können bei der Colitis ulcerosa vorkommen und sollen speziell bei pädiatrischen Patienten (jünger als 10 – 12 Jahre) berücksichtigt werden.	D/KKP	*ECCO statement 4 D* In young children or patients with an aberrant presentation of colitis, UC should always be considered in the differential diagnosis even if the pathology is not typical [EL1b RG B].	EL 1b RG B		
	Die bioptischen Proben sollen bez. der Lokalisation gekennzeichnet sein und durch Informationen zum klinischen Bild ergänzt werden (Endoskopiebefund, Art und Dauer der Symptomatik, Art und Dauer der Behandlung).	D/KKP	*ECCO statement 4K* The term indeterminate colitis (IC) should be restricted to resection specimens. When patients have colitis that has yet to be classified after all clinical, radiologic, endoscopic and histological results are taken into account, then the preferable term is IBD unclassified (IBDU) [EL5 RG D].	EL 5 RG D		
	Die histologische Aufarbeitung der Proben soll in Stufen- oder Serienschnitten erfolgen.	D/KKP				
	Der Pathologiebefund soll eine Aussage zur histologischen Entzündungsaktivität enthalten.	D/KKP	*ECCO statement 4 J* The pathology report should give an indication of the activity of the disease [EL5 RG D].	EL 5 RG D		
Intraepitheliale Neoplasien (IEN) *3.8 – 3.10*	Die Diagnose von intraepithelialen Neoplasien/ Dysplasien bei der Colitis ulcerosa soll nach den seit 2010 gültigen Kriterien der WHO erfolgen; IEN/Dysplasien sollen histopathologisch graduiert werden (niedriger oder hoher Grad).	D/KKP				

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	Bei histologischer Diagnose jeder IEN/Dysplasie soll stets eine externe Zweitbeurteilung eingeholt werden.	C/++				
	Im Falle einer erhabenen Läsion mit IEN/Dysplasie soll eine Unterscheidung zwischen einer CED-assoziierten sogenannten DALM-Läsion (Dysplasie-assoziierte Läsion oder Masse) oder einem sporadischen Adenom beziehungsweise einer adenomartigen IEN/Dysplasie (ALM, „adenoma-like mass“) jeweils mit Angabe des IEN- bzw. Dysplasiegrads (LGIEN oder HGIEN) erfolgen, da diese Aussage von therapeutischer Bedeutung ist. Diese Unterscheidung soll unter Berücksichtigung des makroskopischen bzw. endoskopischen Befunds erfolgen.	C/++				
Proktitis *4.1 – 4.3*	Eine leichte bis mäßig aktive Proktitis soll zunächst mit 5-Aminosalizylaten ≥ 500 mg/d (bei Kindern ≥ 250 mg/d) als Suppositorium behandelt werden.	B/++	*ECCO statement 5A* Suppositories may deliver drug more effectively to the rectum and are better tolerated than enemas [EL3, RG C].	EL3 RG C	*ST 1*: In patients with mild to moderate active ulcerative proctitis, we recommend rectal 5-aminosalicylate (5-ASA), at a dosage of 1 g daily, as first-line therapy to induce symptomatic remission.	h QE /++
	Mesalazinschaum und Mesalazineinläufe stellen eine äquivalente therapeutische Alternative dar.	B/+	*ECCO statement 5A* A mesalazine 1 g suppository once daily is the preferred initial treatment for mild or moderately active proctitis [EL1b, RGA].	EL 1b RG A		
			Mesalazine foam enemas are an alternative [EL1b RG B].	EL 1b RG B		
			Oral mesalazine alone is less effective [EL1b, RG B].	EL 1b RG B		
	Bei Versagen der Monotherapie soll die Kombination der rektalen Mesalazinanwendung mit topischen Steroiden oder der oralen Gabe von 5-ASA-freisetzenden Präparaten eingesetzt werden.	B/++	*ECCO statement 5A* Combining topical mesalazine with oral mesalazine or topical steroid is more effective than either alone and should be considered for escalation of treatment [EL1b, RG B].	EL 1b RG B	*ST 13*: In patients with mild to moderate active left-sided UC or proctitis who fail to respond to rectal 5-ASA therapy, we suggest rectal corticosteroids as second-line therapy to induce complete remission.	Vl QE/+

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			Refractory proctitis may require treatment with immunosuppressants and/or biologics [EL4, RG C].	EL 4 RG C		
			ECCO statement 5A Rectal 5-ASA is the first line in maintenance in proctitis and an alternative in left-sided colitis [EL1b, RG A].	EL 1b RG A	*ST 6*: In patients with oral or rectal 5-ASA–induced complete remission of mild to moderate active left-sided UC or proctitis, we recommend the same therapy be continued to maintain complete remission.	m QE/++
Linksseitenkolitis *4.4 – 4.8*	Eine leichte bis mäßig schwere linksseitige CU soll initial mit rektalen 5-ASA in Form von Einläufen oder Schäumen (≥ 1 g/d) in Kombination mit oralen 5-ASA-freisetzenden Präparaten (≥ 3 g/d) behandelt werden.	B/ ++	*ECCO Statement 5B* Left-sided active ulcerative colitis of mild–moderate severity should initially be treated with an aminosali-cylate enema 1 g/day [EL1b, RG B] combined with oral mesalazine N2 g/day [EL1a, RG A].	EL 1b RG B EL 1a RG A	*ST 2*: In patients with mild to moderate active left-sided UC, we recommend 5-ASA enemas, at a dosage of at least 1 g daily, as an alternative firstline therapy to induce complete remission.	m QE/++
	Eine alleinige orale Gabe von 5-ASA-freisetzenden Präparaten (≥ 3 g/d) kann alternativ eingesetzt werden, ist aber weniger wirksam.	B/ +	*ECCO Statement 5B* Once daily dosing with 5ASA is as effective as divided doses [EL1b, RG A].	EL 1b RG A		
	Die rektale Anwendung von 5-ASA-Einläufen oder –Schäumen (≥ 1 g/d) soll der topischen Steroidtherapie vorgezogen werden.	A/ ++	*ECCO Statement 5B* Topical therapy with steroids or amino-salicy-lates alone [EL1b, RG B] as well as mono-therapy with oral aminosalicylates [EL1a, RG A] is less effective than oral plus topical 5ASA therapy.	EL 1b RG B EL 1a RG A		
			Topical mesalazine is more effective than topical steroid [EL1a, RG A].	EL 1a RG A		
			ECCO Statement 5B Rectal 5-ASA is the first line in maintenance in Proctitis and an alternative in left-sided colitis [EL1b, RG A].	EL 1b RG A		
	Aufgrund der besseren Therapieadhärenz und der größeren Patientenzufriedenheit kann die einmalige orale Gabe von retardiert formulierten 5-ASA-freisetzenden Präparaten gegenüber nicht retardierten vorgezogen werden.	B/ +				

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	Eine systemische Steroidtherapie (0,5 – 1 mg/kg KG/d Prednisolon-äqui-valent) soll begonnen werden, wenn die Symptome der CU nicht auf die unter 4.4. – 4.6. genannte Therapie ansprechen.	C/ ++	*ECCO Statement 5B* Systemic corticosteroids are appropriate if symptoms of active colitis do not respond to mesalazine [EL1b, RG C].	EL 1b RG C	*ST 13*: In patients with mild to moderate active left-sided UC or proctitis who fail to respond to rectal 5-ASA therapy, we suggest rectal corticosteroids as second-line therapy to induce complete remission.	Vl QE/+
					ST 6: In patients with oral or rectal 5-ASA–induced complete remission of mild to moderate active left-sided UC or proctitis, we recommend the same therapy be continued to maintain complete remission.	m QE/++
			ECCO Statement 5B Severe left-sided colitis is usually an indication for hospital admission for intensive treatment with systemic therapy [EL1b, RG B]	EL 1b RG B		
Ausgedehnter Befall *4.9 – 4.10*	Bei ausgedehntem Befall soll eine leicht bis mäßig schwere CU zunächst mit einem oralen 5-ASA-freisetzenden Präparat in einer Dosierung ≥ 3 g/d in Kombination mit Mesalazineinläufen oder -schäumen behandelt werden.	A/ ++	*ECCO Statement 5C* Extensive ulcerative colitis of mild–moderate severity should initially be treated with oral 5-ASA N2 g/day [EL1a, RG A], which should becombined with topical mesalazine to increase remission rates if tolerated [EL1b, RG A].	EL 1b RG A EL 1a RG A	*ST 3*: In patients with mild to moderate active UC of any disease extent beyond proctitis, we recommend an oral 5-ASA preparation, at dosages between 2.0 and 4.8 g/day, as an alternative first-line therapy to induce complete remission.	m QE/++
			Once daily dosing with 5ASA is as effective as divided doses [EL1b, RG A].	EL 1b RG A		
					ST 4: In patients with mild to moderate active UC of any disease extent beyond proctitis, we suggest the combination of a rectal and an oral 5-ASA preparation over oral 5-ASA alone as an alternative first-line therapy to induce complete remission.	L QE/+

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			ECCO Statement 6F Azathioprine/mercaptopurine is recommended for patients with mild to moderate disease activity who have experienced early or frequent relapse whilst taking 5-ASA at optimal dose or who are intolerant to 5-ASA [EL5, RG D], patients that are steroid-dependent [EL1a, RG A] and for patients responding to ciclosporin (or tacrolimus) for induction of remission [EL3, RG C].	EL 5 RG D EL 1a RG A EL 3 RG C		
	Eine systemische Steroidtherapie (0,5 – 1 mg/kg Körpergewicht/ Tag Prednisolonäquivalent) soll begonnen werden, wenn die Symptome der CU nicht auf die unter 4.4 – 4.6 und 4.9 genannte Therapie ansprechen.	C/ ++	*ECCO Statement 5C* Systemic corticosteroids are appropriate if symptoms of active colitis do not respond to mesalazine [EL1b, RG C].	EL 1b RG C	*ST 5*: We recommend that patients with UC be evaluated for lack of symptomatic response to oral/rectal 5-ASA induction therapy in 4 to 8 weeks to determine the need to modify therapy.	vl QE/++
					ST 12: In patients with mild to moderate active UC who fail to respond to 5-ASA therapy, we recommend oral corticosteroids as second-line therapy to induce complete remission.	L QE/++
					ST 9: In patients with UC who have failed to respond to oral 5-ASA, we recommend against switching to another oral 5-ASA formulation to induce complete remission.	L QE/++
					ST 16: We recommend that patients with UC be evaluated for lack of symptomatic response to corticosteroid induction therapy within 2 weeks to determine the need to modify therapy.	Vl QE/++
Schwere CU, beliebige Ausdehnung *4.11 – 4.15*	Definition: Zur Definition einer schweren, aktiven CU können die Kriterien von Truelove und Witts (mehr als 6 blutige Durchfälle/d,	C/++	*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	EL 5 RG D		

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	Fieber, Tachykardie, Anämie, BSG >30 mm/h) angewendet werden.		severe colitis and should be admitted to hospital for intensive treatment [EL5, RG D].			
	Die Behandlung einer schweren, aktiven CU mit Zeichen einer systemischen Beteiligung sollte unter stationären Bedingungen erfolgen.	C/+	*ECCO Statement 5D* Severe extensive colitis is an indication for hospital admission for intensive treatment [EL1b, RG B].	EL 1b RG B		
	Ein schwer verlaufender Schub einer CU mit Zeichen einer systemischen Beteiligung soll mit einer intra-venösen Steroidtherapie (z. B. 1 mg/kg Körpergewicht Prednisolon-äquivalent pro Tag) behandelt werden.	B/++			*ST 11*: In patients with moderate to severe active UC, we recommend oral corticosteroids as firstline therapy to induce complete remission.	M QE/++
					ST 15: In patients with mild to moderate UC of any disease extent, we suggest oral budesonide MMX as an alternative first-line therapy to induce complete remission.	H QE/+
	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.	s. Text/+			*ST 20*: In patients with UC who fail to respond to thiopurines or corticosteroids, we recommend anti-TNF therapy to induce complete corticosteroid-free remission.	H QE/++
			ECCO Statement 6F In patients responding to anti-TNF agents, bothmaintaining remission with azathioprine/ mercaptopurine [EL4, RGC] and continuing anti-TNF therapy with or without thiopurines [EL1a, RGA] are appropriate.	EL 4 RG C EL 1a RG A	*ST 21*: When starting anti-TNF therapy, we recommend it be combined with a thiopurine or methotrexate rather than used as monotherapy to induce complete remission.	M QE/++
					ST 23: We recommend that patients with UC be evaluated for lack of symptomatic response to anti-TNF induction therapy in 8 to 12 weeks to determine the need to modify therapy.	L QE/++

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	Diese Patienten sollen intensiv überwacht und, insbesondere jene mit toxischem Verlauf, in enger Zusammenarbeit von Gastroenterologen/ Kindergastroenterologen und Chirurgen betreut werden.	D/KKP				
Refraktärsystemische Steroidtherapie *4.16 – 4.19*	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.	D/KKP	*ECCO Statement 5E* The response to intravenous steroids is best assessed objectively around the third day [EL2b, RGB].	EL 2b RG B		
					ST 28: In patients with primary failure to an anti-TNF therapy, we recommend switching to vedolizumab over switching to another anti-TNF therapy to induce complete corticosteroid-free remission.	VI QE/++
					ST 29: In patients with secondary failure to an anti-TNF therapy, we recommend switching to another anti-TNF therapy or vedolizumab based on therapeutic drug monitoring results to induce complete corticosteroid-free remission.	M QE/++
	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 Therapie-alternative in Betracht gezogen werden (B).	s. Text/++	*ECCO Statement 5E* Second line therapy with either ciclosporin [EL1b, RG B], or infliximab [EL1b, RG B] or tacrolimus [EL4, RG C] may be appropriate.	EL 1b RG B EL 1b RG B EL 4 RG C		
			ECCO Statement 5G Outpatients with moderately active steroid refractory disease should be treated with anti TNF therapy [EL1b, RG B] or tacrolimus [EL2b, RG C], although surgical	EL 1b RG B EL 2b RG C EL 5		

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			options or admission for parenteral steroid therapy could also be considered [EL5 RG D].	RG D		
			ECCO Statement 5H 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.	EL 1b RG B EL 4 RG C	*ST 20*: In patients with UC who fail to respond to thiopurines or corticosteroids, we recommend anti-TNF therapy to induce complete corticosteroid-free remission.	H QE/++
			Continued medical therapy that does not achieve a clear clinical benefit is not recommended [EL5, RG D]	EL 5 RG D		
			ECCO Statement 6F The prior failure of thiopurines favours maintenance with anti-TNF therapy [EL5, RGD].	EL 5 RG D		
					ST 30: In patients with moderate to severe active UC who fail to respond to corticosteroids, thiopurines, or anti-TNF therapies, we recommend vedolizumab to induce complete corticosteroid-free remission.	M QE/++
	Nach Ansprechen auf eine Therapie kann eine Azathioprin- oder eine 6-Mercaptopurin-Therapie eingeleitet werden.	B/+	*ECCO Statement 6F* In patients with severe colitis responding to intravenous steroids, intravenous ciclosporin or infliximab, azathioprine/ mercaptopurine should be considered to maintain remission [EL2b, RG3]. However, in patients responding to infliximab continuing infliximab is also appropriate [EL4, RGC].	EL2b RG C EL 4 RG C	*ST 17*: In patients with UC, we recommend against the use of thiopurine monotherapy to induce complete remission.	L QE/++
	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.	D/KKP	*ECCO Statement 5H* Treatment options including colectomy should be discussed with patients with severely active UC not responding to intravenous steroids. If there is no improvement within 4 – 7 days of salvage therapy, colectomy is recommended [EL4, RG C].	EL 4 RG C		

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			Third line medical therapy may be considered at a specialist centre [EL4, RG C].	EL 4 RG C		
Schub unter Remission *4.20 – 4.22*	Wird ein 5-ASA-freisetzendes Präparat zur Remissionserhaltung genutzt, soll im Falle eines akuten Schubes mit leichter bis mäßiger Aktivität zunächst die Dosierung auf ≥ 3 g/d erhöht werden.	B/++				
	Führt diese Maßnahme nicht zügig zu einer Besserung der Symptomatik, soll eine systemische Steroidtherapie initiiert werden.	B/++				
	Wird Azathioprin oder 6-Mercaptopurin zur Remissionserhaltung eingesetzt, sollte eine systemische Steroidtherapie begonnen werden.	D/KKP				
Schmerztherapie *4.23 – 4.25*	Schmerzen können in allen Stadien der Erkrankung aus verschiedenen Ursachen auftreten. Eine differenzierte Schmerzanalyse (Krank-heitsaktivität, Nebenwirkungen der Anti-in-flammatorischen Therapie, funktionelle gastrointestinale Störungen, psychische Störungen) soll vor Einleitung einer symptomatischen Schmerztherapie durchgeführt werden.	D/KKP				
	Im akuten Schub und bei chronisch-aktiven Verläufen kann bei anhaltenden Bauchschmerzen trotz anti-inflammatorischer Therapie eine symptomatische Schmerz-therapie mit Metamizol oder ggf. Opioiden durchgeführt werden.	D/+				
	Eine Dauertherapie mit Opioiden sollte vermieden werden.	D/-				
Remission *5.1 – 5.15*	Definition: Die Remission der CU kann klinisch und endoskopisch definiert werden. Kriterien der klinischen Remission sind Abwesenheit	D/+	*ECCO Statement 6A* The goal of maintenance therapy in UC is to maintain steroid-free remission, clini-	EL 1 RG A EL 2 RG B		

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	von Diarrhö (≤ 3 ungeformte Stühle/ d), kein sichtbares Blut im Stuhl und keine durch die CU bedingten intes-tinalen oder extraintestinalen Be-schwerden. Die endos-kopische Remission wird durch das Fehlen entzündlicher Veränderungen be-stimmt.		cally [EL1, RG A] and endoscopically defined [EL2, RG B]			
	Bei Colitis ulcerosa soll eine remissi-onserhaltende Therapie (oral oder rektal) mit Aminosalizylaten erfol-gen.	A/++	*ECCO Statement 6B* Maintenance treatment is recommended for all patients [EL1a, RG A].	EL 1a RG A	*ST 7*: In patients with oral 5-ASA–induced complete remission of mild to moderate active UC of any disease ex-tent, we recommend continu-ed oral therapy of at least 2 g/day to maintain complete remission.	m QE/ ++
			Intermittent therapy is acceptable in a few patients with disease of limited extent [EL5, RG D]	EL 5 RG D		
					Statement 24. In patients with UC who respond to anti-TNF induction therapy, we recom-mend continued anti-TNF therapy to maintain complete remission. vlQE for infliximab and adalimumab hQE for goli-mumab	s. Text/++
			ECCO Statement 6C Choice of maintenance treatment in UC is determined by disease extent [EL1b, RG B], disease course (frequency of fla-res) [EL5, RG D], failure of previous maintenance treatment [EL5, RG D], severity of the most recent flare [EL5, RG D], treatment used for inducing remissi-on during the most recent flare [EL5, RG D], safety of maintenance treatment [EL1b, RG B], and cancer prevention [EL2a, RG B].	EL 1b RG B EL 5 RG D EL 5 RG D EL 5 RG D EL 5 RG D EL 1b RG B EL 2a RG B		
			ECCO Statement 6I Due to limited evidence, no recommen-dation can be given for the duration of treatment with azathio-prine or inflixi-mab, although prolonged use of these	EL 4 RG D		

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			medications may be considered if needed [EL4, RG D].			
	Angesichts des Nebenwirkungsprofils bei nicht unterschiedlicher Effizienz soll 5-ASA der Vorzug gegenüber SASP gegeben werden.	A/++	*ECCO Statement 6 D* Oral 5-aminosalicylate (5-ASA) containing compounds are the first line maintenance treatment in patients responding to 5-ASA or steroids (oral or rectal) [EL1a, RG A].	EL 1a RG A		
			A combination of oral and rectal 5-ASA can be used as a second line maintenance treatment [EL1b, RG B].	EL 1b RG B		
			ECCO Statement 6E Although sulfasalazine is equally or slightly more effective [EL1a, RG A], other oral 5-ASA preparations are preferred for toxicity reasons.	EL 1a RG A		
			All the different available preparations of oral 5-ASA are effective [EL1a, RG A].	EL 1a RG A		
			There is no robust evidence to support the choice of any specific 5-ASA preparation for maintenance [EL1a, RG A].	EL 1a RG A		
	Der Weg der Applikation soll sich nach dem Befallsmuster der Erkrankung richten. Die Proktitis und die distale Kolitis sollen primär topisch therapiert werden.	A/++				
	Es sollen Dosen verwendet werden, für die in Studien Wirksamkeit nachgewiesen wurde (▶ **Tab. 8**).	B/++	*ECCO Statement 6E* The minimum effective dose of oral 5-ASA is 1.2 g per day [EL1a, RG A].	EL 1a RG A		
			For rectal treatment 3 g/week in divided doses is sufficient to maintain remission. The dose can be tailored individually according to efficacy and in some cases higher doses±topical 5-ASA is useful [EL5, RG D].	EL 5 RG D		
	Einzelne Präparate können als tägliche Einmalgabe gegeben werden.	A/+	*ECCO Statement 6E* Once daily administration of 5-ASA has been proven to be at least as effective as twice or three-times daily administra-	EL 1a RG A	*ST 10*: When using oral 5-ASA to induce or maintain complete remission of UC, we suggest oncedaily over more frequent dosing.	m QE/+

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			tion, with no increased side effects [EL1a, RG A].			
	Nach Erreichen der Remission soll die remissionserhaltende Therapie mit Amino-salizylaten mindestens 2 Jahre durchgeführt werden.	B/++	*ECCO Statement 6H* The general recommendation is to continue 5-ASA maintenance treatment long-term [EL3b, RG C] since this may reduce the risk of colon cancer [EL4, RG D].	EL 3b RG C EL 4 RG D		
	Definition: Ein Versagen der remissi-ons-erhaltenden Therapie ist dann gegeben, wenn ein Schub trotz einer geeigneten remissions-erhaltenden Therapie auftritt und eine Schub-therapie erfordert. Eine erneute, remissionserhaltende Therapie setzt zuerst eine Remissionsinduktion durch eine Schubtherapie voraus.	D				
	Bei häufigen oder schweren Schü-ben soll die remissionserhaltende Therapie eskaliert werden.	C/++			*ST 25*: In patients with UC who have a suboptimal response to anti-TNF induction therapy, we recommend dose intensi-fication to achieve complete remission.	Vl QE/++
					ST 26: In patients with UC who lose response to anti-TNF maintenance therapy, we re-commend optimizing dose to recapture complete remissi-on.	Vl QE/++
					ST 27: We recommend that dose optimization for patients with UC be informed by the-rapeutic drug monitoring.	L QE/++
	Möglichkeiten zur stufenweisen Therapie-eskalation sind eine oral/ rektale Kombinations-therapie mit Aminosalizylaten, eine Erhöhung der oralen Dosis von 5-ASA, eine Thera-pie mit Azathioprin/ 6-Mercaptopu-rin oder Infliximab.	A/++			*ST 31*: We recommend that patients with UC be evaluated for lack of symptomatic re-sponse to vedolizumab in-duction therapy in 8 to 14 weeks to determine the need to modify therapy.	vl QE/++

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					ST 32: In patients with UC who respond to vedolizumab, we recommend continued vedolizumab therapy to maintain complete corticosteroidfree remission.	M QE/++
	Methotrexat und Tacrolimus sollten zur Remissionserhaltung der CU eher nicht eingesetzt werden.	B/-			*ST 19*: In patients with UC, we recommend against the use of methotrexate monotherapy to induce or maintain complete remission.	L QE/++
					ST 8: In selected 5-ASA–naive patients with UC who have achieved symptomatic remission on oral corticosteroids, we suggest an oral 5-ASA preparation of at least 2 g/day while being assessed for corticosteroid-free complete remission.	Vl QE/+
	Kortikosteroide sollen zur Remissionserhaltung nicht eingesetzt werden.	A/++			*ST 14*: In patients with UC, we recommend against the use of oral corticosteroids to maintain complete remission because they are ineffective for this indication and their prolonged use is associated with significant adverse effects.	M QE/++
					Statement 28. In patients with primary failure to an anti-TNF therapy, we recommend switching to vedolizumab over switching to another anti-TNF therapy to induce complete corticosteroid-free remission.	Vl QE/++
	Die medikamentösen Therapiemöglichkeiten und -risiken sollen gegen eine Operation abgewogen werden.	B/++				

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	Bei Steroidabhängigkeit soll primär Azathioprin/6-MP eingesetzt werden.	A/++	*ECCO Statement 5F* Patients with steroid-dependent disease should be treated with azathioprine/ mercaptopurine [EL1b, RG B].	EL 1b RG B	*ST 18*: In selected patients with UC who have achieved symptomatic remission on oral corticosteroids, we suggest thiopurine monotherapy as an option to maintain complete corticosteroid-free remission.	L QE/+
					ST 22: In patients with UC who are corticosteroid dependent, we recommend anti-TNF therapy to induce and maintain complete corticosteroid-free remission.	Vl QE/++
	Bei Unverträglichkeit von Aminosalicylaten kann der apathogene Escherichia coli Stamm Nissle 1917 (A) oder bei Kindern das probiotische Präparat VSL#3 (B) eingesetzt werden.	s. Text/+	*ECCO Statement 6G* E coli Nissle is an effective alternative to 5-ASA for maintenance [EL1b, RG A].	EL 1b RG A		
					ST 33: In patients with UC, we recommend against fecal microbial transplant to induce or maintain complete remission outside the setting of a clinical trial.	L QE/++
Infektiologische Probleme *6.1 – 6.22*			/		/	
Chirurgie *7.1 – 7.20*	Als Standardoperation soll eine restaurative Proktokolektomie durchgeführt werden.	D/KKP				
	Die freie oder gedeckte Perforation soll als Notfallindikation operiert werden.	A/++				
	Die therapierefraktäre Blutung soll bei fortge-setzter Transfusionspflichtigkeit im interdisziplinären Kontext dringlich operiert werden.	D/KKP				

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	Patienten mit einem medikamentös therapierefraktären fulminanten Schub sollen dringlich operiert werden.	B/++				
	Ein trotz Einsatz von Immunsuppressiva inkl. Biologika therapierefraktärer Verlauf sollte als absolute Operationsindikation operiert werden.	D/KKP				
	Bei Patienten mit CU und Kolonstenose unklarer Dignität soll operiert werden.	C/++				
	Eine elektive Operation kann bei Patientenwunsch erfolgen. Dabei sind die Risiken der konservativen Behandlungsstrategien gegen die Risiken einer Operation abzuwägen.	D/++				
	Kinder und Jugendliche mit Wachstumsstörungen unter adäquater Therapie nach Ausschluss anderer Ursachen und Konsultation eines Kindergastroenterologen sollen operiert werden.	D/KKP				
	Bei erhöhtem perioperativem Risiko sollte die Proktokolektomie dreizeitig operiert werden.	D/+				
	Bei Mangelernährung (hohes metabolisches Risiko) soll vor elektiver Operation präoperativ eine gezielte Ernährungstherapie für mindestens 7 Tage erfolgen.	B/++				
	Bei der dreizeitigen Proktokolektomie sollte die Kolektomie bis zum rektosigmoidalen Übergang erfolgen.	D/+				
	Bei der ileoanalen Pouchanlage soll die belassene Rektummukosa nicht länger als 2 cm sein.	D/KKP				
	Bei Proktitis ulcerosa in belassener Rektummukosa kann topisches 5-ASA eingesetzt werden. Alternativ kann eine sekundäre transanale Mu-	D/+				

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	kosektomie bei starken Symptomen erfolgreich sein.					
	Unter der Indikation einer intraepithelialen Neoplasie oder eines manifesten Karzinoms soll eine komplette Mukosektomie mit Anastomose an der Linea dentata durchgeführt werden.	D/KKP				
	Pouchchirurgie soll nur in dafür spezialisierten Zentren durchgeführt werden.	D/KKP				
	Patienten mit einer chronischen Pouchitis oder nach Colitis-ulcerosa-assoziiertem Karzinom oder intraepithelialer Neoplasie sollten jährlich endoskopisch überwacht werden.	D/+				
	Die Kolektomie mit ileorektaler Anastomose kann nur für ausgewählte Konstellationen wiez. B. bei dringendem Kinderwunsch empfohlen werden.	D/-				
	Das kontinente Ileostoma nach Kock kann als mögliche Alternative für besondere Fälle angeboten werden.	D/+				
	Bei belassenem Rektum unter ileorektaler Anastomose oder bei endständigem Ileostoma mit Rektumblindverschluss nach Hartmann sollte eine jährliche endoskopische Kontrolle des belassenen Rektums mit Stufenbiopsien erfolgen.	D/+				
	Die laparoskopische restaurative Proktokolektomie kann als gleichwertige Alternative zur offenen Operation angeboten werden.	B/+				
7.21	Bei Colitis indeterminata ohne anorektales Fistelleiden und entsprechender Operationsindikation kann eine restaurative Proktokolektomie unter Aufklärung mit den damit	D/+				

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	verbundenen Risiken dem Patienten angeboten werden.					
Pouchitis *7.22 – 7.27*	Die Diagnose Pouchitis soll unter der Berücksichtigung der Parameter Klinik, Endoskopie und Histologie erfolgen.	C/++	*ECCO Statement 8A* The diagnosis of pouchitis requires the presence of symptoms, together with characteristic endoscopic and histological abnormalities [EL3a, RG B]. Extensive UC, extraintestinal manifestations (i. e. PSC), being a non-smoker, p-ANCA positive serology and NSAID use are possible risk factors for pouchitis [EL3b, RG D]	EL 3a RG B EL 3b RG D		
			ECCO Statement 8B The most frequent symptoms of pouchitis are increased number of liquid stools, urgency, abdominal cramping and pelvic discomfort. Fever and bleeding are rare [EL1c, RG B].	EL 1c RG B		
			Routine pouchoscopy after clinical remission is not required [EL5, RG D].	EL 5 RG D		
	Bei einer chronischen Pouchitis soll eine chirurgisch behandelbare Ursache ausgeschlossen werden.	D/KKP				
	Als Primärtherapie der akuten Pouchitis soll Ciprofloxacin oder Metronidazol eingesetzt werden.	A/++	*Statement 8C* The majority of patients respond to metronidazole or ciprofloxacin, although the optimummodality of treatment is not clearly defined [EL1b, RG B]. Side effects are less frequent using ciprofloxacin [EL1c, RG B]. Antidiarrhoeal drugs may reduce the number of daily liquid stools in patients, independent ofpouchitis [EL5, RG D]	EL 1b RG B EL 1c RG B EL 5 RG D		
	Bei einer chronischen Pouchitis kann eine kombinierte antibiotische Therapie eingesetzt werden.	C/+	*Statement 8 D* In chronic pouchitis a combination of two antibiotics is effective [EL1b, RG B]. Oral budesonide is an alternative [EL2b, RG B]. Infliximab is effective for the treatment of chronic refractory pouchitis [EL4, RG C]	EL 1b RG B EL 2b RG B EL 5 RG C		
		A/+	Statement 8E	EL 1b RG B		

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	Zum Remissionserhalt kann eine probiotische Therapie eingesetzt werden.		Probiotic therapywith VSL#3 (18 × 1011 of 8 bacterial strains for 9 or 12 months) has shown efficacy for maintaining antibiotic-induced remission [EL1b, RG B]. VSL#3 (9 × 1011 bacteria) has also shown efficacy for preventing pouchitis [EL2b, RG C]	EL 2b RG C		
	Nach Pouchanlage sollte eine jährliche Kontrolluntersuchung erfolgen.	D/KKP				
Cuffitis			*Statement 8F* Rectal cuff inflammation (cuffitis) may induce symptoms similar to pouchitis or irritable pouch syndrome, although bleeding is more frequent [EL2a, RG B]. Topical 5-ASA has shown efficacy [EL4, RGD]	EL 2a RG B EL 4 RG D		
Karzinom-Prophylaxe *8.1 – 8.3*	Das kolorektale Karzinomrisiko ist bei Patienten mit Colitis ulcerosa im Vergleich zur Normalbevölkerung erhöht.	B/starker Konsens	*Statement 9A* Patients with longstanding ulcerative colitis have an increased risk of colorectal cancer compared to the general population [EL 1b, RG B]	EL 1b RG B		
	Das Risiko ist hoch bei ausgedehnter Kolitis, erhöht bei Linksseitenkolitis und nicht eindeutig erhöht bei der Proktitis ulcerosa.	B/starker Konsens				
	Das Risiko steigt mit der Dauer der Erkrankung an, korreliert positiv mit der Ausprägung der entzündlichen Aktivität im Verlauf und ist bei einer zusätzlich bestehenden PSC noch stärker erhöht.	EK 2a, b/B/Starker Konsens	*Statement 9B* The risk of colorectal cancer in ulcerative colitis is associated with disease duration and extent [EL 1b, RG B]	EL 1b RG B		
			Statement 9C Concomitant Primary Sclerosing Cholangitis (PSC), post-inflammatory polyps, a family history of CRC and more severe or persistent inflammatory activity confer an additional risk for CRC in ulcerative colitis patients [EL 1b, RG B]	EL 1b RG B		

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Überwachungskoloskopie *8.4 – 8.8*	Da die colitisassoziierte Kolonkarzinommortalität durch eine endoskopische Überwachung gesenkt werden kann, sollen regelmäßige Überwachungskoloskopien erfolgen.	B/++	*Statement 9 D* Regular follow-up colonoscopies could be carried out, because surveillance colonoscopy may permit earlier detection of CRC, with a corresponding improved prognosis [EL 3a, RG B]	EL 3a RG B		
	Zur Festlegung der Überwachungsstrategie soll bei allen CU-Patienten unabhängig von der Krankheitsaktivität eine Kontrollkoloskopie zur Erfassung des Befallsmusters spätestens 8 Jahre nach Beginn der Symptomatik erfolgen.	C/++	*Statement 9E* In all patients with UC irrespective of the disease activity, a screening colonoscopy could be carried out 6 – 8 years after the beginning of symptoms in order to assess the patient's individual risk profile [EL 5, RG D]	EL 5 RG D		
			Statement 9F When disease activity is limited to the rectum without evidence of previous or current endoscopic and/or microscopic inflammation proximal to the rectum, inclusion in a regular surveillance colonoscopy programme is not necessary [EL2a, RG B]	EL 2a RG B		
			Statement 9H The CRC risk profile should be determined at the screening colonoscopy or the first surveillance colonoscopy 6 to 8 years after the first manifestation. Risk stratification mainly depends on extent of disease, severity endoscopic and/or histological inflammation, pseudopolyps, concurrence of PSC, and family history of CRC [EL2b, RG B]	EL 2b RG B		
	Die Überwachungskoloskopien sollten dann bei ausgedehnter CU ab dem 8. Jahr und bei linksseitiger oder distaler CU ab dem 15. Jahr nach Erstmanifestation 1 – 2 jährlich erfolgen.	C/++	*Statement 9I* The individual risk profile dictates surveillance colonoscopy intervals: every 1 – 2 years (high-risk) or every 3 – 4 years (low-risk) from the eighth year after the first manifestation in both extensive UC nd left-sided UC [EL5, RG D]	EL 5 RG D		
	Wenn gleichzeitig eine PSC besteht, sollen die Überwachungskoloskopien unabhängig von der Krank-	C/++	*Statement 9G* In cases with concurrent primary sclerosing cholangitis (PSC), surveillance co-	EL 3a RG B		

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	heitsaktivität und Ausdehnung der CU ab dem Zeitpunkt der PSC-Diagnosestellung jährlich erfolgen.		lonoscopies should be carried out yearly from the point of PSC diagnosis irrespective of disease activity and extent [EL3a, RG B]			
	Nach subtotaler Kolektomie sollen in Analogie die gleichen endoskopischen Überwachungsstrategien wie bei einer CU ohne Resektion erfolgen.	C/++				
8.9 – 8.15	Der geplante Zeitraum der Überwachungskoloskopie soll an die besondere Situation angepasst und die Rückzugszeit bei der Überwachungskoloskopie soll ausreichend lang sein.	C/++				
	Überwachungskoloskopie sollen in einem sauberen Darm durchgeführt werden. Bei Restverschmutzung ist eine Wiederholung erforderlich.	D/KKP	*Statement 9 J* Good bowel preparation is essential for effective surveillance colonoscopy. If faecal residue is present, repeat colonoscopy should be considered [EL5, RG D]	EL5 RG D		
	Biopsien sollen in der Remissionsphase gewonnen werden, da die histomorphologische Abgrenzung von entzündlichen gegenüber neoplastischen Veränderungen schwierig sein kann.	D/KKP	*Statement 9K* Colonoscopic surveillance is best performed when ulcerative colitis is in remission, because it is otherwise difficult to discriminate between dysplasia and inflammation on mucosal biopsies [EL5, RG D]	EL 5 RG D		
	Gezielte Biopsien sollen aus allen endoskopisch suspekten Läsionen entnommen werden.	A/++	*Statement 9 L* Chromoendoscopy with targeted biopsies is the surveillance procedure of choice for appropriately trained endoscopists [EL1b, RG B].	EL 1b RG B		
	Bei einer Überwachungskoloskopie bei CU sollen sowohl ungezielte Biopsien (mindestens 4 alle 10 cm) als auch gezielte Biopsien aus allen auffälligen Arealen entnommen werden.	B/++	9L: Alternatively, random biopsies (quadrant biopsies every 10 cm) and targeted biopsies of any visible lesion should be performed if white light endoscopy is used [EL3, RG B]	EL 3 RG B		
	Alternativ kann eine Chromoendoskopie mit gezielten Biopsien aus allen auffälligen Arealen erfolgen.	A/+				

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	Der Stellenwert der hochauflösenden virtuellen Chromoendoskopie (NBI, FICE, iScan) mit gezielten Biopsien ist nicht ausreichend definiert und soll deshalb nicht als alleinige Strategie verfolgt werden.	A/- –				
Karzinome 8.16 – 8.20	Bei Nachweis von intraepithelialen Neoplasien (IEN) soll eine externe, unabhängige pathologische Zweitbeurteilung eingeholt werden.	A/++				
	Bei Vorliegen einer fraglichen IEN/ Dysplasie soll eine endoskopische Kontrolle ggf. nach Intensivierung der antiinflammatorischen Therapie innerhalb von 3 Monaten durchgeführt werden.	B/++				
			Statement 9N Endoscopically visible dysplastic raised lesions within an area within the extent of ulcerative colitis can be divided in adenoma-like and non-adenoma-like by their macroscopic characteristics [EL 2a, RG B]	EL 2a RG B		
	Bei dem Nachweis einer eindeutigen, durch einen externen Pathologen bestätigten Kolitisassoziierten hochgradigen IEN/Dysplasie (C) oder eines Adenokarzinoms (B) soll eine Proktokolektomie erfolgen.	s. Text/++	*Statement 9O* Presence of low grade or high grade dysplasia should be confirmed by an external second pathologist [EL 1b, RG B]	EL 1b RG B		
	Bei dem Nachweis einer eindeutigen, durch einen externen Referenzpathologen bestätigten, niedrig gradigen IEN/Dysplasie in flacher Mukosa soll dem Patienten nach Aufklärung über das Malignitätsrisiko entweder eine Proktokolektomie (relative Operationsindikation) oder eine endoskopisch-bioptisch Kontrolle innerhalb von 3 Monaten mit anschließend engmaschiger Überwachung angeboten werden.	B/++	*Statement 9S* Flat high-grade dysplasia warrants a recommend-dation of colectomy because of the risk of a concomitant or future colorectal cancer [EL 2a, RG B]	EL 2a RG B		
			Statement 9 T The current evidence is insufficient to assess the balance of risks and benefits of colectomy for flat low-grade dysplasia. The decision to recommend colectomy or continued surveillance is best tailored	EL 5 RG D		

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			to the individual after careful discussion [EL 5, RG D]			
			Statement 9 R Polyps with dysplasia that arise proximal to the segments with macroscopic or histologic involvement are considered as sporadic adenomas and should be treated accordingly [EL 2c, RG B]	EL 2c RG B		
	Scharf begrenzte, erhabene Läsionen mit intraepithelialen Neoplasien, die vom Pathologen als „adenoma-like mass“ (ALM) klassifiziert sind (siehe AG 3), sollen möglichst endoskopisch oder sonst operativ komplett reseziert werden, sofern sich in gezielt aus der Umgebung entnommenen Biopsien und im Restkolon keine IEN zeigen.	B/++	*Statement 9P* Adenoma-like raised lesions can be adequately treated by polypectomy provided the lesion can be completely excised shows absence of dysplasia at the margins of the specimen, and there is no evidence of flat dysplasia elsewhere in the colon, either adjacent to, or distant from, the raised lesion [EL 2a, RG B]	EL 2a RG B		
			Statement 9Q Patients with non-adenoma-like raised lesions should undergo a colectomy, regardless of the grade of dysplasia detected on biopsy analysis because of the high association with meta-chronous, or synchronous, carcinoma [EL 2a, RG B]	EL 2a RG B		
Chemoprävention *8.21 – 8.22*	Zur Prophylaxe des Colitis-assoziierten Kolonkarzinoms können 5-ASA-haltige Präparate eingesetzt werden.	B/+	*Statement 9 M* Chemoprevention with 5-ASA compounds may reduce the incidence of colorectal cancer in UC patients and should be considered for all UC patients [EL2, RG B]. Colorectal cancer chemoprevention with ursodeoxycholic acid should be given to patients with PSC [EL1b, RG B]. There is insufficient evidence to recommend for or against chemoprevention with thiopurines	EL 2 RG B EL 1b RG B		

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	Beim zusätzlichen Nachweis einer PSC kann zur Prophylaxe eines Colitis-assoziierten Kolonkarzinoms Ursodesoxycholsäure eingesetzt werden.	A/+				
Immunsuppr. *8.23*	Patienten unter Therapie mit mindestens 2 Immunsuppressiva sollen regelmäßig dermatologisch untersucht werden und zu konsequentem Sonnenschutz aufgefordert werden.	C/++				
Extraintestinal Gelenke *9.1 – 9.7*	Die Gelenkbeteiligung stellt die häufigste extraintestinale Manifestation bei der Colitis ulcerosa dar. Es wird zwischen dem Befall des Achsenskeletts und dem peripheren Gelenkbefall, der meist in Form von Arthralgien imponiert, unterschieden.	D/starker Konsens	Statement 11A Diagnosis of non-axial arthritis and arthropathy associated with UC is made on clinical grounds based on characteristic features and exclusion of other specific forms of arthritis [EL3b, RG C]. Although HLA B27 is over-represented in axial arthritis related to UC this is not of diagnostic value [EL2b, RG B]	EL 3b RG C EL 2b RG B		
	Die Diagnose der Gelenkbeteiligung soll durch Anamnese, klinische Untersuchung und bei axialem Befall auch bildgebend entsprechend rheumatologischer Kriterien erfolgen.	C/++	11 A: Type I is pauciarticular and affects large joints acutely at times of UC activity Type II is polyarticu-lar, affecting a larger number of peripheral joints independently of UC activity [EL2b, RG B]. Axial arthritis, including sacro-iliitis and ankylosing spondylitis, is diagnosed on conventional rheuma-tological grounds, and is supported by characteris-tic radiological changes, magnetic resonance imaging being the most sensitive [EL2b, RG B].	EL 2b RG B EL 2b RG B		
	Bei schubassoziierter Gelenkbeteiligung soll die Therapie im Rahmen der Behandlung der Grunderkrankung erfolgen.	A/++				
	Bei der akuten Arthritis können begleitende symptomatische Maßnahmen wie Entlastung und Ruhigstellung akut betroffener Gelenke erfolgen.	D/++				

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	A) Bei chronischen Arthralgien kann eine Physiotherapie erfolgen.	D/+	11 B: In axial arthropathy arguments in favour of intensive physiotherapy [EL2a, RG B], associated with NSAIDs are stronger, but safety concerns mean that long-term treatment with NSAIDs is best avoided if possible [EL1b, RG B]. Sulfasalazine [EL1a, RG B], methotrexate [EL1b, RG B] and azathioprine [EL3b, RG C] are generally ineffective, or only marginally effective.	EL 2a RG B EL 1b RG B EL 1a RG B EL 1b RG B EL 3b RG C		
	B) Eine analgetische Therapie nach allgemeinen Empfehlungen zur Schmerztherapie soll durchgeführt werden.	D/+				
	C) NSAR sollten eher nicht eingesetzt werden.	B/-				
	A) Bei peripheren Arthritiden soll primär Sulfasalazin eingesetzt werden.	B/++	*Statement 11B* In peripheral arthritis treatment of the underlying UC is normally effective in relieving symptoms [EL5, RGD]. For persistent symptoms in the absence of active UC there is general support for use of short term treatment with non-steroidal anti-inflammatory agents. Local steroid injections and physiotherapy are also effective [EL4, RG D]. Sulfasalazine has a role in persistent peripheral arthritis [EL1a, RG B].	EL 4 RG C EL 4 RG D EL 1b RG B		
	B) Bei schweren peripheren Arthritiden kann Methotrexat eingesetzt werden.	B/+				
	Schwere, therapierefraktäre Polyarthritiden und die schwere therapierefraktäre Spondylarthropathie (Spondylitis ankylosans) können mit anti-TNF-α-Antikörpern behandelt werden.	B/+	11 B: The efficacy of anti-TNF therapy for patients with ankylosing spondylitis and UC intolerant or refractory to NSAIDs is well established [EL1b, RG B]	EL 1b RG B		
Leber Galle *9.8-*	Klinisch ist die primär sklerosierende Cholangitis (PSC) die bedeutendste hepatobiliäre Erkrankung, die mit einer Colitis ulcerosa assoziiert sein kann. Die Häufigkeit der PSC bei Colitis ulcerosa liegt bei 2 – 10 % der Patienten. Die Autoimmunhepatitis ist eine seltene Begleiterkrankung der Colitis ulcerosa und kann in Form eines Überlappungssyndroms mit einer PSC auftreten.	D/starker konsens				

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	Bei Verdacht auf eine PSC soll eine MRCP als primäre Diagnostik erfolgen. Bei unklaren Fällen oder fortbestehendem klinischem Verdacht soll eine ERC ergänzend durchgeführt werden.	C/++	*Statement 11 J* Diagnosis of hepatobiliary disorders in association with ulcerative colitis follows the standard investigatory pathways prompted by abnormal liver function tests, with ultrasound scanning, and serology to identify specific auto-immune and infective causes [EL2a, RG B]. Magnetic resonance cholangiography is now established as the first-line diagnostic test for primary sclerosing cholangitis [EL2a, RG B]. Primary sclerosing cholangitis substantially increases the risk of both cholangiocarcinoma and colorectal carcinoma [EL1a, RG A]	EL 2a RG B EL 2a RG B EL 1a RG A		
	Ab Diagnosestellung einer PSC sollte eine Dauertherapie mit Ursodeoxycholsäure durchgeführt werden.	B/+	*Statement 11K* Ursodeoxycholic acid improves abnormal liver function tests [EL1b, RG B], but not histology and prognosis in PSC. ERCP should be used to treat dominant strictures by dilatation and/or stenting [EL4, RG C]. Advanced liver disease may necessitate transplantation [EL2a, RG B]	EL 1b RG B EL 2a RG B		
	Zusätzlich soll eine endoskopische Therapie von funktionell wirksamen und erreichbaren Stenosen durchgeführt werden.	D/KKP				
	In fortgeschrittenen Stadien der PSC soll in einem Transplantationszentrum die Möglichkeit einer Lebertransplantation geprüft werden.	A/++				
Haut	Typische Hautmanifestationen sind Erythema nodosum (14 – 19 % der Patienten) und Pyoderma gangraenosum (1 – 2 % der Patienten). Überwiegend treten die Effloreszensen im akuten Schub der Erkrankung auf. Die Diagnose erfolgt klinisch. Serologische Marker existieren nicht.	D/Konsens	Statement 11F Diagnosis of the cutaneous manifestations of IBD is made on clinical grounds, based on their characteristic features and (to some extent) the exclusion of other specific skin disorders; biopsy can be helpful in atypical cases [EL3b, RG C]	EL 3b RG C		

Kapitel nach DGVS-Leitlinie	DGVS (2011)	Evidenzgrad/ Empfehlungs-stärke	ECCO (2013)	Evidenzgrad/ Empfehlungs-stärkstärke	The Toronto Consensus Group (2015)	Evidenzgrad/ Empfehlungs-stärke
	Bei Erythema nodosum und Pyoderma gangrae-nosum sollte eine hoch dosierte Steroid-therapie erfolgen und die Colitis ulcerosa in Remission gebracht werden. In therapieresistenten Fällen sollte eine immunmodulatorische Therapie durchgeführt werden. Eine chirurgische Intervention soll nicht durchgeführt werden.	D/ + + KKP	*Statement 11G* Treatment of erythema nodosum is usually based on that of the underlying Ulcerative Colitis. Systemic steroids are usually required [EL4, RG D]. Pyoderma gangrenosum is initially treated with systemic steroids, topical or oral calcineurin inhibitors [EL4, RG D], infliximab [EL1b, RG C] or adalimumab [EL3b, RG C]	EL 5 RG D EL 4 RG D EL 1b RG C EL 3b RG C		
			Statement 11H Anti-TNF treatment can induce paradoxical inflammation of the skin [EL4] which is a class-drug effect and is usually reversible upon drug cessation [EL4]. When diagnosis is uncertain, referral to a dermatologist for expert opinion is recommended [EL5 RG D]. Treatment is based almost entirely on extra-polation from paradoxical skin inflammation in other chronic diseases and it may include topical steroid therapy, topical keratolytic agents, vitamin D analogues, methotrexate, switching anti-TNF or anti-TNF discontinuation [EL3b RGC]	EL 4 + EL 4 + EL 5 RG D EL 3b RG C		
Augen	Als extraintestinale Manifestationen treten die anteriore Uveitis (Iritis/Iridocyclitis), die Skleritis und die Episcleritis bei 1,4 – 22,9 % der Patienten mit Colitis ulcerosa auf.	D/Konsens				
	Bei Verdacht auf eine okuläre Manifestation bei Colitis ulcerosa soll eine fachärztliche, ophthalmologische Untersuchung durchgeführt werden. Die Episkleritis soll primär nicht systemisch therapiert werden, sondern die topische Gabe von Kortikosteroiden erfolgen. Die Skleritis soll mit systemischen Kortikosteroiden, ggf. auch mit Immunsuppressiva behandelt werden. Die Uveitis soll je nach Lokalisation mit topischen	D/KKP	*Statement 11I* Patients with ocular manifestations should be referred to an ophthalmologist [EL5, RG D]. Episcleritis may not require systemic treatment and will usually respond to topical steroids or NSAID [EL4, RG D]. Uveitis is treated with steroids, and it may be necessary to use both topical and systemic routes [EL3b, RG C]. Immunomodulatory therapy including anti TNF may be helpful in resistant cases [EL4, RG D]	EL 5 RG D EL 4 RG D EL 3b RG D EL 4 RG D		

Kapitel nach DGVS-Leitlinie	DGVS (2011)	Evidenzgrad/ Empfehlungs-stärke	ECCO (2013)	Evidenzgrad/ Empfehlungs-stärkstärke	The Toronto Consensus Group (2015)	Evidenzgrad/ Empfehlungs-stärke
	oder systemischen Kortikosteroiden behandelt werden.					
	Eine immunsuppressive Therapie kann in resistenten Fällen einer okulären Manifestation durchgeführt werden (C). Zusätzlich kann eine Pupillenerweiterung zur Therapie des Spasmus sowie zur Prophylaxe von Synechien durchgeführt werden.	D/+				
Osteoporose	Die Häufigkeit einer Osteoporose bei Patienten mit Colitis ulcerosa schwankt zwischen 7 und 18 %, eine Osteopenie liegt bei 34 – 67 % aller Patienten vor. Das Risiko für Wirbelfrakturen oder Hüftfrakturen ist bei Patienten mit Colitis ulcerosa 1,4-fach gegenüber der Normalbevölkerung erhöht.	C/starker Konsens	*Statement 11C* Diagnosis of osteoporosis in adults is best made from a T score of less than −2.5 on radiographic bone densitometry [EL1a, RG A], all other diagnostic methods having current limitations [EL2b, RG B]. The presence of osteoporosis identifies patients at above average risk for fracture and who should receive treatment [EL2b, RG B]	EL 1a RG A EL 2b RG B EL 2b RG B		
			Statement 11 D Osteopenia may be a prognostic marker for future osteoporosis, but presents little direct risk [EL2b, RG C]. However if the T score is less than −1.5, treatment with calcium and vitamin D should be recommended [EL4, RG C]. Pre-existing history of fracture is of substantial adverse prognostic significance and patients should be treated for osteoporosis even if the T score is normal [EL4, RG C]	EL 2b RG C EL 4 RG C EL 4 RG C		
	Eine Knochendichtemessung (DXA) zur Diagnose einer Osteoporose soll bei Patienten durchgeführt werden, die mit systemischen Steroiden längerfristig behandelt wurden und/ oder eine chronische Entzündungsaktivität aufweisen.	C/++				
	Im Rahmen einer systemischen Steroidmedikation soll eine Substitution mit Kalzium und Vitamin D erfolgen. Die Therapie der Osteopenie	s. Text/++	11 E: Patients receiving systemic steroid therapy should receive calcium and vitamin D for prophylaxis [EL5, RG D] In postmenopausal women with osteoporosis,	EL 5 RG D EL 2 RG C EL 3 RG C		

Kapitel nach DGVS-Leitlinie	DGVS (2011)	Evidenzgrad/ Empfehlungs-stärke	ECCO (2013)	Evidenzgrad/ Empfehlungs-stärkstärke	The Toronto Consensus Group (2015)	Evidenzgrad/ Empfehlungs-stärke
	und der Osteoporose soll durch die Substitution mit Kalzium und Vitamin D erfolgen (C). Bei Patienten mit Frakturen soll eine Amino-bisphosphonattherapie erfolgen (A).		regular use of bisphosphonates, calcitonin and its derivatives, and raloxifene reduce or prevent further bone loss [EL2b, RG C]. Data in males with osteoporosis are less secure but bisphosphonates are probably of value [EL3 b, RG C].			
			Statement 11E Weight-bearing exercise [EL2b, RG B], Stopping smoking [EL3b, RG C], avoiding alcohol excess [EL4, RG D], and maintaining adequate dietarycalcium (N1 g/day) [EL 2b, RG B] are beneficial. Newer data also support the use of strontium salts [EL2a, RG B].	EL 2b RG B EL 3b RG D EL 4 RG D EL 2b RG B EL 2a RG B		
Selten 9.21	Neben den oben behandelten gut definierten extraintestinalen Manifestationen bei Colitis ulcerosa gibt es zusätzlich noch weniger gut definierte kasuistisch belegte extraintestinale Manifestationen im Bereich der Lunge, des Herzen, des Pankreas, der Nieren sowie neurologischer Manifestationen. Zusätzlich treten im Sinne von extraintestinalen Begleiterkrankungen im Vergleich zur Normalbevölkerung häufiger Gallensteine, Nierensteine sowie thromboembolische Komplikationen auf.	D/starker Konsens	*Statement 11 L* The risk of thrombosis and related mortality is doubled in patients with UC compared to controls [EL2, RG C]. In patients at risk for thromboembolism prevention with both mechanical thromboprophylaxis and heparin (LMWH or UFH) should be considered [EL5, RG D]. Treatment of venous thromboembolism in IBD should follow established antithrombotic therapy options [EL 1a, RG A] taking into account the potentially increased risk of bleeding [EL5, RG D]	EL 2 RG C EL 5 RG D EL 5 RG D		
Anämie			*Statement 11 M* Anaemia is defined according to the WHO criteria [EL5, RGD]. The major forms of anaemia in ulcerative colitis are iron-deficient anaemia, anaemia of chronic disease and anaemia of mixed origin [EL5, RG D]	EL 5 RG D		
			Statement 11N Diagnostic criteria for iron deficiency depend on the level of colonic inflammation. In patients without any evidence of inflammation a serum ferritin level b30 mcg/L or transferrin saturation b16% define iron deficiency. In the presence of inflammation, the lower limit of serum	EL 2 RG B EL 2 RG B		

Kapitel nach DGVS-Leitlinie	DGVS (2011)	Evidenzgrad/ Empfehlungs-stärke	ECCO (2013)	Evidenzgrad/ Empfehlungs-stärkstärke	The Toronto Consensus Group (2015)	Evidenzgrad/ Empfehlungs-stärke
			ferritin consistent with normal iron stores is 100 mcg/L [EL2, RG B]. In the presence of biochemical or clinical evidence of inflammation, the diagnostic criteria for anaemia of chronic disease (ACD) are a serum ferritin N100 mcg/L and transferrin saturation b16 %. If the serum ferritin level is between 30 mcg/L and b100 mcg/L a combination of true iron deficiency and ACD is likely [EL 2, RG B]			
			Statement 11O Treatment should be considered for all patientswith a haemoglobin level below normal. The approach to treatment depends mainly on symptoms, the severity of anaemia and aetiology [EL4, RG D]	EL 4 RG D		
			Statement 11P Iron supplementation should be initiated when iron deficiency anaemia is present [EL1, RG A] and considered when there is iron deficiency without anaemia [EL4, RG D]. Intravenous iron is more effective and better tolerated than oral iron supplements [EL1, RG A]. Absolute indications for intravenous iron include severe anaemia (haemoglobin b10.0 g/dL), and intolerance or inadequate response to oral iron [EL1a, RG A]. Intravenous iron should be considered in combination with an erythropoietic agent in selected cases where a rapid response is required [EL5, RG D]	EL 1 RG A EL 4 RG D EL 1 RG A EL 1a RG A EL 5 RG D		
			Statement 11Q Erythropoietic therapy should be considered, when anaemia does not improve in spite of intravenous iron therapy and control of inflammation [EL 2, RG B]. To optimise the effect of erythropoietic agents treatment should be combined with intravenous iron supplementation [EL 2, RGB]	EL 3 RG B EL 2 RG B		

Kapitel nach DGVS-Leitlinie	DGVS (2011)	Evidenzgrad/ Empfehlungs-stärke	ECCO (2013)	Evidenzgrad/ Empfehlungs-stärkstärke	The Toronto Consensus Group (2015)	Evidenzgrad/ Empfehlungs-stärke
			Statement 11 R Blood transfusion should be restricted to very special clinical situations, such as acute severe anaemia with hemodynamic instability, severe anaemia-related weakness and fatigue and/or failure of all other treatments [EL 5 RG D]	EL 5 RG D		
Psychosomatik 10.1 – 10.10	Belastende Lebensereignisse, psychologischer Stress und psychische Störungen sind nicht ursächlich für die Entstehung der Colitis ulcerosa.	B/tarker Konsens	*Statement 10A* There is no conclusive evidence for anxiety, depression and psychosocial stress contributing to risk for UC onset [EL2c, RG D]	EL 2c RG D		
	Subjektive Stressbelastung und affektive Störungen können einen negativen Einfluss auf den Verlauf der Colitis ulcerosa haben.	B/starker Konsens	*Statement 10B* Psychological factors may have an impact on the course of UC. Perceived psychological stress [EL2a, RG B] and depression [EL2a, RG B] are risk factors for relapse of the disease. Depression is associated with low health-related quality of life [EL3a, RG B]. Anxiety is associated with non adherence with treatment [EL4, RG C]	EL 2a RG B EL 2a RG B EL 3a RG B EL 4 RG C		
	Eine hohe Krankheitsaktivität kann mit vermehrter psychischer Symptombelastung einhergehen.	B/starker Konsens				
	Psychische Störungen können einen negativen Einfluss auf den Krankheitsverlauf und die Lebensqualität haben.	B/starker Konsens	*Statement 10C* Psychological distress and mental disorder are more common in patients with active ulcerative colitis than in population-based controls, but not in patients in remission [EL3a, RG B]	EL 3a RG B		
	Patienten mit anhaltenden Bauchschmerzen oder Durchfällen, welche nicht durch die Krankheitsaktivität bzw. Krankheitskomplikationen erklärt werden können, sollten auf das Vorliegen eines Reizdarmsyndroms (RDS) oder einer depressiven Störung untersucht werden. Bei Vorliegen eines RDS bzw. einer depressiven Störung sollten die in Leitlinien empfohlenen Therapieprinzipien angewendet werden.	B/+	*Statement 10 D* Clinicians should particularly assess depression among their patients with active disease and those with abdominal pain in remission [EL 2b, RG B]	EL 2b RG B		

Kapitel nach DGVS-Leitlinie	DGVS (2011)	Evidenzgrad/ Empfehlungs-stärke	ECCO (2013)	Evidenzgrad/ Empfehlungs-stärkstärke	The Toronto Consensus Group (2015)	Evidenzgrad/ Empfehlungs-stärke
	Psychosoziale Faktoren und die krankheitsbezogene Lebensqualität sollen auch unter Berücksichtigung geschlechtsspezifischer Aspekte bei ärztlichen Konsultationen erfragt und in der Therapie berücksichtigt werden.	B/++	*Statement 10E* The psychosocial consequences and healthrelated quality of life of patients should be taken into account in clinical practice at regular visits. Individual information and explanation about the disease should be provided through a personal interview [EL3b, RG B].	El 3b RG B		
	Bei der Behandlung von Patienten mit Colitis ulcerosa sollen Kooperationen mit Psychotherapeuten bzw. Psychosomatikern bestehen.	B/++				
	Die behandelnden Ärzte sollen auf die Selbsthilfe hinweisen und die Patienten über ihre Krankheit informieren.	D/KKP	10 E: Patients' disease control can be improved by combining selfmanagement and patient-centred consultations [EL1b, RG B]	EL 1b RG B		
			10 F: Patients should be informed of the existence of patient associations [EL 5, RG D]	EL 5 RG D		
	Bei Patienten mit Colitis ulcerosa und psychischen Störungen soll eine Psychotherapie durchgeführt werden.	B/++	*Statement 10F* Physicians should screen patients for anxiety, depression and need for additional psychological care and recommend psychotherapy if indicated [EL 2b, RG B].	EL 2b RG B		
			Statement 10G Psychotherapeutic interventions are indicated for psychological disorders and low quality of life associated with ulcerative colitis [EL 1b, RG B]	EL 1b RG B		
			Statement 10H The choice of psychotherapeutic method depends on the psychological disturbance and should best be made by specialists (Psychotherapist, Specialist for Psychosomatic Medicine, Psychiatrist). Psychopharmaceuticals should be prescribed for defined indications [EL 5, RG D]	EL 5 RG D		
	Kindern und Jugendlichen und ihren Familien soll eine psychosoziale Unterstützung angeboten werden.	A/++				

Anhang B: Literaturrecherche

Übersicht	
1.	Recherchen zum Thema „Diagnostik“
1.1	Eisenmangel
1.2	Calprotectin
1.3	Überwachungskoloskopie
1.4	Intraepitheloale Neoplasien
2.	Recherchen zum Thema „Schub“
2.1	Proktitis/ Linksseitenkolitis/Pancolitis
2.2	Steroidrefraktärer Krankheitsverlauf
2.3	Steroidabhängiger Krankheitsverlauf
2.4	Therapieversagen auf Biologika-Therapie
3.	Recherchen zum Thema „Remissionserhaltung“
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3.2	Remissionserhaltung bei distaler Colitis Ulcerosa
3.3	E. coli Stamm Nissle 1917
3.4	Therapieversagen unter Mesalazin
3.5	Biosimilar Infliximab
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5.	Recherchen zum Thema „Chirurgie/ Pouchitis“
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5.2	Postoperative Komplikationen
6.	Recherchen zum Thema „Komplementärmedizin und Ernährung“
6.1	Schlüsselfrage
6.2	Recherche in PubMed
6.3	Recherche in Cochrane
6.4	Ergebnis und PRISMA Flow Chart

1. Recherchen zum Thema „Diagnostik“

1.1 Eisenmangel

1.1.1 Schlüsselfrage

1.1 Wie und wann soll eine Diagnostik bzgl. eines Eisenmangels erfolgen?

Population: Personen mit CU/IBD
Interventions: Iron Defiancy Anemia (IDA), Ferric Maltol, IV Eisen Fer-Inject, Eisencarboxycartose
Comparisons: –
Outcomes: Hämoglobin, Ferritin, Transferrin –Sättigung, Retikulozyten Hb, Ferritinindex, Rezeptor, Erytrhocyten, CRP, Diagnostische Genauigkeit (Sensitivität, Spezifität, positiver oder negativer prädiktiver Wert)

1.1.2 Recherche in PubMed (12.12.16)

AG 1 Diagnostik
1.1 Wie und wann soll eine Diagnostik bzgl. eines Eisenmangels erfolgen?

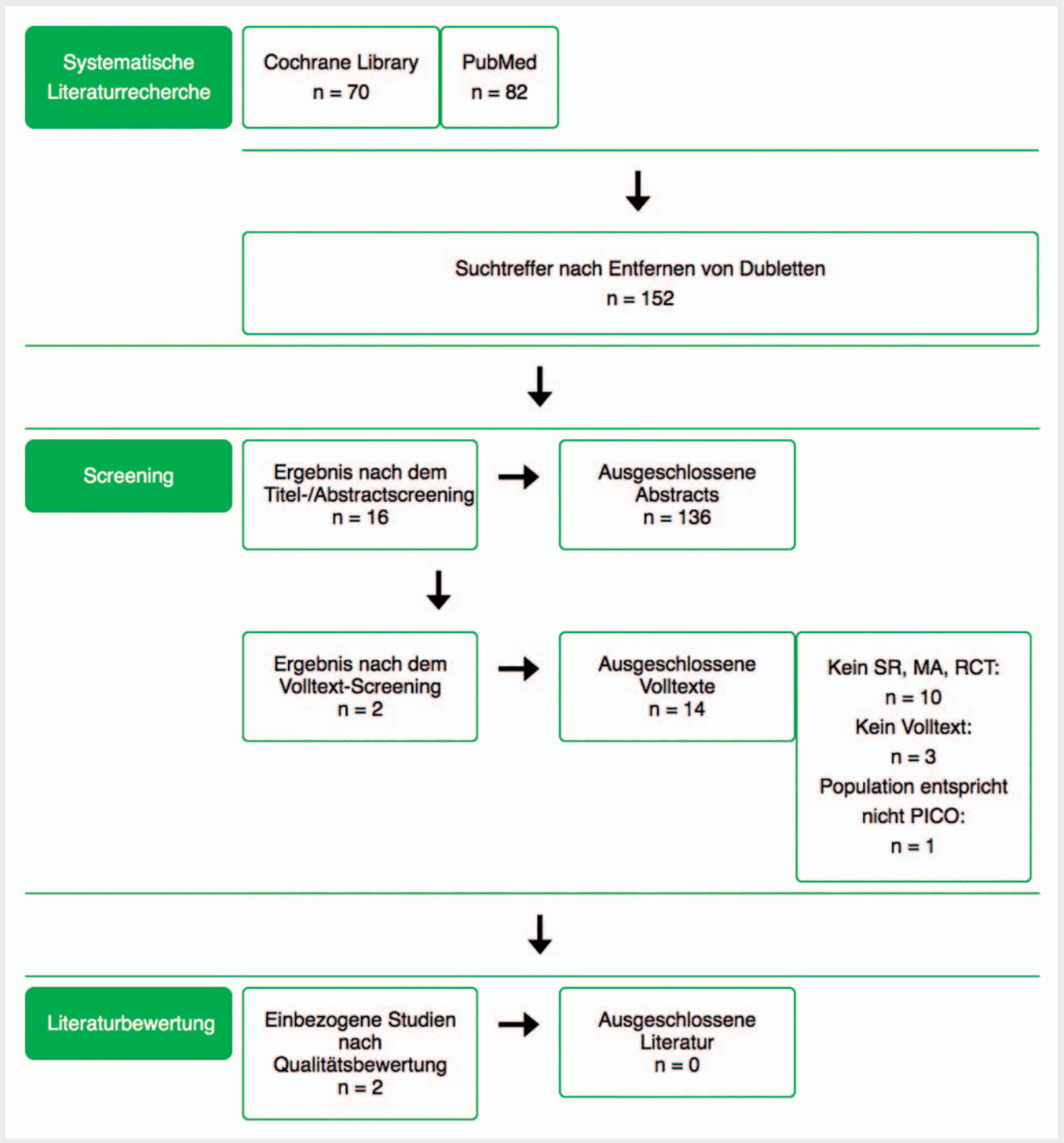
Nr.	Query	Treffer
#1	Colitis, Ulcerative[MeSH] OR "inflammatory bowel diseases"[MeSH:noexp]	43 939
#2	Idiopathic Proctocolitis[tiab] OR Ulcerative Colitis[tiab] OR Colitis Gravis[tiab]	31 861
#3	#1 OR #2	51 006
#4	Diagnostic Techniques and Procedures[MeSH] OR Diagnos*[tiab] OR Screen*[tiab] OR Detect*[tiab] OR Test*[tiab] OR assay[tiab] OR indicat*[tiab] OR quantif*[tiab] OR search[tiab] OR analy*[tiab] OR method*[tiab] or assess*[tiab] OR check*[tiab]	14 843 771
#5	Anemia, Iron-Deficiency[MeSH] OR (Anemi*[tiab] AND Iron-Deficien*[tiab]) OR IDA[tiab] OR Iron Compounds[MeSH] OR Iron[tiab] OR Ferri*[tiab] OR Ferrous*[tiab] OR FerInject[tiab] OR Ferric Carboxymaltose [Supplementary Concept] OR ((Ferri*[tiab] OR Iron[tiab]) AND carboxymaltose[tiab])	220 223
#6	#4 AND #5	143 031
#7	#3 AND #6	332
#8	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomised[tiab] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Systematic Review[pt] OR Systematic Review[tiab] OR Systematic[sb] OR Meta-Analysis[pt] OR Meta-Analysis[tiab] OR Meta-Analysis [sb] OR Cochrane Database Syst Rev[Journal]	4 216 274
#9	animals[mh] NOT humans[mh]	4 271 569
#10	#8 NOT #9	3 672 006
#11	#7 AND #10 Filters: German, English; Publication date from 2009/06/01 to 2016/12/12	82

1.1.3 Recherche in Cochrane (16.12.16)

Search Name: CU_AG1_1
Date Run: 08/12/16 14:26:55.879

ID	Search	Hits
#1	[mh "Colitis, Ulcerative"] or Ulcerative Colitis:ti,ab,kw	2115
#2	[mh "Diagnostic Techniques and Procedures"] OR Diagnos* OR Screen* OR Detect* OR Test* OR assay OR indicat* OR quantif* OR search OR analy* OR method* or assess* OR check*;ti,ab,kw	812 320
#3	[mh "Anemia, Iron-Deficiency"] or (Anemi* and Iron-Deficien*) or IDA or [mh "Iron Compounds"] or Iron or Ferri* or Ferrous* or FerInject or ((Ferri* or Iron) and carboxymaltose); ti,ab,kw	10 187
#4	#2 and #3	8484
#5	#1 and #4	110
#6	#1 and #4 Publication Year from 2009, in Cochrane Reviews (Reviews only), Other Reviews, Trials and Technology Assessments	70

1.1.4 Ergebnis und PRISMA Flow Chart



1.2 Calprotectin

1.2.1 Schlüsselfrage

1.2 Wann und unter welcher Rationale soll eine Calprotectin-Diagnostik durchgeführt werden?

Population: Personen mit CU/ IBD
Interventions: fecal calprotectin, fecal neutrophil marker, Screening, Differentialdiagnostik, Verlaufskontrolle, Homecare-Calpotectin
Comparisons: Keine
Outcomes: Calprotectin level, Diagnostische Genauigkeit (Sensitivität, Spezifität, positiver oder negativer prädiktiver Wert)

1.2.2 Recherche in PubMed (12.12.16)

AG 1 Diagnostik
1.2 Wann und unter welcher Rationale soll eine Calprotectin-Diagnostik durchgeführt werden?

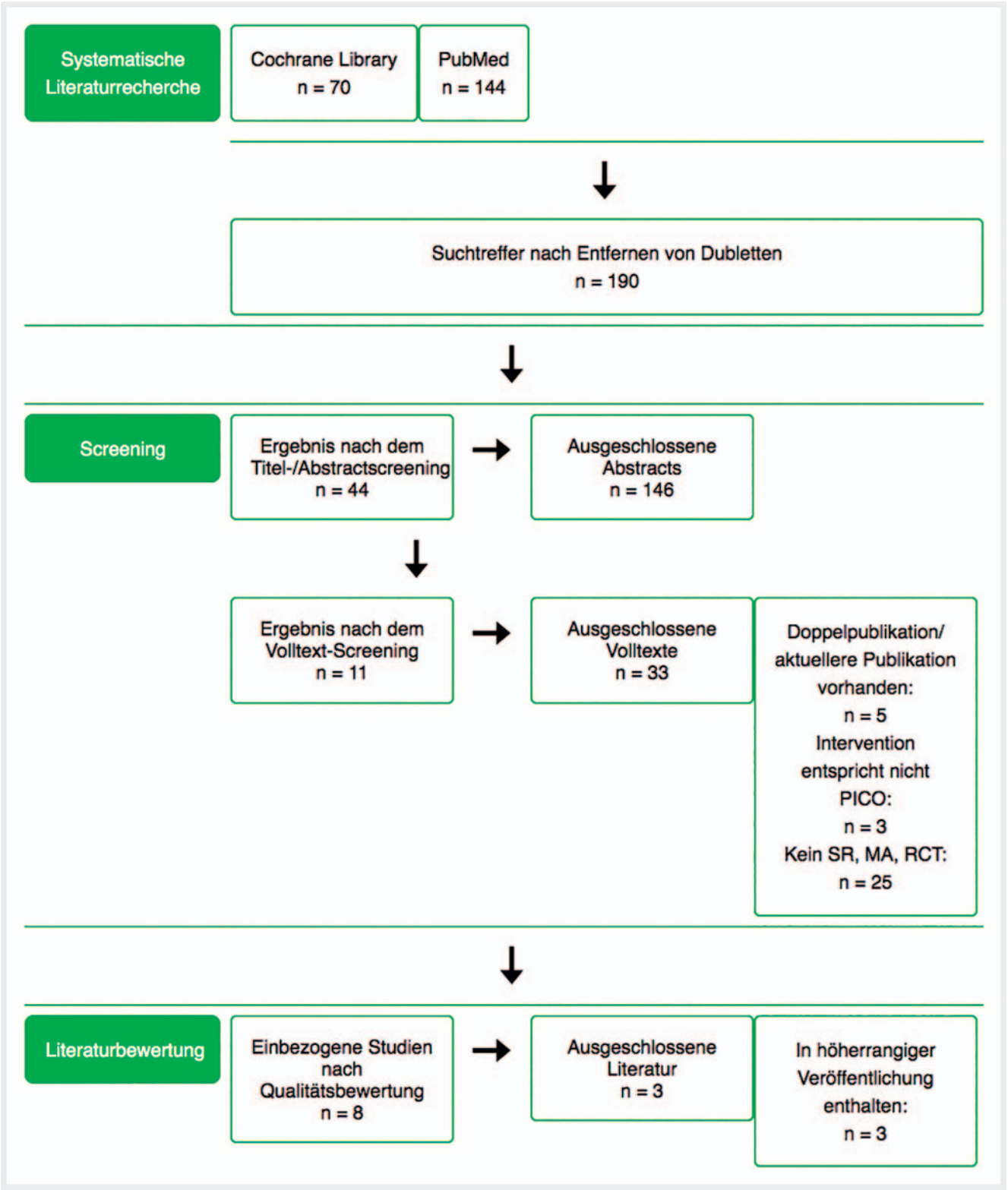
Nr.	Query	Treffer
#1	Colitis, Ulcerative[MeSH] OR "inflammatory bowel diseases"[MeSH:noexp]	43 939
#2	Idiopathic Proctocolitis[tiab] OR Ulcerative Colitis[tiab] OR Colitis Gravis[tiab]	31 861
#3	#1 OR #2	51 006
#4	Diagnostic Techniques and Procedures[MeSH] OR Diagnos*[tiab] OR Screen*[tiab] OR Detect*[tiab] OR Test*[tiab] OR assay[tiab] OR indicat*[tiab] OR quantif*[tiab] OR search[tiab] OR analy*[tiab] OR method*[tiab] or assess*[tiab] OR check*[tiab]	14 843 771
#5	Leukocyte L1 Antigen Complex[MeSH] OR Leukocyte L1 Antigen Complex[tiab] OR Calcium-Binding Myeloid Protein P8,14[tiab] OR Calgranulin[tiab] OR Calprotectin[tiab] OR Migratory Inhibitory Factor-Related Protein MRP[tiab] OR Antigen L1[tiab] OR 27E10 Antigen[tiab] OR Leukocyte L1 Protein	3 589
#6	Leukocyte Elastase[MeSH] OR Leukocyte Elastase[tiab] OR Neutrophil Elastase[tiab] OR PMN Elastase[tiab] OR PMN Elastase[tiab] OR Granulocyte Elastase[tiab] OR Lysosomal Elastase[tiab] OR Neutrophil marker[tiab]	6 433
#7	#5 OR #6	9 998
#8	#4 AND #7	7 407
#9	#3 AND #8	559
#10	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomised[tiab] OR randomized[tiab] OR placebo [tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Systematic Review[pt] OR Systematic Review[tiab] OR Systematic[sb] OR Meta-Analysis[pt] OR Meta-Analysis[tiab] OR Meta-Analysis[sb] OR Cochrane Database Syst Rev[Journal]	4 216 274
#11	animals[mh] NOT humans[mh]	4 271 569
#12	#10 NOT #11	3 672 006
#13	#9 AND #12 Filters: German, English; Publication date from 2009/06/01 to 2016/12/12	144

1.2.3 Recherche in Cochrane (12.12.16)

Search Name: CU_AG1_2
Date Run: 12/12/16 15:50:06.860

ID	Search	Hits
#1	[mh “Colitis, Ulcerative”] or [mh ^ “inflammatory bowel diseases”]	1350
#2	Idiopathic Proctocolitis or Ulcerative Colitis or Colitis Gravis:ti,ab,kw	2299
#3	#1 or #2	2529
#4	[mh “Diagnostic Techniques and Procedures”]	207 504
#5	Diagnos* or Screen* or Detect* or Test* or assay or indicat* or quantif* or search or analy* or method* or assess* or check*:ti,ab,kw	751 764
#6	#4 or #5	769 432
#7	[mh “Leukocyte L1 Antigen Complex”]	98
#8	Leukocyte L1 Antigen Complex or Calcium-Binding Myeloid Protein P8,14 or Calgranulin or Calprotectin or Migratory Inhibitory Factor-Related Protein MRP or Antigen L1 or 27E10 Antigen or Leukocyte L1 Protein:ti,ab,kw	356
#9	[mh Leukocyte Elastase]	170
#10	Leukocyte Elastase or Neutrophil Elastase or PMN Elastase or PMN Elastase OR Granulocyte Elastase or Lysosomal Elastase or Neutrophil marker:ti,ab,kw	834
#11	#7 or #8 or #9 or #10	1172
#12	#6 and #11	1105
#13	#3 and #12 Publication Year from 2009, in Cochrane Reviews (Reviews only), Other Reviews, Trials and Technology Assessments	70

1.2.4 Ergebnis und PRISMA Flow Chart



1.3 Überwachungskoloskopie

1.3.1 Schlüsselfrage

1.3 Wann und wie soll eine Überwachungskoloskopie durchgeführt werden?

Population: Personen mit CU – kontrollierte Patienten
Interventions: Überwachungskoloskopie (surveillance colonoscopy), Biopsie (Anzahl), Chromoendoskopie, virtuelle Chromoendoskopie (NBI, FICE, i-Scan), random biopsy
Comparisons: Keine
Outcomes: RLD, Flat Adenoma, neoplasia/neoplasm, intraepithelial neoplasia IEN, dysplasia, DALM, ALM, cancer, grading risk of cancer, risk of malignancy/malignancies

1.3.2 Recherche in PubMed (12.12.16)

AG 1 Diagnostik
1.3 Wann und wie soll eine Überwachungskoloskopie durchgeführt werden?

Nr.	Query	Treffer
#1	Colitis, Ulcerative[MeSH] OR "inflammatory bowel diseases"[MeSH:noexp]	43 939
#2	Idiopathic Proctocolitis[tiab] OR Ulcerative Colitis[tiab] OR Colitis Gravis[tiab]	31 861
#3	#1 OR #2	51 006
#4	Diagnostic Techniques and Procedures[MeSH] OR Diagnos*[tiab] OR Screen*[tiab] OR Detect*[tiab] OR Test*[tiab] OR assay[tiab] OR indicat*[tiab] OR quantif*[tiab] OR search[tiab] OR analy*[tiab] OR method*[tiab] or assess*[tiab] OR check*[tiab]	14 843 771
#5	surveill*[tiab] OR monitor*[tiab] OR routine*[tiab] OR check-up[tiab] OR Screen*[tiab] OR random*[tiab]	2 301 458
#6	Colonoscopy[MeSH] OR Biopsy[MeSH] OR Colonoscop*[tiab] OR biops*[tiab] OR Chromoendoscop*[tiab] OR Capsule Endoscopy[MeSH] OR Capsule Endoscop*[tiab] OR Virtual Endoscop*[tiab] OR narrowed-spectrum endoscop*[tiab] OR narrow band imaging[tiab] OR flexible spectral imaging color enhancement*[tiab] OR FICE[tiab] OR i-Scan digital contrast*[tiab] OR I-SCAN[tiab] OR autofluorescence imaging[tiab] OR AFI[tiab] OR confocal laser endomicroscop*[tiab]	500 566
#7	#5 AND #6	76 248
#8	#4 AND #7	74 365
#9	#3 AND #8	1 527
#10	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomised[tiab] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Systematic Review[pt] OR Systematic Review[tiab] OR Systematic[sb] OR Meta-Analysis[pt] OR Meta-Analysis[tiab] OR Meta-Analysis[sb] OR Cochrane Database Syst Rev[Journal]	4 216 274
#11	animals[mh] NOT humans[mh]	4 271 569
#12	#10 NOT #11	3 672 006
#13	#9 AND #12 Filters: German, English; Publication date from 2009/06/01 to 2016/12/12	187

1.3.3 Recherche in Cochrane (12.12.16)

Search Name: CU_AG1_3
Date Run: 12/12/16 15:57:21.874

ID	Search	Hits
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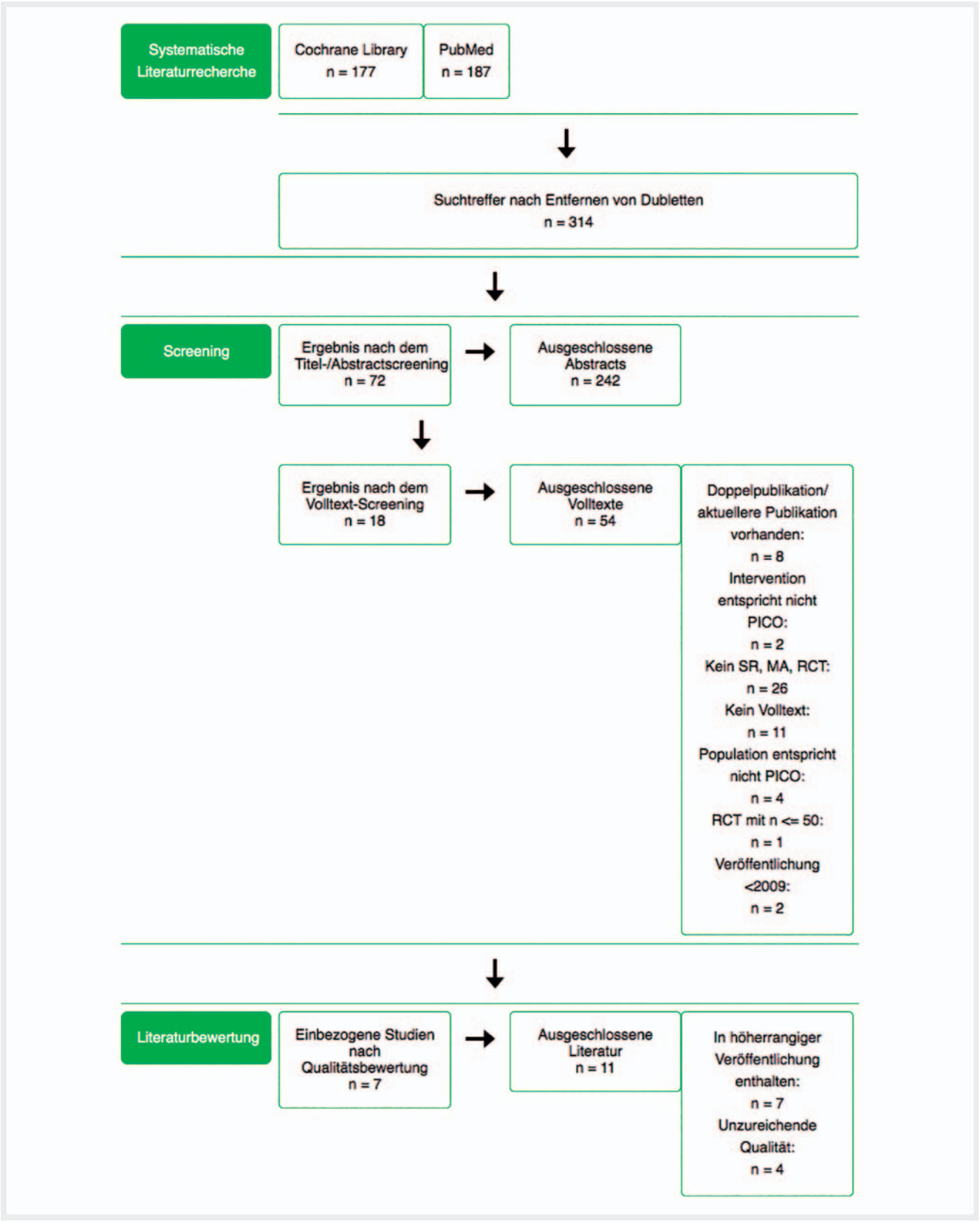
#2	Idiopathic Proctocolitis or Ulcerative Colitis or Colitis Gravis:ti,ab,kw	2299
#3	#1 or #2	2529
#4	[mh "Diagnostic Techniques and Procedures"]	207 504
#5	Diagnos* or Screen* or Detect* or Test* or assay or indicat* or quantif* or search or analy* or method* or assess* or check*:ti,ab,kw	751 764
#6	#4 or #5	769 432
#7	surveill* or monitor* or routine* or check-up or Screen* or random*:ti,ab,kw	603 606
#8	[mh Colonoscopy] or [mh Biopsy] or [mh "Capsule Endoscopy"]	7691
#9	Colonoscop* or biops* or Chromoendoscop* or Capsule Endoscop* or Virtual Endoscop* or narrowed-spectrum endoscop* or narrow band imaging or flexible spectral imaging color enhancement* or FICE or i-Scan digital contrast* or I-SCAN or autofluorescence imaging or AFI or confocal laser endomicroscop*:ti,ab,kw	22 858
#10	#8 or #9	24 058
#11	#7 and #10	17 294
#12	#6 and #11	16 696
#13	#3 and #12 Publication Year from 2009, in Cochrane Reviews (Reviews only), Other Reviews, Trials and Technology Assessments	177

1.3.4 Ergebnis und PRISMA Flow Chart



1.4 Intraepitheloale Neoplasien

1.4.1 Schlüsselfrage

1.4 Wie sollte bei histologischer Diagnosestellung einer niedriggradigen, bzw. hochgradigen IEN vorgegangen werden?

Population: Personen mit CU mit niedriggradigen bzw. hochgradigen intra-intestinale Neoplasien
Interventions: Referenzpathologie (Inhouse oder extern), Therapie: Proktokolektomie, Kontrollen (Intervalle)
Comparisons: Keine
Outcomes: Diagnostische Genauigkeit (Sensitivität, Spezifität, positiver oder negativer prädiktiver Wert), Krankheitsaktivität, scores (MAYO, SCCAI, PUCAI), Quality of life (IBDQ, SIDQ), mucosal healing

1.4.2 Recherche in PubMed (12.12.16)

AG 1 Diagnostik
1.4 Wie sollte bei histologischer Diagnosestellung einer niedriggradigen, bzw. hochgradigen IEN vorgegangen werden?

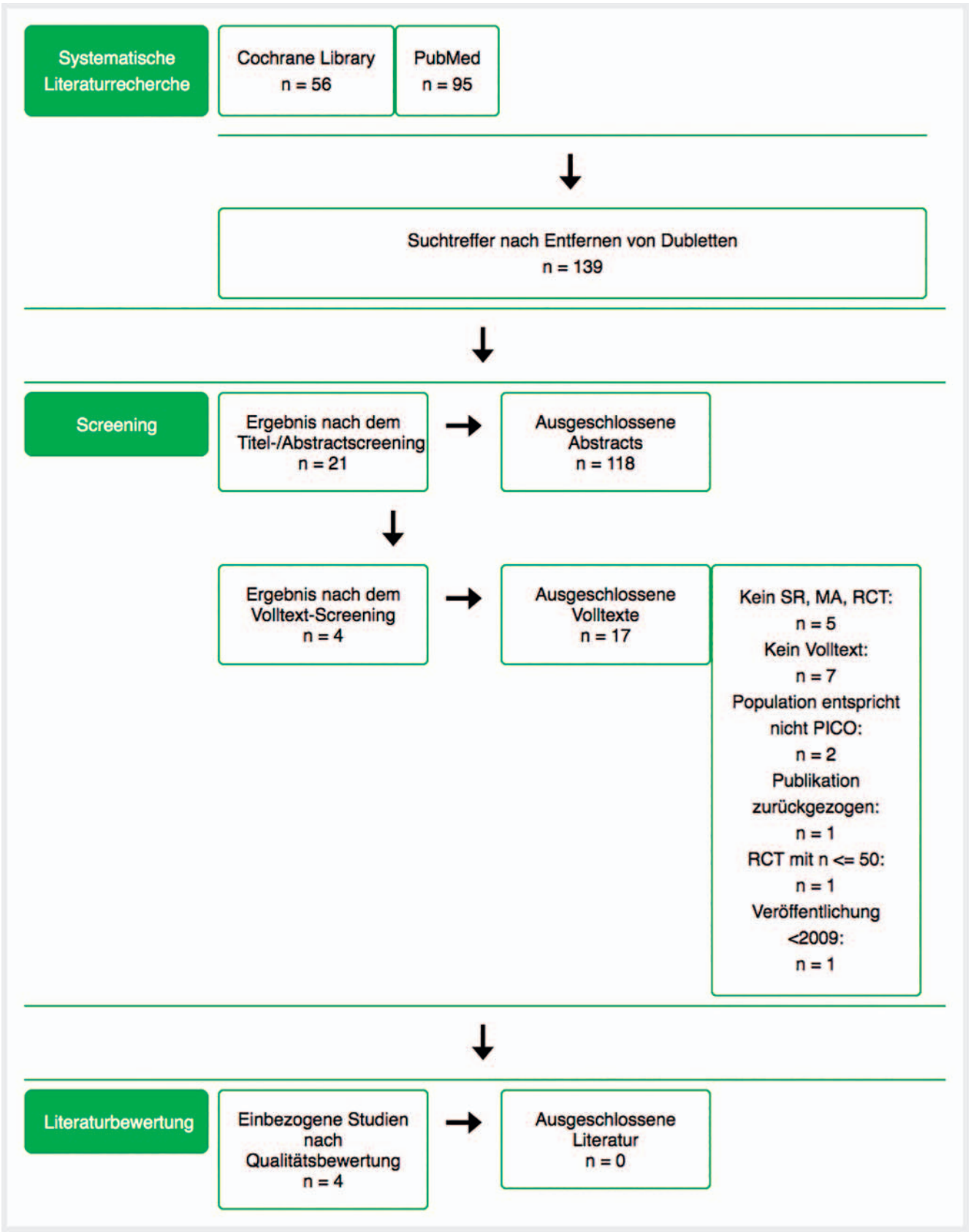
Nr.	Query	Treffer
#1	Colitis, Ulcerative[MeSH] OR "inflammatory bowel diseases"[MeSH:noexp]	43 939
#2	Idiopathic Proctocolitis[tiab] OR Ulcerative Colitis[tiab] OR Colitis Gravis[tiab]	31 861
#3	#1 OR #2	51 006
#4	Carcinoma in Situ[MeSH:noexp] OR Adenocarcinoma in Situ[MeSH] OR Neoplasms[MeSH] OR Intraepithelial Neoplas*[tiab] OR "IEN"[tiab]	2 854 403
#5	Neoplasm Grading[MeSH] OR Classif*[tiab] OR Grad*[tiab] OR differential*[tiab] OR Scor*[tiab]	2 167 739
#6	#4 AND #5	349 872
#7	#3 AND #6	960
#8	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomised[tiab] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Systematic Review[pt] OR Systematic Review[tiab] OR Systematic[sb] OR Meta-Analysis[pt] OR Meta-Analysis[tiab] OR Meta-Analysis[sb] OR Cochrane Database Syst Rev[Journal]	4 216 274
#9	animals[mh] NOT humans[mh]	4 271 569
#10	#8 NOT #9	3 672 006
#11	#7 AND #10 Filters: German, English; Publication date from 2009/06/01 to 2016/12/12	95

1.4.3 Recherche in Cochrane (12.12.16)

Search Name: CU_AG1_4
Date Run: 12/12/16 16:07:27.914

ID	Search	Hits
#1	[mh "Colitis, Ulcerative"] or [mh ^"inflammatory bowel diseases"]	1350
#2	Idiopathic Proctocolitis or Ulcerative Colitis or Colitis Gravis:ti,ab,kw	2299
#3	#1 or #2	2529
#4	[mh ^"Carcinoma in Situ"] or [mh "Adenocarcinoma in Situ"] or [mh Neoplasms]	59 815
#5	Intraepithelial Neoplas* or "IEN":ti,ab,kw	1075
#6	#4 or #5	60 115
#7	[mh "Neoplasm Grading"]	280
#8	Classif* or Grad* or differential* or Scor*	204 642
#9	#7 or #8	204 642
#10	#6 and #9	15 487
#11	#3 and #10 in Cochrane Reviews (Reviews only), Other Reviews, Trials and Technology Assessments	56

1.4.4 Ergebnis und PRISMA Flow Chart



2. Recherchen zum Thema „Schub“

2.1 Proktitis/Linksseitenkolitis/Pancolitis

2.1.1 Schlüsselfrage

2.1 Wie soll eine leicht-bis mittelgradig aktive Proktitis/Linksseitenkolitis/Pancolitis behandelt werden?
2.2 Wie soll eine mittelschwere bis schwere Proktitis/Linksseitenkolitis/ Pancolitis behandelt werden?

Population: Patienten mit Proktitis / Pancolitis, Linksseitenkolitis (leicht – mittelgradig bzw. mittelschwer – schwer)
Interventions:
Medikation: Antibodies, Infliximab, Infliximab biosimilar, Adalimumab, Ustekinumab, Eldelumab, Vedolizumab, Golimumab, biological therapy, Purines, cyclosporine, tacrolimus, aminosalicylic acids, Sulfasalazine, AVX-470, AJM300, steroids, Second generation steroids, Ozanimod, sphingosine-1-phosphate (S1P), receptor targeting compounds, Budesonide MMX, Tofacitinib, Filgotinib, Etrolizumab, Phosphatidylcholine, CTP13, SB2, Methotrexate
Therapien: Leukapheresis, Fecal microbiota transplantation
Comparisons: –
Outcomes: Krankheitsaktivität, scores (MAYO, SCCAI, PUCAI), Quality of life (IBDQ, SIDQ), mucosal healing, adverse events, toxic megacolon, Trough level

2.1.2 Recherche in PubMed (07.12.16)

2.1 und 2.2 Wie soll eine leicht-bis mittelgradig aktive bzw. mittelschwere bis schwere Proktitis/Linksseitenkolitis/ Pancolitis behandelt werden?

Nr.	Query	Treffer
#1	Colitis, Ulcerative[MeSH] OR "inflammatory bowel diseases"[MeSH:noexp]	43 939
#2	Idiopathic Proctocolitis[tiab] OR Ulcerative Colitis[tiab] OR Colitis Gravis[tiab]	31 861
#3	pancolitis[tiab] OR colitis[tiab] OR proctitis[tiab]	55 581
#4	severe[tiab] OR severity[tiab]	3 676 851
#5	(#1 OR #2) AND #3 AND #4	4 980
Interventionen		
#6	"AVX-470" [Supplementary Concept] OR AVX-470[tiab]	4
#7	"CT-P13"[Supplementary Concept] OR "CT-P13"[tiab] OR CTP13[tiab] OR inflectra[tiab] OR SB2[tiab] OR Remsima[tiab] OR Flixabi[tiab] OR "Biosimilar Pharmaceuticals"[MeSH] OR "Pharmaceuticals, Biosimilar"[tiab] OR Biosimilar*[tiab]	1 863
#8	"Infliximab"[MeSH] OR infliximab[tiab] OR "MAb cA2"[tiab] OR "Monoclonal Antibody cA2"[tiab] OR "Antibody cA2, Monoclonal"[tiab] OR"cA2, Monoclonal Antibody"[tiab] OR "Remicade"[tiab] OR originator[tiab]	12 036
#9	"Adalimumab"[MeSH] OR Adalimumab[tiab] OR "D2E7 Antibody"[tiab] OR Humira[tiab]	5 577
#10	Etrolizumab[tiab] OR "rhuMAb Beta7" [Supplementary Concept] OR "rhuMAb Beta7"[tiab] OR PRO145 223[tiab]	34
#11	Golimumab [Supplementary Concept] OR golimumab[tiab] OR Simponi[tiab]	679
#12	("Aminosalicylic Acids"[MeSH] OR "Aminosalicylic Acid"[MeSH] OR ASA*[tiab] OR Aminosalicyl*[tiab] OR 5-ASA[tiab] OR Rezipas [tiab] OR Pamisyl[tiab] OR ((meta[tiab] OR para[tiab] OR acid*[tiab] OR salt[tiab] OR monolithium*[tiab] OR monopotassium*[tiab] OR monosodium*[tiab] Alumino*[tiab]) AND (Aminosalicyl*[tiab] OR ASA[tiab]))	38 274
#13	(Sulfasalazine[MeSH] OR Sulfasalazin*[tiab] OR Sulphasalazin*[tiab] OR Salicylazosulfapyridine[tiab]OR Salazosulfapyridine[tiab] OR Colo-Pleon[tiab] OR "Colo Pleon"[tiab] OR Pleon[tiab] OR "ratio-Sulfasalazine"[tiab] OR "ratio Sulfasalazine"[tiab] OR Ulcol[tiab] OR Ucine[tiab] OR Azulfidine[tiab] OR Azulfadine[tiab] OR Salazopyrin OR Pyralin*[tiab] OR Asulfidine[tiab] OR Azulfidin*[tiab])	5 772
#14	(Mesalamine[MeSH] OR Mesalamin*[tiab] OR (Mesalamin*[tiab] AND (Monosodium[tiab] OR Salt[tiab])) OR Mesalazine[tiab] OR Fivasa[tiab] OR Mesasal[tiab] OR Pentasa[tiab] OR Rowasa[tiab] OR Asacol*[tiab] OR Ascolitin[tiab] OR Canasa[tiab] OR Salofalk[tiab] OR Claversal[tiab] OR Lixacol[tiab])	3 788
#15	Janus Kinases[MeSH] OR JAK*[tiab] OR "janus kinase"[tiab] OR janus-kinase[tiab]	24 684
#16	Filgotinib[tiab] OR GLPG0634[tiab]	15
#17	Tofacitinib [Supplementary Concept] OR tofacitinib[tiab] OR tasocitinib[tiab] OR Xeljanz[tiab] OR Jakvinus[tiab] OR "CP 690,550"[tiab] OR CP690 550[tiab] OR "CP-690 550"[tiab] OR "CP 690 550"[tiab] OR "CP-690,550"[tiab]	539
#18	Glucocorticoids[MeSH] OR glucocorticoid*[tiab] OR "Glucocorticoid Effect*"[tiab] OR steroid*[tiab] OR corticoid*[tiab] OR ((cortico*[tiab] OR hormone[tiab] OR generation[tiab]) AND steroid*[tiab])	286 312
#19	Beclomethasone[MeSH] OR Beclomethason*[tiab] OR Beclometason*[tiab] OR ((Beclomethasone[tiab] OR Beclometason[tiab]) AND Dipropionate[tiab])) OR Beclamet[tiab] OR "Beclo Asma"[tiab] OR "Beclo AZU"[tiab] OR Beclocort[tiab] OR Beclomet[tiab] OR Beclorhinol[tiab] OR Becloturmant[tiab] OR Sanasthmax[tiab] OR Beclovent[tiab] OR Beconase[tiab] OR Becloforte[tiab] OR Becodisk[tiab] OR Becotide[tiab] OR Propaderm[tiab] OR Sanasthmyl[tiab] OR Becodisks[tiab] OR "Beconase AQ"[tiab] OR Bronchocort[tiab] OR Junik[tiab] OR Qvar[tiab] OR Aerobec*[tiab] OR Beclazone*[tiab] OR Ecobec[tiab] OR Filair*[tiab] OR "Nasobec Aqueous"[tiab] OR Prolair[tiab] OR "Respocort"[tiab] OR Ventolair[tiab] OR Vancenase[tiab] OR Vanceril[tiab] OR Aldecin[tiab] OR Viarin[tiab] OR "Apo-Beclomethasone"[tiab]	3 728
#20	Dexamethasone[MeSH] OR Dexamethason*[tiab] OR Dexametason*[tiab] OR Hexadecadrol[tiab] OR Methylfluorprednisolone [tiab] OR Decameth[tiab] OR Decaspray[tiab] OR Dexasone[tiab] OR Dexpak[tiab] OR Maxidex[tiab] OR Millicorten[tiab] OR Oradexon[tiab] OR Decaject[tiab] OR Decaject*[tiab] OR Hexadrol[tiab]	63 579

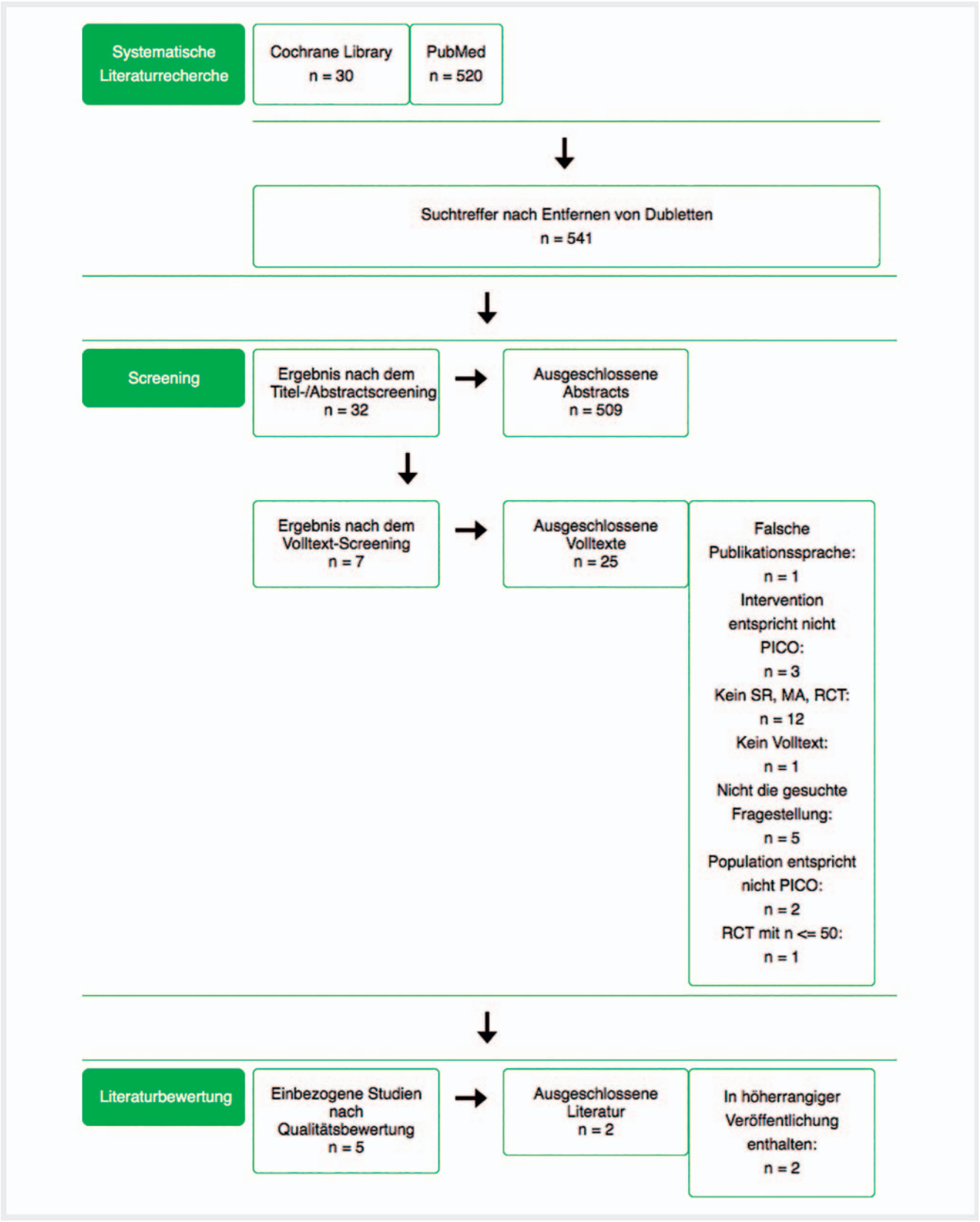
2.1 und 2.2 Wie soll eine leicht-bis mittelgradig aktive bzw. mittelschwere bis schwere Proktitis/Linksseitenkolitis/ Pancolitis behandelt werden?		
Nr.	**Query**	**Treffer**
#21	Budesonide[MeSH] OR Budesonid*[tiab] OR Pulmicort[tiab] OR MMX[tiab] OR Horacort[tiab] OR Rhinocort[tiab]	5 519
#22	Eldelumab[tiab] OR Anti-IP-10[tiab]	37
#23	Ustekinumab[MeSH] OR Ustekinumab[tiab] OR Stelara[tiab] OR "CNTO 1275"[tiab] OR "CNTO-1275"[tiab] OR CNTO1275[tiab]	892
#24	"Vedolizumab" [Supplementary Concept] OR Vedolizumab[tiab] OR Entyvio[tiab] OR MLN0002[tiab]	262
#25	"AJM300" [Supplementary Concept] OR AJM300[tiab] OR "Integrin alpha4"[MeSH] OR "Integrin alpha4"[tiab]	1 019
#26	Cyclosporine[MeSH] OR cyclosporin*[tiab] OR Ciclosporin*[tiab] OR Neoral[tiab] OR CyA-NOF[tiab] OR "CyA NOF"[tiab] OR Sandimmun*[tiab] OR CsA-Neoral[tiab] OR "CsA Neoral" OR CsANeoral[tiab] OR "OL 27 – 400"[tiab] OR "OL 27 400"[tiab] OR "OL 27 400"[tiab]	55 045
#27	Methotrexate[MeSH] OR Methotrexate[tiab] OR Amethopterin[tiab] OR Mexate[tiab]	47 499
#28	Tacrolimus[MeSH] OR tacrolimus[tiab] OR Prograf*[tiab] OR "FR-900 506"[tiab] OR "FR 900 506"[tiab] OR FR900 506[tiab] OR"FK-506"[tiab] OR "FK 506"[tiab] OR "FK506"[tiab]	21 649
#29	"Purines"[MeSH] OR Purin*[tiab]	489 896
#30	Phosphatidylcholines[MeSH] Or phosphatidylcholin*[tiab] OR ((cholin*[tiab]) AND (phosphoglycerid[tiab] OR glycero*[tiab])) OR lecithin*[tiab]	58 424
#31	"Leukapheresis"[MeSH] OR Leukapher*[tiab] OR Leukocytopher*[tiab] OR Leukopher*[tiab] OR Leukocytapher*[tiab] OR Lymphapher*[tiab] OR Lymphocytopher*[tiab] OR Lymphopher*[tiab] OR Lymphocytapher*[tiab]	4 414
#32	Probiotics[MeSH] OR probiotic*[tiab]	17 509
#33	"Receptors, Lysosphingolipid"[MeSH] OR ((sphingosin*[tiab]) AND (phosphat*[tiab] OR receptor*[tiab])) OR S1P[tiab] OR Ozanimod [Supplementary Concept] OR Ozanimod[tiab] OR RPC1063[tiab] OR Etrasimod[tiab] OR APD334[tiab]	6 .279
#34	"Fecal Microbiota Transplantation"[MeSH] OR (Fecal[tiab] OR intestinal[tiab] OR microbiot*[tiab]) AND (Transplant*[tiab] OR transfer*[tiab])) OR ((Transplantation*[tiab] OR transfer[tiab] OR Donor[tiab] OR Infusion[tiab]) AND (Feces[tiab])	13 629
#35	"Azathioprine"[MeSH] OR Azahtioprin*[tiab] OR Imurel[tiab] OR Imuran[tiab] OR Immuran[tiab] OR Azafalk[tiab] OR Azaimmun [tiab] OR Azarek[tiab] OR Colinsan[tiab] OR Immunoprin[tiab] OR Imurek[tiab] OR Zytrim[tiab]	13 807
#36	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35	1 069 147
Filter		
#37	#5 AND #36	1 202
#38	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomised[tiab] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Systematic Review[pt] OR Systematic Review[tiab] OR Systematic[sb] OR Meta-Analysis[pt] OR Meta-Analysis[tiab] OR Meta-Analysis[sb] OR Cochrane Database Syst Rev[Journal]	4 216 274
#39	animals[mh] NOT humans[mh]	4 271 569
#40	#38 NOT #39	3 672 006
#41	#37 AND #40 Filters: German, English; Publication date from 2009/06/01 to 2016/12/07	520

2.1.3 Recherche in Cochrane

Search Name: CU_AG1_1/2
Date Run: 12/01/2017

ID	Search
#1	MeSH descriptor: [Colitis, Ulcerative] explode all trees
#2	MeSH descriptor: [Inflammatory Bowel Diseases] explode all trees
#3	colitis or pancolitis:ti,ab,kw (Word variations have been searched)
#4	MeSH descriptor: [Proctitis] explode all trees
#5	proctitis
#6	(#1 or #2) and (#3 or #4 or #5) Publication Year from 2009

2.1.4 Ergebnis und PRISMA Flow Chart



2.2 Steroidrefraktärer Krankheitsverlauf

2.2.1 Schlüsselfrage

2.3 Welche Therapie soll bei steroidrefraktärem Krankheitsverlauf erfolgen?

Population: Patienten mit steroidrefraktärer Colitis ulcerosa
Interventions:
Medikation: Antibodies, Infliximab, Infliximab biosimilar, Adalimumab, Ustekinumab, Eldelumab, Vedolizumab, Golimumab, biological therapy, Purines, cyclosporine, tacrolimus, aminosalicylic acids, Sulfasalazine, AVX-470, AJM300, steroids, Second generation steroids, Ozanimod, sphingosine-1-phosphate (S1P), receptor targeting compounds, Budesonide MMX, Tofacitinib, Filgotinib, Etrolizumab, Phosphatidylcholine, CTP13, SB2, Methotrexate
Therapien: Leukapheresis, Fecal microbiota transplantation
Comparisons: –
Outcomes: Krankheitsaktivität, scores (MAYO, SCCAI, PUCAI), Quality of life (IBDQ, SIDQ), mucosal healing, adverse events, toxic megacolon, Trough level

2.2.2 Recherche in PubMed (07.12.16)

2.3 Welche Therapie soll bei steroidrefraktärem Krankheitsverlauf erfolgen?

Nr.	Query	Treffer
#1	Colitis, Ulcerative[MeSH] OR "inflammatory bowel diseases"[MeSH:noexp]	43 .939
#2	Idiopathic Proctocolitis[tiab] OR Ulcerative Colitis[tiab] OR Colitis Gravis[tiab]	31 861
#3	(steroid*[tiab] OR glucocorticoid*[tiab]) AND (refract*[tiab] OR resist*[tiab] OR unmanageable[tiab] OR obstinate[tiab])	17 850
#4	(#1 OR #2) AND #3	785
Interventionen		
#5	"AVX-470" [Supplementary Concept] OR AVX-470[tiab]	4
#6	"CT-P13"[Supplementary Concept] OR "CT-P13"[tiab] OR CTP13[tiab] OR inflectra[tiab] OR SB2[tiab] OR Remsima[tiab] OR Flixabi[tiab] OR "Biosimilar Pharmaceuticals"[MeSH] OR "Pharmaceuticals, Biosimilar"[tiab] OR Biosimilar*[tiab]	1 863
#7	"Infliximab"[MeSH] OR infliximab[tiab] OR "MAb cA2"[tiab] OR "Monoclonal Antibody cA2"[tiab] OR "Antibody cA2, Monoclonal"[tiab] OR"cA2, Monoclonal Antibody"[tiab] OR "Remicade"[tiab] OR originator[tiab]	12 036
#8	"Adalimumab"[MeSH] OR Adalimumab[tiab] OR "D2E7 Antibody"[tiab] OR Humira[tiab]	5 577
#9	Etrolizumab[tiab] OR "rhuMAb Beta7" [Supplementary Concept] OR "rhuMAb Beta7"[tiab] OR PRO145 223[tiab]	34
#10	Golimumab [Supplementary Concept] OR golimumab[tiab] OR Simponi[tiab]	679
#11	"Aminosalicylic Acids"[MeSH] OR "Aminosalicylic Acid"[MeSH] OR ASA*[tiab] OR Aminosalicyl*[tiab] OR 5-ASA[tiab] OR Rezipas[tiab] OR Pamisyl[tiab] OR ((meta[tiab] OR para[tiab] OR acid*[tiab] OR salt[tiab] OR monolithium*[tiab] OR monopotassium*[tiab] OR monosodium*[tiab] Alumino*[tiab]) AND (Aminosalicyl*[tiab] OR ASA[tiab])	38 274
#12	Sulfasalazine[MeSH] OR Sulfasalazin*[tiab] OR Sulphasalazin*[tiab] OR Salicylazosulfapyridine[tiab]OR Salazosulfapyridine[tiab] OR Colo-Pleon[tiab] OR "Colo Pleon"[tiab] OR Pleon[tiab] OR "ratio-Sulfasalazine"[tiab] OR "ratio Sulfasalazine"[tiab] OR Ulcol[tiab] OR Ucine[tiab] OR Azulfidine[tiab] OR Azulfadine[tiab] OR Salazopyrin OR Pyralin*[tiab] OR Asulfidine[tiab] OR Azulfidin*[tiab]	5 772
#13	Mesalamine[MeSH] OR Mesalamin*[tiab] OR (Mesalamin*[tiab] AND (Monosodium[tiab] OR Salt[tiab])) OR Mesalazine [tiab] OR Fivasa[tiab] OR Mesasal[tiab] OR Pentasa[tiab] OR Rowasa[tiab] OR Asacol*[tiab] OR Ascolitin[tiab] OR Canasa [tiab] OR Salofalk[tiab] OR Claversal[tiab] OR Lixacol[tiab]	3 788
#14	Janus Kinases[MeSH] OR JAK*[tiab] OR "janus kinase"[tiab] OR janus-kinase[tiab]	24 684
#15	Filgotinib[tiab] OR GLPG0634[tiab]	15
#16	Tofacitinib [Supplementary Concept] OR tofacitinib[tiab] OR tasocitinib[tiab] OR Xeljanz[tiab] OR Jakvinus[tiab] OR "CP 690,550"[tiab] OR CP690 550[tiab] OR "CP-690 550"[tiab] OR "CP 690 550"[tiab] OR "CP-690,550"[tiab]	539
#17	Glucocorticoids[MeSH] OR glucocorticoid*[tiab] OR "Glucocorticoid Effect*"[tiab] OR steroid*[tiab] OR corticoid*[tiab] OR ((cortico*[tiab] OR hormone[tiab] OR generation[tiab]) AND steroid*[tiab])	286 312
#18	Beclomethasone[MeSH] OR Beclomethason*[tiab] OR Beclometason*[tiab] OR ((Beclomethasone[tiab] OR Beclometason [tiab]) AND Dipropionate[tiab])) OR Beclamet[tiab] OR "Beclo Asma"[tiab] OR "Beclo AZU"[tiab] OR Beclocort[tiab] OR Beclomet[tiab] OR Beclorhinol[tiab] OR Becloturmant[tiab] OR Sanasthmax[tiab] OR Beclovent[tiab] OR Beconase[tiab] OR Becloforte[tiab] OR Becodisk[tiab] OR Becotide[tiab] OR Propaderm[tiab] OR Sanasthmyl[tiab] OR Becodisks[tiab] OR "Beconase AQ"[tiab] OR Bronchocort[tiab] OR Junik[tiab] OR Qvar[tiab] OR Aerobec*[tiab] OR Beclazone*[tiab] OR Ecobec [tiab] OR Filair*[tiab] OR "Nasobec Aqueous"[tiab] OR Prolair[tiab] OR "Respocort"[tiab] OR Ventolair[tiab] OR Vancenase [tiab] OR Vanceril[tiab] OR Aldecin[tiab] OR Viarin[tiab] OR "Apo-Beclomethasone"[tiab]	3 728

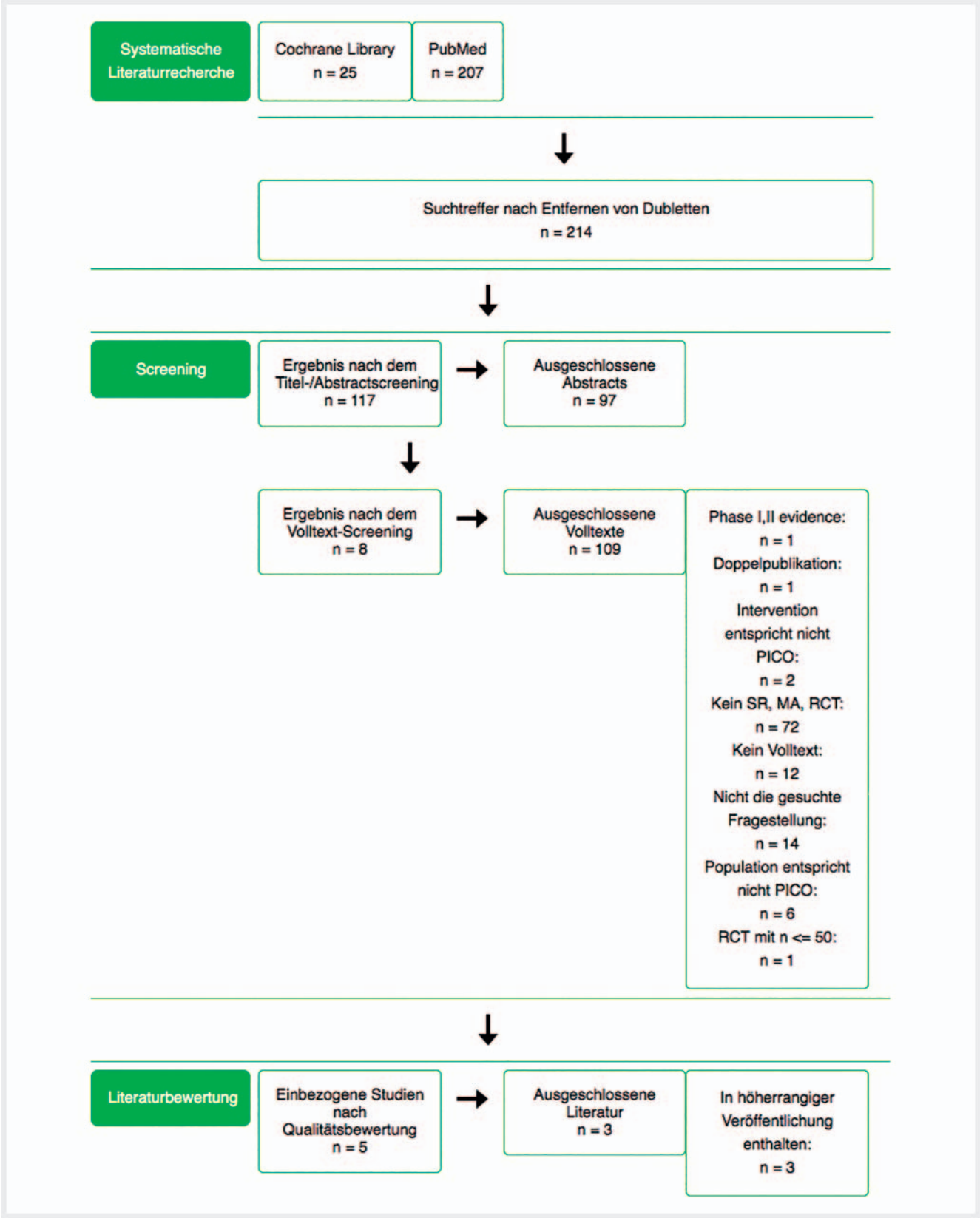
2.3 Welche Therapie soll bei steroidrefraktärem Krankheitsverlauf erfolgen?		
Nr.	**Query**	**Treffer**
#19	Dexamethasone[MeSH] OR Dexamethason*[tiab] OR Dexametason*[tiab] OR Hexadecadrol[tiab] OR Methylfluorprednisolone[tiab] OR Decameth[tiab] OR Decaspray[tiab] OR Dexasone[tiab] OR Dexpak[tiab] OR Maxidex[tiab] OR Millicorten[tiab] OR Oradexon[tiab] OR Decaject[tiab] OR Decaject*[tiab] OR Hexadrol[tiab]	63 579
#20	Budesonide[MeSH] OR Budesonid*[tiab] OR Pulmicort[tiab] OR MMX[tiab] OR Horacort[tiab] OR Rhinocort[tiab]	5 519
#21	Eldelumab[tiab] OR Anti-IP-10[tiab]	37
#22	Ustekinumab[MeSH] OR Ustekinumab[tiab] OR Stelara[tiab] OR "CNTO 1275"[tiab] OR "CNTO-1275"[tiab] OR CNTO1275[tiab]	892
#23	"Vedolizumab" [Supplementary Concept] OR Vedolizumab[tiab] OR Entyvio[tiab] OR MLN0002[tiab]	262
#24	"AJM300" [Supplementary Concept] OR AJM300[tiab] OR "Integrin alpha4"[MeSH] OR "Integrin alpha4"[tiab]	1 019
#25	Cyclosporine[MeSH] OR cyclosporin*[tiab] OR Ciclosporin*[tiab] OR Neoral[tiab] OR CyA-NOF[tiab] OR "CyA NOF"[tiab] OR Sandimmun*[tiab] OR CsA-Neoral[tiab] OR "CsA Neoral" OR CsANeoral[tiab] OR "OL 27 – 400"[tiab] OR "OL 27 400"[tiab] OR "OL 27 400"[tiab]	55 045
#26	Methotrexate[MeSH] OR Methotrexate[tiab] OR Amethopterin[tiab] OR Mexate[tiab]	47 499
#27	Tacrolimus[MeSH] OR tacrolimus[tiab] OR Prograf*[tiab] OR "FR-900 506"[tiab] OR "FR 900 506"[tiab] OR FR900 506[tiab] OR"FK-506"[tiab] OR "FK 506"[tiab] OR "FK506"[tiab]	21 649
#28	"Purines"[MeSH] OR Purin*[tiab]	489 896
#29	Phosphatidylcholines[MeSH] Or phosphatidylcholin*[tiab] OR ((cholin*[tiab]) AND (phosphoglycerid[tiab] OR glycero*[tiab])) OR lecithin*[tiab]	58 424
#30	"Leukapheresis"[MeSH] OR Leukapher*[tiab] OR Leukocytopher*[tiab] OR Leukopher*[tiab] OR Leukocytapher*[tiab] OR Lymphapher*[tiab] OR Lymphocytopher*[tiab] OR Lymphopher*[tiab] OR Lymphocytapher*[tiab]	4 414
#31	Probiotics[MeSH] OR probiotic*[tiab]	17 509
#32	"Receptors, Lysosphingolipid"[MeSH] OR ((sphingosin*[tiab]) AND (phosphat*[tiab] OR receptor*[tiab])) OR S1P[tiab] OR Ozanimod [Supplementary Concept] OR Ozanimod[tiab] OR RPC1063[tiab] OR Etrasimod[tiab] OR APD334[tiab]	6 279
#33	"Azathioprine"[MeSH] OR Azahtioprin*[tiab] OR Imurel[tiab] OR Imuran[tiab] OR Immuran[tiab] OR Azafalk[tiab] OR Azaimmun[tiab] OR Azarek[tiab] OR Colinsan[tiab] OR Immunoprin[tiab] OR Imurek[tiab] OR Zytrim[tiab]	13 807
#34	"Fecal Microbiota Transplantation"[MeSH] OR (Fecal[tiab] OR intestinal[tiab] OR microbiot*[tiab]) AND (Transplant*[tiab] OR transfer*[tiab])) OR ((Transplantation*[tiab] OR transfer[tiab] OR Donor[tiab] OR Infusion[tiab]) AND (Feces[tiab])	13 629
#35	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34	1 069 147
Filter		
#36	#4 AND #35	574
#37	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomised[tiab] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Systematic Review[pt] OR Systematic Review [tiab] OR Systematic[sb] OR Meta-Analysis[pt] OR Meta-Analysis[tiab] OR Meta-Analysis[sb] OR Cochrane Database Syst Rev[Journal]	4 216 274
#38	animals[mh] NOT humans[mh]	4 271 569
#39	#37 NOT #38	3 672 006
#40	#36 AND #39 Filters: German, English; Publication date from 2009/06/01 to 2016/12/07	207

2.2.3 Recherche in Cochrane (01.07.16

Search Name: CU_AG2_3
Date Run: 12/01/2017)

ID	Search
#1	MeSH descriptor: [Colitis, Ulcerative] explode all trees
#2	MeSH descriptor: [Inflammatory Bowel Diseases] explode all trees
#3	((steroid* or glucocorticoid*) and (refract* or resist* or unmanageable or obstinate))
#4	(#1 or #2) and #3 Publication Year from 2009

2.2.4 Ergebnis und PRISMA Flow Chart



2.3 Steroidabhängiger Krankheitsverlauf

2.3.1 Schlüsselfrage

2.4 Welche Therapie soll bei steroidabhängigem Krankheitsverlauf erfolgen?

Population: Patienten mit steroid-abhängiger Colitis Ulcerosa
Interventions:
Medikation: Antibodies, Infliximab, Infliximab biosimilar, Adalimumab, Ustekinumab, Eldelumab, Vedolizumab, Golimumab, biological therapy, Purines, cyclosporine, tacrolimus, aminosalicylic acids, Sulfasalazine, AVX-470, AJM300, steroids, Second generation steroids, Ozanimod, sphingosine-1-phosphate (S1P), receptor targeting compounds, Budesonide MMX, Tofacitinib, Filgotinib, Etrolizumab, Phosphatidylcholine, CTP13, SB2, Methotrexate
Therapien: Leukapheresis, Fecal microbiota transplantation
Comparisons: –
Outcomes: Krankheitsaktivität, scores (MAYO, SCCAI, PUCAI), Quality of life (IBDQ, SIDQ), mucosal healing, adverse events, toxic megacolon, Trough level

2.3.2 Recherche in PubMed (07.12.16)

2.4 Welche Therapie soll bei Steroid-abhängigem Krankheitsverlauf erfolgen?

Nr.	Query	Treffer
#1	Colitis, Ulcerative[MeSH] OR "inflammatory bowel diseases"[MeSH:noexp]	43.939
#2	Idiopathic Proctocolitis[tiab] OR Ulcerative Colitis[tiab] OR Colitis Gravis[tiab]	31.861
#3	(steroid*[tiab] OR glucocorticoid*[tiab]) AND (depend*[tiab] OR addict*[tiab] OR rely*[tiab])	35.794
#4	(#1 OR #2) AND #3	470
Interventionen		
#5	"AVX-470" [Supplementary Concept] OR AVX-470[tiab]	4
#6	"CT-P13"[Supplementary Concept] OR "CT-P13"[tiab] OR CTP13[tiab] OR inflectra[tiab] OR SB2[tiab] OR Remsima[tiab] OR Flixabi[tiab] OR "Biosimilar Pharmaceuticals"[MeSH] OR "Pharmaceuticals, Biosimilar"[tiab] OR Biosimilar*[tiab]	1.863
#7	"Infliximab"[MeSH] OR infliximab[tiab] OR "MAb cA2"[tiab] OR "Monoclonal Antibody cA2"[tiab] OR "Antibody cA2, Monoclonal"[tiab] OR"cA2, Monoclonal Antibody"[tiab] OR "Remicade"[tiab] OR originator[tiab]	12.036
#8	"Adalimumab"[MeSH] OR Adalimumab[tiab] OR "D2E7 Antibody"[tiab] OR Humira[tiab]	5.577
#9	Etrolizumab[tiab] OR "rhuMAb Beta7" [Supplementary Concept] OR "rhuMAb Beta7"[tiab] OR PRO145 223[tiab]	34
#10	Golimumab [Supplementary Concept] OR golimumab[tiab] OR Simponi[tiab]	679
#11	"Aminosalicylic Acids"[MeSH] OR "Aminosalicylic Acid"[MeSH] OR ASA*[tiab] OR Aminosalicyl*[tiab] OR 5-ASA[tiab] OR Rezipas[tiab] OR Pamisyl[tiab] OR ((meta[tiab] OR para[tiab] OR acid*[tiab] OR salt[tiab] OR monolithium*[tiab] OR monopotassium*[tiab] OR monosodium*[tiab] Alumino*[tiab]) AND (Aminosalicyl*[tiab] OR ASA[tiab])	38.274
#12	Sulfasalazine[MeSH] OR Sulfasalazin*[tiab] OR Sulphasalazin*[tiab] OR Salicylazosulfapyridine[tiab]OR Salazosulfapyridine[tiab] OR Colo-Pleon[tiab] OR "Colo Pleon"[tiab] OR Pleon[tiab] OR "ratio-Sulfasalazine"[tiab] OR "ratio Sulfasalazine"[tiab] OR Ulcol[tiab] OR Ucine[tiab] OR Azulfidine[tiab] OR Azulfadine[tiab] OR Salazopyrin OR Pyralin*[tiab] OR Asulfidine[tiab] OR Azulfidin*[tiab]	5.772
#13	Mesalamine[MeSH] OR Mesalamin*[tiab] OR (Mesalamin*[tiab] AND (Monosodium[tiab] OR Salt[tiab])) OR Mesalazine [tiab] OR Fivasa[tiab] OR Mesasal[tiab] OR Pentasa[tiab] OR Rowasa[tiab] OR Asacol*[tiab] OR Ascolitin[tiab] OR Canasa [tiab] OR Salofalk[tiab] OR Claversal[tiab] OR Lixacol[tiab]	3.788
#14	Janus Kinases[MeSH] OR JAK*[tiab] OR "janus kinase"[tiab] OR janus-kinase[tiab]	24.684
#15	Filgotinib[tiab] OR GLPG0634[tiab]	15
#16	Tofacitinib [Supplementary Concept] OR tofacitinib[tiab] OR tasocitinib[tiab] OR Xeljanz[tiab] OR Jakvinus[tiab] OR "CP 690,550"[tiab] OR CP690 550[tiab] OR "CP-690 550"[tiab] OR "CP 690 550"[tiab] OR "CP-690,550"[tiab]	539
#17	Glucocorticoids[MeSH] OR glucocorticoid*[tiab] OR "Glucocorticoid Effect*"[tiab] OR steroid*[tiab] OR corticoid*[tiab] OR ((cortico*[tiab] OR hormone[tiab] OR generation[tiab]) AND steroid*[tiab])	286.312
#18	Beclomethasone[MeSH] OR Beclomethason*[tiab] OR Beclometason*[tiab] OR ((Beclomethasone[tiab] OR Beclometason[tiab]) AND Dipropionate[tiab])) OR Beclamet[tiab] OR "Beclo Asma"[tiab] OR "Beclo AZU"[tiab] OR Beclocort[tiab] OR Beclomet[tiab] OR Beclorhinol[tiab] OR Becloturmant[tiab] OR Sanasthmax[tiab] OR Beclovent[tiab] OR Beconase [tiab] OR Becloforte[tiab] OR Becodisk[tiab] OR Becotide[tiab] OR Propaderm[tiab] OR Sanasthmyl[tiab] OR Becodisks [tiab] OR "Beconase AQ"[tiab] OR Bronchocort[tiab] OR Junik[tiab] OR Qvar[tiab] OR Aerobec*[tiab] OR Beclazone* [tiab] OR Ecobec[tiab] OR Filair*[tiab] OR "Nasobec Aqueous"[tiab] OR Prolair[tiab] OR "Respocort"[tiab] OR Ventolair [tiab] OR Vancenase[tiab] OR Vanceril[tiab] OR Aldecin[tiab] OR Viarin[tiab] OR "Apo-Beclomethasone"[tiab]	3.728

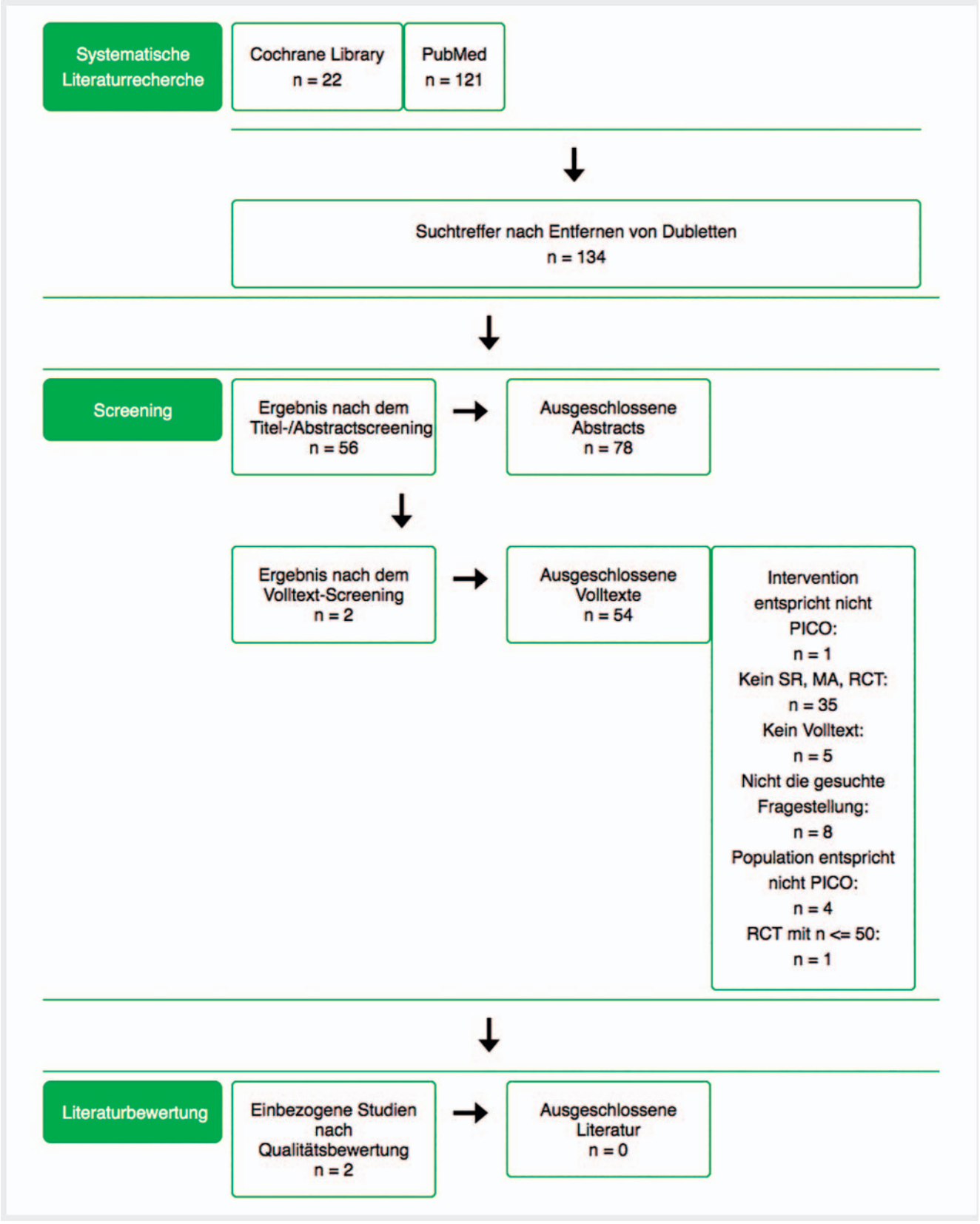
2.4 Welche Therapie soll bei Steroid-abhängigem Krankheitsverlauf erfolgen?		
Nr.	**Query**	**Treffer**
#19	Dexamethasone[MeSH] OR Dexamethason*[tiab] OR Dexametason*[tiab] OR Hexadecadrol[tiab] OR Methylfluor-prednisolone[tiab] OR Decameth[tiab] OR Decaspray[tiab] OR Dexasone[tiab] OR Dexpak[tiab] OR Maxidex[tiab] OR Millicorten[tiab] OR Oradexon[tiab] OR Decaject[tiab] OR Decaject*[tiab] OR Hexadrol[tiab]	63.579
#20	Budesonide[MeSH] OR Budesonid*[tiab] OR Pulmicort[tiab] OR MMX[tiab] OR Horacort[tiab] OR Rhinocort[tiab]	5.519
#21	Eldelumab[tiab] OR Anti-IP-10[tiab]	37
#22	Ustekinumab[MeSH] OR Ustekinumab[tiab] OR Stelara[tiab] OR "CNTO 1275"[tiab] OR "CNTO-1275"[tiab] OR CNTO1275[tiab]	892
#23	"Vedolizumab" [Supplementary Concept] OR Vedolizumab[tiab] OR Entyvio[tiab] OR MLN0002[tiab]	262
#24	"AJM300" [Supplementary Concept] OR AJM300[tiab] OR "Integrin alpha4"[MeSH] OR "Integrin alpha4"[tiab]	1.019
#25	Cyclosporine[MeSH] OR cyclosporin*[tiab] OR Ciclosporin*[tiab] OR Neoral[tiab] OR CyA-NOF[tiab] OR "CyA NOF"[tiab] OR Sandimmun*[tiab] OR CsA-Neoral[tiab] OR "CsA Neoral" OR CsANeoral[tiab] OR "OL 27 – 400"[tiab] OR "OL 27 400"[tiab] OR "OL 27 400"[tiab]	55.045
#26	Methotrexate[MeSH] OR Methotrexate[tiab] OR Amethopterin[tiab] OR Mexate[tiab]	47.499
#27	Tacrolimus[MeSH] OR tacrolimus[tiab] OR Prograf*[tiab] OR "FR-900 506"[tiab] OR "FR 900 506"[tiab] OR FR900 506[tiab] OR"FK-506"[tiab] OR "FK 506"[tiab] OR "FK506"[tiab]	21.649
#28	"Purines"[MeSH] OR Purin*[tiab]	489.896
#29	Phosphatidylcholines[MeSH] Or phosphatidylcholin*[tiab] OR ((cholin*[tiab]) AND (phosphoglycerid[tiab] OR glycero*[tiab])) OR lecithin*[tiab]	58.424
#30	"Leukapheresis"[MeSH] OR Leukapher*[tiab] OR Leukocytopher*[tiab] OR Leukopher*[tiab] OR Leukocytapher*[tiab] OR Lymphapher*[tiab] OR Lymphocytopher*[tiab] OR Lymphopher*[tiab] OR Lymphocytapher*[tiab]	4.414
#31	Probiotics[MeSH] OR probiotic*[tiab]	17.509
#32	"Receptors, Lysosphingolipid"[MeSH] OR ((sphingosin*[tiab]) AND (phosphat*[tiab] OR receptor*[tiab])) OR S1P[tiab] OR Ozanimod [Supplementary Concept] OR Ozanimod[tiab] OR RPC1063[tiab] OR Etrasimod[tiab] OR APD334[tiab]	6.279
#33	"Azathioprine"[MeSH] OR Azahtioprin*[tiab] OR Imurel[tiab] OR Imuran[tiab] OR Immuran[tiab] OR Azafalk[tiab] OR Azaimmun[tiab] OR Azarek[tiab] OR Colinsan[tiab] OR Immunoprin[tiab] OR Imurek[tiab] OR Zytrim[tiab]	13.807
#34	"Fecal Microbiota Transplantation"[MeSH] OR (Fecal[tiab] OR intestinal[tiab] OR microbiot*[tiab]) AND (Transplant*[tiab] OR transfer*[tiab])) OR ((Transplantation*[tiab] OR transfer[tiab] OR Donor[tiab] OR Infusion[tiab]) AND (Feces[tiab])	13.629
#35	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34	1.069.147
Suchzeitraum		
#36	#4 AND #35	309
#37	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomised[tiab] OR randomized[tiab] OR placebo [tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Systematic Review[pt] OR Systematic Review[tiab] OR Systematic[sb] OR Meta-Analysis[pt] OR Meta-Analysis[tiab] OR Meta-Analysis[sb] OR Cochrane Database Syst Rev[Journal]	4.216.274
#38	animals[mh] NOT humans[mh]	4.271.569
#39	#37 NOT #38	3.672.006
#40	#36 AND #39 Filters: German, Englisch; Publication date from 2009/06/01 to 2016/12/07	121

2.3.3 Recherche in Cochrane (12.01.17)

Search Name: CU_AG2_4
Date Run: 12/01/17

ID	Search
#1	MeSH descriptor: [Colitis, Ulcerative] explode all trees
#2	MeSH descriptor: [Inflammatory Bowel Diseases] explode all trees
#3	(steroid* or glucocorticoid*) and (depend* or addict* or rely*):ti,ab,kw (Word variations have been searched)
#4	(#1 or #2) and #3 Publication Year from 2009

2.3.4 Ergebnis und PRISMA Flow Chart



2.4 Therapieversagen auf Biologika-Therapie

2.4.1 Schlüsselfrage

2.5 Wie sollen Patienten behandelt werden, die ein primäres oder sekundäres Therapieversagen auf eine Biologika (anti-TNFalpha)-Therapie zeigen?

Population: Patienten mit Colitis Ulcerosa und Therapieversagen auf anti-TNF-Therapie, primär oder sekundär
Interventions:
Medikation: Antibodies, Infliximab, Infliximab biosimilar, Adalimumab, Ustekinumab, Eldelumab, Vedolizumab, Golimumab, biological therapy, Purines, cyclosporine, tacrolimus, aminosalicylic acids, Sulfasalazine, AVX-470, AJM300, steroids, Second generation steroids, Ozanimod, sphingosine-1-phosphate (S1P), receptor targeting compounds, Budesonide MMX, Tofacitinib, Filgotinib, Etrolizumab, Phosphatidylcholine, CTP13, SB2, Methotrexate
Therapien: Leukapheresis, Fecal microbiota transplantation
Comparisons: –
Outcomes: Krankheitsaktivität, scores (MAYO, SCCAI, PUCAI), Quality of life (IBDQ, SIDQ), mucosal healing, adverse events, toxic megacolon, Trough level

2.4.2 Recherche in PubMed (07.12.16)

2.5 Wie behandeln wir Patienten, die ein primäres oder sekundäres Therapieversagen auf eine Biologika (anti-TNFalpha)-Therapie zeigen?

Nr.	Query	Treffer
#1	Colitis, Ulcerative[MeSH] OR "inflammatory bowel diseases"[MeSH:noexp]	43 939
#2	Idiopathic Proctocolitis[tiab] OR Ulcerative Colitis[tiab] OR Colitis Gravis[tiab]	31 861
#3	"Treatment Failure"[MeSH] OR "Treatment Failure"[tiab] OR (fail*[tiab] AND (Treat*[tiab] OR interven*[tiab])) OR alternative[tiab] NOT "Complementary Therapies"[MeSH]	738 701
#4	"AVX-470" [Supplementary Concept] OR AVX-470[tiab]	4
#5	"CT-P13"[Supplementary Concept] OR "CT-P13"[tiab] OR CTP13[tiab] OR inflectra[tiab] OR SB2[tiab] OR Remsima [tiab] OR Flixabi[tiab] OR "Biosimilar Pharmaceuticals"[MeSH] OR "Pharmaceuticals, Biosimilar"[tiab] OR Biosimilar*[tiab]	1 863
#6	"Infliximab"[MeSH] OR infliximab[tiab] OR "MAb cA2"[tiab] OR "Monoclonal Antibody cA2"[tiab] OR "Antibody cA2, Monoclonal"[tiab] OR"cA2, Monoclonal Antibody"[tiab] OR "Remicade"[tiab] OR originator[tiab]	12 036
#7	"Adalimumab"[MeSH] OR Adalimumab[tiab] OR "D2E7 Antibody"[tiab] OR Humira[tiab]	5 577
#8	Etrolizumab[tiab] OR "rhuMAb Beta7" [Supplementary Concept] OR "rhuMAb Beta7"[tiab] OR PRO145 223[tiab]	34
#9	Golimumab [Supplementary Concept] OR golimumab[tiab] OR Simponi[tiab]	679
#10	#3 AND (#4 OR #5 OR #6 OR #7 OR #8 OR #9)	1 699
#11	(#1 OR #2) AND #10	317
Interventionen		
#12	"Aminosalicylic Acids"[MeSH] OR "Aminosalicylic Acid"[MeSH] OR ASA*[tiab] OR Aminosalicyl*[tiab] OR 5-ASA [tiab] OR Rezipas[tiab] OR Pamisyl[tiab] OR ((meta[tiab] OR para[tiab] OR acid*[tiab] OR salt[tiab] OR monolithium*[tiab] OR monopotassium*[tiab] OR monosodium*[tiab] Alumino*[tiab]) AND (Aminosalicyl*[tiab] OR ASA [tiab])	38 274
#13	Sulfasalazine[MeSH] OR Sulfasalazin*[tiab] OR Sulphasalazin*[tiab] OR Salicylazosulfapyridine[tiab]OR Salazosulfapyridine[tiab] OR Colo-Pleon[tiab] OR "Colo Pleon"[tiab] OR Pleon[tiab] OR "ratio-Sulfasalazine"[tiab] OR "ratio Sulfasalazine"[tiab] OR Ulcol[tiab] OR Ucine[tiab] OR Azulfidine[tiab] OR Azulfadine[tiab] OR Salazopyrin OR Pyralin*[tiab] OR Asulfidine[tiab] OR Azulfidin*[tiab]	5 772
#14	Mesalamine[MeSH] OR Mesalamin*[tiab] OR (Mesalamin*[tiab] AND (Monosodium[tiab] OR Salt[tiab])) OR Mesalazine[tiab] OR Fivasa[tiab] OR Mesasal[tiab] OR Pentasa[tiab] OR Rowasa[tiab] OR Asacol*[tiab] OR Ascolitin [tiab] OR Canasa[tiab] OR Salofalk[tiab] OR Claversal[tiab] OR Lixacol[tiab]	3 788
#15	Janus Kinases[MeSH] OR JAK*[tiab] OR "janus kinase"[tiab] OR janus-kinase[tiab]	24 684
#16	Filgotinib[tiab] OR GLPG0634[tiab]	15
#17	Tofacitinib [Supplementary Concept] OR tofacitinib[tiab] OR tasocitinib[tiab] OR Xeljanz[tiab] OR Jakvinus[tiab] OR "CP 690,550"[tiab] OR CP690 550[tiab] OR "CP-690 550"[tiab] OR "CP 690 550"[tiab] OR "CP-690,550"[tiab]	539
#18	Glucocorticoids[MeSH] OR glucocorticoid*[tiab] OR "Glucocorticoid Effect*"[tiab] OR steroid*[tiab] OR corticoid*[tiab] OR ((cortico*[tiab] OR hormone[tiab] OR generation[tiab]) AND steroid*[tiab])	286 312

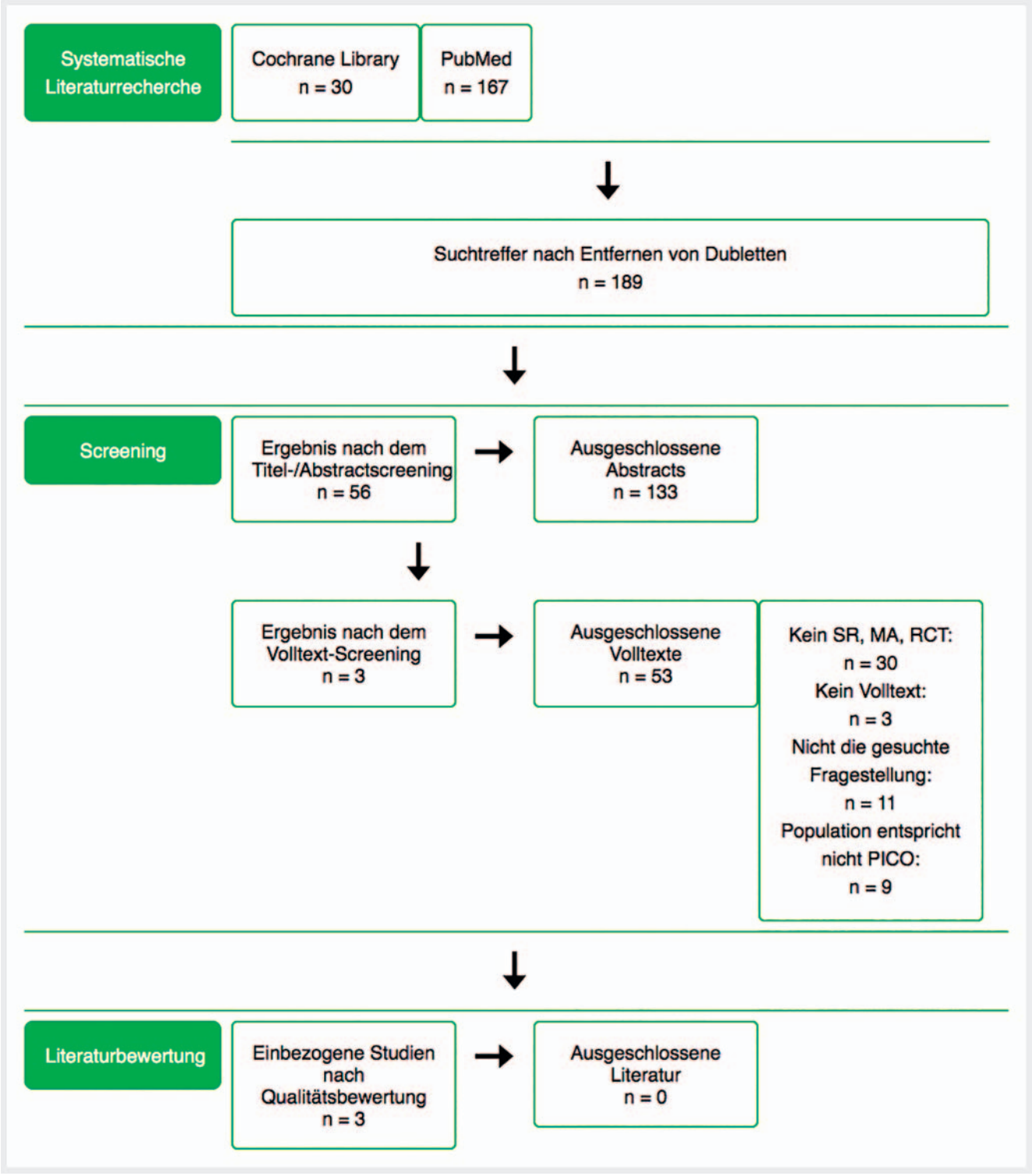
2.5 Wie behandeln wir Patienten, die ein primäres oder sekundäres Therapieversagen auf eine Biologika (anti-TNFalpha)-Therapie zeigen?		
Nr.	**Query**	**Treffer**
#19	(Beclomethasone[MeSH] OR Beclomethason*[tiab] OR Beclometason*[tiab] OR ((Beclomethasone[tiab] OR Beclometason[tiab]) AND Dipropionate[tiab])) OR Beclamet[tiab] OR "Beclo Asma"[tiab] OR "Beclo AZU"[tiab] OR Beclocort[tiab] OR Beclomet[tiab] OR OR Beclorhinol[tiab] OR Becloturmant[tiab] OR Sanasthmax[tiab] OR Beclovent[tiab] OR Beconase[tiab] OR Becloforte[tiab] OR Becodisk[tiab] OR Becotide[tiab] OR Propaderm[tiab] OR Sanasthmyl[tiab] OR Becodisks[tiab] OR "Beconase AQ"[tiab] OR Bronchocort[tiab] OR Junik[tiab] OR Qvar [tiab] OR Aerobec*[tiab] OR Beclazone*[tiab] OR Ecobec[tiab] OR Filair*[tiab] OR "Nasobec Aqueous"[tiab] OR Prolair[tiab] OR "Respocort"[tiab] OR Ventolair[tiab] OR Vancenase[tiab] OR Vanceril[tiab] OR Aldecin[tiab] OR Viarin[tiab] OR "Apo-Beclomethasone"[tiab])	3 728
#20	(Dexamethasone[MeSH] OR Dexamethason*[tiab] OR Dexametason*[tiab] OR Hexadecadrol[tiab] OR Methylfluorprednisolone[tiab] OR Decameth[tiab] OR Decaspray[tiab] OR Dexasone[tiab] OR Dexpak[tiab] OR Maxidex [tiab] OR Millicorten[tiab] OR Oradexon[tiab] OR Decaject[tiab] OR Decaject*[tiab] OR Hexadrol[tiab])	63 579
#21	(Budesonide[MeSH] OR Budesonid*[tiab] OR Pulmicort[tiab] OR MMX[tiab] OR Horacort[tiab] OR Rhinocort[tiab])	5 519
#22	Eldelumab[tiab] OR Anti-IP-10[tiab]	37
#23	Ustekinumab[MeSH] OR Ustekinumab[tiab] OR Stelara[tiab] OR "CNTO 1275"[tiab] OR "CNTO-1275"[tiab] OR CNTO1275[tiab]	892
#24	"Vedolizumab" [Supplementary Concept] OR Vedolizumab[tiab] OR Entyvio[tiab] OR MLN0002[tiab]	262
#25	"AJM300" [Supplementary Concept] OR AJM300[tiab] OR "Integrin alpha4"[MeSH] OR "Integrin alpha4"[tiab]	1 019
#26	Cyclosporine[MeSH] OR cyclosporin*[tiab] OR Ciclosporin*[tiab] OR Neoral[tiab] OR CyA-NOF[tiab] OR "CyA NOF"[tiab] OR Sandimmun*[tiab] OR CsA-Neoral[tiab] OR "CsA Neoral" OR CsANeoral[tiab] OR "OL 27 – 400"[tiab] OR "OL 27 400"[tiab] OR "OL 27 400"[tiab]	55 045
#27	Methotrexate[MeSH] OR Methotrexate[tiab] OR Amethopterin[tiab] OR Mexate[tiab]	47 499
#28	Tacrolimus[MeSH] OR tacrolimus[tiab] OR Prograf*[tiab] OR "FR-900 506"[tiab] OR "FR 900 506"[tiab] OR FR900 506[tiab] OR"FK-506"[tiab] OR "FK 506"[tiab] OR "FK506"[tiab]	21 649
#29	"Purines"[MeSH] OR Purin*[tiab]	489 896
#30	Phosphatidylcholines[MeSH] Or phosphatidylcholin*[tiab] OR ((cholin*[tiab]) AND (phosphoglycerid[tiab] OR glycero*[tiab])) OR lecithin*[tiab]	58 424
#31	"Leukapheresis"[MeSH] OR Leukapher*[tiab] OR Leukocytopher*[tiab] OR Leukopher*[tiab] OR Leukocytapher* [tiab] OR Lymphapher*[tiab] OR Lymphocytopher*[tiab] OR Lymphopher*[tiab] OR Lymphocytapher*[tiab]	4 414
#32	Probiotics[MeSH] OR probiotic*[tiab]	17 509
#33	"Receptors, Lysosphingolipid"[MeSH] OR ((sphingosin*[tiab]) AND (phosphat*[tiab] OR receptor*[tiab])) OR S1P [tiab] OR Ozanimod [Supplementary Concept] OR Ozanimod[tiab] OR RPC1063[tiab] OR Etrasimod[tiab] OR APD334[tiab]	6 279
#34	"Fecal Microbiota Transplantation"[MeSH] OR (Fecal[tiab] OR intestinal[tiab] OR microbiot*[tiab]) AND (Transplant*[tiab] OR transfer*[tiab])) OR ((Transplantation*[tiab] OR transfer[tiab] OR Donor[tiab] OR Infusion[tiab]) AND (Feces[tiab])	13 629
#35	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34	1 057 671
Filter		
#36	#11 AND #35	195
#37	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomised[tiab] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Systematic Review[pt] OR Systematic Review[tiab] OR Systematic[sb] OR Meta-Analysis[pt] OR Meta-Analysis[tiab] OR Meta-Analysis[sb] OR Cochrane Database Syst Rev[Journal]	4 216 274
#38	animals[mh] NOT humans[mh]	4 271 569
#39	#37 NOT #38	3 672 006
#40	#36 AND #39 Filters: German, Englisch; Publication date from 2009/06/01 to 2016/12/07	167

2.4.3 Recherche in Cochrane (12.01.17)

Search Name: CU_AG2_5
Date Run: 12/01/17

ID	Search
#1	MeSH descriptor: [Colitis, Ulcerative] explode all trees
#2	MeSH descriptor: [Inflammatory Bowel Diseases] explode all trees
#3	MeSH descriptor: [Treatment Failure] explode all trees
#4	("Treatment Failure" or (fail* and (Treat* or interven*)) or alternative):ti,ab,kw (Word variations have been searched)
#5	#3 or #4
#6	MeSH descriptor: [Infliximab] explode all trees
#7	MeSH descriptor: [Adalimumab] explode all trees
#8	"2AVX-470" or AVX-470:ti,ab,kw (Word variations have been searched)
#9	MeSH descriptor: [Biosimilar Pharmaceuticals] explode all trees
#10	"CT-P13" or CTP13 or inflectra or SB2 or Remsima or Flixabi or Biosimilar*:ti,ab,kw (Word variations have been searched)
#11	Infliximab or "MAb cA2" or "Monoclonal Antibody cA2" or "Antibody cA2, Monoclonal" or "cA2, Monoclonal Antibody" or Remicade or originator:ti,ab,kw (Word variations have been searched)
#12	Adalimumab or "D2E7 Antibody" or Humira:ti,ab,kw (Word variations have been searched)
#13	Etrolizumab or "rhuMAb Beta7" or "rhuMAb Beta7" or PRO145 223:ti,ab,kw (Word variations have been searched)
#14	Golimumab or Simponi:ti,ab,kw (Word variations have been searched)
#15	(#1 or #2) and #5 and (#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14) Publication Year from 2009

2.4.4 Ergebnis und PRISMA Flow Chart



3. Recherchen zum Thema „Remissionserhaltung“

3.1 Aminosalizylaten

3.1.1 Schlüsselfrage

3.1 Kann bei Patienten mit Colitis ulcerosa die Remission besser mit Aminosalizylaten als mit Placebo erhalten werden?

Population: Patienten mit Colitis ulcerosa (Remissionsphase)
Interventions: Aminosaliycylic acids, 5-ASA, Sulfasalazine
Comparisons: Placebo
Outcomes: Krankheitsaktivität, scores (MAYO, SCCAI, PUCAI), Quality of life (IBDQ, SIDQ), mucosal healing, adverse events, toxic megacolon, Trough level

3.1.2 Recherche in PubMed (07.12.16)

3.1. Kann bei Patienten mit Colitis ulcerosa die Remission besser mit Aminosalizylaten als mit Placebo erhalten werden?

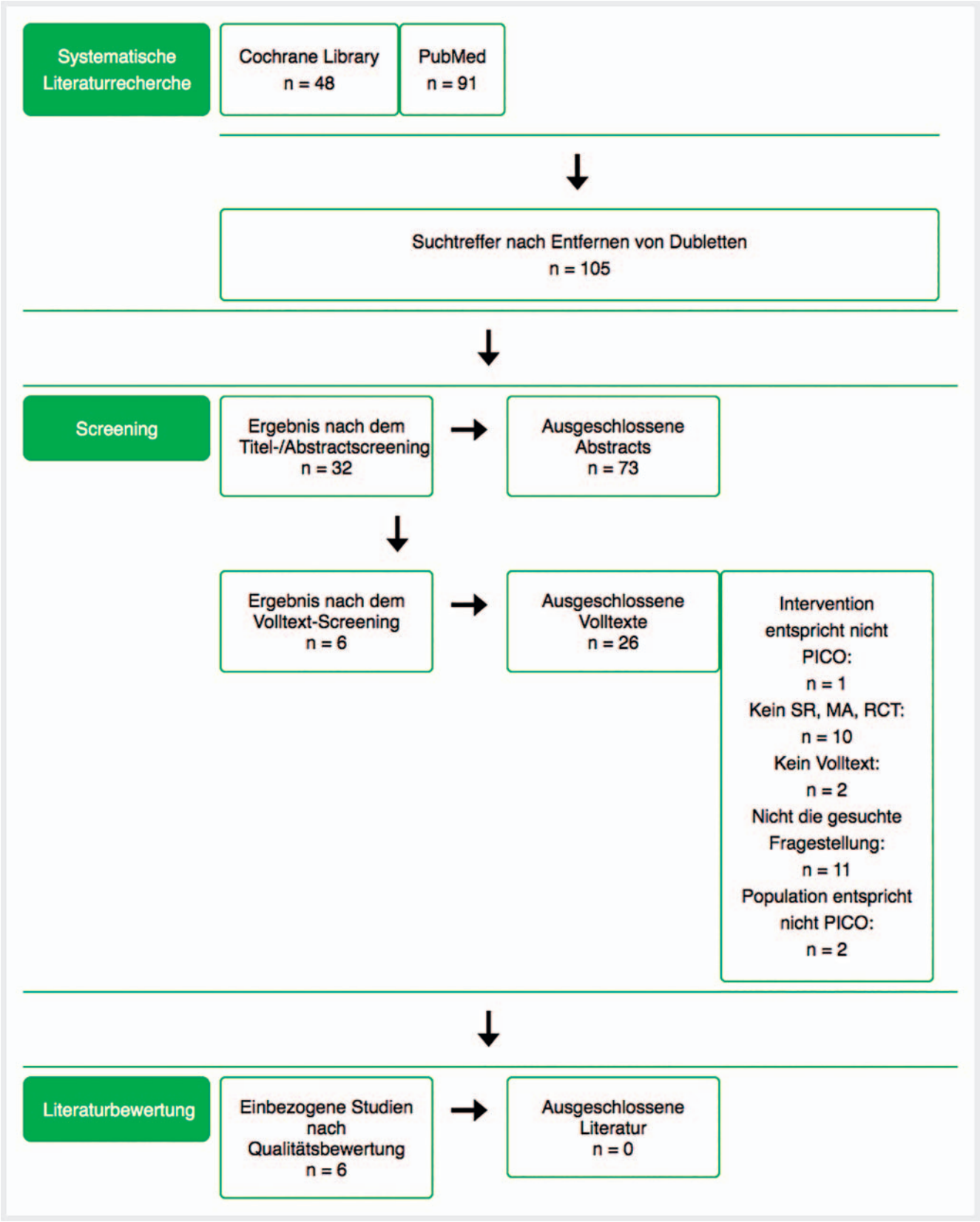
Nr.	Query	Treffer
#1	Colitis, Ulcerative[MeSH] OR "inflammatory bowel diseases"[MeSH:noexp]	43 939
#2	Idiopathic Proctocolitis[tiab] OR Ulcerative Colitis[tiab] OR Colitis Gravis[tiab]	31 840
#3	remission[tiab] OR maintain*[tiab] OR "long term care"[MeSH] OR "long-term"[tiab] OR Care[tiab] OR continu*[tiab] OR prolong*[tiab] OR surveil*[tiab] OR monitor*[tiab] OR stable[tiab] OR stabil*[tiab] OR ((symptom*[tiab]) AND (free[tiab] OR absent[tiab] OR nonpresent[tiab]))	4 338 414
#4	(#1 OR #2) AND 3	11 145
Interventionen		
#5	Placebos[MeSH] OR Placebo*[tiab] OR sham*[tiab] OR "sugar pill"[tiab] OR (inactive[tiab] AND (drug[tiab] OR substance[tiab] OR medicine[tiab])	274 420
#6	"Aminosalicylic Acids"[MeSH] OR "Aminosalicylic Acid"[MeSH] OR ASA*[tiab] OR Aminosalicyl*[tiab] OR 5-ASA[tiab] OR Rezipas[tiab] OR Pamisyl[tiab] OR ((meta[tiab] OR para[tiab] OR acid*[tiab] OR salt[tiab] OR monolithium*[tiab] OR monopotassium*[tiab] OR monosodium*[tiab] Alumino*[tiab]) AND (Aminosalicyl*[tiab] OR ASA[tiab])	38 274
#7	Sulfasalazine[MeSH] OR Sulfasalazin*[tiab] OR Sulphasalazin*[tiab] OR Salicylazosulfapyridine[tiab]OR Salazosulfapyridine[tiab] OR Colo-Pleon[tiab] OR "Colo Pleon"[tiab] OR Pleon[tiab] OR "ratio-Sulfasalazine"[tiab] OR "ratio Sulfasalazine"[tiab] OR Ulcol[tiab] OR Ucine[tiab] OR Azulfidine[tiab] OR Azulfadine[tiab] OR Salazopyrin OR Pyralin*[tiab] OR Asulfidine[tiab] OR Azulfidin*[tiab]	5722
#8	Mesalamine[MeSH] OR Mesalamin*[tiab] OR (Mesalamin*[tiab] AND (Monosodium[tiab] OR Salt[tiab])) OR Mesalazine[tiab] OR Fivasa[tiab] OR Mesasal[tiab] OR Pentasa[tiab] OR Rowasa[tiab] OR Asacol*[tiab] OR Ascolitin[tiab] OR Canasa[tiab] OR Salofalk[tiab] OR Claversal[tiab] OR Lixacol[tiab]	3788
#9	#6 OR #7 OR #8	43 595
#10	#5 AND #9	38 616
Filter		
#11	#4 AND 10	237
#12	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomised[tiab] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Systematic Review[pt] OR Systematic Review[tiab] OR Systematic[sb] OR Meta-Analysis[pt] OR Meta-Analysis[tiab] OR Meta-Analysis[sb] OR Cochrane Database Syst Rev[Journal]	4 216 274
#13	animals[mh] NOT humans[mh]	4 271 569
#14	#12 NOT #13	3 672 006
#15	#11 AND #14 Filters: German, English; Publication date from 2009/06/01 to 2016/12/07	91

3.1.3 Recherche in Cochrane (12.01.2017)

Search Name: CU_AG3_1
Date Run: 12/01/17

ID	Search
#1	MeSH descriptor: [Colitis, Ulcerative] explode all trees
#2	MeSH descriptor: [Inflammatory Bowel Diseases] explode all trees
#3	(remission or maintain* or "long term care" or "long-term" or Care or continu* or prolong* or surveil* or monitor* or stable or stabil* or ((symptom*) and (free or absent or nonpresent))):ti,ab,kw (Word variations have been searched)
#4	(#1 or #2) and #3
#5	MeSH descriptor: [Placebos] explode all trees
#6	Placebo* or sham* or "sugar pill" or (inactive and (drug or substance or medicine))
#7	"Aminosalicylic Acid" or ASA* or Aminosalicyl* or 5-ASA or Rezipas or Pamisyl or ((meta or para or acid* or salt or monolithium* or monopotassium* or monosodium* Alumino*) and (Aminosalicyl* or ASA))
#8	MeSH descriptor: [Aminosalicylic Acids] explode all trees
#9	MeSH descriptor: [Sulfasalazine] explode all trees
#10	Sulfasalazin* or Sulphasalazin* or Salicylazosulfapyridine or Salazosulfapyridine or Colo-Pleon or "Colo Pleon" or Pleon or "ratio-Sulfasalazine" or "ratio Sulfasalazine" or Ulcol or Ucine or Azulfidine or Azulfadine or Salazopyrin or Pyralin* or Asulfidine or Azulfidin*
#11	MeSH descriptor: [Mesalamine] explode all trees
#12	Mesalamin* or (Mesalamin* and (Monosodium or Salt)) or Mesalazine or Fivasa or Mesasal or Pentasa or Rowasa or Asacol* or Ascolitin or Canasa or Salofalk or Claversal or Lixacol
#13	#5 or #6
#14	#7 or #8 or #9 or #10 or #11 or #12
#15	#13 and #14
#16	#4 and #15 Publication Year from 2009

3.1.4 Ergebnis und PRISMA Flow Chart



3.2 Remissionserhaltung bei distaler Colitis Ulcerosa

3.2.1 Schlüsselfrage

3.2 Kann bei Patienten mit distaler Colitis ulcerosa die Remission besser mit topischen Aminosalizylaten als mit topischen Glukokortikoiden erhalten werden?

Population: Patienten mit distaler Colitis ulcerosa (Remissionsphase)
Interventions: topische Aminosaliycylic acids, 5-ASA. Sulfasalazine, Mesalazin
Comparisons: topische Glucocorticoids, Beclometason, Dexamethason, Budenoside MMX, second generation steroids
Outcomes: Krankheitsaktivität, scores (MAYO, SCCAI, PUCAI), Quality of life (IBDQ, SIDQ), mucosal healing, adverse events, toxic megacolon, Trough level

3.2.2 Recherche in PubMed (07.12.16)

3.2 Kann bei Patienten mit distaler Colitis ulcerosa die Remission besser mit topischen Aminosalizylaten als mit topischen Glukokortikoiden erhalten werden?

Nr.	Query	Treffer
#1	Colitis, Ulcerative[MeSH] OR "inflammatory bowel diseases"[MeSH:noexp]	43 939
#2	Idiopathic Proctocolitis[tiab] OR Ulcerative Colitis[tiab] OR Colitis Gravis[tiab]	31 823
#3	distal[tiab]	193 907
#3	remission[tiab] OR maintain*[tiab] OR "long term care"[MeSH] OR "long-term"[tiab] OR Care[tiab] OR continu*[tiab] OR prolong*[tiab] OR surveil*[tiab] OR monitor*[tiab] OR stable[tiab] OR stabil*[tiab] OR ((symptom*[tiab]) AND (free[tiab] OR absent[tiab] OR nonpresent[tiab]))	4 338 414
#5	(#1 OR #2) AND #4	11 145
Interventionen		
#6	"Administration, Rectal"[MeSH] OR "Rectal administration"[tiab] OR Enema[MeSH] OR Enema*[tiab] OR Suppositories [MeSH] OR Suppositor*[tiab] or foam[tiab]	35 334
#7	Glucocorticoids[MeSH] OR glucocorticoid*[tiab] OR "Glucocorticoid Effect*"[tiab] OR steroid*[tiab] OR corticoid* [tiab] OR ((cortico*[tiab] OR hormone[tiab] OR generation[tiab]) AND steroid*[tiab])	286 312
#8	Beclomethasone[MeSH] OR Beclomethason*[tiab] OR Beclometason*[tiab] OR ((Beclomethasone[tiab] OR Beclometason[tiab]) AND Dipropionate[tiab])) OR Beclamet[tiab] OR "Beclo Asma"[tiab] OR "Beclo AZU"[tiab] OR Beclocort[tiab] OR Beclomet[tiab] OR OR Beclorhinol[tiab] OR Becloturmant[tiab] OR Sanasthmax[tiab] OR Beclovent[tiab] OR Beconase[tiab] OR Becloforte[tiab] OR Becodisk[tiab] OR Becotide[tiab] OR Propaderm[tiab] OR Sanasthmyl[tiab] OR Becodisks[tiab] OR "Beconase AQ"[tiab] OR Bronchocort[tiab] OR Junik[tiab] OR Qvar[tiab] OR Aerobec*[tiab] OR Beclazone* [tiab] OR Ecobec[tiab] OR Filair*[tiab] OR "Nasobec Aqueous"[tiab] OR Prolair[tiab] OR "Respocort"[tiab] OR Ventolair [tiab] OR Vancenase[tiab] OR Vanceril[tiab] OR Aldecin[tiab] OR Viarin[tiab] OR "Apo-Beclomethasone"[tiab]	3728
#9	Dexamethasone[MeSH] OR Dexamethason*[tiab] OR Dexametason*[tiab] OR Hexadecadrol[tiab] OR Methylfluorprednisolone[tiab] OR Decameth[tiab] OR Decaspray[tiab] OR Dexasone[tiab] OR Dexpak[tiab] OR Maxidex[tiab] OR Millicorten[tiab] OR Oradexon[tiab] OR Decaject[tiab] OR Decaject*[tiab] OR Hexadrol[tiab]	63 579
#10	Budesonide[MeSH] OR Budesonid*[tiab] OR Pulmicort[tiab] OR MMX[tiab] OR Horacort[tiab] OR Rhinocort[tiab]	5519
#11	"Aminosalicylic Acids"[MeSH] OR "Aminosalicylic Acid"[MeSH] OR ASA*[tiab] OR Aminosalicyl*[tiab] OR 5-ASA[tiab] OR Rezipas[tiab] OR Pamisyl[tiab] OR ((meta[tiab] OR para[tiab] OR acid*[tiab] OR salt[tiab] OR monolithium*[tiab] OR monopotassium*[tiab] OR monosodium*[tiab] Alumino*[tiab]) AND (Aminosalicyl*[tiab] OR ASA[tiab])	38 724
#12	Sulfasalazine[MeSH] OR Sulfasalazin*[tiab] OR Sulphasalazin*[tiab] OR Salicylazosulfapyridine[tiab]OR Salazosulfapyridine[tiab] OR Colo-Pleon[tiab] OR "Colo Pleon"[tiab] OR Pleon[tiab] OR "ratio-Sulfasalazine"[tiab] OR "ratio Sulfasalazine"[tiab] OR Ulcol[tiab] OR Ucine[tiab] OR Azulfidine[tiab] OR Azulfadine[tiab] OR Salazopyrin OR Pyralin*[tiab] OR Asulfidine[tiab] OR Azulfidin*[tiab]	5722
#13	Mesalamine[MeSH] OR Mesalamin*[tiab] OR (Mesalamin*[tiab] AND (Monosodium[tiab] OR Salt[tiab])) OR Mesalazine[tiab] OR Fivasa[tiab] OR Mesasal[tiab] OR Pentasa[tiab] OR Rowasa[tiab] OR Asacol*[tiab] OR Ascolitin[tiab] OR Canasa[tiab] OR Salofalk[tiab] OR Claversal[tiab] OR Lixacol[tiab]	3788
#14	(#7 OR #8 OR #9 OR #10) AND (#11 OR #12 OR #13)	7518
#15	#6 AND #14	194

3.2 Kann bei Patienten mit distaler Colitis ulcerosa die Remission besser mit topischen Aminosalizylaten als mit topischen Glukokortikoiden erhalten werden?		
Nr.	**Query**	**Treffer**
Filter		
#16	#5 AND 15	81
#17	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomised[tiab] OR randomized[tiab] OR placebo [tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Systematic Review[pt] OR Systematic Review[tiab] OR Systematic[sb] OR Meta-Analysis[pt] OR Meta-Analysis[tiab] OR Meta-Analysis[sb] OR Cochrane Database Syst Rev[Journal]	4 216 274
#18	animals[mh] NOT humans[mh]	4 271 569
#19	#17 NOT #18	3 672 006
#20	#16 AND #19 Filters: German, Englisch; Publication date from 2009/06/01 to 2016/12/07	20

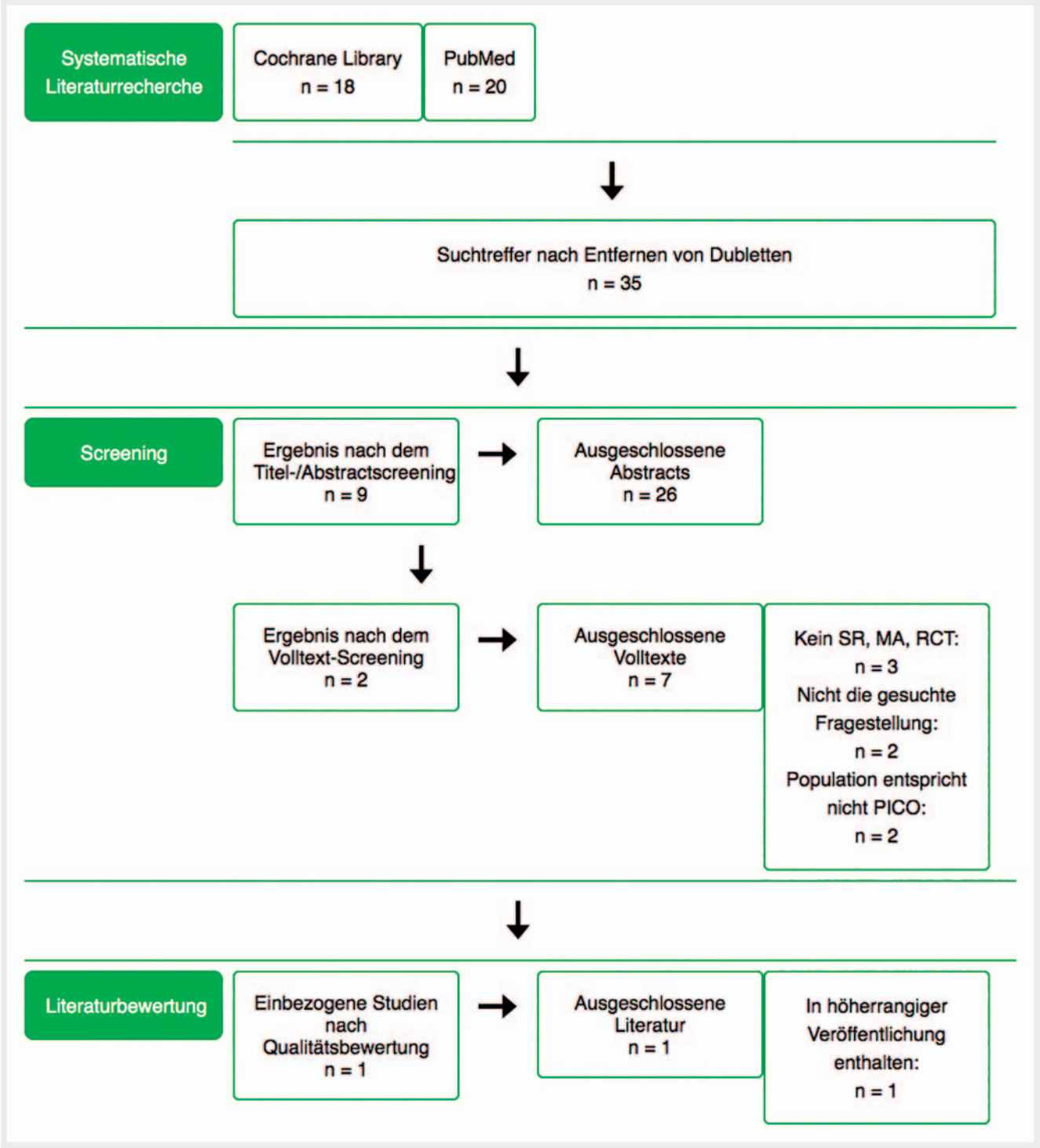
3.2.3 Recherche in Cochrane (12.01.17)

Search Name: CU_AG3_2
Date Run: 12/01/17

ID	Search
#1	MeSH descriptor: [Colitis, Ulcerative] explode all trees
#2	MeSH descriptor: [Inflammatory Bowel Diseases] explode all trees
#3	(remission or maintain* or "long term care" or "long-term" or Care or continu* or prolong* or surveil* or monitor* or stable or stabil* or ((symptom*) and (free or absent or nonpresent))):ti,ab,kw (Word variations have been searched)
#4	MeSH descriptor: [Administration, Rectal] explode all trees
#5	MeSH descriptor: [Enema] explode all trees
#6	MeSH descriptor: [Suppositories] explode all trees
#7	"Rectal administration" or Enema* or Suppositor* or foam
#8	#4 or #5 or #6 or #7
#9	MeSH descriptor: [Glucocorticoids] explode all trees
#10	MeSH descriptor: [Steroids] explode all trees
#11	glucocorticoid* or "Glucocorticoid Effect*" or steroid* or corticoid* or ((cortico* or hormone or generation) and steroid*)
#12	MeSH descriptor: [Beclomethasone] explode all trees
#13	Beclomethason* or Beclometason* or Beclamet or "Beclo Asma" or "Beclo AZU" or Beclocort or Beclomet or Beclorhinol or Becloturmant or Sanasthmax or Beclovent or Beconase or Becloforte or Becodisk or Becotide or Propaderm or Sanasthmyl or Becodisks or "Beconase AQ" or Bronchocort or Junik or Qvar or Aerobec* or Beclazone* or Ecobec or Filair* or "Nasobec Aqueous" or Prolair or Respocort or Ventolair or Vancenase or Vanceril or Aldecin or Viarin or "Apo-Beclomethasone"
#14	Beclomethason* or Beclometason* or Beclamet or "Beclo Asma" or "Beclo AZU" or Beclocort or Beclomet or Beclorhinol or Becloturmant or Sanasthmax or Beclovent or Beconase or Becloforte or Becodisk or Becotide or Propaderm or Sanasthmyl or Becodisks or "Beconase AQ" or Bronchocort or Junik or Qvar or Aerobec* or Beclazone* or Ecobec or Filair* or "Nasobec Aqueous" or Prolair or Respocort or Ventolair or Vancenase or Vanceril or Aldecin or Viarin or "Apo-Beclomethasone":ti,ab,kw (Word variations have been searched)
#15	MeSH descriptor: [Budesonide] explode all trees
#16	Budesonid* or Pulmicort or MMX or Horacort or Rhinocort
#17	MeSH descriptor: [Dexamethasone] explode all trees
#18	Dexamethason* or Dexametason* or Hexadecadrol or Methylfluorprednisolone or Decameth or Decaspray or Dexasone or Dexpak or Maxidex or Millicorten or Oradexon or Decaject or Decaject* or Hexadrol
#19	MeSH descriptor: [Cortisone] explode all trees
#20	MeSH descriptor: [Prednisone] explode all trees
#21	Dehydrocortisone or prednison* or delta-Cortisone or Rectodelt or Sterapred or Ultracorten or Winpred or Apo-Prednisone or Cortan or Cortancyl or Panafcort or Cutason or Decortin or Dacortin or Decortisyl or Deltasone or Encorton* or Enkortolon or Kortancyl or "Liquid Pred" or Meticorten or Orasone or Panasol or "Predni Tablinen" or Prednidib or Predniment or Pronisone or Sone

ID	Search
#22	"Aminosalicylic Acid" or ASA* or Aminosalicyl* or 5-ASA or Rezipas or Pamisyl or ((meta or para or acid* or salt or monolithium* or monopotassium* or monosodium* Alumino*) and (Aminosalicyl* or ASA))
#23	MeSH descriptor: [Aminosalicylic Acids] explode all trees
#24	MeSH descriptor: [Sulfasalazine] explode all trees
#25	Sulfasalazin* or Sulphasalazin* or Salicylazosulfapyridine or Salazosulfapyridine or Colo-Pleon or "Colo Pleon" or Pleon or "ratio-Sulfasalazine" or "ratio Sulfasalazine" or Ulcol or Ucine or Azulfidine or Azulfadine or Salazopyrin or Pyralin* or Asulfidine or Azulfidin*
#26	MeSH descriptor: [Mesalamine] explode all trees #27
#27	Mesalamin* or (Mesalamin* and (Monosodium or Salt)) or Mesalazine or Fivasa or Mesasal or Pentasa or Rowasa or Asacol* or Ascolitin or Canasa or Salofalk or Claversal or Lixacol
#28	#9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #19 or #20 or #21
#29	#22 or #23 or #24 or #25 or #26 or #27
#30	#28 and #29
#31	#30 and #8
#32	(#1 or #2) and #31 Publication Year from 2009

3.2.4 Ergebnis und PRISMA Flow Chart



3.3 E. coli Stamm Nissle 1917

3.3.1 Schlüsselfrage

3.3 Kann bei Patienten mit Colitis ulcerosa die Remission mit E. coli Stamm Nissle 1917 genau so gut wie mit Mesalazin erhalten werden?

Population: Patienten mit Colitis ulcerosa (Remissionsphase)
Interventions: E Coli Nissle 1917
Comparisons: Mesalazin
Outcomes: Krankheitsaktivität, scores (MAYO, SCCAI, PUCAI), Quality of life (IBDQ, SIDQ), mucosal healing, adverse events, toxic megacolon, Trough level

3.3.2 Recherche in PubMed (07.12.16)

3.3 Kann bei Patienten mit Colitis ulcerosa die Remission mit E. coli Stamm Nissle 1917 genau so gut wie mit Mesalazin erhalten werden?

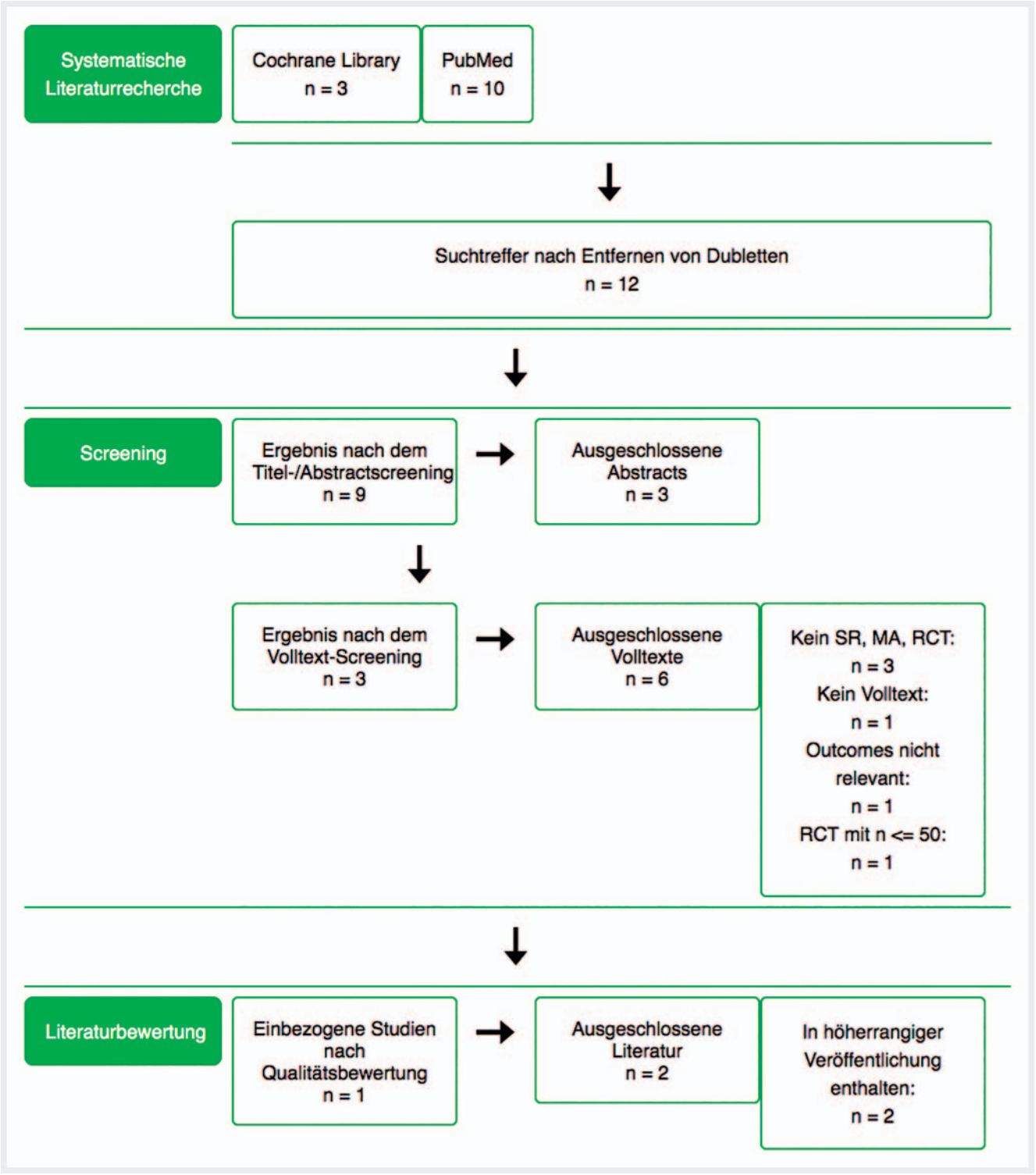
Nr.	Query	Treffer
#1	Colitis, Ulcerative[MeSH] OR "inflammatory bowel diseases"[MeSH:noexp]	43 939
#2	Idiopathic Proctocolitis[tiab] OR Ulcerative Colitis[tiab] OR Colitis Gravis[tiab]	31 861
#3	remission[tiab] OR maintain*[tiab] OR "long term care"[MeSH] OR "long-term"[tiab] OR Care[tiab] OR continu*[tiab] OR prolong*[tiab] OR surveil*[tiab] OR monitor*[tiab] OR stable[tiab] OR stabil*[tiab] OR ((symptom*[tiab]) AND (free[tiab] OR absent[tiab] OR nonpresent[tiab]))	4 338 414
#4	(#1 OR #2) AND 3	11 145
Interventionen		
#5	"Escherichia coli"[MeSH] OR „Escherichia coli“[tiab] OR E.coli[tiab] OR Nissle[tiab] OR 1917[tiab] OR ECN[tiab] OR "E coli"[tiab] OR "Diffusely Adherent Escherichia coli"[tiab] OR "Diffusely Adherent E. coli"[tiab] OR "Enteroinvasive Escherichia coli"[tiab] OR "Enteroinvasive E. coli"[tiab] OR "Alkalescens-Dispar Group"[tiab] OR "Enteroaggregative Escherichia coli"[tiab] OR "EAggEC"[tiab] OR "Enteroaggregative E. coli"[tiab]	351 282
#6	"Aminosalicylic Acids"[MeSH] OR "Aminosalicylic Acid"[MeSH] OR ASA*[tiab] OR Aminosalicyl*[tiab] OR 5-ASA[tiab] OR Rezipas[tiab] OR Pamisyl[tiab] OR ((meta[tiab] OR para[tiab] OR acid*[tiab] OR salt[tiab] OR monolithium*[tiab] OR monopotassium*[tiab] OR monosodium*[tiab] Alumino*[tiab]) AND (Aminosalicyl*[tiab] OR ASA[tiab])	38 274
#7	Sulfasalazine[MeSH] OR Sulfasalazin*[tiab] OR Sulphasalazin*[tiab] OR Salicylazosulfapyridine[tiab]OR Salazosulfapyridine[tiab] OR Colo-Pleon[tiab] OR "Colo Pleon"[tiab] OR Pleon[tiab] OR "ratio-Sulfasalazine"[tiab] OR "ratio Sulfasalazine"[tiab] OR Ulcol[tiab] OR Ucine[tiab] OR Azulfidine[tiab] OR Azulfadine[tiab] OR Salazopyrin OR Pyralin*[tiab] OR Asulfidine[tiab] OR Azulfidin*[tiab]	5 722
#8	Mesalamine[MeSH] OR Mesalamin*[tiab] OR (Mesalamin*[tiab] AND (Monosodium[tiab] OR Salt[tiab])) OR Mesalazine[tiab] OR Fivasa[tiab] OR Mesasal[tiab] OR Pentasa[tiab] OR Rowasa[tiab] OR Asacol*[tiab] OR Ascolitin[tiab] OR Canasa[tiab] OR Salofalk[tiab] OR Claversal[tiab] OR Lixacol[tiab]	3 788
#9	#6 OR #7 OR #8	43 595
#10	#5 AND #9	366
Filter		
#11	#4 AND #10	26
#12	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomised[tiab] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Systematic Review[pt] OR Systematic Review[tiab] OR Systematic[sb] OR Meta-Analysis[pt] OR Meta-Analysis[tiab] OR Meta-Analysis[sb] OR Cochrane Database Syst Rev[Journal]	4 216 274
#13	animals[mh] NOT humans[mh]	4 271 569
#14	#12 NOT #13	3 672 006
#15	#37 AND #40 Filters: German, English; Publication date from 2009/06/01 to 2016/12/07	10

3.3.3 Recherche in Cochrane (12.01.17)

Search Name: CU_AG3_3
Date Run: 12/01/17

ID	Search
#1	MeSH descriptor: [Colitis, Ulcerative] explode all trees
#2	MeSH descriptor: [Inflammatory Bowel Diseases] explode all trees
#3	(remission or maintain* or "long term care" or "long-term" or Care or continu* or prolong* or surveil* or monitor* or stable or stabil* or ((symptom*) and (free or absent or nonpresent))):ti,ab,kw (Word variations have been searched)
#4	(#1 or #2) and #3
#5	"Aminosalicylic Acid" or ASA* or Aminosalicyl* or 5-ASA or Rezipas or Pamisyl or ((meta or para or acid* or salt or monolithium* or monopotassium* or monosodium* Alumino*) and (Aminosalicyl* or ASA))
#6	MeSH descriptor: [Aminosalicylic Acids] explode all trees
#7	MeSH descriptor: [Sulfasalazine] explode all trees
#8	Sulfasalazin* or Sulphasalazin* or Salicylazosulfapyridine or Salazosulfapyridine or Colo-Pleon or "Colo Pleon" or Pleon or "ratio-Sulfasalazine" or "ratio Sulfasalazine" or Ulcol or Ucine or Azulfidine or Azulfadine or Salazopyrin or Pyralin* or Asulfidine or Azulfidin* #9
#9	MeSH descriptor: [Mesalamine] explode all trees
#10	Mesalamin* or (Mesalamin* and (Monosodium or Salt)) or Mesalazine or Fivasa or Mesasal or Pentasa or Rowasa or Asacol* or Ascolitin or Canasa or Salofalk or Claversal or Lixacol
#11	#5 or #6
#12	#7 or #8
#13	#9 or #10
#14	#11 or #12 or #13
#15	MeSH descriptor: [Escherichia coli] explode all trees
#16	Escherichia coli or E.coli or Nissle or 1917 or ECN or "E coli" or EAggEC
#17	#15 or #16
#18	#14 and #17
#19	#4 and #18 Publication Year from 2009

3.3.4 Ergebnis und PRISMA Flow Chart



3.4 Therapieversagen unter Mesalazin

3.4.1 Schlüsselfrage

3.4 Wie kann bei Patienten mit Colitis ulcerosa, die auf Mesalazin nicht adäquat ansprechen, die Remission erhalten werden?

Population: Patienten mit Colitis ulcerosa (Remissionsphase)
Interventions: Azathioprin, anti TNFa Antikörper (Infliximab, Adalimumab, Golimumab) oder Vedolizumab
Comparisons: –
Outcomes: Krankheitsaktivität, scores (MAYO, SCCAI, PUCAI), Quality of life (IBDQ, SIDQ), mucosal healing, adverse events, toxic megacolon, Trough level

3.4.2 Recherche in Pubmed (07.12.2016)

3.4 Wie kann bei Patienten mit Colitis ulcerosa, die auf Mesalazin nicht adäquat ansprechen die Remission erhalten werden?

Nr.	Query	Treffer
#1	Colitis, Ulcerative[MeSH] OR "inflammatory bowel diseases"[MeSH:noexp]	43 939
#2	Idiopathic Proctocolitis[tiab] OR Ulcerative Colitis[tiab] OR Colitis Gravis[tiab]	31 861
#3	remission[tiab] OR maintain*[tiab] OR "long term care"[MeSH] OR "long-term"[tiab] OR Care[tiab] OR continu*[tiab] OR prolong*[tiab] OR surveil*[tiab] OR monitor*[tiab] OR stable[tiab] OR stabil*[tiab] OR ((symptom*[tiab]) AND (free[tiab] OR absent[tiab] OR nonpresent[tiab]))	4 338 414
#4	"Aminosalicylic Acids"[MeSH] OR "Aminosalicylic Acid"[MeSH] OR ASA*[tiab] OR Aminosalicyl*[tiab] OR 5-ASA[tiab] OR Rezipas[tiab] OR Pamisyl[tiab] OR ((meta[tiab] OR para[tiab] OR acid*[tiab] OR salt[tiab] OR monolithium*[tiab] OR monopotassium*[tiab] OR monosodium*[tiab] Alumino*[tiab]) AND (Aminosalicyl*[tiab] OR ASA[tiab])	38 274
#5	Sulfasalazine[MeSH] OR Sulfasalazin*[tiab] OR Sulphasalazin*[tiab] OR Salicylazosulfapyridine[tiab]OR Salazosulfapyridine[tiab] OR Colo-Pleon[tiab] OR "Colo Pleon"[tiab] OR Pleon[tiab] OR "ratio-Sulfasalazine"[tiab] OR "ratio Sulfasalazine"[tiab] OR Ulcol[tiab] OR Ucine[tiab] OR Azulfidine[tiab] OR Azulfadine[tiab] OR Salazopyrin OR Pyralin*[tiab] OR Asulfidine[tiab] OR Azulfidin*[tiab]	5 722
#6	Mesalamine[MeSH] OR Mesalamin*[tiab] OR (Mesalamin*[tiab] AND (Monosodium[tiab] OR Salt[tiab])) OR Mesalazine[tiab] OR Fivasa[tiab] OR Mesasal[tiab] OR Pentasa[tiab] OR Rowasa[tiab] OR Asacol*[tiab] OR Ascolitin[tiab] OR Canasa[tiab] OR Salofalk[tiab] OR Claversal[tiab] OR Lixacol[tiab]	3 788
#7	"Treatment Failure"[MeSH] OR "Treatment Failure"[tiab] OR (fail*[tiab] AND (Treat*[tiab] OR interven*[tiab])) OR alternative[tiab] NOT "Complementary Therapies"[MeSH]	738 701
#8	(#1 OR #2) AND 3	11 145
#9	(#4 OR #5 OR #6) AND #7	2 460
#10	#8 AND #9	243
Interventionen		
#11	"Receptors, Lysosphingolipid"[MeSH] OR ((sphingosin*[tiab]) AND (phosphat*[tiab] OR receptor*[tiab])) OR S1P [tiab] OR Ozanimod [Supplementary Concept] OR Ozanimod[tiab] OR RPC1063[tiab] OR Etrasimod[tiab] OR APD334[tiab]	6 279
#12	("CT-P13"[Supplementary Concept] OR "CT-P13"[tiab] OR CTP13[tiab] OR inflectra[tiab] OR SB2[tiab] OR Remsima [tiab] OR Flixabi[tiab] OR "Biosimilar Pharmaceuticals"[MeSH] OR "Pharmaceuticals, Biosimilar"[tiab] OR Biosimilar*[tiab])	1 863
#13	("Infliximab"[MeSH] OR infliximab[tiab] OR "MAb cA2"[tiab] OR "Monoclonal Antibody cA2"[tiab] OR "Antibody cA2, Monoclonal"[tiab] OR"cA2, Monoclonal Antibody"[tiab] OR "Remicade"[tiab] OR originator[tiab])	12 036
#14	"Adalimumab"[MeSH] OR Adalimumab[tiab] OR "D2E7 Antibody"[tiab] OR Humira[tiab]	5 577
#15	etrolizumab[tiab] OR "rhuMAb Beta7" [Supplementary Concept] OR "rhuMAb Beta7"[tiab] OR PRO145 223[tiab]	34
#16	golimumab [Supplementary Concept] OR golimumab[tiab] OR Simponi[tiab]	679
#17	"vedolizumab" [Supplementary Concept] OR Vedolizumab[tiab] OR Entyvio[tiab] OR MLN0002[tiab]	262
#18	Janus Kinases[MeSH] OR JAK*[tiab] OR "janus kinase"[tiab] OR janus-kinase[tiab]	24 684
#19	Filgotinib[tiab] OR GLPG0634[tiab]	15
#20	Tofacitinib [Supplementary Concept] OR tofacitinib[tiab] OR tasocitinib[tiab] OR Xeljanz[tiab] OR Jakvinus[tiab] OR "CP 690,550"[tiab] OR CP690 550[tiab] OR "CP-690 550"[tiab] OR "CP 690 550"[tiab] OR "CP-690,550"[tiab]	539

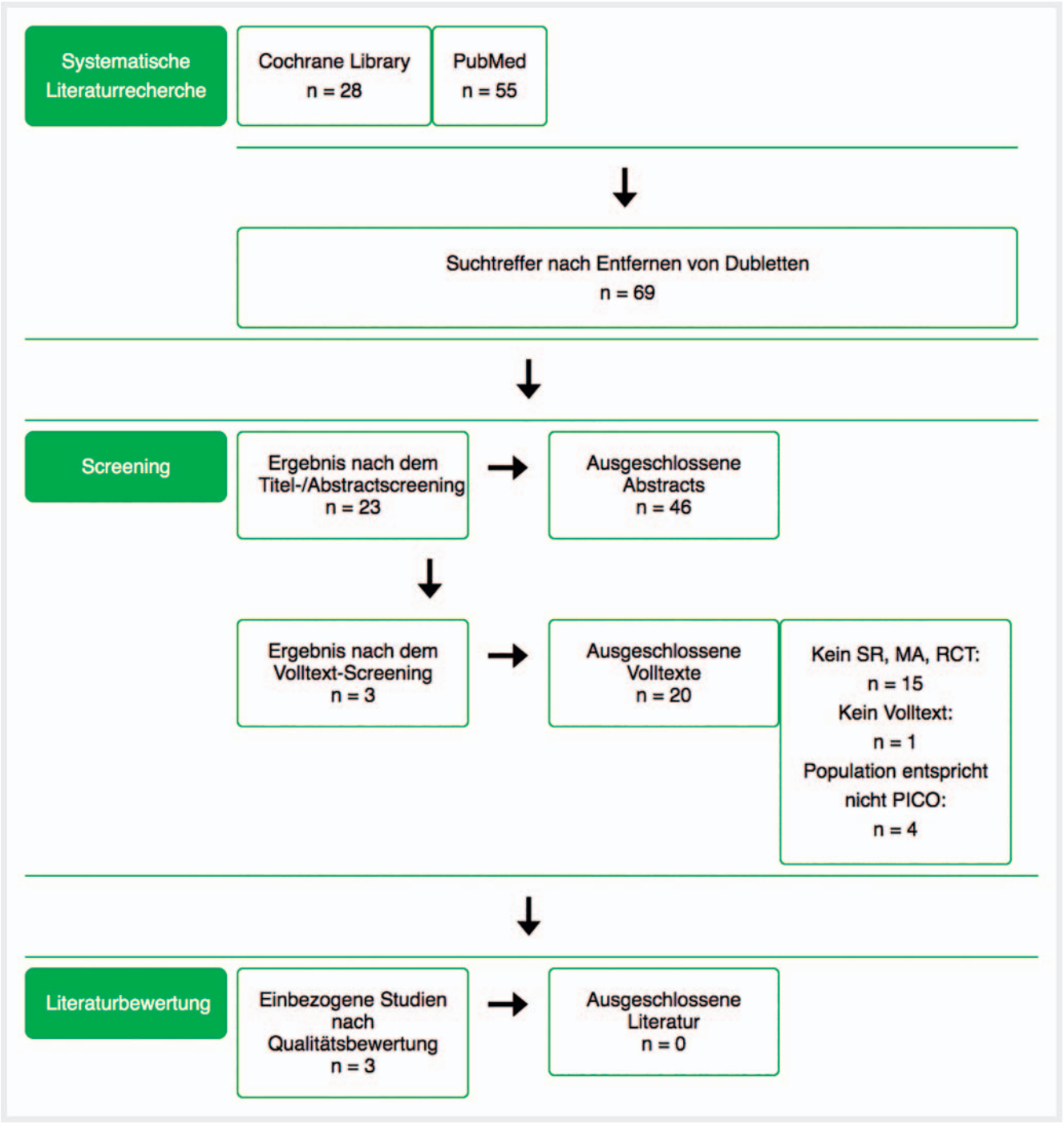
3.4 Wie kann bei Patienten mit Colitis ulcerosa, die auf Mesalazin nicht adäquat ansprechen die Remission erhalten werden?		
Nr.	**Query**	**Treffer**
#21	Glucocorticoids[MeSH] OR glucocorticoid*[tiab] OR "Glucocorticoid Effect*"[tiab] OR steroid*[tiab] OR corticoid*[tiab] OR ((cortico*[tiab] OR hormone[tiab] OR generation[tiab]) AND steroid*[tiab])	286 312
#22	Beclomethasone[MeSH] OR Beclomethason*[tiab] OR Beclometason*[tiab] OR ((Beclomethasone[tiab] OR Beclometason[tiab]) AND Dipropionate[tiab])) OR Beclamet[tiab] OR "Beclo Asma"[tiab] OR "Beclo AZU"[tiab] OR Beclocort[tiab] OR Beclomet[tiab] OR OR Beclorhinol[tiab] OR Becloturmant[tiab] OR Sanasthmax[tiab] OR Beclovent[tiab] OR Beconase[tiab] OR Becloforte[tiab] OR Becodisk[tiab] OR Becotide[tiab] OR Propaderm[tiab] OR Sanasthmyl[tiab] OR Becodisks[tiab] OR "Beconase AQ"[tiab] OR Bronchocort[tiab] OR Junik[tiab] OR Qvar[tiab] OR Aerobec*[tiab] OR Beclazone*[tiab] OR Ecobec[tiab] OR Filair*[tiab] OR "Nasobec Aqueous"[tiab] OR Prolair[tiab] OR "Respocort"[tiab] OR Ventolair[tiab] OR Vancenase[tiab] OR Vanceril[tiab] OR Aldecin[tiab] OR Viarin[tiab] OR "Apo-Beclomethasone"[tiab]	3 728
#23	Dexamethasone[MeSH] OR Dexamethason*[tiab] OR Dexametason*[tiab] OR Hexadecadrol[tiab] OR Methylfluorprednisolone[tiab] OR Decameth[tiab] OR Decaspray[tiab] OR Dexasone[tiab] OR Dexpak[tiab] OR Maxidex[tiab] OR Millicorten[tiab] OR Oradexon[tiab] OR Decaject[tiab] OR Decaject*[tiab] OR Hexadrol[tiab]	63 579
#24	Budesonide[MeSH] OR Budesonid*[tiab] OR Pulmicort[tiab] OR MMX[tiab] OR Horacort[tiab] OR Rhinocort[tiab]	5 519
#25	Cyclosporine[MeSH] OR cyclosporin*[tiab] OR Ciclosporin*[tiab] OR Neoral[tiab] OR CyA-NOF[tiab] OR "CyA NOF"[tiab] OR Sandimmun*[tiab] OR CsA-Neoral[tiab] OR "CsA Neoral" OR CsANeoral[tiab] OR "OL 27 – 400"[tiab] OR "OL 27 400"[tiab] OR "OL 27 400"[tiab]	55 045
#26	Methotrexate[MeSH] OR Methotrexate[tiab] OR Amethopterin[tiab] OR Mexate[tiab]	47 499
#27	Tacrolimus[MeSH] OR tacrolimus[tiab] OR Prograf*[tiab] OR "FR-900 506"[tiab] OR "FR 900 506"[tiab] OR FR900 506[tiab] OR"FK-506"[tiab] OR "FK 506"[tiab] OR "FK506"[tiab]	21 649
#28	"Purines"[MeSH] OR Purin*[tiab]	489 896
#29	Phosphatidylcholines[MeSH] Or phosphatidylcholin*[tiab] OR ((cholin*[tiab]) AND (phosphoglycerid[tiab] OR glycero*[tiab])) OR lecithin*[tiab]	58 424
#30	"Leukapheresis"[MeSH] OR Leukapher*[tiab] OR Leukocytopher*[tiab] OR Leukopher*[tiab] OR Leukocytapher*[tiab] OR Lymphapher*[tiab] OR Lymphocytopher*[tiab] OR Lymphopher*[tiab] OR Lymphocytapher*[tiab]	4 414
#31	"Fecal Microbiota Transplantation"[MeSH] OR (Fecal[tiab] OR intestinal[tiab] OR microbiot*[tiab]) AND (Transplant*[tiab] OR transfer*[tiab])) OR ((Transplantation*[tiab] OR transfer[tiab] OR Donor[tiab] OR Infusion[tiab]) AND Feces[tiab])	13 629
#32	Probiotics[MeSH] OR probiotic*[tiab]	17 509
#33	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #27 OR#28 OR #29 OR#30 OR #31 OR #32	1 029 054
Suchzeitraum		
#34	#10 AND #33	141
#35	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomised[tiab] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Systematic Review[pt] OR Systematic Review[tiab] OR Systematic[sb] OR Meta-Analysis[pt] OR Meta-Analysis[tiab] OR Meta-Analysis[sb] OR Cochrane Database Syst Rev[Journal]	4 216 274
#36	animals[mh] NOT humans[mh]	4 271 569
#37	#35 NOT #36	3 672 006
#38	#34 AND #37 Filters: German, English; Publication date from 2009/06/01 to 2016/12/07	50

3.4.3 Recherche in Cochrane (12.01.17)

Search Name: CU_AG3_4
Date Run: 12/01/17

ID	Search
#1	MeSH descriptor: [Colitis, Ulcerative] explode all trees
#2	MeSH descriptor: [Inflammatory Bowel Diseases] explode all trees
#3	(remission or maintain* or "long term care" or "long-term" or Care or continu* or prolong* or surveil* or monitor* or stable or stabil* or ((symptom*) and (free or absent or nonpresent))):ti,ab,kw (Word variations have been searched)
#4	(#1 or #2) and #3
#5	MeSH descriptor: [Treatment Failure] explode all trees
#6	"Treatment Failure" or (fail* and (Treat* or interven*)) or alternative:ti,ab,kw (Word variations have been searched)
#7	"Aminosalicylic Acid" or ASA* or Aminosalicyl* or 5-ASA or Rezipas or Pamisyl or ((meta or para or acid* or salt or monolithium* or monopotassium* or monosodium* Alumino*) and (Aminosalicyl* or ASA))
#8	MeSH descriptor: [Aminosalicylic Acids] explode all trees
#9	MeSH descriptor: [Sulfasalazine] explode all trees
#10	Sulfasalazin* or Sulphasalazin* or Salicylazosulfapyridine or Salazosulfapyridine or Colo-Pleon or "Colo Pleon" or Pleon or "ratio-Sulfasalazine" or "ratio Sulfasalazine" or Ulcol or Ucine or Azulfidine or Azulfadine or Salazopyrin or Pyralin* or Asulfidine or Azulfidin*
#11	MeSH descriptor: [Mesalamine] explode all trees
#12	Mesalamin* or (Mesalamin* and (Monosodium or Salt)) or Mesalazine or Fivasa or Mesasal or Pentasa or Rowasa or Asacol* or Ascolitin or Canasa or Salofalk or Claversal or Lixacol #13
#13	#5 or #6
#14	#7 or #8 or #9 or #10 or #11 or #12
#15	#13 and #14
#16	#4 and #15 Publication Year from 2009

3.4.4 Ergebnis und PRISMA Flow Chart



3.5 Biosimilar Infliximab

3.5.1 Schlüsselfrage

3.5 Kann bei Patienten mit Colitis ulcerosa die Remission mit Biosimilar Infliximab genauso gut erhalten werden wie mit Originator Infliximab?

Population: Patienten mit Colitis ulcerosa (Remissionsphase), Nichtansprechen auf Mesalazin
Interventions: Azathioprin, anti TNFa Antikörper (Infliximab, Adalimumab, Golimumab) oder Vedolizumab
Comparisons: –
Outcomes: Krankheitsaktivität, scores (MAYO, SCCAI, PUCAI), Quality of life (IBDQ, SIDQ), mucosal healing, adverse events, toxic megacolon, Trough level

3.5.2 Recherche in Pubmed (07.12.2016)

3.5 Kann bei Patienten mit Colitis ulcerosa die Remission mit Biosimilar Infliximab genauso gut erhalten werden wie mit Originator Infliximab?

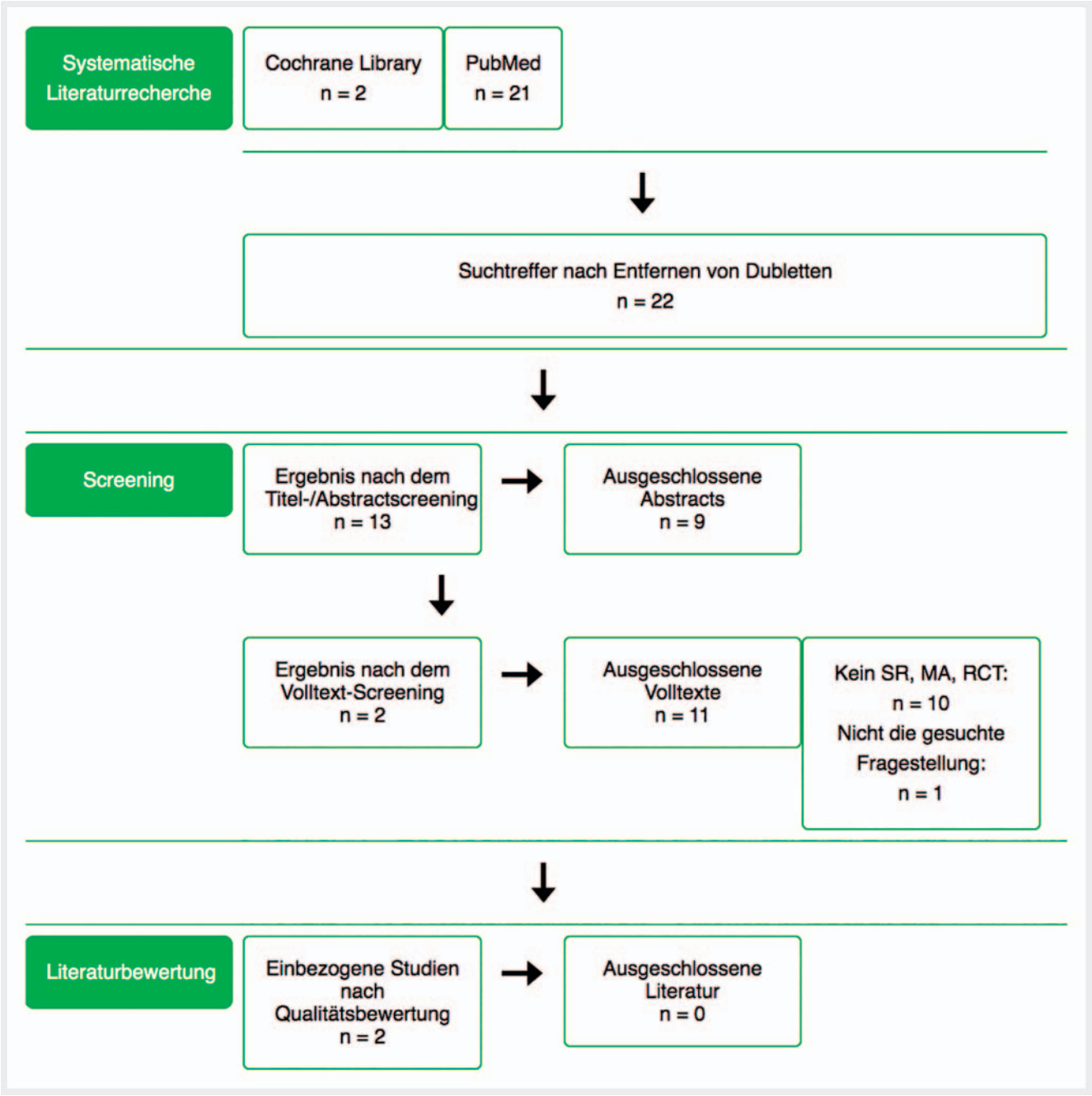
Nr.	Query	Treffer
#1	Colitis, Ulcerative[MeSH] OR "inflammatory bowel diseases"[MeSH:noexp]	43 939
#2	Idiopathic Proctocolitis[tiab] OR Ulcerative Colitis[tiab] OR Colitis Gravis[tiab]	31 840
#3	remission[tiab] OR maintain*[tiab] OR "long term care"[MeSH] OR "long-term"[tiab] OR Care[tiab] OR continu*[tiab] OR prolong*[tiab] OR surveil*[tiab] OR monitor*[tiab] OR stable[tiab] OR stabil*[tiab] OR ((symptom*[tiab]) AND (free[tiab] OR absent[tiab] OR nonpresent[tiab]))	4 338 414
#4	(#1 OR #2) AND 3	11 145
Interventionen		
#5	"CT-P13"[Supplementary Concept] OR "CT-P13"[tiab] OR CTP13[tiab] OR inflectra[tiab] OR SB2[tiab] OR Remsima[tiab] OR Flixabi[tiab] OR "Biosimilar Pharmaceuticals"[MeSH] OR "Pharmaceuticals, Biosimilar"[tiab] OR Biosimilar*[tiab]	1863
#6	"Infliximab"[MeSH] OR infliximab[tiab] OR "MAb cA2"[tiab] OR "Monoclonal Antibody cA2"[tiab] OR "Antibody cA2, Monoclonal"[tiab] OR"cA2, Monoclonal Antibody"[tiab] OR "Remicade"[tiab] OR originator[tiab]	12 036
#7	#5 AND #6	308
Filter		
#8	#4 AND #7	32
#9	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomised[tiab] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Systematic Review[pt] OR Systematic Review[tiab] OR Systematic[sb] OR Meta-Analysis[pt] OR Meta-Analysis[tiab] OR Meta-Analysis[sb] OR Cochrane Database Syst Rev[Journal]	4 214 861
#10	animals[mh] NOT humans[mh]	4 271 569
#11	#9 NOT #10	3 672 006
#12	#8 AND #11 Filters: German, English; Publication date from 2009/06/01 to 2016/12/07	21

3.5.3 Recherche in Cochrane (12.01.17)

Search Name: CU_AG3_5
Date Run: 12/01/17

ID	Search
#1	MeSH descriptor: [Colitis, Ulcerative] explode all trees
#2	MeSH descriptor: [Inflammatory Bowel Diseases] explode all trees
#3	(remission or maintain* or "long term care" or "long-term" or Care or continu* or prolong* or surveil* or monitor* or stable or stabil* or ((symptom*) and (free or absent or nonpresent))):ti,ab,kw (Word variations have been searched)
#4	(#1 or #2) and #3
#5	MeSH descriptor: [Infliximab] explode all trees
#6	MeSH descriptor: [Biosimilar Pharmaceuticals] explode all trees
#7	infliximab or "MAb cA2" or "Monoclonal Antibody cA2" or Remicade or originator
#8	"CT-P13" or CTP13 or inflectra or SB2 or Remsima or Flixabi or Biosimilar*
#9	#5 or #7
#10	#6 or #8
#11	#9 and #10
#12	#4 and #11 Publication Year from 2009

3.5.4 Ergebnis und PRISMA Flow Chart



3.6 Erhaltungstherapie bei Proktitis

3.6.1 Schlüsselfrage

3.6 Wie sollte die Erhaltungstherapie bei Proktitis durchgeführt werden?

Population: Patienten mit Proktitis
Interventions: Erhaltungsttherapie
Comparisons: –
Outcomes: Krankheitsaktivität, scores (MAYO, SCCAI, PUCAI), Quality of life (IBDQ, SIDQ), mucosal healing, adverse events, toxic megacolon, Trough level

3.6.2 Recherche in Pubmed (07.12.2016)

3.6 Wie kann die Erhaltungstherapie bei Proktitis durchgeführt werden?

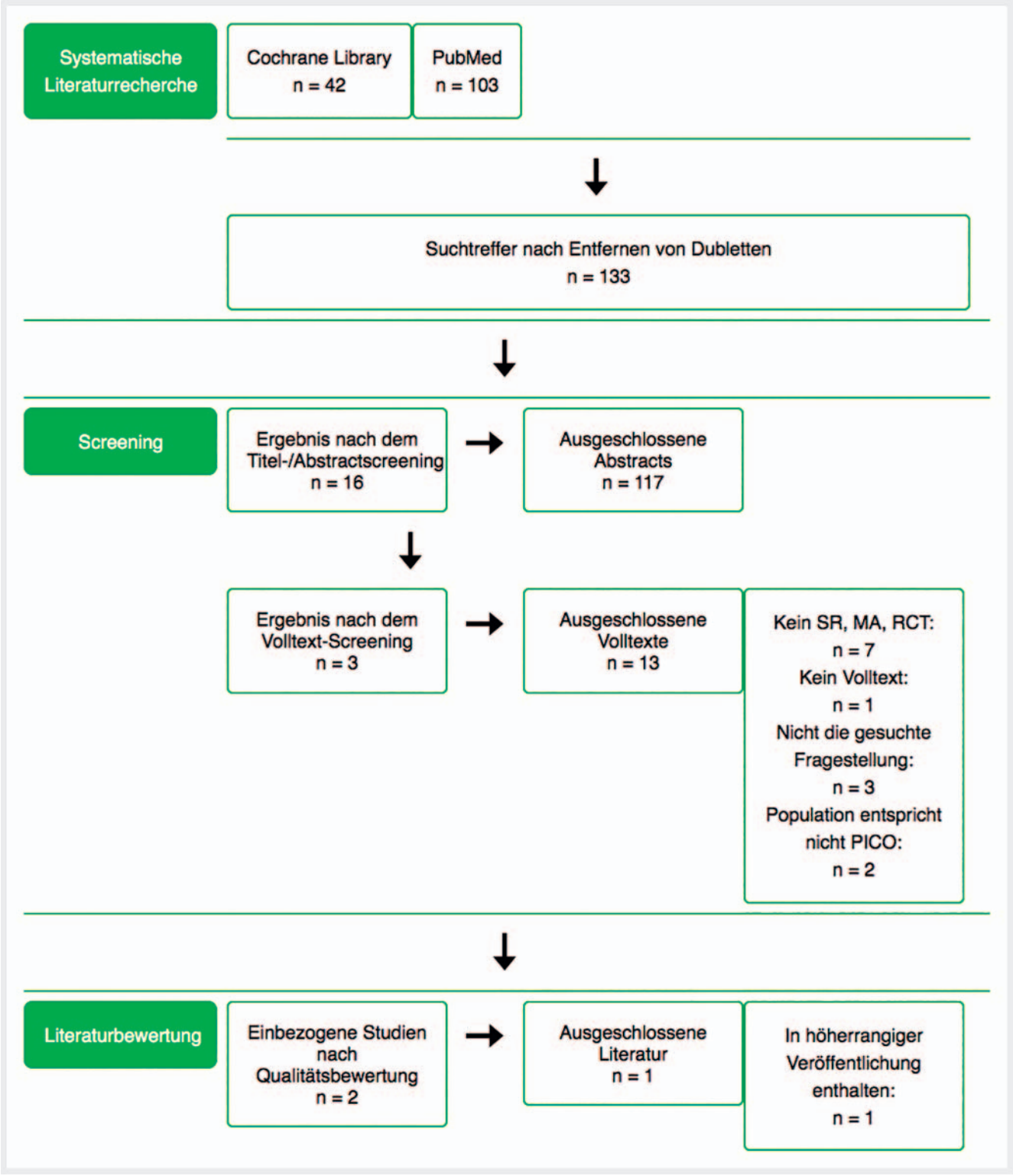
Nr.	Query	Treffer
#1	Colitis, Ulcerative[MeSH] OR "inflammatory bowel diseases"[MeSH:noexp]	43 939
#2	Idiopathic Proctocolitis[tiab] OR Ulcerative Colitis[tiab] OR Colitis Gravis[tiab]	31 840
#3	remission[tiab] OR maintain*[tiab] OR "long term care"[MeSH] OR "long-term"[tiab] OR Care[tiab] OR continu*[tiab] OR prolong*[tiab] OR surveil*[tiab] OR monitor*[tiab] OR stable[tiab] OR stabil*[tiab] OR ((symptom*[tiab]) AND (free[tiab] OR absent[tiab] OR nonpresent[tiab]))	4 364 163
#4	"Proctitis"[MeSH] OR proctitis[tiab] OR proctitides[tiab] OR ((rectal*[tiab] OR rectum[tiab] OR rectum [MeSH]) AND (inflammat*[tiab] OR inflammation[MeSH])	10 270
#5	(#1 OR #2) AND #3 AND #4	726
Filter		
#6	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomised[tiab] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Systematic Review[pt] OR Systematic Review[tiab] OR Systematic[sb] OR Meta-Analysis[pt] OR Meta-Analysis[tiab] OR Meta-Analysis[sb] OR Cochrane Database Syst Rev[Journal]	4 214 861
#7	animals[mh] NOT humans[mh]	4 271 569
#8	#6 NOT #7	3 670 593
#9	#5 AND #8 Filters: German, English; Publication date from 2009/06/01 to 2016/12/07	103

3.6.3 Recherche in Cochrane (12.01.17)

Search Name: CU_AG3_6
Date Run: 12/01/17

ID	Search
#1	MeSH descriptor: [Colitis, Ulcerative] explode all trees
#2	MeSH descriptor: [Inflammatory Bowel Diseases] explode all trees
#3	maintenance or remission
#4	MeSH descriptor: [Proctitis] explode all trees
#5	rectal or rectum and inflammation
#6	#4 or #5
<#7	(#1 or #2) and #3 and #6 Publication Year from 2009

3.6.4 Ergebnis und PRISMA Flow Chart



3.7 Therapieziel

3.7.1 Schlüsselfrage

3.7 Sollte bei endoskopischer Remission und fehlenden Zeichen einer Entzündung bei klinischen Beschwerden eine Therapiemodifikation erfolgen?

Population: Patienten mit Colitis ulcerosa, endoskopische Remissionsphase, keine Anzeichen von Entzündung, aber klinische Symptome
Interventions: Therapiemodifikation
Comparisons: keine Therapiemodifikation
Outcomes: Krankheitsaktivität, scores (MAYO, SCCAI, PUCAI), Quality of life (IBDQ, SIDQ), mucosal healing, adverse events

3.7.2 Recherche in Pubmed (07.12.2016)

3.7 Sollte bei endoskopischer Remission und fehlenden Zeichen einer Entzündung bei klinischen Beschwerden (z. B. Durchfall) eine Therapiemodifikation erfolgen?

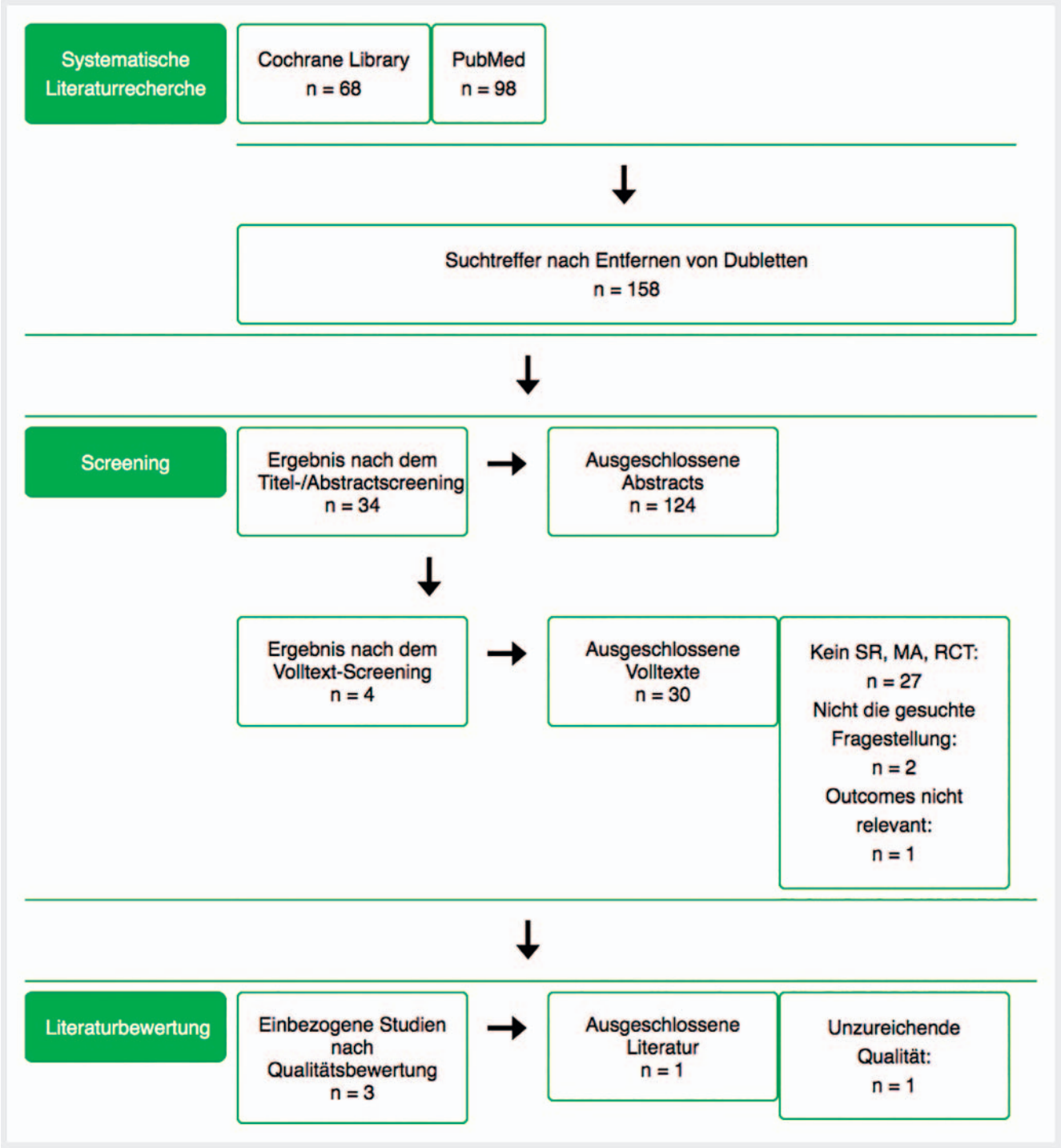
Nr.	Query	Treffer
#1	Colitis, Ulcerative[MeSH] OR "inflammatory bowel diseases"[MeSH:noexp])	43 939
#2	(Idiopathic Proctocolitis[tiab] OR Ulcerative Colitis[tiab] OR Colitis Gravis[tiab])	31 861
#3	remission[tiab] OR maintain*[tiab] OR "long term care"[MeSH] OR "long-term"[tiab] OR Care[tiab] OR continu*[tiab] OR prolong*[tiab] OR surveil*[tiab] OR monitor*[tiab] OR stable[tiab] OR stabil*[tiab] OR ((symptom*[tiab]) AND (free[tiab] OR absent[tiab] OR nonpresent[tiab]))	4 338 414
#4	((endoscop*[tiab] OR colonosc*[tiab]) AND remission[tiab]) OR (inflammation[tiab] AND (absence[tiab]))	15 358
#5	symptoms[tiab] OR diarrhoe[tiab] OR "Abdominal Pain"[MeSH] OR "abdominal pain"[tiab] OR cramp*[tiab] OR "Muscle Cramp"[MeSH] OR "Gastrointestinal Hemorrhage"[MeSH] OR "rectal bleeding"[tiab]	795 841
#6	(#1 OR #2) AND #3 AND #4 AND #5	223
Filter		
#7	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomised[tiab] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Systematic Review[pt] OR Systematic Review[tiab] OR Systematic[sb] OR Meta-Analysis[pt] OR Meta-Analysis[tiab] OR Meta-Analysis[sb] OR Cochrane Database Syst Rev[Journal]	4 214 861
#8	animals[mh] NOT humans[mh]	4 271 569
#9	#7 NOT #8	3 670 593
#13	#6 AND #9 Filters: German, English; Publication date from 2009/06/01 to 2016/12/07	67

3.7.3 Recherche in Cochrane (12.01.2017)

Search Name: CU_AG3_7
Date Run: 12/01/17 15:35:08.270

ID	Search
#1	MeSH descriptor: [Colitis, Ulcerative] explode all trees
#2	maintenance or remission
#3	signs or symptoms or diarrhea or pain or cramp or rectal bleeding
#4	MeSH descriptor: [Signs and Symptoms, Digestive] explode all trees
#5	MeSH descriptor: [Diarrhea] explode all trees
#6	MeSH descriptor: [Abdominal Pain] explode all trees
#7	MeSH descriptor: [Gastrointestinal Hemorrhage] explode all trees
#8	(urge or sudden) and (defec* or stool) or tenesmus
#9	(#1 and #2) and (#3 or #4 or #5 or #6 or #7 or #8) Publication Year from 2009

3.7.4 Ergebnis und PRISMA Flow Chart



4. Recherchen zum Thema „Infektionen“

4.1 Schlüsselfrage

4. Welche diagnostischen Verfahren sind effektiv zur Prophylaxe, Identifikation und Therapie von Infektionen?

Population: Untersuchte Personen mit CU, Neugeborene, die in der Schwangerschaft TNF-AK ausgesetzt waren
Interventions: Immunosuppression, immunosuppressive, immunocompromised, CMV, EBV, Azathioprin, clostridium difficile, Cotrimoxazol, PCP-Prophylaxe, tuberculosis, herpes zoster, viral, vaccination, FMT, complications, hepatitis, pneumonia, salmonella, campylobacter, shigella, norovirus, rota virus, opportunistic infections, prevention, Stuhldiagnostik bei Diarrhoe unter Immunsuppression, Kombinationstherapien
Comparisons: –
Outcomes: Krankheitsaktivität, scores (MAYO, SCCAI, PUCAI), Quality of life (IBDQ, SIDQ), mucosal healing, adverse events, diagnostische Genauigkeit (Sensitivität, Spezifität, positiver oder negativer prädiktiver Wert)

4.2 Recherche in PubMed (04.01.2017)

Welche diagnostischen Verfahren sind effektiv zur Identifikation von Infektionen?

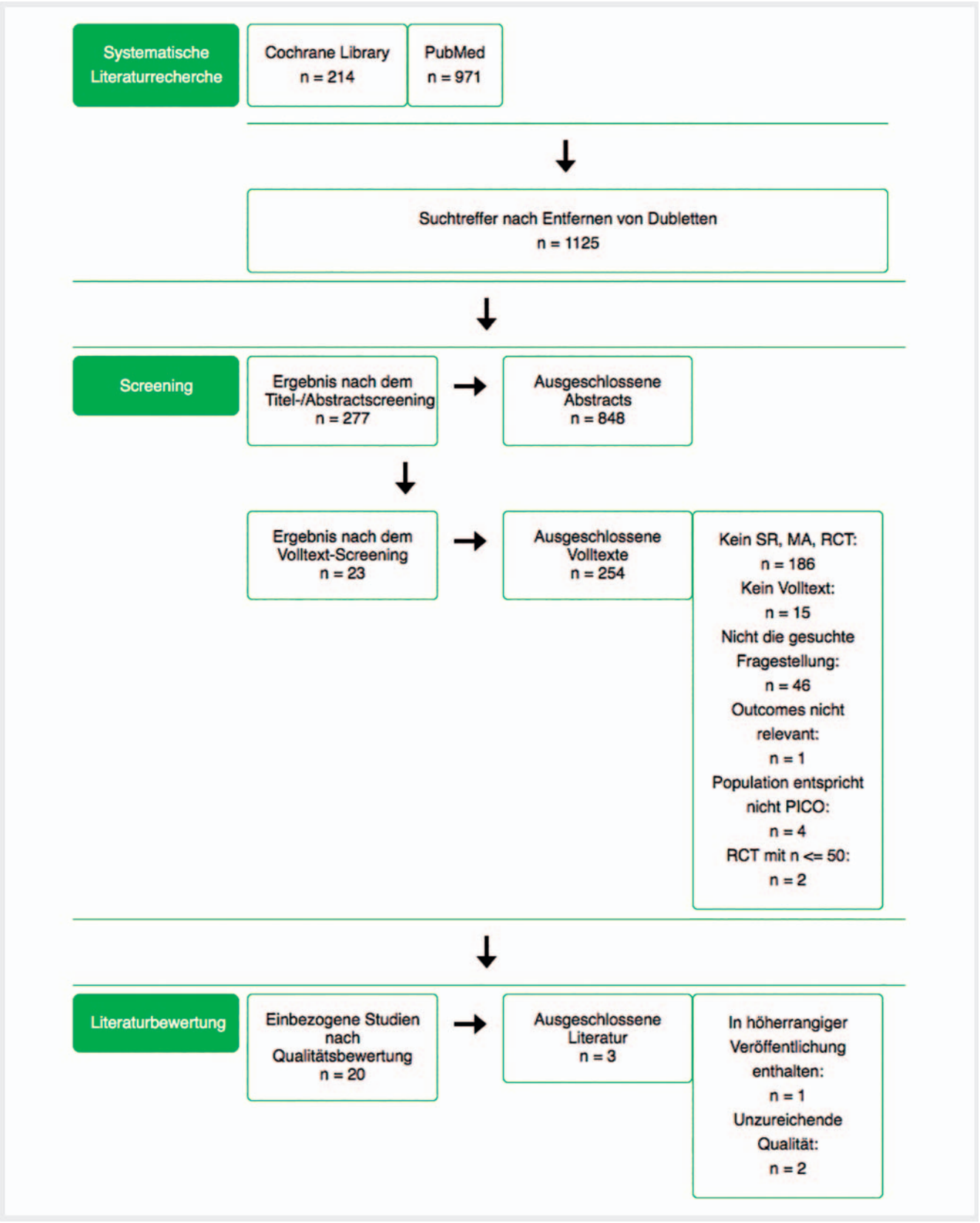
Nr.	Query	Treffer
#1	Colitis, Ulcerative[MeSH] OR "inflammatory bowel diseases"[MeSH:noexp]	44 221
#2	Idiopathic Proctocolitis[tiab] OR Ulcerative Colitis[tiab] OR Colitis Gravis[tiab]	31 976
#3	#1 OR #2	51 230
#4	Infection[MeSH] OR infect*[tiab]	1 840 822
#5	Campylobacter[MeSH] OR Campylobacter[tiab] OR Shigella[MeSH] OR Shigella[tiab] OR Opportunistic Infections [MeSH] OR Salmonella[MeSH] OR Salmonella[tiab]	135 155
#6	Viruses[MeSH] OR Virus*[tiab] OR Viral*[tiab] OR Norovirus[MeSH] OR Norovirus*[tiab] OR Rotavirus[MeSH] OR Rotavirus*[tiab] OR Hepatitis[MeSH] OR Hepatiti*[tiab]	1 062 286
#7	Cytomegalovirus[MeSH] OR Cytomegalovirus*[tiab] OR CMV[tiab] OR HCMV[tiab] OR (Salivary[tiab] AND Gland[tiab] AND Virus*[tiab]) OR "Human Herpesvirus 5"[tiab] OR HHV 5[tiab]	47 803
#8	Clostridium[MeSH] OR Clostridi*[tiab] OR C. difficile[tiab]	41 558
#9	Vaccination[MeSH] OR Vaccinat*[tiab] OR Immunization*[tiab]	208 422
#10	Epstein-Barr Virus Infections[MeSH] OR Epstein-Barr Virus*[tiab] OR Herpesvirus 4[tiab] OR EBV Infection*[tiab]	43 102
#11	Herpes zoster[MeSH] OR Zona[tiab] OR Zoster[tiab] OR Shingles[tiab]	30 010
#12	Tuberculosis[MeSH] OR Tuberculos*[tiab]	226 901
#13	Pneumonia[MeSH] OR Pneumonia*[tiab] OR Lung Inflammation[tiab]	173 702
#14	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	2 859 044
#15	#3 AND #14	6 378
#16	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomised[tiab] OR randomized[tiab] OR placebo [tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Systematic Review[pt] OR Systematic Review[tiab] OR Systematic[sb] OR Meta-Analysis[pt] OR Meta-Analysis[tiab] OR Meta-Analysis[sb] OR Cochrane Database Syst Rev[Journal]	4 245 232
#17	animals[mh] NOT humans[mh]	4 285 703
#18	#16 NOT #17	3 697 620
#19	#15 AND #18 Filters: German, English; Publication date from 2009/06/01 to 2017/01/04	971

4.3 Recherche in Cochrane (04.01.2017)

Search Name: CU_AG4
Date Run: 04/01/17 09:23:35.69

ID	Search	Hits
#1	[mh "Colitis, Ulcerative"] or Ulcerative Colitis:ti,ab,kw	2115
#2	[mh Infection] or infect*:ti,ab,kw	80 073
#3	[mh Campylobacter] or Campylobacter or [mh Shigella] or Shigella or [mh "Opportunistic Infections"] or [mh Salmonella] or Salmonella:ti,ab,kw	1972
#4	[mh Viruses] or Virus* or Viral* or [mh Norovirus] or Norovirus* or [mh Rotavirus] or Rotavirus* or [mh Hepatitis] or Hepatiti*:ti,ab,kw	33 861
#5	[mh Cytomegalovirus] or Cytomegalovirus* or CMV or HCMV or (Salivary and Gland and Virus*) or "Human Herpesvirus 5" or HHV 5:ti,ab,kw	1997
#6	[mh Clostridium] or Clostridi* or C. difficile:ti,ab,kw	1405
#7	[mh Vaccination] or Vaccinat* or Immunization*:ti,ab,kw	11 868
#8	[mh "Epstein-Barr Virus Infections"] or Epstein-Barr Virus* or Herpesvirus 4 or EBV Infection*:ti,ab,kw	627
#9	[mh "Herpes zoster"] or Zona or Zoster or Shingles:ti,ab,kw	1710
#10	[mh Tuberculosis] or Tuberculos*:ti,ab,kw	4327
#11	[mh Pneumonia] or Pneumonia* or Lung Inflammation:ti,ab,kw	13 013
#12	#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11	110 688
#13	#1 and #12 Publication Year from 2009, n Cochrane Reviews (Reviews only), Other Reviews, Trials and Technology Assessments	210

4.4 Ergebnis und PRISMA Flow Chart



5. Recherchen zum Thema „Chirurgie/ Pouchitis“

5.1 Chirugie

5.1.1 Schlüsselfrage

5.1 Wie sollte das chirurgische Vorgehen einer Proktokolektomie am besten gestaltet sein?

Population: CU-Patienten mit Indikation zur Proktokolektomie
Interventions: High-volume-Zentren, laparoskopische Proktokolektomie, primär mit Stoma, darmnahe Rektumresektion
Comparisons: Spezialisierte Zentren, Krankenhäuser der Regelversorgung? offene Proktokolektomie, primär ohne Stoma, Resektion in der TME-Schicht
Outcomes: Mortalität, Quality of Life, Morbidität, Komplikationsrate, Pouchitis, Pouchfunktion, Poucherhalt.

5.1.2 Recherche in PubMed (13.12.2016)

5.1 Wie sollte das chirurgische Vorgehen am besten gestaltet sein?

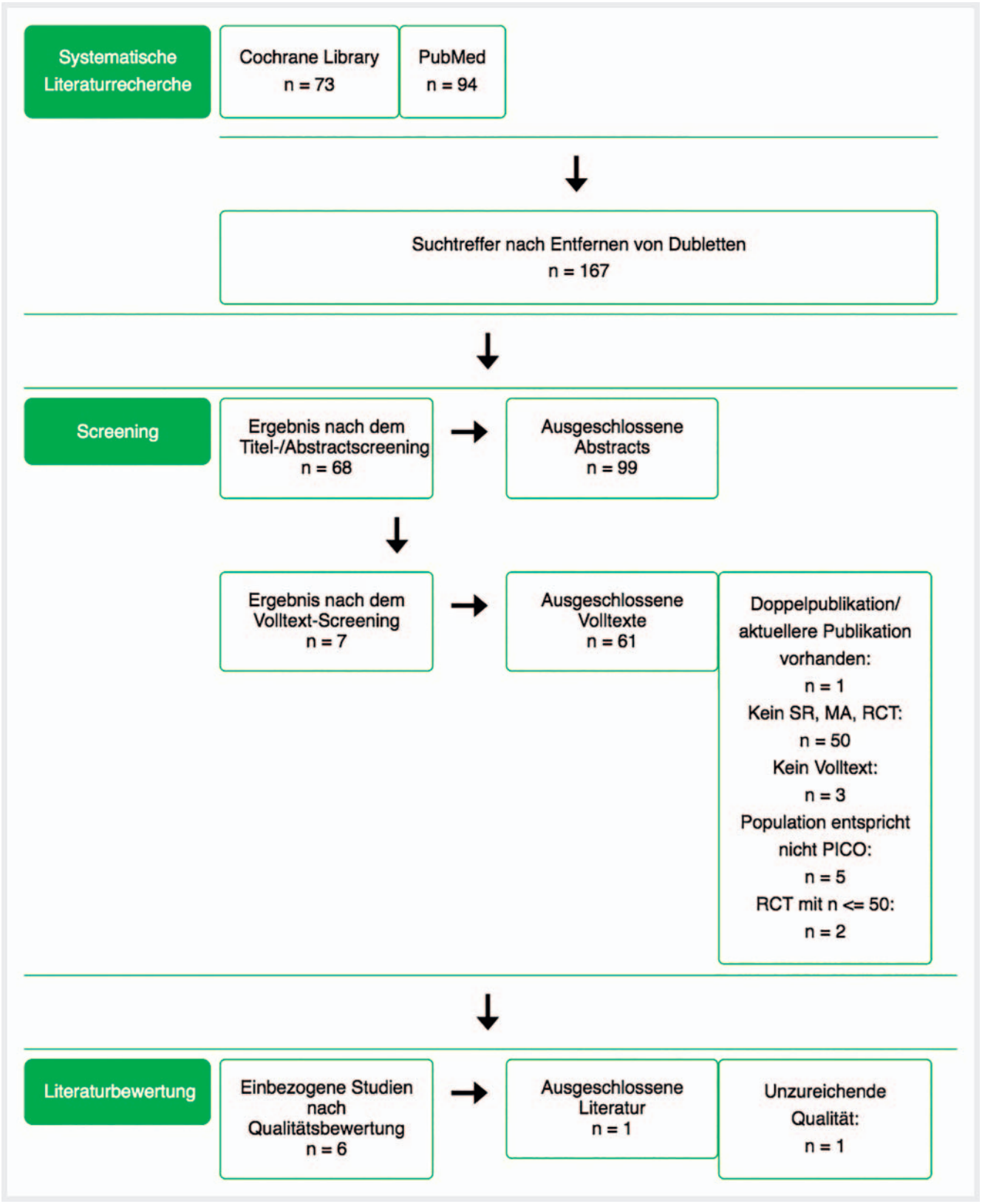
Nr.	Query	Treffer
#1	Colitis, Ulcerative[MeSH] OR "inflammatory bowel diseases"[MeSH:noexp]	43 939
#2	Idiopathic Proctocolitis[tiab] OR Ulcerative Colitis[tiab] OR Colitis Gravis[tiab]	31 861
#3	#1 OR #2	51 066
#4	Digestive System Surgical Procedures[MeSH] OR Surg*[tiab] OR Proctocolectomy, Restorative[MeSH] OR Proctocolectom*[tiab] OR Coloproctectom*[tiab] OR Colonic Pouches[MeSH] OR (Colon*[tiab] AND (Pouch[tiab] OR Pouches[tiab]))	1 836 782
#5	Hospitals, High-Volume[MeSH] OR Hospitals, Low-Volume[MeSH] OR (Volume[tiab] AND Hospital*[tiab])	26 244
#6	Hospitals, Special[MeSH] OR (Special*[tiab] AND Hospital*[tiab])	107 014
#7	Hospitals, General[MeSH] OR (General[tiab] AND Hospital*[tiab])	103 290
#8	#5 AND (#6 OR #7)	3 738
#9	#6 AND (#5 OR #7)	13 923
#10	#7 AND (#5 OR #6)	14 456
#11	Open[tiab] AND (Minimally Invasive Surgical Procedures[MeSH] OR (Minimal*[tiab] OR Surg*[tiab]) OR Laparoscopi*[tiab])	96 461
#12	Surgical Stomas[MeSH] OR Stoma*[tiab]	149 941
#13	((Mesorectal*[tiab] OR Mesenterial*[tiab]) AND (Excision*[tiab] OR Extirpation*[tiab])) OR TME[tiab]	3 368
#14	(Rectum[MeSH] OR rectal*[tiab] OR rectum[tiab]) AND (eversion*[tiab] OR resect*[tiab])	76 248
#15	#13 AND #14	1 511
#16	"Endoscopic Mucosal Resection"[MeSH] OR Mucosectom*[tiab] OR Mucotom*[tiab] OR (Endoscopic*[tiab] AND (Mucosa*[tiab] OR Mucous*[tiab]) AND (Resect*[tiab] OR Dissect*[tiab]) OR Strip Biops*[tiab]	4 757
#17	Anastomosis, Surgical[MeSH] OR Surgical*[tiab] Anastomos*[tiab]	32 532
#18	Surgical Stapling[MeSH] OR Stapl*[tiab]	14 581
#19	Hand*[tiab] AND (Stitch*[tiab] OR Sew*[tiab] OR Sutur*[tiab])	4 385
#20	#17 AND #18	2 302
#21	#17 AND #19	872
#22	#16 OR #20 OR #21	7 977
#23	#8 OR #9 OR #10 OR #11 OR #12 OR #15 OR #22	264 417
#24	#3 AND #4	11 927
#25	#23 AND #24	793
#26	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomised[tiab] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Systematic Review[pt] OR Systematic Review[tiab] OR Systematic[sb] OR Meta-Analysis[pt] OR Meta-Analysis[tiab] OR Meta-Analysis[sb] OR Cochrane Database Syst Rev[Journal]	4 216 274
#27	animals[mh] NOT humans[mh]	4 271 569
#28	#26 NOT #27	3 672 006
#29	#25 AND #28 Filters: German, English; Publication date from 2009/06/01 to 2016/12/13	84

5.1.3 Recherche in Cochrane (16.12.2016)

Search Name: CU_AG5_1
Date Run: 16/12/16 15:14:49.883

ID	Search	Hits
#1	[mh "Colitis, Ulcerative"] or [mh ^"inflammatory bowel diseases"]	1350
#2	Idiopathic Proctocolitis or Ulcerative Colitis or Colitis Gravis:ti,ab,kw	2300
#3	#1 or #2	2530
#4	[mh "Digestive System Surgical Procedures"] or [mh "Proctocolectomy, Restorative"] or [mh "Colonic Pouches"]	14 024
#5	Surg* or Proctocolectom* or Coloproctectom* or ((Colon* or Ileal*) and (Pouch or Pouches));ti,ab,kw	170 997
#6	#4 or #5	176 024
#7	[mh Hospitals, High-Volume] or [mh "Hospitals, Low-Volume"] or (Volume AND Hospital*):ti,ab,kw	589
#8	[mh "Hospitals, Special"] or (Special* AND Hospital*):ti,ab,kw	827
#9	[mh "Hospitals, General"] or (General AND Hospital*):ti,ab,kw	387
#10	#7 and (#8 or #9)	5
#11	#8 and (#7 or #9)	13
#12	#9 and (#7 or #8)	16
#13	Open and ([mh "Minimally Invasive Surgical Procedures"] or (Minimal* or Surg*) or Laparoscopi*):ti,ab,kw	13 976
#14	[mh "Surgical Stomas"] or Stoma*:ti,ab,kw	14 185
#15	((Mesorectal* or Mesenterial*) and (Excision* or Extirpation*)) or TME	391
#16	([mh Rectum] or rectal* or rectum) and (eversion* or resect*)	1814
#17	#15 and #16	214
#18	[mh "Endoscopic Mucosal Resection"] or Mucosectom* or Mucotom* or (Endoscopic* and (Mucosa* or Mucous*) and (Resect* or Dissect*)) or Strip Biops*:ti,ab,kw	456
#19	[mh "Anastomosis, Surgical"] or Surgical* Anastomos*:ti,ab,kw	3203
#20	[mh "Surgical Stapling"] or Stapl*:ti,ab,kw	1190
#21	Hand* and (Stitch* or Sew* or Sutur*):ti,ab,kw	1092
#22	#19 and #20	258
#23	#19 and #21	143
#24	#18 or #22 or #23	750
#25	{or #10-#14, #17, #24}	28 252
#26	#3 and #6	660
#27	#25 and #26 Publication Year from 2009, in Cochrane Reviews (Reviews only), Other Reviews, Trials and Technology Assessments	73

5.1.4 Ergebnis und PRISMA Flow Chart



5.2 Postoperative Komplikationen

5.2.1 Schlüsselfrage

5.2 Wie können postoperative Komplikationen bei Patienten mit Proktokolektomie vermieden/ versorgt werden?

Population: CU-Patienten mit Proktokolektomie (und akuter Pouchitis)
Interventions: Probiotics, antibiotics, Immunsuppressiva, Biologika
Comparisons: –
Outcomes: Mortalität, Quality of Life, Morbidität, Lokalseptische Komplikationen, Pouchitis, Pouchfunktion, Poucherhalt.

5.2.2 Recherche in PubMed (15.12.2016)

5.2 Wie können postoperative Komplikationen bei Patienten mit Proktokolektomie vermieden/versorgt werden?

Nr.	Query	Treffer
#1	Colitis, Ulcerative[MeSH] OR "inflammatory bowel diseases"[MeSH:noexp]	43 939
#2	Idiopathic Proctocolitis[tiab] OR Ulcerative Colitis[tiab] OR Colitis Gravis[tiab]	31 861
#3	#1 OR #2	51 066
#4	Digestive System Surgical Procedures[MeSH] OR Surg*[tiab] OR Proctocolectomy, Restorative[MeSH] OR Proctocolectom*[tiab] OR Coloproctectom*[tiab] OR Colonic Pouches[MeSH] OR ((Colon*[tiab] OR Ileal*[tiab]) AND (Pouch[tiab] OR Pouches[tiab]))	1 841 044
#5	Postoperative Complications[MeSH] OR complication*[tiab] OR "adverse effects" [Subheading] OR complications[Subheading] OR Pneumonia[MeSH] OR Pneunomi*[tiab] OR Inflammation[MeSH] OR Inflammation*[tiab] OR Anastomotic Leak[MeSH] OR Leak*[tiab] OR Abscess[MeSH] OR Abscess[tiab] OR Pouchitis[MeSH] OR Pouch Ileitis[tiab] OR Intestinal Obstruction [MeSH] OR Obstruct*[tiab] OR Ileus[tiab] OR Incisional Hernia[MeSH] OR ((Incisional*[tiab] OR Postoperative[tiab]) AND Hernia*[tiab])	4 797 577
#6	#4 AND #5	788 376
#7	treatment*[tiab] OR "therapy" [Subheading] OR Probiotics[MeSH] OR Probiotic*[tiab]	7 697 435
#8	Therapeutics[MeSH] OR Anti-Bacterial Agents[MeSH] OR Therap*[tiab] OR Anti-Bacterial*[tiab] OR Antibacterial*[tiab] Antibiotic*[tiab] OR Bacteriocidal*[tiab] OR Bacteriostatic*[tiab] OR Ciprofloxacin[MeSH] OR Ciprofloxacin[tiab] OR Metronidazole[MeSH] OR Metronidazol*[tiab] OR Trichopol[tiab] OR Flagyl[tiab] OR Metrogyl[tiab] OR Vancomycin[MeSH] OR Vancomycin*[tiab] OR Vancocin*[tiab]	239 971
#9	"Receptors, Lysosphingolipid"[MeSH] OR ((sphingosin*[tiab]) AND (phosphat*[tiab] OR receptor*[tiab])) OR S1P[tiab] OR Ozanimod [Supplementary Concept] OR Ozanimod[tiab] OR RPC1063[tiab] OR Etrasimod[tiab] OR APD334[tiab]	6 287
#10	"CT-P13"[Supplementary Concept] OR "CT-P13"[tiab] OR CTP13[tiab] OR inflectra[tiab] OR SB2[tiab] OR Remsima[tiab] OR Flixabi[tiab] OR "Biosimilar Pharmaceuticals"[MeSH] OR "Pharmaceuticals, Biosimilar"[tiab] OR Biosimilar*[tiab]	1 871
#11	"Infliximab"[MeSH] OR infliximab[tiab] OR "MAb cA2"[tiab] OR "Monoclonal Antibody cA2"[tiab] OR "Antibody cA2, Monoclonal"[tiab] OR"cA2, Monoclonal Antibody"[tiab] OR "Remicade"[tiab] OR originator[tiab]	12 065
#12	"Adalimumab"[MeSH] OR Adalimumab[tiab] OR "D2E7 Antibody"[tiab] OR Humira[tiab]	5 595
#13	etrolizumab[tiab] OR "rhuMAb Beta7" [Supplementary Concept] OR "rhuMAb Beta7"[tiab] OR PRO145 223[tiab]	34
#14	"AVX-470" [Supplementary Concept] OR AVX-470[tiab]	4
#15	golimumab [Supplementary Concept] OR golimumab[tiab] OR Simponi[tiab]	683
#16	"vedolizumab" [Supplementary Concept] OR Vedolizumab[tiab] OR Entyvio[tiab] OR MLN0002[tiab]	263
#17	Ustekinumab[MeSH] OR Ustekinumab[tiab] OR Stelara[tiab] OR "CNTO 1275"[tiab] OR "CNTO-1275"[tiab] OR CNTO1275[tiab]	896
#18	Eldelumab[tiab] OR Anti-IP-10[tiab]	37
#19	Janus Kinases[MeSH] OR JAK*[tiab] OR "janus kinase"[tiab] OR janus-kinase[tiab]	24 731
#20	Filgotinib[tiab] OR GLPG0634[tiab]	15
#21	Tofacitinib [Supplementary Concept] OR tofacitinib[tiab] OR tasocitinib[tiab] OR Xeljanz[tiab] OR Jakvinus[tiab] OR "CP 690,550"[tiab] OR CP690 550[tiab] OR "CP-690 550"[tiab] OR "CP 690 550"[tiab] OR "CP-690,550"[tiab]	539
#22	(Glucocorticoids[MeSH] OR glucocorticoid*[tiab] OR "Glucocorticoid Effect*"[tiab] OR steroid*[tiab] OR corticoid*[tiab] OR ((cortico*[tiab] OR hormone[tiab] OR generation[tiab]) AND steroid*[tiab]))	286 707

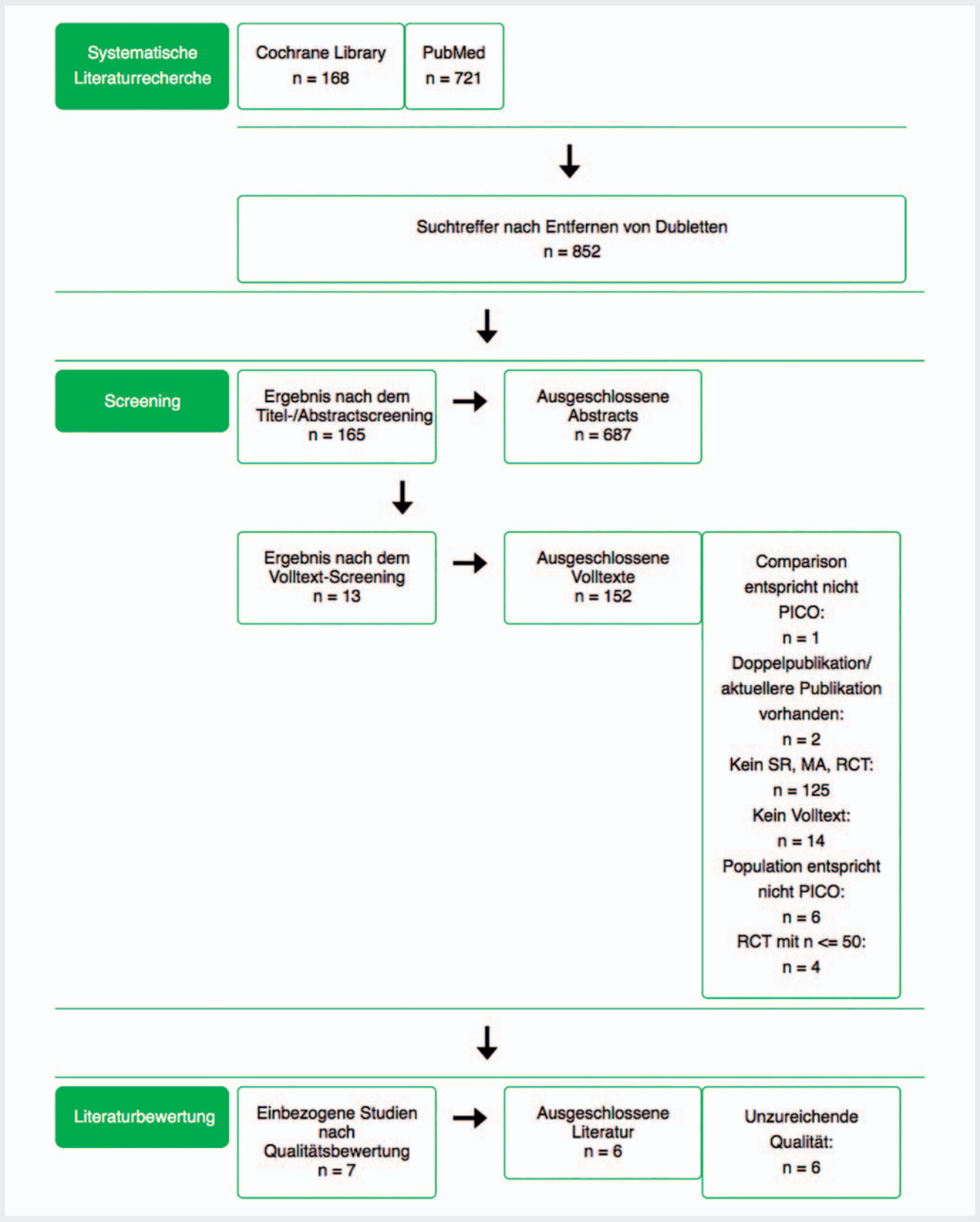
5.2 Wie können postoperative Komplikationen bei Patienten mit Proktokolektomie vermieden/versorgt werden?		
Nr.	**Query**	**Treffer**
#23	Prednisone[MeSH] OR "Cortisone"[MeSH] OR Dehydrocortisone[tiab] OR prednison*[tiab] OR delta-Cortisone[tiab] OR Rectodelt[tiab] OR Sterapred[tiab] OR Ultracorten[tiab] OR Winpred[tiab] OR Apo-Prednisone[tiab] OR Cortan[tiab] OR Cortancyl[tiab] OR Panafcort[tiab] OR OR Cutason[tiab] OR Decortin[tiab] OR Dacortin[tiab] OR Decortisyl[tiab] OR Deltasone [tiab] OR Encorton*[tiab] OR Enkortolon[tiab] OR Kortancyl[tiab] OR "Liquid Pred"[tiab] OR Meticorten[tiab] OR Orasone[tiab] OR Panasol[tiab] OR "Predni Tablinen"[tiab] OR Prednidib[tiab] OR Predniment[tiab] OR Pronisone[tiab] OR Sone[tiab]	67 237
#24	(Beclomethasone[MeSH] OR Beclomethason*[tiab] OR Beclometason*[tiab] OR ((Beclomethasone[tiab] OR Beclometason [tiab]) AND Dipropionate[tiab])) OR Beclamet[tiab] OR "Beclo Asma"[tiab] OR "Beclo AZU"[tiab] OR Beclocort[tiab] OR Beclomet[tiab] OR OR Beclorhinol[tiab] OR Becloturmant[tiab] OR Sanasthmax[tiab] OR Beclovent[tiab] OR Beconase[tiab] OR Becloforte[tiab] OR Becodisk[tiab] OR Becotide[tiab] OR Propaderm[tiab] OR Sanasthmyl[tiab] OR Becodisks[tiab] OR "-Beconase AQ"[tiab] OR Bronchocort[tiab] OR Junik[tiab] OR Qvar[tiab] OR Aerobec*[tiab] OR Beclazone*[tiab] OR Ecobec [tiab] OR Filair*[tiab] OR "Nasobec Aqueous"[tiab] OR Prolair[tiab] OR "Respocort"[tiab] OR Ventolair[tiab] OR Vancenase[tiab] OR Vanceril[tiab] OR Aldecin[tiab] OR Viarin[tiab] OR "Apo-Beclomethasone"[tiab])	3 729
#25	Dexamethasone[MeSH] OR Dexamethason*[tiab] OR Dexametason*[tiab] OR Hexadecadrol[tiab] OR Methylfluorprednisolone [tiab] OR Decameth[tiab] OR Decaspray[tiab] OR Dexasone[tiab] OR Dexpak[tiab] OR Maxidex[tiab] OR Millicorten[tiab] OR Oradexon[tiab] OR Decaject[tiab] OR Decaject*[tiab] OR Hexadrol[tiab]	63 831
#26	Budesonide[MeSH] OR Budesonid*[tiab] OR Pulmicort[tiab] OR MMX[tiab] OR Horacort[tiab] OR Rhinocort[tiab]	5 528
#27	Cyclosporine[MeSH] OR cyclosporin*[tiab] OR Ciclosporin*[tiab] OR Neoral[tiab] OR CyA-NOF[tiab] OR "CyA NOF"[tiab] OR Sandimmun*[tiab] OR CsA-Neoral[tiab] OR "CsA Neoral" OR CsANeoral[tiab] OR "OL 27 – 400"[tiab] OR "OL 27 400"[tiab] OR "OL 27 400"[tiab]	55 094
#28	Tacrolimus[MeSH] OR tacrolimus[tiab] OR Prograf*[tiab] OR "FR-900 506"[tiab] OR "FR 900 506"[tiab] OR FR900 506[tiab] OR"FK-506"[tiab] OR "FK 506"[tiab] OR "FK506"[tiab]	21 685
#29	Methotrexate[MeSH] OR Methotrexate[tiab] OR Amethopterin[tiab] OR Mexate[tiab]	47 657
#30	"Purines"[MeSH] OR Purin*[tiab]	490 654
#31	"Azathioprine"[MeSH] OR Azahtioprin*[tiab] OR Thiopurin*[tiab] OR Imurel[tiab] OR Imuran[tiab] OR Immuran[tiab] OR Azafalk[tiab] OR Azaimmun[tiab] OR Azarek[tiab] OR Colinsan[tiab] OR Immunoprin[tiab] OR Imurek[tiab] OR Zytrim[tiab]	15 358
#32	6-Mercaptopurine[MeSH] OR 6-Mercaptopurin*[tiab] OR Mercaptopurin*[tiab] OR "1,7-Dihydro-6H-purine-6-thione"[tiab] OR 6-Thiohypoxanthin*[tiab] OR 6-Thiopurine[tiab] OR Thiopurin*[tiab] OR Leupurin[tiab] OR Purimethol[tiab] OR "BW 57 – 323H"[tiab] OR "BW 57 323H"[tiab] OR "BW 57 323H"[tiab] OR Purinethol[tiab] OR "Puri-Nethol"[tiab] OR "Puri Nethol"[tiab]	20 848
#33	"AJM300" [Supplementary Concept] OR AJM300[tiab] OR "Integrin alpha4"[MeSH] OR "Integrin alpha4"[tiab]	1 019
#34	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33	8 382 187
#35	#6 AND #34	634 540
#36	#3 AND #35	5 663
#37	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomised[tiab] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Systematic Review[pt] OR Systematic Review[tiab] OR Systematic[sb] OR Meta-Analysis[pt] OR Meta-Analysis[tiab] OR Meta-Analysis[sb] OR Cochrane Database Syst Rev[Journal]	4 230 293
#38	animals[mh] NOT humans[mh]	4 280 967
#39	#37 NOT #38	3 683 796
#40	#36 AND #39 Filters: German, English; Publication date from 2009/06/01 to 2016/12/15	721

5.2.3 Recherche in Cochrane (16.12.2016)

Search Name: CU_AG5_2
Date Run: 16/12/16 15:15:55.428

ID	Search	Hits
#1	[mh "Colitis, Ulcerative"] or [mh ^"inflammatory bowel diseases"]	1350
#2	Idiopathic Proctocolitis or Ulcerative Colitis or Colitis Gravis:ti,ab,kw	2300
#3	#1 or #2	2530
#4	[mh "Digestive System Surgical Procedures"] or [mh "Proctocolectomy, Restorative"] or [mh "Colonic Pouches"]	14 024
#5	Surg* or Proctocolectom* or Coloproctectom* or ((Colon* or Ileal*) and (Pouch or Pouches));ti,ab,kw	170 997
#6	#4 or #5	176 024
#7	Any MeSH descriptor with qualifier(s): [Adverse effects – AE, Complications – CO]	154 012
#8	[mh "Postoperative Complications"] or [mh Inflammation] or [mh "Anastomotic Leak"] or [mh Abscess] or [mh Pneumonia] or [mh Pouchitis] or [mh "Intestinal Obstruction"] or [mh "Incisional Hernia"]	42 336
#9	complication* or Inflammation* or Pneunomi* or Leak* or Abscess or Pouch Ileitis or Obstruct* or Ileus or ((Incisional* or Post-operative) and Hernia*)	164 786
#10	#7 or #8 or #9	260 935
#11	#6 and #10	83 625
#12	Any MeSH descriptor with qualifier(s): [Therapy – TH]	78 683
#13	[mh Probiotics] or [mh Therapeutics] or [mh "Anti-Bacterial Agents "] or [mh Ciprofloxacin] or [mh Metronidazole] or [mh Vancomycin]	279 633
#14	treatment* or Probiotic* or Therap* or Anti-Bacterial* or Antibacterial* Antibiotic* or Bacteriocidal* or Bacteriostatic* or Ciprofloxacin or Metronidazol* or Trichopol or Flagyl or Metrogyl or Vancomycin* or Vancocin*:ti,ab,kw	645 487
#15	[mh "Receptors, Lysosphingo lipid"] or [mh "Biosimilar Pharmaceuticals"] or [mh Infliximab] or [mh Adalimumab] or [mh Ustekinumab] or [mh "Janus Kinases"] or [mh Glucocorticoids] or [mh Prednisone] or [mh Cortisone] or [mh Beclomethasone] or [mh Dexamethasone] or [mh Cyclosporine] or [mh Tacrolimus] or [mh Methotrexate] or [mh Purines] or [mh Azathioprine] or [mh 6-Mercaptopurine] or [mh "Integrin alpha4"]	26 137
#16	((sphingosin*) and (phosphat* or receptor*)) or S1P or Ozanimod or RPC1063 or Etrasimod or APD334 or CT-P13 or CTP13 or inflectra or SB2 or Remsima or Pharmaceuticals, Biosimilar or Biosimilar* or Flixabi or infliximab or MAb cA2 or Monoclonal Antibody cA2 or Antibody cA2, Monoclonal ORcA2, Monoclonal Antibody or Remicade or originator or Adalimumab or D2E7 Antibody or Humira or etrolizumab or rhuMAb Beta7 or PRO145 223 or AVX-470 or golimumab or Simponi or Vedolizumab or Entyvio or MLN0002 or Ustekinumab or Stelara or CNTO 1275 or CNTO-1275 or CNTO1275 or Eldelumab or Anti-IP-10 or JAK* or janus kinase or janus-kinase or Filgotinib or GLPG0634 or tofacitinib or tasocitinib or Xeljanz or Jakvinus or CP 690,550 or CP690 550 or CP-690 550 or CP 690 550 or CP-690,550 or glucocorticoid* or Glucocorticoid Effect* or steroid* or corticoid* or ((cortico* or hormone or generation) and steroid*);ti,ab,kw	33 862
#17	Dehydrocortisone or prednison* or delta-Cortisone or Rectodelt or Sterapred or Ultracorten or Winpred or Apo-Prednisone or Cortan or Cortancyl or Panafcort or Cutason or Decortin or Dacortin or Decortisyl or Deltasone or Encorton* or Enkortolon or Kortancyl or Liquid Pred or Meticorten or Orasone or Panasol or Predni Tablinen or Prednidib or Predniment or Pronisone or Sone;ti,ab,kw	7040
#18	Beclomethason* or Beclometason* or ((Beclomethasone or Beclometason) and Dipropionate) or Beclamet or Beclo Asma or Beclo AZU or Beclocort or Beclomet or Beclorhinol or Becloturmant or Sanasthmax or Beclovent or Beconase or Becloforte or Becodisk or Becotide or Propaderm or Sanasthmyl or Becodisks or Beconase AQ or Bronchocort or Junik or Qvar or Aerobec* or Beclazone* or Ecobec or Filair* or Nasobec Aqueous or Prolair or Respocort or Ventolair or Vancenase or Vanceril or Aldecin or Viarin or Apo-Beclomethasone:ti,ab,kw	2439
#19	Dexamethason* or Dexametason* or Hexadecadrol or Methylfluorprednisolone or Decameth or Decaspray or Dexasone or Dexpak or Maxidex or Millicorten or Oradexon or Decaject or Decaject* or Hexadrol or Budesonid* or Pulmicort or MMX or Horacort or Rhinocort:ti,ab,kw	10 277
#20	cyclosporin* or Ciclosporin* or Neoral or CyA-NOF or CyA NOF or Sandimmun* or CsA-Neoral or CsA Neoral or CsANeoral or OL 27 – 400 or OL 27 400 or OL 27 400 or tacrolimus or Prograf* or FR-900 506 or FR 900 506 or FR900 506 ORFK-506 or FK 506 or FK506 or Methotrexate or Amethopterin or Mexate or Purin*:ti,ab,kw	16 294
#21	Azahtioprin* or Thiopurin* OR Imurel or Imuran or Immuran or Azafalk or Azaimmun or Azarek or Colinsan or Immunoprin or Imurek or Zytrim or 6-Mercaptopurin* or Mercaptopurin* or 1,7-Dihydro-6H-purine-6-thione or 6-Thiohypoxanthin* or 6-Thiopurine or Thiopurin* or Leupurin or Purimethol or BW 57 – 323H or BW 57 323H or BW 57 323H or Purinethol or Puri-Nethol or Puri Nethol or AJM300 or Integrin alpha4:ti,ab,kw	817
#22	{Moss, #12-#21}	701 772
#23	#11 and #22	69 904
#24	#3 and #23 Publication Year from 2009, in Cochrane Reviews (Reviews only), Other Reviews, Trials and Technology Assessments	168

5.2.4 Ergebnis und PRISMA Flow Chart



6. Recherchen zum Thema „Komplementärmedizin und Ernährung“

6.1 Schlüsselfrage

6. Welche komplementärmedizinischen Verfahren sind effektiv zur Behandlung der CU?

Population: Personen mit CU
Interventions:
Complementary therapies (complementary medicine, alternative medicine, alternative therapies, complementary and alternative medicine, complementary and alternative therapies, naturopathy): phytotherapy, phytochemicals, herbs, herbal medicine, balm, passiflora, curcumin, boswellia serrata, aloe vera, glycyrrhiza, belladonna, frankincense, calendula, tormentill, helminths, caraway, myrrh, chamomile, coffee, turmeric, plantago ovata, ginger, nicotine, Trichuris suis ovata, Passionflower, peppermint oil, hydrotherapy, biofeedback, massage, warming, chronotherapy, light, acupuncture, acupressure, chinese medicine, ayurvedic medicine, kampo
Nutrition: Vitamins, nutritional supplement, Supplements, dietary
Exercise: movement, relaxation, pmr, breathing exercises, autogenic training, yoga, lifestyle modification, tai chi, qigong, hypnosis, hypnotherapy, meditation, balneotherapy, antroposophic, aromatherapy, imagery, homeopathy, mindfulness
Comparisons: Standardtherapie, keine Therapie
Outcomes: Krankheitsaktivität, scores (MAYO, SCCAI, PUCAI), Quality of life (IBDQ, SIDQ), mucosal healing, adverse events

6.2 Recherche in PubMed (13.12.2016)

Welche komplementärmedizinischen Verfahren sind effektiv zur Behandlung der CU?

Nr.	Query	Treffer
#1	Colitis, Ulcerative[MeSH] OR "inflammatory bowel diseases"[MeSH:noexp]	43 939
#2	Idiopathic Proctocolitis[tiab] OR Ulcerative Colitis[tiab] OR Colitis Gravis[tiab]	31 834
#3	#1 OR #2	50 979
Komplementärmedizinische Verfahren		
#4	Complementary Therapies[MeSH]	195 947
#5	Complementary Therap*[tiab] OR Complementary Medicine[tiab] OR Alternative Medicine[tiab] OR Alternative Therap*[tiab] OR Naturopathic[tiab] OR Naturopathy[tiab]	19 378
#6	Phytotherapy[tiab] OR Aromatherapy[tiab] OR Phytochemical*[tiab]	14 537
#7	Herb*[tiab] therap*[tiab] OR Herb*[tiab] medicine[tiab] OR balm[tiab] OR passiflora*[tiab] OR passiflora[MeSH] OR Passion[tiab] Flower*[tiab] OR Curcumin[MeSH] OR curcumin[tiab] OR Turmeric[tiab] OR Curcuma[MeSH] OR Curcuma*[tiab] OR Boswellia[MeSH] OR Boswellia[tiab] OR Aloe[MeSH] OR Aloe[tiab] OR Glycyrrhiza[MeSH] OR Glycyrrhiza [tiab] OR Liquorice*[tiab] OR Licorice*[tiab] OR Atropa belladonna[MeSH] OR Belladonna*[tiab] OR frankincense[MeSH] OR Frankincense[tiab] OR Olibanum[tiab] OR Calendula[MeSH] OR Calendula*[tiab] OR Potentilla[MeSH] OR Tormentil*[tiab] OR Septfoil[tiab] OR Helminths[MeSH] OR Therapy with Helminths[MeSH] OR Helminth*[tiab] OR Parasitic Worm*[tiab] OR Aschelminthe*[tiab] OR Nematomorpha*[tiab] OR Gordius[tiab] OR Helminthic Therap*[tiab] OR Carum[MeSH] OR Carum*[tiab] OR Caraway*[tiab] OR Ajowan*[tiab] OR Commiphora[MeSH] OR Commiphora[tiab] OR Myrrh[tiab] OR Chamomile[MeSH] OR Camomile*[tiab] OR Chamomile[tiab] OR Coffee[MeSH] OR Coffee[tiab] OR Caffeine[MeSH] OR Caffein*[tiab] OR Plantago[MeSH] OR Plantago*[tiab] OR Plantain*[tiab] OR Ginger[MeSH] OR Ginger*[tiab] OR Zingiber[tiab] OR Nicotine[MeSH] OR Nicotine[tiab] OR Trichuris[MeSH] OR Trichur*[tiab] OR Trichocephalus[tiab] OR Mentha piperita[MeSH] OR Mentha piperita*[tiab] OR Peppermint*[tiab]	227 198
#8	Hydrotherapy[MeSH] OR Hydrotherap*[tiab] OR Whirlpool*[tiab]	19 156
#9	Biofeedback, Psychology[MeSH] OR Biofeedback*[tiab] OR Myofeedback*[tiab]	11 123
#10	Massage[MeSH] OR Massage*[tiab]	11 176
#11	Hot Temperature[MeSH:noexp] OR Heat[tiab] OR Hot Temperature*[tiab] OR Warming[tiab]	247 455
#12	Chronotherapy[MeSH] OR Chronotherap*[tiab]	1 468
#13	Phototherapy[MeSH] OR Phototherap*[tiab] OR Light therap*[tiab]	35 568
#14	Acupuncture[MeSH] OR Acupuncture Therapy[MeSH] OR Acupuncture[tiab]	24 567
#15	Acupressure[MeSH] OR Acupressure[tiab] OR Shiatsu[tiab] OR Shiatzu[tiab]	1 021
#16	Medicine, Chinese Traditional[MeSH] OR (Chinese[tiab] AND Traditional[tiab] AND Medicine*[tiab]) OR Kampo[tiab] OR Kanpo[tiab]	26 771
#17	(Ayurvedic[tiab] OR Siddha[tiab] OR Hindu[tiab]) AND medicine[tiab]	1 294
#18	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	756 558

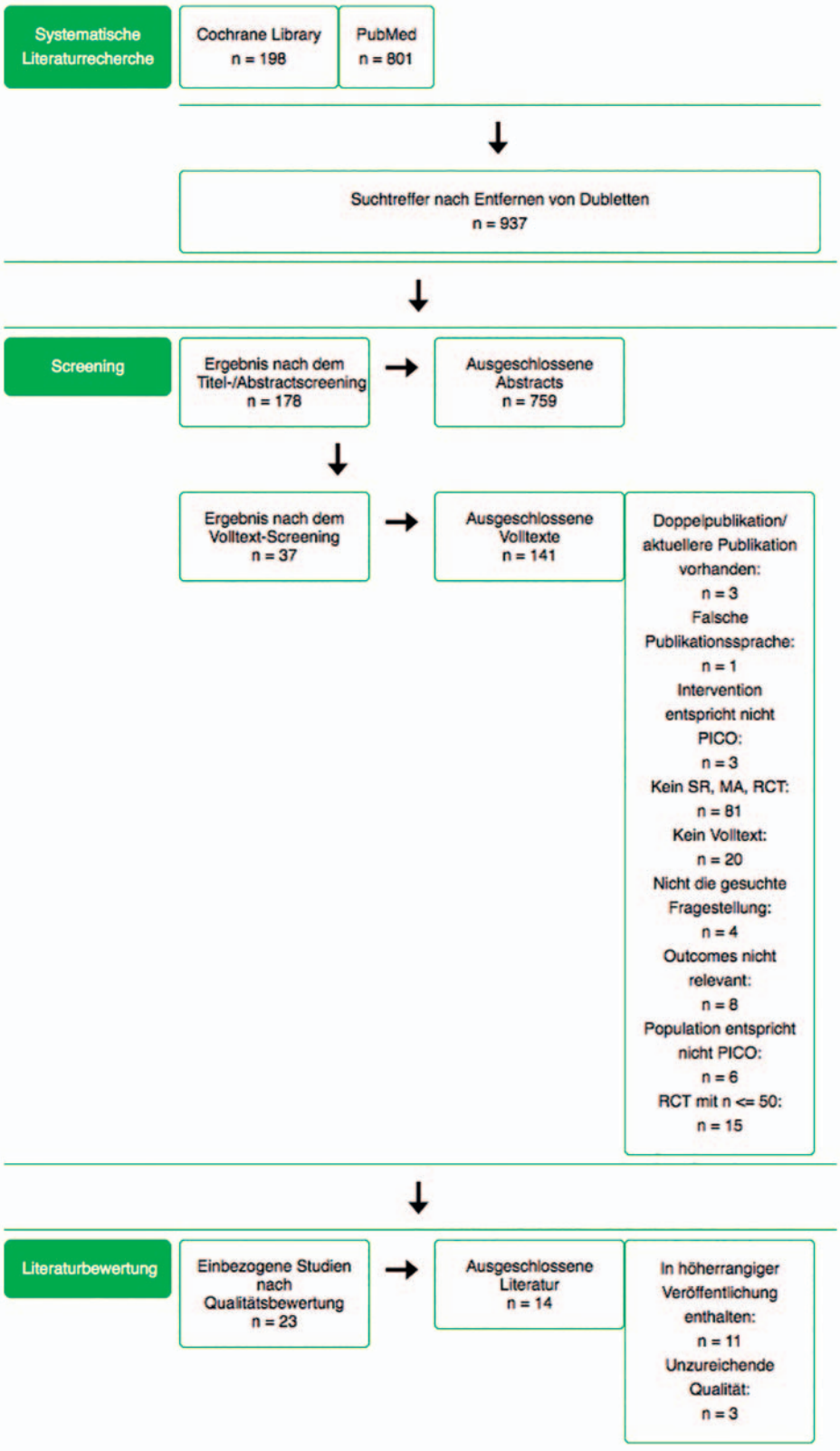
Welche komplementärmedizinischen Verfahren sind effektiv zur Behandlung der CU?		
Nr.	**Query**	**Treffer**
Ernährung		
#19	Diet, Food, and Nutrition[MeSH] OR Nutri*[tiab] OR Diet*[tiab]	1 256 990
#20	Vitamins[MeSH] OR Vitamin*[tiab]	195 710
#21	(Food[tiab] OR Diet*[tiab]) AND Supplement*[tiab]	67 749
#22	#19 OR #20 OR #21	1 374 563
Exercise		
#23	Exercise[MeSH] OR Sport[MeSH] OR Exercise[tiab] OR Sport*[tiab] OR Physical Fitness[tiab]	382 588
#24	Movement[MeSH:noexp] OR Movement[tiab] OR Relaxation[MeSH] OR Relaxation Therapy[MeSH] OR Relaxation[tiab]	348 594
#25	Autogenic Training[MeSH] OR "Autogenic Training"[tiab] OR (progressive[tiab] AND muscle[tiab] AND relaxation[tiab]) OR "PMR"[tiab]	3 792
#26	Breathing exercise*[tiab] OR "Respiratory Muscle Training"[tiab]	1 122
#27	Yoga[tiab] OR Tai Ji[tiab] OR Tai Chi[tiab] OR Tai-ji[tiab] OR Qigong[tiab] OR Qi gong[tiab] OR Meditation[tiab]	7 268
#28	(Life Style[MeSH] OR Health Behavior[MeSH] OR Lifestyle[tiab] OR Life Style[tiab] OR Health Behaviour*[tiab] OR Health Behavior*[tiab]) AND (change[tiab] OR modi*[tiab] OR intervention*[tiab])	75 153
#29	Hypnosis[tiab] OR Hypnoses[tiab] OR Hypnotherap*[tiab]	8 115
#30	Balneology[MeSH] OR Balneology[tiab] OR Balneothera*[tiab]	11 996
#31	Anthroposophy[MeSH] OR Anthroposoph*[tiab]	411
#32	Imager*[tiab] OR (Directed[tiab] AND Reverie[tiab] AND Therap*[tiab])	15 430
#33	Homeopath*[tiab] OR Homoeopath*[tiab]	4 989
#34	Mindfulness[MeSH] OR Mindfulness[tiab]	3 823
#35	#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34	814 368
#36	#18 OR #22 OR #35 – Interventionen gesamt	2 754 198
#37	#3 AND #36	5 751
#38	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomised[tiab] OR randomized[tiab] OR placebo [tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Systematic Review[pt] OR Systematic Review[tiab] OR Systematic[sb] OR Meta-Analysis[pt] OR Meta-Analysis[tiab] OR Meta-Analysis[sb] OR Cochrane Database Syst Rev[Journal]	4 216 274
#39	animals[mh] NOT humans[mh]	4 271 572
#40	#38 NOT #39	3 672 006
#41	#37 AND #40 Filters: German, English; Publication date from 2009/06/01 to 2016/12/13	801

6.3 Recherche in Cochrane (13.12.2016)

Search Name: CU_AG6
Date Run: 13/12/16 10:05:59.610

ID	Search	Hits
#1	[mh "Colitis, Ulcerative"] or Ulcerative Colitis:ti,ab,kw	2115
#2	[mh "Complementary Therapies"] or Phytotherapy or Aromatherapy or Phytochemical* or Herb* therap* or Herb* medicine or balm OR passiflora* or passiflora OR Passion Flower* or curcumin or Turmeric or Curcuma* or Boswellia or Aloe or Glycyrrhiza or Liquorice* or Licorice* or Belladonna* or Frankincense or Olibanum or Calendula* or Potentilla or Tormentil* or Helminth* or Parasitic Worm* or Aschelminthe* or Nematomorpha* or Gordius or Helminthic Therap* or Carum* or Caraway* or Ajowan* or Commiphora or Myrrh or Camomile* or Chamomile or Coffee or Caffein* or Plantago* or Plantain* or Ginger* or Zingiber or Nicotine or Trichur* or Trichocephalus or Mentha piperita* or Peppermint*:ti,ab,kw	32 841
#3	Hydrotherap* or Biofeedback* or Massage* or Warming or Chronotherap* or Phototherap* or Light therap* or Acupunctureor Acupressure or Shiatsu or (Chinese and Traditional and Medicine*):ti,ab,kw	19 445
#4	[mh "Diet, Food, and Nutrition"] or Nutri* or Diet* or [mh Vitamins] or Vitamin* or ((Food or Diet*) and Supplement*):ti,ab,kw	96 518
#5	[mh Exercise] or [mh Sport] or Exercise or Sport* OR Physical Fitness or [mh Relaxation] or [mh "Relaxation Therapy "] or Relaxation or [mh "Autogenic Training"] or Autogenic Training or (progressive AND muscle AND relaxation) or "PMR" or Breathing exercise* or "Respiratory Muscle Training" or Yoga or Tai Ji or Tai Chi or Tai-ji or Qigong or Qi gong or Meditation or (([mh "Life Style "] or [mh "Health Behavior "] or Lifestyle or Life Style or Health Behaviour* or Health Behavior*) and (change or modi* or intervention*)) or Hypnosis or Hypnoses or Hypnotherap* or [mh Balneology] or Balneology or Balneothera* or [mh Anthroposophy] OR Anthroposoph* Imager* or (Directed and Reverie and Therap*) or Homeopath* or Homoeopath* or [mh Mindfulness] or Mindfulness:ti,ab,kw	97 939
#6	#2 or #3 or #4 or #5	208 685
#7	#1 and #6 Publication Year from 2009, in Other Reviews, Trials and Technology Assessments	198

6.4 Ergebnis und PRISMA Flow Chart



Anhang C: Evidenztabellen

AG 1: Wie und wann soll eine Calprotectin-Diagnostik durchgeführt werden?

Bewertungsvorlage:
Oxford SR

Holtman, G.A. et al. Noninvasive Tests for Inflammatory Bowel Disease: A Meta-analysis. Pediatrics. 137. 2016

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** MA of 19 diagnostic studies (14 cohort studies and 5 case-control studies) **Databases:** Medline, Embase **Search period:** inception - Sept. 2014 **Inclusion Criteria:** (1) the study population consisted of children with gastrointestinal symptoms suggestive of IBD; (2) one of the following diagnostic tests was investigated: signs, symptoms, markers (blood, fecal, or urinary), or ultrasonography (3) the reference standard for IBD was endoscopy, including histopathology and/or clinical follow-up (4) the target condition was IBD (5) the study design provided information about the association between tests of interests and the presence or absence of IBD (6) the study report, or the subsequent data requested, enabled the construction of a 2 × 2 table. for the 2 × 2 **Exclusion Criteria:** (1) studies including healthy control subjects and/or patients with known IBD were excluded	**Intervention:** 2806 children with gastrointestinal symptoms (age range: 3 months–21 years), of whom 1265 had IBD. **None of the studies was conducted in nonreferred children.** Noninvasive Tests: Symptoms and Signs, Blood Markers, Fecal Markers, Urinary Markers, Ultrasonography, Combinations of Tests **Comparison**: –	**Primary:** Diagnostic accuracy **Secondary:** – **Results: Symptoms and Signs:** Sensitivity and specificity varied substantially between studies for all symptoms (8 studies). Highest positive likelihood ratio of 2.6 (1.7 – 4.0) for Rectal bleeding. **Blood Markers:** Pooled sensitivities for CRP with and without 2 outliers were 0.63 (0.51 – 0.73) and 0.57 (0.46 – 0.66), respectively, and pooled specificities were 0.88 (0.80 – 0.93) and 0.84 (0.77 – 0.89). *Platelet count:* The pooled sensitivities with and without studies with a cutoff value < 400 × 10/L were 0.55 (0.36 – 0.73) and 0.45 (0.28 – 0.63), respectively the specificities were 0.88 (0.81 – 0.93) and 0.91 (0.87 – 0.94). *Hemoglobin:* Age/gender-specific cutoff values showed increase in pooled sensitivity from 0.37 (0.24 – 0.52) to 0.56 (0.46 – 0.65). Pooled specificity not affected: 0.90 (0.83 – 0.94) and 0.87 (0.77 – 0.93). **Fecal Markers:** FCal exhibited a pooled sensitivity and specificity of 0.99 (0.92 – 1.00) and 0.65 (0.54 – 0.74), and 1.00 (0.86 – 1.00) and 0.69 (0.63 – 0.74), respectively, after exclusion of 2 case-control studies. **Urinary Markers:** One study found that measurement of urinary excretion of cellobiose/mannitol with a cutoff of 0.023 had a sensitivity and specificity of 0.41 (0.22 – 0.61) and 0.67 (0.41 – 0.87), respectively. **Ultrasonography:** The sensitivity of bowel wall thickness > 3 mm and seve-	**Cohort Studies:** Ashorn S (2009) Inflamm Bowel Dis Beattie RM (1995) Arch Dis Child Bonnín TA (2007) Rev Esp Enferm Cabrera-Abreu JC (2003) Arch Dis Child Canani RB (2006) J Pediatr Gastroenterol Nutr Diamanti A (2010) Inflamm Bowel Dis Dubinsky MC (2001) Am J Gastroenterol Fagerberg UL (2005) J Pediatr Gastroenterol Nutr Khan K (2002) Inflamm Bowel Dis Perminow G (2009) Scand J Gastroenterol Sabery N (2007) Pediatrics Sidler MA (2008) Van de Vijver E (2012) Arch Dis Child Ziech ML (2014) Pediatr Radiol **Case- control studies** El-Chammas K (2013) J Pediatr Henderson P (2012) Am J Gastroenterol Leach ST (2007) Scand J Gastroenterol Minar P (2014) Infl amm Bowel Dis Tsampalieros A (2011) J Pediatr	**Funding Sources:** No external funding. **COI:** The authors have indicated they have no potential confl icts of interest to disclose. **Study Quality:** High Risks of Bias regarding Patient Selection in 9 studies (6 unclear). High Risks of Bias regarding Index Test in 3 studies (10 unclear). High Risks of Bias regarding Reference Standard in 8 studies (9 unclear). High Risks of Bias regarding Flow and Timing in 10 studies (8 unclear). Low Applicability Concerns. **Heterogeneity:** Heterogeneity explored regarding explanations (differences in study design or cutoff value) but not presented in I2, Chi- Square-Test or Forest Plot. Analyses with and without outliers. **Publication Bias:** Not investigated. **Notes:** Oxford LoE 1 for validating diagnostic studies.

		ral other parameters measured by using ultrasonography (2 studies) in children with gastrointestinal symptoms ranged from 0.78 to 1.00, and specificity ranged from 0.55 to 0.74. **Combinations of Tests:** Highest specificity (0.96) of combination for hemoglobin and ESR. **Author's Conclusion:** In children whose pediatrician is considering an endoscopy, symptoms are not accurate enough to identify low- risk patients in whom an endoscopy can be avoided. FCal, CRP, and albumin findings are potentially of clinical value, given their ability to select children at low risk (negative FCal test result) or high risk (positive CRP or albumin test result) for IBD.		
Degraeuwe P.L. et al. Faecal calprotectin in suspected paediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 60. 339 – 346. 2015				
Evidence level/ Study Types	**Population**	**Outcomes/Results**	**Literature/references**	**Methodical Notes**
Evidence level: 1 **Study type:** MA with 9 cohort studies **Databases:** MEDLINE, EMBASE, the Database of Abstracts of Reviews of Effects (DARE) of the Centre for Reviews and Dissemination, the MEDION database of the University of Maastricht **Search period:** Inception to April 2012 **Inclusion Criteria:** (1) Only cohort studies evaluating the diagnostic performance of FC concentration in paediatric patients; (2) FC measurement and reference standard available for all of the paediatric participants (or a follow-up period long enough to exclude IBD); (3) sufficient data to calculate 2 × 2 tables **Exclusion Criteria:** –	**Intervention:** Faecal calprotectin (FC) assessed in 853 pediatric patients. Age range: 0.9 – 19.9. **Comparison:** –	**Primary:** Test accuracy **Secondary:** – **Results:** Sensitivity for diagnosing IBD: 0.97 (95 % CI 0.92 – 0.99) Specificity: 0.70 (0.59 – 0.79) FC cutoff level: At an FC cutoff level of 50 mg/g there would be 17 % (95 % CI 15 – 20) false-positive and 2 % (1 – 3) false-negative results (based on patient-level pooled analysis of 742 patients from 8 diagnostic accuracy studies). Regression modelling identified FC concentration and age as independently associated with the diagnosis of IBD. **Author's Conclusion:** In high- prevalence circumstances, FC can be used as a noninvasive biomarker of paediatric IBD with only a small risk of missing cases. To quantify the individual patients' risk, we developed a simple prediction model based on FC concentration and age. Although the derived prediction rule cannot substitute the clinical diagnostic process, it can help in selecting patients for endoscopic evaluation.	Van de Vijver E (2012) Arch Dis Child Sidler MA (2008) Inflamm Bowel Dis Perminow G (2009) Scand J Gastroenterol Kolho KL (2006) Scand J Gastroenterol Henderson P (2012) Am J Gastroenterol Fagerberg UL (2005) J Pediatr Gastroenterol Nutr Diamanti A (2010) Inflamm Bowel Dis Berni Canani RB (2006) J Pediatr Gastroenterol Nutr Ashorn S (2009) Inflamm Bowel Dis	**Funding Sources:** P.H. was funded by a Medical Research Council patient cohorts research initiative grant for PICTS to D.C. W. by the Medical Research Council, UK (no. G0800 675), and K.-L.K. received grants from the Finnish Pediatric Research Foundation and a Helsinki University Central Hospital Grant. A.S.D.: received payment for advisory board membership and educational presentations from Janssen U.L.F.: institution received lecture fees from Tillotts AB, MSD, and AbbVie and travel grants from Tillotts AB and Otsuka Pharma Scandinavia AB K.-L.K.: received consultation fee from Tillotts Pharma, payment for advisory board membership from MSD and Abbvie, and support for travel from Biocodex P.F. v.R. received consultation fee (supply of reagents free of charge) from Buhlmann Laboratories AG and an unrestricted start-up grant from Ferring-NL B.V. D.C. W. received consultation fees or honoraria from Pfizer and MSD, a research grant from MSD, lecture honoraria from MSD and Dr Falk, and support for travel from Ferring. **COI:** A.S.D. reports conflicts of interest as stated above. The

				other authors report no conflicts of interest. **Study Quality:** Well-known shortcomings in the quality and reporting of diagnostic research led to exclusion of nearly half of the paediatric accuracy studies because they used a case- control design known for introducing spectrum bias. None of the studies prespecified a target value for sensitivity, specificity, predictive accuracy, and a minimal acceptable lower confidence limit, enabling sample size calculation. **Heterogeneity:** Q = 1133.20, df = 8.00, p = 0.00 I2 = 99.29 [99.14 – 99.45]. Between-study differences were shown for age and FC concentration. The prevalence of IBD varied from 51 % to 84 %, and the false-positive rate ranged from 0 % to 29 % suggesting dissimilar study entry criteria. **Publication Bias:** Publication bias was assessed by Deeks' funnel plot asymmetry test for small study effect/publication bias. The nonsignificant slope (P = 0.62) indicates that no bias was found. **Notes:** Oxford LoE 1 for validating diagnostic studies.

Mosli, M.H. et al. C-Reactive Protein, Fecal Calprotectin, and Stool Lactoferrin for Detection of Endoscopic Activity in Symptomatic Inflammatory Bowel Disease Patients: A Systematic Review and Meta-Analysis. Am J Gastroenterol. 110. 802 – 819 quiz 820. 2015

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** MA of 18 prospective cohort studies, 1 retrospective analysis **Databases:** MEDLINE, EMBASE, the Cochrane Library, ISI Web of Knowledge **Search period:** Inception to 6 November 2014 **Inclusion Criteria:** – Cohort and case–control studies that evaluated the diagnostic accuracy of serum CRP, FC, and SL for assessment of endoscopic disease activity. ▪ Patients with previously diagnosed UC or CD presenting with symptoms suggestive of endoscopically active disease	**Intervention:** Serum CRP, FC, and SL assessed in 2102 IBD patients (1069 UC, 1033 CD) **Comparison:** 397 controls, who were either patients with IBS or healthy volunteers.	**Primary:** TP, TN, FP, FN, sensitivity, specificity, and positive and negative likelihood ratios **Secondary:** – **Results: Fecal Calprotectin for UC:** Sensitivity: 0.88 (0.84 – 0.92) Specificity: 0.79, 95 % CI: 0.68 – 0.87. Pooled positive and negative likelihood ratios for UC: 4.2 (95 % CI 2.8 – 6.4) and 0.15 (95 % CI 0.11 – 0.20). Stool Lactoferrin for IBD: Sensitivity: 0.82 (95 % CI 0.73 – 0.88) Specificity: 0.79 (95 % CI 0.62 – 0.89) C-Reactive Protein for IBD: Sensitivity: 0.49 (95 % CI 0.34 – 0.64) Specificity: 0.92 (95 % CI 0.72 – 0.98) **Author's Conclusion:** This systematic review indicates	Af Bjorkesten CG (2012) Scand J Gastroenterol D'Haens G (2012) Inflamm Bowel Dis D'Inca R (2007) Int J Colorectal Dis Filik L (2006) Adv Ther Inoue K (2014) J Gastroenterol Hepatol Karoui S (2011) Dig Dis Sci Lobaton T (2013) Inflamm Bowel Dis Langhorst J (2008) Am J Gastroenterol Lobaton T (2013) J Crohns Colitis Masoodi I (2009) J Gastroenterol Hepatol Nancy S (2013) Inflamm Bowel Dis Onal IK (2012) Turk J Gastroenterol Primas C (2013) Gastroenterology Schoepfer AM (2009) Inflamm Bowel Dis	**Funding Sources:** Funding for the IBD/FBD Review Group (1 September 2010—31 August 2015) has been provided by the Canadian Institutes of Health Research (CIHR) Knowledge Translation Branch (CON—105 529) and the CIHR Institutes of Nutrition, Metabolism and Diabetes (INMD), and Infection and Immunity (III) and the Ontario Ministry of Health and Long-Term Care (HLTC3968FL-2010-2235). Miss Ila Stewart has provided support for the IBD/FBD Review Group through the Olive Stewart Fund. **COI:** N.C.: has received fees for consultancy from Abbott/AbbVie and Ferring, fees for lectures from Abbott and Janssen, travel expenses from Merck, and has stock/ stock options in Pfizer, Glaxo Smith Kline, Proctor and Gamble, and Johnson and Johnson. All of these financial activi-

▪ All studies regardless of publication status or language. **Exclusion Criteria:** –		that serum CRP, FC, and SL are potentially useful diagnostic tools that might aid in triaging patients with an established diagnosis of IBD for endoscopic evaluation when they present with symptoms of active disease. However, their utility is highly specific to the clinical context. Larger studies are needed to further characterize these biomarkers and determine their optimal applications in clinical practice.	Shastri Y (2008) Gastroenterology Schoepfer AM (2010) Am J Gastroenterol Schoepfer AM (2013) Inflamm Bowel Dis Sipponen T (2008) Inflamm Bowel Dis Yamamato T (2013) United European Gastroenterol J	ties are outside the submitted work. W.J.S.: has received consultancy fees from Abbvie, Abbott Laboratories, ActoGeniX NV, AGI Therapeutics, Alba Therapeutics Corporation, Albireo, Alfa Wasserman, Amgen, AMPharma BV, Anaphore, Astellas Pharma, Athersys, Atlantic Healthcare Limited, Axcan Pharma (now Aptalis), BioBalance Corporation, Boehringer-Ingelheim, Bristol Meyers Squibb, Celegene, Celek Pharmaceuticals, Cellerix SL, Cerimon Pharmaceuticals, ChemoCentryx, CoMentis, Cosmo Technologies, Coronado Biosciences, Cytokine Pharmasciences, Eagle Pharmaceuticals, Eisai Medical Research, Elan Pharmaceuticals, EnGene, Eli Lilly, Enteromedics, Exagen Diagnostics, Ferring Pharmaceuticals, Flexion Therapeutics, Funxional Therapeutics Limited, Genzyme Corporation, Genentech (now Roche), Gilead Sciences, Given Imaging, Glaxo Smith Kline, Human Genome Sciences, Ironwood Pharmaceuticals (previously Microbia), Janssen (previously Centocor), KaloBios Pharmaceuticals, Lexicon Pharmaceuticals, Lycera Corporation, Meda Pharmaceuticals (previously Alaven Pharmaceuticals), Merck Research Laboratories, MerckSerono, Millennium Pharmaceuticals (subsequently merged with Takeda), Nisshin Kyorin Pharamceuticals, Novo Nordisk A/S, NPS Pharmaceuticals, Optimer Pharmaceuticals, Orexigen Therapeutics, PDL Biopharma, Pfi zer, Procter and Gamble, Prometheus Laboratories, ProtAb Limited, Purgenesis Technologies, Relypsa, Salient Pharmaceuticals, Salix, Santarus, Schering Plough Corporation (acquired by Merck), Shire Pharmaceuticals, Sigmoid Pharma Limited, Sirtris Pharmaceuticals (a GSK company), S.L.A. Pharma (UK) Limited, Targacept, Teva Pharmaceuticals, Therakos, Tillotts Pharma AG (acquired by Zeria Pharmaceuticals), TxCell SA, UCB Pharma, Viamet Pharmaceuticals, Vascular Biogenics Limited (VBL), Warner Chilcott UK Limited, Wyeth (now Pfizer). Dr Sandborn's grant and research funding include: Abbott Laboratories, Bristol Meyers Squibb, Genentech, Glaxo Smith Kline, Janssen (previously Cento-

				cor), Millennium Pharmaceuticals (now Takeda), Novartis, Pfizer, Procter and Gamble Pharmceuticals, Shire Pharmaceuticals, and UCB Pharma. Payments for lectures including service on speakers' bureaus are from Abbott Laboratories, Bristol Meyers Squibb, and Janssen (previously Centocor). All of these financial activities are outside the submitted work. B.G.F.: discloses that he has received Grants or Research Support from Abbott/ AbbVie, Amgen, Astra Zeneca, Bristol-Myers Squibb (BMS), Janssen Biotech (Centocor), JnJ/ Janssen, Roche/Genentech, Millennium, Pfizer, Receptos, Santarus, Sanofi, Tillotts, UCB Pharma has consulted for Abbott/ AbbVie, Actogenix, Albireo Pharma, Amgen, Astra Zeneca, Avaxia Biologics Inc., Avir Pharma, Axcan, Baxter Healthcare, Biogen Idec, Boehringer-Ingelheim, Bristol-Myers Squibb, Calypso Biotech, Celgene, Elan/Biogen, En-Gene, Ferring Pharma, Roche/ Genentech, GiCare Pharma, Gilead, Given Imaging, GSK, Ironwood Pharma, Janssen Biotech (Centocor), JnJ/Janssen, Kyowa Kakko Kirin, Lexicon, Lilly, Merck, Millennium, Nektar, Novonordisk, Pfizer, Prometheus Therapeutics and Diagnostics, Protagonist, Receptos, Salix Pharma, Serono, Shire, Sigmoid Pharma, Synergy Pharma, Takeda, Teva Pharma, TiGenix, Tillotts, UCB Pharma, Vertex Pharma, Warner- Chilcott, Wyeth, Zealand, Zyngenia is a speaker for Abbott/AbbVie, JnJ/Janssen, Takeda, Warner-Chilcott, UCB Pharma is a member of the scientific advisory board of Abbott/ AbbVie, Amgen, Astra Zeneca, Avaxia Biologics, Bristol-Myers Squibb, Celgene, Centocor, Elan/Biogen, Ferring, JnJ/ Janssen, Merck, Novartis, Novonordisk, Pfizer, Prometheus Laboratories, Protagonist, Salix Pharma, Takeda, Teva, TiGenix, Tillotts Pharma AG, and UCB Pharma an **Study Quality:** 3 studies included a small number of healthy controls that did not undergo colonoscopy. Low risk of partial or differential verification or incorporation bias among studies. **Heterogeneity:** Substantial differences between studies in clinical and endoscopic end point

				criteria and test cut-off points. Sensitivity for CU: Q = 39.56, df = 15.00, P = 0.00 I2 = 62.08 (41.54 – 82.62). Specificity: Q = 67.59, df = 15.00, P = 0.00 I2 = 77.81 (67.32 – 88.30) **Publication Bias:** No statistically significant risk of publication bias was observed for all three biomarkers (CRP: coefficient = −19.34, P = 0.117 95 % CI: −44.96 to 6.27, FC: coefficient = −9.712 078, P = 0.085 95 % CI: −20.86 to 1.43, and SL: P = 0.277 95 % CI: −63.49 to 21.81) Oxford LoE 1 for validating diagnostic studies.

Lin, J.F. et al. Meta-analysis: fecal calprotectin for assessment of inflammatory bowel disease activity. Inflamm Bowel Dis. 20. 1407 – 1415. 2014

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** MA of 13 prospective studies **Databases:** Medline, Web of Science, Cochrane Library, EMBASE **Search period:** ?–Dec. 2013 **Inclusion Criteria:** (1) Study evaluated FC for monitoring IBD activity (2) An endoscopic scoring system was used as reference standard to assess inflammatory activity (3) Study provided sufficient details to construct a 2-by-2 table. **Exclusion Criteria:** (1) Pediatric patients with IBD	**Intervention:** FC diagnostic and endoscopic evaluation. 1471 patients with IBD (744 UC 727 CD) **Comparison:** –	**Primary:** Diagnostic Accuracy of FC for disease activity **Secondary:** – **Results:** Sensitivity in CU: 0.88 (95 % CI 0.85 – 0.91) Specificity in CU: 0.82 (95 % CI 0.77 – 0.86) **Author's Conclusion:** The FC test is a reliable marker for assessing IBD disease activity and may have greater ability to evaluate disease activity in UC than CD.	Af Bjorkesten CG (2012) Scand J Gastroenterol D'Haens G (2012) Inflamm Bowel Dis Langhorst J (2008) Am J Gastroenterol Lobaton T (2013) J Crohns Colitis Nancey S (2013) Inflamm Bowel Dis Onal IK (2012) Turk J Gastroenterol Schoepfer AM (2009) Inflamm Bowel Dis Schoepfer AM (2010) Am J Gastroenterol Schoepfer AM (2013) Inflamm Bowel Dis Sipponen T (2008) Inflamm Bowel Dis Vieira A (2009) BMC Res Notes Yamamato T (2013) United European Gastroenterol J	**Funding Sources:** B. Nie and B. Jiang were co-corresponding authors of the article. Supported by the NanFang Hospital Fund for Distinguished Young Scholars, Grant 2013JQ03. COI: The authors have no conflicts of interest to disclose. **Study Quality:** Only 1 study with representative spectrum. 1 study without acceptable reference standard, 1 study without acceptable delay between tests, 1 study did not avoid differential verification. **Heterogeneity:** Moderate Heterogeneity. **Sensitivity-Anaylses:** Q-Value 15.07 (P = 0.0351, I^2 = 53.5 %) **Specificity-Anaylses:** Q-Value 20.91 (P = 0.0039, I^2 = 66.5 %) **Publication Bias:** Funnel plot indicated asymmetry Deeks' test showed statistically nonsignificant value (P = 0.425), indicating no publication bias **Notes:** Oxford LoE 1 for validating diagnostic studies.

Mao, R. et al. Fecal calprotectin in predicting relapse of inflammatory bowel diseases: a meta-analysis of prospective studies. Inflamm Bowel Dis. 18. 1894 – 1899. 2012

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** MA of 6 prospective studies **Databases:** MEDLINE, EMBASE, Web of Science, Cochrane Database **Search period:** ? – August 2011 **Inclusion Criteria:** (1) prospective studies about using FC in predicting IBD relapse (2) FC level for	**Intervention:** Fecal Calprotectin assessment in 672 IBD patients (UC: 318 CD: 354) **Comparison:** –	**Primary:** Predictive Capacity of Fecal Calprotectin in IBD Relapse IBD **Secondary:** – **Results:** Sensitivity for CU: 0.77 (95 % CI 0.67 – 0.85) Specificity for CU: 0.71 (95 % CI 0.64 – 0.77) PLR for CU: 2.47 (95 % CI 1.92 – 3.19) NLR for CU: 0.36 (95 % CI 0.24 – 0.53)	Kallel L (2010) Eur J Gastroenterol Hepatol García-Sánchez V (2010) J Crohns Colitis Gisbert JP (2009) Gastroenterol Hepatol D'Inca R (2008) Am J Gastroenterol Costa F (2005) Gut Tibble JA (2000) Gastroenterology	**Funding Sources: Not stated** COI: Not stated **Study Quality:** One study used an old method assay (Roseth) to investigate FC. Due to the limited number of included studies, study quality scores (QUADAS) were not taken into account for meta- analysis. **Heterogeneity:** Q-Value for Sensitivity: 3.47 (P = 0.32)

predicting IBD relapse was measured at remission (3) estimates of diagnostic accuracy (such as sensitivity or specificity) (4) the identification of relapse is based on clinical activity indices or endoscopic findings (5) studies were conducted in human, nonpediatric populations **Exclusion Criteria:** –		DOR for CU: 7.70 (95 % CI 3.93 – 15.09) AUC: 0.78 (SEM: 0.04) **Author's Conclusion:** In conclusion, the current evidence suggests a potential role for FC in predicting relapse of quiescent IBD. Although the overall test performance including sensitivity and specificity is not as high as expected, measuring FC levels at clinical remission can be used to predict IBD relapse due to its simplicity and noninvasiveness.		Q-Value for Specificity: 3.22 (P = 0.36) PLR for CU: 2.94 (P = 0.40) NLR for CU: 3.08 (P = 0.38) DOR for CU: 3.60 (P = 0.31) **Publication Bias:** Significant potential for publication bias: Egger test showed significant result (P < 0.05). **Notes:** Oxford LoE 1 for validating diagnostic studies.

Jellema, P. et al. Inflammatory bowel disease: a systematic review on the value of diagnostic testing in primary care. Colorectal Dis. 13. 239 – 254. 2011

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 Study type: MA of 24 primary diagnostic studies (13 cohort studies, 10 [nested] case–control studies, 1 study with both designs) **Databases:** PubMed, Embase **Search period:** ? to February 2009 **Inclusion Criteria:** (1) studies with populations consisting of adult patients consulting a physician because of nonacute gastrointestinal symptoms; (2) primary care or open- access clinics setting; (3) studies carried out in an outpatient population with a prevalence of IBD of 25 % or less; (4) cohort design and case– control designs in which control subjects were diagnosed with the irritable bowel syndrome or in whom organic gastrointestinal disease was excluded (5) studies using colonoscopy, histology, barium enema and/or clinical follow up to diagnose IBD **Exclusion Criteria:** (1) case–control study designs with healthy control subjects or control subjects with a specific disease; (2) studies for which no two-by-two table could be extracted or reconstructed (including case series consisting solely of IBD	**Intervention:** (i) signs and symptoms (including alarm symptoms), individual or in combination (including symptom- based classification systems) (ii) blood and faecal tests (iii) abdominal ultrasonography **No. of included patients not reported on study or overall level.** **Comparison:** Not reported.	**Primary:** Diagnostic performance: **Results for IBD** **Secondary:** – **Results: Symptoms:** No pooled result due to high heterogeneity. **Blood and faecal tests:** CRP: Highly variable performance. Sensitivity from 0.55 (cut-off 5 mg/l) to 1.00 (cut-off 2.3 mg/l), Specificity from 0.42 (cut-off 6 mg/l) to 0.90 (cut-off 5 mg/l). *ESR:* Sensitivity from 0.56 (cut-off not reported) to 0.78 (cut-off 15 mm/h). Specificity from 0.75 (cut-off not reported) to 0.96 (cut-off 10 mm/h). *Calprotectin:* Sensitivity from 0.61 (cut-off 60 mg/kg) to 1.0 (varying cut-off level ranging 10 mg/l–170 µg/g). Specificity from 0.71 (cut-off 50 µg/g) to 1.0 (varying cut-off level ranging 15 µg/g - 90 µg/g) **Ultrasonography:** Pooled estimate for sensitivity: 0.73 (95 % CI 0.65 – 0.80). Pooled estimate for specificity: 0.95 (95 % CI 0.91 – 0.97). **Author's Conclusion: -** Although calprotectin and ultrasonography showed consistent and promising findings, none of the studies was performed in primary care. To assist primary care physicians in diagnostic decision making, we urgently need high quality studies performed in primary care.	Astegiano M (2001) Eur J Gastroenterol Hepatol Bellentani S (1990) Fam Pract Bozkurt T (1994) J Clin Ultrasound Brewster NT (1994) Br J Surg Carroccio A (2003) Clin Chem Chalubinski K (1987) Wien Klein Wochenschr D'Inca R (2007) Int J Colorectal Dis Dolwani S (2004) Aliment Pharmacol Ther Duerr RH (1991) Gastroenterology Fine KD (1998) Am J Gastroenterol Kaiser T (2007) investigated. Gut **Notes:** Kruis W (1984) Gastroenterology Limburg PJ (2000) Am J Gastroenterol Metcalf JV (1996) Br J Gen Pract Otten CM (2008) Clin Chem Lab Med Pallotta N (2005) Inflamm Bowel Dis Poullis AP (2002) Eur J Gastroenterol Hepatol Schroder O (2007) Aliment Pharmacol Ther Sheridan MB (1993) Clin Radiol Shine B (1985) Clin Chim Acta Thompson WG (1984) Gut Tibble J (2000) Gut Wassell J (2004) Ann Clin Biochem	**Funding Sources:** This study was supported by a grant (no. 945-06-001) from The Netherlands Organization for Health Research and Development (ZonMw), The Hague, The Netherlands. **COI: Not stated.** **Study Quality:** Potential sources of bias most frequently identified related to selection of study participants, appropriateness of reference standard and differential verification bias. The following aspects were poorly described (score 'unclear'): time between index and reference test and withdrawals. Generally, seven studies performed well, receiving a positive assessment of at least 8 of 11 QUADAS items. **Heterogeneity:** Only stated as substantial and reason for refraining from certain subgroup analyses. **Publication Bias:** Not Oxford LoE 2 for validating diagnostic studies. Search strategy only available on request.

patients); (3) studies written in languages other than English, Dutch, German or French; (4) reviews, editorials, case reports; (5) studies using sigmoidoscopy as the single reference test			Whitehead WE (2006) Aliment Pharmacol Ther	

Menees, S. B. et al. A meta-analysis of the utility of C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin, and fecal lactoferrin to exclude inflammatory bowel disease in adults with IBS. Am J Gastroenterol. 110. 444 – 454. 2015

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** MA of 12 prospective diagnostic cohort studies **Databases:** Medline (1950 to March 2014), EMBASE (1947 to March 2014), Cochrane library (1993 to March 2014), Web of Science (1900 to March 2014), and PubMed (1950 to March 2014). **Search period:** Inception - March 2014 **Inclusion Criteria:** (i) human studies in adults that compare CRP, ESR, fecal calprotectin, or fecal lactoferrin with confirmed diagnosis of IBD with IBS or healthy control (HC) subjects (ii) studies that utilize the enzyme-linked immunosorbent assay for fecal calprotectin, not the point of care testing (iii) used Manning or Rome Criteria for IBS diagnosis (iv) provided sufficient data (studies must give medians and either confidence intervals for the median, interquartile ranges, or ranges). **Exclusion Criteria:** If there were multiple papers published based on the same or overlapping data sets, then only the paper with the highest number of subjects, the most detailed results, and the longest follow-up time was included.	I**ntervention:** N = 2145: 1059 IBD, 595 IBS, and 491 HC. The IBD, IBS, and HC cohorts were 52.7 %, 29.9 %, and 53.5 % male, respectively. The mean age for the IBD, IBS, and HC cohorts was 40.7 (± 13.3), 40.0 (± 18.2), and 38.7 (± 13.8) years, respectively. **Comparison:** –	**Primary:** Utility of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fecal calprotectin, and fecal lactoferrin to distinguish between patients with IBS and inflammatory bowel disease (IBD) and healthy controls (HCs). **Secondary:** – **Results: C-reactive protein:** A CRP level of ≥ 1.7 mg/dl has a > 52 % predictive probability of IBD. Levels > 2.7 mg/dl have more than a 90 % likelihood of IBD. A CRP of ≤ 0.5 predicted a 1 % or lower likelihood of IBD. **Erythrocyte sedimentation rate:** An elevated level of ESR was not predictive of IBD and did not discriminate IBD patients from those with IBS or HCs. **Fecal calprotectin:** For IBD, as the level of fecal calprotectin increases, so does the likelihood of IBD with the maximal predictive value of 78.7 % at 1000 µ /g. However, a patient with a level of < 40 µ g/g has a 1 % chance or less of having IBD. On the other hand, a low or high level of fecal calprotectin could not completely exclude IBS. **Fecal lactoferrin:** In IBD, the maximal predictive likelihood of disease for fecal lactoferrin was 20.4 % at 1810 µg/g. A level of 10 µg/g had a 2 % probability of IBD. **Author's Conclusion:** CRP and calprotectin of ≤ 0.5 or 40, respectively, essentially excludes IBD in patients with IBS symptoms. The addition of CRP and calprotectin to symptom-based criteria may improve the confident diagnosis of IBS.	Costa F (2003) Dig Liver Dis Carroccio A (2003) Clin Chem Dolwani S (2004) Aliment Pharmacol Ther Schoepfer AM (2013) Inflamm Bowel Dis Schroder O (2007) Aliment Pharmacol Ther Li XG (2006) Beijing Da Xue Xue Bao Strid H (2013) J Crohns Colitis Boehm D (2012) Clin Chem Lab Med Oikonomou KA (2012) J Gastroenterol Sidhu R (2010) Aliment Pharmacol Ther Wassell J (2004) Ann Clin Biochem	**Funding Sources:** This study was supported by Division of Gastroenterology, University of Michigan Health System. **COI:** Potential competing interests: William D. Chey is a consultant for Salix Pharmaceuticals. Stacy Menees, Corey Powell, Jacob Kurlander, and Akash Goel declare no conflict of interest. **Study Quality:** Overall, the applicability of the included studies was fair for the aim of the present study. The areas called into question through the QUADAS tool included the representative spectrum of the diagnostic studies as 8 of the 12 had recruited patients with the target disorders (IBS and IBD) and HCs. For seven studies, some participants received verification of their diagnosis of IBD using a different reference standard. Five of the studies did not have clear selection criteria described nor was the selection of who received the index test random. Finally, there were unclear data for the delay between the tests, blinding of the reference test, and details regarding whether the reference standard was independent of the index test. **Heterogeneity:** For CRP IBD, IBS, and HC groups, the I2 statistic was 76.4 %, 94.6 %, and 0 %, respectively. **Publication Bias:** Not investigated. **Notes:** Oxford LoE 1 for exploratory diagnostic studies.

Boon, G.J. et al. Are faecal markers good indicators of mucosal healing in inflammatory bowel disease?. World J Gastroenterol. 21. 11 469 – 480. 2015

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** SR of 36? **Databases:** Medline **Search period:** ? – February 2015 (Inclusion criteria: 1990 and February 2014) **Inclusion Criteria:** (1) Studies assessing mucosal inflammation by endoscopic and/or histological means and compared these findings to faecal marker concentrations in IBD patient cohorts; (2) Articles published between 1990 and February 2014; (3) Publication in English **Exclusion Criteria:** (1) Comparisons of faecal biomarker concentration between patients with IBD and controls or other disease group; (2) Use of serum biomarkers; (3) Heterogeneous study population; (4) Assessment of post-operative disease.	**Intervention:** No explicit information on overall sample size: Studies comprised variable numbers of study participants, considered CD (15-164 participants) or UC (12-152 participants) separately or as a combined group (11-252 participants). 8 Studies with pediatric population. **Comparison:** Faecal markers concentrations: 33 studies on feacal calprotectin, 13 studies on faecal lactoferrin, 1 study on S100A12.	**Primary:** Ability of FC to determine endoscopic disease activity **Secondary:** – **Results:** Available data do not indicate the optimal roles of markers. Wide range of correlation between faecal markers and endoscopic disease activity across all markers: r values ranging from 0.32 to 0.87, P values ranging from < 0.0001 to 0.7815). Few studies evaluated faecal calprotectin and/or faecal lactoferrin and their relationship with endoscopic disease activity showing inconsistent results. **Author's Conclusion:** Future studies should report the results of faecal inflammatory markers in the context of mucosal healing with clear validated cut offs.	af Björkesten CG (2012) Scand J Gastroenterol Aomatsu T (2011) Dig Dis Sci Bunn SK (2001) J Pediatr Gastroenterol Nutr Canani RB (2008) Dig Liver Dis Cellier C (1994) Gut D'Incà R (2007) Int J Colorectal Dis D'Haens G (2012) Inflamm Bowel Dis Denis MA (2007) Inflamm Bowel Dis Fagerberg UL (2007) J Pediatr Gastroenterol Nutr Falvey JD (2015) Inflamm Bowel Dis Hanai H (2004) Dig Dis Sci Jones J (2008) Clin Gastrenterol Kaiser T (2007) Gut Kolho KL (2006) Scand J Gastroenterol Komraus M (2012) Mediators Inflamm Kristensen V (2015) J Crohns Colits Langhorst J (2008) AM J Gastrenterol Lobatón T (2013) J Crohns Colitis Molander P (2013) J Crohns Colits Moran A (1995) Scand J Gastroenterol Nakarai A (2013) Am J Gastroenterol Nancey S (2013) Inflamm Bowel Dis Pfefferkorn MD (2010) J Pediatr Gastroenterol Nutr Røseth AG (2004) Scand J Gastroenterol Røseth AG (2007) Digestion Schoepfer AM (2007) Dis Colon Rectum Schoepfer AM (2009) Inflamm Bowel Dis Schoepfer AM (2010) AM J Gastroenterol Schoepfer AM (2010) AM J Gastroenterol Silberer H (2005) Clin Lab Sipponen T (2008) Aliment Pharmacol Ther Sipponen T (2008a) Inflamm Bowel Dis Sipponen T (2008b) Inflamm Bowel Dis Sipponen T (2010) Scand J Gastroenterol Vieira A (2009) BMC Res Notes	**Funding Sources:** No specific funding was obtained for this study. **COI:** There is no relevant conflict of interests for the authors contributing to this study. **Study Quality:** No systematic selection or assessment of study quality. No statement of included study types. Widely heterogeneous study populations. **Heterogeneity:** High due to inconsistent cutoff values, inflammation scores, study populations. **Publication Bias:** Not investigated. **Notes:** Bibliographical search only in MEDLINE. No detailed information on search query. Exclusion criteria "heterogeneous study population" not elaborated. Insufficient information on selection process. No assessment of study quality.

AG 1: Wie und wann soll eine Eisenmangel-Diagnostik durchgeführt werden?

Bewertungsvorlage:
Oxford SR

Avni, T. et al. Treatment of anemia in inflammatory bowel disease–systematic review and meta-analysis. PLoS One. 8. e75 540. 2013

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** MA of 9 RCT **Databases:** MEDLINE, CENTRAL, The Cochrane Library, NLM gateway, American Society of Gastroenterology, www.controlled-trials.com, www.clinicaltrials.gov, www.clinicaltrials.nci.nih.gov. **Search period:** MEDLINE: 1/1966 - 1/2013, Conference proceedings: 2007 onwards **Inclusion Criteria:** (1) Randomized controlled trials; (2) Comparison of any treatment for anemia in patients with IBD; (3) No restriction on publication status (published, conference proceedings, or unpublished), trial years or language **Exclusion Criteria:** –	**Intervention:** 973 patients (395 CD, 578 CU) Range of median age: 26 – 46 60.8 % Women. Oral vs. IV iron preparations, ESAs versus placebo **Comparison:** –	**Primary:** Hemoglobin response **Secondary:** Disease severity scores (Inflammatory Bowel Disease Questionnaire (IBDQ) scores, The Harvey-Bradshaw Simple Index scores (HBSI), Crohn's Disease Activity Index (CDAI) diary card and UC) iron indices (ferritin concentration and transferrin saturation (TSAT), Hb levels or absolute change in Hb level at the end of follow- up red blood cell transfusion requirements, inflammatory markers CRP levels) number of patients with treatment failure adverse effects (AEs) (severe AEs, AEs leading to discontinuation and by involved organ), QOL scores, and mortality. **Results: IV versus oral iron:** *Hemoglobin response:* IV iron associated with higher rate of achieving a 2 g/dl increase in Hb concentration in comparison to oral iron RR 1.25 (95 % CI 1.04 – 1.51, I2 = 2 %, 4 trials), risk difference: 0.13 (number needed to treat: 7.69). After exclusion of 1 trial with unclear risk for bias: RR 1.21 95 % CI 1.01 – 1.46, I2 = 0 %, 3 trials. *Iron indices:* IV iron treatment superior to oral iron preparation: WMD = 107.5 ng/mL (95 % CI 24.7 – 190.2, I2 = 99 %, random effects model). *Clinical parameters:* No significant effects by IV iron regarding CRP levels (WMD 0.35 mg/l, 95 % CI-1.51 – 2.42, I2 = 75 %, random effects model) or Disease activity indexes (for UC, CAI score, WMD: 0.45 points, 95 % CI 0.82 – 1.71, I2 = 88 %, random effects model). No data on QoL or all-cause mortality. *Adverse events:* No increase in SAEs with IV iron (RR = 1.03 95 % CI 0.4 – 2.6.	Erichsen K (2005) Scand J Gastroenterol Erichsen K (2005) Aliment Pharmacol Ther Evstatiev R (2011) Gastroenterology Gasche C (1997) Ann Intern Med Kulnigg S (2008) Am J Gastroenterol Kulnigg-Dabsch S (2013) Inflamm Bowel Dis Lindgren S (2009) Scand J Gastroenterol Schreiber S (1996) N Engl J Med Schröder O (2005) Am J Gastroenterol	**Funding Sources:** The authors have no support or funding to report. **COI:** The authors have declared that no competing interests exist. **Study Quality:** Allocation generation was adequate (low risk for bias) in 6 trials allocation concealment was adequate in 5. One trial was double blinded. In 5 trials, the primary outcome was analysed by intention to treat. **Heterogeneity:** Low to high heterogeneity due to different interventions, inclusion and exclusion criteria and follow-up time, the clinical outcomes (Hb response, disease severity scores and AEs) **Publication Bias:** Not investigated. **Notes:** Thorough search for unpublished/grey literature.

		I2 = 41 %). Decrease in AEs that required discontinuation of intervention with IV iron (RR = 0.13, 95 % CI 0.05 – 0.38, I2 = 0 %) and decrease in gastrointestinal AEs (RR 0.25, 95 % CI 0.06 – 0.95, I2 = 61 %, random effects model). Increase in nonserious transfusion reaction (RR 3.07, 95 % CI 1.23 – 7.6, I2 = 30 %). **ESAs versus placebo:** *Hemoglobin response:* ESA administration associated with non-significant increase in achieving a 2 g/dl increase in HB levels: RR 1.99 (95 % CI 0.56 – 7.14, I2 = 87 %, random effects model). No data available for clinical outcomes. *Iron indices and Hb level:* Hb levels increased with ESA by a WMD of 2.32 g/L (95 % CI 1.33 – 3.32, I2 = 63 %). Adverse Events: Statistically insignificant effect for transfusion reactions to ESAs: RR 3.21 (95 % CI 0.54 – 19.11). **Author's Conclusion:** Treatment for anemia in IBD should include IV iron and not oral iron replacement, due to improved Hb response, no added toxicity and no negative effect on disease activity.		

Filmann, N. et al. Prevalence of anemia in inflammatory bowel diseases in european countries: a systematic review and individual patient data meta-analysis. Inflamm Bowel Dis. 20. 936 – 945. 2014

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** MA of 6? **Databases:** PubMed, Embase **Search period:** January 2007 - May 2012 **Inclusion Criteria:** (1) Original full- paper publications from Europe that evaluated the prevalence of anemia in patients with IBD. **Exclusion Criteria:** (1) reviews, letters to the editor, abstracts; (2) data from countries outside Europe, data of children, or of in-hospital patients; (3) patient data does not include any laboratory tests showing anaemia	**Intervention:** 2192 IBD patients with assessment of anemia **Comparison:** –	Primary: Prevalence of anemia **Secondary:** – **Results:** Overall prevalence of anemia in IBD patients: 24 % (95 % CI, 18 – 31) Overall prevalence of severe anemia in IBD patients: 2.75 % (95 % CI, 1.4 – 4.5) Prevalence of anemia in CU-patients: patients 21 % (95 % CI, 15 – 27). Iron deficiancy in IBD: 57.32 % of anemic patients had transferrin saturation below 16 % or serum ferritin below 30 mg/L (patients in remission)/below 100 mg/L (patients during active disease)	Bager P (2011) Scand J Gastroenterol Blumenstein I (2008) Inflamm Bowel Dis/ Blumenstein I (2011) J Crohns Colitis Oustamanolakis P (2011) J Crohns Colitis Bergamaschi G (2010) Haematologica Bager P (2011) Scand J astroenterol	**Funding Sources:** Not stated. **COI:** The authors have no relevant conflicts of interest to disclose. **Study Quality:** Selection of included study samples with high risk of bias regarding representativity of study population. High prevalences of anemia in studies from Greece (42 %) and Italy (37 %) partly explained by the differing health care systems. **Heterogeneity:** Stated as high but not quanitified. **Publication Bias:** Not investigated. **Notes:** Last search ended 2 years before publication. Search query likely missed relevant publications. German data set to different research question and only available as additional sup-

		Author's Conclusion: In summary, the present meta-analysis with individual patient data from 6 studies with overall 2192 patients revealed a homogeneous prevalence of anemia of around 24 % patients with IBD in Europe.		plement document included without comprehensive description of reasons for inclusion. No quality assessment of these data possible due to missing information on all characteristics. Study design of included studies not stated.

AG 1: Wie sollte bei histologischer Diagnosestellung einer niedriggradigen, bzw. hochgradigen IEN vorgegangen werden?

Bewertungsvorlage:
Oxford SR

Iannone, A. et al. Chromoendoscopy for surveillance in ulcerative colitis and Crohn's disease: a systematic review of randomized trials. Clin Gastroenterol Hepatol 2016

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** SR of 10 RCT **Databases:** MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials **Search period:** Inception – Sep 2016 **Inclusion Criteria:** (1) Randomized controlled trials which compared chromoendoscopy with other endoscopic techniques for the surveillance of dysplasia in people with ulcerative colitis and Crohn's disease; (2) Studies enrolling patients with a long course of ulcerative colitis or Crohn's disease (more than 8 years) and measuring the efficacy of chromoendoscopy and compared interventions **Exclusion Criteria:** (1) Trials comparing endoscopic techniques different from chromoendoscopy; (2) Trials evaluating surveillance data in general population and hereditary polyposis syndromes in the analyses	**Intervention:** 1500 participants with IBD. **Comparison:** 3 trials: chromoendoscopy vs. standard- definition white light endoscopy: 497 patients with UC 2 trials: chromoendoscopy vs. high-definition white light endoscopy: 313 patients with UC 4 trials: chromoendoscopy vs. narrow band imaging: 475 patients, 440 with UC 1 trial: chromoendoscopy vs. both high- definition white light endoscopy and i-SCAN: 225 patients without classification.	**Primary:** Of direct evidence: all-cause mortality, colorectal cancer-related mortality and time to interval cancer **Secondary:** Of indirect evidence: No. of patients diagnosed with one or more dysplastic lesions, No. of dysplastic lesions detected by targeted biopsies, test sensitivity and specificity (using histological examination as reference standard), procedural time **Results: All-cause mortality, colorectal cancer-related mortality and time to interval cancer:** No trial reported relevant data. **Number of patients diagnosed with one or more dysplastic lesions:** Higher likelihood with chromoendoscopy compared to **Morphological subtypes of dysplastic lesions:** No statistically significant differences in the likelihood of detecting non-polypoid or polypoid dysplastic lesions between chromoendoscopy and other techniques (RR = 1.26, 95 % CI 0.56 – 2.81 and RR = 0.65, 95 %CI 0.21 – 1.97). **Histological subtypes of dysplastic lesions:** No statistically significant differences. **Number of dysplastic lesions detected by targeted**	Kiesslich R (2003) Gastroenterology Kiesslich R (2007) Gastroenterology Feitosa F (2011) Inflamm Bowel Dis Pellisé M (2011) Gastrointest Endosc Bisschops R (2012) Gastrointest Endosc Freire P (2014) Inflamm Bowel Dis Mohammed N (2015) Gastrointest Endosc Iacucci M (2016) Gastroenterology Park SJ (2016) Gastroenterology Watanabe K (2016) Gastrointest Endosc	**Funding Sources:** All authors declare no financial, professional, or personal conflict. **COI:** All authors declare no financial, professional, or personal conflict. **Study Quality:** Random sequence generation adequate in 3 trials, unclear in the other 7. Allocation concealment inadequate in 2 studies, unclear in the other 8. 4 trials with adequate and 6 trials with unclear blinding of participants + investigators + outcome assessment. Per protocol-analysis in 4 studies and not reported in 6. Withdrawal of randomly assigned participants from analyses < 10 % in 2 trials, > 10 % in 2 trials, not reported in 6. **Heterogeneity:** Number of patients diagnosed with one or more dysplastic lesions: $Chi^2 = 9.75$, $I^2 = 0\,\%$ **Morphological subtypes of dysplastic lesions:** Moderate heterogeneity in detection of non-polypoid ($Chi^2 = 3.84$, $I^2 = 48\,\%$) and polypoid ($Chi^2 = 5.85$, $I^2 = 66\,\%$) dysplastic lesions **Procedural time:** High heterogeneity ($Chi^2 = 106.31$, $I^2 = 97\,\%$) **Publication Bias:** Not investigated. **Notes:** Search query presented in Supplement (not available).

		biopsies: No statistically significant differences. **Procedural time:** Significant longer time of procedure comparing chromoendoscopy to other techniques (4 trials, 623 participants, MD = 8.91 minutes, 95 % CI 1.37 – 16.45). **Test sensitivity and specificity:** *Chromoendoscopy:* Test sensitivity ranging from 63 % to 100 %, Specificity from 90 % to 98 %. *Standard-definition white light endoscopy and narrow band imaging:* Test sensitivity between 50 % to 80 % and between 50 % to 100 %. *High-definition white light endoscopy:* Test sensitivity from 94 % to 100 %, Specificity of 85 %. *i-SCAN:* Sensitivity: 72 %, Specificity: 92 %. **Author's Conclusion:** In surveillance of inflammatory bowel diseases, chromoendoscopy identifies more patients with dysplasia only when compared to standard- definition white light endoscopy. It is associated with longer procedural time with no direct evidence of effect on preventing all-cause/cancer-specific mortality or time to interval cancer.		

Subramanian, V et al. Meta-analysis: the diagnostic yield of chromoendoscopy for detecting dysplasia in patients with colonic inflammatory bowel disease (Structured abstract). Alimentary Pharmacology and Therapeutics. 33. 304 – 312. 2011

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** MA of 6 (2 RCT, 4 prospective cohort) **Databases:** Pubmed (1965 - February 2010), Embase (1974 -February 2010), Ovid (1965 -February 2010), CINAHL (1982 -February 2010), Zetoc (1993 - February 2010), Ingenta (1991 -February 2010) **Search period:** – **Inclusion Criteria:** (1) prospective inclusion of patients with colonic inflammatory bowel disease; (2) surveillance colonoscopy and comparison of CE with standard	**Intervention:** Four studies with UC patients (over 8 years duration, in remission), 1 study pancolitis patients (over 5 years duration), 1 study with extensive UC and CD (involving more than one third of the colon). No details on age/ sex. WLE followed by CE: 259 patients CE compared to different controls: 700 patients 267 patients randomized 1:1 to WLE or CE **Comparison:** –	**Primary:** Incremental yield (IY) of detecting any dysplastic lesions **Secondary:** Differences in proportion of lesions detected by targeted biopsies, differences in proportion of flat lesions detected, differences in proportion of dysplastic lesions detected by random biopsy alone (miss rates), time taken for the procedure **Results:** Pooled IY of CE over WLE for the detection of any grade of dysplasia on a per patient basis: 7 % (95 % CI 3.2 – 11.3, no P-value). Differences in proportion of lesions detected by targe-	Kiesslich R 2003 Gastroenterology Matsumoto T 2003 Am J Gastroenterol Rutter MD 2004 Gut Hurlstone DP 2005 Endoscopy Kiesslich R 2007 Gastroenterology Marion JF 2008 Am J Gastroenterol	**Funding Sources:** Declaration of funding interests: None. **COI:** Krish Ragunath has received research funding from Olympus (Keymed, UK). Subramanian conceived the study, abstracted data, data analysis and manuscript preparation. Mannath abstracted data, data analysis and manuscript preparation. Ragunath and Hawkey were involved in critical review and editing of the manuscript. **Study Quality:** 1 study with unclear description of selection criteria. 3 studies with unclear description of reference standard. All studies without or unclear description of uninterpretable/intermediate test results. All studies without or

WLE; (3) sufficient information to allow calculation of yield of dysplasia (and 95 % CI's); (4) published as a full journal article; (5) any language **Exclusion Criteria:** –		ted biopsies: pooled increase in targeted dysplastic (low or high grade) lesion detection of CE over WLE: 44 % (95 % CI 28.6 – 59.1, no P-value). Detection of flat lesions: pooled increase in flat dysplastic (low or high grade) lesion detection of CE over WLE: 27 % (95 % CI 11.2 – 41.9, no P-value). Miss rates: pooled reduction in dysplastic lesions detected by random biopsy alone of CE over WLE: –40 % (95 % CI –52.8 to –27, no P-value). Duration of the procedure: pooled weighted difference in means between CE and WLE: 11 min (95 % CI 10 min 15 s to 11 min 43 s, no P-value). False positive results: Only data with CE available. No pooled analyses. **Author's Conclusion:** In summary, CE is superior to WLE for dysplasia detection in patients with colonic IBD undergoing surveillance colonoscopy. IY of CE over WLE is 7 % for all dysplastic lesions, primarily due to increased yield of targeted biopsies from visualisation of additional lesions by CE. As this analysis was designed to evaluate the yield of CE and WLE, it is not clear whether these results will translate into superior patient outcomes with CE. Randomised controlled trials are needed to clarify this issue.		unclear description of withdrawals. Heterogeneity: Pooled IY: Moderate heterogeneity (Cochran's Q = 8.1, P = 0.14 and I^2 = 38 %). Lesions detected by targeted biopsies: moderate heterogeneity (Cochran's Q = 9.1, P = 0.1 and I^2 = 45.03 %) Detection of flat lesions: low heterogeneity (Cochran's Q = 1, P = 0.8 and I^2 = 0 %) Miss rates: low heterogeneity (Cochran's Q = 3.3, P = 0.3 and I^2 = 9.3 %). Duration of the procedure: low heterogeneity (Cochran's Q = 2.8, P = 0.4 and I^2 = 0 %). **Publication Bias:** Detection of any dysplasia: Excluded by Egger's regression asymmetry test (P = 0.53, intercept = –0.99 and 95 % CI: –5.02 to 3.03) Yield of any dysplasia from targeted biopsies: Excluded by Egger's regression asymmetry test (P = 0.93, intercept = –0.23 and 95 % CI: –7.3 to 6.8) Detection of flat lesions: Excluded by Egger's regression asymmetry test (P = 0.18, intercept = 1.44 and 95 % CI: –1.6 to 4.5) Miss rates: Excluded by Egger's regression asymmetry test (P = 0.9, intercept = –2.7 and 95 % CI: –11.4 to 10.9). Duration of the procedure: Excluded by Egger's regression asymmetry test (P = 0.96, intercept = 0.05 and 95 % CI: –4.3 to 4.4) **Notes:** Oxford LoE 2 for validating diagnostic studies. Thorough search strategy. Simple pooled analyses of data without being weighted.

Wanders, L.K. et al. Cancer risk after resection of polypoid dysplasia in patients with longstanding ulcerative colitis: a meta-analysis. Clin Gastroenterol Hepatol. 12. 756 – 764. 2014

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** SR of 10 cohort studies **Databases:** MEDLINE (1966–February 2012) EMBASE (1986–February 2012), PubMed (February 2011–February 2013), The Cochrane library (?) Search period: – **Inclusion Criteria:** (1) Follow-up studies with histologically proven ulcerative colitis and defined	**Intervention:** 376 patients with inflammatory bowel disease (IBD) who had resected polypoid dysplasia and follow-up. 322 patients with reliable diagnosis of UC. **Comparison:** –	**Primary:** CRC risk after resection of polypoid dysplasia **Secondary:** – **Results:** Average duration of colitis before first detection of polypoid dysplastic lesion: 15.7 years (range, 0 – 57). Pooled CRC incidence: 5.3 (95 % CI, 2.7 – 10.1) per 1000 years of patient follow-up	Blonski W (2008) Scand J Gastroenterol Goldstone R (2011) Gastrointest Endosc Jess T (2006)Inflamm Bowel Dis Kisiel JB (2012) Inflamm Bowel Dis Medlicott SA (1997) Am J Gastroenterol Odze RD (2004) Clin Gastroenterol Hepatol Pekow JR (2010) Inflamm Bowel Dis	**Funding Sources:** Not stated. **COI:** These authors disclose the following: Evelien Dekker received research funding and equipment on loan from Olympus. Simon P.L. Travis received consulting fees from Abbott, Asahi-Kasei, Bristol- Myers Squibb, Cosmo Technologies, Coronado Biosciences, Ferring Pharmaceuticals, Genentech, Genzyme Corp, GlaxoSmithKline, Janssen, Lexicon Pharmaceuticals, Merck Research laboratories, Millenni-

polypoid lesions and raised lesions that were removed by polypectomy; (2) Clearly defined follow-up and outcomes (CRC, HGD, or DALM at colectomy and/or surveillance) **Exclusion Criteria:** (1) studies with data only on CRC in colitis; (2) studies focused on only flat LGD as primary outcome (defined as endoscopically normal mucosa or non-polypoid lesions); (3) studies with inadequate follow-up data (outcome data in the subgroup of patients with polypoid dysplasia during follow-up to at least CRC were not documented in the studies)		Pooled CRC + HGD incidence: 7.0 (95 % CI, 4.0 – 12.4) per 1000 patient years Pooled all dysplasia incidence:65 (95 % CI, 54 – 78) per 1000 patient years **Author's Conclusion:** In conclusion, the risk estimate of developing CRC after resection of polypoid dysplasia in colitis is low with narrow CIs, providing support for the strategy in recent guidelines, and is approximately one-third of previous estimates for flat dysplasia. However, the rate of development of any form of dysplasia is 10-fold higher than the CRC rate, necessitating close endoscopic follow-up of patients where this strategy is undertaken.	Rozen P (1995) Gastroenterology Rubin PH (1999) Gastroenterology Vieth M (2006) Gut	um Pharmaceuticals, Nisshin Kyorin Pharmaceuticals, Novartis, Novo Nordisk, NPS Pharmaceuticals, PDL Biopharma, Pfizer, Procter and Gamble, Santarus, Schering Plough, Shire Pharmaceuticals, Sigmoid Pharma Ltd, Tillotts Pharma AG, TxCell SA, UCB Pharma, and Warner Chilcott UK Ltd research grants from Abbott, Genentech, GlaxoSmithKline, Janssen, Novartis, Pfizer, Procter and Gamble, Shire Pharmaceuticals, and UCB Pharma payments for lectures/speakers bureaus from Abbott, Janssen, Ferring Pharmaceuticals, and Warner Chilcott and holds no stock/stock options. James E. East is on the Advisory board at Cosmo Pharmaceuticals and is a speaker for Abbott Laboratories. The remaining authors disclose no conflicts. **Study Quality:** 1 study with potential selection bias, 3 studies with compromised comparability, medium quality for outcome/exposure for all studies. **Heterogeneity:** CRC rate: Q-Value: 6.0 (9 degrees of freedom, P = 0.74), I^2 = 0.0 %. CRC/HGD: Q-Value: 10.9 (9 degrees of freedom, P = 0.28), I^2 = 17.3 %. All dysplasia rate: Q-Value: 45.4 (9 degrees of freedom, P< 0.001), I^2 = 80.2 %. **Publication Bias:** Publication bias was examined by funnel plots. No evidence of publication bias was found for CRC, CRC/HGD and all dysplasia outcomes. **Notes:** Search query likely missed relevant publications.

Broek, F J et al. Systematic review of narrow-band imaging for the detection and differentiation of neoplastic and nonneoplastic lesions in the colon (Structured abstract). Gastrointestinal Endoscopy. 69. 124 – 135. 2009

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** MA of 16 studies (14 RCT, 2 Cohort) **Databases:** Pubmed, EMBASE **Search period:** ? – April 3, 2008 **Inclusion Criteria:** Not described in detail, only studies in English were obtained. **Exclusion Criteria:** Not described.	**Intervention: RCT** : NBI: 537 patiens **Cohort:** NBI: 102 patients **Comparison: RCT:** WLE: 536 patients **Cohort** : WLE: 102 patients	**Primary:** Detection **Secondary:** Differentiation **Results: Detection:** No consistent or significant results. **Differentiation:** Sensitivity: 92 % (95 % CI, 89-94) Specificity: 86 % (95 % CI, 80-91) Overall accuracy: 89 % (95 % CI, 87-91) **Author's Conclusion:** In conclusion, this systematic review evaluated all available evidence on the diagnostic value of NBI with respect to the detection of colon neoplasia/adenomas	Rastogi A (2008) Gastrointest Endosc Machida H (2004) Endoscopy Su MY (2006) Am J Gastroenterol Chiu HM (2007) Gut East JE (2007) Gastrointest Endosc Hirata M (2007) Gastrointest Endosc Tischendorf JJ (2007) Endoscopy Katagiri A (2008) Aliment Pharmacol Ther	**Funding Sources:** Not stated. **COI:** The following authors report no disclosures relevant to this publication: J.B. Reitsma, E. Dekker. The following authors have disclosed actual or potential conflicts: F.J.C. van den Broek is supported by an unrestricted educational grant from Olympus Inc, Hamburg, Germany. W.L. Curvers is supported by an unrestricted research grant from Astra Zeneca, the Netherlands. P. Fockens has received a research grant from Olympus Inc. Tokyo, Japan. The department of Gastroenterology and Hepatology

		and the differentiation between neoplastic and nonneoplastic colon polyps. NBI is a relatively new technique that has extensively been studied in the last few years as it has become commercially available all over the world. Until now, NBI has failed to demonstrate an improved detection of neoplasia in the colon, and therefore its use in routine clinical practice will likely not improve the yield of neoplasia. The value of NBI for differentiating neoplastic from nonneoplastic colon polyps has proven to be associated with high sensitivity and specificity in experienced hands. Results on differentiation with NBI seem comparable to results achieved with chromoendoscopy however, future research should focus on defining learning curves, interobserver variation, and validation in general practice.		of the Academic Medical Centre Amsterdam has been provided with loan endoscopic equipment by Olympus Inc, Tokyo, Japan. **Study Quality:** Low or unclear quality regarding patient selection in 6 of 8 studies. Low or unclear quality regarding possibility for replication of the index test and reference standard in 5 of 8 studies. Low or unclear quality regarding applicability of results in daily practice in 7 of 8 studies. **Heterogeneity:** Not investigated **Publication Bias:** Not investigated **Notes:** Execution of search not presented comprehensively: Different strategy for PubMed and Embase. Presented search results not possibly retrieved with search query (too few). No description of inclusion/exclusion criteria. Heterogeneity not investigated.

AG 1: Wie und wann soll eine Überwachungskoloskopie durchgeführt werden?

Bewertungsvorlage:
Oxford SR

Iannone, A. et al. Chromoendoscopy for surveillance in ulcerative colitis and Crohn's disease: a systematic review of randomized trials. Clin Gastroenterol Hepatol 2016

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** SR of 10 RCT **Databases:** MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials **Search period:** Inception - Sep 2016 **Inclusion Criteria:** (1) Randomized controlled trials which compared chromoendoscopy with other endoscopic techniques for the surveillance of dysplasia in people with ulcerative colitis and Crohn's disease; (2) Studies enrolling patients with a long course of ulcerative colitis or Crohn's disease (more than 8 years) and measuring the efficacy of	**Intervention:** 1500 participants with IBD. **Comparison:** 3 trials: chromoendoscopy vs. standard- definition white light endoscopy:497 patients with UC 2 trials: chromoendoscopy vs. high-definition white light endoscopy: 313 patients with UC 4 trials: chromoendoscopy vs. narrow band imaging: 475 patients, 440 with UC 1 trial: chromoendoscopy vs. both high-definition white light endoscopy and i-SCAN: 225 patients without classification.	**Primary:** Of direct evidence: all-cause mortality, colorectal cancer-related mortality and time to interval cancer **Secondary:** Of indirect evidence: No. of patients diagnosed with one or more dysplastic lesions, No. of dysplastic lesions detected by targeted biopsies, test sensitivity and specificity (using histological examination as reference standard), procedural time **Results: All-cause mortality, colorectal cancer-related mortality and time to interval cancer:** No trial reported relevant data. **Number of patients diagnosed with one or more dysplastic lesions:** Higher	Kiesslich R (2003) Gastroenterology Kiesslich R (2007) Gastroenterology Feitosa F (2011) Inflamm Bowel Dis Pellisé M (2011) Gastrointest Endosc Bisschops R (2012) Gastrointest Endosc Freire P (2014) Inflamm Bowel Dis Mohammed N (2015) Gastrointest Endosc Iacucci M (2016) Gastroenterology Park SJ (2016) Gastroenterology Watanabe K (2016) Gastrointest Endosc	**Funding Sources:** All authors declare no financial, professional, or personal conflict. **COI:** All authors declare no financial, professional, or personal conflict. **Study Quality:** Random sequence generation adequate in 3 trials, unclear in the other 7. Allocation concealment inadequate in 2 studies, unclear in the other 8. 4 trials with adequate and 6 trials with unclear blinding of participants + investigators + outcome assessment. Per protocol-analysis in 4 studies and not reported in 6. Withdrawal of randomly assigned participants from analyses < 10 % in 2 trials, > 10 % in 2 trials, not reported in 6. **Heterogeneity:** Number of patients diagnosed with one or

chromoendoscopy and compared interventions **Exclusion Criteria:** (1) Trials comparing endoscopic techniques different from chromoendoscopy; (2) Trials evaluating surveillance data in general population and hereditary polyposis syndromes in the analyses		likelihood with chromoendoscopy compared to **Morphological subtypes of dysplastic lesions:** No statistically significant differences in the likelihood of detecting non-polypoid or polypoid dysplastic lesions between chromoendoscopy and other techniques (RR = 1.26, 95 % CI 0.56 – 2.81 and RR = 0.65, 95 %CI 0.21 – 1.97). **Histological subtypes of dysplastic lesions:** No statistically significant differences. **Number of dysplastic lesions detected by targeted biopsies:** No statistically significant differences. **Procedural time:** Significant longer time of procedure comparing chromoendoscopy to other techniques (4 trials, 623 participants, MD = 8.91 minutes, 95 % CI 1.37 – 16.45). **Test sensitivity and specificity:** *Chromoendoscopy:* Test sensitivity ranging from 63 % to 100 %, Specificity from 90 % to 98 %. *Standard-definition white light endoscopy and narrow band imaging:* Test sensitivity between 50 % to 80 % and between 50 % to 100 %. *High-definition white light endoscopy:* Test sensitivity from 94 % to 100 %, Specificity of 85 %. *i-SCAN:* Sensitivity: 72 %, Specificity: 92 %. **Author's Conclusion:** In surveillance of inflammatory bowel diseases, chromoendoscopy identifies more patients with dysplasia only when compared to standard-definition white light endoscopy. It is associated with longer procedural time with no direct evidence of effect on preventing all- cause/ cancer-specific mortality or time to interval cancer.		more dysplastic lesions: $Chi^2 = 9.75$, $I^2 = 0$ % **Morphological subtypes of dysplastic lesions:** Moderate heterogeneity in detection of non-polypoid ($Chi^2 = 3.84$, $I^2 = 48$ %) and polypoid ($Chi^2 = 5.85$, $I^2 = 66$ %) dysplastic lesions **Procedural time:** High heterogeneity ($Chi^2 = 106.31$, $I^2 = 97$ %) **Publication Bias:** Not investigated. **Notes:** Search query presented in Supplement (not available).

Omata, F. et al. Image-enhanced, chromo, and cap-assisted colonoscopy for improving adenoma/neoplasia detection rate: a systematic review and meta-analysis. Scand J Gastroenterol. 49. 222 – 237. 2014

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** MA of 42 RCT, 6 RCT with CU patients	**Intervention:** Image-enhanced endoscopy (IEE), autofluorescence imaging (AFI), flexible	**Primary:** Adenoma/neoplasia detection rate **Secondary:** –	van den Broek FJ (2008) Gut van den Broek FJ (2009) Clin Gastroenterol Hepatol	**Funding Sources:** Not stated. **COI:** The authors report no conflicts of interest. The authors

Databases: MEDLINE, EMBASE, Cochrane library **Search period:** ? – June 2012 **Inclusion Criteria:** (1) Full papers written in English **Exclusion Criteria:** (1) Non- randomized studies; (2) Non- parallel back-to- back studies	spectral imaging color enhancement (FICE), i- scan, narrow band imaging (NBI), chromoendoscopy (CE), and cap-assisted colonoscopy (CAC). **No description of study populations available.** **Comparison:** –	**Results:** In 3 of 14 NBI studies conducted in chronic UC patients, the pooled estimate of RR was 1.32 (95 % CI: 0.66 – 2.66) (Fixed-Effects-Model, FEM). In 2 of 9 CE studies conducted in chronic UC patients using methylene blue, the pooled estimates of RR was 2.39 (95 % CI: 1.18 – 4.84) (FEM). **Author's Conclusion:** In conclusion, neither AFI, FICE/i-scan, NBI nor CAC can confidently claim to improve ADR over standard/high-definition white light endoscopy. CE may improve ADR. For surveillance of intraepithelial neoplasia (low- and high-grade dysplasia) in chronic UC patients, CE using methylene blue is effective, while NBI is not. Additional RCTs for more efficient adenoma/neoplasia detection using IEE modalities, such as AFI, FICE/i-scan, and NBI, with brighter light are expected in the future.	Takeuchi Y (2010) Gastrointest Endosc Kuiper T (2011) Gastroenterology Rotondano G (2012) Int J Colorectal Dis Pohl J (2009) Gut Aminalai A (2010) Am J Gastroenterol Cha JM (2010) Dig Dis Sci Chung SJ (2010) Gastrointest Endosc Hong SN (2012) Gastrointest Endosc Dekker E (2007) Endoscopy Rex DK (2007) Gastroenterology Adler A (2008) Gut Inoue T (2008) J Gastroenterol Kaltenbach T (2008) Gut Adler A (2009) Gastroenterology Paggi S (2009) Clin Gastroenterol Hepatol Sabbagh LC (2011) BMC Gastroenterol Rastogi A (2011) Gastrointest Endosc Gross SA (2011) Endoscopy Boparai KS (2011) Endoscopy van den Broek FJ (2011) Endoscopy Ignjatovic A (2012) Am J Gastroenterol Ikematsu H (2012) J Gastroenterol Brooker JC (2002) Gastrointest Endosc Hurlstone DP (2004) Gut Lapalus MG (2006) Endoscopy Le Rhun M (2006) Clin Gastroenterol Hepatol Stoffel EM (2008) Cancer Prev Res Kiesslich R (2003) Gastroenterology Kiesslich R (2007) Gastroenterology Park SY (2008) Scand J Gastroenterol Pohl J (2011) Gut Kondo S (2007) Am J Gastroenterol Harada Y (2009) Gastrointest Endosc Lee YT (2009) Am J Gastroenterol Tee HP (2010) World J Gastroentero Takeuchi Y (2010) Gastrointest Endosc Dai J (2010) J Dig Dis Hewett DG (2010) Gastrointest Endosc	alone are responsible for the content and writing of the paper. **Study Quality:** The quality of studies was assessed in terms of both allocation sequence and concealment of allocation. Of the 42 studies, 17 used computer-generated random numbers for randomization concealment of allocation was reported in 28 of 42 studies. Regarding quality of colonoscopy, overall adenoma detection rate was > 30 % in 27 studies and cecal intubation rate was > 95 % in all studies in which randomization was performed before cecal intubation. **Heterogeneity: NBI** studies: $I^2 = 0$ % **CE** studies: $I^2 = 0$ % **Publication Bias:** Egger's test suggested publication bias or small study effect only in the meta-analysis of 14 NBI studies ($p = 0.026$). **Notes:** RR is not appropriate to determine validity of diagnostic tests.

			Prachayakul V (2012) Surg Endosc Rastogi A (2012) Gut de Wijkerslooth TR (2012) Gut	

Subramanian, V. et al. Meta-analysis: the diagnostic yield of chromoendoscopy for detecting dysplasia in patients with colonic inflammatory bowel disease. Aliment Pharmacol Ther. 33. 304 – 312. 2011

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** MA of 6 studies (2 RCT, 4 prospective cohort studies) **Databases:** Pubmed (1965 to February 2010), Embase (1974 to February 2010) and Ovid (1965 to February 2010), Cumulative index to nursing and allied health (CINAHL, 1982 to February 2010), Zetoc (1993 to February 2010), Ingenta (1991 to February 2010) **Search period:** - **Inclusion Criteria:** (1) prospective inclusion of patients with colonic inflammatory bowel disease; (2) surveillance colonoscopy and comparison of CE with standard WLE; (3) sufficient information to allow calculation of yield of dysplasia (and 95 % CI's); (4) published as a full journal article; (5) any language **Exclusion Criteria:** –	**Intervention:** Four studies with UC patients (over 8 years duration, in remission), 1 study pancolitis patients (over 5 years duration), 1 study with extensive UC and CD (involving more than one third of the colon). No details on age/ sex. WLE followed by CE: 259 patients CE compared to different controls: 700 patients 267 patients randomized 1:1 to WLE or CE **Comparison:** –	**Primary:** Incremental yield (IY) of detecting any dysplastic lesions **Secondary:** Differences in proportion of lesions detected by targeted biopsies, differences in proportion of flat lesions detected, differences in proportion of dysplastic lesions detected by random biopsy alone (miss rates), time taken for the procedure **Results:** Pooled IY of CE over WLE for the detection of any grade of dysplasia on a per patient basis: 7 % (95 % CI 3.2 – 11.3, no P-value). Differences in proportion of lesions detected by targeted biopsies: pooled increase in targeted dysplastic (low or high grade) lesion detection of CE over WLE: 44 % (95 % CI 28.6 – 59.1, no P-value). Detection of flat lesions: pooled increase in flat dysplastic (low or high grade) lesion detection of CE over WLE: 27 % (95 % CI 11.2 – 41.9, no P-value). Miss rates: pooled reduction in dysplastic lesions detected by random biopsy alone of CE over WLE: –40 % (95 % CI –52.8 to –27, no P-value). Duration of the procedure: pooled weighted difference in means between CE and WLE: 11 min (95 % CI 10 min 15 s to 11 min 43 s, no P-value). False positive results: Only data with CE available. No pooled analyses. **Author's Conclusion:** In summary, CE is superior to WLE for dysplasia detection in patients with colonic IBD undergoing surveillance colonoscopy. IY of CE over WLE is 7 % for all dysplastic lesions, primarily due to increased yield of targeted	Kiesslich R (2003) Gastroenterology Kiesslich R (2007) Gastroenterology Rutter MD (2004) Gut Matsumoto T (2003) Am J Gastroenterol Hurlstone DP (2005) Endoscopy Marion JF (2008) Am J Gastroenterol	**Funding Sources:** Declaration of funding interests: None.Declaration of funding interests: None. **COI:** Krish Ragunath has received research funding from Olympus (Keymed, UK). Subramanian conceived the study, abstracted data, data analysis and manuscript preparation. Mannath abstracted data, data analysis and manuscript preparation. Ragunath and Hawkey were involved in critical review and editing of the manuscript. **Study Quality:** Quality of included studies rated qith QUADAS (2 studies with rating of 12/14, 4 with 11/14). 1 study with unclear description of selection criteria. 3 studies with unclear description of reference standard. All studies without or unclear description of uninterpretable/intermediate test results. All studies without or unclear description of withdrawals. **Heterogeneity:** Pooled IY: Moderate heterogeneity (Cochran's Q = 8.1, P = 0.14 and I^2 = 38 %). Lesions detected by targeted biopsies: moderate heterogeneity (Cochran's Q = 9.1, P = 0.1 and I^2 = 45.03 %) Detection of flat lesions: low heterogeneity (Cochran's Q = 1, P = 0.8 and I^2 = 0 %) Miss rates: low heterogeneity (Cochran's Q = 3.3, P = 0.3 and I^2 = 9.3 %). Duration of the procedure: low heterogeneity (Cochran's Q = 2.8, P = 0.4 and I^2 = 0 %). **Publication Bias:** Pooled IY: Publication bias excluded by funnel plot and regression asymmetry (P = 0.53, intercept = –0.99 and 95 % CI: –5.02 to 3.03). Lesions detected by targeted biopsies: excluded by funnel plot and regression asymmetry (P = 0.93, intercept = –0.23 and 95 % CI: –7.3 to 6.8) Detection of flat lesions: excluded by Egger's regression asymmetry test (P = 0.18, intercept = 1.44 and 95 % CI: –1.6 to 4.5)

		biopsies from visualisation of additional lesions by CE. As this analysis was designed to evaluate the yield of CE and WLE, it is not clear whether these results will translate into superior patient outcomes with CE. Randomised controlled trials are needed to clarify this issue.		Miss rates: excluded by Egger's regression asymmetry test (P = 0.9, intercept = –2.7 and 95 % CI: –11.4 to 10.9). Duration of the procedure: excluded by Egger's regression asymmetry test (P = 0.96, intercept = 0.05 and 95 % CI: –4.3 to 4.4). **Notes:** Oxford LoE 2 for validating diagnostic studies. Thorough search strategy. Simple pooled analyses of data without being weighted.
Meyer, R. et al. Combining aneuploidy and dysplasia for colitis' cancer risk assessment outperforms current surveillance efficiency: a meta- analysis. Int J Colorectal Dis. 2016				
Evidence level/ Study Types	**Population**	**Outcomes/Results**	**Literature/References**	**Methodical Notes**
Evidence level: 2 **Study type:** MA of 11/12 studies (3 retrospective, 8 prospective, 1 follow-up study) **Databases:** PubMed **Search period:** ? - Jan 2016 **Inclusion Criteria:** (1) surveillance studies; (2) assessment of ploidy status; (3) assessment of risk by rating neoplastic mucosal changes for individual cancer risk during disease development **Exclusion Criteria:** (1) studies on patients after colectomy; (2) studies on inflammatory bowel diseases other than UC	**Intervention:** Assessment of DNA aneuploidy and dysplasia in surveillance colonoscopy **Comparison:** –	**Primary:** OR for detection of dysplasia and aneuploidy and occurrence of UC-associated carcinoma (UCC) **Secondary:** – **Results:** OR for detection of dysplasia and occurrence of UCC: OR 4.93 (95 % CI 1.61, 15.11) OR for detection of aneuploidy and occurrence of UCC: OR 5.31 (95 % CI CI 2.03, 13.93) OR for combined assessment of dysplasia plus aneuploidy and UCC occurrence: OR 8.99 (95 % CI 3.08, 26.26) **Author's Conclusion:** In conclusion, our meta- analysis revealed that aneuploidy is an equally effective parameter for UCC risk assessment as dysplasia. Strikingly, the combined assessment of dysplasia and aneuploidy is superior compared to applying each parameter alone. Thus, detection of dysplasia and/or aneuploidy will indicate high-risk patients affording timely follow-up. Conversely, patients with normal findings on DNA content and histopathologic evaluation can be examined less frequently. Thus, aneuploidy assessment should become part of consensus guidelines as complementing risk parameter.	Choi WT (2015) Hum Pathol Sjoqvist U (2004) Anticancer Res Habermann J (2001) Scand J Gastroenterol Holzmann K (2001) Dis Colon rectum Lindberg JO (1999) Br J Surg 86 Karlen P (1998) Gastroenterology Befrits R (1994) Dis Colon rectum Rubin CE (1992) Gastroenterology Lofberg R (1992) Gastroenterology Rutegard J (1989) Dis Colon rectum Rutegard J (1988) Dis Colonpotential rectum **Notes:** Lofberg R (1987) Gut	**Funding Sources:** This study was conducted in connection to the North German Tumor Bank of Colorectal Cancer (ColoNet), generously supported by the German Cancer Aid Foundation (DKH e. V. #108 446). Rüdiger-Meyer is supported by a Mildred Scheel postdoctoral scholarship of the German Cancer Aid. **COI:** The authors declare that they have no conflicts of interest. **Study Quality:** Quality of included study not investigated. **Heterogeneity:** Test for heterogeneity not described. 6 studies with preselected patients for certain specific phenotypes including the presence of dysplasia and/or aneuploidy. 6 studies with patients chosen for having UC for a certain duration or extent. Different study designs, surveillance periods, intervals of colonoscopy, numbers of biopsy sites, analysis methods with regard to sample preparation, staining, and evaluation criteria. Yet, test for heterogeneity not significant. **Publication Bias:** Funnel plots and rank correlation tests revealed no evidence for a publication bias. **Data not shown**. Oxford LoE 2 for exploratory diagnostic studies. Only one database searched, relevant studies possibly missed. No assessment of study quality. Test for heterogeneity not described. Random-Effects- Model despite low heterogeneity not conclusive. Lindberg et al. 1999 included in 1 of 3 pooled analyses without explanation. Huge calculated CI for OR for included studies. Overestimation of effect probable.

AG 1: Wie und wann soll eine Überwachungskoloskopie durchgeführt werden?

Bewertungsvorlage:
OXFORD Appraisal Sheet: RCT

Manes, G. et al. Colon Cleansing for Colonoscopy in Patients with Ulcerative Colitis: Efficacy and Acceptability of a 2L PEG Plus Bisacodyl Versus 4L PEG. Inflamm Bowel Dis. 21. 213744. 2015

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 2 **Study type:** RCT **Number of Patient:** 216 patients randomized and included in ITT analyses **Recruitung Phase:** May - Dec 2013 **Inclusion Criteria:** (1) Adult outpatients with ulcerative colitis aged 18 to 85 years; (2) colonoscopy with different indications **Exclusion Criteria:** (1) previous major abdominal surgery, previous colon resection, ileus, intestinal obstruction, toxic megacolon; (2) severe heart failure (NYHA class III or IV), acute cardiovascular disease, uncontrolled arterial hypertension (systolic pressure > 170 mm Hg, diastolic pressure > 100 mm Hg); (3) severe liver cirrhosis (Child-Pugh score C) or renal failure (creatinine clearance, 30 mL/min), ascites, phenylketonuria, and glucose6phosphate dehydrogenase deficiency; (4) Pregnant or breastfeeding women	**Intervention:** PEGBIS preparation for colon cleansing: 108 patients randomized and included in ITT analyses. Surveillance colonoscopy in 52.8 % Mean age: 52.4 (SD 15.3). Sex: 59.4 % male. **Comparison:** 4L PEG preparation for colon cleansing: 108 patients randomized and included in ITT analyses. Mean age: 48.7 (SD 13.6). Sex: 60 % male. Surveillance colonoscopy in 34.3 %	**Primary:** Quality of overall colon cleansing assessed by the endoscopist **Secondary:** Quality of cleansing in right colon, amount of bubbles in bowel lumen, patients' acceptance, tolerability and compliance with cleansing regimen, assessment of safety based on severity of adverse events **Results:** Quality of overall colon cleansing: Adequate in PEGBIS: 81.5 % and in 4L PEG: 75 % (ITT, no Pvalue reported). **Following results presumably by PerProtocol-Analyses:** *Quality of cleansing:* Assessed by Ottawa Bowel Preparation Scale similar in groups for whole (4.7 ± 2.7 vs 5.2 ± 3.0) and right colon (1.7 ± 0.8 vs 1.7 ± 0.9), no Pvalue reported. Presence of bubbles: significantly higher in PEGBIS group (76/106 patients, 71.7 %) as compared with 4L PEG group (38/105 patients, 36.2 %) (P < 0.001). *Compliance:* Poor (less than 75 % solution intake) in 2/106 patients in PEGBIS group, 15/105 patients in the 4L PEG group (OR = 0.11, 95 % CI, 0.02 – 0.52, P = 0.002). *Tolerability and Safety:* No or mild discomfort from preparation intake in 83 % of patients with PEGBIS and 44.8 % with 4L PEG (P < 0.0001). *Acceptance:* Willingness to repeat preparation by 94.3 % in PEGBIS group and 61.9 % in 4L PEG group (P < 0.001). *Safety:* No SAE in both groups. **Author's Conclusion:** In conclusion, our study demonstrates that lowvolume PEG solution plus bisacodyl may represent a valid alternative to standard 4L PEG solution, with a better patient compliance, tolerance, and acceptability these factors may have a positive impact on the quality of colonoscopy and may play an important role on patients' adherence to surveillance programs. The study also demonstrates that the clinical characteristics of the disease activity do not influence the safety and efficacy of preparation. Finally, the study confirms that several concepts regarding bowel cleansing are true for both general population and patients with UC: in particular, the time interval from solution intake and colonoscopy is the most important factor affecting quality of bowel cleansing and should be shortened to less than 6 hours.	**Funding Sources:** Not stated. **COI:** The authors have no conflicts of interest to disclose. **Randomization:** Computer-generated sequence. Treatment allocation was concealed and was accomplished at the screening visit through nonresearch medical personnel. **Blinding:** Endoscopistblinded: To guarantee investigators' blindness, endoscopists entered into the endoscopic suite only after the nurse had administered the above-mentioned questionnaire. Patients were instructed not to discuss their preparation with the endoscopist. **Dropout Rate/ITT Analysis:** PEGBIS group: 2 excluded for major protocol violation. 4L PEG group: 2 excluded for major protocol violation, 1 excluded for incomplete data report. **Notes:** Investigators but not patients blinded. Secondary outcomes patients dependent. Indication for colonoscopy (surveillance) differed significantly between groups.

Watanabe, T. et al. Comparison of Targeted vs Random Biopsies for Surveillance of Ulcerative ColitisAssociated Colorectal Cancer. Gastroenterology. 151. 11221130. 2016

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 3 **Study type:** RCT **Number of Patient:** 246 patients randomized (124 target group, 122 random group), 221 patients included in full analysis set (114	**Intervention:** Target biopsy: 124 patients randomized, 114 analyzed. Mean age: 50.7 (SD 13.9). Sex: 63 % male. Disease extent (n): 44 left	**Primary:** No. of neoplastic lesions detected in a singe surveillance colonoscopy **Secondary:** Proportion of surveillance colonoscopic examinations in which neoplastic lesions are detected out of all surveillance colonoscopic examinations, examination time, No. of biopsies, economic efficiency, incidence of examination	**Funding Sources:** This study was supported by a GrantinAid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, an Intractable Diseases, the Health and Labour Sciences Research Grant

target group, 107 in random group) **Recruitung Phase:** Oct 01, 2008 - Dec 31, 2010 **Inclusion Criteria:** (1) Patients who are clinically and histologically diagnosed with UC; (2) Cases in which the simple clinical colitis activity index is 8 or less; (3) Cases in which the activity index of Truelove and Witts is mild; (4) Patients who understand the main purpose of the study and provide consent for participation. **Exclusion Criteria:** (1) Patients with a history of tumors or colorectal cancer associated with UC; (2) Patients who are clinically suspected of having a hemorrhagic diathesis or who present with coagulopathy in examinations; (3) Patients with renal dysfunction (serum creatinine level [1.2 mg/dl); (4) Patients who are pregnant or nursing; (5) Other patients deemed ineligible for registration by a physician.	sided colitis, 64 pancolitis, 6 other. **Comparison:** Step (random) biopsy: 122 patients randomized, 107 analyzed. Mean age: 48.5 (SD 13.6). Sex: 70 % male. Disease extent (n): 27 left sided colitis, 75 pancolitis, 5 other.	complications requiring special treatments, risk factors of neoplasia **Results: Primary:** Mean number of biopsy samples with neoplasia in each surveillance colonoscopy was 0.211 (24 of 114) in target group and 0.168 (18 of 107) in random group (ratio 1.251 [95 % CI 0.679, 2.306]). **Secondary:** *Proportion of positive colonoscopies:* Not reported. *Examination time:* Significantly longer in random group than in target group (41.7 vs 26.6 minutes P < 0.001). *No. of biopsies:* Mean number of biopsy samples in each colonoscopy significantly larger in random group than in target group (34.8 vs 3.1 P < 0.001). *Economic efficiency:* Not reported. *Complications requiring special treatments:* None in any group. *Risk factors:* Duration of the disease positively associated with neoplasia (OR 1.07 [95 % CI 1.01, 1.13 p = 0.02]). **Author's Conclusion:** In conclusion, a targeted biopsy is as effective as a random biopsy for the detection of neoplasia in surveillance for UC. Considering costeffectiveness, a targeted biopsy seems to be more effective than a random biopsy. When performing a targeted biopsy, it is recommended that a random biopsy sample be taken from the rectum. On the other hand, when performing a random biopsy, obtaining biopsy specimens from areas without any signs of present or past inflammation can be omitted, which can reduce the number of unnecessary biopsies and increase the efficacy of the random biopsy.	from Ministry of Health, Labour and Welfare of Japan and Grants by JSCCR (to Toshiaki Watanabe). The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. **COI:** The authors disclose no conflicts. **Randomization:** Unique random sequence generated by the Data Center an stratified for facilities and severity of UC, was sequentially applied to each patient allocation. Unclear allocation concealment. **Blinding:** No blinding of researchers or patients. Blinding of pathologist would have been possible. **Dropout Rate/ITTAnalysis:** Full analysis set analysis instead of ITT. **Notes:** 2 groups are stated as similar in baseline characteristics, but no test described. No ITT-analysis. Certain endpoints from study protocol not reported. No blinding of investigators.

Ogawa, T. et al. Evaluation of discomfort during colonoscopy with conventional and ultrathin colonoscopes in ulcerative colitis patients. Dig Endosc. 27. 99105. 2015

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 3 **Study type:** RCT **Number of Patient:** 86 patients with CU randomized, 84 patients analyzed **Recruitung Phase:** Apr – Oct 2012 **Inclusion Criteria:** (1) Acceptable indication was estimation for mucosal inflammation by routine medical examination; (2) Patients with diagnosis of UC before colonoscopy; (3) Patients who were able to provide written informed consent to total colonoscopy, basically without sedation, and randomization; (4) Patients aged ≥ 18 years **Exclusion Criteria:** (1) Indication for detailed colonoscopy to survey for colon cancer or dysplasia was excluded; (2) No consent available; (3) Patients who preferred to receive sedation/ analgesia from the start; (4) Patients who had undergone prior partial colonic resection; (5) Patients who had known stenosis or adhesions; (6) cases with megacolon or toxic megacolon; (7) clinically severe and/or fulminant UC; (8) Incomplete preparation before colonoscopy	**Intervention:** Ultrathin flexible scope (PCF PQ260 9.2 mm):43 patients randomized, 42 patients analyzed. Age (SD): 43.7 ± 14.1. Sex (male/female): 31/11 **Comparison:** Conventional scope (PCF Q260A 11.3 mm): 43 patients randomized, 42 patients analyzed. Age (SD): 48.1 ± 16.2. Sex (male/female): 30/12	**Primary:** Patients' rating of procedural discomfort: Pain related to colonoscopy by visual analogue scale (VAS) **Secondary:** Cecal intubation time, rate of complete intubation (to reach the cecum) and rate of procedural complications **Results:** Pain: Newscope group vs. conventional scope group mean ± SD, median (range) 19.3 ± 16.9, 14 (0 – 62) vs. 32.0 ± 21.6, 31.8 (0 – 100), (P = 0.005). **Cecal intubation rate** (n, %): 41 (97.6 %) in both groups **Cecal intubation time** (min, SD): Newscope group vs. conventionalscope group 4.5 ± 1.7 vs. 5.4 ± 3.2 (P = 0.57) **Complications:** 0 in both groups There was no patient who requested sedation during the colonoscopy procedure. **Author's Conclusion:** The new ultrathin flexible colonoscope PCFPQ260 applied to UC patients was efficient to reduce patient discomfort. This scope should improve patient tolerance of the procedure and should potentially contribute to establishing a better treatment strategy for patients with active UC.	**Funding Sources:** Not stated. Both colonoscope from Olympus. **COI:** Authors declare no conflict of interests for this article. **Randomization:** Stratified permuted block method. **Blinding:** Patients, but not endoscopists, were blinded to the type of colonoscope used. All patients reported the VAS score within 1 h after colonoscopy to a medical assistant blinded to the type of instrument used. **Dropout Rate/ITTAnalysis:** No ITT Analysis. **6 patients excluded for poor bowel preparation listet as excluded before randomization. No description of assessment for poor bowel preparation**. 1 patient without features of CU excluded in each group. **Notes:** Patients did not receive sedation/analgesia from the start but were provided with sedation if desired. If outcomes result from smaller diameter or increased flexibility unclear.

AG 2: Wie behandeln wir eine mittelschwere bis schwere Proktitis/Linksseitenkolitis/Pancolitis?

Bewertungsvorlage:
Oxford SR

Sherlock, Mary E et al. Oral budesonide for induction of remission in ulcerative colitis. Cochrane Database of Systematic Reviews. 2015

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** Systematic Review and Meta analysis of 6 randomized studies (total n = 1808). **Databases:** MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Inflammatory Bowel Disease (IBD) Group Specialised Register and ongoing trials were identified using the registry link http://ClinicalTrials.gov **Search period:** Inception to 28.04.2015 **Inclusion Criteria:** Randomised trials evaluating the use of oral budesonide for induction of remission in ulcerative colitis. Eligible trial designs included parallel arm, placebo-controlled trials or trials comparing two active agents. Cross-over designs were also eligible for inclusion. Studies of human subjects, published in all languages were considered. Studies published in abstract format within the past 3 years were considered only if sufficient outcome data could be retrieved from the abstract or following contact with the authors. articipants of all ages with a confirmed diagnosis of active UC, using a combination of clinical symptoms and signs, radiologic, endoscopic and histologic criteria, were eligible for inclusion in the review. Acceptable activity indices included: Ulcerative Colitis Disease Activity Index (UCDAI), the Clinical Activity Index (CAI), the Powell-Tuck Index, the Simple Clinical Colitis Activity Index, Beattie's Colitis Symptom Score, Lichtiger Symptom Score for acute Ulcerative Colitis, the Mayo Index,	**Intervention:** Oral budesonide. All doses and formulations of budesonide as well as different durations of therapy were eligible for inclusion. **Comparison:** Control (Placebo or an active agent such as a traditional corticosteroid or 5-ASA product).	**Primary:** induction of remission of active ulcerative colitis. Clinical remission was defined by the primary studies and was expressed as the percentage of patients randomised (intention-to-treat analysis). **Secondary:** clinical, endoscopic and histologic improvement as defined by the authors; endoscopic mucosal healing, change in disease activity index score, quality of life; **Results: Primary:** *Budesonide versus placebo* Data from three studies (900 participants) were combined in a meta-analysis. The primary outcome was a combined clinical and endoscopic remission. Budesonide-MMX® 9 mg daily was superior to placebo for inducing remission at eight weeks. 15 % (71/462) of patients in the budesonide-MMX® 9 mg group achieved remission compared to 7 % (30/438) placebo group (RR 2.25, 95 % CI 1.50 to 3.39). A GRADE analysis indicated that the quality of evidence supporting the primary outcome was moderate. A pooled analysis of two studies (440 participants) suggests that a lower dose of budesonide-MMX® 6 mg was not superior to placebo for induction of remission. Eleven per cent (25/230) of patients in the budesonide-MMX® 6 mg group achieved remission compared to 6 % (13/210) of placebo patients (RR 1.80, 0.94 to 3.42). A GRADE analysis indicated that the quality of evidence supporting the primary outcome was low due to very sparse data. *Subgroup analysis: remission rates according to concurrent mesalamine use:* In two study populations, in which mesalamine users where excluded a priori, budesonide-MMX®	D'Haens GR, (2010) Journal of Crohn's and Colitis Gross V, (2011) Journal of Crohn's and Colitis Löfberg R, (1996) Gastroenterology Rubin D, (2014) Inflammatory Bowel Diseases Sandborn WJ, (2012) Gastroenterology Travis S, (2014) Gut	**Funding Sources:** Funding for the IBD/FBD Review Group (September 1, 2010-August 31, 2015) has been provided by the Canadian Institutes of Health Research (CIHR) Knowledge Translation Branch (CON-105 529) and the CIHR Institutes of Nutrition, Metabolism and Diabetes (INMD); and Infection and Immunity (III) and the Ontario Ministry of Health and Long Term Care (HLTC3968FL-2010 – 2235). **COI:** MES: Dr. Sherlock has received fees for consultancy from Abbvie Canada for attending an advisory board meeting. All of the fees received are outside the scope of the submitted work. AMG: Anne Marie Griffiths has received fee(s) from Johnson and Johnson for Board membership; fee(s) from Janssen, Abbvie and Ferring for consultancy; grants or grants pending from Johnson and Johnson and Abbive; lecture fee(s) from: Abbvie and Merck and payment for development of educational presentations from Ferring. All of these activities are outside the submitted work. AHS: Hillary Steinhart has received fee(s) from Janssen, Abbvie, Shire, Pendopharm, Pfizer, and Takeda for consultancy; and lecture fee(s) from: Janssen, Abbvie, Shire, Warner Chilcott, Aptalis, and Takeda. His institution has received grants or grants pending from Janssen, Abbvie, Pfizer, Amgen, Takeda and Actavis. All of these activities are outside the submitted work. JKM: None known. CHS: Dr. Cynthia Seow has served as a consultant and on advisory boards for Janssen Pharmaceuticals, Abbvie, Takeda, Actavis, and Shire. She has a grant through Janssen Pharmaceuticals. Dr. Seow has also provided lectures for Janssen Pharmaceuticals and Warner Chilcott. All of these activities are outside the submitted work. **Study Quality:** We assessed the quality of included studies using the Cochrane risk of bias tool. We used the GRADE (Grading of Re-

the Seo Index, the Truelove and Witt's Severity Index, and the Paediatric Ulcerative Colitis Activity Index and the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) **Exclusion Criteria:** There were no exclusions based on patient age or the type, dose, duration orformulationof budesonide therapy.		9 mg patients achieved remission in 18 % (41/232) of patients compared to 6 % of placebo patients. The relative risk was 2.89 (95 % CI 1.59 to 5.25;), suggesting that budesonide-MMX® may be more effective in patients who are not mesalamine-refractory, which did not change when sensitivity analysis was applied. *Subgroup analysis: Remission rates according to disease location:* A pooled analysis of two studies (Sandborn 2012; Travis 2014), shows that budesonide-MMX® 9 mg daily was significantly more efficacious than placebo for treatment of patients with left-sided disease (289 patients) but not for patients with extensive disease (145 patients). Among those with left-sided disease 22 % (32/145) of budesonide-MMX® 9 mg patients entered remission com- pared to 8 % (11/144) of placebo patients (RR 2.98, 95 % CI 1.56 to 5.67). Among those with extensive disease 9 % (8/85) of budesonide-MMX® 9 mg patients entered remission compared to 3 % (2/60) of placebo patients (RR 2.41, 95 % CI 0.61 to 9.56).8. **Secondary:** *Adverse Events: Budesonide versus placebo* A pooled analysis of three studies (971 participants) showed no statistically significant difference in the proportion of patients who experienced at least one adverse event. 45 %(217/485) of budesonide MMX® 9 mg patients experienced at least one adverse event compared to 41 % (200/486) of placebo patients (RR 1.09, 95 % CI 0.95 to 1.26). A GRADE analysis indicated that the quality of evidence supporting this outcome was moderate due to moderate heterogeneity (I2 = 54 %). Similar results were found for the comparison budesonide MMX® 6 mg versus placebo (2 studies, 512 participants). Sixty-one per cent (154/254) of budesonide MMX® 6 mg patients experi-		commendations, Assessment, Development and Evaluation) criteria to assess the overall quality of evidence supporting the primary outcome and selected secondary outcomes. **Heterogeneity:** Two authors independently evaluated the eligible studies for clinical and methodological heterogeneity. We used the Chi^2 test to assess heterogeneity, with a P-value of < 0.10 considered statistically significant. To estimate the degree of heterogeneity across studies, we used the I^2 statistic. A value of 25 % is considered to indicate low heterogeneity, 50 % moderate heterogeneity and 75 % high heterogeneity. **Publication Bias:** "We planned to assess publication bias by means of a funnel plot. However, given that we identified only six eligible studies, three of which were not suitable for combined analysis, a funnel plot was not constructed." **Notes:** Due to differences of study design, not all studies could be used for the same meta-analysis.

		enced at least one adverse event compared to 53 % of placebo patients (RR 1.13, 95 % CI 0.97 to 1.32). A GRADE analysis indicated that the quality of evidence supporting this outcome was very low due to a high level of heterogeneity (I2 = 86 %) and sparse data. Commonly reported adverse events include worsening ulcerative colitis, headache, pyrexia, insomnia, back pain, nausea, abdominal pain, diarrhoea, flatulence and na- sopharyngitis. **Author's Conclusion: -** Moderate quality evidence to support the use of oral budesonide-MMX® at a 9 mg daily dose for induction of remission in active ulcerative colitis, particularly in patients with left-sided colitis. Budesonide-MMX® 9 mg daily is effective for induction of remission in the presence or absence of concurrent 5-ASA therapy. Further, budesonide-MMX® appears to be safe, and does not lead to significant impairment of adrenocorticoid function compared to placebo. Moderate quality evidence from a single study suggests that mesalamine may be superior to standard budesonide for the treatment of active ulcerative colitis. Low quality evidence from one study found no difference in remission rates between budesonide MMX® and mesalamine. Very low quality evidence from one small study showed no difference in endoscopic remission rates between standard budesonide and prednisolone. Low quality evidence from one study showed no difference in remission rates between budesonide-MMX® and standard budesonide. Adequately powered studies are needed to allow conclusions regarding the comparative efficacy and safety of budesonide versus prednisolone, budesonide- MMX® versus standard budesonide and budesonide versus mesalamine.		

Lie, M R et al. Drug therapies for ulcerative proctitis: systematic review and meta-analysis. Inflamm Bowel Dis. 20. 2157 – 2178. 2014

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Systematic Review and Meta-analysis of 18 RCTs (n = 1546) **Databases:** Embase, Medline OvidSP, Cochrane Central Register of Controlled Trials, Web of Science, and Pubmed **Search period:** x – 28.04.2014 **Inclusion Criteria:** *Study type:* Randomized controlled trials comparing the efficacy of any drug versus another active therapy or placebo for remission induction in Ulcerative Proctitis (UP). *Population:* Adults (16 years or older), with a diagnosis of ulcerative colitis limited to 20 cm from the anal verge (i. e. ulcerative proctitis) at endoscopy. Studies were allowed to investigate both patients with a first presentation and patients with a relapse of previously established disease. *Intervention:* Any drug therapy be compared to either another drug therapy or placebo. All formulations (e. g. oral, suppository, enema) were accepted. The duration of treatment had to be at least 4 weeks in induction studies. Studies were grouped based on the type of treatment (i. e. induction, maintenance) and based on drug class (e. g. 5-ASA, corticosteroids). Additionally, these groups were further subdivided by drug formulation (e. g. suppository, enema). **Exclusion Criteria:** 133 articles were excluded. Due to the following reasons. Articles only published as abstracts, uncontrolled, non-randomized or retrospective studies. Also lack specific proctitis group, short time of treatment (15 days-3 weeks), insuf-	**Intervention:** 5-ASA, corticosteroids, thiopurines, anti-TNF-a agents **Comparison:** Other interventions or placebo.	**Primary:** *Primary outcomes:* Clinical remission induction rate and maintained clinical remission rate. **Secondary:** *Secondary outcomes:* Endoscopic remission and histological remission rates. **Results:** Twenty-three studies (1834 patients) were included. Eighteen trials investigated induction and 5 studied maintenance of remission. Topical 5-ASA was significantly superior to placebo for induction (RR, 2.39; 95 % CI, 1.63 – 3.51) and maintenance (RR, 2.80; 95 % CI, 1.21 – 6.45) of clinical remission, regardless of dose or formulation. Subgroup analysis of 5-ASA suppositories also showed superiority over placebo for induction of clinical (RR, 3.07; 95 % CI, 1.70 – 5.55) and endoscopic remission (RR, 2.64; 95 % CI, 1.85 – 3.77). **Author's Conclusion:** The effectiveness of topical 5-ASA for inducing remission is confirmed. The ability of topical 5-ASA to induce clinical remission was clearly shown in several placebo-controlled studies. Patients receiving topical 5-ASA were 2.39 times more likely to achieve clinical remission than those receiving placebo. No clear dose response relationship was found between topical 5-ASA and clinical remission, although only 2 studies compared different 5-ASA doses. Additionally, endoscopic evaluations in 4 studies showed a clear benefit of topical 5-ASA over placebo. Histological remission rates were assessed in only 2 studies and showed no clear benefit of topical 5-ASA over placebo.	Andus T, (2010) Inflamm Bowel Dis Ardizzone S, (1996) Aliment Pharmacol Ther Betamethasone 17-valerate, prednisolone 21-phosphate retention enemata in proctocolitis (1971) Br Med J Campieri M, (1988) J Clin Gastroenterol Campieri M, (1990) Scand J Gastroenterol Campieri M, (1990) Int J Colorectal Dis Eliakim R, (2007) Aliment Pharmacol Ther Farup PG, (1995) Scand J Gastroenterol Gionchetti P, (1997) Aliment Pharmacol Ther Gionchetti P, (1998) Dis Colon Rectum Gross V, (2006) Aliment Pharmacol Ther Hanauer SB, (2005) Am J Gastroenterol Larnet M, (2005) Inflamm Bowel Dis Pokrotnieks J, (2000) Aliment Pharmacol Ther van Hees PAM, (1980) Gut van Hogezand RA, (1988) Aliment Pharmacol Ther Watanabe M, (2013) Aliment Pharmacol Ther Williams CN, (1987) Dig Dis Sci	**Funding Sources:** n.a. **COI:** The authors have no conflicts of interest to disclose. **Study Quality:** "The risk of bias was assessed independently by each of the 2 primary reviewers, according to the scheme described in the Cochrane Handbook for Systematic Review of Interventions.32 This assessment involved judgment on selection, performance, attrition, and detection bias. The "Risk of bias tool" in the pub- lically available program RevMan 5.2 was used to report possible bias in included studies." Results for quality of the included studies are provided. **Heterogeneity:** Where applicable, studies were pooled using a random- effect model, regardless of statistical heterogeneity. Heterogeneity was tested using the x2 test, the I- squared test, and visual inspec- tion of forest plots. If heterogeneity was present, we attempted to investigate the cause thereof (such as methodological factors or the outcome assessment). Given the limited number of included studies, subgroup analysis or meta-regression was not considered useful. In the case of high heterogeneity (I2. 75 %), studies were pooled only if the direction of their results was consistent. **Publication Bias:** n.a. **Notes:** No investigation of publication bias. The authors rate the majority of the included studies to be poor with high risk of bias. In addition the follow-up times are short so mucosal healing is likely to be underestimated. Also most studies apparently use different scoring systems to define clinical remission.

ficient number of included participants, non-reporting of clinical remission rates, not drug related intervention, not original work articles.				

Cohen, R D et al. Systematic Review: Rectal Therapies for the Treatment of Distal Forms of Ulcerative Colitis. Inflamm Bowel Dis. 21. 1719 – 1736. 2015

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Systematic review of 48 studies. **Databases:** PubMed **Search period:** 01.01.2004 – 31.12.2013 first search. no restriction on second search for clinical trials. **Inclusion Criteria:** Articles were restricted to those involving adult humans and included comparative studies, meta- analyses, and (systematic) reviews. **Exclusion Criteria:** Clinical studies of pouchitis or cuffitis and case reports were excluded from the review.	**Intervention:** *Interventions:* rectal therapies: suppository, foam, gel, and enema formula- tions of 5-ASAs, corticosteroids, and non–5-ASA agents, and provides ratings for the quality of the evidence. **Comparison:** Placebo, or different forms of administration of the same drug.	**Primary:** Efficacy of the treatment (induction or maintenance). **Secondary: Safety outcomes:** AE, drug-related AE, AE causing discontinuation of the drug treatment. **Results:** The current literature supports the use of rectal therapies for both induction and maintenance of remission in patients with distal forms of UC. *Efficacy:* A greater percentage of patients with distal forms of UC receiving 5-aminosalicylic acids or corticosteroid rectal formulations derived greater therapeutic benefit after treatment compared with patients receiving placebo. Most uncontrolled studies of rectal therapies reported that patients with distal forms of UC had marked improvement from baseline after treatment. *Safety:* The overall safety profile of rectal therapies was favorable. Treatment with second-generation corticosteroids, such as budesonide and beclomethasone dipropionate, did not increase the incidence of steroid-related adverse effects. **Author's Conclusion:** Overall, most rectal therapies, regardless of formulation, were shown to be well tolerated and efficacious for both the treatment of active UC and for the maintenance of UC remission. Avoiding systemic corticosteroid exposure by using non–steroid-containing agents or therapies with second-generation corticosteroids, such as budesonide and BDP, should be emphasized when selecting topical therapies for patients with these conditions.	Gross VB, (2006) Aliment Pharmacol Ther Andus T, (2010) Inflamm Bowel Dis. 2010 Watanabe M, (2013) Aliment Pharmacol Ther Campieri M, (1990) Int J Colorectal Dis Campieri M, (1990) Scand J Gastroenterol Lamet M, (2005) Inflamm Bowel Dis Eliakim R, (2007) Aliment Pharmacol Ther Pokrotnieks J, (2000) Aliment Pharmacol Ther Aumais G, (2005) Drugs RD Sutherland LR, (1987) Gastroenterology Connolly MP, (2009) Digestion Cortot A, (2008) Am J Gastroenterol Marteau P, (2005) Gut Vecchi M, (2001) Aliment Pharmacol Ther 2001;15:251 – 256 Hanauer SB, (1998) Inflamm Bowel Dis Campieri M, (1991) Gut Sutherland LR, (1987) Dig Dis Sci Hammond A, (2004) Hepato-gastroenterology Hartmann F, (2010) Aliment Pharmacol Ther Biancone L, (2007) Dig Liver Dis Gionchetti P, (2005) J Clin Gastroenterol Lindgren S, (2002) Scand J Gastroenterol Hanauer SB, (1998) Gastroenterology Danielsson Å, (1993) Aliment Pharmacol Ther Danielsson Å, (1992) Scand J Gastroenterol Cobden I, (1991) Aliment Pharmacol Ther Ginsberg AL, (1988) Ann Intern Med Gandolfo J, (1987) Dig Dis Sci Selby WS, (1984) Digestion	**Funding Sources:** n.a. **COI:** R.D. Cohen—Speakers Bureau: Abbvie, Entera Health, Salix Pharmaceuticals, Shire PLC. Consultant: Abbive, Cellgene, Entera Health, Hospira, Janssen, Prome- theus, Salix Pharmaceuticals, Sandoz Biopharmaceuticals, Shire PLC, Takeda, UCB Pharma. S. R. Dalal has no conflicts of interest to disclose. **Study Quality:** An adaptation of the GRADE system was used to determine the quality of evidence for the efficacy of rectal therapies for inducing or maintaining UC remission. The quality of the evidence was categorized as "high," "moderate," "low," or "very low." **Heterogeneity:** n.a. **Publication Bias:** n.a. **Notes:** Search for articles was restricted to PubMed, and no Mesh terms were applied and no information how keywords are linked through operators. Two searches were performed, one with restriction on publication date, the second without. It is possible that important articles were missed. Inclusion criteria were only vaguely defined. No information on total n, study characteristics or types. The definition of remission differed among studies.

			Miner PB Jr, (2006) Aliment Pharmacol Ther 2006; 23: 1403 – 1413 Miner PB Jr, (2006) Aliment Pharmacol Ther 2006; 23: 1427 – 1434 van Deventer SJ, (2006) Aliment Pharmacol Ther van Deventer SJ, (2004) Gut Ingram JR, (2005) Clin Gastroenterol Hepatol Mahmood A, (2005) Aliment Pharmacol Ther Sinha A, (2003) N Engl J Med Sandborn WJ, (1994) Gastroenterology Pedersen G, (2010) Am J Gastroenterol Miyata M, (2005) Dig Dis Sci van Dieren JM, (2009) Inflamm Bowel Dis	

AG 2: Wie behandeln wir eine mittelschwere bis schwere Proktitis/ Linksseitenkolitis/ Pancolitis?

Bewertungsvorlage:
OXFORD Appraisal Sheet: RCT

Ito, H et al. Direct comparison of two different mesalamine formulations for the induction of remission in patients with ulcerative colitis: a double-blind, randomized study. Inflammatory bowel diseases. 16. 1567 – 1574. 2010

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 2 **Study type:** Randomized placebo-controlled study, multicentric setup (53 centers in Japan) **Number of Patient:** 229 **Recruitung Phase:** 2005 – 2007 **Inclusion Criteria:** Outpatients aged 16 – 64 years of age at the time of informed consent, patients who had mild-to-moderate active UC defined by UC disease activity index (UC-DAI) of 3 – 8 and a bloody stool score of 1 or greater. **Exclusion Criteria:** 1) severe UC, chronic continuous type UC or acute fulminating type UC; oral mesalamine more than 2.25 g daily, oral salazosulfapyridine more than 4.5 g daily, mesalamine enemas, salazosulfapyridine suppositories, corticosteroids (oral preparations, enemas, suppositories, injections and/or remedies for hemorrhoidal diseases) and/or cytapheresis within 14 days before the start of the investigational drug; immunosuppressants within 90 days before the start of the investigational drug; any other investigational drug within six months	**Intervention:** Population: 229 participants with mild to moderate active UC, 84 with proctitis *Interventions:* ▪ PH-dependent release formulation at 2.4 g/day (pH-2.4 g) Mesalamine (Eudragit-S (Asa- col 400 mg tablet, Tillotts Pharma AG, Ziefen, Switzerland, supplied by ZERIA Pharmaceutical, Tokyo, Japan) or ▪ PH-dependent release formulation at 3.6 g/day (pH-3.6 g) Mesalamine (Eudragit-S (Asa- col 400 mg tablet, Tillotts Pharma AG, Ziefen, Switzerland, supplied by ZERIA Pharmaceutical, Tokyo, Japan) or ▪ Time-dependent release formula-	**Primary:** *Change in UC-DAI:* Each patient recorded the condition of their bloody stools, stool frequency and drug compliance in their diary and visited the medical center every two weeks. Each component of UC-DAI, except the mucosal appearance score, was assessed at each visit. Colonoscopy was performed at eight weeks or at withdrawal from the study, and UC-DAI was calculated at that time. **Secondary:** Remission was defined as patients with a UC- DAI of 2 or less and a bloody stool score of 0 at the final assessment. *Efficacy:* Efficacy was defined as remission or improvement. Improvement was defined as patients with the decrease in UC-DAI by two points or more, except patients who experienced a remission *Safety:* To evaluate safety, clinical laboratory data and vital signs were checked at the time of informed consent and four weeks and eight weeks after enrolment (or upon withdrawal). The presence or absence of adverse events (AEs) and adverse drug reactions (ADRs) were recorded by investigators at each visit. **Results: Primary:** *Change in UC-DAI:* In the full analysis set (n = 225) the decrease in UC-DAI in each group was 1.5 in pH-2.4 g, 2.9 in pH-3.6 g, 1.3 in Time-2.25 g and 0.3 in Placebo, respectively. These results demonstrate the superiority of pH-3.6 g over Time-2.25 g (P = 0.003) and the non-inferiority of pH-2.4 g to Time-2.25 g. Among the patients with proctitis-type UC, a significant decrease in UC-DAI was observed in	**Funding Sources:** n.a. **COI:** Drs. Ito, Iida and Suzuki received consulting fees from ZERIA Pharmaceutical. Drs. Matsumoto and Hibi received consulting fees and grant support from ZERIA Pharmaceutical. No other potential conflicts of interest related to this article were reported. This study was made possible by the cooperation of the many participants in the study, the physicians in charge and associated staff members. We thank all of those involved in supporting this study. In addition, the authors thank Dr. Fumiaki Ueno of Ofuna Chuo Hospital, Dr. Masahiro Igarashi of the Cancer Institute Hospital of JFCR and Dr. Haruhiko Ogata of Keio University for the members of independent image assessment committee, Prof. Hideki Origasa of the University of Toyama for statistical advice, Prof. Ulrich Mittmann and the staff of Tillotts Pharma AG for scientific advice regarding the article and the planning of the study, and Hayato Koyama of ZERIA Pharmaceutical for review of article and writing assistance. **Randomization:** Treatment assignments were balanced according

before informed consent; a history of hypersensitivity to mesalamine or salicylate drugs, severe cardiac disease, severe pulmonary disease and/or severe hematological diseases; severe hepatopathy, severe nephropathy and/or malignant tumors; and pregnant or lactating participants.	tion at 2.25 g/day (Time-2.25 g) Mesalamine (Pentasa 250 mg tablet, Nisshin Kyorin Pharmaceutical, Japan). The investigational drugs were administered three times daily for eight weeks. **Comparison:** Placebo (Placebo) each adminstered daily.	pH-2.4 g and pH-3.6 g as compared to Placebo, but not in Time-2.25 g. **Secondary:** *Remission:* The proportion of patients who experienced a remission was 30.3 % (CI, 19.6 – 42.8) in pH-2.4 g, 45.3 % (CI, 32.9 – 58.2) in pH-3.6 g, 28.6 % (CI, 17.9 – 41.3) in Time-2.25 g, and 9.4 % (CI, 2.0 – 25.0) in Placebo. There were statistically significant differences from Placebo in all active-drug groups. *Efficacy* was archived in 45.5 % (CI, 33.2 – 58.1) in pH-2.4 g, 64.1 % (CI, 51.1 – 75.6) in pH-3.6 g, 49.2 % (CI, 36.4 – 62.1) in Time-2.25 g, and 28.1 % (CI, 13.8 – 46.7) in Placebo. There were significant differences from Placebo in both pH-3.6 g and Time-2.25 g. *Safety:* No differences were observed in the safety profiles. **Author's Conclusion:** this is the first study to directly compare the efficacy and safety of two different mesalamine formulations for the induction of remission in patients with UC. The results of our study clearly showed superior efficacy of the pH-dependent release formulation administered at a dose of 3.6 g/day and superior characteristics of this formulation to treat patients with proctitis-type UC. However, it is unknown whether the formulation is also efficacious in patients with more severe UC because the subjects in this study were patients with mild-to-moderate active UC. Mesalamine is considered safer than corticosteroids. Accordingly, further research will be necessary to fully evaluate the role of mesalamine formulations for the treatment of severe UC. If this is accomplished, it is likely that mesalamine contributes to the improvement in the quality of life of patients with UC.	to the inflamed areas (proctitis-type or others) and the severity of the disease (range of UC-DAI at initial assessment: 3 – 5 or 6 – 8) with the use of a biased-coin minimization algorithm. Balance within each medical center was also taken into consideration. A person independent from the study was in charge of the random allocation. Seven patients were assigned as a block as follows: 2,2,2,1(placebo). The randomization code was sealed and stored until the blind was removed. **Blinding:** Double blind study. **Dropout Rate/ITT-Analysis:** No intention treat analysis was performed, only per protocol and analysis of the full analysis set (neither one includes dropouts). "Concerning the withdrawal cases, their adoption was to be decided before the blind was removed." **Notes:** *No intention to treat analysis was performed, instead full analysis set (which is not standard procedure).* In total 4 dropouts were excluded from analysis from 225 total (which were not equally distributed across study arms). Given the small amount of total dropout the effect on outcomes is possibly small. No tests for group differences were performed, but the characteristics appear similar.

Crispino, P et al. Efficacy of mesalazine or beclomethasone dipropionate enema or their combination in patients with distal active ulcerative colitis. Eur Rev Med Pharmacol Sci. 19. 2830 – 2837. 2015

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 3 **Study type:** Randomized controlled single blind study. Single center in Italy. **Number of Patient:** 120 **Recruitung Phase:** "A total of 120 patients (40 for each group) were recruited in our Gastroenterology Outpatient Unit" no information on the timeframe was provided. **Inclusion Criteria:** The inclusion criteria were: age of at least 18 years, standard endoscopic and histological diag- nosis of distal UC (left-sided, procto-sigmoiditis and proctitis), mild or moderate disease activity assessed by the modified Colitis Activity Index (CAI): in particular the disease was classified as mild if baseline CAI was > 4 but ≤ 8 and as moderate if CAI > 8 but < 12, with proved endo- scopic activity according to Baron et al criteria and histological activity according to Truelove and Richards criteria.	**Intervention:** Patient's disease was defined in activity if CAI > 4, Baron > 0 and Tru- elove and Richards > 0. *Intervention:* Eligible patients continued oral treatment with mesalazine 2.4 g/day and were randomized to receive one of the following topical formulations for eight weeks: Group C, (Asalex® granular form plus Clipper®) enema, mixing 1.5 g of granular mesalazine and BDP enema 3 mg/60 ml, every night. **Comparison:** Group A, mesalazine 4 g/60 ml every night as retention enema or	**Primary:** *Complete remission:* achievement of the simultaneous clinical, endoscopic and histological disease remission at eight weeks. Patients were defined in complete remission when the CAI clinical score resulted less than 4, there was an endoscopic remission (presence of a mat mucosa, ramifying vascular pattern clearly visible through- out, no spontaneous bleeding, no bleeding to light touch) and a histological remission (absence of active inflammation into the mucosa, erosions or crypt abscesses; the surface of glandular epithelial cells was intact, even if general architecture of the mucosa was disturbed, with glands appearing reduced in number; oedema and fibrosis of the lamina propria with occasional foci of lympho- cytes found in specimens). **Secondary:** *CAI score* changes from the baseline observation, to 4 and 8 weeks 25. *Efficacy:* according to disease extension and drugs tolerability. **Results: Primary:** *Complete remission:* After eight weeks, complete remission rates were of 52 %, 47 % and 65 % respectively, in group A (topical Mesalazine), B (topical BDP) and C (both). The difference between remission rates in the three treatment groups was found statistically not significant. Remission rates were the highest in ulcerative proc-	**Funding Sources:** n.a. **COI:** The Authors declare that there are no conflicts of interest. **Randomization:** Patients were assigned to the treatment groups based on a computer- generated randomization scheme. **Blinding:** This study was a single-centre randomized investigator blind trial. **Dropout Rate/ITT- Analysis:** Intention-to treat analysis was performed. **Notes:** Sample size is insufficient to detect a significant difference in the rate of clinical remission. The author's expected a difference of at least 30 % and enrolled patients accordingly. According to the authors the stratification by inflammation locus was not considered before the start of the investigation. No blinding of participants.

Exclusion Criteria: patients with steroid-refractory disease treated with immunosuppressive agents, disease extension beyond the splenic flexure, presence of lesions in the proximal tract of the colon, patients who underwent topical steroids or mesalazine less than three months before study, patients intolerant to steroids or mesalazine, pregnancy and lactation, concomitant diseases requiring oral steroids or any other severe systemic syndrome.	Group B, BDP 3 mg/ 60 ml every night as retention enema; (both are considered standard treatments)	titis in all groups: A (57 %), B (67 %) C (86 %). In procto- sigmoiditis the remission rates reduced, to A: 61 % B: 40 % and C: 56 %. In left-sided colitis the remission rates were A: 40 % B: 33 % and C: 53 %. **Secondary:** *CAI score* changes From baseline to 4 and 8 weeks the CAI score decreased significantly in all the three groups ($p < 0.0001$). Safety: All the 120 patients were analyzed to detect any adverse events. No serious adverse event re- lated to the study drugs was reported in patients of the three treatment groups. **Author's Conclusion:** All the three combinations achieved equivalent results in terms of symptoms in inducing symptoms relief and mucosa healing in distally active UC. The combination therapy with BDP and mesalazine was not better that any agent alone in inducing distal active UC remission.		

AG 2: Welche Therapie soll bei Steroid-refraktärem Krankheitsverlauf erfolgen?

Bewertungsvorlage:
Oxford SR

Lv, R et al. Tumor necrosis factor alpha blocking agents as treatment for ulcerative colitis intolerant or refractory to conventional medical therapy: a meta-analysis. PLoS One. 9. e86 692. 2014

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** Systematic Review and Meta **Analysis:** 2122 participants from 7 RCTs (8 trials) **Databases:** Pubmed, Embase, and the Cochrane **Search period:** published between 1991 and July 20, 2013 **Inclusion Criteria:** The studies had to be randomized controlled trials (RCTs) comparing anti-TNF-a therapies (e. g. adalimumab, certolizumab, golimumab, or infliximab) with the administration of a placebo or other intervention, and published in the English language, (ii) the UC patients of any age included had to have UC resistant to conventional therapy of corticosteroids and/or immunosuppressive agents, or refractory to intravenous corticosteroids, and, (iii) the patients had to have been given TNF-a blockers at least twice and monitored for at least 12 weeks after the initial dose of TNF-a blocker or control drug.	**Intervention:** Anti-TNF-a therapies (e. g. adalimumab, certolizumab, golimumab, or inflix- imab) **Comparison:** Placebo or other therapy.	**Primary:** Frequency of clinical remission **Secondary:** Frequency of long-term mucosal healing, steroid-free remission, colectomy, serious side effects **Results:** *Frequency* of clinical remission of patients treated with TNF-a blockers was studied in 6 trials that consisted of 1279 patients. Of these 6 trials, 3 trials were controlled by administering a placebo. Patients were treated with infliximab in 2 of the trials and adalimumab in 1. No significant heterogeneity was detected between these trials ($I2 = 0\,\%$, $p = 0.57$). A pooled analysis using fixed-effects models showed that the TNF-a blocker was significantly superior to placebo for maintenance of clinical remission (RR = 2.29; 95 % [1.73, 3.03], Z = 5.78, p,0.00 001) *Steroid free remission:* 698 patients, reported discontinued corticosteroid use and sustained steroid-free remission during their study. Of these, infliximab treatment efficacy was examined in 2 trials and adalimu-	Armuzzi A, (2004) European Review for Medical and Pharmacological Sciences Gavalas E, (2007) Hepatogastroenterology Laharie D, (2012) Lancet Ochsenkühn T, (2004) European Journal of Gastroenterology & Hepatology Rutgeerts P, (2005) The New England Journal of Medicine Sandborn WJ, (2009) Gastroenterology Sandborn WJ, (2012) Gastroenterology	**Funding Sources:** This study was funded by National Natural Science Foundation of China, grant number [No. 81173240]. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. **COI:** The authors have declared that no competing interests exist. **Study Quality:** "Overall, the quality of the studies ranged from moderate to high (Jadad score ≥ 3). Two studies were rated at high risk of bias due to lack of proper blinding control. All data were analyzed in accordance with the intention-to- treat principle." **Heterogeneity:** "Heterogeneity between studies was quantified by calculating I2 where p,0.10 was determined significant. Where there was evidence of heterogeneity, a random- effects model was used for pooling. Otherwise, a fixed-effects model was used." **Publication Bias:** "Due to an insufficient number of studies to produce a meaningful analysis, funnel plots were not used to investigate publication bias." **Notes:** Differences in co-therapy between individual studies, and follow up times. Differences

Exclusion Criteria: - Reviews, case reports and abstracts that lacked sufficient information to determine if the above parameters were met were excluded.		mab in 1 trial. No heterogeneity was detected when comparing the 3 trials (I2 = 4 %, p = 0.35). A pooled analysis utilizing fixed-effects models was conducted. It was shown that the proportion of patients who achieved steroid-free remission was higher in groups that received the TNF-a blockers than in the placebo treated groups (RR = 2.97; 95 % [1.77, 4.96], p,0.0001). *Mucosal* healing was evaluated in 5 trials, consisting of 1345 patients, to determine TNF-a blocker treatment efficacy. Of these, 3 trials compared anti-TNF-a agents with a placebo control. Patients were given infliximab in 2 trials and adalimumab in the third trial. No heterogeneity was detected when comparing these 3 trials (I2 = 37 %, p = 0.20). A pooled analysis using fixed-effects models showed the TNF-a blocker was significantly superior to placebo for healing of the mucosa (RR = 1.89; 95 % [1.55, 2.31], p,0.00 001) The *rate of colectomy* was only reported within 3 of the included trials, which evaluated a total of 863 patients. The data demonstrated that more patients in the placebo group (36/244) than in the infliximab group (46/484) had a colectomy, as shown in Fig. 7. This difference in colectomy rate is statistically significant (RR = 0.64; 95 % [0.43, 0.97], p = 0.03, Figure. 7), indicating the benefit of infliximab treatment. **Data synthesis:** Serious side effects *Serious side effects* were reported in 6 of the trials, consisting of 2088 patients. Within these trials, the frequency of serious side effects was 16.9 % in the anti-TNF-a group, 20.0 % in the placebo group and 24.7 % in cyclosporine group. Of these, 4 trials administered a placebo as a control and 1 used cyclosporine. Significant heterogeneity was not		are also appearant in UC severity and definition of steroid- refractory status.

		detected when comparing these trials (I2 = 34 %, p = 0.19). A pooled analysis using fixed effects models showed the occurrence of serious side effects was equivalent between TNF-a and placebo receiving patients (RR = 0.83; 95 %[0.69, 1.00], Z = 1.98, p = 0.05) **Author's Conclusion:** In summary, this meta- analysis has updated the UC treatment field and demonstrated that TNF-a blockers were superior for patient treatment as compared to placebo. This conclusion was based on increased achievement of clinical remission and mucosal healing and reduction in the need for colectomy, combined with no significant, severe side effects. Using anti-TNF-a also spares patients the effects of corticosteroid treatment, which is used when the patients have refractory UC nonresponsive to conventional treatment. Additionally, infliximab and cyclosporine are comparable when used as rescue therapy in acute severe steroid- refractory UC, although, more randomized trials are needed to further evaluate the efficacy of these agents. So, in selected patients with moderate to severe active ulcerative colitis who have failed to respond or are poorly responsive to standard pharmacologic forms of treatment with corticosteroids and immunosuppressive agents, therapy with an anti-TNF-a agent may be considered. In addition, it may be necessary to identify biomarkers that indicative of patients who will respond to the TNF-a inhibitor.		

Komaki, Y et al. Pharmacologic therapies for severe steroid refractory hospitalized ulcerative colitis: a network meta-analysis. J Gastroenterol Hepatol 2016

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Network meta analysis (8 RCTs, 421 participants).	**Intervention:** 421 steroid refractory participants with acute UC. Interventions were	**Primary:** Clinical response, severe adverse events. **Secondary:** colectomy free rate	Ogata H, (2006) Gut Ogata H, (2012) Inflamm Bowel Dis Lichtiger S, (1994) N Engl J Med	**Funding Sources:** n.a. **COI:** One author was supported by the Pediatric Oncology Research Fellowship of the Chil-

Databases: MEDLINE, Google Scholar, EMBASE, Cochrane Central Register of Controlled Trials. **Search period:** 1993 – November 2015 **Inclusion Criteria:** "Only randomized controlled trials evaluating the efficacy of pharmacologic therapy of UC that compared outcomes between intervention and control arms were included. Control arms were placebo or alternative treatments. There were no restrictions regarding age, sex, and duration of study. We imposed no geographic or language restrictions and articles in languages other than English or Japanese were translated if necessary." **Exclusion Criteria:** Studies that reported events on neither treated nor control groups were excluded from analysis.	Cyclosporin, Infliximab, Tacrolimus. **Comparison:** Placebo or alternative treatment (Cyclosporin, Infliximab, Tacrolimus).	**Results: Clinical response:** The rank of probability of efficacy interpreted by SUCRA (surface under the cumulative ranking) was Infliximab (SUCRA = 0.79, 95 % CI = 0.53 – 1.05), cyclosporine (SUCRA = 0.77, 95 % CI = 0.39 – 1.14), tacrolimus (SUCRA = 0.43, 95 % CI = –0.12 – 0.99) and placebo (SUCRA = 6.67*10^-3, 95 % CI = – = 6.4*10^–3 – 0.02). **Colectomy free rate:** The relative effect of efficacy (number of patients experiencing colectomy free) are analyzed by the network meta-analysis. The rank probability of efficacy interpreted by SUCRA was as follows infliximab (SUCRA = 0.74, 95 % CI = 0.47 – 1.01), cyclosporine (SUCRA = 0.59, 95 % CI = 0.17 – 1.01), tacrolimus (SUCRA = 0.53, 95 % CI = 0.25 – 0.80) and placebo (SUCRA = 0.13, 95 % CI = –0.033 – 0.29). **Severe adverse events:** The network of all treatment comparisons analyzed for severe adverse events leading to discontinuation was performed. The rank probability of risk interpreted by SUCRA was as follows (No.1 is the worst); infliximab (SUCRA = 0.91, 95 % CI = 0.79 – 1.04), tacrolimus (SUCRA = 0.71, 95 % CI = 0.21 – 1.20), cyclosporine (SUCRA = 0.33, 95 % CI = –0.24 – 0.90) and placebo (SUCRA = 0.040, 95 % CI = –0.020 – 0.10). **Author's Conclusion:** We found that among the 3 pharmacologic treatments and placebo, infliximab was the most effective, followed by cyclosporine, tacrolimus, and placebo, though the differences between the three agents were small.	Sands BE, (2001) Inflamm Bowel Dis Jarnerot G, (2005) Gastroenterology Aoki H, (2012) Gastroenterology Bossa F, (2009) Dig Liver Dis Laharie D, (2012) Lancet	dren's Cancer Association of Japan. **Study Quality:** The Jadad score and Cochrane Risk of Bias Assessment Instrument were used to evaluate the methodological quality of the RCTs **Heterogeneity:** "We evaluated the presence of heterogeneity across trials of each therapy by using the I2 statistic. An I2 value of < 25 % indicates low heterogeneity, 25 – 75 % moderate heterogeneity, and > 75 % high heterogeneity. We also evaluated the presence of heterogeneity across trials of each therapy by using the statistic Q (Q) and used a P value of < 0.10 as evidence of statistically significant heterogeneity." **Publication Bias:** "To account for the fact that each set of studies estimates a different summary effect, we created comparison- adjusted funnel plots with Stata software version 14 with studies that compared active treatment versus placebo. In the absence of small study effects the comparison-adjusted funnel plot should be symmetric around the zero line" **Notes:** The number of studies in each Meta-Analyses was small (1 – 2), which makes comparison of efficacy more difficult. Differences in assessing clinical response (DAI, Lichtiger's index, Truelove-Witts score). Differencs in study duration (2 – 14 weeks). The investigated outcomes were not primary outcomes in all of the included studies.

Narula, N et al. Systematic Review and Meta-Analysis: Infliximab or Cyclosporine as Rescue Therapy in Patients With Severe Ulcerative Colitis Refractory to Steroids. Am J Gastroenterol. 111. 477 – 491. 2016

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** Systematic Review and Meta Analysis:	**Intervention:** 1473 steroid refractory participants in 16 Studies, three RCTs and 13 non-	**Primary:** short-term symptomatic response to therapy. **Secondary:** Rate of colectomy at 3 and 12 months	Laharie D, (2012) Lancet Scimeca D, (2012) Paper presented at the United	**Funding Sources:** None. **COI:** Potential competing interests: Walter Reinisch has served as a speaker, a consultant, and/or

16 Studies (3 RCT, 13 non-randomized) **Databases:** MEDLINE, Embase, PubMed **Search period:** 1950 to September 2015 **Inclusion Criteria:** observational design (prospective or retrospective cohort or case–control) or interventional design (randomized or non-randomized); (ii) subjects with acute severe UC who had failed a course of intravenous or oral steroids prior to treatment with a rescue therapy; (iii) IFX and cyclosporine administered as rescue therapies with outcomes reported for both cohorts; and (iv) subjects not treated pre- viously with IFX or cyclosporine therapy during the same presentation of acute UC.a **Exclusion Criteria:** Studies were excluded, if patients had already been given IFX or cyclosporine after failing the other rescue therapy during the same presentation acute severe UC.	randomized trials. Treatment with Infliximab (IFX) **Comparison:** Cyclosporin A (CSA)	**Results: Primary** *Therapeutic Response:* Eleven studies reported therapeutic response in 565 IFX and 648 CSA receiving participants. The pooled OR for therapeutic response among three randomized trials was 1.08 (95 % CI 0.73 – 1.60, $\chi2 = 0.28$, I2 = 0 %). The pooled response rate in randomized studies is 43.8 % for IFX and 41.7 % for CSA. In non- randomized studies, significantly higher therapeutic response was seen with IFX, with a pooled OR of 2.96 (95 % CI 2.12 – 4.14, $\chi2 = 6.50$, I2 = 0 %). The pooled response rate in non- randomized studies is 74.8 % (IFX) and 55.4 % (CSA), for an absolute risk reduction of 19.4 % and a number needed to treat of 5 for IFX compared with CSA. The median time of evaluation of therapeutic response was 3 months. **Secondary:** *Three month colectomy:* 10 studies + reported colectomy rates within 3 months (416 IFX and 447 cyclosporine). Two RCTs reported colectomy rates at 3 months and reported no difference between the two groups (OR 1.00, 95 % CI 0.64 – 1.59, $\chi2 = 0.34$, I2 = 0 %). The pooled 3-month colectomy rate among randomized studies was 26.6 % (IFX) and 26.4 %(CSA). In non-randomized studies the pooled OR for 3-month colectomy was 0.53 (95 % CI 0.22 – 1.28, $\chi2 = 22.73$, I2 = 69 %), demonstrating no significant difference between the two groups. The pooled 3-month colectomy rate among non- randomized studies was 24.1 % among those receiving IFX and 42.5 % among those receiving cyclosporine. *12 months colectomy rate:* 12 studies reported 12-month colectomy rates in 620 IFX and 649 CSA receivers. Three RCTs reported colectomy rates at 12 months, that did not differ between the two groups (OR 0.76,	European Gastroenterology Week 2012 Williams JG, (2004) paper presented at the United European Gastroenterology Week 2014 Croft A, (2013) Aliment Pharmacol Daperno M, (2004) Dig Liver Dis Dean K, (2012) J Gastroenterol Hepatol Govani S, (2014) Gastroenterology Kim EH, (2015) Gut Liver Lynch R, (2013), Aliment Pharmacol Ther Mocciaro F, (2012) J Crohns Colitis Naves JE, (2014) Inflamm Bowel Dis Protic M, (2013) Gastroenterology Radojcic M, (2014) J Gastroenterol Hepatol Sjoberg M, (2012) Inflamm Bowel Dis Yoshimura N, (2013) Gastroenterology	an advisory board member for Abbott Laboratories, Abbvie, Aesca, Amgen, AM Pharma, Aptalis, Astel- las, Astra-Zeneca, Avaxia, Bioclinica, Biogen IDEC, Bristol-Myers Squibb, Cellerix, Chemocentryx, Celgene, Centocor, Danone Austria, Elan, Falk Pharma GmbH, Ferring, Galapagos, Genentech, Grünenthal, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid erapeutics, Millenium, Mitsubishi Tanabe Pharma Corporation, MSD, Novartis, Ocera, Otsuka, PDL, Pharmacosmos, Pfizer, Procter & Gamble, Prometheus, Robarts Clinical Trial, Schering-Plough, Setpointmedical, Shire, Takeda, erakos, Tigenix, UCB, Vifor, Yakult, Zyngenia, and 4SC. Jean-Frederic Colombel has served as a consultant, an advisory board member, or a speaker for Abbvie, Amgen, Bristol Meyers Squibb, Celltrion, Ferring, Genen- tech, Giuliani SPA, Merck & Co., Mitsubishi, Nestle Nutrition Sci- ence Partners Ltd., P zer Inc., Prometheus Laboratories, Receptos, Takeda/Millenium Pharmaceuticals Inc., UCB Pharma, Vertex, and Dr August Wol GmbH & Co. John K. Marshall has received hono- raria from Janssen, AbbVie, Aptalis, Astra-Zeneca, Ferring, Forest, Optimer, Procter & Gamble, Shire, Takeda, and Warner-Chilcott. The remaining authors declare no conflict of interest. **Study Quality:** The quality of randomized studies was evaluated using domain-based risk of bias tables as recommended by the Cochrane Collaboration. The quality of non- randomized studies was assessed using the Newcastle–Ottawa scale, a tool that allows for quality appraisal of non-randomized studies in meta-analyses. The results from the quality assessment are provided in the Supplementary Materials. **Heterogeneity:** "We tested for heterogeneity using the $\chi2$-test and the I2-test. The I2-test describes the percentage of variability in e ect estimates that is due to heterogeneity rather than chance, wherein an I2-test> 50 % suggests signi cant heterogeneity. A random-e ects model was used given the variation among study designs, as this provides a

		95 % CI 0.51 – 1.14, $\chi 2 = 1.59$, $I2 = 0$ %). In non-randomized studies, the 12-month colectomy rate was lower for IFX, with a pooled OR of 0.42 (95 % CI, 0.22 – 0.83, $\chi 2 = 30.94$, $I2 = 71$ %;). The pooled rate of colectomy at 12 months in the non-randomized studies was 20.7 % for the IFX group compared with 36.8 % in the CSA, for an absolute risk reduction of 16.1 % and a number needed to treat of 6. **Author's Conclusion:** In conclusion, this meta-analysis does not find any defnitive preference with regard to IFX and cyclosporine for steroid-refractory acute severe UC. Optimized dosing of IFX requires 3-dose induction and possibly higher or more frequent doses guided by therapeutic drug monitoring, but more prospective data are needed. Observational data suggest better treatment response and lower risk of colectomy at 12 months with IFX compared with cyclosporine, with comparable short-term adverse events; however, this increase in apparent benefit from observational studies may well reflect residual confounding rather than true causality. Studies are ongoing to determine how to maximize the therapeutic benefit of IFX in the setting of acute severe UC and prospective studies comparing dose-optimized IFX to cyclosporine may provide more definitive insight into this debate.		more conservative estimate than a mixed-effects model." Heterogeneity was low between RCTs and high between non-randomized studies (I^2:69 and 71 % for 3 and 12 month colectomy rate). **Publication Bias:** Symmetrical distribution of the studies on the plot suggests no publication bias. Egger's test similarly showed no publication bias (Egger's t value = 0.89, P value = 0.39). **Notes:** The effect favouring infliximab in non- randomized studies is potentially caused by residual confounding. No information on age or sex of study participants. Medication Regimen not uniform in the compared studies (x mg/kg). Additional influence through concomitant medication (AZA, Methotrexate, Thiopurine or unclear)

AG 2: Welche Therapie soll bei Steroid-refraktärem Krankheitsverlauf erfolgen?

Bewertungsvorlage:
OXFORD Appraisal Sheet: RCT

Williams, J G et al. Comparison Of iNfliximab and ciclosporin in STeroid Resistant Ulcerative Colitis: pragmatic randomised Trial and economic evaluation (CONSTRUCT). Health Technol Assess. 20. 1 – 320. 2016

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 3 **Study type:** "open-label parallel-group, pragmatic randomised trial", multicentric design (52 UK hospitals) **Number of Patient:** 270 **Recruitung Phase:** "Sixty-four sites recruited patients to the cohort and 52 of these recruited participants to the trial. The first site was activated in March 2010 with the first cohort patient recruited in May 2010 and the first trial participant randomised in June 2010. We randomised the last trial participant in February 2013 and completed follow-up in February 2014." **Inclusion Criteria:** The study included patients who had been were admitted unscheduled with severe colitis (by the criteria of Truelove and Witts, a Mayo score of at least 2 on endoscopic finding, or clinical judgement); who then failed to respond to about 2 – 5 days of intravenous hydrocortisone; and also had a proven histological diagnosis of UC, indeterminate colitis where clinical judgement suggested a diagnosis of UC rather than Crohn's disease, or symptoms typical of UC awaiting histology. **Exclusion Criteria:** Study excluded patients: patients aged < 18 years; from vulnerable groups or unable to consent; with an enteric infection or histological diagnosis inconsistent with UC; who were pregnant, lactating, or fertile but unwilling to use contraception for 6 months after randomisation; suffering current malignancy, except for basal cell carcinoma; with serious comorbidity, including immunodeficiency, recent myocardial infarction, heart failure, acute stroke, respiratory failure, renal failure, hepatic failure, or severe infection; with known hypersensitivity to infliximab, ciclosporin or polyethoxylated oils; using tacrolimus or rosuvastatin; whose English was poor in the absence of local translator services; needing emergency colectomy without further medical	**Intervention:** 270 participants of steroid refractory participants. Participants were randomly assigned to one group of 135, which received either a) 5 mg/kg of intravenous infliximab at 0, 2 and 6 weeks or b) 2 mg/kg/day of intravenous ciclosporin for 7 days followed by 5.5 mg/kg/day of oral ciclosporin until 12 weeks from randomization n **Comparison:** –	**Primary:** QAS (quality adjusted survival): the area under the curve (AUC) of scores derived from Crohn's and Ulcerative Colitis Questionnaires completed by participants at 3 and 6 months, and then 6-monthly over 1 – 3 years, more frequently after surgery. **Secondary:** (a) Disease- specific QoL, measured by the CUCQ. (b) and (c) Generic QoL, measured by the SF-12.62 (d) Mortality. (e) Colectomies, both emergency and planned. (f) AEs. (g) Readmissions, including those for causes other than UC. (h) Malignancies. (i) Serious infections. (j) Renal disorders. (k) Disease activity, using the criteria proposed by Truelove and Witts. **Results: Primary** *QAS*: No significant difference between IFX and CSA in QAS [mean difference in AUC/day 0.0297 favouring CSA, 95 % confidence interval (CI) –0.0088 to 0.0682; p = 0.129]; **Secondary:** *EQ-5 D scores* (quality-adjusted life-year mean difference 0.021 favouring ciclosporin, 95 % CI –0.032 to 0.096; p = 0.350); Short Form questionnaire-6 Dimensions scores (mean difference 0.0051 favouring ciclosporin, 95 % CI –0.0250 to 0.0353; p = 0.737). *colectomy rates:* no statistically significant difference in [odds ratio (OR) 1.350 favouring infliximab, 95 % CI 0.832 to 2.188; p = 0.223]; *numbers of serious adverse reactions* (event ratio = 0.938 favouring ciclosporin, 95 % CI 0.590 to 1.493; p = 0.788); *participants with serious adverse reactions* (OR 0.660 favouring ciclosporin, 95 % CI 0.282 to 1.546; p = 0.338); *numbers of serious adverse events* (event ratio 1.075 favouring infliximab, 95 % CI 0.603 to 1.917; p = 0.807); *serious adverse events* (OR 0.999 favouring infliximab, 95 % CI 0.473 to 2.114; p = 0.998); *deaths* (all three who died received infliximab; p = 0.247) or concomitant use of immunosuppressants. The lower cost of ciclosporin led to lower total NHS costs (mean difference –£5632, 95 % CI –£8305 to –£2773; p < 0.001). Interviews highlighted the debilitating effect of UC; participants were more positive about infliximab than ciclosporin. Professionals reported advantages and disadvantages with both drugs, but nurses disliked the intravenous ciclosporin. **Author's Conclusion:** Total cost to the NHS was considerably higher for infliximab than ciclosporin. Nevertheless, there was no significant difference between the two drugs in clinical effectiveness, colectomy rates, incidence of SAEs or reactions, or mortality, when measured 1 – 3 years post treatment. Further studies will be needed to evaluate the efficacy and effectiveness of new anti- tumour necrosis factor drugs and formulations of ciclosporin.	**Funding Sources:** This project was funded by the NIHR Health Technology Assessment programme and will be published in full in Health Technology Assessment; Vol. 20, No. 44. See the NIHR Journals Library website for further project information. **COI:** First author was a member of the National Institute for Health Research (NIHR) Efficacy and Mechanism Evaluation Board from 2008 to 2011 and the NIHR Health Services and Delivery Research Researcher-Led Board from 2009 to 2014. **Randomization:** Web-based adaptive randomisation algorithm. **Blinding:** Blinding was possible only for data analysts. **Dropout Rate/ITT- Analysis:** High dropout rates for follow ups: Only 13 % remained (17 out of 135 in each group) participants participated in the last follow-up at 36 months. Similar amount of dropouts in each group. Intention to treat analysis was performed: "This is a pragmatic trial, and analysis will be by intention-to-treat." **Notes:** Not a controlled, double-blinded trial. Only clinicians were blinded. This is likely to introduce bias. However subjective scores (f.e well-being) are more likely to be influenced than objective measures (f.e. mortality). Appearantly QoL outcome measures were completed by participants before steroid treatment and subsequent randomization. Large amount of losses to follow- up (only 13 % remain after 36 weeks follow-up).

treatment; currently participating in another clinical trial; treated with either infliximab or ciclosporin within 3 months of admission; or showing any other contraindication to treatment with infliximab or ciclosporin.			

Sandborn, W J et al. Anti-CD3 antibody visilizumab is not effective in patients with intravenous corticosteroid-refractory ulcerative colitis. Gut. 59. 1485 – 1492. 2010

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 3 **Study type:** Multicentric, randomised, double-blind, placebo-controlled study conducted globally at 75 sites in 14 countries. **Number of Patient:** 127 patients with severly active UC despite treatment with ≥ 5 days of intravenous corticosteroids. **Recruitung Phase:** Pilot studies with visilizumab, a humanised monoclonal antibody to CD3, suggest efficacy for corticosteroid-refractory ulcerative colitis (UC). A placebo-controlled trial was warranted. **Inclusion Criteria:** gible patients included men or women at least 18 years of age with a diagnosis of ulcerative colitis for whom oral corti- costeroid treatment had failed or who were newly diagnosed and hospitalised and who currently had severely active intravenous corticosteroid-refractory disease. Severely active intravenous corticosteroid-refractory ulcerative colitis was defined by a modified Truelove and Witts Severity Index score (MTWSI, also known as the Lichtiger score)6 26 $10 points on or after the fifth consecutive day of intravenous corticosteroids (methy- prednisolone $40 mg/day or equivalent) and within 1 day before randomisation. In addition, patients were required to have a Mayo score26 27 of $10 points and a Mayo sigmoidoscopy subscore of $2 points. The Mayo score was calculated on the day of sigmoidoscopy by a blinded gastroenterologist, after a minimum of three consecutive days (ie, on or after the fourth consecutive day) of intravenous corticosteroids. In addition to intravenous corticosteroids, patients could be receiving mesal- amine, azathioprine, 6-mercaptopurine, or methotrexate. **Exclusion Criteria:** Patients were excluded from study participation if they had an ileostomy,	**Intervention:** Visilizumab intravenous injection 5 mikrogram/kg for 2 days. **Comparison:** Placebo nondescript.	**Primary:** Induction of response on day 45 (MTWSI score of ≤ 9 points) **Secondary:** Remission (total Mayo score of < 3 points, with no individual subscore > 1 point), Mucosal healing at day 45 (defined as an absolute endoscopy subscore of #1 point), symptomatic response at day 15, colectomy. **Results: Efficacy:** At day 45, there were no significant differences between the treatment groups in the rates of response, remission or mucosal healing. Similarly, at day 15 there were no significant differences between the treatment groups in the rates of symptomatic response. The median (95 % CI) time to symptomatic response was 11 (8 to 15) days in the visilizumab group and 11 (8 to 30) days in the placebo group. Disease progression occurred in 26 % (22 of 84) of patients in the visilizumab group and 33 % (14 of 43) of patients in the placebo group. Of these patients, 19 in the visilizumab group (23 %) and 11 in the placebo group (26 %) received salvage treatment with an anti-tumour necrosis factor agent (infliximab or adalimumab). **Colectomy:** The proportions (95 % CI) of patients who under- went colectomy were 18 % (10 % to 28 %; 15 of 84 patients) in the visilizumab group and 7 % (2 % to 19 %; 3 of 43 patients) in the placebo group. **Safety:** Adverse events occurred in 77 % of patients in the placebo group and 96 % of patients in the visilizumab group. Grades 2, 3 and 4 adverse events occurred more frequently in the visilizumab group. The proportions of patients with serious adverse events were similar in the placebo and visilizumab groups. One patient in the visilizumab group developed hepatic focal nodular hyperplasia. No patient developed cancer and no patient died. The incidence of infections was slightly lower in the placebo group than in the visilizumab group. **Author's Conclusion:** The results of our study show that visilizumab administered at a dose of 5 mikrog/kg for two consecutive days is not effective in achieving symptomatic response at day 15; response, remission, or mucosal healing at day 45; prolongation of time to disease progression; or corticosteroid discontinuation in patients with severe intravenous corticosteroid- refractory ulcerative colitis. The patients who received visilizumab had a trend towards a greater rate of colectomy and were more likely to experience signs and symptoms of cytokine release, including cardiac and vascular disorders, some of which were severe and/or serious. Based on this unfavourable benefit to risk profile identified during an interim analysis, the trial was discontinued prematurely.	**Funding Sources:** Supported by a research grant from Facet Biotech (previously PDL BioPharma), Redwood City, California, USA. COI: WS, JFC, DH, LM, ST, SRT, GV and STa have served as consultants and received research support from PDL BioPharma. PS and DCB have received research support from PDL BioPharma, MF and JNL are former employees of PDL BioPharma. **Randomization:** Centralized, adaptive randomization method **Blinding:** n.a. **Dropout Rate/ITT- Analysis:** 18 out of 43 (Placebo group) vs 32 out of 84 (control group) **Notes:** *Trial was stopped in progress because the intervention had an insufficient safety* profile! "On 24 August 2007 an independent Data Safety Monitoring Board reviewed the interim efficacy and safety data on 91 patients and recommended that the trial be stopped because of insufficient efficacy and an inferior safety profile for visilizumab compared with placebo." Blinding procedures is not adequatly described in all cases. Analysis must have been carried out prematurely ahead of schedule to determine efficacy and safety of the drug.

proctocolectomy or subtotal colectomy with ileor- ectal anastomosis, or required immediate surgical, endoscopic, or radiological intervention for massive haemorrhage, perforation, sepsis, intra-abdominal or perianal abscess, or toxic megacolon. Patients were also excluded if they had had a positive Clostridium difficile test within 10 days before the first dose of study drug, active medically significant infections (particularly those of viral aetiology such as cytomegalovirus colitis), any medically significant opportunistic infection within the past 12 months, vaccination with a live virus within 6 weeks, or were seroposi- tive for human immunodeficiency virus, hepatitis B virus surface antigen, or hepatitis C virus antibody. Additional exclusion criteria included significant renal, liver, central nervous system, pulmonary, vascular, gastrointestinal, or endocrine conditions or laboratory abnormalities (eg, white blood cell count < 2.53 103/ml; platelet count < 1503 103/ml; haemoglobin concentration < 8 g/dl; creatinine $1.6 mg/dl; alanine aminotransferase or aspartate aminotransferase $2 times the upper limit of normal; alkaline phosphatase $1.5 times the upper limit of normal); a non-therapeutic level of a chronic anti-convulsant drug within 4 days, or medically significant cardiac conditions, including a history of myocardial infarction, coronary artery disease, congestive heart failure, or arrhythmias within 6months. Patients were also excluded if they had a history of lympho- proliferative disorder or malignancy within the past 5 years (except for non- melanoma skin cancer or carcinoma in situ of the cervix). Patient's who had received the first dose of infliximab, or another anti-tumour necrosis factor drug within 4 weeks of randomisation or a subsequent dose within 2 weeks of randomisation, ciclosporin or tacrolimus (FK506) within 2 weeks, or any investigational treatment within 60 days, were excluded. Pregnant and/or lactating women were also excluded from study participation.			

AG 2: Welche Therapie soll bei Steroid-abhängigem Krankheitsverlauf erfolgen?

Bewertungsvorlage:
Oxford SR

Chande, N et al. Methotrexate for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. Cd006 618. 2014

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Systematic review of two RCTS, total n = 101 **Databases:** MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and the Cochrane IBD/FBD. Review papers on ulcerative colitis, and references from identified papers were also searched in an effort to identify additional studies. Abstracts from major gastroenterological meetings were searched to identify research published in abstract form only. **Search period:** x – June 26, 2014 **Inclusion Criteria:** Randomized controlled trials comparing methotrexate with placebo or an active comparator were considered for inclusion. **P:** Adult patients with active ulcerative colitis defined by a combination of clinical, radiographic, endoscopic and histological criteria were included. **I:** Methotrexate given by any route. C:Placebo or other standard treatment. **O:** The number of patients achieving clinical remission and complete withdrawal from steroids as defined by the studies and expressed as a percentage of the number of patients randomized. Secondary outcomes measures included: a) Endoscopic remission as defined by the authors; b) Clinical, histological or endoscopic improvement as defined by the authors; c) The occurrence of adverse events; and d) Improvements in quality of life as measured by a validated instrument.	**Intervention:** Population consisted of 101 steroid dependent patients with active UC. Methotrexate given by any route. **Comparison:** Placebo or other standard treatment.	**Primary:** The number of patients achieving clinical remission and complete withdrawal from steroids as defined by the studies and expressed as a percentage of the number of patients randomized. **Secondary:** a) Endoscopic remission as defined by the authors; b) Clinical, histological or endoscopic improvement as defined by the authors; c) The occurrence of adverse events; and d) Improvements in quality of life as measured by a validated instrument. **Results:** One study (n = 67) compared oral methotrexate (12.5 mg/week) to placebo. The other study (n = 34) compared oral methotrexate (15 mg/week) to 6- mercaptopurine (1.5 mg/kg/day) and 5-aminosalicylic acid (3 g/day). The placebo-controlled study was judged to be at low risk of bias. The other study was judged to be at high risk of bias due to an open-label design. In the placebo- controlled trial two patients (7 %) were withdrawn from the methotrexate group due to adverse events (leucopenia, migraine) compared to one patient (3 %) who had a rash in the placebo group (RR 2.47, 95 % CI 0.23 to 25.91). Adverse events experienced by methotrexate patients in the active comparator study included nausea and dyspepsia, mild alopecia, mild increase in aspartate aminotransferase levels, peritoneal abscess, hypoalbuminemia, severe rash and atypical pneumonia. **Author's Conclusion:** Although methotrexate was well- tolerated, the studies showed no benefit for methotrexate over placebo or active comparators. The results for ef-	Maté-Jiménez J, (2000) Eur J Gastroenterol Hepatol Oren R, (1996) Gastroenterology	**Funding Sources:** Funding for the IBD/FBD Review Group (September 1, 2010 – August 31, 2015) has been provided by the Canadian Institutes of Health Research (CIHR) Knowledge Translation Branch (CON – 105 529) and the CIHR Institutes of Nutrition, Metabolism and Diabetes (INMD); and Infection and Immunity (III) and the Ontario Ministry of Health and Long Term Care (HLTC3968FL- 2010–2235). Miss Ila Stewart has provided support for the IBD/FBD Review Group through the Olive Stewart Fund. **COI:** Nilesh Chande has received fees for consultancy from Abbott/AbbVie and Ferring, fees for lectures from Abbott and Janssen, travel expenses from Merck and has stock/stock options in Pfizer, Glaxo Smith Kline, Proctor and Gamble and Johnson and Johnson. All of these financial activities are outside the submitted work. The other authors have no known declarations of interest. **Study Quality:** "The methodological quality of the included studies was evaluated using the Cochrane risk of bias tool." **Heterogeneity:** n.a. **Publication Bias:** n.a. **Notes:** Poor overall evidence, with 2 RCTs available with different comparators. One has a sample size of only 32 besides having three arms and a high risk of bias. Both included original articles would not have been included in a literature search due to their original publication date (1996 and 2000). Dissimilarities between the studies exist, but are not relevant because they are not directly comparable. Steroid- dependence was not defined a priori as an inclusion criterion – the included studies just happen to include these patients.

Exclusion Criteria: - Missing placebo or active comparator group. Wrong study type: none-RCT.		ficacy outcomes between methotrexate and placebo, methotrexate and 6-mercaptopurine and methotrexate and 5- aminosalicylic acid were uncertain. Whether a higher dose or parenteral administration would be effective is unknown. At present there is no evidence supporting the use of methotrexate for induction of remission in active ulcerative colitis.		

AG 2: Welche Therapie soll bei Steroid-abhängigem Krankheitsverlauf erfolgen?

Bewertungsvorlage:
OXFORD Appraisal Sheet: RCT

Carbonnel, F et al. Methotrexate Is Not Superior to Placebo for Inducing Steroid-Free Remission, but Induces Steroid-Free Clinical Remission in a Larger Proportion of Patients With Ulcerative†Colitis. Gastroenterology. 150. 380 – 388.e4. 2016

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 3 **Study type:** Double-blind, placebo-controlled trial. Multicentric setup (26 european medical centers). Number of Patient: 111 **Recruitung Phase:** 2007 – 2009 **Inclusion Criteria:** Adults younger than 75 years of age, diagnosed with UC for at least 6 months and were steroid- dependent, as defined by at least one unsuccessful attempt to discontinue steroids during the last 12 weeks before inclusion. Steroid therapy may have completely stopped if it had been restarted within the last 90 days. At inclusion, the daily dose of steroids had to range between 10 and 40 mg prednisone or equivalent. Patients could have active or inactive disease at inclusion, as defined by a Mayo Clinic score (range 0 – 12, with higher scores indicating more active disease) of > 2 or 2. At the beginning of the trial, patients included had to have inactive disease, but in November 2009, due to slow recruitment, an amendment allowed inclusion of patients with active or inactive disease. Patients with a child- bearing poten- tial were required to use an adequate method of contraception throughout the study. **Exclusion Criteria:** Patients were ineligible if they were initially refractory to oral steroids (no	**Intervention:** Steroid dependent UC; participants younger than 75 years, diagnosed with UC for at least 6 months, at least one unsuccesful attempt to discontinue steroids durng the last 12 weeks before exclusion. At inclusion the daily dose of steroids ranges between10 and 40 mg. Intervention: Methotrexate parenteral: intramuscularly or subcutaneously **Comparison:** Placebo, administered parenteral: intramuscularly or subcutaneously	**Primary:** Steroid- free remission at week 16, defined as remission with a Mayo score 2 with no item > 1 and complete withdrawal of steroids and no use of another immunosuppressives (IS) or anti-TNF therapy or colectomy. **Secondary:** Steroid-free remission at week 24, remission at week 16 and 24, endoscopic healing (Mayo endoscopic subscore = 0 or 1), clinical remission (defined as Mayo clinical subscore ≤ 2 with no item > 1), all without ste- roids, IS, anti-TNF, or colectomy at week 16 and/or 24 as well as adverse events, either severe or not. Additionally, the proportion of patients with CRP concentration < 5 mg/L and In- flammatory Bowel Disease Questionnaire score ≥ 170 without steroids at week 16 were determined. **Results: Primary** *Steroid-free remission at week 16* was achieved by 19 of 60 patients given methotrexate (31.7 %) and 10 of 51 patients given placebo (19.6 %) — a difference of 12.1 % (95 % confidence interval [CI]: 4.0 % to 28.1 %; P 1⁄4.15). **Secondary:** The proportion of patients in steroid-free clinical remission at week 16 was 41.7 % in the methotrexate group and 23.5 % in the placebo group, for a difference of 18.1 % (95 % CI: 1.1 % to 35.2 %; P 1⁄4.04). The proportions of patients with steroid-free endoscopic healing at week 16 were 35 % in the methotrexate group and 25.5 % in the placebo group—a difference of 9.5 % (95 % CI: 7.5 % to 26.5 %; P 1⁄4.28). No differences were observed in other secondary end points. More patients receiving placebo discontinued the study because of adverse events (47.1 %), mostly caused by UC, than patients receiving methotrexate (26.7 %; P 1⁄4.03). A higher proportion of patients in the methotrexate group had nausea and vomiting (21.7 %) than in the placebo group (3.9 %; P 1⁄4.006).	**Funding Sources:** This study was funded by the French Ministry of Health (PHRC National), an anonymous patient treated by Prof Pierre Michetti, the Association François Aupetit, and the Société Nationale Française de Gastroentérologie. The study sponsors were not involved in the study design in the collection, analysis, and interpretation of data. **COI:** These authors disclose the following: Franck Carbonnel: advisory board for Genentech, Otsuka, Vifor, and speaker for Hospira. Jean Frédéric Colombel: served as consultant or advisory board member for Abbvie, ABScience, Amgen, Bristol Meyers Squibb, Celltrion, Danone, Ferring, Genentech, Giuliani SPA, Given Imaging, Janssen, Immune Pharmaceuticals, Medimmune, Merck & Co., Millenium Pharmaceuticals Inc., Neovacs, Nutrition Science Partners Ltd., Pfizer Inc., Prometheus Laboratories, Protagonist, Receptos, Sanofi, Schering Plough Corporation, Second Genome, Shire, Takeda, Teva Pharmaceuticals, Tigenix, UCB Pharma, Vertex, Dr. August Wolff GmbH & Co.; and has served as speaker for Abbvie, Falk, Ferring, Janssen, Merck & Co., Nutrition Science Partners Ltd., and Takeda. Jérome Filippi: Abbvie, Astellas Pharma Ferring, Given Imaging, Jansen, MSD, and Takeda. Konstantinos H. Katsanos: served as speaker for MSD and Abbvie. Laurent Peyrin-Biroulet: Consulting fees from Merck, Abbott, Janssen, Genentech, Mitsubishi, Fer-

improvement after 2 weeks of 40 mg prednisone), had received anti-TNFs within 60 days before enrollment, or had received azathioprine, mercaptopurine, cyclosporine, nonsteroidal anti-inflammatory drugs, cotrimoxazole, or probenecid within 30 days before enrollment. Other exclusion criteria included indication for colectomy, alcohol consumption, chronic obstructive pulmo- nary disease, renal failure, liver disease, pregnancy or lactation, patients without efficacious contraception, patients infected with human immunodeficiency virus, hepatitis B virus, hepatitis C virus, a history of a malignant condition, obesity (defined by body mass index > 30 kg/m2), or diabetes mellitus.		**Author's Conclusion:** In conclusion, our study failed to show that parenteral methotrexate is beneficial for induction of steroid-free remission in UC. However, methotrexate induced clinical remission without steroids at week 16 more frequently than placebo, and was associated with better control of disease- related symptoms. Additional studies are required to define the potential benefit of methotrexate as a maintenance therapy.	ring, Norgine, Tillots, Vifor, Shire, Therakos, Pharmacosmos, Pilège, BMS, UCB-Pharma, Hospira, Celltrion, Takeda, Biogaran, Boerhinger-Ingelheim, Lilly, Pfizer, HAC-Pharma; lecture fees from Merck, Abbott, Takeda, Janssen, Ferring, Norgine, Tillots, Vifor, Therakos, and HAC-pharma. Matthieu Allez received honoraria from Novo Nordisk, MSD, Abbvie, Ferring, Genentech, TxCell, Janssen, Pfizer, GSK, Hospira, and UCB. Maria Nachury: lecture fees from Abbvie, MSD, and Ferring. Gottfried Novacek: Honoraria from AbbVie, MSD, Ferring, Merck, Astro-Pharma, and Takeda. Silvio Danese: served as speaker, consultant, and advisory board member for Abbvie, Astra Zeneca, MSD, Novo Nordisk, Takeda Millennium, Salix Pharmaceuticals, and Pfizer. Fabrizio Bossa: MSD, Abbvie, and Takeda. Jacques Moreau: MSD, Abbvie, Norgine, Ferring, and Vifor. Gilles Bommelaer: Abbvie (lecture fees). Xavier Roblin: Abbvie, MSD, HAC Pharma, Ferring, Takeda, and Theradiag. Mathurin Fumery: lecture fees: Abbvie, MSD, and Ferring. Yoram Bouhnik: Consultancies: BMS, Shire, Sanofi, Norgine Pharma, MSD, Abbvie, Astra Zeneca, Roche, Takeda Millenium; stock ownership in Inception IBD, San Diego, CA; honoraria from BMS, MSD, Abbvie, Teva, Ferring, Vifor Pharma, HAC, Mayoli-Spindler; and paid expert testimony for Abbvie; travel grants: Abbvie, MSD, Ferring, Takeda. Philippe Seksik: consulting fees from Abbvie, Merck-MSD, and Biocodex; grants from Biocodex; sponsored travel from Merck-MSD and Takeda. Walter Reinisch: served as a speaker for Abbott Laboratories, Abbvie, Aesca, Aptalis, Centocor, Celltrion, Danone Austria, Elan, Falk Pharma GmbH, Ferring, Mitsubishi Tanabe Pharma Corporation, MSD, Otsuka, PDL, Pharmacosmos, Schering-Plough, Shire, Takeda, Therakos, Vifor, and Yakult; as a consultant for Abbott Laboratories, Abbvie, Aesca, Amgen, AM Pharma, Astellas, Astra Zeneca, Avaxia, Bioclinica, Biogen IDEC, Bristol-Myers Squibb, Cellerix, Chemocentryx, Celgene, Centocor, Celltrion, Danone Austria, Elan, Falk Pharma GmbH, Ferring, Galapagos, Genentech, Grünenthal, ICON, Inova, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, MedImmune, Millenium, Mitsubishi Tanabe Pharma Corporation, MSD, Nestle, Novartis, Ocera, Otsuka, PDL, Pharmacosmos, Pfizer, Procter & Gamble,

			Prometheus, Robarts Clinical Trial, Schering-Plough, Setpointmedical, Takeda, Therakos, Tigenix, UCB, Vifor, Zyngenia, and 4SC; as an advisory board member for Abbott Laboratories, Abbvie, Aesca, Amgen, AM Pharma, Astellas, Astra Zeneca, Avaxia, Biogen IDEC, Bristol-Myers Squibb, Cellerix, Chemocentryx, Celgene, Centocor, Celltrion, Danone Austria, Elan, Ferring, Galapagos, Genentech, Grünenthal, Inova, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, MedImmune, Millenium, Mitsubishi Tanabe Pharma Corporation, MSD, Nestle, Novartis, Ocera, Otsuka, PDL, Pharmacosmos, Pfizer, Procter & Gamble, Prometheus, Schering-Plough, Setpointmedical, Takeda, Therakos, Tig **Randomization:** Randomization was centralized and balanced by center. The 1:1 randomization sequence was generated independently of the investigators by the Clinical Investigation Center of Lille University Hospital, using a computer procedure, with a block size of 4. The placebo and the active treatment were numbered according to the randomization code and then distributed by Eurofins. **Blinding:** Patients, caregivers, investigators, and data analysis personnel were unaware of the treatment assignment. An independent blinded observer supervised the study and recorded any adverse effects of treatment. **Dropout Rate/ITT-Analysis:** All analyses were performed on a full intent-to-treat basis; patients withdrawn before week 16 were considered as failures. **Notes:** Broad confidence interval with a possibility the effect could be nil or point towards placebo being superior: Difference between I and C: 12.1 % 95 %CI (-4 %; + 28 %). Higher amount of dropout in the placebo group (51 % vs 33 % dropout). Readings of endoscopic images was not centralized, which could introduce inter-rate bias. Inclusion of patients regardless of their UC activity status: “At the beginning of the trial, patients included had to have inactive disease, but in November 2009, due to slow recruitment, an amendment allowed inclusion of patients with active or inactive disease.”

AG 2: Welche Therapie soll bei Patienten erfolgen, die ein primäres oder sekundäres Therapieversagen auf eine Biologika (anti-TNFalpha)- Therapie zeigen?

Bewertungsvorlage:
Oxford SR

Feuerstein, J D et al. Systematic review and meta-analysis of third-line salvage therapy with infliximab or cyclosporine in severe ulcerative colitis. Ann Gastroenterol. 29. 341 – 347. 2016

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Systematic Review and Meta-Analysis of 6 observational studies **Databases:** Pubmed **Search period:** 1960 – 01.01.2015 **Inclusion Criteria:** Any article published and indexed on PubMed that assessed the use of in iximab or cyclosporine as third- line salvage therapy following the initial failure of intravenous corticosteroids and either in iximab or cyclosporine. In order to be included, the use of the third- line agent had to be within 60 days of cessation of the prior drug. **Exclusion Criteria:** Articles not indexed on PubMed, Abstracts only presented at a medical conference but not published as a manuscript, case reports of only a single patient and review articles were also excluded.	**Intervention:** Poupulation:The mean age of the patients was 42 and 43 % (13/30) of patients were female. The average duration of disease was 6.7 years and the majority of patients (77 %, 23/30) had extensive colitis. Seventy-three percent (22/30) of patients were previously or concomitantly on a thiopurine or methotrexate. **Interventions:** Cylcosporin (CSA) following Infliximab (IFX) as third line treatment or Infliximab (IFX) following Cylcosporin (CSA) as third line treatment (not reported here) **Comparison:** –	**Primary:** Our primary outcomes were clinical remission and serious adverse events associated with each drug and in aggregate. **Secondary:** Secondary outcomes included clinical response and 12 month colectomy rates. **Results:** Two studies assessed salvage therapy with CSA following IFX: There was a mean of 20 days (range 19 – 21) between the last dose of IFX and starting CSA. Overall response and remission event rates were 60 % (95 % CI 43 – 78 %) and 18 % (95 %CI 4 – 31 %) respectively at three months. The 12-month colectomy event rate was 57 % (95 %CI 39 – 74 %). No deaths among patients occurred, but 10 % (3/30) of all the patients developed an infectious complication. Other complications included renal and hepatic abnormalities, fatigue, leg cramps, weakness, cough, and pancreatitis. Serious adverse event rate was 12 % (95 %CI 0.01 – 23 %), and total adverse event rate was 31 % (95 %CI 16 – 47 %). **Author's Conclusion:** In conclusion, third-line salvage therapy with either CSA or IFX is efficacious in some patients but carries a significant risk of complications. Importantly, 41 – 57 % of these patients will end up requiring a colectomy within 12 months. Future studies are needed to prospectively evaluate the bene ts and risks of this strategy compared to colectomy.	Leblanc S, (2011) Am J Gastroenterol Maser EA, (2008) Clin Gastroenterol Hepatol	**Funding Sources:** n.a. **COI:** Dr Adam Cheifetz: Consulting from the following: Abbvie Laboratories, Janssen Pharmaceuticals, UCB, Takeda, Given Imaging, Prometheus Labs, Pfizer **Study Quality:** "Given the few studies that were available on this topic, all studies were included." **Heterogeneity:** Heterogeneity was assessed by the Q and I2 statistics **Publication Bias:** n.a. **Notes:** Only PubMed Database was searched, which can be considered as a non-systematic literature search. Quality of the studies was not assessed due to the small amount of literature available to inclusion. No investigation of publication bias or small study effects. Sample size is extremely small with 33 participants in two studies receiving CSA after IFX treatment failure, which explains broad confidence intervals for effect estimates.

Gisbert, J P et al. Systematic review with meta-analysis: the efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed. Aliment Pharmacol Ther. 41. 613 – 623. 2015

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Systematic review (8 cohort studies on UC) and meta-analysis (not in case of UC). **Databases:** PubMed and Embase **Search period:** x – October 2014 **Inclusion Criteria:** Prospective and retrospective studies assessing the efficacy of second-line anti-TNF therapies in IBD patients, after failure or intolerance to another anti-TNF agent; Infliximab (IFX), Adalimumab (ADA), and/or Certolizumab Pegol (CZP) as the first- and second-line drugs; outcomes of interest were efficacy of the switch strategy in terms of remission and/or response to second-line therapy. Articles published in any language were included. **Exclusion Criteria:** Any study mixing different kinds of first-line therapies that could not be separated were excluded. Unspecified discontinuation of the first antiTNF also lead to study exclusion. Reference lists from the articles selected by elec- tronic searching were hand- searched to identify further relevant studies. If a study was duplicated, the most recent one fulfilling the inclusion criteria was included.	**Intervention:** Second anti- TNF drug, after failure (primary and secondary) or intolerance of primary anti-TNF. All 8 eight studies identified investigated the efficacy of treatment with ADA, after unsuccessful primary treatment with IFX. **Comparison: –**	**Primary:** Percentage of Remission/Response, depending on the reason for first line anti-TNF failure. **Secondary:** Incidence of severe AEs or SAEs related to the second anti-TNF given. **Results: Secondary:** In UC patients, AE rates ranged from 20 % to 39 %, with SAEs ranging from 0 % to 7 %, and discontinuation of therapy related to AEs ranging from 0 % to 48 %. **Author's Conclusion:** The efficacy of switching an anti- TNF agent in CD patients largely depends on the reason for switching. Based on the present meta-analysis, the remission rate was higher when the reason for withdrawing the first anti-TNF agent was intolerance (61 %) than when it was secondary failure (45 %) or primary failure (30 %).	Afif W, (2009) Inflamm Bowel Dis Armuzzi A, (2013) Dig Liver Dis Baert F, (2014) Aliment Pharmacol Ther Garcia-Bosch O, (2013) J Crohns Colitis Oussalah A, (2008) Aliment Pharmacol Ther Peyrin-Biroulet L, (2007) World J Gastroenterol Sandborn WJ, (2012) Gastroenterology Taxonera C, (2011) Aliment Pharmacol Ther	**Funding Sources:** Declaration of funding interests: None. **COI:** Declaration of personal interests: JP Gisbert and M Chaparro have served as speakers, consultants and advisory members for, and have received research funding from MSD and Abbvie. AC Marin and AG McNicholl: none. **Study Quality:** n.a. **Heterogeneity:** The I2 statistic was used to assess the heterogeneity of the studies following the recommendation of the Handbook for Systematic Reviews of Interventions of The Cochrane Collaboration, 8 as follows: 0 – 40 % not important heterogeneity; 40 – 75 % moderate heterogeneity; 75 – 100 % considerable heterogeneity. **Publication Bias:** The publication/reporting bias was also assessed by funnel plots only in those analyses including more than 10 studies. (Not in the UC studies) **Notes:** Search profile could have been improved to include Mesh terms, or Anti TNF in general. Gray literature was not considered. It is therfor possible that relevant studies were missed. Golimumab was not considered in the search. Importantly, there was no evaluation of study quality. Despite the discovery of eight studies investigating UC and switch IFX to ADA, no meta-analysis was performed. Which brings up the question if the selection criteria should have been been more stringent to allow for comparison. "as follow-up times were not consistent and most authors did not subdivide results regarding the reason for switching. Consequently, the heterogeneity in study design prevented us from pooling efficacy estimates through a formal meta-analysis."

Narula, N et al. Systematic Review: Sequential Rescue Therapy in Severe Ulcerative Colitis: Do the Benefits Outweigh the Risks?. Inflamm Bowel Dis. 21. 1683 – 1694. 2015

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Systematic Review and meta-analysis (1 prospective, 9 retro-	**Intervention:** steroid refractory population; 5 Studies on sequential use of CSA upon IFX	**Primary:** The primary outcome was the short-term symptomatic response to therapy.	Chaparro M, (2012), Aliment Pharmacol Ther Leblanc S, (2011), Am J Gastroenterol	**Funding Sources:** n.a. **COI:** W. Reinisch has served as a speaker, a consultant, and/or an advisory board member for

spective cohort studies, 314 participants in total) **Databases:** MEDLINE, Embase **Search period:** 1950 to May 2014 **Inclusion Criteria:** observational design (prospective or retrospective cohort or case–control) or interventional design (ran- domized or nonrandomized), (2) subjects with acute severe UC who had failed a course of intravenous or oral steroids before treatment with a rescue therapy, (3) subjects treated initially with either IFX or a calcineurin inhibitor as rescue therapy, (4) subjects were subsequently treated with IFX or a calcineurin inhibitor during the same presentation of acute UC after failure of initial rescue therapy, loss of response to initial rescue therapy, or adverse events attributed to initial rescue therapy, and (5) less than 3 months lapsed between time of cessation of 1 rescue ther- apy and commencement of the second salvage therapy. **Exclusion Criteria:** Some studies did not report failure of a rescue therapy in previous UC flares or report whether patients were naive to previous treatment with rescue therapy but were not excluded for that reason. Where studies did not provide sufficient information, authors were con- tacted to obtain additional data.	non-response and 5 Studies on sequential use of IFX upon CSA non-response and Intervention: IFX, followed by sequential CSA **Comparison:** CSA, followed by sequential IFX or initial failed IFX than Tacrolimus	**Secondary:** Secondary outcomes included the rates of remission, colectomy at 3 and 12 months, adverse drug events, serious infections, and mortality during the observational period. **Results:** 314 patients underwent sequential therapy with a calcineurin inhibitor and IFX. Most patients *responded* to third-line rescue therapy (62.4 %; 95 % CI, 57.0 %–67.8 %; 196/314), with remission in 38.9 % (122/314; 95 % CI, 33.5 %–44.3 %). The overall colectomy rate was 28.3 % (51/180; 95 % CI, 21.7 %–34.5 %) at 3 months and 42.3 % (101/239; 95 % CI, 36.0 %–48.6 %) at 12 months. *Adverse events* were encountered by 23.0 % (55/239; 95 % CI, 17.7 %–28.3 %) of patients, including *serious infections* in 6.7 % (17/252; 95 % CI, 3.6 %–9.8 %) and *mortality* in 1 % (3/314; 95 % CI, 0 %–2.1 %). **Author's Conclusion:** When both corticosteroids and initial rescue therapy fail, a second salvage agent can be considered. The risk of sequential therapy in steroid-refractory UC seems lower than initially reported. However, the evidence is limited as data from prospective controlled trials are missing. The sequence of IFX followed by calcineurin inhibitors, or vice versa, appear to have similar treatment outcomes regarding avoidance of colectomy and risk of adverse events. Sequential rescue therapy should only be performed at specialized referral centers familiar with the use of calcineurin inhibition. Early tapering of corticosteroids may help lower the risk of serious infectious complications. The optimal time interval between rescue agents is not clear from this systematic review, but assessing for clearance of initial drug used before initiation of a sequential the-	Ordas I, (2013), Gastroenterology Maser E, (2008), Clin Gastroenterol Hepatol Manosa M, (2009), Digestion Yamamoto S, (2010), J Gastroenterol Hepatol Herrlinger K, (2010), Aliment Pharmacol Ther Tsukamoto H, (2013), Eur J Gastroenterol Hepatol Takeuchi K, (2013), Gastroenterology Minami N, (2014), Gastroenterology	Abbott Laboratories, AbbVie, Aesca, Amgen, AM-Pharma, Aptalis, Astellas, AstraZeneca, Avaxia, BioClinica, Biogen Idec, Bristol-Myers Squibb, Cellerix, Chemo-Centryx, Celgene, Centocor, Danone Austria, Elan, Falk Pharma GmbH, Ferring, Galapagos, Genentech, Grünenthal, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, Millennium, Mitsubishi Tanabe Pharma Corporation, MSD, Novartis, Ocera, Otsuka, PDL, Pharmacosmos, Pfizer, Procter & Gamble, Prometheus, Robarts Clinical Trials, Schering- Plough, Setpoint Medical, Shire, Takeda, Therakos, TiGenix, UCB, Vifor, Yakult, Zyngenia, and 4SC. J-F. Colombel has served as a consultant, an advisory board member, or a speaker for AbbVie, Amgen, Bristol-Myers Squibb, Celltrion, Ferring, Genentech, Giuliani SPA, Merck & Co., Mitsubishi, Nestle Nutrition Science Partners Ltd., Pfizer Inc., Prometheus Laboratories, Receptos, Takeda/Millennium Pharmaceuticals Inc., UCB Pharma, Vertex, and Dr. August Wolff GmbH & Co. J.K. Marshall has served as a consultant, an advisory board member, or a speaker for AbbVie, Aptalis, AstraZeneca, Celltrion, Cubist, Ferring, Forest, Janssen, Optimer, Procter & Gamble, Shire, Takeda, and Warner Chilcott. The remaining authors have no conflicts of interest to disclose. **Study Quality:** "We used the Grading of Recommendations Assessment, Devel- opment and Evaluation (GRADE) system to determine the quality of evidence. GRADE uses several domains, including design, consistency, precision, directness, and publication bias, to rate the quality of evidence as high, moderate, low, or very low." "We downgraded the rating to "very low" due to the risk of bias in some of the observational studies, mainly due to inclusion of abstracts where the risk of bias was largely unclear." **Heterogeneity:** n.a. **Publication Bias:** n.a. **Notes:** Inclusion criteria for salvage therapy are heterogeneous, as well as the time elapsed between salvage therapies. Treatment dosage of Cyclosporin A

		rapy may help minimize toxicity associated with salvage therapies. Regardless, decisions about response to rescue therapy should be made in a timely manner, as postoperative complications are increased in those who have prolonged medical therapy before colectomy. Certain situations require urgent colectomy, such as refractory megacolon, perforation, or severe hemorrhaging, and use of sequential rescue therapy should be avoided in these cases. More prospec- tive controlled trials could further inform outcomes with sequential rescue therapy compared with urgent colectomy in a setting of failed medical management and determine whether IFX or calcineurin inhibitors should be given first, or administered as combination, in patients with steroid-refractory UC.		(CSA) and Infliximab (IFX) differed between studies. Study participants received additional medication during the sequential rescue that was not the same in all observed studies (thiopurines, corticosteroids). No information on gender or age. No forest plot for evaluation of publication bias. Overall quality of included studies is rated as very low.

AG 3: Kann bei CU Patienten die Remission besser mit Aminosalizylaten als mit Placebo erhalten werden?

Bewertungsvorlage:
Oxford SR

Feagan, Brian G et al. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. Cochrane Database of Systematic Reviews. 10. Cd000 544. 2012

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** Systematic Review and Meta- Analysis (38 studies, total n = 8127). **Databases:** MEDLINE, EMBASE and the Cochrane Library. **Search period:** inception to January 20, 2012. **Inclusion Criteria:** *Types of studies* Prospective, randomized controlled trials of parallel design, minimum treatment duration of six months *Types of participants* Patients of any age with mild-to- moderate ulcerative colitis (UC) in remission defined by Truelove and Witts	**Intervention:** *Population:* Patients of any age with mild-to- moderate UC in remission (defined by Truelove and Witts). *Intervention*: Oral 5-aminosalicylic acid (5-ASA) **Comparison:** Placebo, Sulfasalazine (SASP), different 5- ASA formulation or dosing.	**Primary:** Efficacy: Endoscopic or Clinical relapse as defined by the authors of each study. **Secondary:** ▪ the proportion of patients who failed to adhere with their medication regimen ▪ the proportion of patients who experienced at least one adverse event ▪ the proportion of patients who withdrew due to adverse events ▪ the proportion of patients excluded or withdrawn after entry **Results:** 5-ASA versus Placebo *Efficacy:* 5-ASA was significantly superior to placebo for maintenance of clinical	Andreoli A, (1987) Clin Con Inflam Bowel Dis Ardizzone S, (1995) J Clin Gastroenterol Ardizzone S, (1999) Aliment Pharmacol and Ther Courtney MG, (1992) Lancet D'Haens G, (2012) Am J Gastroenterol Dew MJ, (1983) Br Med J Dignass AU, (2009) Clin Gastroenterol Hepatol Fockens P, (1995) Eur J Gastroenterol Hepatol Giaffer MH, (1992) Aliment Pharmacol Ther Green JRB, (1992) Aliment Pharmacol Ther Green JR, (1998) Aliment Pharmacoland Ther Hanauer SB, (1996) Ann Int Med	**Funding Sources:** Funding for the IBD/FBD Review Group (September 1, 2010 – August 31, 2015) has been provided by the Canadian Institutes of Health Research (CIHR) Knowledge Translation Branch (CON – 105 529) and the CIHR Institutes of Nutrition, Metabolism and Diabetes (INMD); and Infection and Immunity (III) and the Ontario Ministry of Health and Long Term Care (HLTC3968FL-2010-2235). Miss Ila Stewart has provided support for the IBD/ FBD Review Group through the Olive Stewart Fund. **COI:** Brian Feagan has received lecture fee(s) from: GlaxoSmith-Kline, Procter & Gamble Pharmaceuticals, Salix Pharmaceuticals Inc, Shire Pharmaceuticals Inc, Tillotts Pharma AG and Merck. John MacDonald has served as a

Types of interventions Trials of oral 5-ASA therapy for treatment of patients with UC in remission compared with placebo, SASP sulphasalazine or other formulations of 5-ASA were included. Studies that compared once daily 5-ASA treatment with conventional dosing of 5-ASA (two or three times daily) and 5-ASA dose ranging studies were also included.
Types of outcome measures Outcome measures included endoscopic or clinical relapse, or early withdrawal, as defined by the authors of each study.
Exclusion Criteria: Not RCT, wrong treatment duration, wrong comparison, wrong intervention, pooled analysis.

or endoscopic remission. 41 % of 5-ASA patients relapsed compared to 58 % of placebo patients (7 studies, 1298 patients; RR 0.69, 95 % CI 0.62 to 0.77). There does not appear to be any difference in efficacy among the various 5-ASA formulations. Thirty-eight per cent of patients in the 5-ASA group relapsed compared to 37 % of patients in the 5-ASA comparator group (5 studies, 457 patients; RR 1.01, 95 % CI 0.80 to 1.28).
Adverse effects: Common adverse events included flatulence, abdominal pain, nausea, diarrhea, headache, dyspepsia, and nasopharyngitis. There were no statistically significant differences in the incidence of adverse events between 5-ASA and placebo, 5- ASA and SASP, once daily and conventionally dosed 5-ASA, 5- ASA and comparator 5-ASA formulations and 5-ASA dose ranging studies.
Author's Conclusion: It is clear that oral 5-ASA preparations have yet to be proven to be more clinically beneficial than SASP. Male infertility is associated with SASP and not with 5-ASA, so 5- ASA may be preferred for patients concerned about fertility. 5-ASA therapy is more expensive than SASP, so SASP may be the preferred option where cost is an important factor. 5-ASA could also be offered to patients who are intolerant to SASP. Oral 5-ASA administered once daily is as effective and safe as conventional dosing (twice or three times daily) for maintenance of remission in quiescent ulcerative colitis. Once daily dosing does not appear to enhance adherence in the clinical trial setting. There does not appear to be any difference in efficacy or safety between the various formulations of 5-ASA. Patients with extensive ulcerative colitis or with frequent relapses may benefit from a higher dose of

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Wright JP, (1993) Dig Dis Sci

consultant for Tillotts Pharma AG. All of these financial activities are outside the submitted work.
Study Quality: "We used the GRADE approach for rating the overall quality of evidence for primary outcomes and selected secondary outcomes of interest. Randomized trials start as high quality evidence, but may be downgraded due to: (1) limitations in design and imple- mentation (risk of bias), (2) indirectness of evidence, (3) inconsistency (unexplained heterogeneity), (4) imprecision (sparse data), and (5) reporting bias (publication bias)." "The GRADE analysis indicated that the overall quality of the evidence for the primary outcome for the placebo- controlled studies (failure to maintain clinical or endoscopic remission) was high."
Heterogeneity: "The presence of hetero- geneity among studies was assessed using the Chi2 test (a P value of 0.10 was regarded as statistically significant) and the I^2 statistic (Higgins 2003). If statistically significant heterogeneity was identified, the RR and 95 % CI were calculated using a random-effects model. We conducted sensitivity analyses as appropriate to investigate heterogeneity. We also conducted sensitivity analyses excluding studies with a high risk of bias." Heterogeneity was low (I^2 = 15 %) in the meta analysis of the RR for relapse of UC in the comparison 5- ASA vs placebo.
Publication Bias: Publication biased was assessed by the GRADE approach (see section study on study quality).
Notes: Exclusion criteria not specifically listed, but for every excluded study.

		maintenance therapy. High dose therapy appears to be as safe as low dose and is not associated with a higher incidence of adverse events. When selecting among the various 5-ASA formulations, physicians and patients should consider dose-response data, adherence issues and price.		

Lie, M R et al. Drug therapies for ulcerative proctitis: systematic review and meta-analysis. Inflamm Bowel Dis. 20. 2157 – 2178. 2014

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Systematic Review and Meta-analysis of 18 RCTs (n = 1546) for induction and 5 studies on maintenance (n = 288) **Databases:** Embase, Medline OvidSP, Cochrane Central Register of Controlled Trials, Web of Science, and Pubmed **Search period:** x – 28.04.2014 **Inclusion Criteria:** *Study type:* Randomized controlled trials comparing the efficacy of any drug versus another active therapy or placebo for remission induction in Ulcerative Proctitis (UP). *Population:* Adults (16 years or older), with a diagnosis of ulcerative colitis limited to 20 cm from the anal verge (i. e. ulcerative proctitis) at endoscopy. Studies were allowed to investigate both patients with a first presentation and patients with a relapse of previously established disease. *Intervention:* Any drug therapy be compared to either another drug therapy or placebo. All formulations (e. g. oral, suppository, enema) were accepted. The duration of treatment had to be at least 4 weeks in induction studies. Studies were grouped based on the type of treatment (i. e. induction, maintenance) and based on drug class (e. g. 5- ASA, corticosteroids). Additionally, these groups were further subdivided by drug formula-	**Intervention:** *Population:* Adults (16 years or older), with a diagnosis of ulcerative colitis limited to 20 cm from the anal verge (i. e. ulcerative proctitis) at endoscopy. Studies were allowed to investigate both patients with a first presentation and patients with a relapse of previously established disease. *Intervention:* 5- ASA, corticosteroids, thiopurines, anti- TNF-a agents **Comparison:** Other interventions or placebo.	**Primary: Primary outcomes:** Clinical remission induction rate and maintained clinical remission rate. **Secondary: Secondary outcomes:** Endoscopic remission and histological remission rates. **Results:** Twenty-three studies (1834 patients) were included. Eighteen trials investigated induction and 5 studied maintenance of remission. Topical 5-ASA was significantly superior to placebo for induction (RR, 2.39; 95 % CI, 1.63 – 3.51) and maintenance (RR, 2.80; 95 % CI, 1.21 – 6.45) of clinical remission, regardless of dose or formulation. Subgroup analysis of 5-ASA suppositories also showed superiority over placebo for induction of clinical (RR, 3.07; 95 % CI, 1.70 – 5.55) and endoscopic remission (RR, 2.64; 95 % CI, 1.85 – 3.77). **Author's Conclusion:** The effectiveness of topical 5-ASA for inducing remission is confirmed. The ability of topical 5-ASA to induce clinical remission was clearly shown in several placebo-controlled studies. Patients receiving topical 5-ASA were 2.39 times more likely to achieve clinical remission than those receiving placebo. No clear dose response relationship was found between topical 5-ASA and clinical remission, although only 2 studies compared different 5-ASA doses.	Andus T, (2010) Inflamm Bowel Dis Ardizzone S, (1996) Aliment Pharmacol Ther Betamethasone 17-valerate, prednisolone 21-phosphate retention enemata in proctocolitis (1971) Br Med J Campieri M, (1988) J Clin Gastroenterol Campieri M, (1990) Scand J Gastroenterol Campieri M, (1990) Int J Colorectal Dis Eliakim R, (2007) Aliment Pharmacol Ther Farup PG, (1995) Scand J Gastroenterol Gionchetti P, (1997) Aliment Pharmacol Ther Gionchetti P, (1998) Dis Colon Rectum Gross V, (2006) Aliment Pharmacol Ther Hanauer SB, (2005) Am J Gastroenterol Larnet M, (2005) Inflamm Bowel Dis Pokrotnieks J, (2000) Aliment Pharmacol Ther van Hees PAM, (1980) Gut van Hogezand RA, (1988) Aliment Pharmacol Ther Watanabe M, (2013) Aliment Pharmacol Ther Williams CN, (1987) Dig Dis Sci	**Funding Sources:** n.a. **COI:** The authors have no conflicts of interest to disclose. **Study Quality:** "The risk of bias was assessed independently by each of the 2 primary reviewers, according to the scheme described in the Cochrane Handbook for Systematic Review of Interventions. This assessment involved judgment on selection, performance, attrition, and detection bias. The "Risk of bias tool" in the publically available program RevMan 5.2 was used to report possible bias in included studies." Results for quality of the included studies are provided. **Heterogeneity:** Where applicable, studies were pooled using a random-effect model, regardless of statistical heterogeneity. Heterogeneity was tested using the x2 test, the I-squared test, and visual inspec- tion of forest plots. If heterogeneity was present, we attempted to investigate the cause thereof (such as methodological factors or the outcome assessment). Given the limited number of included studies, subgroup analysis or meta-regression was not considered useful. In the case of high heterogeneity ($I^2 = 75\,\%$), studies were pooled only if the direction of their results was consistent. **Publication Bias:** n.a. **Notes:** No investigation of publication bias. The authors rate the majority of the included studies to be poor with high risk of bias. In addition the follow-up times are short so mucosal healing is likely to be underestimated. Also most studies apparently use different scoring systems to define clinical remission.

tion (e. g. suppository, enema). **Exclusion Criteria:** 133 articles were excluded. Due to the following reasons. Articles only published as abstracts, uncontrolled, non- randomized or retrospective studies. Also lack specific proctitis group, short time of treatment (15 days-3 weeks), insufficient number of included participants, non-reporting of clinical remission rates, not drug related intervention, not original work articles.		Additionally, endoscopic evaluations in 4 studies showed a clear benefit of topical 5-ASA over placebo. Histological remission rates were assessed in only 2 studies and showed no clear benefit of topical 5-ASA over placebo.		

Marshall, John K et al. Rectal 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. Cochrane Database of Systematic Reviews 2012

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Systematic Review and Meta-Analysis (9 RCTs, total n = 484 participants). **Databases:** MEDLINE, Cochrane Inflammatory Bowel Disease and Functional Bowel Disorders (IBD/ FBD) Review Group Specialized Trials Register, Hand search of five gastroenterologic journals (Am J Gastroenterol, Can J Gastroenterol, Gastroenterology, Gastrointest Endosc, Gut, Scand J Gastroentero). **Search period:** 1966 to August 30, 2012 **Inclusion Criteria:** *Types of studies:* RCT *Types of participants:* age≥ 12 years, UC disease extent less than 60 cm from the anal verge or distal to the splenic flexure, as determined by barium enema or endoscopy. Subjects were also expected to have been in remission at the time of randomization. *Types of interventions:* At least one treatment arm was required to administer rectal 5- ASA as an enema, foam or suppository for a minimum duration of six months. Eligible comparators were	**Intervention:** *Population:* UC patients (age≥ 12 year) with diseases extent less than 60 cm from the anal verge or distal to the splenic flexure, as determined by barium enema or endoscopy and in remission at the time of randomization. *Intervention:* Rectal 5-ASA (foam, suppository, enema). **Comparison:** Placebo, oral 5-ASA.	**Primary:** Remission: Symptomatic, endoscopic or histologic criteria. **Secondary:** Time to relapse, change in disease activity index (DAI) **Results:** 62 % of patients in the rectal 5-ASA group maintained symptomatic remission compared to 30 % of patients in the placebo group (4 studies; 301 patients; RR 2.22, 95 % CI 1.26 to 3.90; $I^2 = 67$ %; $P < 0.01$). A GRADE analysis indicated that the overall quality of the evidence for the primary outcome was low due to imprecision (i. e. sparse data 144 events) and inconsistency (i. e. unexplained heterogeneity). **Author's Conclusion:** The limited data available suggest that rectal 5-ASA is superior to placebo and may be as effective as oral 5-ASA for maintaining remission of mild to moderately active UC.	Andreoli A, (1994) Ital J Gastroenterol Biddle WL, (1988) Gastroenterology d'Albasio G, (1990) Dis Colon Rectum d'Albasio G, (1998) Am J of Gastroenterol D'Arienzo A, (1990) Am J of Gastroenterol Hanauer S, (2000) Am J of Gastroenterol Mantzaris GJ, (1994) Dis Colon Rectum Marteau P, (1998) Gut Sutherland LR, (1987) Can J Gastroenterol	**Funding Sources:** Funding for the IBD/FBD Review Group (September 1, 2010 –August 31, 2015) has been provided by the Canadian Institutes of Health Research (CIHR) Knowledge Translation Branch (CON – 105 529) and the CIHR Institutes of Nutrition, Metabolism and Diabetes (INMD); and Infection and Immunity (III) and the Ontario Ministry of Health and Long Term Care (HLTC3968FL- 2010 – 2235). Miss Ila Stewart has provided support for the IBD/FBD Review Group through the Olive Stewart Fund. **COI:** Dr. Marshall has received honoraria for speaking and/or consulting from Axcan, Aptalis, Ferring, Shire, Warner-Chilcott, Janssen, Abbott and Takeda, and has received research funds from Abbott, Janssen, Centocor, GKS, Amgen and Pfizer. Dr. Steinhart has received honoraria for speaking and/or consulting from Aptalis, Shire, Janssen and Abbott, and has received research funds from Abbott, Janssen, Centocor, Amgen, Pfizer, GSK and Millenium. Dr. Thabane has no conflicts of interest. Dr. Irvine has received honoraria for speaking and/or consulting from Abbott, Shire and Procter & Gamble, and has received research funds from Abbott. Dr. Newman has no conflicts of interest. Dr. Anand has no conflicts of interest.

placebo and oral 5-ASA formulations. *Types of outcome measures:* Continued remission by clinical, endoscopic or histologic criteria. Secondary analyses included time to relapse and change in disease activity indices (DAI). Subgroup analyses by disease extent and 5- ASA dose were also planned. **Exclusion Criteria:** Non randomized trial, wrong population (pancolitis, total colitis), follow up period too short.				**Study Quality:** "The methodological quality of each trial was assessed using the Cochrane risk of bias tool and the Jadad scale." A GRADE analysis indicated that the overall quality of the evidence for the primary outcome was low due to imprecision (i. e. sparse data 144 events) and inconsistency (i. e. unexplained heterogeneity). **Heterogeneity:** Heterogeneity was assessed using the Chi^2 test and visual inspection of forest plots. If no significant heterogeneity was identified (P> 0.10 for Chi^2) a fixed-effect model (Mantel- Haenstzel) was used. If heterogeneity was significant, a random-effects model was used. **Publication Bias:** Publication bias was assessed using the Cochrane bias tool. Risk of bias due to selective reporting was low in all studies. **Notes:** Only PubMed database was searched alongside Cochrane database and journal records. Heterogeneity was high in the primary analysis of symptomatic remission. Overall quality was rated as low, therefor caution should be advised in the interpretation of the results.

Ford, A C et al. Efficacy of 5-aminosalicylates in ulcerative colitis: systematic review and meta-analysis. Am J Gastroenterol. 106. 601 – 616. 2011

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Systematic Review and Meta Analysis (37 RCTs, 18 of which in quiescent UC) **Databases:** MEDLINE, EMBASE, Cochrane central register of controlled trials, Cochrane Inflammatory Bowel Disease Group Specialized Trials Register **Search period:** MEDLINE (1966 to December 2010) EMBASE (1984 to December 2010) Cochrane central register of controlled trials (Issue 4, October 2010). **Inclusion Criteria:** *Study type:* RCT *Population:* Adult patients (90 % ≥over 16 years old) *Intervention:* 5-Aminosalicylic acid (5-ASA) Comparison: Placebo or alternative dose of the same 5-ASA drug	**Intervention:** *Population:* Adult patients (90 % ≥over 16 years old) *Intervention:* 5-Aminosalicylic acid (5-ASA) **Comparison:** Placebo or alternative dose of the same 5-ASA drug	**Primary:** Efficacy of 5-ASA drugs: UC relapse: endoscopic evidence of any degree of relapse, endoscopic evidence and clinical assessment as relapsed, clinical assessment as relapsed, recognized scoring system as relapsed (e. g., Truelove and Witt), or other author-defined criteria for relapse. UC remission: endoscopic evidence of complete remission (most stringent definition available, e. g., complete mucosal healing), endoscopic evidence and clinical assessment as complete remission, clinical assessment as complete remission, recognized scoring system of complete remission (e. g., Truelove and Witt), or other author-defined criteria for remission. **Secondary:** Adverse effects, duration of therapy, compliance with therapy	Misiewicz JJ, (1965) Lancet Dissanayake AS, (1973) Gut Riis P, (1973) Scand J Gastroenterol Sandberg- Gertzen H, (1986) Gastroenterology Lauritsen K, (1988) Gut Wright JP, (1993) Dig Dis Sci Miner P, (1995) Dig Dis Sci The Mesalamine Study Group. (1996) Ann Intern Med Hawkey CJ, (1997) Gastroenterology Ardizzone S, (1999) Aliment Pharmacol Ther Lichtenstein GR, (2010) Aliment Pharmacol Ther	**Funding Sources:** This study was funded by the American College of Gastroenterology and performed to inform their monograph on inflammatory bowel disease. We thank Maria T. Abreu, Charles N. Bernstein, Marla C. Dubinsky, Stephen B. Hanauer, William J. Sandborn, and Thomas A. Ullman for their contributions to the discussion concerning the role of 5-ASAs in the treatment of ulcerative colitis. **COI:** Alexander C. Ford, Jean-Paul Achkar, Khurram J. Khan, Nicholas J Talley, and John K. Marshall: none. Sunanda V. Kane: has served as a consultant to Shire and Warner-Chilcott, and has received research support from Shire. Paul Moayyedi: chair at McMaster University partly funded by an unre- stricted donation by AstraZeneca, and has received consultant's and speaker's bureau fees from AstraZeneca, AxCan Pharma, Nycomed, and Johnson and Johnson.

Exclusion Criteria: Wrong comparison, outcome, intervention, population or study type; pooled analysis, duplicate publication, data not extractable, review article		**Results:** There were 11 RCTs comparing 5-ASAs with placebo in preventing relapse of quiescent UC, with the RR of relapse of 0.65 (95 % CI 0.55 – 0.76; NNT = 4). Doses of ≥ 2.0 g/day appeared more effective than < 2.0 g/day for preventing relapse (RR = 0.79; 95 % CI 0.64 – 0.97). **Author's Conclusion:** In summary, this systematic review and meta-analysis has demonstrated a clear benefit of 5- ASAs, particularly mesalamine and sulfasalazine, over placebo in both the induction of remission of active UC and in preventing relapse in quiescent UC. Increas- ing the total daily dose of 5-ASA used, to at least 2.0 g, appears to both increase the likelihood of achieving remission and reduce the risk of disease relapse.		**Study Quality:** Risk of bias was assessed as described in the Cochrane handbook (14), by recording the method used to generate the randomization schedule, the method used to conceal allocation, whether blinding was implemented, what proportion of patients completed follow- up, whether an intention-to-treat analysis was extractable, and whether there was evidence of selective reporting of outcomes. **Heterogeneity:** $I^2$was used as a measure of heterogeneity. A value < 25 % was arbitrarily chosen to represent low levels of heterogeneity. We also evaluated heterogeneity using the $\chi 2$ test with P values < 0.15 indicating statistically significant heterogeneity. Where the degree of statistical heterogeneity was greater than this between trial results in this meta-analysis, possible explanations were investigated using sensitivity analyses according to the dosage and duration of therapy, compliance with therapy, criteria used to define remission or relapse, duration of disease, proportion with new-onset disease, and high risk of bias and unclear risk of bias vs. low risk of bias trials, where trial reporting allowed this. These were exploratory analyses only, and may explain some of the observed variability, but the results should be interpreted with caution. **Publication Bias:** There was statistically significant funnel plot asymmetry (Egger test, P = 0.02), suggesting evidence of publication bias or other small study effects. **Notes:** Certain overlap of cited literature with SR on oral 5-ASA Feagan BG 2012 Cochrane Database of Systemic Review (5/11). Evidence of small study effect or publication bias in particular. Heterogeneity between trials in regard to the preferred (efficacy of 5-ASAs vs. placebo for both induction of remission of active UC and prevention of relapse of quiescent UC. Inconsequent definition of population and illegibility criteria (adults, 90 %> 16 years).

Cohen, R D et al. Systematic Review: Rectal Therapies for the Treatment of Distal Forms of Ulcerative Colitis. Inflamm Bowel Dis. 21. 1719 – 1736. 2015

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Systematic review of 48 studies. **Databases:** PubMed **Search period** : 01.01.2004 – 31.12.2013 first search. no restriction on second search for clinical trials. **Inclusion Criteria:** Articles were restricted to those involving adult humans and included comparative studies, meta- analyses, and (systematic) reviews. **Exclusion Criteria:** Clinical studies of pouchitis or cuffitis and case reports were excluded from the review.	**Intervention:** *Interventions:* rectal therapies: suppository, foam, gel, and enema formula- tions of 5-ASAs, corticosteroids, and non–5-ASA agents, and provides ratings for the quality of the evidence. **Comparison:** Placebo, or different forms of administration of the same drug.	**Primary:** Efficacy of the treatment (induction or maintenance). **Secondary:** Safety outcomes: AE, drug-related AE, AE causing discontinuation of the drug treatment. **Results:** The current literature supports the use of rectal therapies for both induction and maintenance of remission in patients with distal forms of UC. *Efficacy:* A greater percentage of patients with distal forms of UC receiving 5-aminosalicylic acids or corticosteroid rectal formulations derived greater therapeutic benefit after treatment compared with patients receiving placebo. Most uncontrolled studies of rectal therapies reported that patients with distal forms of UC had marked improvement from baseline after treatment. *Safety:* The overall safety profile of rectal therapies was favorable. Treatment with second-generation corticosteroids, such as budesonide and beclomethasone dipropionate, did not increase the incidence of steroid-related adverse effects. **Author's Conclusion:** Overall, most rectal therapies, regardless of formulation, were shown to be well tolerated and efficacious for both the treatment of active UC and for the maintenance of UC remission. Avoiding systemic corticosteroid exposure by using non–steroid-containing agents or therapies with second-generation corticosteroids, such as budesonide and BDP, should be emphasized when selecting topical therapies for patients with these conditions.	Gross VB, (2006) Aliment Pharmacol Ther Andus T, (2010) Inflamm Bowel Dis. 2010 Watanabe M, (2013) Aliment Pharmacol Ther Campieri M, (1990) Int J Colorectal Dis Campieri M, (1990) Scand J Gastroenterol Lamet M, (2005) Inflamm Bowel Dis Eliakim R, (2007) Aliment Pharmacol Ther Pokrotnieks J, (2000) A-limentPharmacol Ther Aumais G, (2005) Drugs RD Sutherland LR, (1987) Gastroenterology Connolly MP, (2009) Digestion Cortot A, (2008) Am J Gastroenterol Marteau P, (2005) Gut Vecchi M, (2001) Aliment Pharmacol Ther 2001; 15: 251 – 256 Hanauer SB, (1998) Inflamm Bowel Dis Campieri M, (1991) Gut Sutherland LR, (1987) Dig Dis Sci Hammond A, (2004) Hepato-gastroenterology Hartmann F, (2010) Aliment Pharmacol Ther Biancone L, (2007) Dig Liver Dis Gionchetti P, (2005) J Clin Gastroenterol Lindgren S, (2002) Scand J Gastroenterol Hanauer SB, (1998) Gastroenterology Danielsson Å, (1993) A-liment Pharmacol Ther Danielsson Å, (1992) Scand J Gastroenterol Cobden I, (1991) Aliment Pharmacol Ther Ginsberg AL, (1988) Ann Intern Med Gandolfo J, (1987) Dig Dis Sci Selby WS, (1984) Digestion Miner PB Jr, (2006) Aliment Pharmacol Ther 2006; 23: 1403 – 1413 Miner PB Jr, (2006) Aliment Pharmacol Ther 2006; 23: 1427 – 1434	**Funding Sources:** n.a. **COI:** R.D. Cohen—Speakers Bureau: Abbvie, Entera Health, Salix Pharmaceuticals, Shire PLC. Consultant: Abbive, Cellgene, Entera Health, Hospira, Janssen, Prometheus, Salix Pharmaceuticals, Sandoz Biopharmaceuticals, Shire PLC, Takeda, UCB Pharma. S. R. Dalal has no conflicts of interest to disclose. **Study Quality:** An adaptation of the GRADE system was used to determine the quality of evidence for the efficacy of rectal therapies for inducing or maintaining UC remission. The quality of the evidence was categorized as "high," "moderate," "low," or "very low." **Heterogeneity:** n.a. **Publication Bias:** n.a. **Notes:** Search for articles was restricted to PubMed, and no Mesh terms were applied and no information how keywords are linked through operators. Two searches were performed, one with restriction on publication date, the second without. It is possible that important articles were missed. Inclusion criteria were only vaguely defined. No information on total n, study characteristics or types. The definition of remission differed among studies.

			van Deventer SJ, (2006) Aliment Pharmacol Ther van Deventer SJ, (2004) Gut Ingram JR, (2005) Clin Gastroenterol Hepatol Mahmood A, (2005) Aliment Pharmacol Ther Sinha A, (2003) N Engl J Med Sandborn WJ, (1994) Gastroenterology Pedersen G, (2010) Am J Gastroenterol Miyata M, (2005) Dig Dis Sci van Dieren JM, (2009) Inflamm Bowel Dis	

AG 3: Kann bei CU Patienten die Remission besser mit Aminosalizylaten als mit Placebo erhalten werden?

Bewertungsvorlage:
OXFORD Appraisal Sheet: RCT

Gordon, G L et al. Once-daily Mesalamine Formulation for Maintenance of Remission in Ulcerative Colitis: A Randomized, Placebo- controlled Clinical Trial. J Clin Gastroenterol. 50. 318 – 325. 2016

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 3 **Study type:** Randomized placebo-controlled trial, multinational (America and Russia) **Number of Patient:** 257 **Recruitung Phase:** 2004 – 2007 **Inclusion Criteria:** Patients ≥ 1 8 years, historically confirmed diagnosis of mild to moderate UC (as deter- mined by either physician letter for newly or recently diagnosed patients, or by medical records for previously diagnosed patients) in remission [defined as having both a revised Sutherland Disease Activity Index (SDAI) rectal bleeding score of 0 and a screening sigmoidoscopy score of≤ 1 for mucosal appearance] for ≥ Z1 month, but not for > 12 months, were eligible for enrollment. Additional criteria were UC flare with symptoms occurring in the previous 1 to 12 months that required therapeutic intervention and no use of steroids or immunosuppressive agents within 30 days of screening. **Exclusion Criteria:** Exclusion criteria included a history of allergy or intolerance to aspirin, mesalamine, or other salicylates; impaired immune function; positive serology tests for HIV or hepatitis B or C; any infectious, ischemic, or immunologic disease with gastro-intestinal involvement; uncontrolled, clinically significant	**Intervention:** *Population:* 257 Patients ≥ 18 years, historically confirmed diagnosis of mild to moderate UC (as determined by either physician letter for newly or recently diagnosed patients, or by medical records for previously diagnosed patients) in remission [defined as having both a revised Sutherland Disease Activity Index (SDAI) rectal bleeding score of 0 and a screening sigmoidoscopy score of≤ 1 for mucosal appearance] for ≥Z1 month, but not for > 12 months *Intervention:* Mesalamine granules 1.5 g once daily for 6 months. **Comparison:** Matching placebo (4 capsules) once daily for 6 months.	**Primary:** *Efficacy of remission maintenance:* "Percentage of patients in UC remission at 6 months. Relapse, or treatment failure, was defined as: (1) revised SDAI scores ≥Z1 for rectal bleeding and ≥Z2 for mucosal appearance; (2) UC flare and/or initiation of therapy previously used for the treatment of UC; or (3) study discontinuation due to lack of efficacy or UC-related adverse event (AE). Secondary efficacy measures included the percentage of patients maintaining a revised SDAI of r2 with no individual component of the revised SDAI score of > 1 and a score of 0 for rectal bleeding at 6 months; the percentage of patients with a change from baseline in scores for stool frequency, rectal bleeding, and physician's rating of disease activity at 1, 3, and 6 months; the percentage of patients with a change from baseline in mucosal appearance score at 6 months; the mean change from baseline in the revised SDAI at 6 months; and duration of remission (defined as the number of days between the start of study drug and the day the relapse was first detected, or early termination from the study, plus 1 d)." **Secondary:** "*Safety assessments:* included monitoring of AEs, clinical laboratory tests (eg, hematology, blood chemistry, and urinalysis), and vital signs. Compliance was evaluated for the safety population and calculated with the following equation: % compliance = [(number of capsules dispensed – number of capsules returned)/(4*number of days of exposure)] *100. Patients were considered compliant to treatment if > 70 % of the study drug was administered." **Results:** *Efficacy:* A significantly greater percentage of patients receiving mesalamine granules versus placebo were in remission at 6 months (79.9 % vs. 66.7 %; P = 0.03). A greater percentage of patients receiving mesalamine granules maintained a revised Sutherland Disease Activity Index (SDAI)≤r2	**Funding Sources:** Supported by Salix, a Division of Valeant Pharmaceuticals North America LLC, Bridgewater, NJ. Technical editorial and medical writing assistance was provided, under the direction of the authors, by Sophie Bolick, PhD, Synchrony Medical Communications LLC, West Chester, PA. Funding for this support was provided by Salix. **COI:** G.L.G. is a consultant and on the speakers' bureau for, and has received research grants from Salix, a Division of Valeant Pharmaceuticals North America LLC, Bridgewater, NJ. He is also a consultant to and on the speakers' bureau for AbbVie; Aptalis; Janssen Pharmaceuticals Inc.; Prometheus Laboratories Inc.; sanofi-aventis US; Takeda; UCB; and Warner Chilcott; receives research grants from AbbVie; Aptalis; Avaxia; Coronado; Cubist; Dr Falk; Evoke; Ferring; Furiex; GlaxoSmithKline; Hutchinson; Janssen Pharmaceuticals Inc.; Lexicon; Pfizer Inc.; Prometheus Laboratories Inc.; Red Hill BioPharma; Revogenex; sanofi-aventis US; Shire; Takeda; Theravance; Tranzyme; UBC; UCB; Ventrus; and Warner Chilcott. S.Z. serves as a principal investigator on several studies sponsored by Salix. He also is a consultant and speaker for the company, holds shares in the company, and is a recipient of grants from the company. In addition, he is a con- sultant,

renal disease (≥Z1.5 times the upper limit of normal of serum creatinine or blood urea nitrogen levels); creatinine clearance levels of ≤ r60 mL/min; and ≥ Z twice the upper limit of normal for liver function tests including alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), alkaline phosphatase, and bilirubin. Concomitant use of immunosuppressants, anti-tumor necrosis factor-a therapy, methotrexate, cyclosporine, corticosteroids, psyllium-containing products, loperamide and opioids or opiates for diarrhea, anticholinergics or sucral- fate, rifampin, spironolactone/furosemide, lactulose, or similar agents that lower stool pH, alternative or comple- mentary treatments for UC, and mesalamine products was prohibited during the study. At the initial screening visit, patients were requested to discontinue prohibited medications, including mesalamine products.		with no individual component of revised SDAI > 1 and rectal bleeding = 0 at 6 months (72.0 % vs. 58.1 %; P = 0.04). No significant differences between groups were observed for change from baseline to 6 months for total SDAI score or its components (ie, stool frequency, rectal bleeding, mucosal appearance, physician's rating of disease). Mesalamine granules treatment resulted in a significantly longer remission duration versus placebo (P = 0.02) and decreased patients' risk of relapse by 43 % (hazard ratio = 0.57; 95 % confidence interval, 0.35 – 0.93; P = 0.02). *Safety:* Mesalamine granules were well tolerated, and adverse events related to hepatic, renal, and pancreatic function— potential concerns with long-term treatment—occurred at a rate similar to placebo. **Author's Conclusion:** The results of this randomized, double-blind, placebo-controlled trial demonstrated that treatment with mesalamine granules 1.5 g once daily for up to 6 months was efficacious and well tolerated for the maintenance of UC remission and provided significant protection from UC recurrence.	speaker, and investigator for GlaxoSmithKline, Novartis, and Pfizer Inc. S.S. is on the speaker's bureau for Abbott Corpo- ration. A.C.B., E. B., C.P., and W.P.F. are former employees of Salix. G.R.L. is a consultant to Abbott Corporation/AbbVie; Alaven; Elan; Ferring; Hospira; Janssen Orthobiotech; Millenium Pharmaceuticals; Ono Pharmaceuticals; Pfizer; Prometheus Labo- ratories Inc.; Salix; Santarus Inc., previously a wholly owned subsidiary of Salix; Shire; Takeda; UCB; and Warner Chilcott. He has received research funding from Bristol-Myers Squibb; Ferring; Janssen Orthobiotech; Prometheus Laboratories Inc.; Salix; Santarus Inc.; Shire; UCB; and Warner Chilcott. He has also received honoraria (CME program) from Ironwood and Luitpold Pharmaceuticals Inc./American Regent Inc. U.M. and R.P. declare that they have nothing to disclose. **Randomization:** Assignment was randomized, but methods or sequence were not described. Only that participants were assigned intervention and comparison 2:1. **Blinding:** Double-blind study. **Dropout Rate/ITT-Analysis:** Dropout rate was not equal in both groups: n = 45(27.7 %) and n = 36(38.7 %) in mesalamine and in the placebo group. All analyses were carried out as ITT. **Notes:** Randomization sequence was not described. No tests for differences in baseline group characteristics were performed. Results may not apply to all UC patients (only mild to moderate UC cases were selected).

AG 3: Kann bei CU Patienten die Remission besser mit topischen Aminosalizylaten als mit topischen Glukokortikoiden erhalten werden?

Bewertungsvorlage:
Oxford SR

Cohen, R D et al. Systematic Review: Rectal Therapies for the Treatment of Distal Forms of Ulcerative Colitis. Inflamm Bowel Dis. 21. 1719 – 1736. 2015

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Systematic review of 48 studies. **Databases:** PubMed **Search period:** 01.01.2004 – 31.12.2013 first search. no restriction on second search for clinical trials.	**Intervention:** *Population:* Patients with ulcerative proctitis, ulcerative proctosigmoiditis, or left-sided colitis in remission or active *Interventions:* rectal therapies: suppository, foam, gel, and enema formula- tions of 5-	**Primary:** Efficacy of the treatment (induction or maintenance). **Secondary:** Safety outcomes: AE, drug-related AE, AE causing discontinuation of the drug treatment. **Results:** The current literature supports the use of rectal therapies for both	Gross VB, (2006) Aliment Pharmacol Ther Andus T, (2010) Inflamm Bowel Dis 2010 Watanabe M, (2013) Aliment Pharmacol Ther Campieri M, (1990) Int J Colorectal Dis Campieri M, (1990) Scand J Gastroenterol	**Funding Sources:** n.a. **COI:** R.D. Cohen—Speakers Bureau: Abbvie, Entera Health, Salix Pharmaceuticals, Shire PLC. Consultant: Abbive, Cellgene, Entera Health, Hospira, Janssen, Prome- theus, Salix Pharmaceuticals, Sandoz Biopharmaceuticals, Shire PLC, Takeda, UCB

Inclusion Criteria: Articles were restricted to those involving adult humans and included comparative studies, meta-analyses, and (systematic) reviews. **Exclusion Criteria:** Clinical studies of pouchitis or cuffitis and case reports were excluded from the review.	ASAs, corticosteroids, and non–5-ASA agents, and provides ratings for the quality of the evidence. **Comparison:** Placebo, or different forms of administration of the same drug.	induction and maintenance of remission in patients with distal forms of UC. *Efficacy:* A greater percentage of patients with distal forms of UC receiving 5-aminosalicylic acids or corticosteroid rectal formulations derived greater therapeutic benefit after treatment compared with patients receiving placebo. Most uncontrolled studies of rectal therapies reported that patients with distal forms of UC had marked improvement from baseline after treatment. *Safety:* The overall safety profile of rectal therapies was favorable. Treatment with second-generation corticosteroids, such as budesonide and beclomethasone dipropionate, did not increase the incidence of steroid-related adverse effects. **Author's Conclusion:** Overall, most rectal therapies, regardless of formulation, were shown to be well tolerated and efficacious for both the treatment of active UC and for the maintenance of UC remission. Avoiding systemic corticosteroid exposure by using non–steroid-containing agents or therapies with second-generation corticosteroids, such as budesonide and BDP, should be emphasized when selecting topical therapies for patients with these conditions.	Lamet M, (2005) Inflamm Bowel Dis Eliakim R, (2007) Aliment Pharmacol Ther Pokrotnieks J, (2000) Aliment Pharmacol Ther Aumais G, (2005) Drugs RD Sutherland LR, (1987) Gastroenterology Connolly MP, (2009) Digestion Cortot A, (2008) Am J Gastroenterol Marteau P, (2005) Gut Vecchi M, (2001) Aliment Pharmacol Ther 2001;15:251 – 256 Hanauer SB; (1998) Inflamm Bowel Dis Campieri M, (1991) Gut Sutherland LR, (1987) Dig Dis Sci Hammond A, (2004) Hepato-gastroenterology Hartmann F, (2010) Aliment Pharmacol Ther Biancone L, (2007) Dig Liver Dis Gionchetti P, (2005) J Clin Gastroenterol. Lindgren S, (2002) Scand J Gastroenterol Hanauer SB, (1998) Gastroenterology Danielsson Å, (1993) Aliment Pharmacol Ther Danielsson Å, (1992) Scand J Gastroenterol Cobden I, (1991) Aliment Pharmacol Ther Ginsberg AL, (1988) Ann Intern Med Gandolfo J, (1987) Dig Dis Sci Selby WS, (1984) Digestion Miner PB Jr, (2006) Aliment Pharmacol Ther 2006;23:1403 – 1413 Miner PB Jr, (2006) Aliment Pharmacol Ther 2006;23:1427 – 1434 van Deventer SJ, (2006) Aliment Pharmacol Ther van Deventer SJ, (2004) Gut Ingram JR, (2005) Clin Gastroenterol Hepatol Mahmood A, (2005) Aliment Pharmacol Ther Sinha A, (2003) N Engl J Med Sandborn WJ, (1994) Gastroenterology Pedersen G, (2010) Am J Gastroenterol Miyata M, (2005) Dig Dis Sci van Dieren JM, (2009) Inflamm Bowel Dis	Pharma. S. R. Dalal has no conflicts of interest to disclose. **Study Quality:** An adaptation of the GRADE system was used to determine the quality of evidence for the efficacy of rectal therapies for inducing or maintaining UC remission. The quality of the evidence was categorized as "high," "moderate," "low," or "very low." **Heterogeneity:** n.a. **Publication Bias:** n.a. **Notes:** Search for articles was restricted to PubMed, and no Mesh terms were applied and no information how keywords are linked through operators. Two searches were performed, one with restriction on publication date, the second without. It is possible that important articles were missed. Inclusion criteria were only vaguely defined. No information on total n, study characteristics or types. The definition of remission differed among studies.

AG 3: Kann bei CU Patienten die Remission mit E.Coli Stamm Nissle 1917 genau so gut wie mit Aminosalizylaten erhalten werden?

Bewertungsvorlage:
Oxford SR

Losurdo, G. et al. Escherichia coli Nissle 1917 in Ulcerative Colitis Treatment: Systematic Review and Meta-analysis. J Gastrointestin Liver Dis. 24. 499 – 505. 2015

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Systematic review and Meta- Analysis (5 RCTs, 1 open label pilot study) **Databases:** PubMed, MEDLINE, Science Direct and EMBASE. **Search period:** Inception – 06.2015 **Inclusion Criteria:** RCTs **Exclusion Criteria:** Review articles, experimental *in vivo* or *in vitro* studies, abstracts	**Intervention:** *Population:* Adult population, pediatric population (1 study). *Intervention:* Escherichia coli Nissle 1917 (EcN) **Comparison:** Mesalazine	**Primary:** Rates for induction of remission, relapse of UC [%]. **Secondary:** Occurence of side effects [%]. **Results:** *Induction therapy:* EcN induced remission in 61.6 % of cases, while in the control group (mesalazine) the remission was achieved in 69.5 % of cases, with a mean difference of 7.9 %. The pooled OR was 0.92 (95 % CI 0.15 – 9.66, p = 0.93). A single study showed a better performance of EcN than the placebo. *Maintenance therapy:* A relapse of the disease occurred in 36.8 % in the EcN group and in 36.1 % in the control group (mesalazine), with a mean difference of 0.8 %, OR = 1.07, with a 95 % CI of 0.70 – 1.64 (p = 0.74). Side effects were comparable (OR = 1.44, 95 % CI 0.80 – 2.59, p = 0.22). **Author's Conclusion:** EcN is equivalent to mesalazine in preventing disease relapse, thus confirming current guideline recommendations. EcN seems to be as effective as controls in inducing remission and therefore, its use cannot be recommended as in one study the comparison was performed against placebo. Further studies may be helpful for this subject. ECN 1917 is a valid probiotic for UC treatment and its use could represent an effective option even if indications need to be better detailed through new trials able to provide a more reliable support for a further meta-analysis.	Kruis W, (1997) Aliment Pharm Therap Kruis W, (2004) Gut Matthes H, (2010) BMC Complement Altern Med Petersen AM, (2014) J Crohns Colitis Rembacken BJ, (1999) Lancet Henker J, (2008) Z Gastroenterol	**Funding Sources:** n.a. **COI:** None to declare. **Study Quality:** Finally, the Jadad scale was selected in order to evaluate the methodological quality of eligible trials [23]. A score ≥ 3 points indicated an adequate quality of the trial. **Heterogeneity:** "Heterogeneity was assessed by using the $\chi 2$ and I^2 statistics. In particular, heterogeneity was considered to be present if the $\chi 2$ test delivered a $p < 0.05$ and, therefore, I^2 statistic was used to quantify the proportion of heterogeneity between the studies. In the presence of heterogeneity, a revision of included studies was carried out to assess the main reason explaining the phenomenon and, therefore, the subgroup analysis was performed. Only if this attempt failed, a random effects model was employed, otherwise a fixed effects model was adopted." **Publication Bias:** "Additionally, we provided funnel plots to determine the risk of publication bias: absence of signi cant publication bias occurred when symmetry in the graph appeared." Funnel plots .... "demonstrating the symmetry of the study distribution, thus excluding the possibility of publication bias." **Notes:** Unclear definition of inclusion criteria. Differences in study duration for maintenance of remission limit comparability (12 weeks – 9 months). Small n = 34 open label study does not on pediatric patients should not have been included. Funnel plots for publication bias are usually only applied if the number of studies ≥ 10.

AG 3: Wie kann bei CU Patienten die auf Mesalazin nicht ansprechen, die Remission erhalten werden?

Bewertungsvorlage:
Oxford SR

Bickston, Stephen J et al. Vedolizumab for induction and maintenance of remission in ulcerative colitis. Cochrane Database of Systematic Reviews 2014

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** Systematic Review and Meta-analysis (4 RCTs, 606 patients) **Databases:** PubMed, MEDLINE, EMBASE and CENTRAL **Search period:** Inception – 15.06.2014 **Inclusion Criteria:** *Types of studies* Randomized controlled trials. *Types of participants* Adult patients (> 18 years of age) with active or quiescent UC as defined by conventional clinical, histological or endoscopic criteria were considered for inclusion. *Interventions* Vedolizumab *Comparison:* Placebo or control medication *Types of outcome measures* Proportion of patients who failed to achieve clinical remission and the proportion of patients who relapsed as defined by the included studies. Proportion of patients who failed to have a clinical response, failure to enter endoscopic remission, failure to have an endoscopic response, endoscopic relapse, disease-specific quality of life, adverse events, withdrawal due to adverse events and serious adverse events. **Exclusion Criteria:** Pooled analyses, open label studies.	**Intervention:** *Population:* 606, Adult patients (> 18 years of age) with active or quiescent UC as defined by conventional clinical, histological or endoscopic criteria. *Intervention:* Vedolizumab independent of dose. **Comparison:** Placebo or control medication.	**Primary:** Proportion of patients who failed to achieve clinical remission and the proportion of patients who relapsed as defined by the included studies. **Secondary:** Secondary outcomes included the proportion of patients who failed to have a clinical response, failure to enter endoscopic remission, failure to have an endoscopic response, endoscopic relapse, disease-specific quality of life, adverse events, withdrawal due to adverse events and serious adverse events **Results: Primary:** *Induction data not summarized. Relapse of UC*: After 52 weeks of therapy, 54 % of vedolizumab patients had a clinical relapse compared to 84 % of placebo patients (RR 0.67, 95 % CI 0.59 to 0.77; 1 study, 373 patients). GRADE analyses indicated that the overall quality of the evidence for the primary outcomes was high for induction of remission and moderate for relapse (due to sparse data 246 events). **Secondary:** *Adverse events:* There was no statistically significant difference between vedolizumab and placebo in terms of the risk of any adverse event (RR 0.99, 95 % CI 0.93 to 1.07), or serious adverse events (RR 1.01, 95 % CI 0.72 to 1.42). There was a statistically significant difference in withdrawals due to adverse events. Six per cent of vedolizumab patients withdrew due to an adverse event compared to 11 % of placebo patients (RR 0.55, 95 % CI 0.35 to 0.87; 2 studies, 941 patients). Adverse events commonly reported across the studies included: worsening ulcerative colitis,	Feagan B, (2000) Gastroenterology Feagan BG, (2005) N Eng J Med Feagan BG, (2013) N Eng JMed Parikh A, (2012) Inflam Bow Dis	**Funding Sources:** Funding for the IBD/FBD Review Group (September 1, 2010 – August 31, 2015) has been provided by the Canadian Institutes of Health Research (CIHR) Knowledge Translation Branch (CON – 105 529) and the CIHR Institutes of Nutrition, Metabolism and Diabetes (INMD); and Infection and Immunity (III) and the Ontario Ministry of Health and Long Term Care (HLTC3968FL- 2010 – 2235). Miss Ila Stewart has provided support for the IBD/FBD Review Group through the Olive Stewart Fund. **COI:** Stephen Bickston's institution has received grant funding from Janssen for the PREVENT clinical trial. This activity is outside of the submitted work. Brian Behm's institution received funding to be a site for the GEMINI clinical trials. Brian Feagan is an author of three manuscripts that were included in this review. He has received fee(s) from Abbott/AbbVie, Amgen, Astra Zeneca, Avaxia Biologics Inc., Bristol-Myers Squibb, Celgene, Centocor Inc., Elan/Biogen, Ferring, JnJ/Janssen, Merck, Novartis, Novonordisk, Pfizer, Prometheus Laboratories, Protagonist, Salix Pharma, Takeda, Teva, Tillotts Pharma AG, UCB Pharma for Board membership; fee(s) from Abbott/AbbVie, Actogenix, Albireo Pharma, Amgen, Astra Zeneca, Avaxia Biologics Inc., Axcan, Baxter Healthcare Corp., Boehringer- Ingelheim, Bristol- Myers Squibb, Calypso Biotech, Celgene, Elan/Biogen, EnGene, Ferring Pharma, Roche/Genentech, GiCare Pharma, Gilead, Given Imaging Inc., GSK, Ironwood Pharma, Janssen Biotech (Centocor), JnJ/Janssen, Kyowa Kakko Kirin Co Ltd., Lexicon, Lilly, Merck, Millennium, Nektar, Novonordisk, Pfizer, Prometheus Therapeutics and Diagnos- tics, Protagonist, Receptos, Salix Pharma, Serono, Shire, Sigmoid Pharma,

		headache, nasopharyngitis, upper respiratory tract infection, nausea, and abdominal pain. **Author's Conclusion:** Moderate to high quality data from four studies shows that vedolizumab is superior to placebo for induction of clinical remission and response and endoscopic remission in patients with moderate to severely active ulcerative colitis and prevention of relapse in patients with quiescent ulcerative colitis. Moderate quality data from one study suggests that vedolizumab is superior to placebo for prevention of relapse in patients with quiescent ulcerative colitis. Adverse events appear to be similar to placebo. Future trials are needed to define the optimal dose, frequency of administration and long-term efficacy and safety of vedolizumab used for induction and maintenance therapy of ulcerative colitis. Vedolizumab should be compared to other currently approved therapies for ulcerative colitis in these trials.		Synergy Pharma Inc., Takeda, Teva Pharma, Tillotts, UCB Pharma, Vertex Pharma, Warner-Chilcott, Wyeth, Zealand, and Zyngenia for consultancy; and lecture fee(s) from: Abbott/AbbVie, JnJ/Janssen, Takeda, Warner-Chilcott, and UCB Pharma. Reena Khanna has received fee(s) from AbbVie for Board membership and fee(s) from Takeda for consultancy. All of these activities are outside the submitted work. The other authors have no known declarations of interest. **Study Quality:** "The methodological quality of the included studies was assessed using the Cochrane risk of bias tool." "All of the studies were rated as having a low risk of bias." **Heterogeneity:** Heterogeneity is not an issue when the data is from a single RCT (in case of relapse/maintenance of UC). **Publication Bias:** Disagreement among authors regarding risk of bias was resolved by consensus. In future updates of this review publication bias will be assessed by examining the authors and institutions involved, journal of publication, funding sources, and the affiliation of authors with manufacturers. **Notes:** Evidence for the outcome of interest (maintenance/relapse of UC) was rated as moderate, but the data is from a single RCT (with 236 interventions and 126 controls). Current version of the review article does not include assessment of publication bias.
Timmer, A et al. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev Cd000 478. 2016				
Evidence level/ Study Types	**Population**	**Outcomes/Results**	**Literature/References**	**Methodical Notes**
Evidence level: 2 **Study type:** Systematic review and meta-analysis (7 studies, RCTs and 3 randomized controlled open label, total n = 302 patients) **Databases:** MEDLINE, EMBASE and Cochrane Library. **Search period:** Inception – 30.06.2015 **Inclusion Criteria:** *Types of studies:* RCTs of at least 12 months duration. Open label studies were also considered.	**Intervention:** *Population:* 302 Patients in whom azathioprine or 6-mercaptopurine were used to treat UC in remission, with or without a preceding period of induction of remission. Remission of ulcerative colitis was defined as mild or absent symptoms with complete discontinuation of corticosteroids, irrespective of the use of prophylactic medication, and continuing	**Primary:** The primary outcome was defined as failure to maintain clinical or endoscopic remission at 12 months from randomization or later, i. e. clinical or endoscopic relapse, or early withdrawal from the study as defined by the investigators. For studies where life table analysis was used the estimated probability of relapse over time was to be examined. Patients failing to achieve clinical remission during an induction phase were considered treatment	Hawthorne AB, (1992) BMJ Jewell DP, (1974) BMJ Mate-Jimenez J, (2000) Eur J of Gastroen Hepat Paraskeva KD, (2000) Gut Sood A, (2000) Indian J Gastroenterol Sood A, (2002) J Gastroenterol Sood A, (2003) Indian J Gastroenterol	**Funding Sources:** Funding for the IBD/FBD Review Group (September 1, 2010 – August 31, 2015) has been provided by the Canadian Institutes of Health Research (CIHR) Knowledge Translation Branch (CON – 105 145) and the CIHR Institutes of Nutrition, Metabolism and Diabetes (INMD); and Infection and Immunity (III) and the Ontario Ministry of Health and Long Term Care (HLTC3968FL- 2010–2235). Miss Ila Stewart has provided support for the IBD/FBD Review

Types of participants: Patients in whom azathioprine or 6-mercaptopurine were used to treat UC in remission, with or without a preceding period of induction of remission. Remission of ulcerative colitis was defined as mild or absent symptoms with complete discontinuation of corticosteroids, irrespective of the use of prophylactic medication, and continuing evidence on sigmoidoscopy of an uninflamed or grade 1 mucosa.
Types of interventions Oral azathioprine or 6-mercaptopurine for the treatment of patients with UC in remission. This included trials in which these drugs were added to the treatment of patients in remission, withdrawal studies and studies in which there was more than one phase (e. g. active followed by maintenance).
Comparison: Placebo, or other active maintenance therapies.
Types of outcome measures: Failure to maintain clinical or endoscopic remission at 12 months from randomization or later; occurrence of any adverse event and withdrawal due to adverse events.
Exclusion Criteria: Patients with chronic active disease were not included.

evidence on sigmoidoscopy of an uninflamed or grade 1 mucosa.
Intervention: Oral azathioprine (AZA) or oral 6-mercaptopurine (6MP).
Comparison: Placebo or other maintenance therapies f.e 5-aminosalicylate (5-ASA).

failures to maintenance therapy in an intention-to-treat approach.
Separate analyses were performed excluding these cases.
Secondary: Secondary outcomes included the occurrence of any adverse event (particularly opportunistic infection, pancreatitis, bone marrow suppression, cancer and death) and withdrawal due to adverse events. Data were extracted to investigate the influence of the dose of azathioprine or 6-mercaptopurine treatment, the duration of previous azathioprine or 6-mercaptopurine treatment (for with- drawal trials), and the effect of other concurrent therapies.
Results: Failure to maintain remission: *AZA vs Placebo:* AZA was significantly superior to placebo for maintenance of remission. 44 % (51/115) of AZA failed to maintain remission compared to 65 % (76/117) of placebo patients (4 studies, 232 patients; RR 0.68, 95 % CI 0.54 to 0.86). A GRADE analysis rated the overall quality of the evidence for this outcome as low due to risk of bias and imprecision (sparse data).
6MP and AZA vs 5-ASA sulfasalazine Two trials compared 6-mercaptopurine to mesalazine, or azathioprine to sulfasalazine showed significant heterogeneity and thus were not pooled. 50 % (7/14) of 6-mercaptopurine patients failed to maintain remission compared to 100 % (8/8) of mesalazine patients (1 study, 22 patients; RR 0.53, 95 % CI 0.31 to 0.90). 58 % (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).
Adverse events: When placebo-controlled studies were pooled with 5-ASA studies to assess adverse events, there was no significant difference between

Group through the Olive Stewart Fund.
COI: Antje Timmer received grants (paid to institution) from Sanofi-Aventis, Bayer, Takeda, Celgene, and Novartis for pharmacoepidemi- ological studies prior to 2014; and payment for lectures from Abbott, Ferring, The Falk Foundation, and MSD Sharp. All of these activities are outside the submitted work.
Petrease H Patton: None known.
Nilesh Chande has received fees for consultancy from Abbott/AbbVie, Ferring, and Actavis; fees for lectures from Abbott, travel expenses from Merck and has stock/stock options in Pfizer, Glaxo Smith Kline, Proctor and Gamble and Johnson and Johnson. All of these financial activities are outside the submitted work.
John WD McDonald: None known. John K MacDonald: None known.
Study Quality: Study quality was assessed using the Cochrane risk of bias tool. The risk of bias was high in three of the studies due to lack of blinding.
Heterogeneity: "The presence of heterogeneity among studies was assessed using the chi2 test, a P value of 0.10 was regarded as statistically significant. The I2 statistic was used to quantify inconsistency (Higgins 2003). This statistic describes the percentage of the variability in effect estimates that are due to heterogeneity rather than sampling error. A value greater than 50 % was considered evidence of substantial heterogeneity. In the presence of significant heterogeneity, pooled analysis was not performed. If homogeneity was likely (I2 < 0.03), pooled RR with 95 % confidence intervals were calculated using a fixed-effect model based on the method by Mantel and Haenszel as a primary analysis."
High heterogeneity (P = 0.03; I2 = 79 %) prevented the the compared analysis of 6-MP to 5-ASA and AZA to sulfasalazine.
Publication Bias: "The number of eligible trials was too small to assess the occurrence of publication bias, or any bias arising from differences in methodological quality."

		AZA and control in the incidence of adverse events. 9 % (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 AZA were at significantly increased risk of withdrawing due to adverse events. Eight per cent (8/101) of AZA 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, plus 1 case on cyclosporin) and significant bone marrow suppression (5 cases). Deaths, opportunistic infection or neoplasia were not reported. **Author's Conclusion:** 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.		In the risk of bias assessment for the individual studies, 4 were judged to be at low risk of reporting bias, in 3 studies reporting bias was unclear to the investigators. **Notes:** Inclusion of unblinded trials introduces bias to the investigation. Overall n is small and important comparisons between interventions were prevented due to heterogeneity. The comparison of Azathioprin with Placebo yields the most meaningful results.

AG 3: Wie kann bei CU Patienten die auf Mesalazin nicht ansprechen, die Remission erhalten werden?

Bewertungsvorlage:
OXFORD Appraisal Sheet: RCT

Sandborn, W J et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 146. 96 – 109.e1. 2014

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 3 **Study type:** Multicentric, placebo controlled, double blind, randomized withdrawal study. (251 centers) **Number of Patient:** 464 **Recruitung Phase:** 2007 – 2011 **Inclusion Criteria:** Extracted from referenced article: "Eligible patients had an established diagnosis of UC and moderate-to-severe disease activity, defined as a Mayo score of 6 – 12, with an endoscopic subscore ≥ 2. No minimum disease duration was prespecified. Patients had an inadequate response to, or had failed to tolerate, 1 or more of the following conventional therapies: oral 5-aminosalicylates, oral corticosteroids, azathioprine (AZA), and/or 6-mercaptopurine; or were corticosteroid dependent. Patients concurrently treated with oral 5- aminosalicylates or corticosteroids were to receive a stable dose for at least 2 weeks before baseline, and patients receiving AZA and/or 6- mercaptopurine were to receive a stable dose for at least 4 weeks before baseline. Patients were required to maintain stable doses of their concomitant UC medications during the study." **Exclusion Criteria:** Extracted from referenced article: "Patients with a history of, or at imminent risk for, colectomy; who required gastrointestinal surgery within 2 months before screening; had colitis limited to 20 cm of the colon (patients with ulcerative proctitis often have rectal bleeding as the primary clinical manifestation of the disease, thus, the utility of the Mayo score in this patient population is less clear); or had a history of colonic mucosal dysplasia or adenomatous colonic polyps that were not removed, were ineligible. Patients were excluded if their screening stool study was positive for enteric pathogens or Clostridium difficile toxin. Earlier use of the following medications also	**Intervention:** *Population:* 464 Patients with established diagnosis of UC and moderate- to-severe disease activity, defined as a Mayo score of 6 – 12, with an endoscopic subscore ≥ 2 with inadequate response to, or had failed to tolerate, 1 or more of the following conventional therapies: oral 5-aminosalicylates, oral corticosteroids, azathioprine (AZA), and/or 6- mercaptopurine; or were corticosteroid dependent *Intervention:* Golimumab (Simponi; Janssen Biotech, Inc, Horsham, PA) 50 mg, or golimumab 100 mg every 4 weeks through week 52. **Comparison:** Subcutaneous placebo every 4 weeks through week 52.	**Primary: Primary:** *Maintenance of clinical response* through week 54 among golimumab- induction responders. Patients were assessed for UC disease activity using the Mayo score at weeks 30 and 54 and by partial Mayo score every 4 weeks (loss of response was confirmed by endoscopy) to substantiate that patients had maintained clinical response at each visit. Therefore, patients who maintained clinical response were considered to be in a state of continuous clinical response through week 54. **Secondary: Secondary:** The analysis population for major secondary end points was golimumab- induction responders. Prespecified major secondary end points were as follows: (1) clinical remission at both weeks 30 and 54; (2) mucosal healing at both weeks 30 and 54; (3) clinical remission at both weeks 30 and 54 among patients who had clinical remission at PURSUIT- M baseline; and (4) corticosteroid-free clinical remission at week 54 among patients receiving concomitant corticosteroids at PURSUIT-M baseline. **Results: Primary:** *Clinical response was maintained* through week 54 in 47.0 % of patients receiving 50 mg golimumab, 49.7 % of patients receiving 100 mg golimumab, and 31.2 % of patients receiving placebo (P = .010 and P<.001 respectively> **Secondary:** *Clinical remission:* At weeks 30 and 54, a higher percentage of patients who received 100 mg golimumab were in clinical remission and had mucosal healing (27.8 % and 42.4 %) than patients given placebo (15.6 % and 26.6 %; P = .004 and P = .002, respectively) or 50 mg golimumab (23.2 % and 41.7 % espectively). *serious adverse events* Occurred in 7.7 %, 8.4 %, and 14.3 % among patients given placebo, 50 mg, or 100 mg golimumab, respectively; percentages of serious infections were 1.9 %, 3.2 %, and 3.2 %, respectively. Among all patients given golimumab in the study, 3 died (from sepsis, tuberculosis, and cardiac failure, all in patients who received 100 mg goli- mumab) and 4 developed active tuberculosis. **Author's Conclusion:** both golimumab doses administered as an every-4-weeks SC maintenance regimen in patients with moderate- to-severe active UC who were induced into clinical response with golimumab were effective in maintaining clinical response through 1 year. Further, patients receiving the 100-mg golimumab dose achieved long- term clinical remission and mucosal healing at both weeks 30 and 54, in addition to showing positive trends for maintenance of clinical remis- sion through 1 year. There was a positive relationship between the maintenance of clinical response and serum golimumab concentration. Maintenance treatment with golimumab resulted in an overall safety profile in this UC population that was consistent with those reported for other TNFa- antagonists and with golimumab in other approved indications.	**Funding Sources:** The study was funded by Janssen Research & Development, LLC (Spring House, PA). **COI:** The authors disclose the following: William Sandborn has received consulting fees from Abbott, ActoGeniX NV, AGI Therapeutics, Inc, Alba Therapeutics Corp, Albireo, Alfa Wasserman, Amgen, AM-Pharma BV, Anaphore, Astellas, Athersys, Inc, Atlantic Healthcare, Ltd, Aptalis, BioBalance Corp, Boehringer- Ingelheim, Bristol-Myers Squibb, Celgene, Celek Pharmaceuticals, Cellerix SL, Cerimon Pharmaceuticals, ChemoCentryx, CoMentis, Cosmo Technologies, Coronado Biosciences, Cytokine Pharmasciences, Eagle Pharmaceuticals, EnGene, Inc, Eli Lilly, Enteromedics, Exagen Diagnostics, Inc, Ferring Pharmaceuticals, Flexio Therapeutics, Inc, Funxional Therapeutics, Ltd, Genzyme, Corp, Gilead Sciences, Given Imaging, GlaxoSmithKline, Human Genome Sciences, Ironwood Pharmaceuticals, Janssen Research and Development, LLC, KaloBios Pharmaceuticals, Lexicon Pharmaceuticals, Lycera Corp, Meda Pharmaceuticals, Merck Research Laboratories, Merck Serono, Millenium Pharmaceuticals, Nisshin Kyorin Pharmaceuticals, Novo Nordisk, NPS Pharmaceuticals, Optimer Pharmaceuticals, Orexigen Therapeutics, Inc, PDL Biopharma, Pfizer, Procter and Gamble, Prometheus Laboratories, ProtAb, Ltd, Purgenesis Technologies, Inc, Relypsa, Inc, Roche, Salient Pharmaceuticals, Salix Pharmaceuticals, Santarus, Schering Plough, Shire Pharmaceuticals, Sigmoid Pharma, Ltd, Sirtris Pharmaceuticals, SLA Pharma UK, Ltd, Targacept, Teva Pharmaceuticals, Therakos, Tilliotts Pharma AG, TxCell SA, UCB Pharma, Viamet Pharmaceuticals, Vascular Biogenics, Ltd, Warner Chilcott UK, Ltd, and Wyeth; has received research grants from Abbott, Bristol-Myers Squibb, Genentech, GlaxoSmithKline, Janssen Research and Development, LLC, Milennium Pharmaceuticals, Novartis, Pfizer, Procter and Gamble, Shire Pharmaceuticals, and UCB Pharma;

precluded study participation: biologic anti- TNF agent(s) natalizumab or other agents target- ing the a-4 integrin, B-cell depleting agents (rituximab), or T-cell depleting agents (alemtuzumab, visilizumab) within 12 months of the first study-agent injection (or continued B- or T-cell depletion > 12 months after completing therapy with lymphocyte-depleting agents); oral corticosteroids at a dose > 40 mg prednisone or its equivalent per day; receipt of cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil within 8 weeks before the first study agent injection; or use of an investigational agent within 5 half-lives of that agent before the first study agent injection."			has received payments for lectures/ speakers bureau from Abbott, Bristol-Myers Squibb, and Janssen Research and Development, LLC; and holds stock/stock options in Enteromedics. Brian Feagan has received consulting fees from Millennium, Merck, Janssen Research and Development, LLC, Elan/Biogen, Janssen-Ortho, Teva Pharmaceuticals, Bristol-Myers Squibb, Celgene, UCB Pharma, Abbott, Astra Zeneca, Serono, Genentech, Tillotts, Unity Pharmaceuticals, Albireo Pharma, Given Imaging, Inc, Salix Pharm, Novonordisk, GlaxoSmithKline, Actogenix, Prometheus Therapeutics and Diagnostics, Athersys, Axcan, Gilead, Nektar, Pfizer, Shire, Wyeth, Zealand Pharm, Zyngenia, glCare Pharma, Inc, and Sigmoid Pharma; has received research grants from Merck, Millennium, Tillotts, Abbott, Protein Design Labs, Novartis, Janssen Research and Development, LLC, Elan/Biogen, UCB Pharma, Bristol-Myers Squibb, Genentech, CombinatoRx, ActoGeniX, and Wyeth; has received payments for lectures/speakers bureau from UCB, Abbott, Janssen Research and Development, LLC; and has served as a Scientific Advisory Board member for Astra Zeneca, Elan/Biogen, Merck, Celgene, Novartis, UCB Pharma, Salix Pharmaceuticals, Abbott Laboratories, Pfizer, Tillotts Pharma AG, and Prometheus Laboratories. Jean-Federic Colombel has served as a consultant, advisory board member, or speaker for Abbott Laboratories, Bristol Meyers Squibb, Ferring, Genentech, Giuliani SPA, Given Imaging, Janssen Research and Development, LLC, Merck & Co, Millenium Pharmaceuticals, Inc, Pfizer, Inc, Prometheus Laboratories, Sanofi, Schering Plough Corporation, Takeda, Teva Pharmaceuticals, and UCB Pharma (previously named Celltech Therapeutics, Ltd). Walter Reinisch has served as a speaker, consultant, and/or advisory board member for Abbott Laboratories, Aesca, Amgen, Astellas, Astra Zeneca, Biogen IDEC, Bristol- Myers Squibb, Cellerix, Chemocentryx, Celgene, Janssen Research and Development, LLC, Danone Austria, Elan, Ferring, Genentech, Grünenthal, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, Millenium, Mitsubishi Tanabe Pharma Corporation, MSD, Novartis, Ocera, Otsuka, PDL, Pharmacosmos, Pfizer, Procter & Gamble, Prometheus, Roba

			Randomization: Treatment allocation used an adaptive randomization procedure based on 3 factors: (1) investigative site, (2) a 4-level cross-classification of clinical remission status and corticosteroid use at PURSUIT-M baseline, and (3) previous induction therapy (IV golimumab 1 mg/kg, 2 mg/kg, or 4 mg/kg; SC golimumab 100/50 mg, 200/100 mg, or 400/200 mg). **Blinding:** Double blind study **Dropout Rate/ITT-Analysis: -** Dropouts: "Among randomized patients, 75.6 % (351 of 464) of patients completed the study through week 54; more than 70 % of patients completed the study in each group." "456 of 464 randomized golimumab-induction responders were analyzed: 8 patients (1.7 %) were excluded because of noncompliance with good clinical practice at three sites. 7 randomized patients were retrospectively excluded following identification of noncompliance after acceptance of the original manuscript for publication in this journal." **Notes:** No tests for similarity were performed to compare characteristics of the randomized groups were performed. 7 patients were retrospectively excluded following identification of noncompliance, which is questionable.

AG 3: Kann bei CU Patienten die Remission mit Infliximab Biosimilar genau so gut erhalten werden wie mit Originator Infliximab?

Bewertungsvorlage:
Oxford SR

Jacobs, I et al. Biosimilars for the Treatment of Chronic Inflammatory Diseases: A Systematic Review of Published Evidence. BioDrugs. 30. 525 – 570. 2016

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Systematic review **Databases:** MEDLINE/MEDLINE In-Process and EMBASE (searched using the OVIDSP interface), and ISI Web of Science **Search period:** Inception – 3.09.2015 **Inclusion Criteria:** Articles published in the English language. **Exclusion Criteria:** n.a.	**Intervention:** Population includes: rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), psoriasis, Crohn's disease (CD), and ulcerative colitis (UC) patients. Proposed biosimilars for adalimumab, etanercept, infliximab, and rituximab. Approved biosimilars include infliximab CT-	**Primary:** Evidence for biosimilarity of originator and biosimilar: Analytical studies; Nonclinical studies; PK/safety studies or preliminary safety/efficacy studies; Comparative safety/efficacy studies; Post-marketing/ observational studies. **Secondary:** n.a. **Results:** Several observational studies have been reported for CT-P13 that investigated the efficacy and impact of switching	Molnar T, (2015) J Crohns Colitis Yoon Suk J, (2015) J Crohns Colitis Jung YS, (2015) J Gastroenterol Hepatol Kang HW, (2014) J Crohns Colitis Kang Y-S, (2015) Dig Dis Sci Murphy C, (2015) J Crohns Colitis Farkas K, (2015) Expert Opin Biol Ther Gecse K, (2015) Z Gastroenterol	**Funding Sources:** The SLR to support this manuscript was sponsored by Pfizer Inc. **COI:** IJ, DP and KLS are full-time employees and shareholders of Pfizer. LI was a full-time employee of Pfizer Inc. at the time the study was conducted. SL is a full-time employee of Envision Pharma Group, who were paid consultants to Pfizer in connection with the development of the SLR report that forms the basis of this manuscript. He was not compensated for his role in

	P13, SB2, and etanercept SB4. **Comparison:** Originator treatment.	from the biologic originator to CT-P13 in patients with UC or CD (n = 336). In one study of 110 patients with CD or UC, the clinical response to the treatment at 8 weeks was 87 % in patients who had not been previously treated with an anti-TNF agent and 67 % in those who had switched from another anti-TNF. Another prospective study in 90 patients with CD or UC found decreases in scores of disease activity after 6 weeks of treatment with the biosimilar. One of these observational cohort studies explored the use of CT-P13 in pediatric patients with CD (n = 32). The results of these studies should be interpreted with a degree of caution based on the underlying limitations of the study designs. Following the launch of CT-P13 in several major European countries, health economic studies have emerged evaluating the budget impact and cost effectiveness (from a payer or patient perspective) of introducing the biosimilar into the chronic inflammatory disease market. Published studies to date have explored the potential cost savings realized from substituting the originator with CT-P13 for the treatment of CD, UC, RA, AS, and PsA across multiple European countries. The totality of evidence from these studies points towards substantial cost savings, with the degree of budget impact dependent on the rate of interchangeability, patient number, and eligibility of treatment with the biosimilar (i. e., whether patients are treatment-naive or treatment-experienced), along with the acquisition cost of the biosimilar. These authors have attempted to quantitatively demonstrate that the introduction of a biosimilar may provide additional budget to treat more patients (including, for example, those with	Kierkus J, (2015) Gastroenterology	the development of this manuscript. **Study Quality:** In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a validated tool matched to the study type was used to assess the strength/validity of the empirical data for each individual study. The assessment of the quality of randomized controlled trials (RCTs) was carried out using recommendations from the National Institute for Health and Care Excellence (NICE) single technology appraisal (STA) manufacturer's template and the Jadad scoring system. The Downs and Black instrument was used to assess the quality of all non-randomized studies. As studies published as abstracts in conference proceedings have limited information, the Downs and Black instrument was modified to include only the most relevant qualifying parameters. **Heterogeneity:** n.a. **Publication Bias:** n.a. **Notes:** 4 out 9 articles also included in the SR by Radin et al. 2016. PICO questions, inclusion and exclusion criteria, as well as outcomes were only vaguely defined. The scope of the article is too ambitious, available evidence is mostly observational, and as a consequence the conclusion drawn from the evidence can only be vague.

		earlier- stage disease) on an annual basis, which could potentially alleviate both the short- and longer-term cost burden among health-care payers and providers. **Author's Conclusion: -** While most agents display a moderate to high degree of similarity to their originator in the published studies identified, large discrepancies persist in the overall amount and type of data available in the public domain. Significant gaps exist particularly for intended copies, reinforcing the need to maintain a clear differentiation between these molecules and true biosimilars.		
Radin, M. et al. Infliximab Biosimilars in the Treatment of Inflammatory Bowel Diseases: A Systematic Review. BioDrugs 2016				
Evidence level/ Study Types	**Population**	**Outcomes/Results**	**Literature/References**	**Methodical Notes**
Evidence level: 2 **Study type:** Systematic Review (11 studies) **Databases:** Medline, EMBASE, Cochrane register of controlled trials, Scopus **Search period:** 2012 – 09.2016 **Inclusion Criteria:** Clinical study of IBD treated with infliximab biosimilar, more than 5 patients included. **Exclusion Criteria:** n.a.	**Intervention:** *Population:* 435 UC patients (127 switched and 308 naive). *Intervention:* Infliximab biosimilar **Comparison:** Originator anti TNF-a Antibody (switch patients)	**Primary:** Efficacy **Secondary:** Safety **Results:** "Overall no significant difference in efficacy and safety between the originator infliximab and its biosimilar CT-P13 was observed. When assessing the safety of CT-P13, we found that 9.2 % of patients experienced adverse effects (4.1 % infusion-related reactions and 4.3 % infections)." **Author's Conclusion:** "Despite no trials addressing the use of CTP-13 in IBD in a randomized fashion, the current literature, including observational studies about the clinical experience of CT- P13, is promising. The analyzed studies did not report a significant difference in terms of efficacy, safety and immunogenicity when comparing the clinical experience with CT-P13 with the available literature data on originator treatment in IBD. However, some debate is ongoing regarding interchangeability and immunogenicity."	Smits LJT, (2016) J Crohns Colitis Farkas K, (2015) Expert Opin Biol Ther Park SH (2015) Expert Rev Gastroenterol Hepatol Jung YS, (2015) J Gastroenterol Hepatol Gecse KB, (2015) J Crohns Colitis Kang YS, (2015) Dig Dis Sci Farkas K, (2016) J Crohns Colitis Keil R, (2016) Scand J Gastroenterol Jahnsen J, (2015) Expert Rev Gastroenterol Hepatol Scieczkowska J, (2016) J Crohns Colitis Buer LCT, (2016) J Crohns Colitis	**Funding Sources:** none. **COI:** M. Radin, S. Sciscia, D. Roccatello and M.J. Cuadrado declare no conflicts of interest. **Study Quality:** Heterogeneity: n.a. **Publication Bias:** n.a. **Notes:** Evidence is based on uncontrolled, retrospective studies. Author's claim no RCTs have investigated treatment of IBD comparing biosimilar with originator. Differences in outcomes and length of treatments between studies. No assessment of the quality of primary studies.

AG 3: Wie kann die Erhaltungstherapie bei CU Patienten mit Proktitis durchgeführt werden?

Bewertungsvorlage:
Oxford SR

Marshall, J.K. et al. Rectal 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 11. Cd004 118. 2012

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** Systematic Review and Meta-Analysis (9 RCTS) **Databases:** MEDLINE database, Cochrane library, Cochrane Inflammatory Bowel Disease and Functional Bowel Disorders (IBD/ FBD) Review Group Specialized Trials Register and manual review of bibliographies and abstracts submitted to major gastroenterology meetings (1997 to 2011) published in the following Journals: Am J Gastroenterol; Can J Gastroenterol; Gastroenterology; Gastrointest Endosc Gut; Scand J Gastroentero. **Search period:** 1966 – 30.08.2012 **Inclusion Criteria:** *Types of studies* randomized controlled clinical trials were eligible for inclusion. *Types of participants* Age≥ 12 years of age, UC disease extent less than 60 cm from the anal verge or distal to the splenic flexure, as determined by barium enema or endoscopy. Subjects were also expected to have been in remission at the time of randomization. *Types of interventions* One treatment arm was required to administer rectal 5-ASA as an enema, foam or suppository for a minimum duration of six months. Eligible comparators were placebo and oral 5-ASA formulations. *Types of outcome measures* The principal outcome measure was continued remission by clinical, endoscopic or histologic criteria. Pre-planned secondary analyses included time to relapse and change in disease activity indices (DAI). Subgroup	**Intervention:** *Population:* 484 patients with UC in remission, Age≥ 12 years of age, UC disease extent less than 60 cm from the anal verge or distal to the splenic flexure, as determined by barium enema or endoscopy. *Intervention:* Rectal 5-ASA as an enema, foam or suppository for at least six months. **Comparison:** *Intervention:* Rectal Placebo as and enema, foam or suppository for at least six months.	**Primary:** *Continued remission:* by clinical, endoscopic or histologic criteria. **Secondary:** Time to relapse and change in disease activity indices (DAI). Subgroup analyses by disease extent and 5-ASA dose were also planned. Because of anticipated heterogeneity in the definition of these outcomes, those of the original authors were accepted. **Results: Primary:** *Continued remission*: 62 % of patients in the rectal 5-ASA group maintained symptomatic remission compared to 30 % of patients in the placebo group (4 studies; 301 patients; RR 2.22, 95 % CI 1.26 to 3.90; $I^2 = 67$ %; P< 0.01). A GRADE analysis indicated that the overall quality of the evidence for the primary outcome was low due to imprecision (i. e. sparse data 144 events) and inconsistency (i. e. unexplained heterogeneity). **Secondary:** *Adverse events:* There was no statistically significant difference in the proportion of patients who experienced at least one AE. 16 % of patients in the rectal 5-ASA group compared to 12 % of placebo patients (2 studies; 160 patients; RR 1.35, 95 % CI 0.63 to 2.89; $I^2 = 0$ %; P = 0.44). The most commonly reported adverse events were anal irritation and abdominal pain. No statistically significant differences between rectal and oral 5- ASA were identified for either symptomatic or endoscopic remission over a period of six months. *Rectal vs. oral 5-ASA:* 80 % of patients in the rectal 5-ASA group maintained symptomatic remission compared to 65 % of patients in the oral 5-ASA group (2 studies; 69 patients; RR 1.24, 95 % CI 0.92 to 1.66; $I^2 = 0$ %;	Andreoli A, (1994) Ital J Gastroenterol Biddle WL, (1988) Gastroenterology d'Albasio G, (1990) Dis Colon Rectum d'Albasio G, (1998) Am J Gastroenterol D'Arienzo A, (1990) Am J Gastroenterol Hanauer S, (2000) Am J Gastroenterol Mantzaris GJ, (1994) Dis Colon Rectum Marteau P, (1998) Gut Sutherland LR, (1987) Can J Gastroenterol	**Funding Sources:** Funding for the IBD/FBD Review Group (September 1, 2010 – August 31, 2015) has been provided by the Canadian Institutes of Health Research (CIHR) Knowledge Translation Branch (CON – 105 529) and the CIHR Institutes of Nutrition, Metabolism and Diabetes (INMD); and Infection and Immunity (III) and the Ontario Ministry of Health and Long Term Care (HLTC3968FL- 2010 – 2235). Miss Ila Stewart has provided support for the IBD/FBD Review Group through the Olive Stewart Fund. **COI:** Dr. Marshall has received honoraria for speaking and/or consulting from Axcan, Aptalis, Ferring, Shire, Warner-Chilcott, Janssen, Abbott and Takeda, and has received research funds from Abbott, Janssen, Centocor, GKS, Amgen and Pfizer. Dr. Steinhart has received honoraria for speaking and/or consulting from Aptalis, Shire, Janssen and Abbott, and has received research funds from Abbott, Janssen, Centocor, Amgen, Pfizer, GSK and Millenium. Dr. Thabane has no conflicts of interest. Dr. Irvine has received honoraria for speaking and/or consulting from Abbott, Shire and Procter & Gamble, and has received research funds from Abbott. Dr. Newman has no conflicts of interest. Dr. Anand has no conflicts of interest. **Study Quality:** The methodological quality of each trial was assessed using the Cochrane risk of bias tool and the Jadad scale. We used the GRADE approach for rating the overall quality of evidence for the primary outcomes and selected secondary outcomes of interest. Six studies were rated as low risk of bias. Three studies were rated as high risk of bias due to blinding (two open label and one single-blind). **Heterogeneity:** "Heterogeneity was assessed using the Chi^2 test

analyses by disease extent and 5-ASA dose were also planned. Because of anticipated heterogeneity in the definition of these outcomes, those of the original authors were accepted. **Exclusion Criteria:** n.a.		P = 0.15). A GRADE analysis indicated that the overall quality of the evidence for the primary outcome was low due to imprecision (i. e. sparse data 50 events) and high risk of bias (i. e. both studies in the pooled analysis were open label). 80 % of patients in the rectal 5-ASA group maintained endoscopic remission compared to 70 % of patients in the oral 5-ASA group (2 studies; 91 patients; RR 1.14, 95 % CI 0.90 to 1.45; I^2 = 0 %; P = 0.26). **Author's Conclusion:** The limited data available suggest that rectal 5-ASA is superior to placebo and may be as effective as oral 5-ASA for maintaining remission of mild to moderately active UC.		and visual inspection of forest plots. If no significant heterogeneity was identified (P > 0.10 for Chi^2) a fixed-effect model (Mantel-Haenstzel) was used. If heterogeneity was significant, a random-effects model was used." **Publication Bias:** n.a. **Notes:** No investigation of publication bias. GRADE evidence quality was considered low for the primary outcome due to sparse data and unexplained heterogeneity.

Lie, M.R. et al. Drug therapies for ulcerative proctitis: systematic review and meta-analysis. Inflamm Bowel Dis. 20. 2157 – 2178. 2014

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Systematic Review and Meta analysis (23 studies total; 5 on maintenance of remission, of which 4 double blind studies, one with unclear blinding) **Databases:** Embase (including Medline), Medline OvidSP, Cochrane Central Register of Controlled Trials, Web of Science, and Pubmed **Search period:** inception – 28.04.2014 **Inclusion Criteria:** *Types of study*: Randomized controlled trials comparing the efficacy of any drug versus another active therapy or placebo for remission induction or maintenance of remission in UP. *Types of participants*: Adults (age ≥ 16 years), with a diagnosis of ulcerative colitis limited to 20 cm from the anal verge (i. e. ulcerative proctitis) at endoscopy, both first presentation of UC and patients with a relapse. For maintenance of remission studies, subjects had to be in remission for	**Intervention:** *Population*: (total n = 288 for maintenance); Adults (age ≥ 16 years), with a diagnosis of ulcerative colitis limited to 20 cm from the anal verge (i. e. ulcerative proctitis) at endoscopy, both first presentation of UC and patients with a relapse. For maintenance of remission studies, subjects had to be in remission for at least 4 weeks prior to enrollment. *Intervention*: Any drug therapy. All formulations (e. g. oral, suppository, enema). The duration of treatment had to be at least 4 weeks in induction studies, and at least 3 months in maintenance studies. Studies were grouped based on the type of treatment (i. e. induction, maintenance) and based on drug class (e. g. 5-ASA, corticosteroids). Additionally, these groups were further subdivided by	**Primary:** Clinical remission for induction studies. Sustained clinical remission for maintenance studies. **Secondary:** Endoscopic remission rates, histological remission rates, time to relapse. **Results:** *Topical 5-ASA Versus Placebo* Three trials (N = 193) examined topical 5-ASA (suppositories, daily dose 500 – 1000 mg) versus placebo. Patients treated with 5-ASA maintained clinical remission in 65.5 %, but in patients receiving placebo, only 26.0 % maintained their remission. The pooled RR of maintaining clinical remission for all trials was 2.80 (95 % CI, 1.21 – 6.45; I^2 = 66 %; P = 0.02) using a random-effects model. A subgroup analysis (N = 140) of the studies examining 500 mg 5-ASA suppositories showed a 57.7 % maintained clinical remission rate for 5-ASA compared with 26.1 % for placebo. The pooled RR of maintaining clinical remission with this dose of 5-ASA was 2.52 (95 % CI, 0.64 – 9.86; I2 ¼ 85 %; P ¼ 0.18)	d'Albasio G, (1998) Am J Gastroenterol d'Arienzo A, (1990) Am J Gastroenterol Hanauer SB, (2000) Am J Gastroenterol Nilsson A, (1995) Am J Gastroenterol Travis SPL, (1994) Gut	**Funding Sources:** n.a. **COI:** The authors have no conflicts of interest to disclose. **Study Quality:** "The risk of bias was assessed independently by each of the 2 primary reviewers, according to the scheme described in the Cochrane Handbook for Systematic Review of Interventions. This assessment involved judgment on selection, performance, attrition, and detection bias. The "Risk of bias tool" in the publically available program RevMan 5.2 was used to report possible bias in included studies." The studies included in the analysis for maintenance were of acceptable to high methodological quality. **Heterogeneity:** Where applicable, studies were pooled using a random- effect model, regardless of statistical heterogeneity. Heterogeneity was tested using the x^2 test, the I^2 test, and visual inspec- tion of forest plots. If heterogeneity was present, we attempted to investigate the cause thereof (such as methodological factors or the outcome assessment). Given the limited number of included studies, subgroup analysis or meta-regression was not considered useful. In the case of high heterogeneity (I^2 > 75 %),

at least 4 weeks prior to enrollment. *Types of interventions*: Any drug therapy compared to either another drug therapy or placebo. All formulations (e. g. oral, suppository, enema) were accepted. The duration of treatment had to be at least 4 weeks in induction studies, and at least 3 months in maintenance studies. Studies were grouped based on the type of treatment (i. e. induction, maintenance) and based on drug class (e. g. 5-ASA, corticosteroids). Additionally, these groups were further subdivided by drug formulation (e. g. suppository, enema). Primary outcomes: Clinical remission for induction studies. Sustained clinical remission for maintenance studies. Secondary outcomes were endoscopic remission rates and histological remission rates. For maintenance studies, time to relapse was also considered a secondary outcome. **Exclusion Criteria:** Studies that were only published as abstracts, Uncontrolled, non-randomized or retrospective studies.	drug formulation (e. g. suppository, enema). **Comparison:** Another drug therapy or placebo.	using a random-effects model. *Topical 5-ASA, Different Doses* One trial (N = 76) compared OD 500 mg 5-ASA suppositories with BID 500 mg suppositories. The maintained clinical remission rates were 72.5 % and 91.7 %, respectively, a statistically significant difference in favor of the higher 5-ASA dose (P = 0.03). *Oral SASP and Olsalazine* One study (N = 69) compared a daily dose of 1000 mg oral SASP with 2000 mg oral olsalazine. In this study, remission was maintained in 69.0 % and 58.1 % for the SASP and olsalazine groups, respectively, although this difference was not statistically significant. **Author's Conclusion:** The role of topical 5-ASA as first line treatment for UP has been confirmed in this review, both for induction and maintenance of remission. Additionally, there is limited evidence available for the superiority of topical 5-ASA compared with oral 5-ASA in UP. As such, this review will not change the first line treatment for patients with UP. Because of the paucity of studies examining other drugs than 5-ASA, this review cannot draw any conclusions on which drug is the most optimal second line therapy in UP. Similarly, this review cannot reliably assess the efficacy of corticosteroids, thiopurines, or anti-TNFa therapy in patients with UP.		studies were pooled only if the direction of their results was consistent. **Publication Bias:** No funnel plots or tests were applied, only the assessment of reporting bias using the Cochrane handbook for systematic review. "The risk of reporting bias was considered low because no studies reported post-hoc analyses." **Notes:** No investigation of publication bias. High heterogeneity despite random effects models. These are likely caused by differences in medication study length and small size of the individual studies.

AG 3: Welche Endpunkte sind als Therapieziel bei der Erhaltungstherapie von CU-Patienten geeignet.

Bewertungsvorlage:
Oxford SR

Shah, S. C. et al. Mucosal Healing Is Associated With Improved Long-term Outcomes of Patients With Ulcerative Colitis: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 14. 1245 – 1255.e8. 2016

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** Systematic review (13 studies observational and interventional) **Databases:** PubMed, Cochrane Library CENTRAL, Embase. **Search period:** inception – 05.05.2015. **Inclusion Criteria:** (1) observational (prospective or post hoc analysis of prospectively obtained cohort) or interventional design (randomized or non- randomized); (2) established diagnosis of UC by accepted criteria not in clinical or endoscopic remission at study outset; (3) no prior colectomy; (4) clear definition of MH; (5) at least 1 endoscopic assessment after initiation of UC therapy performed between 1 and 6 months from study outset to assess for MH (defined as MH1); (6) follow-up clinical and/or endoscopic data available ≥ 52 weeks from study outset. **Exclusion Criteria:** Analyses were excluded because of high risk of publication bias. Studies with exclusively pediatric patients (≤ 15 years), a diagnosis of Crohn's disease, indeterminate colitis, or an unclear diagnosis of UC were also excluded.	**Intervention:** *Population*: 2073 UC patient with active UC. Intervention: no intervention other than continuation of current prescribed. **Comparison:** no comparison.	**Primary:** Long term clinical remission (CR): defined as CR at ≥ 52 weeks and at least 6 months after endoscopic assessment for MH1. **Secondary:** Long-term colectomy-free rate, MH rate, and CS-free CR rate at ≥ 52 weeks and at least 6 months after MH1 assessment. **Results:** We analyzed 13 studies comprising 2073 patients with active UC. Patients with MH1 had pooled odds ratio of 4.50 for achieving long-term (after at least 52 weeks) clinical remission (95 %CI, 2.12 – 9.52), 4.15 for remaining free of colectomy (95 % CI, 2.53 – 6.81), 8.40 for achieving long-term MH (95 % CI, 3.13 – 22.53), and 9.70 for achieving long-term corticosteroid-free clinical remission (95 % CI, 0.94 – 99.67), compared with patients without MH1. We found no difference in outcomes if patients achieved MH1 while receiving biologic versus non-biologic therapy. **Author's Conclusion:** Targeting MH may be associated with better long-term outcomes compared with targeting patient-reported outcomes alone and has been shown to be a predictor of improved disease course and long-term prognosis, consistent with the results presented in this meta-analysis of more than 2000 active UC patients. On the basis of our findings and in the absence of published prospective RCTs, it seems reasonable that achieving MH should be the goal of UC treatment, and interval endoscopic assessment should be performed after initiating new therapies to evaluate response and gui-	Paoluzi OA, (2002) Aliment Pharmacol Ther Arias MT, (2015) Clin Gastroenterol Hepatol Armuzzi A, (2013) Inflamm Bowel Dis Froslie KF, (2007) Gastroenterology Gustavsson A, (2010) Aliment Pharmacol Ther Kato K, (2014) Aliment Pharmacol Ther Tursi A, (2014) Ann Gastroenterol Cabriada JL, (2010) Dig Liver Dis Dai C, (2014) PLoS One Parente F, (2010) Am J Gastroenterol Yamamoto T, (2010) Inflamm Bowel Dis Colombel JF, (2011) Gastroenterology Tursi A, (2014) Eur J Intern Med	**Funding Sources:** n.a. **COI:** The authors disclose no conflicts. **Study Quality:** Quality assessment was performed independently by two investigators by using the Newcastle– Ottawa Scale (NOS) for nonrandomized studies and the Cochrane Risk of Bias tool for RCTs, with discrepancies resolved by consensus. For the NOS, studies scoring ≥ 7 (of 9) were considered high quality, consistent with other meta-analyses. All nonrandomized studies were high quality, and the 2 RCTs had low risk of bias. **Heterogeneity:** There was significant heterogeneity among the studies for the outcomes long-term CR (chi^2, P< 0.00 001, I^2 = 85 %), MH rate (chi^2, P< 0.00 001, I^2 = 85 %), and CS-free CR (chi^2, P< 0.0001, I^2 = 91 %), but not colectomy-free rate (chi^2, P = 0.4, I^2 = 3 %). **Publication Bias:** "A funnel plot generated for the primary outcome suggested no publication bias, as did Egger test (t value = 1.53, P = 0.158). However, publication bias may still exist because of the number of studies excluded as a result of lack of access to additional data." **Notes:** Large amount of heterogeneity, due to differences in study design, population, lenght, medication (prior/concomitant) and time of assessment of Mucosal healing.

		de further therapeutic management. Whether this treat-to-target strategy alters the natural disease course of UC, including prevention of dysplasia and colorectal carcinoma, or whether such a strategy is favorable from a risk versus benefit and cost- effectiveness standpoint re- mains to be evaluated with well-designed prospective, clinical trials.		

Alrubaiy, L. et al. Systematic review of health-related quality of life measures for inflammatory bowel disease. J Crohns Colitis. 9. 284 – 292. 2015

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Systematic Review. **Databases:** MEDLINE, EMBASE, and PsychoINFO. **Search period:** Inception – 01.10.2013 **Inclusion Criteria:** English articles describing the development and/or the evaluation of one or more measurement properties [e. g. internal consistency, reliability, validity, responsiveness] of the HRQoL measures specific for patients with IBD. Articles were included if they sought to assess at least one domain of quality of life in IBD. **Exclusion Criteria:** n.a.	**Intervention:** *Population:* Patients with IBD *Interventions*: Different HRQoL scores specific to IBD: IBDQ; SIBDQ; IBDQ-9; RFIPC; EIBDQ; IBD disability score, IBD disability index, SICC- IBD; CPWDQ; CD burden. **Comparison:** no direct comparison.	**Primary:** *Identification of disease-specific HRQoL measures IBD*: For each questionnaire we identified the dimensions of HRQoL that were assessed [e. g. social, work, disease burden, etc.]. *Measurement properties:* we assessed the measurement properties of each HRQoL measure using the quality properties checklist proposed by Terwee et al, which were: [1] reliability [including internal consistency, reliability, and measurement error]; [2] validity (including content validity, structural validity and hypothesis testing [construct validity]); and [3] responsiveness. *Methodology qualities of the HRQoL measures* The methodological quality of the original development studies for the included HRQoL measures using the COSMIN [COnsensus-based Standards for the selection of health Measurement Instruments] checklist.23.24 The COSMIN checklist assesses the methodology quality of the internal consistency, reliability, measurement error, responsiveness, content validity, construct validity, and factor analysis. Each measurement property methodology was assessed against certain quality standards and rated on a 4-point scale [1 = poor, 2 = fair, 3 = good, or 4 = excellent]. The overall score for the methodological	Guyatt G, (1989) Gastroenterology Irvine EJ (1999) J Pediatr Gastroenterol Nutr Irvine EJ, (1996) Am J Gastroenterol Alcala MJ, (2004) Inflamm Bowel Dis Drossman DA, (1991) Psychosom Med Davey Smith G, (2002) Int J Nurs Stud Allen PB, (2013) Aliment Pharmacol Ther Peyrin-Biroulet L, (2012) Gut Smith JJ, (2012) Colorectal Dis Vergara M, (2011) Inflamm Bowel Dis Wilcox AR, (2010) Inflamm Bowel Dis	**Funding Sources:** This work was supported by the Welsh Clinical Academic training [WCAT] scheme and is a collaboration between Swansea University, Wales Deanery and the Welsh Government. **COI:** None. **Study Quality:** n.a. **Heterogeneity:** n.a. **Publication Bias:** n.a. **Notes:** This articles identifies and compares HRQoL questionnaires specific to IBD regarding criteria such as validity, consistency. Since these tests are applicable to all forms of IBD (with the exception of 2 CD tests), as well as activity stages, the investigated population is not homogeneous. This might affect several of the outcomes. Many methods of SR in the evidence table do not apply to this type of articles (heterogeneity, publication bias), study quality of the primary cohort studies could have been assessed. Case-control studies were included therfor 3a rating.

		quality of a certain property is determined by taking the lowest rating. *Level of credibility of the HRQoL measures* Levels of the HRQoL measure establishment or use in literature: Cohen's criteria were used to determine the level of establishment of each specific HRQoL measure. **Secondary:** n.a. **Results:** *Identification of disease-specific HRQoL measures IBD*: 10 IBD-specific HRQoL measures that covered different aspects of patients' lives were identified. *Measurement properties:* Internal consistency, construct validity, and content validity were the commonly evaluated measurement properties. Seven HRQoL measures scored positive for at least four of eight measurement properties. The majority of studies were rated as 'fair' to 'poor' when assessing their methodology quality. *Level of credibility of the HRQoL measures* The most established HRQoL measure in the literature was the Inflammatory Bowel Disease Questionnaire [IBDQ]. **Author's Conclusion:** To our knowledge, this is the first systematic review of HRQoL measures in IBD that systematically appraised the measurement properties and the methodological quality of the HRQoL measures using a robust and standardized approach. This facilitates good comparison between the HRQoL measures on the quality of their measurement properties. This review will better guide the use of HRQoL in various clinical and research settings. It will also help clinicians, researchers, and the general public to better assess the scientific literature on HRQoL in IBD. Several new HRQoL measures are emerging, and our study showed that most of the HRQoL are supported by evidence of at least one type of reliability or validity		

		and further validation studies might support their use. The choice of HRQoL measure in future will depend on the context for which it will be used [for example, social, disease burden, disability, etc.]. Until then, the IBDQ has the strongest published evidence of reliability and validity and it is well established in the literature.		

Mosli, M.H. et al. Histologic evaluation of ulcerative colitis: a systematic review of disease activity indices. Inflamm Bowel Dis. 20. 564 – 575. 2014

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Systematic review (88 clinical studies and 21 reviews) **Databases:** MEDLINE, EMBASE, PubMed, the Cochrane Library (CENTRAL), and DDW **Search period:** Inception – 02.2013 **Inclusion Criteria:** All studies that used histological indices of disease activity in patients with UC; randomized and/or controlled trials, case-controlled studies, and cohort studies were included. **Exclusion Criteria:** Case reports, editorials, clinical guidelines, commentary, letters to the editor, meeting reports.	**Intervention:** *Population:* UC patients *Intervention:* Different histological scoring indices in UC: Truelove and Richards, Matts Score, Watts Score, Keren Score, Friedman Index, Gomes Score, Saverymuttu Index, Floren Index, Hanauer Index, Odze Index, Sandborn Index, Scheppach/ D'Argenio Score, Harpaz Index, Initial Riley Score, Riley Score, Modified Riley Score, Geboes Score, Chicago Score. **Comparison:** n.a.	**Primary:** Extent of use, Level of validation. **Secondary: Results:** After systematically applying inclusion criteria, we identified 108 scientific articles including 88 clinical studies and 21 related clinical reviews. Eighteen indices of histological activity in UC were identified and reviewed. **Author's Conclusion:** In summary, histopathology is an important component of UC assessment both in clinical practice and for clinical trials, with potential long-term implications for predicting remission rates, future surgery, and malignancy risk. Currently, the use of a partially validated score such as the Geboes score or the MRS seems optimal for clinical research purposes, but requires further validation. Ideally, improvements to current indices or development of new indices will lead to standardized methods of histological assessment that can be employed in both clinical practice and in clinical trials.	Truelove SC, (1956) Br Med J Riley SA, (2000) Gut Matts SG, (1961) Q J Med Watts JM, (1966) Gut Keren DF, (1984) Hum Pathol Friedman L, (1985) Gastroenterology Gomes P, (1986) Gut Saverymuttu SH, (1986) Gastroenterology Floren CH, (1987) Scand J Gastroenterol Hanauer S, (1993) Am J Gastroenterol Odze R, (1993) Am J Surg Pathol Sandborn WJ, (1993) Am J Gastroenterol Scheppach W, (1992) Gastroenterology D'Argenio G, (2001) Dig Dis Sci Fiel M, (2003) Mod Pathol Riley SA, (1988) Gastroenterology Feagan BG, (2005) N Engl J Med Rubin DTHD, (2007) Gastroenterology	**Funding Sources:** n.a. **COI:** Disclosures: M.H. Mosli has no financial disclosures. B.G. Feagan has received grant/ research support from Millennium Pharmaceuticals, Merck, Tillotts Pharma AG, Abbott Labs, Novartis Pharmaceuticals, Centocor Inc., Elan/Biogen, UCB Pharma, Bristol-Myers Squibb, Genentech, ActoGenix, Wyeth Pharmaceuticals Inc.; Consulting fees from Millennium Pharmaceuticals, Merck, Centocor Inc., Elan/Biogen, Janssen- Ortho, Teva Pharmaceuticals, Bristol-Myers Squibb, Celgene, UCB Pharma, Abbott Labs, Astra Zeneca, Serono, Genentech, Tillotts Pharma AG, Unity Pharmaceuticals, Albireo Pharma, Given Imaging Inc., Salix Pharmaceuticals, Novonordisk, GSK, Actoge- nix, Prometheus Therapeutics and Diagnostics, Athersys, Axcan, Gilead, Pfizer, Shire, Wyeth, Zealand Pharma, Zyngenia, GiCare Pharma Inc. Sigmoid Pharma; Speakers Bureau for UCB, Abbott, J&J/Janssen. W.J. Sandborn has received consulting fees from Abbott, ActoGeniX NV, AGI Therapeutics Inc, Alba Therapeutics Corp, Albireo, Alfa Wasserman, Amgen, AM-Pharma BV, Anaphore, Astellas, Athersys Inc, Atlantic Healthcare Ltd, Apta- lis, BioBalance Corp, Boehringer-Ingelheim, Bristol-Myers Squibb, Celgene, Celek Pharmaceuticals, Cellerix SL, Cerimon Pharmaceuticals, ChemoCentryx, CoMentis, Cosmo Technolo- gies, Coronado Biosciences, Cytokine Pharmasciences, Eagle Pharmaceuticals, EnGene Inc, Eli Lilly, Enteromedics, Exagen Diagnostics Inc, Ferring Pharmaceuticals, Flexio Therapeutics Inc, Funxional The-

				rapeutics Ltd, Genzyme Corp, Gilead Scien- ces, Given Imaging, GSK, Human Genome Sciences, Ironwood Pharmaceuticals, Kalo-Bios Pharmaceuticals, Lexicon Pharma- ceuticals, Lycera Corp, Meda Pharmaceuticals, Merck Research Laboratories, Merck Serono, Millenium Pharmaceu-ticals, Nisshin Kyorin Pharma-ceuticals, Novo Nordisk, NPS Pharmaceuticals, Optimer Phar-maceuticals, Orexigen Therapeu-tics Inc, PDL Bio- pharma, Pfizer, Procter and Gamble, Prome-theus Laboratories, ProtAb Ltd, Purgenesis Technologies Inc, Re-lypsa Inc, Roche, Salient Pharma-ceuticals, Salix Pharmaceuticals, Santarus, Scher- ing Plough, Shire Pharmaceuticals, Sigmoid Pharma Ltd, Sirtris Pharmaceu-ticals, SLA Pharma UK Ltd, Tar-gacept, Teva Pharma- ceuticals, Therakos, Tillotts Pharma AG, TxCell SA, UCB Phar- ma, Viamet Pharmaceuticals, Vascular Biogen-ics Ltd, Warner Chilcott UK Ltd and Wyeth; research grants from Abbott, Bristol- Myers Squibb, Genentech, GSK, Janssen, Milen-nium Pharmaceuticals, Novartis, Pfizer, Procter and Gamble, Shire Pharmaceuticals and UCB Phar-ma; payments for lectures/spe-ak- ers bureaux from Abbott, Bristol-Myers Squibb and Jans-sen; and holds stock/stock opti-ons in Enteromedics. G. D'Haens has received grant/research sup-port from Merck, Abbott Labs, Cen- tocor Inc., Given Imaging, UCB Pharma, ActoGenix, Consul-ting fees from Boehringer- Ingel-heim, Cosmo Technologies, EnGene Inc, Ferring Pharmaceu-ticals, Millennium Pharmaceuti-cals, Merck, Centocor Inc., Elan/ Biogen, Janssen- Ortho, Teva Pharma- ceuticals, UCB Pharma, Abbott Labs, Astra Zeneca, Shire, Tillotts Pharma AG, Novonordisk, GSK, Actogenix, Pfizer, Sigmoid Pharma. C. Behling has received consulting fees from Robarts Clinical Trials. K. Kaplan has no disclosures. D. Driman has no disclosures. L. Shackelton has no disclosures. K.A. Baker had no disclosures. J.K. MacDonald has no disclosures. M.K. Vandervoort has no disclosures. K. Geboes has no disclosures. B.G. Levesque has received consulting fees from Santarus Inc. and Prometheus labs, Speakers bureau for Warner

				Chilcott, Salix, and UCB Pharma, and research grant support from Robarts Clinical Trials. **Study Quality:** n.a. **Heterogeneity:** n.a. **Publication Bias:** n.a. **Notes:** No quality assessment of primary studies. Unclear status regarding severity or disease activity or location.

AG 4: Welche therapeutischen Verfahren sind effektiv bei Vorliegen einer Infektion?

Bewertungsvorlage:
Oxford SR

Khan, K.J. et al. Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis. Am J Gastroenterol. 106. 661 – 673. 2011

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Systematic Review + Meta Analysis with 10 RCTs **Databases:** Medline, EMBASE, Cochrane Central Register **Search period:** 1966 – 2010 **Inclusion Criteria:** Randomized controlled trials. Adults (> 90 %of patients aged > 16 years) with Crohn ' s disease (CD) or ulcerative colitis (UC). Compared antibiotic therapy with placebo or no therapy. Other inflammatory bowel disease therapy allowed provided this was the same in both arms of the trial. Minimum duration of therapy of 7 days in trials reporting induction of remission of active CD and UC with maximum time point to assess remission of 17 weeks. Did not specifi cally evaluate post-operative CD patients. Minimum follow-up of 6 months in trials reporting prevention of relapse of quiescent CD and UC. Assessment of failure of remission in active CD/UC, or relapse of disease activity in quiescent CD/UC, at last time point of assessment in the trial according to a predefi ned hierarchy. **Exclusion Criteria:** –	**Intervention:** Antimycobacterial drugs, traditional broad-spectrum antibiotics, antimycobacterial and antibiotics in combination. The minimum duration of therapy that was eligible was 10 days. 702 patients **Comparison:** Either placebo or no intervention 458 patients	**Primary:** Outcome of interest: failure of remission in active luminal Crohn's disease (CD) or active ulcerative colitis (UC), relapse of disease activity in quiescent luminal CD or UC. Hierarchy of reporting of outcomes used: Luminal CD remission: Crohn's disease activity index (CDAI) < 150 (or other validated index), endoscopic evidence of complete remission (most stringent definition available, e. g., complete mucosal healing), clinical assessment of complete remission, other author-defined criteria for remission. Luminal CD relapse: CDAI ≥ 150, endoscopic / radiological evidence of relapse (most stringent definition available), other CDAI cutoff, clinical assessment as relapsed, other author-defined criteria for relapse. UC remission: endoscopic evidence of complete remission (most stringent definition available, e. g., complete mucosal healing), clinical assessment as complete remission, recognized scoring system of complete remission (e. g., Truelove and Witt), other author-defi ned criteria for remission. UC relapse: endoscopic evidence of relapse, clinical assessment of symptomatic relapse, recognized scoring system defining relapse,	Afdhal NH, (1991) Dig Dis Sci Arnold GL, (2002) Inflamm Bowel Dis Burke DA, (1990) Aliment Pharmacol Ther Dickinson RJ, (1985) Gut Gionchetti P, (1999) Dig Dis Sci Graham DY, (1995) Gastroenterology Leiper K, (2008) Aliment Pharmacol Ther Maeda Y, (2010) Br J Surg Mantzaris GJ, (1994) Am J Gastroenterol Mantzaris GJ, (2001) Scand J Gastroenterol Ohkusa T, (2005) Scand J Gastroenterol Ohkusa T, (2010) Am J Gastroenterol Prantera C, (1994) Am J Gastroenterol Prantera C, (2006) Aliment Pharmacol Ther Prantera C, (2010) Gut Selby W, (2007) Gastroenterology Steinhart AH, (2002) Gastroenterology Sutherland L, (1991) Gut Thia KT, (2009) Inflamm Bowel Dis West RL, (2004) Aliment Pharmacol Ther	**Funding Sources:** American College of Gastroenterology **COI:** Paul Moayyedi chairperson at McMaster University partly funded by an unrestricted donation by AstraZeneca, and has received consultant' s and speaker' s bureau fees from AstraZeneca, AxCan Pharma, Nycomed, and Johnson and Johnson. The remaining authors declare no confl ict of interest **Study Quality:** Antibiotics for induction of remission of CD: only one low risk of bias trial. Antibiotics for induction of remission of UC: only one low risk of bias trial. It is therefore possible that the trend to overall benefit seen with antibiotics for UC and CD is an artifact due to bias. **Heterogeneity: Antibiotics for induction of remission of CD:** There was moderate heterogeneity between results ($I^2 = 44\,\%$). No statistically significant funnel plot asymmetry. **Antibiotics for induction of remission of UC:** There was moderate heterogeneity between results ($I^2 = 69\,\%$). Statistically significant funnel plot asymmetry, suggesting publication bias or other small study effects. **Antibiotics for maintenance of remission in quiescent UC and CD:** no significant heterogeneity between results ($I^2 = 0\,\%$) **Publication Bias:** Th e main limitation of the review is that there were only four trials with low risk of bias

		other author-defined criteria for relapse. Time of outcome assessment: last time point of assessment in the trial. Denominator used: true intention-to-treat analysis, if not available then all evaluable patients **Secondary:** – **Results:** Antibiotics for induction of remission of CD: We identified 10 RCTs involving 1160 patients that evaluated the efficacy of antibiotic therapy at inducing remission in CD. Patients tended to have moderate CD. There was a statistically significant effect of antibiotics to induce remission in active CD compared with placebo (RR of active CD not in remission = 0.85; 95 % CI = 0.73 – 0.99, P = 0.03). A diverse number of antibiotics were tested either alone or in combination. Difficult to evaluate whether any particular antibiotic was effective in active CD. Analysis of specific classes, alone or in combination: Fluoroquinolone: 2 Trials, n = 218, no statistically significant effect (RR = 0.86; 95 % CI = 0.55 – 1.35. Heterogeneity: I 2 = 83 %. Macrolides: 3 Trials, n = 269, no statistically significant effect (RR = 0.76; 95 % CI = 0.42 – 1.36). Heterogeneity: I 2 = 79 %. Metronidazole: no statistically significant effect (RR = 0.99; 95 % CI = 0.83 – 1.18). Heterogeneity: I 2 = 0 %. Rifamycin: 4 trials, n = 738, statistically significant effect (RR = 0.78; 95 % CI = 0.67 – 0.91). Heterogeneity: I 2 = 0 %. Clofazamine: 3 trials, n = 303, statistically significant effect (RR = 0.70; 95 % CI = 0.53 – 0.94). Heterogeneity: I 2 = 0 %. Ethambutol: 1 trial, n = 40, no statistically significant effect (RR = 2.45; 95 % CI = 0.28 – 21.62). Antibiotics for induction of remission of UC: 9 trials involving 662 patients with		**Notes:** Cave: nur 4 Studien mir niedrigem RoB. Die Schlussfolgerungen der Autoren sind sehr positiv in Anbetracht der meist geringen Patientenzahlen in Kombination mit sehr moderater Studienqualität pro Antibiotika-Klasse.

		active UC that gave remission as an outcome. Patients with moderately active UC. Overall, there was a statistically significant effect in favor of antibiotics (RR of active UC not in remission = 0.64; 95 % CI = 0.43 – 0.96, P = 0.03). The NNT was 7 (95 % CI = 4 – 25). Antibiotics for maintenance of remission in quiescent UC and CD: 3 RCTs treating 186 patients with quiescent CD. Statistically significant effect of antibiotics in preventing CD relapse compared with placebo (RR of relapse = 0.62; 95 % CI = 0.46 – 0.84). NNT was 4 (95 % CI = 3 – 10). Perianal fistulae in CD: 3 RCTs, n = 131, ciprofloxacin or metronidazole, statistically significant effect (RR = 0.80; 95 % CI = 0.66 – 0.98). Heterogeneity: I^2 = 0 %. **Author's Conclusion:** Our data suggest antibiotic therapy may induce remission in active UC and CD, as well as prevent relapse in patients with quiescent CD. This supports a number of studies that suggest a bacterial origin for IBD. The strongest effect was seen in preventing relapse of CD with an NNT of 4 (95 % CI = 3 – 10) and all antibiotic combinations studied had some antimycobacterial properties. [...] However, the antibiotic combinations were diverse and this is only based on three trials so there is currently insufficient data to recommend antibiotic therapy to a variety of single antibiotics and antibiotic combinations were evaluated, so it is not possible to recommend a specific antibiotic therapy for IBD. The exception to this is the use of either ciprofl oxacin or metronidazole for treating CD perianal fistulas.		

Nguyen, D.L. et al. Effect of Immunosuppressive Therapies for the Treatment of Inflammatory Bowel Disease on Response to Routine Vaccinations: A Meta-Analysis. Dig Dis Sci. 60. 2446 – 2453. 2015

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Systematic Review and Meta Analysis of 9 prospective case series **Databases:** MEDLINE/ PubMed, Cochranedatabases, CINAHL, Scopus, Google Scholar, **Search period:** – November 2014 **Inclusion Criteria:** Studies on adult IBD patients that evaluated immune response to various vaccinations while on immunosuppressive therapy compared to healthy controls or IBD patients not on immunosuppressive therapies **Exclusion Criteria:** –	**Intervention:** IBD patients with immune response to various vaccinations while on immunosuppressive therapy. N = 945 patients. **Comparison:** Healthy controls or IBD patients not on immunosuppressive therapies, n = 529.	**Primary:** Effect of immunosuppressive therapy for the treatment of IBD on response to routine vaccinations **Secondary: –** **Results:** Overall Rate of Vaccine Response: a 60 % lower chance of achieving adequate seroprotection in the group that received immunosuppressive therapies compared to the group that was not on immunosuppressive therapies (OR 0.41 95 % CI 0.30, 0.55, p < 0.001). Vaccine Response to Anti-TNF Monotherapy: 7 studies (N = 728). Nearly a 70 % lower chance of achieving adequate immune response in the group on anti-TNF monotherapy compared to the group receiving no immunosuppressive therapy (OR 0.32 95 % CI 0.21, 0.49, p < 0.001). Vaccine Response to Immunomodulator Monotherapy: 6 studies (N = 890). Nearly 40 % lower chance of achieving adequate response to vaccinations among patients on immunomodulatory monotherapy compared to patients not on mmunosuppressive therapy (OR 0.63 95 % CI 0.42, 0.95, p = 0.03). Rate of Vaccine Response to ≥ 2 Immunosuppressants: 7 studies (N = 654). A 65 % lower chance of achieving adequate response to vaccinations among patients on ≥ 2 immunosuppressive therapies compared to patients not on immunosuppressive therapy (OR0.35 95 % CI 0.23, 0.54). Patients on immunomodulator monotherapy had a twofold higher probability of achieving adequate immune response to vaccination, compared to patients on anti-TNF monotherapy (OR 1.92 95 % CI 1.30, 2.84).	Altunoz ME, (2012) Dig Dis Sci Andrisani G, (2013) J Crohns Colitis Cossio-Gil Y, (2014) J Gastroenterol Hepatol Cullen G, (2012) Gut Gisbert JP, (2012) Am J Gastroenterol Lee CK, (2014) J Crohns Colitis Park SH, (2014) Inflamm Bowel Dis	**Funding Sources:** – **COI:** none **Study Quality:** prospective case series Heterogeneity: no statistically significant heterogeneity **Publication Bias:** – **Notes:** –

		Author's Conclusion: In conclusion, IBD patients on immunosuppressive therapy have a significantly lower response to routine vaccinations. The greatest effect is seen among patients on anti-TNF and combination immunosuppressive therapy. Routine monitoring of vaccine titers post-vaccination is important to ensure that adequate immunologic response has been achieved among IBD patients.		

Shukla, T. et al. Antiviral Therapy in Steroid-refractory Ulcerative Colitis with Cytomegalovirus: Systematic Review and Meta- analysis. Inflamm Bowel Dis. 21. 2718 – 2725. 2015

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Systematic Review and Meta Analysis of Fifteen observational studies **Databases:** PubMed (Medline), EMBASE, Web of Science, Cochrane Library, Google Scholar **Search period:** January 1, 1948 – July 31, 2014 **Inclusion Criteria:** Cohort, case– control, and case series studies with a minimum of 5 patients. (1) patients with UC; (2) serum or tissue diagnosis of CMV; (3) reported use of antiviral therapy; (4) stratified colectomy rates by antiviral treatment exposure (exposed and unexposed) **Exclusion Criteria:** (1) patient follow-up was less than 3 months after the diagnosis of CMV; (2) colectomy rates were not stratified by antiviral treatment exposure; (3) the diagnosis of CMV was made exclusively from colectomy specimens; (4) studies that included patients with CD.	**Intervention:** Antiviral Therapy, n = 144 patients **Comparison:** Without antiviral therapy, n = 189 patients	**Primary:** Risk of colectomy compared for CMV-positive patients treated with and without antiviral therapy, for the overall UC population and in a subset of patients refractory to CS. **Secondary:** – **Results:** , n = 333. 43.2 % (n = 144) treated with antiviral agents, 56.8 % (n = 189) not treated. Risk of Colectomy in All Patients with UC with CMV: 15 studies. No difference in the risk of colectomy between patients treated with antiviral therapy and those without treatment (OR, 0.92; 95 % CI, 0.31 – 2.76). Subgroup analysis: no significant difference in the risk of colectomy based on the method of CMV diagnosis or geographical location. Risk of Colectomy in Patients with CS-Refractory UC with CMV: 8 studies (n = 77 antiviral therapy, n = 62 not). Definition of CS- refractory disease varied. On meta-analysis, the risk of colectomy was significantly lower in patients with CS-refractory UC treated with antiviral therapy than in patients not treated with antiviral therapy (OR, 0.20; 95 % CI, 0.08 – 0.49). Subgroup analysis: method of diagnosis of CMV.The risk of colectomy was lower only in patients in whom CMV was diagnosed based on	Criscuoli V, (2011) World J Gastroenterol Domenech E, (2008) Inflamm Bowel Dis Jones A, (2014) Clin Gastroenterol Hepatol Kambham N, (2004) Am J Surg Pathol Kim YS, (2012) J Clin Gastroenterol Kopylov U, (2013) World J Gastrointest Pathophysiol Maruyama Y, (2012) Gastroenterology Matsuoka K, (2007) Am J Gastroenterol Minami M, (2007) World J Gastroenterol Omiya M, (2010) Intern Med Park SH, (2013) Dig Dis Sci Roblin X, (2011) Am J Gastroenterol Wada Y, (2003) Dis Colon Rectum Yoshino T, (2007) Inflamm Bowel Dis Zeki SS, (2010) Gastroenterology	**Funding Sources:** – **COI:** – **Study Quality:** The quality of evidence supporting the use of antiviral therapy for decreasing the risk of colectomy in all patients with UC with CMV was graded as very low. **Heterogeneity:** Risk of Colectomy in All Patients with UC with CMV: Moderate heterogeneity in the overall analysis (I2 = 65 %) Risk of Colectomy in Patients with CS- Refractory UC with CMV: No heterogeneity (I2 = 0 %) **Publication Bias:** There was no evidence of publication bias based on visual examination for funnel plot asymmetry (data not shown) or on quantitative analysis (P = 0.35). **Notes:** –

		H&E and/or IHC but not based on tissue PCR. No significant differences in colectomy risk based on geographical location. **Author's Conclusion:** In summary, this study demonstrates that antiviral therapy is not required for all patients with UC with CMV disease but may be beneficial in a subgroup of patients who are refractory to CS. However, the quality of evidence supporting colectomy risk and antiviral therapy was low and therefore insufficient to change current clinical practice. Further prospective controlled trials will help to confirm these findings and to identify subgroups of patients who might benefit from antiviral therapy.		

Kopylov, U. et al. Antiviral therapy in cytomegalovirus-positive ulcerative colitis: a systematic review and meta-analysis. World J Gastroenterol. 20. 2695 – 2703. 2014

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Systematic Review and Meta Analysis of 9 comparative prospective and retrospective cohort studies **Databases:** Pubmed, Embase and World of Science. Manually scanned the abstracts presented at the following medical conferences: DDW, UEGW, ECCO for the years 2004 – 2012 **Search period:** January 1966 and March 2013 **Inclusion Criteria:** Prospective and retrospective cohort studies comparing outcomes of treated and untreated CMV- positive UC patients. For studies involving mixed cohorts (CD and UC), only the UC data were analyzed. **Exclusion Criteria:** (1) Studies including less than 4 patients in one or more of the arms; (2) Studies pertaining exclusively to CD patients; (3) Studies describing antiviral treatment with an antiviral agent other than gancyclovir, valgancyclovir or foscarnet; (4) Series	**Intervention:** Antiviral treated CMV- positive patients, 70 patients. **Comparison:** Untreated CMV-positive patients, 106 patients.	**Primary:** Rate of colectomy during the hospitalization period or within 30 d of diagnosis. **Secondary:** Secondary outcomes was colectomy rate for the available follow-up duration (3 mo since the index hospitalization). **Results:** 9 studies were included, 4 studies were prospective and 5 retrospective. n = 176 patients. Patients who had received antiviral treatment had a higher risk of requiring a subsequent colectomy (OR = 2.40; 95 %CI: 1.05 – 5.50;I2 = 37.2 %). No significant difference was found in the rate of colectomy during follow-up period (OR = 1.43; 95 %CI: 0.61 – 2.96;I2 = 36.4 %). Subgroup analysis: 1. CMV diagnosis was based on immunohistochemistry (IHC) same trend: (OR = 3.41; 95 %CI: 0. 39 – 29.83), 5 studies, Heterogeneity I2 = 56.9 %. 2. only the prospective studies (n = 4) or studies with moderate (n = 3) vs high risk of bias (n = 6)	Al-Zafiri R, (2012) Gastroenterol Hepatol (N Y) Kim YS, (2012) J Clin Gastroenterol Kopylov U, (2013) World J Gastrointest Pathophysiol Maconi G, (2011) Gastroenterology Maruyama Y, (2012) Gastroenterology Minami M, (2007) World J Gastroenterol Omiya M, (2010) Intern Med Roblin X, (2011) Am J Gastroenterol Zeki SS, (2010) Gastroenterology	**Funding Sources:** – **COI:** – **Study Quality:** Prospective and retrospective cohort studies. The overall quality of the studies was moderate-low; no study met the criteria for high quality. Adverse effects were not clearly reported in the majority of the included studies. **Heterogeneity:** The included studies were heterogeneous with regards to the severity of disease, as well as the clinical severity score employed **Publication Bias: –** **Notes: –**

exclusively reporting colectomy data, i. e. only patients who reached the outcome of colectomy, were included. Patients were excluded from the analysis if they underwent colectomy before gancyclovir treatment was considered or the results of CMV assessment were available.		showed the same trend, but without reaching statistical significance because of small group size and wide CI. 3. comparing studies conducted in Europe (n = 4) to those taken place in Asia (n = 3). Asia: No case of colectomy during hospitalization Europe: no difference between the two groups (OR = 19.85; 95 %CI: 1.94 – 203.61; and OR = 0.81; 95 %CI: 0.24 – 2.79 for studies taken in Asia and in Europe, respectively). **Author's Conclusion:** No positive association between antiviral treatment and a favorable outcome was demonstrated. These findings should be interpreted cautiously due to primary studies' quality and potential biases.		

Cascio, A. et al. Cytomegalovirus pneumonia in patients with inflammatory bowel disease: a systematic review. Int J Infect Dis. 16. e474 – e479. 2012

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Systematic Review of 12 case reports **Databases:** PubMed and SCOPUS **Search period: –** **Inclusion Criteria:** Reported detailed data on patients with IBD who presented with pneumonia due to CMV. CMV pneumonia was diagnosed in the presence of at least: (1) positive radiology or autopsy findings of pneumonia, and (2) pp65 antigenemia and/or CMV DNA in blood and/or positive anti-CMV IgM and IgG titers, and (3) absence of other cause of pneumonia. In the presence of another cause of pneumonia, the detection of CMV inclusion bodies/immunohistochemical stain/culture in biopsies/autopsy, or PCR on bronchoalveolar lavage(BAL) fluid was considered necessary. **Exclusion Criteria:** –	**Intervention:** IBD paitents with CMV pneumonia n = 13 patients **Comparison:** –	**Primary:** Risk factors treatment **Secondary:** – **Results:** Analysis: Female/male ratio of 5.5:1. Disease subtype: CD was the underlying disease in 77 % of the cases. Eleven (85 %) patients were on treatment with thiopurines (nine with azathioprine and two with 6- mercaptopurine) when they developed CMV pneumonia. The chest X-ray was initially negative in two patients. HLH was contextually present in six cases, probably triggered by the CMV infection. **Author's Conclusion:** CMV pneumonia should always be suspected in IBD patients who present with fever and tachypnea, especially if the latter is worsening and/or is associated with dyspnea. Treatment must be early and specific.	12	**Funding Sources:** – **COI:** – **Study Quality:** Case Reports **Heterogeneity:** – **Publication Bias:** – **Notes: –**

Anderson, J.L. et al. Systematic review: faecal microbiota transplantation in the management of inflammatory bowel disease. Aliment Pharmacol Ther. 36. 503 – 516. 2012

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 4 **Study type:** Systematic review (17 case series articles) **Databases:** MEDLINE; EMBASE; CENTRAL (The Cochrane Library); CINAHL; Web of Science; BIOSIS; SCOPUS; BIOMED CENTRAL; NHS Evidence + hand searching of journals: Gastroenterology; Gut; Journal of Crohn's and Colitis; Inflammatory Bowel Diseases. **Search period:** Inception – 10.2011 **Inclusion Criteria:** Patients with IBD of any age; intervention fecal microbiota transplantation, with or without comparator group; outcomes: any relevant outcome. Any RCT, non-randomised controlled trials, uncontrolled trials, case series or case reports of any study duration. English and foreign language reports included. **Exclusion Criteria:** Animal or in vitro studies.	**Intervention:** *Patients:* 41 patients, (27 CU patients). *Intervention:* Fecal microbiota transplantation (FMT). **Comparison:** Any comparator or none.	**Primary:** Management of IBD **Secondary:** Managment of C.difficile in IBD patients **Results:** There were nine case series/case reports of patients receiving FMT for management of their IBD, and eight where FMT was for the treatment of infectious diarrhoea in IBD. These 17 articles reported on 41 patients with IBD (27 UC, 12 Crohn's, 2 unclassified) with a follow-up period of between 2 weeks and 13 years. Where reported, FMT was administered via colonoscopy/enema (26/33) or via enteral tube (7/33). In patients treated for their IBD, the majority experienced a reduction of symptoms (19/25), cessation of IBD medications (13/17) and disease remission (15/24). There was resolution of C. difficile infection in all those treated for such (15/15). **Author's Conclusion:** Despite the relative paucity of information specifically in IBD, there is limited, weak evidence that FMT has the potential to be an effective and safe treatment for IBD, at least when standard treatments have failed or are unacceptable to the patient. Well-designed randomised, controlled trials are necessary to confirm the positive findings from case reports, to evaluate safety and to develop optimal protocols for the use of FMT in IBD, prior to this becoming a standard part of clinical therapy.	Aas J, (2003) Clin Infec Dis Grehan (2010) J Clin Gastroenterol Borody TJ, (2008) Gastroenterology Wettstein A, (2007) United European Gastroenterology Federation Borody TJ, (1989) Med J Australia Mellow M, (2010) Am J Gastroenterol Borody T, (2011) Am J Gastroenterol You D, (2011) Am J Gastroenterol Borody T, (2011) Am J Gastroenterol Borody T, (2001) Probiotics, Prebiotics and New Foods Conference, Universita Urbaniana, Rome Vermeire S, (2012) Gastroenterology Zainah H, (2012) Case Rep Infect Dis Borody TJ, (2003) J Clin Gastroenterol Bennet JD, (1989) Lancet Angelberger S, (2012) In ECCO Conference Abstracts Watson JB, (2012) Gastroenterology Neelakanta A, (2012) Gastroenterology	**Funding Sources:** The systematic review was internally funded. **COI:** KW has served as a speaker for DDW, DDF and Danone, and has received research funding from Crohn's and Colitis UK, British Dietetic Association, Healthcare Quality Improvement Partnership and Californian Dried Plum Board. KW is an employee of King's College London. **Study Quality:** n.a. **Heterogeneity:** n.a. **Publication Bias:** n.a. **Notes:** No assessment of study quality. Lack of primary literature presented in the article, despite thorough search. No separate results for UC patients. Variability and missing details in the protocol of FMT regarding preparation and administration. Very limited evidence available.

AG 4: Welche diagnostischen Verfahren sind effektiv zur Identifikation von Infektionen?

Bewertungsvorlage:
Oxford SR

Ford, A.C. et al. Opportunistic infections with anti-tumor necrosis factor-alpha therapy in inflammatory bowel disease: meta- analysis of randomized controlled trials. Am J Gastroenterol. 108. 1268 – 1276. 2013

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Systematic Review and Meta Analysis of 22 RCTs **Databases:** Medline, Cochrane, Embase **Search period:** – November 2012 **Inclusion Criteria:** Randomized controlled trials. Adults (> 90 %of patients aged > 16 years) with inflammatory bowel disease. Compared anti-TNF α therapies (adalimumab, certolizumab, golimumab, or infl iximab) with placebo. Minimum duration of therapy of 14 days. 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, Mycobacterium avium complex infection, herpes simplex infection, or other unspecifi ed opportunistic infections) during randomized double-blind treatment period reported in both arms of the trial. **Exclusion Criteria:** –	**Intervention:** n = 4135 anti-TNFα antibody treated patients with IBD. **Comparison:** n = 2919 patients with IBD assigned to Placebo.	**Primary:** Occurrence of any opportunistic infection with anti-TNFα, compared with placebo. (Mycobacterium tuberculosis, oral or esophageal candidiasis, varicella-zoster virus infection, herpes zoster infection, cytomegalovirus or Epstein–Barr virus infection, Nocardia infection, Pneumocytsis jirovecii infection, Histoplasma capsulatum infection, Mycobacterium avium complex infection, herpes simplex infection, or other unspecified opportunistic infections) **Secondary:** More serious opportunistic infections (excluding oral or esophageal candidiasis and herpes zoster infection), and deaths from opportunistic infection **Results:** n = 39 (0.9 %) with opportunistic infections compared with n = 9 (0.3 %)among the placebo patients. Among patients receiving active therapy these included eight cases of Mycobacterium tuberculosis, eight cases of herpes simplex infection, six cases of oral or esophageal candidiasis, six cases of herpes zoster infection, two cases of varicella-zoster virus infection, two cases of cytomegalovirus or Epstein–Barr virus infection, and one case of Nocardia infection. The RR of developing an opportunistic infection was significantly higher with anti-TNF α therapy (2.05; 95 % CI 1.10 – 3.85. The NNH with anti-TNF α therapy to cause one opportunistic infection was 500 (95 % CI 200 – 1567). Subgroup analyses not significant: CD compared to UC, duration of therapy etc.	Colombel JF (2007) Gastroenterology Colombel JF (2010) N Engl J Med Hanauer SB (2002) Lancet Lemann M (2006) Gastroenterology Present DH (1999) N Engl J Med 1999 Probert CJ (2003) Gut 2003 Regueiro M (2009) Gastroenterology Reinisch W (2011) Gut Rutgeerts P (1999) Gastroenterology Rutgeerts P (2005) N Engl J Med Sandborn W (2012) Am J Gastroenterol Sandborn WJ (2007) N Engl J Med Sandborn WJ (2007) Ann Intern Med Sandborn WJ (2007) Gut 2007 Sandborn WJ (2011) Clin Gastroenterol Hepatol Sandborn WJ (2012) Gastroenterology Sands BE (2004) N Engl J Med Schreiber S (2005) Gastroenterology Schreiber S (2007) N Engl J Med Panaccione R (2011) J Crohns Colitis Watanabe M (2012) J Crohns Colitis 2012	**Funding Sources:** None. **COI:** Alexander C. Ford has received speaker ' s fees from MSD. Laurent Peyrin- Biroulet has served as a consultant to Merck, Abbott, and UCB Pharma, and received speaker ' s fees from Merck and Abbott. **Study Quality:** no information given. **Heterogeneity:** No statistically signifi cant heterogeneity detected between studies **Publication Bias:** No evidence of funnel plot asymmetry **Notes:** no risk of bias table, i. e. no information about study quality

		The RR of tuberculosis infection was 2.52 (95 % CI 0.62 – 10.21). **Author's Conclusion:** 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.		

Shahidi, N. et al. Performance of interferon-gamma release assays in patients with inflammatory bowel disease: a systematic review and meta-analysis. Inflamm Bowel Dis. 18. 2034 – 2042. 2012

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Systematic Review and Meta Analysis of n = 9 studies **Databases:** Medline, Embase **Search period: –** June 2011 **Inclusion Criteria:** Studies that assess Interferon-gamma release assays (IGRAs)(QFT-2G, QFT-3G, TSPOT.TB) to detect latent tuberculosis infection (LTBI) in patients with IBD **Exclusion Criteria:** Studies that 1. were not written in English; 2. evaluated a noncommercial, in-house or older generation IGRA; 3. reported insufficient data on desired outcomes (e. g., no IGRA outcomes); 4. lacked appropriate study design (e. g., assessed TB diagnostic tests to decipher between TB and IBD); 5. had fewer than 10 IBD participants; 6. lacked IBD-specific outcomes; 7. were review articles or commentaries.	**Intervention:** n = 1309 IBD patients **Comparison: –**	**Primary:** Evaluating the performance of IGRAs (QuantiFERONTB Gold [QFT-2G], QuantiFERON-TB Gold In-Tube [QFT-3G] and T-SPOT.TB) in individuals with IBD **Secondary: –** **Results:** The pooled concordance between the TST and QFT-2G/QFT-3G was 85 % (95 %CI 77 %–90 %). The concordance of the TST and TSPOT.TB was 72 % (95 % CI 64 %–78 %). Studies assessing agreement reported more IGRA-/TST+ results versus IGRA+/TST- results. The pooled percentage of indeterminate results was 5 % (95 % CI 2 %–9 %) for QFT-2G/QFT-3G. TSPOT.TB showed similar results. Both positive QFT-2G/QFT-3G results (pooled odds ratio [OR] 0.37, 95 % CI 0.16 – 0.87) and positive TST results (pooled OR 0.28, 95 % CI 0.10 – 0.80) were significantly influenced by IST (both P = 0.02). **Author's Conclusion: -** While it remains difficult to determine superiority between the IGRAs and the Tuberculin skin test TST, both are negatively affected byimmunosuppressive therapy. Therefore, screening prior to initiation of IST should be considered. Nevertheless, it is imperative that all patients receive screening prior to anti-TNF therapy.	Arias M (2011) Gastroenterology Belard E (2011) Inflamm Bowel Dis Del Tedesco E (2010) Gastroenterology Greveson K (2010) Gastroenterology Guidi L (2010) Gastroenterology Ministro P (2011) Gastroenterology Papay P (2011) Inflamm Bowel Dis Qumseya BJ (2011) Inflamm Bowel Dis Schoepfer AM (2008) Am J Gastroenterol	**Funding Sources:** – **COI:** – **Study Quality: –** **Heterogeneity:** Agreement Between IGRA and TST: significant heterogeneity between studies (I^2 = 74.5 %, P = 0.0015) Proportion of Indeterminate Results: significant heterogeneity between studies (I^2 = 83.5 %, P < 0.0001) **Publication Bias:** – **Notes: –**

Luther, J. et al. Association between Helicobacter pylori infection and inflammatory bowel disease: a meta-analysis and systematic review of the literature. Inflamm Bowel Dis. 16. 1077 – 1084. 2010

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Systematic Review and Meta Analysis of 24 studies Databases: MEDLINE, EMBASE, Google Scholar, the Cochrane Central Register of Controlled Trials,→ACP Journal Club, DARE, CMR, HTA **Search period:** – March 2009 **Inclusion Criteria:** 1. H. pylori infection diagnosed by serology (IgG antibodyantibody), urea breath test (UBT), fecal antigen test (FAT), rapid urease test (RUT), or histology; 2. inclusion of a control group; 3. IBD and control groups were similar in age, sex, and from the same catchment area; 4. studies of human; 5. data were reported that were sufficient to calculate H. pylori infection rates in both the IBD and control groups. **Exclusion Criteria:** Using data from a previously published study	**Intervention:** H. pylori infection in IBD, n = 5903 patients **Comparison: -** Controls, n = 3001 patients.	**Primary:** Relative risk (RR) of H. pylori infection in IBD versus controls **Secondary:** – **Results:** 24 studies met the inclusion criteria (subjects N = 5903). 27.1 % of IBD patients had evidence of H. pylori infection, 40.9 % in the control groups. RR 0.64 (95 % CI: 0.54 – 0.75). Subgroup analyses: trend toward a greater effect for CD (RR: 0.60, 95 % CI: 0.49 – 0.72) compared to UC (RR: 0.75, 95 %CI: 0.62 – 0.90). Subgroup analyses to explain the observed heterogeneity. Data division based on the method of H. pylori diagnosis, method of IBD, study location, study population age. None explained the observed heterogeneity. After separation into CD and UC and re-analysis: statistically significant reduction in the RR of H. pylori infection in CD patients diagnosed with H. pylori by non-serologic methods (RR: 0.71, 95 % CI: 0.58 – 0.87; I2: 54 %). **Author's Conclusion:** These results suggest a protective benefit of H. pylori infection against the development of IBD. Heterogeneity among studies and the possibility of publication bias limit the certainty of this finding. Further studies investigating the effect of eradication of H. pylori on the development of IBD are warranted. Because environmental hygiene and intestinal microbiota may be strong confounders, further mechanistic studies in H. pylori mouse models are also necessary to further define the mechanism of this negative association.	Corrado G (1998) Scand J Gastroenterol D'Inca R (1998) Dig Dis Sci Duggan AE (1998) Gut el-Omar E (1994) Scand J Gastroenterol Feeney MA (2000) Eur J Gastroenterol Hepatol Furusu H (2002) Hepatogastroenterology Guslandi M (2002) Helpatogastroenterology Mantzaris GJ (1995) Am J Gastroenterol Meining A (1997) Scand J Gastroenterol et al. (50) Oberhuber G (1997) Gastroenterology Oliveira AG (2004) J Clin Microbiol Oliveira AG (2006) Helicobacter Parente F (1997) Scand J Gastroenterol Parente F (2000) Am J Gastroenterol Parlak E (2001) J Clin Gastroenterol Pascasio JM (2003) Pediatr Dev Pathol Pearce CB (2000) Eur J Gastroenterol Hepatol Piodi LP (2003) J Clin Gastroenterol Pronai Ö (2004), Helicobacter Sladek M (2007) Przegl Lek Triantafillidis JK (2003) Am J Gastroenterol Vare PO (2001) Scand J Gastroenterol Wagtmans MF (1997) Scand J Gastroenterol	**Funding Sources:** – **COI:** – **Study Quality:** prospective, retrospective studies, case series with control groups **Heterogeneity:** There was significant heterogeneity in the included studies (I2 ¼ 75.8 %). **Publication Bias:** A possible bias against small studies demonstrating high RR. **Notes:** –

Romkens, T.E. et al. Cytomegalovirus in inflammatory bowel disease: A systematic review. World J Gastroenterol. 22. 1321 – 1330. 2016

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** Systematic Review of 52 non- randomized studies **Databases:** ubMed, EMBASE, Cochrane central register **Search period: –** December 2014 **Inclusion Criteria:** All types of evidence, observational studies, case-control studies and retrospective studies **Exclusion Criteria:** Non-English literature, case reports, case series with n < 10 cases and review articles	**Intervention:** Cytomegalovirus (CMV)infection and intestinal disease in inflammatory bowel disease (IBD), diagnostics and prevalence of CMV in IBD. **Comparison:** –	**Primary:** (1) a list with all used definitions of CMV infection or CMV intestinal disease in IBD patients; (2) prevalence numbers to assess the effect that the applied definition has on the reported prevalence of CMV in IBD patients **Secondary:** (1) prevalence of CMV in subpopulations as ulcerative colitis (UC), Crohn's disease (CD), steroid refractory disease; (2) prevalence of CMV in different regions of the world. Results: 21 different definitions for CMV infection, 8 definitions for CMV intestinal disease and 3 definitions for CMV reactivation. Prevalence numbers depend on used definition, studied population and region. The highest prevalence for CMV infection was found when using positive serum PCR as a definition, whereas for CMV intestinal disease this applies to the use of tissue PCR > 10 copies/mg tissue. Most patients with CMV infection and intestinal disease had steroid refractory disease and came from East Asia. **Author's Conclusion:** We detected multiple different definitions used for CMV infection and intestinal disease in IBD patients, which has an effect on prevalence numbers and eventually on outcome in different trials.	52	**Funding Sources:** – **COI:** – **Study Quality:** None of the included studies was randomized and most of the study designs were single centre (n = 42/50) with more than half of them using a retrospective design (26/48). Some used blinding for the reviewing pathologist (6/43) or endoscopist (2/43). **Heterogeneity:** – **Publication Bias:** – **Notes:** –

Skamnelos, A. et al. CD4 count remission hypothesis in patients with inflammatory bowel disease and human immunodeficiency virus infection: a systematic review of the literature. Ann Gastroenterol. 28. 337 – 346. 2015

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Systematic Review of 13 case-control studies, case series and case reports **Databases:** PubMed **Search period:** – September 2013 **Inclusion Criteria:** 1. Studies irrespective of study design that recruited at least one	**Intervention:** Adolescents presenting with both IBD and HIV infection, n = 47 patients **Comparison:** –	**Primary:** CD4 count remission **Secondary:** – **Results:** 13 papers: 2 case-control studies, 2 case series, and 9 case reports. N = 47 patients with IBD and HIV infection (43 male; 27 with Crohn's disease, 19 with ulcerative colitis, and 1 with indeterminate colitis).	Bernstein CN (1991) Am J Gastroenterol Bernstein BB (1994) Am J Gastroenterol Bongiovanni M (2006) AIDS Christ AD (1996) Scand J Gastroenterol Dhar JM (1984) BMJ James S (1988) Gastroenterology Lautenbach E J (1997) Clin Gastroenterol	**Funding Sources:** – **COI:** – **Study Quality:** 2 case-control studies, 2 case series, and 9 case reports **Heterogeneity:** – **Publication Bias:** – **Notes:** –

group of adults or adolescents presenting with both IBD and HIV infection regardless of which diagnosis preceded. 2. Studies including patients with a simultaneous diagnosis of IBD and HIV infection 3. English language **Exclusion Criteria:** Studies in which IBD was reported as an HIV related opportunistic infection, and studies without primary data.		CD4 count-related IBD remission hypothesis: Remission was described for patients with IBD and HIV infection in 5 studies. Seven of the 9 case reports reported no remission for the patients while one case report provided no data on remission. Four of the five studies with cases presenting with remission referred to the CD4 count related IBD remission hypothesis. However, only two of them mentioned a CD4 count cut-off point in relation to CD4 count remission hypothesis. 7 of the 9 case reports argued against the CD4 count-related IBD remission hypothesis. They described an active IBD or IBD relapse even when patients were in severe immunosuppression. Four case reports described IBD as a new onset (event) in an HIV-infected patient. There is a paucity of data in the literature to support or reject the hypothesis that CD4 count depletion may induce remission of bowel inflammation in IBD patients. There is a trend supporting the CD4 hypothesis and most reports seem to suggest that IBD might be less aggressive in patients infected with HIV. **Author's Conclusion:** Current literature cannot support or reject the CD4 count remission hypothesis in IBD patients with HIV infection. Prospective studies using uniform criteria on IBD and HIV disease course and CD4 counts are needed.	Liebowitz D (1986) J Clin Gastroenterol Pospai D (1998) Dig Dis Sci Sharpstone D (1996) Eur J Gastroenterol Hepatol Sturgess I (1992) Gut 1992 Viazis N (2010) Inflamm Bowel Dis Yoshida E (1996) J Clin Gastroenterol	

AG 4: Welche Verfahren sind effektiv zur Prophylaxe von Infektionen?

Bewertungsvorlage:
Oxford SR

Conway, R. et al. Methotrexate use and risk of lung disease in psoriasis, psoriatic arthritis, and inflammatory bowel disease: systematic literature review and meta-analysis of randomised controlled trials. Bmj. 350. h1269. 2015

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** Systematic Review and Meta Analysis of n = 7 RCTs **Databases:** PubMed, Cochrane, Embase **Search period:** – 9 January 2014 **Inclusion Criteria:** Double blind randomised controlled trials; patients with psoriasis, psoriatic arthritis, or inflammatory bowel disease; studies in English; studies consisting of a minimum of two arms, at least one receiving methotrexate and at least one not receiving methotrexate; studies including only adults (≥ 18 years); trials of 12 weeks or more duration; studies of 50 patients or more; studies reporting respiratory side effects for methotrexate and comparator groups separately **Exclusion Criteria:** –	**Intervention:** n = 818 receiving methotrexate **Comparison:** n = 812 comparator treatments (Placebo or drug)	**Primary:** Methotrexate associated increased risk of lung disease in adults with psoriasis, psoriatic arthritis, and inflammatory bowel disease. **Secondary:** – **Results:** No association between an increased risk of total adverse respiratory events compared with comparator agents (relative risk 1.03, 95 % CI 0.90 to 1.17). n = 3 studies with n = 343 CD patients (n = 197 CD under Methotrexate, n = 147 controls) RR 1.07 (0.85 to 1.34) **Author's Conclusion:** Methotrexate did not increase the risk of respiratory adverse events in the diseases studies These results should give doctors and patients the confidence to consider the use of this effective treatment as part of the shared decision making process.	Feagan BG (2014) Gastroenterology Feagan BB (2000) N Engl J Med Feagan BG (1995) N Engl J Med Gottlieb AB (2012) Br J Dermatol Kingsley GH (2012) Rheumatology (Oxford) Reich K (2011) N Engl J Med Saurat JH (2008) Br J Dermatol	**Funding Sources:** no specific funding **COI:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. **Study Quality:** low risk of bias **Heterogeneity:** low **Publication Bias:** funnel plot suggested a low risk of bias **Notes:** –

Lorenzetti, R. et al. Higher risk of tuberculosis reactivation when anti-TNF is combined with immunosuppressive agents: a systematic review of randomized controlled trials. Ann Med. 46. 547 – 554. 2014

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** Systematic Review of n = 40 RCTs, n = 7 RCTs dealing with CD, n = 1 RCT with UC **Databases:** Medline, Cochrane databases **Search period:** January 2010 – March 2012 **Inclusion Criteria:** RCTs english language anti-TNF used in more than one disease, namely IFX, ADA, and CERT that are applied in RA, ankylosing spondylitis (AS), inflammatory bowel diseases (IBD), psoriasis, and psoriatic arthritis (PA). **Exclusion Criteria:** < 30 patients or with a follow-up duration < 12 weeks	**Intervention:** total n = 10 100 CD patients total n = 1867, UC patients total n = 728 (controls included) Treatment: n = 2 CD trials: IFX n = 3 CD trials: certolizumab CERT n = 2 CD trial: infliximab IFX+ AZA n = 1 UC trial: IFX **Comparison:** total n = 4673 Treatment: n = 2 CD-Trials: Placebo + Azathioprine (AZA) n = 5 CD Trials: Placebo n = 1 UC Trial: Placebo	**Primary:** The risk of TB in the anti-TNF arms compared with control group, and whether there was an association of such risk with other variables, such as the type of disease or concomitant medications. **Secondary:** – **Results:** Overall, 26 (0.26 %) out of 10 010 patients developed TB in the active treatment group, corresponding to an incidence rate of 481 cases per 100 000 patient-years. No cases of TB were observed in the 4673 patients receiving placebo or placebo plus immunosuppressive therapy (OR 24.8; 95 % CI 2.4 – 133; P < 0.01).	Colombel JF (2010) N Engl J Med Lemann M (2006) Gastroenterology. Present DH (1999) N Engl J Med Sandborn WJ (2007) N Engl J Med Sandborn WJ (2009) Gastroenterology Schreiber S (2005) Gastroenterology Targan SR (1997) N Engl J Med Winter TA (2004) Aliment Pharmacol Ther	**Funding Sources:** – **COI:** The authors declare no confl icts of interest. **Study Quality:** low RoB **Heterogeneity:** – **Publication Bias:** – **Notes:** –

		Stratifying for concomitant therapy: Higher TB risk: not significant: anti-TNF in monotherapy (2/5769 vs 0/4673; OR 4; 95 % CI 0.2 – 15.7; P < 0.5) significant: anti-TNF agents + MTX or AZA (24/4241 vs 0/4673; OR 54; 95 % CI 5.3 – 288; P < 0.001) Differentiating between the two types of controls: Higher risk: Combination therapy vs placebo alone (24/4241 vs 0/2941; OR 34; 95 % CI 3.3 – 181; P < 0.001) Combination therapy vs placebo plus immunosuppressive agents (24/4241 vs 0/1732; OR 20; 95 % CI 2 – 107; P < 0.001) Differentiating combined therapy and monotherapy: TB risk higher (24/4241 vs 2/5769; OR 13.3; 95 % CI 3.7 – 100; P < 0.001), in the former group an incidence rate of 832 cases per 100 000 patient-years and of 91 in latter group. **Author's Conclusion:** TB risk with anti-TNF agents appeared to be increased when these agents were used in combination with methotrexate or azathioprine as compared with monotherapy regimen. TB risk seemed to be higher than placebo, even when monotherapy is prescribed.		

Luthra, P. et al. Systematic review and meta-analysis: opportunistic infections and malignancies during treatment with anti-integrin antibodies in inflammatory bowel disease. Aliment Pharmacol Ther. 41. 1227 – 1236. 2015

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Systematic review and meta-analysis (12 RCTs, 5 of which on UC). **Databases:** MEDLINE, EMBASE, EMBASE Classic, the Cochrane central register of controlled trials, and the Cochrane IBD Group Specialised Trials Register. **Search period:** Inception – 12.2014. **Inclusion Criteria:** *Study type: RCTs Popoulation:* Adults (> 90 % of patients aged > 16 years) with	**Intervention:** *Population: Intervention:* Non-gut specific (natalizumab targeting integrins containing the a4 subunit) or gut specific (vedolizumab targeting a4b7, and etrolizumab targeting a4b7 and aEb7) anti- integrin antibodies. **Comparison:** Placebo	**Primary:** *Occurrence of any opportunistic infection or malignancy* with non-gut specific or gut specific anti-integrin antibodies. Includes infection by Mycobacterium tuberculosis, JC virus oral or oesophageal candidiasis, varicella-zoster virus infection, herpes zoster infection, cytomegalovirus or Epstein–Barr virus infection, Nocardia infection, Pneumocytsis jirovecii infection, Histoplasma capsulatum infection, Mycobacterium avium complex infection, herpes simplex infection or other	Ghosh S, (2003) N Engl J Med Feagan BG, (2005) N Engl J Med Feagan BG, (2013) N Engl J Med Sandborn WJ, (2005) N Engl J Med Sandborn WJ, (2013) N Engl J Med Feagan BG, (2008) Clin Gastroenterol Hepatol Parikh A, (2012) Inflamm Bowel Dis Sands BE, (2014) Gastroenterology Vermeire S, (2014) Lancet Rutgeerts PJ, (2013) Gut	**Funding Sources:** None. **COI:** Pavit Luthra: None. Laurent Peyrin-Biroulet: has served as a consultant to Merck, Abbott, and UCB Pharma and received speaker's fees from Merck and Abbott. Alexander C Ford: has received speaker's fees from MSD. **Study Quality:** "This was performed independently by two investigators, with disagreements resolved by discussion, and was assessed according to methods described in the Cochrane handbook. The method used to generate the randomisation schedule, the method used to conceal allocation, whether blinding was implemented, what proportion

inflammatory bowel disease. *Intervention:* Anti-integrin antibodies with minimum duration of therapy of 2 weeks. *Comparison:* Placebo. *Outcome:* Opportunistic infections or malignancies during randomised double-blind treatment period reported in both arms of the trial. Opportunistic infections include: Mycobacterium tuberculosis, JC virus, oral or oesophageal candidiasis, varicella-zoster virus infection, herpes zoster infection, Epstein–Barr virus or cytomegalovirus infection, Nocardia infection, Pneumocytsis jirovecii infection, Mycobacterium avium complex infection, herpes simplex infection or other unspecified opportunistic infections. **Exclusion Criteria:** Single infusion of anti-integrin antibody, lack of comparison arm.		unspecified opportunistic infections. compared with placebo. **Secondary:** n.a. **Results:** 12 studies were found eligible (four trials of natalizumab, six of vedolizumab and two of etrolizumab). The RR of developing an opportunistic infection was not significantly higher with non-gut specific (2.34; 95 % CI 0.05 – 108.72) or gut specific anti-integrin antibodies (1.55; 95 % CI 0.16 – 14.83). The RR was generally higher in trials of non-gut specific anti- integrin antibodies with duration of therapy ≥ 52 weeks (RR = 15.00; 95 % CI 0.86 – 261), but remained non-significant. The RR of malignancy was not elevated with non-gut specific (1.57; 95 % CI 0.19 – 12.74) or gut specific anti-integrin antibodies (0.78; 95 % CI 0.15 – 4.02). **Author's Conclusion:** Absolute numbers of opportunistic infections were higher with anti-integrin antibodies, but this difference is not statistically significant. There was no increased risk of malignancy detected. Long-term data in large prospective cohorts are needed to further assess this issue.	Targan SR, (2007) Gastroenterology Sands BE, (2007) Inflamm Bowel Dis	of patients had incomplete outcomes data, and whether there was evidence of selective reporting of outcomes were all recorded. Studies were judged as low risk of bias, if they were low risk across all these domains." Risk of bias was low (4) and unclear (8 studies). **Heterogeneity:** "The value of I^2 ranges from 0 % to 100 %, with 0 % representing no observed heterogeneity, and larger values indicating increasing heterogeneity. A value ≤ 25 %, accompanied by a P value of > 0.10 for the chi^2 test, was arbitrarily chosen to represent low levels of heterogeneity." There was significant heterogeneity between studies (I^2 = 69 %, P = 0.07) in the primary analysis for non gut specific anti-integrin antibodies. **Publication Bias:** "There were too few studies containing the events of interest to reliably assess for evidence of publication bias, or other small study effects." **Notes:** Pooling of results from UC and CD studies likely causes bias and problems in reproducing the findings. Study quality was unclear in 8 out of 12 studies. Despite the considerable sample size the opportunistic infection rates are low, which naturally aggravates statistical analysis and the presented results are non- significant.

Narula, N. et al. Meta-analysis: peri-operative anti-TNFalpha treatment and post-operative complications in patients with inflammatory bowel disease. Aliment Pharmacol Ther. 37. 1057 – 1064. 2013

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** Systematic Review and Meta Analysis of 18 studies (n = 17 retrospect cohort, n = 1 prospect case-control) **Databases:** MEDLINE, Embase and PubMed **Search period:** 1950 - December 2012 **Inclusion Criteria:** (i) observational design (prospective or retrospective cohort or case control) or treatment design (randomised or nonrandomised); (ii) association between preoperative treatment with any anti-TNFa agent and post-ope-	**Intervention:** Post OP infectious complcations: N = 15 studies with n = 987 Patients under anti- TNF-therapy **Comparison:** Post OP infectious complcations: N = 15 studies with n = 2257 controls	**Primary:** Rate of subjects experiencing infectious complications within 30 days of surgery among those receiving vs. not receiving TNFa inhibitor **Secondary:** Rates of non-infectious complications and overall complications **Results:** OR for infectious post-operative complications was 1.56 (95 % CI, 1.09 – 2.24, Chi^2 = 30.92)p = 0.006. The rate of infectious complications was 21.7 % compared to 14.5 % in the control group, for an absolute risk increase of 7.2 % and a number needed to harm of 14.	Appau K (2008) J Gastrointest Surg Bregnbak D (2012), J Crohns Colitis Canedo J (2011) Colorectal Dis Coquet-Reinier B (2010) Surg Endosc Eshuis E (2013) J Crohns Colitis Ferrante M (2009) Inflamm Bowel Dis Kasparek M (2012) Inflamm Bowel Dis Kunitake H (2008) J Gastrointest Surg Marchal L (2004) Aliment Pharmacol Ther Mascarenhas C (2012) Am J Surg	**Funding Sources:** Declaration of personal and funding interests: None. **COI:** Declaration of personal and funding interests: None. **Study Quality:** No RCTs, only one prospective study. **Heterogeneity:** Post OP infectious complications: moderate heterogeneity: I^2 = 55 % **Publication Bias:** No publication bias. **Notes:** –

rative complications after any surgical intervention reported; (iii) similar outcomes reported in a control group; (iv) complications either reported as infectious or non-infectious, or listed individually to allow classification by the reviewer. **Exclusion Criteria:** –		Sensitivity analysis after exclusion of one study with the largest effect: (OR 1.49, 95 % CI 1.05 – 2.11)still statistically significant. Studies limited to CD, statist significant increase in infectious complications (OR 1.93, 95 % CI 1.28 – 2.89). Studies limited to UC, increase was statist not significant. **Author's Conclusion:** Anti-TNFa therapies appear to increase the risk of post-operative complications. The increase in risk is small, and may well reflect residual confounding rather than a true biological effect. Nevertheless, physicians should exercise caution when continuing biological therapies during the peri-operative period.	Mor I (2008), Dis Colon Rectum Nasir B (2010) J Gastrointest Surg Nørgard B (2012) Aliment Pharmacol Ther Rizzo G (2011) Int J Colorectal Dis Schluender S (2007) Dis Colon Rectum Selvasekar C (2007), J Am Coll Surg Syed A (2013) Am J Gastroenterol Waterman M (2012) Gut	

Toussi, S. S. et al. Infections in children and adolescents with juvenile idiopathic arthritis and inflammatory bowel disease treated with tumor necrosis factor-alpha inhibitors: systematic review of the literature. Clin Infect Dis. 57. 1318 – 1330. 2013

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 3 **Study type:** Systematic Review with n = 39 studies on pediatric pIBD, n = 11 prospective, n = 17 retrospective, n = 11 case reports/series **Databases:** PubMed **Search period:** 2000 – 2012 **Inclusion Criteria:** English Language Original studies that evaluated TNF- α inhibitor therapy (infliximab, etanercept, or adalimumab) in pediatric (0 – 18 years) JIA or pIBD patients **Exclusion Criteria:** Studies that did not mention collecting data on the occurrence of infection or that did not describe any infection in the manuscript.	**Intervention:** prospective + retrospective studies n = 1648 n = 1407 Infliximab, n = 241 Adalimumab **Comparison:** –	**Primary:** Infection – incidence, screening, prevention **Secondary:** – **Results:** In pIBD patients treated with either adalimumab or infliximab, the incidence of mild infections ranged from 3 % (1/38) to 77 % (46/60), and from 0 % (0/66) to 10 % (6/60) for serious infections **Author's Conclusion:** Pediatric patients with JIA and IBD can frequently develop mild infections and, less commonly, severe infections when treated with infliximab, etanercept, or adalimumab. Bacterial, viral, and fungal infections were all important etiologies of serious infections. Importantly, few pediatric patients developed M. tuberculosis, likely owing to effective screening for latent tuberculosis. Unfortunately, the majority of the studies reviewed had significant limitations, making it difficult to adequately assess the extent of infections that occurred in this cohort. This includes limited information about	39	**Funding Sources:** T.J.W. is a Scholar of the Henry Schueler Foundation and a Scholar of Pediatric Infectious Diseases of the Sharpe Family Foundation, and receives support from the SOS Kids Foundation (grant numbers: R34HL117 352, 1R01AI103 315 – 01A1). **COI:** T.J.W. is a board member of iCo; has served as a consultant for Astellas, ContraFect, Drais, iCo, Novartis, Pfizer, Methylgene, SigmaTau, and Trius; has received research grants for experimental and clinical antimicrobial pharmacotherapeutics from Astellas, Novartis, Merck, ContraFect, and Pfizer. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed. **Study Quality:** he majority of the studies reviewed had significant limitations **Heterogeneity:** – **Publication Bias:** – **Notes:** –

		the frequency, sites of infection, and microbiology. As mentioned, studies included heterogeneous populations on concomitant immunosuppressive therapy and were not designed to effectively evaluate for mild and/or severe infections. Future prospective studies with larger patient populations, more frequent follow-up, and a more thorough assessment of mild and serious infections would significantly help clinicians better understand the implications of starting a patient with JIA or pIBD on TNF-α inhibitors, and ultimately help to improve prevention strategies and management.		

Bultman, E. et al. Systematic review: steroid withdrawal in anti-TNF-treated patients with inflammatory bowel disease. Aliment Pharmacol Ther. 32. 313 – 323. 2010

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Systematic review (3 studies on UC, 2 RCTs 1 cohort study). **Databases:** Medline. **Search period:** Inception – 2009. **Inclusion Criteria:** English publications; human participants, Paediatric or adult patients with non- fulminant active UC or active luminal CD. Patients received IFX treatment either as induction therapy (1 – 3 infusions within 10 weeks) or as maintenance therapy (induction therapy followed by scheduled infusions), or adalimumab (ADA) treatment. Articles needed to describe the effect of anti-TNF on concomitant steroid- usage with a follow-up of at least 26 weeks. Patients in control-groups may have received either placebo or conventional medication, or may have served as their own control by comparing steroid usage before and after anti-TNF therapy. Non-randomized and⁄or non- controlled trials were included to ensu-	**Intervention:** Maintenance therapy using Infliximab (in case of UC), discontinuation of corticosteroids. **Comparison:** –	**Primary:** Discontinuation of corticosteroids (%) during Infliximab maintenance therapy. **Secondary:** – **Results:** Overall, between 24 % and 38 % of the adult patients treated with corticosteroids at baseline during infliximab maintenance therapy were able to discontinue corticosteroids. Of the adult patients not treated with corticosteroids at baseline, between 72 % and 91 % stayed off steroids without surgery during follow-up. **Author's Conclusion:** In conclusion, although consensus on the definition of corticosteroid- sparing is lacking, it seems that up to two-thirds of the patients are still in need of concomitant corticosteroid treatment despite treatment with infliximab. It seems that in children with a shorter duration of disease, the corticosteroid-sparing is higher compared with that in the adult population. To avoid combination therapy with immunosuppressants and thus to lower the risk of severe infections, it may be	Rutgeerts P, (2005) N Eng J Med Cucchiara S, (2008) Dig Liver Dis	**Funding Sources:** None. **COI:** C.J. van der Woude has served as a speaker, a consultant and an advisory board member for Abbott Laboratories, Shire, Schering- Plough and Centocor, and has received research funding from Abbott Laboratories and Schering-Plough. We thank Centocor and Abbott Laboratories for providing additional data. **Study Quality:** The quality of the studies was assessed by one author. The risk for bias was rated by assessing sequence gene-ra- tion, allocation concealment, blinding, incomplete out- come data and selective outcome reporting. **Heterogeneity:** n.a. **Publication Bias:** n.a. **Notes:** Only one database was searched (Medline). Certain search terms could have been rephrased to included more studies (f.e. steroid- sparing). Selection, extraction and assessment of study data and quality was performed by a single investigator. Study quality was investigated but not reported, neither as individual results nor as overall quality. Outcome of steroid sparing lacks consensus between the studies. Results for pediatric

re a broad overview about the steroid-sparing effect of anti-TNF. **Exclusion Criteria:** Exclusion criteria were: no full paper available, no clear distinction between UC and CD patients, patients with fistulizing disease or fulminant colitis, anti-TNF treatment schedule unknown or episodic IFX treatment.		necessary to introduce biologicals earlier in the course of disease.		studies should not be considered due to sample size (n = 8).

Wu, X.W. et al. Helicobacter pylori infection and inflammatory bowel disease in Asians: a meta-analysis. World J Gastroenterol. 21. 4750 – 4756. 2015

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** Systematic Review and Meta Analysis with n = 10 case-control studies **Databases:** PubMed, EMBASE, the Cochrane Library **Search period:** –June 2014 **Inclusion Criteria:** studies that (1) investigated the relationship between H. pylori infection and IBD; (2) used a case-control, crosssectional, or cohort design; (3) specifically included an Asian population **Exclusion Criteria:** studies that (1) used data from a previously published study; (2)included a pediatric population.	**Intervention:** n = 1299 IBD patients **Comparison:** n = 1817 controls	**Primary:** H. pylori detection **Secondary:** – **Results:** *1. IBD* The pooled RR of H. pylori infection rate in IBD patients compared to controls was 0.48 (95 %CI:0.43 – 0.54; P < 0.001). *2. CD patients* Nine studies included 751 CD patients and 1696 controls. The rate of H. pylori infection in CD patients was 21.3 % compared with 47.7 % in the control groups (RR = 0.43, 95 %CI: 0.37 – 0.50; P < 0.001). *3. UC* Six studies included 548 UC patients and 1025 controls (Fig. 4). The rate of H. pylori infection was 29.9 % in UC patients vs 52.5 % in the control groups (RR = 0.55, 95 %CI: 0.48 – 0.64; P < 0.001). **Author's Conclusion:** The H. pylori infection rate in Asian IBD patients is significantly lower than in non-IBD patients, indicating that infection protects against the development of IBD.	Ando T (2008) J Gastroenterol Hepatol Furusu H (2002) Hepatogastroenterology Hong CH (2009) Korean J Gastroenterol Jin X (2013) Int J Med Sci Matsumura M (2001) J Gastroenterol Moriyama T (2005) Aliment Pharmacol Ther Pang Z (2009) Shijie Huaren Xiaohua Zazhi Song MJ (2009) Korean J Gastroenterol Xiang Z (2013) World J Gastroenterol Zhang S (2001) J Clin Microbiol	**Funding Sources:** – **COI:** – **Study Quality:** case-control studies **Heterogeneity:** 1) IBD no significant heterogeneity (I2 = 21 %). 2) Crohns significant heterogeneity (I2 = 43 %). 3) UC no significant heterogeneity(I2 = 0 %). **Publication Bias:** no statistically significant evidence of publication bias (P = 0.203). **Notes:** –

Rokkas, T. et al. The association between Helicobacter pylori infection and inflammatory bowel disease based on meta-analysis. United European Gastroenterol J. 3. 539 – 550. 2015

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Meta-Analysis (33 cohort and case control studies) **Databases:** PubMed, MEDLINE and Embase **Search period:** Inception – 09.2014.	**Intervention:** 4400 IBD patients (1940 UC patients) and 4763 controls. **Comparison:** –	**Primary:** Association analysis between H.pylori infection in IBD patients vs. controls. **Secondary:** Percentage of H.pylori infection in IBD cases and controls, subgroup analysis for CD, CU.	el-Omar E, (1994) Gut Mantzaris GJ, (1995) Am J Gastroentero Halme L, (1996) J Clin Pathol Meining A, (1997) Scand J Gastroenterol	**Funding Sources:** This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. **COI:** None declared. Study Quality: No assessment of individual study quality was performed.

Inclusion Criteria: - Inclusion criteria were: (1) published as full article, (2) include data for retrieval on the association between H. pylori infection and IBD in humans and (3) H. pylori infection was confirmed by serology and/or histology and/or urea breath test (UBT) and/or rapid urea test (RUT) and/or culture. **Exclusion Criteria:** Studies that did not meet the aforementioned criteria and duplicate publications were excluded. When two papers reported the same study, the publication that was more informative was selected.		**Results:** Overall 26.5 % of IBD patients were positive for H. pylori infection, compared to 44.7 % of individuals in the control group. There was significant heterogeneity in the included studies (Q = 137.2, df (Q) = 32, I^2 = 77 %, p < 0.001) and therefore the random-effects model of meta-analysis was used. The obtained pool RR estimation was 0.62 (95 % confidence interval (CI) 0.55 – 0.71, test for overall effect Z = –7.04, p < 0.001). There was no evidence of publication bias. **Subgroup analyses:** showed significant results for both diseases, with a greater effect for CD (0.38 (0.31 – 0.47), Z = -8.98, p < 0.001) when compared to UC (0.53 (0.42 – 0.67), Z = -5.39, p < 0.001). Significant heterogeneity in the included studies for both diseases; CD: Q = 66.67, df (Q) = 27, I2 = 59.5 %, p < 0.001 and UC: Q = 55.33, df (Q) = 21, I^2 = 62 %, p < 0.001. **Author's Conclusion:** The results of this meta-analysis showed a significant negative association between H. pylori infection and IBD that supports a possible protective benefit of H. pylori infection against the development of IBD.	Oberhuber G, (1997) Gastroenterology Parente F, (1997) Scand J Gastroenterol Wagtmans MJ, (1997) Scand J Gastroenterol D'Inca R, (1998) Dig Dis Sci Duggan AE, (1998) Gut Pearce CB, (2000) Eur J Gastroenterol Parente F, (2000) Am J Gastroenterol Matsumura M, (2001) J Gastroenterol Parlak E, (2001) J Clin Gastroenterol Vare PO, (2001) Scand J Gastroenterol Feeney MA, (2002) Eur J Gastroenterol Hepatol Furusu H, (2002) Hepatogastroenterology Guslandi M, (2002) Hepatogastroenterology Pascasio JM, (2003) Pediatr Dev Pathol Piodi LP, (2003) J Clin Gastroenterol Triantafillidis JK, (2003) Hepatogastroenterology Oliveira AG, (2004) J Clin Microbiol Prónai L, (2004) Helicobacter Oliveira AG, (2006) Helicobacter Sladek M, (2007) Przegl Lek Ando T, (2008) J Gastroenterol Hepatol Lidar M, (2009) Ann N Y Acad Sci Song MJ, (2009) Korean J Gastroenterol Garza-González E, (2010) Int J Immunogenet Pellicano R, (2010) Rev Esp Enferm Dig Varas-Lorenzo MJ (2010) Rev Esp Enferm Dig Zhang S, (2011) J Clin Microbiol Jin X, (2013) Int J Med Sci Xiang Z, (2013) World J Gastroenterol	**Heterogeneity:** Heterogeneity between studies was evaluated with the Cochran Q-test and it was considered to be present if the Q-test provided a p value of less than 0.10. In addition I^2 statistic was used to measure the proportion of inconsistency in individual studies that could not be explained by chance, with I^2 > 50 % representing substantial heterogeneity. **Publication Bias:** The likelihood of publication bias was assessed by constructing funnel plots, which were obtained by plotting the log RRs vs SE of individual studies. Their symmetry was estimated by Egger's regression test and the Begg and Mazumdar adjusted rank correlation test whereas the adjustment for publication bias, i. e. calculation of the number of studies missing from the meta-analysis was estimated using Duval and Tweedie's nonparametric "trim and fill" rank-based method. **Notes:** No assessment of individual study quality was performed. Forrest plots do no display sample sizes and weight of individual studies. High amount of heterogeneity between the studies (Q = 137.2, df (Q) = 32, I^2 = 77 %, p < 0.001). This was addressed and explored using subgroup analyses, meta-regression by publication year, and sensitivity analysis, but there heterogeneity is still substantial.

Anderson, J.L. et al. Systematic review: faecal microbiota transplantation in the management of inflammatory bowel disease. Aliment Pharmacol Ther. 36. 503 – 516. 2012

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 4 **Study type:** Systematic review (17 case series articles) **Databases:** MEDLINE; EMBASE; CENTRAL (The Cochrane Library);	**Intervention:** Patients: 41 patients, (27 CU patients). Intervention: Fecal microbiota transplantation (FMT). **Comparison:** Any comparator or none.	**Primary:** Management of IBD **Secondary:** Managment of C.difficile in IBD patients **Results:** There were nine case series/case reports of patients receiving FMT for	Aas J, (2003) Clin Infec Dis Grehan (2010) J Clin Gastroenterol Borody TJ, (2008) Gastroenterology	**Funding Sources:** The systematic review was internally funded. **COI:** KW has served as a speaker for DDW, DDF and Danone, and has received research funding from Crohn's and Colitis UK, British Dietetic Association,

CINAHL; Web of Science; BIOSIS; SCOPUS; BIOMED CENTRAL; NHS Evidence + hand searching of journals: Gastroenterology; Gut; Journal of Crohn's and Colitis; Inflammatory Bowel Diseases. **Search period:** Inception –10.2011 **Inclusion Criteria:** Patients with IBD of any age; intervention fecal microbiota transplantation, with or without comparator group; outcomes: any relevant outcome. Any RCT, non-randomised controlled trials, uncontrolled trials, case series or case reports of any study duration. English and foreign language reports included. **Exclusion Criteria:** Animal or in vitro studies.		management of their IBD, and eight where FMT was for the treatment of infectious diarrhoea in IBD. These 17 articles reported on 41 patients with IBD (27 UC, 12 Crohn's, 2 unclassified) with a follow-up period of between 2 weeks and 13 years. Where reported, FMT was administered via colonoscopy/enema (26/33) or via enteral tube (7/33). In patients treated for their IBD, the majority experienced a reduction of symptoms (19/25), cessation of IBD medications (13/17) and disease remission (15/24). There was resolution of C.difficile infection in all those treated for such (15/15). **Author's Conclusion:** Despite the relative paucity of information specifically in IBD, there is limited, weak evidence that FMT has the potential to be an effective and safe treatment for IBD, at least when standard treatments have failed or are unacceptable to the patient. Well-designed randomised, controlled trials are necessary to confirm the positive findings from case reports, to evaluate safety and to develop optimal protocols for the use of FMT in IBD, prior to this becoming a standard part of clinical therapy.	Wettstein A, (2007) United European Gastroenterology Federation Borody TJ, (1989) Med J Australia Mellow M, (2010) Am J Gastroenterol Borody T, (2011) Am J Gastroenterol You D, (2011) Am J Gastroenterol Borody T, (2011) Am J Gastroenterol Borody T, (2001) Probiotics, Prebiotics and New Foods Conference, Universita Urbaniana, Rome Vermeire S, (2012) Gastroenterology Zainah H, (2012) Case Rep Infect Dis Borody TJ, (2003) J Clin Gastroenterol Bennet JD, (1989) Lancet Angelberger S, (2012) In ECCO Conference Abstracts Watson JB, (2012) Gastroenterology Neelakanta A, (2012) Gastroenterology	Healthcare Quality Improvement Partnership and Californian Dried Plum Board. KW is an employee of King's College London. **Study Quality:** n.a. **Heterogeneity:** n.a. **Publication Bias:** n.a. **Notes:** No assessment of study quality. Lack of primary literature presented in the article, despite thorough search. No separate results for UC patients. Variability and missing details in the protocol of FMT regarding preparation and administration. Very limited evidence available.

Dulai, P.S. et al. Risks of serious infection or lymphoma with anti-tumor necrosis factor therapy for pediatric inflammatory bowel disease: a systematic review. Clin Gastroenterol Hepatol. 12. 1443 – 1451; quiz e88 – e89. 2014

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 3 **Study type:** Systematic review (5 RCTs, 7 case series, 53 cohort studies). **Databases:** MEDLINE/ Pubmed, Cochrane Library, Web of Knowledge, Embase. **Search period:** Inception – 2013. **Inclusion Criteria:** Randomized controlled trials, cohort studies, or case series; 5 or more consecutive patients (to avoid selection bias); published articles or meeting abstracts; treatment inclu-	**Intervention:** *Population:* 5528 Patients and 9516 years of patient- years of follow up. Pediatric (≤ 18 years) and Adult patients (> 18 years). Mean age 13.6 ± 2.2 years, 56 % male. 11 % UC patients (608). *Intervention*: Treatment with anti-TNF therapy (infliximab, adalimumab). **Comparison:** immunemodulator therapy; adult IBD patients.	Primary: Absolute rate of serious infection, lymphoma, and death. Secondary: Rate of lymphoma with anti-TNF therapy in pediatric IBD with the expected rate of lymphoma among pediatric subjects not exposed to anti-TNF agents and adult IBD patients exposed to anti-TNF agents. Results: Infection risk: The rate of serious infections among pediatric patients treated with anti-TNF agents (352/10 000 Patient years follow	Hyams J, (2012) Clin Gastroenterol Hepatol Turner D, (2010) Gastroenterology Ruemmele FM, (2009) Inflamm Bowel Dis Baldassano R, (2003) Am J Gastroenterol Gasparetto M, (2012) Acta Gastroenterol Belg Noe JD, (2008) Inflamm Bowel Dis Mamula P, (2002) J Pediatr Gastroenterol Nutr Romano C, (2010) J Pediatr Gastroenterol Nutr Rosenbach Y, (2010) Dig Dis Sci	**Funding Sources:** n.a. **COI:** Corey Siegel serves on the advisory board, as a consultant, and has received grant support from Abbvie, Janssen, and UCB, and is supported by grant 1R01HS021 747 – 01 from the Agency for Healthcare Research and Quality; and Marla Dubinsky serves as a consultant to Abbvie, Janssen, UCB, and Takeda. The remaining authors disclose no conflicts. **Study Quality:** n.a. **Heterogeneity:** n.a. **Publication Bias:** n.a. **Notes:** No evaluation of study quality, publication bias.

ded infliximab (IFX) for Crohn's disease, ulcerative colitis, or indeterminate colitis, and/or adalimumab (ADA) for Crohn's disease; population of pediatric patients (≤ 18 y); clearly reported adverse outcomes and follow-up evaluation. Studies including both adult (> 18 y) and pediatric patients were included if pediatric data were reported separately or if the median age at anti-TNF initiation was 18 years or younger. **Exclusion Criteria:** eview articles and case series with fewer than 5 patients were excluded. Given the lack of a clear denominator at risk, studies reporting on adverse event registry databases were excluded. Studies with insufficient data for adverse outcomes and follow-up evaluation were excluded only after attempting to contact the primary author(s).		up (PYF) was similar to that of pediatric patients who received immunomodulator monotherapy (333/10 000 PYF; standardized incidence ratios (SIR), 1.06; 95 % confidence interval [CI], 0.83 – 1.36), but significantly lower than the expected rate for pediatric patients treated with steroids (730/10 000 PYF; SIR, 0.48; 95 % CI, 0.40 – 0.58) or adults treated with anti-TNF agents (654/10 000 PYF; SIR, 0.54; 95 % CI, 0.43 – 0.67). Mortality: Five treatment-related deaths occurred (4 from sepsis and 1 from arrhythmia). Lymphoma: Two patients developed lymphoma (2.1/10 000 PYF). This value was similar to the expected rate of lymphoid neoplasia in the entire pediatric population (5.8/100 000 PYF; SIR, 3.5; 95 % CI, 0.35 – 19.6), and lower than the population of pediatric patients receiving thio- purine monotherapy (4.5/10 000 PYF; SIR, 0.47; 95 % CI, 0.03 – 6.44), and among adults treated with anti- TNF agents (6.1/10 000 PYF; SIR, 0.34; 95 % CI, 0.04 – 1.51). Author's Conclusion: Based on a systematic review, the risk of lymphoma was no greater among children with IBD who received anti-TNF therapy than those treated with other IBD therapies or adults treated with anti-TNF agents. The rate of serious infection was significantly lower among pediatric patients with IBD treated with anti-TNF agents than those treated with steroids, or adults with IBD who received anti-TNF therapy.	Czaja-Bulsa G, (2012) Przeglad Gastroenterologiczny Szychta M, (2013) J Crohns Colitis Colletti R, (2013) J Crohns Colitis Baldassano R, (2013) J Crohns Colitis Alvisi P, (2013) J Crohns Colitis Yokoyama Y, (2012) Gastroenterology Rosh JR, (2012) Gastroenterology Pfefferkorn MD, (2012) Gastroenterology Kierkus J, (2012) Przeglad Gastroenterologiczny Kierkus J, (2012) Eur J Gastroenterol Hepatol Christenson K, (2012) Inflamm Bowel Dis Assa A, (2013) J Crohns Colitis Absah I, (2012) Inflamm Bowel Dis Wanty C, (2011) Arch Pediatr Russell RK, (2011) Aliment Pharmacol Ther Kim MJ, (2011) Acta Paediatr Kelsen J, (2011) Inflamm Bowel Dis Hyams J, (2011) Curr Med Res Opin De Bie CI, (2011) Aliment Pharmacol Ther Tiemi J, (2010) J Pediatr Gastroenterol Nutr De Greef E, (2012) Acta Gastroenterol Belg Lee JS, (2010) World J Gastroenterol Hyams JS, (2010) Am J Gastroenterol Roche S, (2009) J Pediatr Gastroenterol Nutr Duricova D, (2009) Aliment Pharmacol Ther Wynands J, (2008) J Pediatr Gastroenterol Nutr de Ridder L, (2008) Inflamm Bowel Dis Kolho KL, (2007) Acta Paediatr Feldman TL, (2007) Gastroenterology Fanjiang G, (2007) J Pediatr Gastroenterol Nutr Afzal NA, (2007) Dig Dis Sci Deslandres C, (2006) Gastroenterology Lamireau T, (2004) Inflamm Bowel Dis de Ridder L, (2004) J Pediatr Gastroenterol	

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AG 5: Ist das laparoskopische dem offenen Vorgehen bei der restaurativen Proktokolektomie vorzuziehen?

Bewertungsvorlage:
Oxford SR

Ahmed, Ali Usama et al. Open versus laparoscopic (assisted) ileo pouch anal anastomosis for ulcerative colitis and familial adenomatous polyposis. Cochrane Database of Systematic Reviews 2009

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** MA of 11 trials (1 RCT, 4 prospective non- RCT, 6 non-RCT with retrospective or not described data- collection) **Databases:** Cochrane IBD/FBD Group Specialized Trial Register, Cochrane Library (including The Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), The Cochrane Central Register of Controlled Trials (CENTRAL), Health Technology Assessment (HTA) Database, NHS Economic Evaluation Database), MEDLINE, EMBASE, ISI Web of Knowledge (Web of Science), Web casts of the annual meetings of the American Society of Colon and Rectal Surgeons (ASCRS) **Search period:** 1990 – April 2007	**Intervention:** Overall: 607 patients (516 patients with UC and 89 with familial adenomatous polyposis [FAP]). Laparoscopic IPAA (253 patients [41 %]): Procedures started as laparoscopic procedure, with creation of any kind of pneumoperitoneum (by Veress needle or open introduction) or mechanical abdominal wall lift, irrespective of the number of trocars used. Laparoscopic- assisted IPAA: Procedures in which an additional small incision laparotomy was used (e. g. Pfannenstiel or subumbilical midline incision) to facilitate the laparoscopic IPAA procedure. Age (range): 25 (12 – 61) – 32 (16 –	**Primary: Mortality** **Complications:** *Intraoperative complications:* all complications occurring and detected intraoperatively, like small bowel perforation and severe intraoperative bleeding. *Procedure specific complications:* pouch failure, pelvic sepsis, pouch fistula, anastomotic leakage and strictures. *Severe postoperative complications:* e. g. intra-abdominal abscesses, bleeding, sepsis, burst abdomen (Platzbauch) and myocardial infarction. *Total complications:* total number of all complications per study. *Procedure specific complications:* Pouch failure: pouch excision or a non-functioning pouch at 12 months after IPAA procedure. Pelvic sepsis: pelvic abscess, anastomotic leakage or dehis-	Araki Y (2001) Kurume Medical Journal Berdah SV (2004) Annales de Chirurgie Brown SR (2001) Diseases of the Colon & Rectum Dunker MS (2001) Diseases of the Colon & Rectum Hashimoto A (2001) Surgery Today Larson DW (2005) Diseases of the Colon & Rectum Larson DW (2006) Annals of Surgery Maartense S (2004) Annals of Surgery Marcello PW (2000) Diseases of theColon & Rectum Otani Y (2001) Japanese Journal of Gastroenterological Surgery Schmitt SL (1994) International Journal of Colorectal Disease	**Funding Sources:** Not stated. **COI:** Declarations of Interest: None. **Study Quality:** Assessed with modified MINORS. Differences only in 3 items: ▪ Prospective collection of data: 5 trials (45 %) scored 'adequate', 6 trials (55 %) scored 'unclear/ inadequate', ▪ Contemporary groups of cases and controls: 7 trials (64 %) scored 'adequate' and 4 trials (36 %) scored 'unclear/inadequate', ▪ Baseline equivalence of groups: 7 trials (64 %) scored 'adequate', 4 four trials (36 %) scored 'inadequate'. **Heterogeneity:** No heterogeneity found apart in analyses of operative time ($Chi^2 = 11.02$, $p = 0.01$, $I^2 = 73$ %), blood loss ($Chi^2 = 2.70$, $p < 0.10$, $I^2 = 63.0$ %), time to bowel movement ($Chi^2 = 6.74$, $p = 0.03$, $I^2 = 70$ %). **Publication Bias:** Funnel plot on total complications did not indicate arguments for bias.

Inclusion Criteria: **Types of studies** (1) Randomised clinical trials and non-randomised controlled clinical trials comparing open IPAA versus LA-IPAA; (2) Direct comparison of open IPAA vs LA-IPAA, irrespectively of randomisation, prospective data collection, number of patients or language of the article **Types of participants:** Patients with UC or FAP who underwent an IPAA procedure **Types of Interventions:** Any type of open IPAA compared to any type of LAIPAA. **Types of outcome measures:** Primary outcome measures: Mortality and complications (except minor complications). Secondary outcome measures: All other outcomes assessed in the comparison of the two operative techniques. These included minor complications, operative time, operative blood loss, time to bowelmovement, time to regular diet, hospital stay, readmission rate, reoperation rate, incision length, cosmesis, functional outcome (faecal and sexual function) and costs. **Exclusion Criteria:** Studies including mainly patients with other diseases (unless data presented for UC and FAP patients separately). When multiple studies have overlapping patient populations, only the most recent publication was included.	69) years. Sex (M:F): 6:27 – 15:5. **Comparison:** Open IPAA (354 [59 %] patients): All other cases than interventions described as laparoscopic. Age (Mean/ range): 26 (9 – 61) – 39.6 (17.7) years. Sex (M:F): 6:27 – 15:5.	cence or pelvic/perineal wound infection. Pouch fistula: any pouch related fistula. Stricture: anastomotic fibrosis necessitating dilatation. *Functional outcome:* Defecation frequency: times of defecation per day, night or per 24 hours. Mild faecal incontinence: soiling or spotting in underwear. Severe faecal incontinence: regularly severe leakage or faecal loss or passive faecal incontinence. Urge faecal incontinence: inability to defer defecation more than 15 minutes after first urge. Sexual dysfunction: retrograde ejaculation, erection disorder or dyspareunia. *Secondary:* All other outcomes assessed: minor complications, operative time, operative blood loss, time to bowelmovement, time to regular diet, hospital stay, readmission rate, reoperation rate, incision length, cosmesis, functional outcome (faecal and sexual function) and costs. *Mild postoperative complications:* e. g. including prolonged ileus, wound infections, urinary tract infections, urinary retention, pleural effusion, late incisional hernia, and deep venous thrombosis. Other postoperative complications were categorized appropriately at first encounter. **Results:** Mortality reported in the 9 trials including 232 patients in laparoscopic group + 323 patients in open group. 1 study with one death in open group. No statistically significant difference. **Complications:** *Intraoperative complications* reported in the 5 trials including 130 patients in laparoscopic group + 230 patients in open group. No statistically significant difference. *Procedure specific complications* reported in the 8 trials. Differences not statistically significant (RR = 0.81; 95 % CI 0.32, 2.02).		**Notes:** Last search ended 2 years before publication. Most study reported only short-term outcomes (6 studies until discharge, 1 study until 30 days, 1 study until 90 days, 1 study > 12 months, 1 study with mean 16 months, 1 study > 3 years). High risk of bias due to inclusion of non-randomised studies.

		Severe complications reported in 9 trials. Differences not statistically significant (RR = 0.65; 95 % CI 0.29, 1.48). *Minor complications* reported in 9 trials. Differences not statistically significant (RR = 1.05; 95 % CI 0.78, 1.41). *Total complications* consisted of sum of all complications in aforementioned categories. No significant differences (RR = 0.91; 95 % CI 0.73, 1.14). *Operative time* sufficiently reported in 5 trials. RCT showed increase in median operative time from 133 (range 97 to 260) for open IPAA to 214 (range 149 to 400) for laparoscopic approach ($p < 0.001$). Meta-analysis of 4 non-RCTs showed significantly longer operative time in laparoscopic group (weighted mean difference [WMD] = 92 minutes; 95 % CI 53 to 130). *Blood loss* sufficiently reported in 3 trials. No significant difference in RCT and pooled analyses of non-RCT. *Time to bowel movement* reported by three non-RCTs including 141 in laparoscopic group and 231 patients in open group. Only pooled data from sensitivity analyses imputing data for means and SD from 2 trials available. Significant shorter time to bowel movement in laparoscopic group (WMD = –1.96 days; 95 % CI –3.45, –0.46). *Time to regular diet* reported in 6 trials. No significant difference in RCT and pooled analyses of non-RCT. Hospital stay reported in 9 trials. No significant difference showed in RCT. Pooled analyses of 4 non-RCTs including 48 patients in the laparoscopic and 40 in the open group: Significantly shorter hospital stay for laparoscopic procedure compared to open technique (WMD –2.66 days; 95 % CI – 4.28, –1.04).		

		Readmission rate reported in 2 trials. Differences not statistically significant. *Re-operation rate* reported in 7 trials. Differences not statistically significant (RR 0.74; 95 % CI 0.32 to 1.71). *Incision* length reported in 2 studies. Sensitivity analysis with imputed data including 27 patients in laparoscopic and 30 patients in open group: significantly shorter incision in laparoscopic group (WMD –7.79 cm; 95 % CI –9.68, –5.9). *Cosmesis* reported in 2 studies. RCT showed significant increase from mean of 14.7 points in open group to 18.5 in laparoscopic groups (SD not reported, p = 0.01). 1 Non-RCT reported increase from a mean of 16 (4.6) points in the open to 19.8 (4.6) in the laparoscopic group (p = 0.03). **Functional outcome:** *Defecation* frequency reported in 4 trials. Pooling data not possible due to inconsistencies in reporting of results. *Faecal incontinence* reported in 4 trials. Pooling data not possible due to inconsistencies in reporting of results. *Costs* reported in 1 trial. Operative costs significantly higher in laparoscopic group. No significant difference in overall total costs (including costs for hospital stay, relaparotomies and readmission, etc). **Author's Conclusion:** The laparoscopic IPAAis a safe procedure, that could be performed successfully in centres experienced in laparoscopic and restorative pouch surgery. The laparoscopic approach seems to be associated with some short-term advantages regarding postoperative recovery, but these advantages seem to be limited and their clinical significance is arguable. For a complex operation like the IPAA other outcomes, like specific complications, long-term functional outcome, cosmesis and costs aremore likely to influence the choice		

		of the operative technique. This review have shown that for cosmesis there are some data favouring the laparoscopic approach, but that the evidence is still inconclusive and more research is needed before a general recommendation can be made. There is also some evidence that costs, a crucial item in today's health care, may not become a decisive item in the decision between open and laparoscopic IPAA.		

Bartels S. A. et al. Systematic review and meta-analysis of laparoscopic versus open colectomy with end ileostomy for non-toxic colitis. Br J Surg. 100. 726 – 733. 2013

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** MA of 9 studies (6 cohort, 3 case-matched studies) **Databases:** MEDLINE (PubMed), Embase (Ovid), Cochrane Database of Systematic Reviews and Central Register of Controlled Trials (Wiley) **Search period:** Inception – Jun 12 2012 **Inclusion Criteria:** Not described. **Exclusion Criteria:** Not described.	**Intervention:** Total: 966 patients included. **4 studies included CD and UC patients.** Mean age comparable between groups in 6 studies, 3 studies with significantly different age at baseline. Other baseline data relatively homogeneous; sex did not differ between groups in any study, baseline difference in BMI in 1/7 studies that detailed it. Duration of (short-term) follow-up 30 days in 3 studies and not defined in remaining studies. 2 studies included only patients who also had completion proctectomy in a second stage. Laparoscopic colectomy with end ileostomy: 421 patients. Included Procedures: (Sub)Total colectomy, two- or three-stage restorative proctocolectomy, end ileostomy and mucous fistula, sigmoidostomy. Included interventions: Hand-assisted laparoscopic surgery (i. a. via Pfannenstiel incision), straight laparoscopy, single-incision laparoscopic surgery, extraction via stoma site or transrectally, extraction via 7-cm paramedian incision, extraction via hand port,	**Primary:** *Conversion rate:* defined as unplanned laparotomy or extension of the initial extraction site, any unplanned incision or a planned incision longer than 6 cm for specimen extraction, a midline incision, or no definition was given. **Secondary:** **Duration of operation:** operating room time, time from skin incision to wound closure, or no definition was provided. **Reoperation:** further operation within 30 days after the index operation or no definition was given. **Wound infection:** signs of infection or purulent drainage, requiring deliberate opening of the wound or antibiotic treatment, and a positive culture or no definition was given. **Ileus:** absence of adequate bowel function on day 5 after surgery, or the need to insert a nasogastric tube because of abdominal distension, nausea or emesis after starting a liquid diet, in the absence of mechanical obstruction(imaging studies or operation) or no definition was given. *Gastrointestinal bleeding and intra-abdominal abscess:* not defined in any of the studies that reported on these outcomes. *Length of stay:* total postoperative stay, hospital stay including readmission for complications, overall	Gu J (2012) Dis Colon Rectum Bartels SA (2012) Surg Endosc Telem DA (2010) Surg Endosc Watanabe K (2009) Dis Colon Rectum Chung TP (2009) Dis Colon Rectum Ouaissi M (2008) Surg Laparosc Endosc Percutan Tech Marceau C (2007) Surgery Marcello PW (2001) Dis Colon Rectum Dunker MS (2000) Surg Endosc	**Funding Sources:** Not stated. **COI:** Disclosure: The authors declare no conflict of interest. **Study Quality:** Data collected retrospectively in 7 studies. Assessment of the endpoints was not unbiased (unblinded) in any of the studies. Overall quality stated as "average", but results of quality assessment with MINORS not presented. **Heterogeneity:** *Conversion rate:* Not stated. *Duration of operation:* No meta-analysis possible due to considerable variation in definitions and statistical heterogeneity. *Reoperation:* $I^2 = 0\,\%$ *Wound infection:* Chi- Square = 4.03, 6 df, P = 0.67; $I^2 = 0\,\%$ *Ileus:* $I^2 = 40\,\%$ Gastrointestinal bleeding: $I^2 = 1\,\%$ *Intra-abdominal abscess:* Chi-Square = 0.04, 2 df, P = 0.98; $I^2 = 0\,\%$ *Length of stay:* Chi- Square = 0.85, 5 df, P = 0.97; $I^2 = 0\,\%$ Mortality: $I^2 = 0\,\%$ **Publication Bias:** Not investigated. **Notes:** No inclusion/ exclusion criteria described. Combined analyses of UC and CD patients since 4 studies included CD and UC patients. High risk of selection bias resulting from included study types. **Overestimation of effect likely.**

	suprapubic or left lower quadrant incision or stoma site, extraction via (5-cm) incision in right iliac fossa, extraction via incision in right lower quadrant. **Comparison:** Laparoscopic colectomy with end ileostomy: 545 patients.	length of stay, or no definition was given. Mortality: death within 30 days after index operation, and/or death occurring in hospital, or no definition was given. **Results:** *Conversion rate:* 9 studies with 421 patients: 5.5 % (95 % CI; 3.6, 8.4) for the laparoscopic group. *Duration of operation:* No meta- analysis possible due to considerable variation in definitions and statistical heterogeneity. *Reoperation:* 8 studies with 918 patients: RR = 0.83 (95 % CI; 0.51, 1.34; P = 0.44) in favour of laparoscopic resection. *Wound infection:* 7 studies with 824 patients: RR = 0.60 (95 % CI; 0.38, 0.95; P = 0.03, I^2 = 0 %) indicating a significant difference in favour of the laparoscopic group. Risk difference = 6 % (95 % CI; 2, 9). NNT = 19 (95 % CI; 11, 70). *Ileus:* 7 studies with 824 patients: RR = 0.83 (95 % CI; 0.43, 1.61; P = 0.58). *Gastrointestinal bleeding:* 5 studies with 367 patients: RR = 1.03 (95 % CI; 0.25, 4.24; P = 0.97) *Intra-abdominal abscess:* 3 studies with 186 patients: RR = 0.27 (95 % CI; 0.08, 0.91; P = 0.04, I^2 = 0 %) in favour of laparoscopic resection. Risk difference = 9.1 % (95 % CI; 1.6, 16.8). NNT = 11 (95 % CI; 6, 63). *Length of stay:* Data from 6 studies with 758 patients available: Mean difference = 3.17 days (95 % CI; 2.37, 3.98; P < 0.001, I^2 = 0 %) favouring laparoscopic surgery. *Mortality:* 8 studies with 918 patients: RR = 0.46 (95 % CI; 0.07, 3.07; P = 0.42). **Author's Conclusion:** Where the procedure can be completed laparoscopically, there may be short-term benefits over open colectomy for colitis. These results cannot be generalized to critically ill patients in need of an emergency subtotal colectomy.		

Wu, X.J. et al. The role of laparoscopic surgery for ulcerative colitis: systematic review with meta-analysis. Int J Colorectal Dis. 25. 949 – 957. 2010

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** SR of 16 controlled clinical studies **Databases:** Medline (PubMed)Embase, Web of Science, Best Evidence, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, Cochrane Controlled Trials Register, Chinese biomedical databases CBM-disk and CNKI **Search period:** Jan 1992 – May 2008 **Inclusion Criteria:** (1) All controlled studies comparing laparoscopic surgery with open surgery for UC; (2) Patients with different degrees and stages in each study; (3) Studies which had been published in full text; (4) Trials primarily comparing at least one of the following outcomes on laparoscopic surgery were eligible: overall complication rate, peritoneal abscess, anastomotic leakages, postoperative bowel obstruction, wound infection, bleeding amount, mortality, operating time, postoperative hospital stay, postoperative fasting time, and re-operation rate. **Exclusion Criteria:** (1) Studies that did not provide statement of informed consent, patient selection, study design, and measurement index; (2) Studie only available as abstract; Multiple published reports from the same study and incomplete studies.	**Intervention:** Overall: 923 patients included. When stated, no significant differences were found among these trials in the following aspects: age, sex, weight index, diagnosis, clinical stage, and surgical methods. Laparoscopic surgery: 396 patients. No details on sex/ age stated. **Comparison:** Open surgery: 527 patiens. No details on sex/ age stated.	**Primary:** Safety in laparoscopic surgery: Overall complication rate, peritoneal abscess, anastomotic leakages, postoperative bowel obstruction, wound infection, bleeding amount, and mortality **Secondary:** Efficacy in laparoscopic surgery: Operating time, postoperative hospital stay, postoperative fasting time, and re-operation rate **Results: Overall complication rate: 12 studies with 833 patients: OR = 0.65 (95 % CI; 0.49, 0.87, P = 0.004)** *Peritoneal abscess:* 6 studies with 530 patients: OR = 0.59 (95 % CI; 0.26, 1.30, P = 0.19) *Anastomotic leakages:* 6 studies with 503 patients: OR = 1.74 (95 % CI; 0.55, 5.47; i>P = 0.34) *Postoperative bowel obstruction:* 6 studies with 571 patients: OR = 0.76 (95 % CI; 0.42, 1.38; i>P = 0.36) Incisional infection: 7 studies with 574 patients: OR = 1.05 (95 % CI; 0.56, 1.95; i>P = 0.88) *Bleeding amount:* No meta-analysis performed. Mortality: No meta-analysis performed. *Operating time:* 5 studies with 530 patients: WMD = 69.29 (95 % CI; 3.68, 134.91; i>P = 0.04), great and significant heterogeneity. *Bowel function recovery:* 5 studies with 163 patients: OR = –0.87 (95 % CI; –2.24, 0.50; no i>P-value presented); great and significant heterogeneity reported but not presented. *Postoperative hospital stay:* 7 studies with 175 patients: WMD = –3.22 (95 % CI; –4.20, –2.24; i>P < 0.01) *Postoperative fasting time:* 5 studies with 162 patients: WMD = –1.37 (95 % CI; –2.15, –0.58 i>P < 0.01) *Re-operation rate:* 8 studies with 635 patients:	Wexner SD (1992) Dis Colon Rectum Araki Y (1998) Kurume Med J Dunker MS (2000) Surg Endosc Araki Y (2001) Kurume Med J Seshadri PA (2001) Surg Endosc Bell RL (2002) Surg Endosc Proctor ML (2002) J Pediatr Surg Marceau C (2007) Surgery Schmitt SL (1994) Int J Colorect Dis Marcello PW (2000) Dis Colon Rectum Dunker MS (2001) Dis Colon Rectum Hashimoto A (2001) Surg Today Brown SR (2001) Dis Colon Rectum Maartense S (2004) Ann Surg Larson DW (2006) Ann Surg Zhang HF (2007) Minim Invasive Ther Allied Technol	**Funding Sources:** Not stated. **COI:** Not stated. **Study Quality:** Quality of each recruited trial was assessed based on the Cochrane Quality Criteria for RCT (not adequate), including randomization, blindness, assessment of compliance, and the baseline similarity between groups for important outcomes. Results of quality assessment not reported. **Heterogeneity:** *Overall complication rate:* I^2 = 34.7 % P = 0.10 *Peritoneal abscess:* I^2 = not presented. P = 0.67 *Anastomotic leakages:* I^2 = not presented. P = 0.80 *Postoperative bowel obstruction:* I^2 = not presented. P = 0.51 *Incisional infection:* I^2 = not presented. P = 0.39 *Bleeding amount:* No meta- analysis possible due to statistical heterogeneity. I^2 and P not reported. *Mortality:* No meta-analysis possible due to statistical heterogeneity. I^2 and P not reported. *Operating time:* I^2 = 90.0 % P < 0.00 001 *Postoperative hospital stay:* I^2 = 0 % P = 0.97 *Postoperative fasting time:* I^2 = 0 % P = 0.99 *Re-operation rate:* I^2 = not presented. P = 0.81 **Publication Bias:** Funnel plots presented but not interpreted. 2/3 funnel plots futile due to lack of studies. **Notes:** All included studies stated as “controlled clinical studies”. Last date of search ended 2 years before publication. Results of quality assessment not stated. Authors refrained from combination of data on mortality and bleeding amount but pooled data on operating time and bowel function recovery with great and significant heterogeneity. Some P- values and results of heterogeneity-test not presented.

		OR = 0.74 (95 % CI; 0.37, 1.46; i>P > 0.05) **Author's Conclusion:** In conclusion, laparoscopic surgery for UC was at least as safe as open surgery according to less fasting time, shorter hospital stay, and lower overall complication rate. Specific complications such as peritoneal abscess, anastomotic leakage, and intestinal obstruction did not differ between laparoscopic group and open group. However, clinical value of laparoscopic surgery for UC needed further evaluation with more well-designed and long-term followup studies.		

AG 5: Ist die darmnahe Rektumresektion der Resektion in der TME-Schicht überlegen?

Bewertungsvorlage:
OXFORD Appraisal Sheet: RCT

Bartels, Sa et al. Short-term morbidity and quality of life from a randomized clinical trial of close rectal dissection and total mesorectal excision in ileal pouch-anal anastomosis. The British journal of surgery. 102. 281 – 287. 2015

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 2 **Study type:** Single-blind randomized clinical trial (single center in the Netherlands). **Number of Patient:** 60 **Recruitung Phase:** Patients were included between June 2007 and August 2011. **Inclusion Criteria:** Patients aged over 18 years with American Society of Anesthesiologists fitness grade I or II, scheduled for single- or multiple- stage ileal pouch–anal anastomosis (IPAA) in an elective setting, were eligible for the study. **Exclusion Criteria:** n.a.	**Intervention:** All single-stage procedures were done hand-assisted with pouch creation via a Pfannenstiel incision. In two-stage procedures, a midline or Pfannenstiel incision was used, depending on the approach (open or laparoscopic) of the emergency colectomy. A 10-cm J-pouch was created with a double- stapled ileoanal anastomosis. A defunctioning ileostomy was created selectively. All procedures were performed by three experienced colorectal surgeons. After ligation of the superior rectal artery, TME dissection was performed in the areolar avascular plane along the mesorectal fascia down to the pelvic floor.	**Primary:** The primary outcome was long-term pouch compliance, determined by barostat measurements; these results will be published at a later stage. **Secondary:** Secondary outcomes were 30-day or in- hospital morbidity, QoL and pouch function in the first year after surgery. Complications were graded according to the Clavien–Dindo classification of surgical complications. If a patient had multiple complications, only the most severe complication was graded. Anastomotic leakage was considered to be present when diagnosed by CT or during reintervention. **Results:** 59 patients were included, (28 CRD and 31 TME). Baseline data were similar, except for more previous abdominal surgery in the TME group. Operating time was longer for patients having CRD (195 min vs. 166 min for TME; P = 0.008). More patients in the TME group had a primary defunctioning ileostomy (7 of 31 versus 1 of 28 for CRD; P = 0.055). Severe complications occurred more frequently in the TME group (10 of 31 versus 2 of 28 for CRD). QoL was better in the CRD group for several subscales of the questionnaires measured at 1, 3 and 6 months after surgery. At 12 months, QoL was similar in the two groups for all subscales. **Author's Conclusion:** CRD led to a lower severe complication rate and better short-term QoL than wide TME.	**Funding Sources:** The authors thank P. van Koperen and M. Vlug for their help in design of the trial and patient inclusion. W.A.B. has received an unrestricted research grant from Ethicon EndoSurgery (Europe). **COI:** The authors declare no other conflict of interest. **Randomization:** "After giving written informed consent, patients were randomized in a 1:1 ratio using sealed, opaque, sequentially numbered envelopes by means of block randomization (block sizes of 6 and 8)." **Blinding:** All patients were blinded for the type of dissection during the entire study period. Medical staff were not blinded. **Dropout Rate/ITT- Analysis:** "All analyses were carried out according to the intention-to-treat (ITT) principle", but according to the flow diagram one patient was excluded due to the development of rectal cancer. **Notes:** No definition of exclusion criteria. Not all patients were CU patients, but also familial adenomatous polyposis and unspecified IBD patients. No tests were performed to ascertain similarity of baseline characteristics. ITT analysis

	Comparison: When using the CRD technique, the superior rectal artery was not ligated. The mesorectum was left in place and dissected in the non- anatomical perimuscular plane, thereby preserving the mesorectal fat. The dissection was performed close to the muscular tube of the rectum using an ultrasonic device.		does not include all patients that were randomized.

AG 5: Soll die restaurative Proktokolektomie primär mit oder ohne Stoma operiert werden?

Bewertungsvorlage:
Oxford SR

Mennigen, R. et al. Morbidity of loop ileostomy closure after restorative proctocolectomy for ulcerative colitis and familial adenomatous polyposis: a systematic review. J Gastrointest Surg. 18. 2192 – 2200. 2014

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Systematic review (26 studies) **Databases:** PubMed **Search period:** Inception – 28.10.2011 **Inclusion Criteria:** patients with ileostomy reversal after restorative proctocolectomy for UC or familial adenomatomous polyposis; sufficient data extraction (calculation of exact number of affected patients) is possible; one of the defined outcome criteria is reported: (1. Demographic data on study populations, such as age, gender, and underlying disease 2. Surgical details of ileostomy reversal 3. Morbidity of ileostomy reversal, including early complications and late complications 4. Mortality of ileostomy reversal.) **Exclusion Criteria:** Study does not include patients with ileostomy reversal after restorative proctocolectomy; defined outcome criteria are not reported, Double publication, data extraction is not possible; Case reports	**Intervention:** *Population:* Total n = 2724 patients with ileostomy reversal after restorative proctocolectomy, the indication for restorative proctocolectomy was ulcerative colitis in 94.3 %. *Intervention:* non interventional study. **Comparison:** non interventional study.	**Primary:** 1. Demographic data on study populations, such as age, gender, and underlying disease (ulcerative colitis or fa- milial adenomatous polyposis). 2. Surgical details of ileostomy reversal (e. g., type of anastomosis, need for laparotomy, and length of hospital stay). 3. Morbidity of ileostomy reversal, including early complications (such as redo operation, anastomotic dehiscence at the stoma closure site, postoperative bowel obstruction, and wound infection) and late complications (stoma site hernia and bowel obstruction later than 30 days after ileostomy reversal). 4. Mortality of ileostomy reversal. **Secondary:** – **Results:** *Details of Ileostomy Reversal* 15 studies provided data on the time interval between proctocolectomy and ileostomy reversal. The weighted mean duration of fecal diversion was 92 days, range of reported means was 61 – 128 days. Ileostomy reversal technique, as reported in 8 publications was hand- sewn anastomosis in 56.6 % and	Tulchinsky H, (2011) Int J Colorectal Dis Fajardo AD, (2010) J Am Coll Surg Heuschen UA, (2001) Ann Surg Shea BJ, (2007) BMC Med Res Methodol Dolejs S, (2011) J Surg Res Selvaggi F, (2010) Am Surg Gunnarsson U, (2004) Colorectal Dis Fonkalsrud EW, (2000) J Am Coll Surg Dolgin SE, (1999) J Pediatr Surg Edwards DP, (1998) Ann R Coll Surg Engl Bain IM, (1996) Ann R Coll Surg Engl Khoo RE, (1994) Am J Surg Seow-Choen F, (1994) J R Coll Surg Edinb Braun J, (1992) Chirurg Poppen B, (1992) Dis Colon Rectum de Silva HJ, (1991) Br J Surg Sugerman HJ, (1991) Ann Surg Sutter PM, (1991) Schweiz Med Wochenschr Lewis P, (1990) Ann R Coll Surg Engl Matikainen M, (1990) Dis Colon Rectum Wexner SD, (1990) Am J Surg	**Funding Sources:** There was no funding for this study. **COI:** n.a. **Study Quality:** n.a. **Heterogeneity:** n.a. **Publication Bias:** As a visual aid to detect a possible publication bias or system- atic heterogeneity of the studies, a funnel plot of effect size (reported morbidity of ileostomy reversal) against study size (number of ileostomy reversals included in the respective study) was created. The funnel plot shows a roughly symmetric inverted funnel shape which makes publication bias unlikely. Reported morbidity values of larger studies are close to the average morbidity (16.5 %), whereas smaller studies report lower and higher values without systematic preference. **Notes:** Only one database was searched. No assessment of study quality!

studies, Case series reporting exclusively patients developing complications (morbidity 100 %); article languages other than English or German.		stapler anastomosis in 43.4 %. A laparotomy was needed for stoma reversal in 8.0 % as reported in six publications. *Morbidity of Ileostomy Reversal:* Early *Complications* Overall morbidity was 16.5 %; there was no mortality. Postoperative complications mandated redo surgery in 3.0 % of patients. Anastomotic dehiscence at the stoma closure site occurred in 2.0 %, postoperative bowel obstruction in 7.6 %. Most cases of postoperative bowel obstruction could be managed conservatively; however, 2.9 % required laparotomy for postoperative bowel obstruction. The rate of wound infection after ileostomy reversal was 4.0 %.Despite the routine endoscopy and pouchography before ileostomy reversal, pouch- related septic complications (including dehiscence of the pouch-anal anastomosis, pouch fistula, and pelvic abscess) developed early after stoma reversal in 1.9 % (as reported in eight studies). *Morbidity of Ileostomy Reversal:* Late *Complications* Stoma site hernias and bowel obstruction (developing later than 30 days after ileostomy reversal) were studied as late complications; they occurred in 1.9 and 9.4 %, respectively.In 3.5 % of patients, the initial diagnosis of ulcerative colitis was revised to Crohn′s disease during follow-up (as reported in nine studies).19,22,27 – 29,31,34,37,39 Although this cannot be considered as “surgical” late complication, Crohn′s disease led to pouch failure at a later stage in 2.4 % of patients in these studies. **Author’s Conclusion:** The considerable morbidity of ileostomy reversal after restorative proctocolectomy reduces the benefit of temporary fecal diversion. However, ileostomy crea-	Feinberg SM, (1987) Am J Surg Harms BA, (1987) Surgery Nasmyth DG, (1986) Br J Surg Metcalf AM, (1985) Annals of surgery	

		tion is still recommended, as it effectively reduces the total number of pouch-related septic complications, which in turn are the main risk factor for bad pouch function, impaired quality of life, or even pouch failure.		

AG 5: Welche Faktoren beeinflussen das Risiko für Chirurgie und postoperative Komplikationen?

Bewertungsvorlage:
Oxford SR

Singh, S. et al. Postoperative Mortality Among Patients With Inflammatory Bowel Diseases: A Systematic Review and Meta-analysis of Population-Based Studies. Gastroenterology. 149. 928 – 937. 2015

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** MA of 21 studies, 17 with UC patients (presumably cohort studies) **Databases:** Medline, Embase **Search period:** 1990 – 2015 **Inclusion Criteria:** (1) Studies with original data and population-based estimates of postoperative mortality (defined as those that studied the entire population of a defined region, used probability sampling, or recruited from medical centers serving a population of known size), (2) studies reporting postoperative mortality for intestinal resection for either CD and/or UC **Exclusion Criteria:** (1) Studies that reported postoperative mortality for only IBD (CD or UC not distinguished)	**Intervention:** 67.057 UC patients, no details on sex/ age available. Shortest follow-up: 1 year Longest follow-up: 14 years **Comparison:** –	**Primary:** Risk of postoperative mortality **Secondary:** – **Results:** Postoperative mortality was significantly lower for elective (0.7 %; 95 % CI, 0.6 %– 0.9 %) vs. emergent surgery (5.3 %; 95 % CI, 3.8 %–7.4 %) for UC ($P < 0.05$). Risk of postoperative mortality in UC did not decrease significantly between 1990 and 2014 (group difference test not decribed). Postoperative mortality did not differ between Europe and North America for UC (group difference test not decribed). **Author's Conclusion:** Based on a systematic review and meta-analysis, postoperative mortality was high after emergent, but not elective, intestinal resection in patients with UC or CD. Optimization of management strategies and more effective therapies are necessary to avoid emergent surgeries.	Ellis MC (2011) World J Surg Hoie O (2007) Gastroenterology Jess T (2007) Inflamm Bowel Dis Kaplan GG (2008) Gastroenterology de Silva S (2011) Clin Gastroenterol Hepatol Nguyen GC (2014) Inflamm Bowel Dis Faiz O (2010) J Am Coll Surg Tottrup A (2012) BMJ Open Longo WE (2003) Am J Surg Roberts SE (2007) BMJ Lesperance K (2009) J Gastrointest Surg Nørgård BM (2013) Aliment Pharmacol Ther Nordenvall C (2014) Aliment Pharmacol Ther Frolkis AD (2014) Inflamm Bowel Dis Vester-Andersen MK (2014) Am J Gastroenterol Velayos FS (2009) Gastroenterology Lynch RW (2012) Gut Causey MW (2011) Dis Colon Rectum Patel SS (2013) Am J Surg Nguyen GC (2014) Gastroenterology	**Funding Sources:** Supported by a New Investigator Award from the Canadian Institute of Health Research and a Population Health Investigator Award from Alberta-Innovates Health-Solutions (G.K.), and by an Alberta Innovates Health Solutions studentship (A.F.). This research was supported by the Alberta IBD Consortium, which is funded by an Alberta Heritage Foundation for Medical Research interdisciplinary team grant (Alberta Heritage Foundation for Medical Research is now Alberta Innovates–Health Solutions). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. **COI:** These authors disclose the following: Gilaad Kaplan has served as a speaker for Janssen, Merck, Schering-Plough, Abbott, and UCB Pharma, has participated in advisory board meetings for Janssen, Abbott, Merck, Schering-Plough, Shire, and UCB Pharma, and has received research support from Merck, Abbott, GlaxoSmith Kline, and Shire; Remo Panaccione has served as a speaker, a consultant, and an advisory board member for Abbott Laboratories, Merck, Schering-Plough, Shire, Centocor, Elan Pharmaceuticals, and Procter and Gamble, has served as a consultant and speaker for Astra Zeneca, has served as a consultant and an advisory board member for Ferring and UCB, has served as a consultant for GlaxoSmith Kline and Bristol Meyers

				Squibb, has served as a speaker for Byk Solvay, Axcan, Janssen, and Prometheus, has received research funding from Merck, Schering-Plough, Abbott Laboratories, Elan Pharmaceuticals, Procter and Gamble, Bristol Meyers Squibb, and Millennium Pharmaceuticals, and has received educational support from Merck, Schering-Plough, Ferring, Axcan, and Janssen; Subrata Ghosh has served as a speaker for Merck, Schering-Plough, Centocor, Abbott, UCB Pharma, Pfizer, Ferring, and Procter and Gamble, has participated in ad hoc advisory board meetings for Centocor, Abbott, Merck, Schering-Plough, Proctor and Gamble, Shire, UCB Pharma, Pfizer, and Millennium, and has received research funding from Procter and Gamble, Merck, and Schering-Plough; Cynthia Seow has served as a speaker for Janssen, Warner-Chilcott, and Schering-Plough, has participated in advisory board meetings for AbbVie, Janssen, and Takeda, and has received research support from Janssen; and Yvette Leung has received research support from and served as a speaker for Janssen, and has participated in advisory board meetings for Abbott, Janssen, and Shire. The remaining authors disclose no conflicts. **Study Quality:** Assessed by adapting guidelines for assessing the quality of prevalence studies and the Cochrane Collaboration bias assessment used in Randomized Controlled Trials – no standard tool. Use of validated criteria for disease diagnosis unclear in 2 UC studies. Patient retention > 70 % not reported in all but 1 UC study. Lost to follow-up not reported in all but 1 UC study. No objections regarding definition of target population, probability sampling or inclusion of entire population, representation of target population with study sample. **Heterogeneity:** *Postoperative mortality in elective surgery:* $I^2 = 0\,\%$, Q = 5.3, df = 6, P = 0.5121, not significant. *Postoperative mortality in emergent surgery:* $I^2 = 85.5\,\%$, Q = 41.5, df = 6, P < 0.0001, significant. *Postoperative mortality 1999 and Earlier:* $I^2 = 85.3\,\%$, Q = 47.5, df = 7, P < 0.0001, significant.

				Postoperative mortality 2000 and Later: $I^2 = 89.5\,\%$, Q = 57.2, df = 6, P < 0.0001, significant. *Postoperative mortality in Europe:* $I^2 = 89.3\,\%$, Q = 74.7, df = 8, P < 0.0001, significant. *Postoperative mortality in North America:* $I^2 = 94.7\,\%$, Q = 94.1, df = 5, P < 0.0001, significant. **Publication Bias:** Begg and Mazumdar rank correlation test for asymmetry used to test for presence of publication bias. Results only stated as "We did not observe publication bias in any of the analyses." **Notes:** Included study types not clearly defined but presumably cohort studies since "population-based" studies were included.

Peng, J.C. et al. The impact of Clostridum difficile on surgical rate among ulcerative colitis patients: A systemic review and meta- analysis. Saudi J Gastroenterol. 21. 208 – 212. 2015

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** SR of 5 studies (4 cohort study, 1 case-control study) **Databases:** MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, ACP Journal Club, DARE, CMR, HTA **Search period:** Inception to December 2013 **Inclusion Criteria:** (1) Cohort or case–control studies involved a comparison group that lacked CDI; (2) patients were given a primary diagnosis of UC; (3) diagnosis of CDI evaluated by enzyme immunoassay of stool for C. difficile toxin A and B or C. difficile stool culture; (4) studies evaluated surgical rate; (5) studies reported an estimate of relative risk or odds ratio, accompanied by a corresponding measure of uncertainty [ie, 95 % confidence interval (CI), standard error, variance, or P value]. **Exclusion Criteria:** (1) Age was younger than 18 years; (2) patients had no known history of IBD; (3) outcome of interest was not reported; (4) incomplete data	**Intervention:** Patients with CDI: 366 patients **Comparison:** Patients with non-CDI: 2.109 patients	**Primary:** Risk for colectomy: Pooled weighted mean of 1 study with 3 month risk, 2 studies with 1 year risk, 1 study with 3 year risk and 1 study with 5 year risk **Secondary:** – **Results:** OR of surgical rate in UC-CDI patients compared with controls: 1.76 (95 % CI = 1.36 – 2.28, P< 0.0001) **Author's Conclusion:** In summary, our analysis suggested an association between C. difficile infection and surgical risks among UC patients. Although no significant heterogeneity was found among the included studies, the number of included studies was small. Therefore, the result should be interpreted with caution and further clinical studies investigating the effect of C. difficile infection on UC patients are warranted. In our analysis, we found CDI increased the surgical rate in UC patients. If it is found that C. difficile does indeed exacerbate UC, this will have profound influence not only on the way we approach C. difficile testing, but also on the way we approach the treatment of UC patients complicated with C. difficile.	Murthy SK (2012) Aliment Pharmacol Ther Kaneko T (2011) Clin Res Hepatol Gastroenterol Navaneethan U (2012) J Crohns Colitis Jodorkovsky D (2009) Dig Dis Sci Kariv R (2010) J Crohns Colitis	**Funding Sources:** Source of Support: This work was supported by the National Natural Science Foundation of China (No. 81 000 161 and No.81 170 362). **COI:** None declared. **Study Quality:** All included studies had NOS scores ≥ 7, which were considered as high quality. Not further elaborated. **Heterogeneity:** No significant: $Chi^2 = 8.15$, df = 4 (P = 0.09); $I^2 = 51\,\%$. **Publication Bias:** Assessed with funnel plot (not appropriate): Visual inspection of funnel plot was symmetrical in distribution indicating no significant publication bias. **Notes:** Funnel plot not appropriate since less then 10 studies included. Fixed- effects-model marginally acceptable since borderline significance regarding heterogeneity. Calculation with random-effects- model would have been useful for comparison.

Yang, Z. et al. Meta-analysis: effect of preoperative infliximab use on early postoperative complications in patients with ulcerative colitis undergoing abdominal surgery. Aliment Pharmacol Ther. 36. 922 – 928. 2012

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** Systematic review and Meta-Analysis (13 observational studies) **Databases:** PubMed and Embase **Search period:** Inception – 03.08.2012 **Inclusion Criteria:** i) population: patients with UC undergoing abdominal operation; (ii) intervention: infliximab treatment prior to surgery; (iii) comparator: controls not receiving infliximab preoperatively; (iv) outcomes: the primary outcome was the total complication rate in a short term after surgery (usually 30 days). Secondary outcomes were the rate of infectious and non-infectious complications in the above period. **Exclusion Criteria:** Studies that did not contain UC patients exclusively (along with Crohn's disease patients).	**Intervention:** Population: 2933 UC patients Internvention: Infliximab treatment prior to surgery. **Comparison:** No treatment with Infliximab prior to surgery.	**Primary:** Total complication rate in a short term after surgery (usually 30 days). **Secondary:** Rate of infectious and non- infectious complications in the above period. **Results:** A total of 13 studies involving 2933 patients were included in our Meta-Analysis. There was no significant association between infliximab therapy preoperatively and total (OR = 1.09, 95 % CI: 0.87 – 1.37, P = 0.47), infectious (OR = 1.10, 95 % CI: 0.51 – 2.38, P = 0.81) and non-infectious (OR = 1.10, 95 % CI: 0.76 – 1.59, P = 0.61) postoperative complications respectively. Infliximab might be a protective factor against infection for the use within 12 weeks prior to surgery (OR = 0.43, 95 % CI: 0.22 – 0.83, P = 0.01). **Author's Conclusion:** In conclusion, preoperative infliximab use does not increase the risk of early postoperative complications in patients with UC undergoing abdominal surgery. The current practice of some doctors to delay operation and to discontinue infliximab for 8 – 12 weeks prior to elective surgery in UC patients may not be warranted. A globally multicentre prospective study is required to confirm the findings of this meta- analysis.	Järnerot G, (2005) Gastroenterology Selvasekar CR, (2007) J Am Coll Surg Schluender SJ, (2007) Dis Colon Rectum Mor IJ, (2008) Dis Colon Rectum Ferrante M, (2009) Inflamm Bowel Dis Coquet-Reinier B, (2010) Surg Endosc Gainsbury ML, (2011) J Gastrointest Surg de Silva S, (2011) Clin Gastroenterol Hepatol Kennedy R, (2012) J Pediatr Surg Schaufler C, (2012) J Pediatr Gastroenterol Bregnbak D, (2012) J Crohns Colitis Nørgård BM, (2012) Aliment Pharmacol Ther	**Funding Sources:** Declaration of funding interests: This study was funded in part by the National Natural Science Foundation of China (grant no.81 172 062 and 81 000 988). The funding source had no role in the design and conduct of the study; collection, analysis, and interpretation of the data; preparation or review of the manuscript; or the decision to submit the manuscript for publication. **COI:** Declaration of personal interests: None. **Study Quality:** "The quality of the study reports was evaluated using the Newcastle-Ottawa scale (NOS), which was developed to assess the quality of nonrandomised studies with its design, content and ease-of-use directed to the task of incorporating the quality assessment in the interpretation of meta- analytic results. The full score of NOS is 9. Study with 7 or above on the NOS was considered as high quality." "Only 7 out of 13 studies were considered as high-quality ones based on the NOS." **Heterogeneity:** "We assessed heterogeneity using the Chi-squared- based Q-test and the I^2 measure of inconsistency. If significant heterogeneity had a Q-test P-value < 0.10 or I2 > 50 %, a random-effect model was replaced." **Publication Bias:** Publication bias was examined using the Egger's test as well as the funnel plots. No publication bias was found. **Notes:** No use of Mesh terms in the search strategy.

Selvaggi, F. et al. Effect of preoperative biologic drugs on complications and function after restorative proctocolectomy with primary ileal pouch formation: systematic review and meta-analysis. Inflamm Bowel Dis. 21. 79 – 92. 2015

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Systematic review and Meta analysis: (7 articles: 5 cohort studies (4 retrospective, 1 prospective), 2 retrospective case matched studies) in the primary analysis.	**Intervention:** *Population:* Patients undergoing IPAA for UC. (162 receiving biologicals, 468 controls). *Intervention:* Infliximab (IFX) treatment before IPAA. (Other- than- IFX agents were also evaluated for inclusion).	Primary: Infectious IPAA-related complications within 30 days after surgery with primary IPAA formation with loop ileostomy, complications occurring after ileostomy closure, and function after IPAA performed while receiving biologic drugs or not.	Selvasekar CR, (2007) J Am Coll Surg Mor IJ, (2008) Dis Colon Rectum Coquet- Reinier B, (2010) Surg Endosc Rizzo G, (2011) Int J Colorectal Dis Kennedy R, (2012) J Pediatr Surg	**Funding Sources:** n.a. **COI:** The authors have no conflicts of interest to disclose. **Study Quality:** "We assessed the quality with 2 scores: the STROBE (STrengthening the Reporting of OBser- vational studies in Epidemiology) Statement,13 which has a similar aim as the CONSORT Statement, but

Databases: PubMed/ MEDLINE, Scopus, EMBASE, Cochrane Database of Systematic Reviews, Google search. **Search period:** 01.2005 – 04.2014 **Inclusion Criteria:** Study design: Prospective or retrospective cohort studies Population: Patients undergoing IPAA for UC Intervention: Infliximab (IFX) treatment Comparison: no Infliximab treatment Outcome: Postoperative complications; Studies mentioning patients with UC, indeterminate colitis, and Crohn's disease were included only if patients with UC were identifiable. Studies were evaluated for potential replication of data. Studies were only included if adequate information concerning both treated groups was available. In the case of duplicate publication or similar data from the same institutions, studies were matched and data were merged. Only studies published as fulltext article were included. Studies evaluating the effects of other- than- IFX agents were evaluated for inclusion. Articles published in English, French, Spanish, Dutch, or Italian were included. **Exclusion Criteria:** Experimental articles. Studies in which the nutritional and general health status and concomitant medications and comorbidities were not reported were excluded from evaluation.	**Comparison:** No Infliximab (IFX) treatment before IPAA	Secondary: Secondary outcomes were infectious and noninfectious complications after any type of surgery for UC (subtotal colectomy or IPAA) in patients receiving biologics or not. Infectious complications were classified as IPAA-related and non-IPAA–related complications. Infectious IPAA-related complications were those directly related to ileoanal anastomosis (i. e., anastomotic leak, pelvic sepsis, abscess, and fistula). We included all anastomotic leaks of the IPAA as local infectious com- plications, even if not classified as such by the authors. Infectious non-IPAA–related complications were infectious complications that are not specific of pouch surgery (i. e., pneumonia and urinary tract infection). When assessing the complications of any type of surgery, anastomotic and (colo)rectal stump leaks and sur- gical site infection (SSI) were all classified as infectious complications, independently from authors' definition, when possible. Results: Patients receiving IFX were more likely developing early (OR = 4.12; 95 % CI, 2.37 – 7.15; P< 0.001) and post-ileostomy closure (OR = 2.27; 95 % CI, 1.27 – 4.05; P = 0.005) ileal pouch–anal anastomosis–related complications. Number needed to harm was calculated to be 5 and 4, respectively. Having received at least 3 IFX effusions increased the risk of early complications (OR 1⁄4 9.59; 95 % CI, 2.92 – 31.44; P 1⁄4 0.0002), whereas an interval of, 12 weeks since last effusion did not (OR 1⁄4 2.35; 95 % CI, 0.98 – 5.64; P 1⁄4 0.06). Meta- analyses of 14 studies reporting on any type of surgery found that IFX showed a trend toward higher total and infectious complications, but no significant differences were observed. Biologics were associated with lower surgical site infection (OR 1⁄4	Eshuis EJ, (2013) J Crohns Colitis Gu J, (2013) Dis Colon Rectum	is designed for observational studies, consisting of a checklist covering 22 items under the head- ings: title and abstract, introduction, methods, results, discussion, and other information. Study quality was classified as high, accept- able, low, and poor according to the STROBE. Also, a personal score was used, which is obtained by the sum of the following variables: number of patients (0 point, < 10 patients per group; 1 point, 11 – 20 patients per group; 2 point, > 20 patients per group), study nature (prospective versus retrospective 1 versus 0 points), patient assessment (0, poor; 1, acceptable; 2, good), disease and IPAA assessment (0, poor; 1, acceptable; 2, good; 3, excellent), pouch-related complication assessment (0 – 1 point), follow-up, and outcome description (0 – 1 point). Articles scored below 3 and those classified as "poor" with STROBE were excluded from evaluation." **Heterogeneity:** Heterogeneity was assessed by means of x^2 test for heterogeneity and I^2 measure of inconsistency. **Publication Bias:** n.a. **Notes:** Risk of bias due to concomitant medication or alternative medication (CyclosporinA, Adalimumab) in the included studies. IFX alternatives are included according to the inclusion criteria, but they are not described or listed before inclusion. Consecutively the terms "biological treatment" and "IFX" are used somewhat interchangeably in the manuscript, which is imprecise. No investigation of publication bias.

		0.67; 95 % CI, 0.45 – 0.99; P ¼ 0.04). **Author's Conclusion:** "When considering patients undergoing any type of abdominal procedure for UC, preoperative use of biologics did not seem to be associated with significant increase of postoperative complications, suggesting that the influence of important confounding factors can hardly be removed. However, early pouch-specific complications and complications occurring after ileostomy closure were significantly higher in patients undergoing IPAA with primary pouch formation receiving IFX. This can be attributed to adverse effect by biologics themselves, but a correlation between recent biological therapy and complications— possibly due to a more severe disease (e. g., clinically masked by a partial response of the antibodies) rather than an effect of the biologics themselves— cannot be ruled out, at least in some pa- tients. In any event, we would suggest delaying the pouch construc- tion in patients who have received biologics. The effects of dose and the optimal interval between the last effusion and surgery need to be further elucidated.		

Billioud, V. et al. Preoperative use of anti-TNF therapy and postoperative complications in inflammatory bowel diseases: a meta- analysis. J Crohns Colitis. 7. 853 – 867. 2013

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Systematic review and Meta-analysis (21 observational studies, including case control studies). **Databases:** MEDLINE **Search period:** Inception – 01.2012. **Inclusion Criteria:** - Observational studies; Adults (> 50 % of patients aged > 16 years); IBD patients: Crohn's disease, ulcerative colitis, and/or IBD unspecified; Patients undergoing abdominal surgery; Compared	**Intervention:** *Population:* 4251 adult IBD patients (> 50 % of patients aged > 16 years); (Crohn's disease, ulcerative colitis, and/or IBD unspecified) undergoing surgery. 977 were treated with anti_TNF, *Intervention:* Non interventional studies: Comparison of preoperative anti- TNF treatment (Infliximab, adalimumab or certolizumab) before under-	**Primary:** Early overall, infectious, or non-infectious postoperative complications. **Secondary:** – **Results:** 21 studies, containing 4251 subjects, reported the prevalence of postoperative complications according to preoperative anti-TNF treatment. Any Postoperative complications: Pooled prevalence n was 21 %, 35 %, and 26 % in Crohn's disease (CD), ulcerative colitis (UC) or inflammatory bowel disease unspecified (IBD-U). The	Canedo J, (2011) Colorectal Dis Colombel JF, (2004) Am J Gastroenterol Indar AA, (2009) World J Surg Kasparek MS, (2012) Inflamm Bowel Dis Kunitake H, (2008) J Gastrointest Surg Marchal L, (2004) Aliment Pharmacol Ther Nasir BS, (2010) J Gastrointest Surg Rizzo G, (2011) Int J Colorectal Dis Tay GS, (2003) Surgery	**Funding Sources:** none. **COI:** The authors declare the following personal interests: VB declares no conflict of interest. ACF has received speaker's fees from Shire and MSD. EDT declares no conflict of interest. JFC has received consulting and lecture fees from Abbott and Merck. XR has received consulting and lecture fees from Abbott and Merck. LPB has received consulting and lecture fees from Abbott and Merck. **Study Quality:** n.a. **Heterogeneity:** Heterogeneity between studies was assessed using the I^2 statistic with a cutoff

patients preoperatively treated or not treated with anti-TNF (Infliximab, adalimumab or certolizumab) Assessment of early overall, infectious, or non-infectious postoperative complications (within 30 days postoperatively) **Exclusion Criteria:** Studies investigating pediaritic patients exclusively.	going abdominal surgery. **Comparison:** –	prevalence of any postoperative complication was increased in IBD patients who underwent preoperative anti-TNF therapy (OR: 1.25; 95 % CI: 1.02 – 1.53). In CD patients who underwent preoperative anti-TNF therapy (OR: 1.45; 95 % CI: 1.03 – 2.05). The confounding effect of concomitant therapies could not be studied. Infectious postoperative complications. Pooled prevalence was was 16 %, 17 %, and 15 % in CD, UC/IBD-U and IBD. The prevalence of infectious postoperative complications was increased in CD patients who underwent preoperative anti-TNF therapy (OR: 1.45; 95 % CI: 1.03 – 2.05). The confounding effect of concomitant therapies could not be studied. **Author's Conclusion:** In conclusion, the present study suggests that preopera- tive anti-TNF therapy could be associated with a higher rate of overall post-operative complications in IBD patients, with an increased risk of postoperative infections in CD. UC patients receiving preoperative anti-TNF treatment do not seem to be at an increased risk of experiencing post-operative complications. In the present study, the confounding effect of concomitant therapies could not be studied. Further prospective studies about the relationship between anti-TNF and post-operative complications, able to control potential confounding factor and using homogeneous classification of postoperative complications, are keenly awaited before definitive recommendations can be made.	Appau KA, (2008) J Gastrointest Surg Bregnbak D, (2012) J Crohns Colitis Coquet-Reinier B, (2010) Surg Endosc Gainsbury ML, (2011) J Gastrointest Surg de Silva S, (2011) Clin Gastroenterol Hepatol Ferrante M, (2009) Inflamm Bowel Dis Regadas FS, (2011) Colorectal Dis Schluender SJ, (2007) Dis Colon Rectum Selvasekar CR, (2007) J Am Coll Surg Syed A, (2011) Gastroenterology Eshuis EJ, (2010) Gut Mor IJ, (2008) Dis Colon Rectum	of 50 %, and the χ^2 test with a P value < 0.10, used to define a statistically significant degree of heterogeneity. **Publication Bias:** We planned to assess for the evidence of publication bias by applying Egger's test to funnel plots of Ors when a sufficient number of studies (more than ten) existed. **Notes:** Only one database was searched. No assessment of study quality. Age definition for adults seems arbitrary. Heterogeneity was assessed but funnel plots were not shown. No overall effect, weighting of studies or heterogeneity tests are displayed in the forest plots.

AG 5: Welche Faktoren beeinflussen das Risiko für Chirurgie und postoperative Komplikationen?

Bewertungsvorlage:
OXFORD Appraisal Sheet: RCT

Oshima, T et al. Preoperative oral antibiotics and intravenous antimicrobial prophylaxis reduce the incidence of surgical site infections in patients with ulcerative colitis undergoing IPAA. Diseases of the colon and rectum. 56. 1149 – 1155. 2013

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 3 **Study type:** Randomized non-blinded clinical trial (single-center). **Number of Patient:** 200 **Recruitung Phase:** 01.01.2006 – 30.04.2009 **Inclusion Criteria:** 200 consecutive patients with UC undergoing elective IPAA were entered into the study. **Exclusion Criteria:** Subjects with wound class 4, emergent surgery, allergy to antibiotics, and given antibiotics within 2 weeks before surgery were excluded.	**Intervention:** Group A: Combined use of preoperative oral antibiotics and intravenous antimicrobial prophylaxis. **Comparison:** Group B: Intravenous antimicrobial prophylaxis alone.	**Primary:** Rate of overall surgical site infection (SSI) according to intention-to- treat (ITT) analysis. **Secondary:** *Intervention:* Clinical outcome per protocol (PP)- based analysis; Rate of Clostridium difficile (CD) toxin detected from stool in group A compared pre- and post-surgery; occurrence of CD-related disease. *Surgical procedure for both groups:* All surgeries were done with the open approach, and the incision was made in the wall of the median lower abdomen. all patients had restorative proctocolectomy with the creation of an ileal J-pouch reservoir. ileal J-pouch was made by using a linear stapler, the mucosal surface was turned over to achieve complete hemostasis, and the opened bowel was closed by albert-lembert sutures with the use of absorbable suture material (Vicryl 3 – 0). IPAA was performed by using a transanal handsewn technique. the wound was protected by an alexis wound retractor, and the abdominal cavity was irrigated with 3000 ml of saline before closure. the gloves of all participants in the surgery were changed every 2 hours. the peritoneum and fascia were sutured. the wound was irrigated with 200 ml of saline solution before closure. skin was closed with a stapler. intraperitoneal drains were inserted through a separate incision. **Results:** The incidence of overall surgical site infection was significantly lower in group A (6/97 patients, 6.1 %) than in group B (22/98 patients, 22.4 %) (p = 0.0024). In multivariate analysis, the administration of oral antibiotics (OR, 0.178; 95 % CI, 0.057 – 0.552; p = 0.003) and ASA score ≥ 3 (OR, 5.343; 95 % CI, 1.595 – 17.891; p = 0.007) were independent risk factors for surgical site infection. **Author's Conclusion:** "Our study shows that a combination of oral non- absorbable antibiotics and intravenous antibiotics significantly lowers the incidence of SSI compared with intravenous antibiotics alone. We therefore recommend the use of oral nonabsorbable antibiotics in addition to parenteral anti-biotics and mechanical bowel preparation in patients with UC undergoing IPAA.	**Funding Sources:** none reported. **COI:** n.a. **Randomization:** Assignment was randomized to group A or B in 1:1 ratio. *Randomization key*/scheme/algorithm/sequence *is not described*. **Blinding:** No blinding was performed, open label study. **Dropout Rate/ITT-Analysis:** ITT analysis was performed, in which the dropouts (3/2 out of 100 in group A/B) were NOT considered. Consecutive protocol violations (6/7) in group A/B were included in the ITT analysis. 9 % dropout in each group taking the protocol violations in account. **Notes:** The open label design is the major limitation. Blinding could have been easily achieved by administering an oral placebo with similar appearance compared to the oral antibiotics. The objective is not entirely objective and observer bias due to lack of blinding can potentially influence the outcome. Randomization sequence is not described. ITT analysis excludes patients lost to follow up!

AG 5: Welche Verfahren sind effektiv zur Behandlung einer Pouchitis?

Bewertungsvorlage:
Oxford SR

Singh, Siddharth et al. Treatment and prevention of pouchitis after ileal pouch-anal anastomosis for chronic ulcerative colitis. Cochrane Database of Systematic Reviews 2015

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** Sytematic Review and Meta-Analysis (13 RCTs, 2 for Meta-analysis). **Databases:** MEDLINE, EMBASE and the Cochrane Library. **Search period:** Inception – 10.2014. **Inclusion Criteria:** *Types of studies:* RCTs; placebo or other treatment as comparison *Types of participants:* Adult patients (age ≥ 18 years) who had undergone IPAA for chronic ulcerative colitis and were at risk of, or had developed acute or chronic pouchitis. Pouchitis was variably defined by 1) solely clinical criteria; 2) clinical criteria in combination with endoscopic and histologic criteria; or 3) PDAI. Pouchitis was categorized by disease activity, as active (defined clinically as the presence of mild-to-severe symptoms or by a PDAI ≥ 7) or in remission (absence of symptoms or by a PDAI < 7), or by disease duration as acute (symptom duration ≤ 4 weeks) or chronic (symptom duration > 4 weeks). *Types of interventions:* 1. Oral metronidazole 20 mg/kg/day, or 500 mg twice daily; 2. Oral VSL#3 probiotic bacterial formulation containing 300 billion bacteria per gram of viable lyophilized bacteria with four strains of Lactobacilli, three strains of Bifidobacterium and one strain of Streptococcus salivarius subspecies Thermophilus; 6 g/day, 3 g/day, 3 g twice daily, 3 g once per day; 3. Bismuth carbomer foam enemas containing	**Intervention:** Population: Adult patients total n = 517 in 13 studies, age ≥ 18 years who had undergone IPAA for chronic ulcerative colitis and were at risk of, or had developed acute or chronic pouchitis. Pouchitis was variably defined by 1) solely clinical criteria; 2) clinical criteria in combination with endoscopic and histologic criteria; or 3) PDAI. Pouchitis was categorized by disease activity, as active (defined clinically as the presence of mild-to-severe symptoms or by a PDAI ≥ 7) or in remission (absence of symptoms or by a PDAI < 7), or by disease duration as acute (symptom duration ≤ 4 weeks) or chronic (symptom duration > 4 weeks). *Types of interventions:* 1. Oral metronidazole 20 mg/kg/day, or 500 mg twice daily; 2. Oral VSL#3 probiotic bacterial formulation containing 300 billion bacteria per gram of viable lyophilized bacteria with four strains of Lactobacilli, three strains of Bifidobacterium and one strain of Streptococcus salivarius subspecies Thermophilus; 6 g/day, 3 g/ day, 3 g twice daily, 3 g once per day; 3. Bismuth carbomer foam enemas containing 513 mg bismuth citrate (270 mg metallic bismuth) complexed with carbomer (a synthetic high-molecular weight polymer of acrylic acid cross	**Primary:** *Clinical improvement or remission of pouchitis* in patients with acute or chronic pouchitis (treatment of pouchitis); *Proportion of patients without episodes of pouchitis after IPAA* (prevention of pouchitis). The exact definition of improvement and remission varied from study to study limiting the ability to make comparisons across studies. However, the definition of improvement or remission used in each study was used for extraction of data from the individual studies for the purposes of this systematic review. **Secondary:** Adverse events **Results:** *Treatment of acute pouchitis:* The results of one small study (16 participants) suggest that ciprofloxacin may be more effective than metronidazole for the treatment of acute pouchitis. One hundred per cent (7/7) of ciprofloxacin patients achieved remission at two weeks compared to 33 % (3/9) of metronidazole patients. A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was very low due to high risk of bias (no blinding) and very sparse data (10 events). There was no difference in the proportion of patients who had at least one adverse event (RR 0.18, 95 % CI 0.01 to 2.98). Adverse events included vomiting, dysgeusia or transient peripheral neuropathy. There were no differences between metronidazole and budesonide enemas in terms of clinical remission, clinical improvement or adverse events. Adverse events included anorexia, nausea, head-	Brown SJ, (2004) Gastroenterology Gionchetti P, (2000) Gastroenterology Gionchetti P, (2003) Gastroenterology Ha CY, (2010) Gastroenterology Isaacs KL, (2007) Inflam Bowel Dis Joelsson M, (2001) Scand J Gastroenterolo Kuisma J, (2003) Aliment Pharm Therap Mimura T, (2004) Gut Pronio A, (2008) Inflamm Bowel Dis Sambuelli A, (2002) Aliment Pharm Therap Shen B, (2001) Gastroenterology Tremaine WJ, (1997) Aliment Pharm Therap Wischmeyer P, (1993) Mayo Clin Proc	**Funding Sources:** Funding for the IBD/FBD Review Group (September 1, 2010 – August 31, 2015) has been provided by the Canadian Institutes of Health Research (CIHR) Knowledge Translation Branch (CON – 105 529) and the CIHR Institutes of Nutrition, Metabolism and Diabetes (INMD); and Infection and Immunity (III) and the Ontario Ministry of Health and Long Term Care (HLTC3968FL-2010 – 2235). Miss Ila Stewart has provided support for the IBD/FBD Review Group through the Olive Stewart Fund. **COI:** Siddharth Singh: None known Andrea M Stroud: None known Stefan D Holubar: None known Darrell S Pardi has received (fee(s) from Seres Therapeutics, Cubist, Pfizer, Santarus and Optimer for consultancy; grants or grants pending from Salix, Cubist, Janssen, Rebiotix, Seres Health, and Viropharma and payment for development of educational presentations from Merck, Cubist and Optimer. None of my competing interests are directly related to this Cochrane review. Dr. William J Sandborn – has received consulting fees from Abbott, ActoGeniX NV, AGI Therapeutics Inc, Alba Therapeutics Corp, Albireo, Alfa Wasserman, Amgen, AM-Pharma BV, Anaphore, Astellas, AthersysInc, Atlantic Healthcare Ltd, Aptalis, BioBalance Corp, Boehringer-Ingelheim, Bristol-Myers Squibb, Celgene, Celek Pharmaceuticals, Cellerix SL, Cerimon Pharmaceuticals, ChemoCentryx, CoMentis, Cosmo Technologies, Coronado Biosciences, Cytokine Pharmasciences, Eagle Pharmaceuticals, EnGeneInc, Eli Lilly, Enteromedics, Exagen Diagnostics Inc, Ferring Pharmaceuticals, Flexio Therapeutics Inc, Funxional Therapeutics Ltd, Genzyme Corp, Gilead Sciences, Given Imaging, GlaxoSmithKline, Human Genome Sciences, Ironwood Pharmaceuticals, Janssen

513 mg bismuth citrate (270 mg metallic bismuth) complexed with carbomer (a synthetic high-molecular weight polymer of acrylic acid cross linked with poly alkenyl polyether) administered once nightly; 4. Glutamine suppositories containing 1 g of L-glutamine in a polyethylene glycol base administered twice daily; 5. Butyrate suppositories containing 40 mmol sodium butyrate in a polyethylene glycol base administered twice daily; 6. Ciprofloxacin 1000 mg daily; 7. Rifaximin 400 mg orally three times daily; 8. Lactobacillus GG in two gelatine capsules orally twice daily versus microcrystalline cellulose- only gelatin placebocapsules; 9. Budesonide enema 2 mg/100 mL at bedtime plus oral placebo tablets (Sambuelli 2002); 10. Allopurinol 100 mg twice daily; 11. Tinidazole 500 mg daily; and 12. Bifidobacterium longum BB- 536.

Types of outcome measures Proportion of patients with clinical improvement or remission of pouchitis in patients with acute or chronic pouchitis (treatment of pouchitis), or the proportion of patients with no episodes of pouchitis after IPAA (prevention of pouchitis). The exact definition of improvement and remission varied from study to study limiting the ability to make comparisons across studies. However, the definition of improvement or remission used in each study was used for extraction of data from the individual studies for the purposes of this systematic review. The proportion of patients who developed at least one adverse event was a secondary outcome.

Exclusion Criteria: Inclusion criteria not met.

linked with poly alkenyl polyether) administered once nightly; 4. Glutamine suppositories containing 1 g of L-glutamine in a polyethylene glycol base administered twice daily; 5. Butyrate suppositories containing 40 mmol sodium butyrate in a polyethylene glycol base administered twice daily; 6. Ciprofloxacin 1000 mg daily; 7. Rifaximin 400 mg orally three times daily; 8. Lactobacillus GG in two gelatine capsules orally twice daily versus microcrystalline cellulose-only gelatin placebocapsules; 9. Budesonide enema 2 mg/100 mL at bedtime plus oral placebo tablets (Sambuelli 2002); 10. Allopurinol 100 mg twice daily; 11. Tinidazole 500 mg daily; and 12. Bifidobacterium longum BB-536.

Comparison: Placebo or other medical treatment.

ache, asthenia, metallic taste, vomiting, paraesthesia, and depression.

There were no differences between rifaximin and placebo in terms of clinical remission, clinical improvement, or adverse events. Adverse events included diarrhea, flatulence, nausea, proctalgia, vomiting, thirst, candida, upper respiratory tract infection, increased hepatic enzyme, and cluster headache.

There was no difference in clinical improvement between Lactobacillus GG and placebo.

The results of these studies are uncertain due to very low quality evidence.

Treatment of chronic pouchitis: A pooled analysis of two studies (76 participants) suggests that VSL#3 may be more effective than placebo for maintenance of remission. 85 % (34/40) of VLS#3 patients maintained remission at 9 to 12 months compared to 3 % (1/36) of placebo patients (RR 20.24, 95 % CI 4.28 to 95.81). A GRADE analysis indicated that the quality of evidence supporting this outcome was low due to very sparse data (35 events). Adverse events included abdominal cramps, vomiting and diarrhea. There was no difference in effectiveness between glutamine and butyrate suppositories for maintenance of remission. There was no difference in clinical improvement or adverse event rates between bismuth carbomer foam enemas and placebo. Adverse events included diarrhea, worsening symptoms, cramping, sinusitis, and abdominal pain. The results of these studies are uncertain due to very low quality evidence.

Prevention of pouchitis: The results of one small study (40 participants) suggest that VSL#3 may be more effective than placebo for prevention of pouchitis. 90 % (18/20) of VSL#3 patients had no episodes of

Biotech, Inc.; Kalo- Bios Pharmaceuticals, Lexicon Pharmaceuticals, Lycera Corp, Meda Pharmaceuticals, Merck Research Laboratories, Merck Serono, Millenium Pharmaceuticals, Nisshin Kyorin Pharmaceuticals, Novo Nordisk, NPS Pharmaceuticals, Optimer Pharmaceuticals, Orexigen Therapeutics Inc, PDL Biopharma, Pfizer, Procter and Gamble, Prometheus Laboratories, ProtAb Ltd, Purgenesis Technologies Inc, RelypsaInc, Roche, Salient Pharmaceuticals, Salix Pharmaceuticals, Santarus, Schering Plough, Shire Pharmaceuticals, Sigmoid Pharma Ltd, Sirtris Pharmaceuticals, SLA Pharma UK Ltd, Targacept, Teva Pharmaceuticals, Therakos, TilliottsPharma AG, TxCell SA, UCB Pharma, Viamet Pharmaceuticals, Vascular Biogenics Ltd, Warner Chilcott UK Ltd and Wyeth; research grants from Abbott, Bristol- Myers Squibb, Genentech, GlaxoSmithKline, Janssen Pharmaceutical Research & Development, LLC, Milennium Pharmaceuticals, Novartis, Pfizer, Procter and Gamble, Shire Pharmaceuticals and UCB Pharma; payments for lectures/speakers bureau from Abbott, Bristol-Myers Squibb and Janssen Pharmaceutical Research & Development, LLC; and holds stock/stock options in Enteromedics.

Study Quality: Methodological quality was assessed using the Cochrane risk of bias tool as described in the Cochrane Handbook for Systematic Reviews of Interventions. Three studies were judged to be of high quality. Two studies were judged to be low quality and the quality of the other studies was unclear. The overall quality of the evidence supporting the primary and secondary outcomes was evaluated using the GRADE approach. The evidence for all outcomes was considered to be very low.

Heterogeneity: Not described, but Chi^2 and I^2 was calculated. $I^2 = 0$ % and NS in the only Meta-analysis.

Publication Bias: n.a.

Notes: Inclusion criteria section already contain references to articles. This section is oddly specific suggesting post hoc definition of incclusion criteria. No

		acute pouchitis during the 12 month study compared to 60 % (12/20) of placebo patients (RR 1.50, 95 % CI 1.02 to 2.21). A GRADE analysis indicated that the quality of evidence supporting this outcome was low due to very sparse data (30 events). Another small study (28 participants) found that VLS# 3 was not more effective than no treatment for prevention of pouchitis. Bifidobacterium longum, allopurinol and tinidazole were not more effective than placebo for prevention of pouchitis. The results of these studies are uncertain due to very low quality evidence. **Author's Conclusion:** For acute pouchitis, very low quality evidence suggests that ciprofloxacin may be more effective than metronidazole. For chronic pouchitis, low quality evidence suggests that VSL#3 may be more effective than placebo for maintenance of remission. For the prevention of pouchitis, low quality evidence suggests that VSL#3 may be more effective than placebo. Well designed, adequately powered studies are needed to determine the optimal therapy for the treatment and prevention of pouchitis.		investigation or discussion of publication bias. Quality of the evidence was judged to be very low for all outcomes, mainly due to sparsity of data. Only 2 of the 13 studies could be meta-analyzed together.

AG 5: Wie soll der Pouch bei der restaurativen Proktokolektomie gestaltet sein?

Bewertungsvorlage:
OXFORD Appraisal Sheet: RCT

McCormick, P H et al. The ideal ileal-pouch design: a long-term randomized control trial of J- vs W-pouch construction. Dis. Colon Rectum. 55. 1251 – 1527. 2012

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 2 **Study type:** RCT **Number of Patient:** 94 patients (64 analyzed) **Recruitung Phase:** May 1998 – Jan 2003 **Inclusion Criteria:** All patients with preoperative diagnosis of ulcerative colitis who presented to the 3 participating surgeons for IPAA **Exclusion Criteria:** Not described.	**Intervention:** J-pouch: 49 patients (26 men, 23 women); Mean age: 37.6 years; Mean weight: 71.8 kg. Designed with efferent loop length of 20 cm. Creation of enterotomy, pouch was formed with 3 firings of 75-mm linear stapler, blue	**Primary:** Follow up after 1 year (85 % of the patients) and long-term follow-up after an average of 8.7 years after initial pouch functioning (68 % of the patients). Functional characteristics: stool frequency, nocturnal frequency, pad usage, incontinence nature and frequency, antidiarrheal medication requirements, subsequent complications/procedures, occurrence of pouchitis. **Secondary:** Quality of Life: Assessment made with the Mayo Clinic validated instrument, incontinence assessed by using a modified Wexner scoring system.	**Funding Sources:** Not stated. **COI:** Financial disclosure: None reported. **Randomization:** Randomization process centralized in RBWH and conducted by the use of batches of sealed envelopes. **Blinding:** Patients and data collectors were blinded to pouch type until analysis. **Dropout Rate/ITT- Analysis:** No ITT- analyses (30 participants [31.9 % of study population] not

	3.8- mm cartridge (Ethicon), or 2 firings of 100-mm stapler. End of the ileum amputated with stapler to close efferent limb of the pouch. A handsewn 2/0 prolene pursestring used to secure circular stapler anvil in the pouch, formation of anastomosis with a double- stapled technique to the top of the anal canal with the use of a 29- or 33-mm circular cutting stapler. No mucosectomy was performed, and none of the patients had a pre- or postoperative diagnosis of high-grade dysplasia low in the rectum. **Comparison: -** W-pouch: 45 patients (21 men and 24 women); Mean age: 36.6 years; Mean weight: 68.3 kg. Constructed by using 4 limbs of terminal ileum measuring 12, 12, 10, and 12 cm from distal to proximal *(Harms modification)*. Each limb opened on antimesenteric border, continuous handsewn full-thickness 3 – 0 polydiaxanone sulfate suture (Ethicon) opposed each cut limb edge, with exception of immediate area of intended circular stapler insertion where interrupted polydiaxanone sulfate sutures used. Final continuous suture brought the edge of the most proximal and distal limbs together closing the pouch with a double- stapled technique to the top of the anal canal with the use of a 29- or 33-mm circular cutting stapler.	**Results: Operation Details:** Average operating time for W-pouch was 215 minutes and 195 minutes (no CI stated, $p < 0.05$) for J-pouch. 77 % of the J-pouch group and 74 % of the W-pouch group with defunctioning ileostomy, p = not significant (ns). 29-mm circular stapler used in 72 of cases, 33-mm stapler used in 22 cases (*no group distribution reported*). 81 % of patients with previous colectomy (*no group distribution reported*, p = ns). No difference in length of stay (no details reported). **Reversal:** Removal of 3 pouches reported at long term follow-up (2 in W-pouch group: 1 fistulas, 1 poor function; 1 in J-pouch group: 1 pelvic sepsis postoperatively). No significant difference in leak rates or postoperative complications between groups. **Bowel Frequency:** At 12-month assessment, W-pouch group had median of 5 (interquartile range (IQR) 4 – 6) bowel movements over a 24-hour period, J-pouch group had a 24-hour frequency of 7 (IQR 6 – 8) ($p < 0.001$). Daytime frequency at 1 year in W-pouch group was 4 (IQR 3 – 5) and 6 (IQR 4 – 7) in the J-pouch group ($p < 0.001$). Nocturnal frequency was 1 (IQR 1 – 1) in the W- pouch group and 1 (IQR 1 – 2) in the J-pouch group, p = 0.190. At long-term follow-up, W-pouch frequency over 24-hours was 6 (IQR 4 – 8) and 6.5 (IQR 5 – 8) in the J- group frequency (p = 0.36). Frequency of 5 in the W- pouch group at daytime (IQR 3.5 – 6.5) and 5.5 (IQR 4 – 7) in the J-group (p = 0.233). Nocturnal frequency of 1 (IQR 0 – 1) in both groups (p = 0.987). **Urgency:** No significant difference between groups at either time point. **Pad Usage:** No significant difference between groups at either time point. **Incontinence:** No significant difference between groups at either time point. **Quality of Life:** No significant difference between groups at either time point. **Medication Usage:** At long-term follow-up, use of antidiarrheal medication more common in the J-pouch group (34 % of patients with J-pouch and 17 % of patients with W-pouch were taking loperamide, $p < 0.05$). 9 % of patients with J-pouch and 3 % of patients with a W-pouch were taking codeine phosphate (p = ns). **Postoperative Complications and Pouchitis:** 3 episodes of postoperative pelvic sepsis in each group, managed successfully with antibiotics and drainage (1 patient in W-group lost pouch due to a leak). Conservatively managed small-bowel obstruction or ileus in 3 patients with J-pouch, 4 with a W-pouch. 2 wound infections requiring drainage in patients with a J-pouch, 1 patient with a W-pouch had a pulmonary embolism. No statistical difference between the groups regarding these complications. Long-term complications: 1 or more episodes of pouchitis in 53 % of patients with J-pouch and 33 % of patients with W-pouch (p = ns). **Author's Conclusion:** This study demonstrates that the W-pouch has lower daytime frequency in comparison with the J-pouch at 1 year, but, in regard to all other functional assessment parameters, there are no differences between the groups and, reassuringly, no variation in quality of life at this	analyzed). "Of the 30 patients that were not followed up […], 8 were successfully contacted but did not complete the questionnaire, 3 had died, and the remaining 19 were not traceable". **Notes:** Unclear, if groups were similar at baseline: 5 more men in J-pouch group, no p-value stated. Only weight and age reported (no significant differences). No ITT-analyses (31.9 % of study population not analyzed, *deaths not analyzed but excluded*). Long-term complication data based on patients' own evaluations.

		time point. In the longer-term assessment, however, even this disparity between the groups is extinguished, and there is no discernible difference between the 2 pouch designs. We conclude that this study compellingly demonstrates that the J-pouch is the present ideal pouch design, because it has been clearly shown to be easier to construct, while having minimal functional disadvantages, which are attenuated over time and which have no significant impact on the patient's quality of life.	

AG 6: Welche komplementärmedizinischen Verfahren sind effektiv zur Behandlung der CU?

Bewertungsvorlage:
Oxford SR

Fujiya, M. et al. Probiotic treatments for induction and maintenance of remission in inflammatory bowel diseases: a meta-analysis of randomized controlled trials. Clin J Gastroenterol. 7. 1 – 13. 2014

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** MA of 20 RCTs (CU: 16 studies, CD: 5 studies, Pouchitis: 2 studies) **Databases:** PubMed and the Cochrane Controlled Trials Register **Search period:** 1997 to August 2013 **Inclusion Criteria:** 1) english language 2)randomized controlled studies 3) studies comparing probiotics with standard treatments used for IBD or placebo 4) adult and pediatric studies 5) High- quality RCTs which scored three points or more (in Jadad score) **Exclusion Criteria:** Reviews, case reports, and abstracts and presentations of meetings	**Intervention:** Probiotic treatment on patients with IBD (CU, CD and pouchitis). total number of patients: 1-Respoonse rate: total of 362 patients (probiotic treatments n = 184, placebo n = 178 patients with or without conventional therapies). 2-remission induction rate: total of 230 patients (probiotic treatments n = 140 patients, placebo n = 90 patients with or without conventional therapies). 3-maintenance therapy: total of 638 patients (probiotic treatments n = 316 patients, n = 322 patients standard therapy (mesalazine)) **Comparison:** probiotic treatment (Escherichia coli, Lactobacillus, VSL#3 and Bifidobacterium) vs conventional therapy (mesalazine, balsalazide) or placebo.	**Primary:** 1) response rate 2) the remission induction rate 3) maintenance therapy for UC. **Secondary:** relapse time **Results:** 1) response rate (5 studies): probiotic treatment group was 51.1 % (94/184), placebo group was 28.7 % (51/178). RR = 1.81, 95 % CI: 1.40 – 2.35. 2) remission induction rate (6 studies): probiotics therapy group was 53.6 % (75/140) vs.non-probiotics therapy 38.9 % (35/90). RR = 1.56, 95 % CI was 0.95 – 2.59. 3) maintenance of remission (5 studies): The total relapse rate of the probiotics therapy group was 25.0 % (84/336) and that in the mesalazine group was 26.3 % (88/334). RR = 1.00, 95 % CI was 0.79 – 1.26. **Author's Conclusion:** In summary, the present study identified 20 high- quality RCTs which investigated the effects of probiotics on the induction or maintenance of remission in IBD. From the results of the validation of these RCTs, probiotic treatment is a practical option for UC patients as both remission induction and maintenance therapy, but such treatment is not effective in CD patients. Because there were many	Sood A (2009) Clin Gastroenterol Hepatol. Tursi A (2010) Am J Gastroenterol Kato K (2004) Aliment Pharmacol Ther Oliva S (2012) Aliment Pharmacol Ther Furrie E (2005) Gut 2005 Rembacken BJ (1999) Lancet Tursi A (2004) Med Sci Monit Miele E (2009) Am J Gastroenterol Matthes H (2010) BMC Complement Altern Med Kruis W (1997) Aliment Pharmacol Ther Kruis W (2004) Gut Zocco MA (2006) Aliment Pharmacol Ther Wildt S (2011) J Crohns Colitis.	**Funding Sources:** n.s. **COI:** The authors declare that they have no conflict of interest. **Study Quality:** Risk of bias for: Random sequence generation: 8x low, 6x unclear Allocation concealment: 8x low, 6x unclear blinding: 4x high, 10 × low incomplete outcome data: 1 × high, 13 × low selective reporting: low **Quality:** Jadad score > = 3. **Heterogeneity:** 1) heterogeneity of these five studies was very low (P = 0.43, I2 = 0 %) 2) inter-study heterogeneity was high (P = 0.048, I2 = 58.4 %) 3) inter-study heterogeneity was very low (P = 0.7075, I2 = 0 %), **Publication Bias:** 1) low publication bias 2) low publication bias 3) low publication bias **Notes:** –

		variations in the conditions among the studies, future studies on the value of probiotic treatment in IBD should consider the effects of different probiotics and different regimens, together with the specific patient populations which are most likely to benefit from probiotic treatment.		

Garg, Sushil K et al. Helminth therapy (worms) for induction of remission in inflammatory bowel disease. Cochrane Database of Systematic Reviews 2014

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** SR of 2 RCTs (1 c UC, 1 × CD) **Databases:** Cochrane InflammatoryBowelDisease and Functional Bowel Disorders (IBD/FBD)Group SpecialisedRegister; the CochraneCentral Register of Controlled Trials (CENTRAL, The Cochrane Library); PubMed; EMBASE; CINAHL; LILACS; KoreaMed; IndMed; PakMediNet; CAB Abstracts;Web of Science; BIOSIS Previews; CNKI; ISCTRN; ClinicalTrials.gov; ICTRP; and Google. **Search period:** Inception to July 2013. **Inclusion Criteria:** 1) Randomised controlled trials using adequate or quasi methods of randomisation were considered for inclusion. Single-blind, double- blind, triple-blind or open label studies were all eligible for inclusion. 2) patients with active UC or CD, confirmed by a combination of clinical, endoscopic and histological criteria. 3) exposure to a helminth species or combination of species not normally found in humans. **Exclusion Criteria:** 1) Helminth-derived molecular products	**Intervention:** human participants were exposed to a helminth species or combination of species: ▪ at any developmental stage of the parasite (eggs, cysts, larvae, cercariae, adult worms); ▪ in any dose; ▪ by any route (oral, percutaneous, other); and ▪ for any duration of exposure (hours, days, weeks, months). We considered studies where the intervention was exposure to a helminth species or combination of species not normally found in humans. UC Study: 54 patientes: n = 30, placebo n = 24) **Comparison:** The control group received placebo (i. e. sham helminth exposure), no treatment or any other active intervention. Included study: 2500 T.suis eggs vs placebo orally ad 2-weeks interval for 12 weeks.	**Primary:** The proportion of patients who achieved clinical remission as defined by primary studies and expressed as a percentage of those participants randomised to the intervention (i. e. intention-to-treat analysis). **Secondary:** 1. Clinical, histologic, endoscopic improvement as defined by the authors. 2. Endoscopic mucosal healing (endoscopic remission). 3. Change in disease activity index score. 4. Quality of life. 5. Hospital admissions. 6. Requirement for intravenous corticosteroids. 7. Surgery. 8. Adverse events. 9. Study withdrawal. **Results:** Induction of remission at 12 weeks: There was no statistically significant difference in the proportion of participants who achieved clinical remission at 12 weeks. Ten per cent (3/30) of patients in the T. suis arm achieved clinical remission compared to 4.2 % (1/24) of patients in the placebo arm (RR 2.40, 95 % CI 0.27 to 21.63). Clinical improvement at 12 weeks: no statistically significant difference (43 % (13/30) in T. suis group achieved clinical improvement compared to 17 % (4/24) of placebo patients (RR: 2.60, 95 %CI 0.97 to 6.95). Histologic, endoscopic improvement, Endoscopic	Summers RW (2005) Gastroenterology.	**Funding Sources:** Funding for the IBD/FBD Review Group (September 1, 2010 –August 31, 2015) has been provided by the Canadian Institutes of Health Research (CIHR) Knowledge Translation Branch (CON – 105 529) and the CIHR Institutes of Nutrition, Metabolism and Diabetes (INMD); and Infection and Immunity (III) and the Ontario Ministry of Health and Long TermCare (HLTC3968FL- 2010 – 2235). Miss Ila Stewart has provided support for the IBD/FBD Review Group through the Olive Stewart Fund. **COI:** PB is a scientific consultant for Coronado Biosciences Inc, a company involved in the development of Trichuris suis egg therapy. The other authors have no financial conflicts of interest and declare that they do not have any association with any manufacturers or promoters of pharmaceutical or helminth products, or with any parties who may have vested interests in the results of this review. **Study Quality:** Both included studies used adequate methods of randomization, blinding, and allocation concealment and were rated as low risk of bias for these items. Both studies were rated as low risk of bias for incomplete outcome data, selective reporting and other potential sources of bias. Quality of the evidence: quality of the evidence low for the primary outcome (i. e. remission at three months) due to serious imprecision (GRADE). Study withdrawal. There was no statistically significant difference in the proportion of patients who

		mucosal healing not reported. Ulcerative Colitis Disease Activity Index (UCDAI) at 12 weeks: The mean UCDAI score was lower in the T. suis egg group compared to the placebo group after 12 weeks of treatment (MD –1.40, 95 % CI –1.75 to –1.05). Frequency and nature of adverse events: no statistically significant difference. Three per cent (1/30) of patients in the T. suis group experienced an adverse event compared to 12 % (3/24) of placebo patients (RR 0.27, 95 % CI 0.03 to 2.40). Quality of life, Hospital admissions and Surgery not reported. **Author's Conclusion:** Currently, there is insufficient evidence to allow any firm conclusions regarding the efficacy and safety of helminths used to treat patients with IBD. The results for our primary efficacy outcomes in this review come froma single trial in patients with active ulcerative colitis. The findings of this study need to be interpreted with caution as they are based on a small number of patients and the overall quality of the evidence was low. We do not have enough evidence to determine whether helminths are safe when used in patients with ulcerative colitis and Crohn's disease. Further randomised controlled trials are needed to assess the efficacy and safety of T. suis ova therapy in ulcerative colitis and Crohn's disease. Trials should be adequately powered and should include clinically relevant outcomes including mucosal healing. These studies should investigate different doses and duration of T.suis treatment. From the study on ulcerative colitis patients, and based on the clinical improvement rates achieved in the placebo group at 12 weeks, we estimate that at least 91 participants per		withdrew before study completion. One patient in each group discontinued treatment (RR 0.80, 95 % CI 0.05 to 12.14). **Heterogeneity:** not possible due to the study number **Publication Bias:** funnel plot not possible due to included study number **Notes:** –

		study arm would need to be enrolled in any future study, to detect a 20 % increase in the proportion of participants with clinical improvement from helminth therapy (assuming alpha error of 0.05 and power of 80 %). To satisfy safety concerns, there is a need for research on helminths with little pathogenic potential, which would not be ablemultiply in their human host or be spread easily to other people.		
Garg, Sushil K et al. Curcumin for maintenance of remission in ulcerative colitis. Cochrane Database of Systematic Reviews 2012				
Evidence level/ Study Types	**Population**	**Outcomes/Results**	**Literature/References**	**Methodical Notes**
Evidence level: 1 **Study type:** SR of 1 RCT **Databases:** 1. Cochrane Central Register of Controlled Trials; 2. Cochrane Inflammatory Bowel Disease and Functional Bowel Disorders (IBD/FBD) Group Specalised Trial Register; 3. Pubmed 4. MEDLINE 5. EMBASE 6. Ongoing trials were identified using the registry link http://ClinicalTrials.gov. **Search period:** Inception to July 11, 2012 **Inclusion Criteria:** 1) Participants of any age 2) diagnosed with ulcerative colitis as confirmed by clinical and endoscopic criteria 3) in remission at the time of enrolment (as defined by any activity index) 4) Any duration of follow-up was allowed **Exclusion Criteria: –**	**Intervention:** curcumin preparations to placebo or other agents Total number of patients: n = 89 (49 male; 45 patients to curcumin and 44 patients to placebo) with quiescent ulcerative colitis, defined by typical clinical, radiographic, endoscopic, and pathological criteria. The enrolled patients were randomised to either curcumin 2 g/day (n = 45) or placebo (n = 44). All patients were receiving maintenance therapy with sulfasalazine ormesalamine at entry and continued to receive these medications throughout the study. **Comparison:** treatment group received curcumin at any dose versus a comparison group receiving placebo, no treatment, or any other active intervention were considered for inclusion.	**Primary:** 1) proportion of patients who experienced clinical or endoscopic relapse **Secondary:** 2) Frequency and nature of adverse events; 3) Changes in disease activity score (modified Mayo Score); 4) Changes in the endoscopy score (Mayo Score); 5) Time to relapse; and 6) Changes in laboratory measures of inflammation (haemoglobin, platelet count, erythrocyte sedimentation rate, and serum albumin). **Results:** 1) Relapse rate at 6 months: 4 % curcumin vs. 18 % (placebo) (RR 0.24, 95 %CI 0.05 to 1.09; P = 0.06). relapsed at 12 months: 22 % curcumin vs. 32 % of placebo patients (RR 0.70, 95 % CI 0.35 to 1.40; P = 0.31). A total of nine 2) adverse events: seven patients. 3) CAI at six months was significantly lower in the curcumin group compared to the placebo group (1.0 + 2.0 versus 2.2 + 2.3;MD-1.20, 95 %CI –2.14 to –0.26). 4) The endoscopic index (EI) at six months was significantly lower in the curcumin group than in the placebo group (0.8 + 0.6 versus 1.6 + 1.6; MD –0.80, 95 % CI –1.33 to –0.27). 5 + 6) not reported	Hanai H (2006) Clinical Gastroenterology and Hepatology.	**Funding Sources:** Funding for the IBD/FBD Review Group (September 1, 2010 – August 31, 2015) has been provided by the Canadian Institutes of Health Research (CIHR) Knowledge Translation Branch (CON – 105 529) and the CIHR Institutes of Nutrition, Metabolism and Diabetes (INMD); and Infection and Immunity (III) and the Ontario Ministry of Health and Long TermCare (HLTC3968FL- 2010 – 2235). Miss Ila Stewart has provided support for the IBD/FBD Review Group through the Olive Stewart Fund. ACM is supported by NIDDK (K23DK084 338) and the Dept of Medicine, BIDMC. **COI:** Dr. Vineet Ahuja was an investigator for RCTs of oral curcumin for induction of remission in ulcerative colitis and rectal curcumin enema for induction of remission in ulcerative colitis. Mr Sushil Kumar participated in these studies as part of the research team (studies unpublished as of April 2011). ACM has received grant support from Proctor & Gamble, Salix and Shire. He has acted on advisory boards for Abbott, UCB and Salix. He has received speaker's honoraria from Abbott and Schering-Plough. The other authors have no known declarations of interest. **Study Quality:** low risk of bias. They used adequate methods of randomization, allocation concealment, and blinding. There were more dropouts in the placebo group (n = 5) than in the curcumin group (n = 2).

		Author's Conclusion: Curcumin may be a safe and effective therapy for maintenance of remission in quiescent UC when given as adjunctive therapy along with mesalamine or sulfasalazine. However, further research in the form of a large scale methodologically rigorous randomized controlled trial is needed to confirm any possible benefit of curcumin in quiescent UC.		Three patients withdrew from the study due to adverse events (1 from the placebo group and 2 from the curcumin group). Attrition bias, however, does not appear to be a serious limitation as the total dropouts were only 7 % and intention-to-treat analyses were used. **Heterogeneity:** Not applicable. **Publication Bias:** n.s. **Notes:** –

Nikfar, S. et al. Systematic review and meta-analysis of the efficacy and tolerability of nicotine preparations in active ulcerative colitis. Clin Ther. 32. 2304 – 2315. 2010

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** MA of 5 RCTs **Databases:** Scopus (EMBASE), PubMed, Web of Science, and the Cochrane Central Register of Controlled Trials **Search period:** 1966–August 2010 **Inclusion Criteria:** 1) studies assessing the efficacy and tolerability of nicotine **Exclusion Criteria:** 1) Jada scor < 3 2) pharmacokinetic studies, commentaries and cross over studies 3) reviews, case studies, uncontrolled trials, trials that did not have institutional review board approval, and trials published in languages other than English.	**Intervention:** nicotine preparations on remission of UC total number of patients: n = 324 **Comparison:** 1) nicotine preparations vs. placebo (3 studies n = 233 patients) 2) nicotine preparations vs. corticosteroids (2 studies n = 81 patients)	**Primary:** Efficiacy, Tolerability in remission **Secondary:** – **Results:** 1) Efficiacy: RR (95 % CI) 1.40 (0.63 – 3.12) P(NS) 1) Tolerability: Adverse effects: RR (95 % CI) 1.95 (1.38 – 2.78); P < 0.001; withdrawals: RR (95 % CI) 3.44 (0.71 – 16.71) P = NS 2) Efficiacy: RR (95 % CI)0.74 (0.5 – 1.09) (PNS); withdrawals due to AE: RR (95 % CI)2.28 (0.76 – 6.83) (P = NS) **Author's Conclusion:** The findings from this meta-analysis do not support the efficacy or tolerability of nicotine preparations for induction of remission in UC.	Sandborn WJ (1997) Ann Intern Med Pullan RD (1994) N Engl J Med Ingram JR (2005) Clin Gastroenterol Hepatol Thomas GA (1996) Eur J Gastroenterol Hepatol Guslandi M (1998) Eur J Gastroenterol Hepatol	**Funding Sources:** n.s. **COI:** The authors have indicated that they have no conflicts of interest with regard to the content of this article. **Study Quality:** Jadad Score: 1 study 5 points, 2 studies three points and 2 studies 4 points. Randomization: 1 × 1 point, 4 studies 2 points. Blinding: one study without blinding, 3 studies with 1 point, one study two points. All described dropout rates. **Heterogeneity:** The studies were not statistically heterogeneous. **Publication Bias:** n.s. **Notes:** –

Langhorst, J. et al. Systematic review of complementary and alternative medicine treatments in inflammatory bowel diseases. J Crohns Colitis. 9. 86 – 106. 2015

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** SR of 29 studies (26 RCTs and 3 non-randomized controlled trials) **Databases:** Pubmed/ MEDLINE, Scopus, Cochrane central register of controlled trials and PsycInfo. **Search period:** from inception until March 12, 2014 **Inclusion Criteria:** 1] Types of study designs: controlled clinical trials, ran-	**Intervention:** herbs and botanicals: boswellia serrata (n = 4); artemisia absinthium (n = 2); andrographis paniculata (n = 2); and curcumin (n = 2); and 1study each on aloe vera, cannabis, germinated barley, Myrrhinil intest®, plantago ovata, silymarin, sophora, super evening primrose, and wheat grass juice.	**Primary:** induction or maintenance of remission, disease activity or symptom severity, quality of life, or psychological variables. **Secondary:** Safety would also be addressed. **Results:** A total of: 26 RCT and 3 CT for herbal medicine, eg aloe-vera gel, andrographis paniculata, artemisia absinthium, barley foodstuff, boswellia serrata, cannabis, curcumin, evening primrose oil, Myrrhinil intest®, plantago ovata, si-	Ben-Arte E (2002) Scand J Gastroenterol. Merrill JW (2014) J Crohns Colitis Elsenbruch S (2005) Psychother Psychosom. Fernandez- Banates F(1999) Am J Gastroenterol. Gerhardt H (2001) Z Gastroenterol Greenfield SM (1993) Aliment Pharmacol Ther Gupta I (2001) Planta Med Gupta I (1997) Eur J Med Res	**Funding Sources:** This review was supported by the Rut- und Klaus- Bahlsen-Foundation. **COI:** None declared. **Study Quality:** Data on compliance were not provided in almost half of the trials. Blinding of participants, providers, and outcome assessors was satisfactory in trials on herbal medicine, but not feasible in trials on behavioral interventions. Finally, although the drop- out rate in many trials was acceptable, only the minority of trials analyzed primary results in an intention-to-treat analysis.

domized controlled trials, randomized controlled cross-over trials, cluster randomized trials. Studies that investigated the effects of therapies within one group only [eg dosage-finding studies] were not considered eligible.
2] Types of participants: Studies of patients diagnosed with ulcerative colitis and/or Crohn's disease were eligible, regardless of age, condition's duration or the state [remission, active]. Studies were not included if IBS was not the targeted disease but was associated with the targeted disease. No restrictions regarding diagnostic procedures were applied.
3] Types of interventions: Studies that investigated CAM therapies according to the NIH definition16 were eligible. These included natural products such as herbs, botanicals, or helminthes; mind/ body interventions such as meditation, relaxation techniques, stress management except for psychotherapy, mindfulness-based stress reduction, comprehensive lifestyle modification programs, hypnosis, yoga, tai chi or qigong, fasting, traditional Chinese medicine interventions, ayurvedic, anthroposophic or homeopathic therapies, balneotherapy, acupuncture, acupressure and cataplasm.
4] Types of outcomes: Studies were eligible if they assessed at least one of the following outcomes: induction or maintenance of remission, disease activity or symptom severity, quality of life, or psychological variables. Safety would also be addressed.
5] Length of follow-up: No restrictions regarding length of follow-up were applied.
6] Accessibility of data: Studies were eligible only

mind/ body medicine (n = 4): Lifestyle modification, Mindfulness-based interventions, Hypnotherapy, Relaxation training. acupuncture (n = 2), and trichuris suis ova (n = 1).
Total number of patients n = 1927; Patients with either ulcerative colitis, Crohn's disease or inflammatory bowel disease [both UC or CD]
Comparison: Boswellia vs mesalazin, sulfasalazin or placebo Artemisia vs. standard treatment or placebo (+steroid or prednisolone), Andrographis vs. placebo (+mesalamin) Curcurmin vs. placebo (+mesalamin or sulfasalazine) other vs. mesalamin, sulfasalzin, olive oil, 5- ASA-steroids, mesalazin or placebo Mind and body medicine vs. standard care, usual care

lymarin, sophora, tormentil, wheatgrass- juice and wormwood; 1 RCT for trichuris suis ovata; 7 RCT for mind/body interventions such as lifestyle modification, hypnotherapy, relaxation training and mindfulness; and 2 RCT in acupuncture; were found. Best evidence was found for herbal therapy, ie plantago ovata and curcumin in UC maintenance therapy, wormwood in CD, mind/ body therapy and self-intervention in UC, and acupuncture in UC and CD.
Author's Conclusion: Addressing the fact that IBD are caused and upheld by multifactorial processes, which include genetic predisposition, immune dysregulation, barrier dysfunction and altered microbial flora,83 – 85 as well as environmental and lifestyle factors, it seems plausible that subgroups of patients might benefit from a tailored therapy with emphasis on individually differing modalities.
Whereas the various herbal treatment approaches in principle are using the same pathogenetic paradigm as conventional pharmacotherapy, TCM/acupuncture and, especially, mind/body medicine widen the spectrum of therapy and add a resource- orientated salutogenetic dimension to introduce a multimodal integrative treatment approach. Patients try to find the most effective and safest therapy for their disorder, including every available option for treatment. In this context, they are likely to perceive CAM and mainstream medicine as equally available treatment options, and to exercise their freedom of choice on their way to a consumer-driven optimal treatment. A more individualized multimodal treatment approach and further high-quality designs in health research are warranted, to help tailor the right individualized tre-

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Tong ZQ (2010) Chin J Integr Med.

The risk of bias was quite heterogeneous, from studies with a high risk in almost all domains to studies with no apparent risk of bias in any domain. The most critical domains for risk of bias were random sequence generation and allocation concealment, with one-third of the studies not reporting adequate methods.
Heterogeneity: The possibility of meta- analysis was considered separately for every field of CAM presented but could not be performed due to heterogeneous study designs and outcome measures.
Publication Bias: The risk of bias was quite heterogeneous.
Notes: Oxford LoE 1 for randomized and non-randomized controlled trials.

if they were published as full papers, and only English or German language publications were considered eligible. **Exclusion Criteria:** Massages and manipulative therapies were beyond the scope of this review and not included. Studies investigating probiotics or omega-3 fatty acids, fish oils, or essential oils as well as vitamins and minerals were also excluded.		atment modalities for IBD patients, include salutogenetic approaches like MBSR, and appropriate trials to picture these.		
Ling, W. et al. Common Mechanism of Pathogenesis in Gastrointestinal Diseases Implied by Consistent Efficacy of Single Chinese Medicine Formula: A PRISMA-Compliant Systematic Review and Meta-Analysis. Medicine (Baltimore). 94. e1111. 2015				
Evidence level/ Study Types	**Population**	**Outcomes/Results**	**Literature/References**	**Methodical Notes**
Evidence level: 1 **Study type:** SR of 83 randomized controlled studies (6 studies were postgraduate candidate thesis, and 77 journal articles). All studies were conducted in China. Ulcerative colitis was assessed in 3 studies. **Databases:** Chinese National Knowledge Infrastructure (CNKI), the Chinese Science and Technology Periodical Database, the Wanfang Database and the PubMed. **Search period:** ?-March 2014 **Inclusion Criteria:** 1) randomized controlled trials stating the phrase "randomization" (no restriction was imposed on studies with respect to blinding and type of design such as parallel or cross-over); 2) participants with GERD, peptic ulcer, duodenogastric reflux, functional dyspepsia, chronic gastritis, IBS, or ulcerative colitis, 3) irrespective of age, sex, ethnic origin, and geography; 4) the patients were diagnosed using the latest guideline by the year of the study conducted; 5) intervention was SNS, whereas control could be western conventional medicine,	**Intervention:** treatment of CU with SNS (Si-Ni-San) (traditional chinese medicine) Total number of patients: n = 7763 patients (4250 in SNS groups and 3513 in control groups) Only CU: 135 SNS group & 11 control group. **Comparison:** SNS (Si-Ni-San) vs conventional therapy (Sulfasalzin)	**Primary:** clinical efficacy defined by symptom relief (normalization of GI endoscopies, radiology, and pathology) according to the latest specific guideline. **Secondary:** common mechanisms of pathogenesis **Results:** SNS showed higher efficacy rates than conventional treatment (OR = 2.40, 95 % CI = 1.21 – 4.75) **Author's Conclusion:** In this study, we have used synthesized clinical data of the single TCM formula as a tool indirectly to validate the common mechanisms of pathogenesis of GI disorders. The findings are positive for common GI disorders implicated by similar pathogenesis. The present study has limitations such as inherited risk bias and low quality of some included trials. Validation of our findings warrants high-quality clinical studies based on different geographic locations or using different therapeutic agents.	Xu LD (2012) Jilin J Tradit Chin Med. Hu JZ (2010) Chin Med Mod Dist Edu Chin. W Z. (2002) Chengdu university of traditional chinese medicine	**Quality:** Randomization, blinding and dropout rates were not mentioned in the 3 studies referring. Jada score for each study was 1 (low quality). One study mentioned advers effects (not further specified). **Heterogeneity:** P < 0.0001, I2 = 32%. **Publication Bias:** The funnel plot demonstrated no apparent asymmetry.

6) English and Chinese full- texts **Exclusion Criteria:** 1) duplication (the same data of patients with the same authors published in different journals); 2) information of diagnostic criteria, participants, interventions, or outcomes were not defined; 3) observational studies, reviews, and case series reports; 4) studies not meeting the inclusion criteria. 5) pregnant, lactating women, and patients with serious medical conditions were excluded 6) studies with co-intervention additional to SNS were excluded if they were given to both groups.				

Lu, C. et al. Association between 25(OH)D Level, Ultraviolet Exposure, Geographical Location, and Inflammatory Bowel Disease Activity: A Systematic Review and Meta-Analysis. PLoS One. 10. e0132 036. 2015

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** SR and MA (21 controlled clinical trials) **Databases:** PubMed, Clinical Trials. gov, and EBSCO databases **Search period:** January 1, 2000 to November 1, 2014 **Inclusion Criteria:** 1) data on vitamin D levels, sun exposure, latitude, and IBD with or without mention of disease severity. 2) inflammatory bowel disease, IBD, Crohn's disease, CD, ulcerative colitis, UC, vitamin D 3) pediatric and adult participants **Exclusion Criteria:** papers that did not provide original data, animal studies, in vitro studies, studies without a normal control and studies focused on conditions affected by vitamin D metabolism.	**Intervention:** VD3, sun exposure, latitude. A total of 1832 Patients were included in the SR (796 for CD, 275 for CU and 761 as control). **Comparison:** 1) association between CD and vitamin D levels 2) relationship between UC and vitamin D levels. 3) In addition, eight studies were used to analyze dichotomous exposure (vitamin D deficiency) in CD of which three studies also referred to UC. 4) relation of vitamin D and IBD activity.	**Primary:** Vitamin D levels in CD/CU patients vs control **Secondary:** Crohn's Disease Activity Index (CDAI) Pediatric Crohn's Disease Activity Index (PCDAI) **Results:** 1) Association of CD with vitamin D: The average 25(OH)D level in CD patients < controls SMD = 0.26 nmol/L, 95 % CI = 0.09 – 0.42 nmol/L Without children (131/796 CD patients, 212/761 controls) SMD = 0.25 nmol/L, 95 % CI = 0.06 – 0.44 nmol/L,). SMD between pediatric CD and control nonsignificant. 2) vitamin D levels and UC: UC patients < control (SMD = 0.5 nmol/L, 95 % CI = 0.15 – 0.85 nmol/L) adult UC patients/ pediatric UC patients nonsignificant effects 3) CD patients were 1.95 times (OR = 1.95, 95 % CI = 1.48 – 2.57, more likely to suffer vitamin D deficiency than controls. UC patients were 2.02 times (OR = 2.02, 95 % CI = 1.13 – 3.60) 4)patients with active CD (CD Activity Index150) were	Garg M, (2013) Inflammatory bowel diseases Middleton JP (2013) Journal of pediatric gastroenterology and nutrition. Dunn OJ (2009) John Wiley & Sons. El-Matary W (2011) Digestive diseases and sciences. Veit LE (2014) PloS one. De Bruyn JR (2014) Journal of Crohn's & colitis. Dumitrescu G (2014) World journal of gastroenterology: Grünbaum A. (2013) Nutrition journal. Jorgensen SP (2013) Journal of Crohn's & colitis. Joseph AJ (2009) The Indian journal of medical research. Souza HN (2008) Arquivos brasileiros de endocrinologia e metabologia. Suibhne TN (2012) Journal of Crohn's & colitis. Tajima M (2004) Journal of gastroenterology. Tan B (2014) Journal of digestive diseases. McCarthy D (2005) Alimentary pharmacology & therapeutics.	**Funding Sources:** n.s. **COI:** n.s. **Study Quality:** no randomization, drop out rates not specified. Disease durations, years of follow-up since diagnosis, and surgical treatment were not included due to the lack of data. **Heterogeneity:** 1)CD and VD3:, I2 = 54.1 %, P = 0.01 wo children: I2 = 54.9 %, P = 0.018 2) CU and CD3: I2 = 77.5 %, P< 0.01 3) CD patients Probability to suffer from VD3 deficiency: I2 = 0, P = 0.866); CU patients: I2 = 0, P = 0.773. **Publication Bias:** no publication bias was found under Egger's test (P = 0.383). Selection bias may exist because the diagnostic criteria for IBD were not stated. **Notes:** Oxford LoE 1 for randomized and non-randomized controlled trials.

		more likely to have low vitamin D levels. **Author's Conclusion:** We have demonstrated that vitamin D levels are lower in IBD patients, suggesting that vitamin D plays an important role in the pathogenesis of IBD. However, we still do not know which specific mechanism plays the main role in this relationship. Potential mechanisms included the Relationship between IBD and 25(OH)D Level. immune-mediated mechanisms, the anti-inflammatory action of vitamin D, and gene regulation related to vitamin D levels.		

Timmer, Antje et al. Psychological interventions for treatment of inflammatory bowel disease. Cochrane Database of Systematic Reviews 2011				
Evidence level/ Study Types	**Population**	**Outcomes/Results**	**Literature/References**	**Methodical Notes**
Evidence level: 1 **Study type:** SR of 21 studies (RCT's, QRST's and NRCT's) The results of 9 studies could be used for the subgroup analysis for UC.3 studies reported results solely for CD. **Databases:** MEDLINE, EMBASE, and CENTRAL. For MEDLINE and EMBASE; Lilacs, Psyndex, and Psychinfo, Thieme, Karger, Kluwer, Somed, Social SciSearch, Science direct. Conference registers: conferences: DDW 2009 and 2010, DGVS 2008 and 2009, P-IBD2009, ECCO2009 and 2010, UEGW/WCOG 2008 and 2009, GPGE 2009 and 2010). DARE, HTAD and NHS-EED **Search period:** Inception until (last performed in) April 2010 **Inclusion Criteria:** 1) All controlled clinical trials (randomized (RCT), quasi-randomized (QRCT) and non randomized (NRCT)). 2) Follow up was to be at least 2 months for induction trials, and 6 months for maintenance. 3) Studies were included if published in any form and language. 4) Unpublished studies, and studies published in abstract form could be	**Intervention:** Psychological interventions (psychotherapy, educational interventions, relaxation techniques and combinations) as supportive therapy for inflammatory bowel disease (ulcerative colitis or Crohn's disease, or both, with or without unclassified IBD or indeterminate colitis. Total number of patients: n = 1745 Study size ranged from 21 patients to 532 patients. Most studies were small (< 50 patients). There were two studies performed in adolescents. **Comparison:** no treatment, or any other type of therapy, including other psychosocial therapy, sham or standard medical therapy. Concomitant medication was allowed, if applied to both groups.	**Primary:** HRQL, coping/stress management skills and emotional status, in particular depression and anxiety (after 6 or 12 months) **Secondary:** Induction and maintenance of remission, time off work or school, improvement of associated psychopathology, adverse events and trial withdrawal. However, most of these outcomes were not sufficiently reported. Secondary outcome assessment was therefore restricted to the comparison of patients not in remission over or at the respecified time (short term 2 to 8 months, long term 9 to 18 months) and disease activity at follow up. **Results:** In adults, psychotherapy had no effect on quality of life at around 12 months (3 studies, 235 patients, SMD –0.07; 95 % CI –0.33 to 0.19), emotional status (depression, 4 studies, 266 patients, SMD 0.03; 95 % CI –0.22 to 0.27) or proportion of patients not in remission (5 studies, 287 patients, OR 0.85; 95 % CI 0.48 to 1.48). Results were similar at 3 to 8 months. In adolescents, there were positive short term effects	Bregenzer N (2005) Zeitschrift fur Gastroenterologie. Grootenhuis MA (2009) Eur J Gastroenterol Hepatol. Jaghult S (2007) Scandinavian Journal of Gastroenterology. Kennedy A (2003) Health & Social Care in the Community. Kennedy A (2004) Gut. Lange A (1996) Zeitschrift fur Gastroenterologie. Langhorst J (2007) Scandinavian Journal of Gastroenterology. Larsson K (2003) Scandinavian Journal of Gastroenterology. Lecouturier J (2003) Quality of Life Research. Milne B (1986) Journal of Advanced Nursing. Oliveira S (2007) Inflammatory Bowel Diseases. Oxelmark L (2007) Inflamm Bowel Dis. Schmidt CF (1992) Hypnos Schreiber (1999) Gastroenterology. Schwarz (1991) Behaviour Research & Therapy. Smith (2002) Journal of Advanced Nursing. Szigethy (2007) Journal of the American Academy of Child and Adolescent Psychiatry. Waters (2005) Canadian Journal of Gastroenterology.	**Funding Sources:** Funding for the IBD/FBD Review Group (September 1, 2010 – August 31, 2015) has been provided by the Canadian Institutes of Health Research (CIHR) Knowledge Translation Branch (CON – 105 529) and the CIHR Institutes of Nutrition, Metabolism and Diabetes (INMD); and Infection and Immunity (III). Miss Ila Stewart has provided support for the IBD/FBD Review Group through the Olive Stewart Fund. **COI:** Günther Jantschek (deceased) was involved in studies included in this review. Both he and Gabriele Moser served as coauthors on clinical practice guidelines in IBD focusing on issues of psychological therapy. **Study Quality:** Quality of the evidence: very low (GRADE). The risk of bias was high for all studies (especially for selection bias, performance and detection bias and reporting bias). None of the studies applied blinding of the patients or investigators using any sham procedures, but a few tried blinded outcome assessment. On average, 27 % of the treated patients, and 29 % of the control patients dropped out or were lost to follow up (RR: 0.98; 95 % CI 0.92 to 1.05). Results based on HRQL suggest small study bias. **Heterogeneity:** There was no evidence for statistical heteroge-

included if sufficient information was available for the assessment 5) any age 6) Trials not separating type of IBD were also included. **Exclusion Criteria:** 1) Trials with mixed populations, such as functional bowel disease and IBD		of psychotherapy on most outcomes assessed including quality of life (2 studies, 71 patients, SMD 0.70; 95 % CI 0.21 to 1.18) and depression (1 study, 41 patients, SMD –0.62; 95 % CI –1.25 to 0.01). Educational interventions had no effect on quality of life at 12 months (5 studies, 947 patients, SMD 0.11; 95 % CI –0.02 to 0.24), depression (3 studies, 378 patients, SMD –0.08; 95 % CI –0.29 to 0.12) and proportion of patients not in remission (3 studies, 434 patients, OR 1.00; 95 % CI 0.65 to 1.53). No adverse events were reported in any of the included studies. **Author's Conclusion:** There is no evidence for efficacy of psychological therapy in adult patientswith IBD in general. In adolescents, psychological interventions may be beneficial, but the evidence is limited. Further evidence is needed to assess the efficacy of these therapies in subgroups identified as being in need of psychological interventions, and to identify what type of therapy may be most useful.		neity or subgroup effects based on type of disease or intensity of the therapy. **Publication Bias:** The results of the linear regression test of funnel plot asymmetry (Egger's Test) did not show evidence of bias (t = 0.5734, df = 10, P = 0.579). **Notes:** 4 of the included studies reported incomplete data. This studies were not included in the pooled results.

Charlebois, A. et al. The Impact of Dietary Interventions on the Symptoms of Inflammatory Bowel Disease: A Systematic Review. Crit Rev Food Sci Nutr. 56. 1370 – 1378. 2016

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** SR of 12 cohort studies **Databases:** MEDLINE (OvidSP), EMBASE (OvidSP) and CNIHL **Search period:** ? - September 2012. **Inclusion Criteria:** 1) adults diagnosed with inflammatory bowel disease (either Crohn's disease or ulcerative colitis), 2) clinical trial study design, 3) an intervention that involved dietary manipulation using a regular diet (i. e. no formulas or supplements used), 4) symptoms of IBD objectively measured before	**Intervention:** 1) low residue/low fiber diets 2) exclusion diets, 3) other specific diets **Comparison:** normal vs dietary nutrition in either CD or UC patients	**Primary:** effects on disease outcome— most notably clinical response. **Secondary:** Results: 1) low residue/low fiber diets there was no difference in outcome between the groups. 2) exclusion diets: five trials for exclusion diet category —all of which showed significant improvements in symptoms post diet intervention 3) There were five studies that met our criteria which did not fall under low fiber/ low residue or exclusion diets, but that were instead very specific and different from one another. Among the five, three assessed symptom outcome of a diet intervention in CD patients,	Levenstein S (1985) Gut. Ritchie, J.K. (1987) BMJ. Jones, V.A. (1985) The Lancet. Riordan, A.M. (1993) The Lancet. Candy, S. (1985) SAMJ. Rajendran, N. (2011) Colorectal. Disease. Bentz, S. (2010) Digestion. Lomer, M.C.E. (2005) Eur J Gastroenterol. Hepatol. Croagh, C. (2007) Inflamm Bowel. Dis. Bartel, G. (2008) Inflamm Bowel Dis. Chiba, M. (2010) World J Gastroenterol. Grimstad, T. (2011) Scand J. Clin Lab Invest	**Funding Sources:** n.s. **COI:** n.s. **Study Quality:** Most of the studies were randomized, but not all (Grimstadt et al. (2011) and Rajendran and Kumar (2010) both no comparison group), Croagh et al. (2007) retrospective). **Study quality:** n.s. **Heterogeneity:** n.s. **Publication Bias:** n.s. **Notes:** –

and after the intervention. All studies were reviewed by a registered dietician (AC) and verified by a senior gastroenterology resident (GR). **Exclusion Criteria:** Twenty-one trials were excluded after screening titles and abstracts— 1) 12 because they did not involve a regular diet (most used an elemental diet) 2) 9 because they involved the use of dietary supplements 3) one trial that was excluded due to not objectively measured symptoms after the diet intervention.		and two assessed similar outcomes in patients with UC. **Author's Conclusion:** In conclusion, our systematic review evaluating dietary manipulations on symptoms of IBD found 12 studies, most of which were poorly controlled cohort studies. Nevertheless, we were able to identify several potential dietary manipulations which may prove beneficial for improving the symptoms of IBD. Further research using more precise methods of implementing exclusion diets, as well as, the low FODMAP diet are two areas identified in this review that show promise for having therapeutic benefits for patients with inflammatory bowel disease.		

Wedlake, L. et al. Fiber in the treatment and maintenance of inflammatory bowel disease: a systematic review of randomized controlled trials. Inflamm Bowel Dis. 20. 576 – 586. 2014

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** SR of 23 RCT's (Ten studies were in patients with UC (6 open label and 4 double blind placebo controlled trials; 12 were in CD) **Databases:** MEDLINE (U.S. National Library of Medicine); EMBASE (Elsevier B.V., The Netherlands); CINAHL (CINAHL Information Systems, United States); CENTRAL (The Cochrane Library, Chichester, United Kingdom); Nutrition and Food Sciences (CAB International, United Kingdom); Web of Science (ISI Thomson Scientific, United Kingdom); and Scopus (Elsevier). **Search period:** ? – December 2012 **Inclusion Criteria:** 1) Open label, wholly or partially blinded or placebo-controlled nutritional interventional studies 2) Single or multicenter. 3) English or foreign language.	**Intervention:** Oral pharmacological fiber supplement, food supplement, or dietary advice to increase or decrease fiber intake were eligible. Fiber interventions were required to meet the acknowledged definitions of fiber and therefore included prebiotic fibers. Synbiotic preparations containing a named prebiotic fiber complying with the cited fiber definitions were also eligible irrespective of probiotic species and strain(s) used. The 23 studies comprised 1296 patients of which 35 % were male. This included 447 patients with UC (46 % remission; 26 % active disease; 28 % "mixed" disease activity), 829 with CD (56 % remission; 23 % active; 21 % mixed), and 20 with pouchitis, all in remission. The methods used to classify disease	**Primary:** Clinical: remission, relapse, mortality, morbidity, medication use, symptoms, and quality of life. Physiological: gastrointestinal inflammation including histology, inflammatory and immunological markers, microbiota, and metabolic substrates. **Secondary:** Presence or absence of adverse events related to interventional substrate. **Results:** Fiber supplementation had a positive effect on disease outcomes in 3/10 studies in UC and in the sole pouchitis study. In contrast, none of the 12 studies in CD showed a benefit with 5/12 studies reporting no effect on disease outcomes and 3/12 equivalence. Despite this, a number of studies reported favorable intragroup effects on physiological outcomes including fecal butyrate, fecal calprotectin, inflammatory cytokines, microbiota, and gastrointestinal symptom indices.	Fernandez-Banates F (1999) Am J Gastroenterol. Hallert C (1991) Scand J Gastroenterol. Copaci I (2000) Dig Liver Dis. Faghfoori Z (2011) Ann Clin Biochem. 2011. Federico A (2009) Eur Rev Med Pharmacol Sci. Furrie E (2005) Gut. Casellas F (2007) Aliment Pharmacol Ther. Kanauchi O (2002) J Gastroenterol. Ishikawa H (2011) Digestion. Fujimori S (2009) Nutrition.	**Funding Sources:** The systematic review was internally funded. **COI:** The authors have no conflicts of interest to disclose. **Study Quality:** Serious adverse events were inconsistently reported and where reported were unrelated to intervention. No studies were terminated on safety grounds. Most studies clearly reported patient withdrawals (19/23). Few studies were of high quality with only 17 % (4/23) scoring the maximum 5 points, 26 % (6/23) 4 points, 22 % (5/23) 3 points, 17 % (4/23) 2 points, and 17 % (4/23) 1 point on the Jadad score. For UC: 2 × 1 point, 1 × 2 points, 3 × 3 points, 3 × 4 points and 1 × 5 points of Jadad score. **Heterogeneity:** In view of the variation in patient groups, stage of disease (remission and active), interventions, comparators, and the definition and methods of measuring outcomes, meta-analysis of the studies were deemed not possible. **Publication Bias:** n.s. **Notes:** Oxford LoE 2 for SR of randomized and non- randomized controlled trials. Database search terms, timeframes, and host interfaces are de-

4) Adult (inpatients or outpatients) older than 18 years of age with 5) CD, UC, or pouchitis in remission or relapse. 6) Original cohorts only (i. e., excluding previous or abbreviated reports and abstracts of the same patient group) to avoid duplication of patient numbers. 7) Oral pharmacological fiber supplement, food supplement, or dietary advice to increase or decrease fiber intake **Exclusion Criteria:** Animal studies, reports comparing different doses of fiber without any other comparator group, non-RCTs and uncontrolled trials.	activity varied between and within diseases. Where employed (16/23 studies), 10 different indices were used. Use of concomitant medications was reported in 20/23 studies. Adult, older than 18 years. **Comparison:** Fiber supplements (17 studies) and dietary interventions (6 studies). Comparator group of either a placebo, no dietary intervention, an alternative dietary intervention, or a pharmacological intervention (Mesalamine).	**Author's Conclusion:** In summary, this review has demonstrated the potential for the efficacy of fiber in IBD. There is limited, weak evidence of the effectiveness of isphagula in maintenance of remission of UC, germinated barley in active UC, and inulin in the maintenance of remission in pouchitis. Many within-group effects were observed and given the paucity of high-quality studies, these within group observations merit further exploration in adequately powered and controlled clinical trials. Future studies should consider measurement of physiological outcomes to further elucidate fiber's mechanism of action, taking into account the possible confounding effect of medication. It is recommended that in patients with IBD without overt risk of obstruction, the restriction of dietary fiber is unnecessary, but all patients should be appropriately monitored regarding their tolerance to fiber intake.		tailed in Data, Supplemental Digital Content 1, http://links.lww.com/IBD/A354.

Cabre, E. et al. Omega-3 fatty acids and inflammatory bowel diseases – a systematic review. Br J Nutr. 107 Suppl 2. S240 – S252. 2012

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** SR of 19 RCTs (n = 7 for active UC, and n = 4 for inactive UC; active CD n = 2, inactive CD n = 6) **Databases:** MEDLINE via PubMedq, EMBASEq, and Latin American and Caribbean Heath Sciences Literature (LILACS). **Search period:** From inception to April 2011. **Inclusion Criteria:** 1) studies regarding Fish oils, Fatty acids, omega- 3 PUFA 2) both active and inactive UC or CD, Total number of patients: n = 555 (for UC-studies). **Exclusion Criteria:** 1) Studies dealing with conventional diets enriched with fish foods were not considered eligible since the dose of omega-3	**Intervention:** Fish oil or omega-3 PUFA therapy in both active and inactive UC or CD. **Comparison:** ▪ liquid fish oil was compared to sunflower oil as placebo, ▪ fish oil capsules vs. capsules with a mixture of fatty acids (mostly oleic acid) ▪ sulfasalazine capsules as comparator instead of placebo ▪ nutritional supplement enriched with omega-3 PUFA, prebiotics (fructooligosaccharides, Arabic gum), and antioxidant micronutrients, with a sucrose-based placebo supplement ▪ Olive oil, corn oil, and sunflower oil.	**Primary:** 1) remission rate (for active patients) and 2) relapse rate (for patients in remission) during the observation period. **Secondary:** 3) change in disease activity scores (either clinical or endoscopic), 4) time to remission, time to first relapse, 5) adverse events, hospitalization rate, steroid sparing effect, disease activity at the end of follow-up period, and 6) quality of life **Results:** Available data do not allow to support the use of omega-3 PUFA supplementation for the treatment of both active and inactive inflammatory bowel disease. Negative results are quite consistent in trials assessing the use of omega-3 PUFA to maintain disease remission, particularly ulce-	Aslan A (1992) Am J Gastroenterol. Hawthorne AB (1992) Gut. Stenson WF (1992) Ann Intern Med. Loeschke K (1996) Dig Dis Sci. Stack WA (1997) Gut. Almallah YZ (1998) Am J Gastroenterol. Dichi I (2000) Nutrition. Varghese TJ (2000) Br J Surg. Middleton SJ (2002) Aliment Pharmacol Ther. Seidner DL (2005) Clin Gastroenterol. Mantzaris GJ (1996) Hellen J Gastroenterol.	**Funding Sources:** There was no specific funding for this work. **COI:** The authors have no conflict of interest to declare. **Study Quality:** Oxford Quality score: 5 points: n = 2, 4 points: n = 2, 3 points n = 4, 2 points n = 4 Randomization and allocation concealment: 4 studies described both adequate, one had adequate randomization but unclear allocation concealment, and the other 6 trials didn't described any. Blinding: 3 studies adequate, 2 unblinded, 6 not described. ITT: 4 studies yes, 6 no, 1 unknown. other bias: one study had a significant higher drop out rate in the active group, and a higher CAI index in the active group. **Heterogeneity:** n.s. **Publication Bias:** n.s. **Notes:** –

PUFA is not clear in these studies. 2) Papers reporting pooled results in UC and CD, or in active and inactive patients were also excluded. 3) Studies reporting only surrogate outcomes, such as serum/tissue levels of cytokines, eicosanoids or other inflammatory markers		rative colitis, and to a lesser extent Crohn's disease. Trials on their use in active disease do not allow to draw firm conclusions mainly because the heterogeneity of design (ulcerative colitis) or their short number (Crohn's disease). In most trials, the appropriateness of the selected placebo is questionable. **Author's Conclusion:** In summary, although the available data are in general discouraging, the present systematic review does not allow to make firm recommendations about the usefulness of omega-3 PUFA in IBD. Extra attention about the manufacturing of placebo (perhaps using edible mineral oil) should be paid in future large-sized, high quality trials.		
Ge, J. et al. Meat intake and risk of inflammatory bowel disease: A meta-analysis. Turk J Gastroenterol. 26. 492 – 497. 2015				
Evidence level/ Study Types	**Population**	**Outcomes/Results**	**Literature/References**	**Methodical Notes**
Evidence level: 1 **Study type:** MA of 9 studies (2 cohort and 7 case–control studies). **Databases:** Pubmed and EMBASE **Search period:** July 1966 to July 2015 **Inclusion Criteria:** 1) inflammatory bowel disease, ulcerative colitis, Crohn's disease, and meat consumption (including red meat, processed meat, white meat, poultry, beef, pork, lamb, and goat). 2) without language limitations 3) case–control or cohort design 4) evaluation of the association between meat consumption (including total meat, red meat, processed meat, and white meat) and IBD risk 5) the availability of odds ratio, relative risk (RR), and hazard ratio estimates with 95 % confidence interval (CI) statistical data. **Exclusion Criteria:** –	**Intervention:** Meat consumption Total number of cases: UC: 2019, CD: 683, and IBD: 160. **Comparison:** low, medium and high meat consumption in patients with UC, CD or IBD.	**Primary:** IBD, UC CD risk Secondary: geographic area, study design, and type of meat consumed, esophageal cancer **Results:** red meat consumption and IBD risk: significant association (RR: 2.37, 95 % CI: 1.40 – 3.99). white meat and IBD: no significant association (RR: 1.20, 95 % CI: 0.73 – 1.97) processed meat and IBD: no significant association (RR: 1.60, 95 % CI: 0.53 – 4.78) total meat intake and UC risk: significant association (RR: 1.47; 95 % CI: 1.01 – 2.15) total meat intake and CD risk: no association (summary RR: 1.50, 95 % CI: 0.98 – 2.28). total meat consumption and IBD risk (summary RRs: 2.92, 95 % CI 1.59 – 5.34) in cohort studies and total meat consumption and IBD risk (summary RRs: 1.33 95 % CI 1.02 – 1.72) in case–control studies. total meat consumption and IBD risk in studies that were conducted in European populations: significant association (summary RR: 1.61; 95 % CI: 1.16 – 2.21)	Higashi A (1991) Nihon Eiseigaku Zasshi. Akihito M (1994) J Clin Gastroenterol. Sakamoto N (2005) Inflamm Bowel Dis. Bernstein CN (2006) Am J Gastroenterol. D'Souza S (2008) Inflamm Bowel Dis. Maconi G (2010) World J Gastroenterol. Wang YF (2013) World J Gastroenterol.	**Funding Sources:** The authors declared that this study has received no financial support. **COI:** No conflict of interest was declared by the authors. **Study Quality:** All studies included in this meta-analysis scored six or higher in the Newcastle–Ottawa Scale. Randomization and dropout rates n.s. **Heterogeneity:** Meat consumption and IBD risk: significant heterogeneity UC ($Q = 29.98$, $p = 0.001$, $I2 = 66.6$ %) and CD ($Q = 11.51$, $p = 0.074$, $I2 = 47.9$ %). Meat consumption and IBD risk: significant for case control studies ($Q = 30.51$, $p = 0.010$, $I2 = 50.8$ %) but not significant in cohort studies ($Q = 3.44$, $p = 0.179$, $I2 = 41.9$ %). total meat consumption and IBD risk in studies that were conducted in European populations: statistical heterogeneity ($Q = 28.71$, $p = 0.007$, $I2 = 54.7$ %). no statistical heterogeneity in Asian studies ($Q = 5.23$, $p = 0.265$, $I2 = 23.5$ %). significant evidence of heterogeneity among studies for esophageal cancer ($Q = 45.31$, $p < 0.001$, $I2 = 60.3$ %).

		total meat consumption and IBD risk in Asian populations: significant association (summary RR: 1.15, 95 % CI: 0.85 – 1.56). The summary RRs for esophageal cancer in the highest versus lowest consumption groups were 1.50 (95 % CI: 1.15 – 1.95) for total meat, 2.37 (95 % CI: 1.40 – 3.99) for red meat, 1.60 (95 % CI: 0.53 – 4.78) for processed meat, and 1.20 (95 % CI: 0.73 – 1.97) for white meat. **Author's Conclusion:** The results of this meta-analysis indicate that high intake of meat is associated with an increased IBD risk. Further cohort studies are warranted to confirm this association.		**Publication Bias:** No publication bias as determined by either the Egger's test (p = 0.245) or Begg's funnel plot (p = 0.327). **Notes:** –

Liu, X. et al. Dietary fiber intake reduces risk of inflammatory bowel disease: result from a meta-analysis. Nutr Res. 35. 753 – 758. 2015

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** MA of 8 studies (2 cohort studies, 1 nested case-control study, and 5 case-control studies) **Databases:** PubMed, Embase, and Web of Knowledge **Search period:** ? – November 2014 **Inclusion Criteria:** 1) "inflammatory bowel disease," "ulcerative colitis," "Crohn's disease," and "fiber" 2) observational studies published as an original article 3) the study of interest was dietary fiber intake 4) the outcome of interest was UC and/or CD 5) relative risks (RRs) or odds ratio estimates (we presented all results with RRs in this study) with their 95 % confidence intervals (CIs) were available or could be calculated 6) for dose- response analysis, the number of cases and person- years for each category of fiber must be provided (or data must be available to calculate them). If data were the same in more than 1	**Intervention:** dietary fiber intake. Number of cases: UC n = 972; CD n = 834 **Comparison:** no comparison	**Primary:** IBD risk (CU or/ and CD) **Secondary:** – **Results:** Dietary fiber intake: Among the 7 studies, 3 studies reported that dietary fiber intake could decrease the risk of CD, whereas no association was found in the other 4 studies. The pooled RR with 95 % CI of CD for the highest vs lowest categories of dietary fiber intake was 0.44 (0.29 – 0.69, Pfor significance = .000) Dietary fiber intake and UC: Among the 8 studies, 1 study reported that dietary fiber intake could decrease the risk of UC, but the other studies showed no significant association. The summary RR with 95 % CI of UC for the highest vs lowest categories of dietary fiber intake was 0.80 (0.64 – 1.00, Pfor significance = .054) **Author's Conclusion:** The present meta- analyses confirmed that dietary fiber intake may decrease the risk of IBD. Given the increasing prevalence of IBD and its underlying threat to humans, the observed associations between dietary	Nakamoto N (2005) Inflamm Bowel Dis. Reif S (1997) Gut. Persson PG (1992) Epidemiology. Hansen TS (2011) J Crohns Colitis. Ananthakrishnan AN (2013) Gastroenterology. Amre DK (2007) Am J Gastroenterol. Hart AR (2008) Digestion. Geerling BJ (2000) Am J Gastroenterol.	**Funding Sources:** n.s. **COI:** The authors report no conflicts of interest. **Study Quality:** No Randomization due to study design. No further details of study quality specified. **Heterogeneity:** fiber and CD: I2 = 56.1 %, Pfor heterogeneity = .034 fiber and CU: I2 = 48.0 %, Pfor heterogeneity = .062 **Publication Bias:** The visual inspection of the funnel plot and Egger test showed no evidence of publication bias for the analysis of dietary fiber with CDrisk (P = .705) and UC risk (P = .459), respectively. **Notes:** Limitations by the author's: 1.a meta-analysis of observational studies is susceptible to recall bias, which is inherent in the original studies, especially for case-control studies. 2. the number of cases and studies involved in this meta-analysis was not large enough. 3. diet assessment methods differed among the studies. Oxford LoE 1 for MA.

study, we included the latest one or the one with the largest number of cases. **Exclusion Criteria:** 1) 39 investigated the pathogenesis, diagnosis, or therapy of CD or UC; 2) 13 were systematic reviews; 3) 11 did not provide RRs or corresponding 95 % CI 4) 6 explored the diet effect on relapse of IBD.		fiber and IBD might have clinical and public health importance.		

Barclay, A.R. et al. Systematic review: the role of breastfeeding in the development of pediatric inflammatory bowel disease. J Pediatr. 155. 421 – 426. 2009

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 1 **Study type:** MA and SR of 7 studies (one only UC, two only CD, four studies both diseases (one excluded in parts of the analysis, due to the lack of data's) (case control and cohort studies). **Databases:** Ovid databases Medline, Old Medline, Cochrane Library, CAB abstracts, Embase, Cinahl, and ACP Journal Club Database of Abstracts of Reviews of Effectiveness, Pubmed on NCBI. **Search period:** Ovid databases Medline (1966-January 2008), Old Medline 1951 – 1965, Cochrane Library (1991- first quarter 2008), CAB abstracts 1973 – 2008, Embase (1980-week 4, 2008), Cinahl (1982- January 2008), and ACP Journal Club Database of Abstracts of Reviews of Effectiveness (1991-first quarter 2008). Pubmed on NCBI (1960s- January 2008) **Inclusion Criteria:** 1) studies describing outcomes for patients exclusively < 16 years old, early onset with predominantly < 16 years old (> 50 % < 16 years; all < 21 years), or when the data for patients < 16 years old could be extracted separately. 2) We reported breastfeeding for "any exposure," because definitions and	**Intervention:** breast feeding, mixed feeding, or artificial feeding. total number of patients: n = 657 (UC) n = 1014 (control) **Comparison:** healthy controls; The selection of control subjects varied between studies.	**Primary:** early onset of CU/ IBD **Secondary:** – **Results:** Data for all IBD showed a significant protective effect of breastfeeding (OR, 0.69; 95 % CI, 0.51 – 0.94; P = 0.02). There was no significant protective effect from breast milk exposure for the development of UC alone (UC: OR, 0.72; 95 % CI, 0.51 – 1.02; P = 0.06) After exclusion of one study because of incomplete datas, the following results were calculated: A significant protective effect in all IBD and in UC (IBD: OR,0.60; 95 % CI, 0.39 – 0.91; P = .02; UC: OR, 0.61; 95 % CI, 0.44 – 0.84; P = .003) was shown in META-analysis. **Author's Conclusion:** The current evidence demonstrates a possible protective effect for breast milk in the development of early onset IBD. However, the quality of existing data is generally poor. These findings need to be investigated in well-designed prospective studies.	Baron S (2005) Gut. *Gilat T (1987) Scand J Gastroenterol. Koletzko S (1991) BMJ. Rigas A (1993) Ann Epidemiol. Urashima H (1999) Yonago Acta Med.	**Funding Sources:** Dr Andrew Barclay acknowledges the support of the Yorkhill Children's Foundation. The authors acknowledge the support of the GI/ Nutrition Research fund, Child Life and Health, University of Edinburgh. **COI:** The authors declare no conflicts of interest. **Study Quality:** SIGN: 4 studies rated "2 +"; 3 studies "2–". 2 = case control and cohort studies, non randomized interventions; + = well constructed methods, low risk of confounding bias; – = high risk of confounding bias or non-causal relationship. The potential for recall bias was present in all the studies analyzed. Of the 7 studies included in our review, 2 failed to use standard criteria; all 3 failed to describe the criteria used. Only 2 studies referenced published criteria for diagnosis. Failure to use a recognized diagnostic scheme decreases the accuracy of the study, allowing both potential inclusion of non-IBD cases and also misclassification between different types of IBD. Many of the studies highlighted in this systematic review were underpowered to answer the study question, leading to inconclusive results for CD or UC. None of the included studies in our systematic review described an appropriate power calculation to predict what number of subjects would be necessary to detect a significant effect of breastfeeding. **Heterogeneity:** Before exclusion: Heterogeneity for this data

durations of feeding practice are variable **Exclusion Criteria:** 1) studies which did not present original data on breastfeeding and outcomes in IBD 2) no early-onset data separately 3) identified the mean duration of breastfeeding as opposed to "any exposure" to breast milk, and data on absolute exposure could not be retrieved for the population < 16 years of age separately.				was moderate to high (I2 values: IBD, 71.4 %; UC, 43.3 %). After exclusion: The heterogeneity of studies was still high for all IBD and CD, but not for UC (I2 values: IBD, 73.1 %; UC, 0 %). **Publication Bias:** n.s. **Notes:** The MA combining these results was hindered by the lack of OR and CIs for exposure to breast milk in 1 published study.
Ji, J. et al. Review of Clinical Studies of the Treatment of Ulcerative Colitis Using Acupuncture and Moxibustion. Gastroenterol Res Pract. 2016. 9248 589. 2016				
Evidence level/ Study Types	**Population**	**Outcomes/Results**	**Literature/References**	**Methodical Notes**
Evidence level: 2 **Study type:** SR of 63 studies (58 in chinese and 5 in english language) study type: journal articles and graduate student degree dissertations (not further specified) **Databases:** Medline, EMBASE, and the Cochrane Library, China National Knowledge Infrastructure Database (CNKI), the Chongqing VIP Chinese Science and Technology Periodical Database (VIP), and the Chinese Biomedical Literature Database (CBM). **Search period:** January 1, 1995, to December 31, 2015 **Inclusion Criteria:** (1) Study subjects: patients with a definitive diagnosis of UC were included. There were no restrictions on race, age, or gender. (2) Study design: RCTs of UC treatment using acupuncture and moxibustion were included.The languages were limited to Chinese and English. (3) Intervention measures of experimental groups: experimental groups mainly received acupuncture and moxibustion therapy (including filiform needle acupuncture, electroacupuncture, moxibustion,	**Intervention:** acupuncture and moxibustion in UC patients total number of patients: n = 5404. **Comparison:** n.s.	**Primary:** 1) Use of diagnostic standards 2) Use of Acupuncture and Moxibustion Therapy **Secondary:** 3) Methods for acupuncture and moxibustion 4) Duration of treatment **Results:** 1) Use of diagnostic standards: consensus opinions formulated by Chinese industry associations or expert committees (n = 8), the practical guidelines for the diagnosis and treatment of inflammatory bowel diseases of the World Gastroenterology Organization (n = 1) and standards from different types of teaching materials books ("1993 ulcerative colitis diagnostic criteria from the Taiyuan National conference on chronic noninfectious intestinal diseases" and the "2000 diagnostic standards from the Chengdu conference on inflammatory bowel disease of the Chinese Society of Gastroenterology, Chinese Medical Association.") 2) Use of Acupuncture and Moxibustion Therapy: 1. acupuncture and moxibustion therapy combined with drug treatment (drugs are either western medicine or chinese medicine) and 2. acupuncture andmoxibustion alone or in combination. 3) Methods used: acupuncture, electroacu-	Ma S. (1997) Chinese Acupuncture & Moxibustion. Dao Y.(1997) Journal of Sichuan Continuing Education College of MS. Wu HG. (1999) Acupuncture Research. Li HQ (2008) Journal of Clinical Acupuncture and Moxibustion. Mo YX. (2010) Chinese Nursing Research. Guy X. (2010) China's Naturopathy. Yang HJ. (2011) Journal of Qilu Nursing. Zhou GY. (2008) Chinese Archives of Traditional Chinese Medicine. Han SH. (2012) Journal of Nursing and Rehabilitation. Jiang XP. (2012) Clinical Journal of Chinese. Zhou JH. (2003) Jiangsu Journal of Traditional Chinese Medicine. Ding H. (2009) Acta Academiae Medicinae CPAF. Wu HG. (2000) World Journal of Gastroenterology. Wen LJ. (2003) Journal of Jiangxi College of Traditional Chinese Medicine. Wang SM. (2003) Qianwei Journal of Medicine. Xu YL. (2010) Chinese Acupuncture & Moxibustion. Zhang HP. (2012) Nei Mongol Journal of Traditional Chinese Medicine. Chi LL. (2011) Journal of Practical Traditional Chinese Internal Medicine. Luo	**Funding Sources:** This work was supported by National Natural Sciences Foundation of China, nos. 81 303 033; National Basic Research Program of China (973 Program), nos. 2009CB522 900 and 2015CB554 501; Shanghai Municipal Commission of Health and Family Planning, no. 20 134 013; Shanghai Health System outstanding academic leader, no. XBR2013 106; China Postdoctoral Science Foundation, no. 2015M570 380. **COI:** The authors declare that they have no competing interests. **Study Quality:** study quality: The quality of the methodology and reporting of the included articles was generally low. Six studies reported follow- up conditions. An evaluation the quality of the 63 included articles using modified Jadad scoring showed that 3 articles represented high-quality literature. Randomization/blinding: Four articles reported using blind methods; however, the descriptions of these methods in two articles were unclear. Dropout rates: Two studies reported the numbers of cases removed from the trials and the reasons for removal. ITT-analysis: Two trials performed an estimation of sample size before the study. **Heterogeneity:** n.s. **Publication Bias:** 17 articles reported methods for the generation of random sequences and 3 articles used proper allocation

and cupping therapy) alone or combined with other treatment methods (such as drug therapy). In addition, needling methods, acupoint selection, and needle material were not further classified. For acupuncture and moxibustion combined with drug therapy, the drugs administered to experimental groups and control groups in the same study should be consistent. (4) There were no restrictions on the intervention measures used in control groups. (5) Literature with full articles or abstracts that provided sufficient information was included. **Exclusion Criteria:** (1) study subjects and intervention measures that did not conform to the inclusion criteria; (2) RCTs without clear diagnostic standards, basic information on subjects, or intervention measure-related information; (3) series of observations, case reports, expert experiences, and descriptive analyses without controlled cases; (4) literature with duplicated detection or duplicated publication.		puncture, moxibustion, warm needling, acupoint catgut embedding, acupoint application, balance cupping, and auricular point sticking. **Author's Conclusion:** The experimental design, methods, diagnosis, treatment, and efficacy assessment should be improved to provide high- quality evidence for clinical decision-making. With the methods and results of medical researches, the treatment effect of acupuncture and moxibustion on UC will be better observed in the future.	YH. (2009) Jiangxi Journal of Traditional Chinese Medicine. Li DP. (2006) Shaanxi Journal of Traditional Chinese Medicine. Tian JR. (2012) Hebei Journal of Traditional Chinese Medicine. Chen J. (2004) Sichuan Journal of Traditional Chinese Medicine. Li HJ. (2006) Chinese Acupuncture &Moxibustion. Duan DJ. (2012) Hebei Journal of Traditional Chinese. Sun YT. (1998) Chinese Acupuncture Moxibustion. Wang SL. (2008) Chinese Community Doctors. Ma TA. (2005) Central Plains Medical Journal. Cui J. (2010) Hebei Medical Journal. Guo XY. (2007) Liaoning Journal of Traditional Chinese. Wang DM. (2009) Practical Pharmacy and Clinical Remedies. Long ZJ. (2010) Chinese Journal of Coloproctology. Chen HJ. (2010) Chinese and Foreign Medical Research. Sun GH. (2001) Journal of Practical Traditional Chinese Medicine. Wang SM. (2006) Chinese Acupuncture & Moxibustion. Shi YQ. (2006) Hubei Journal of Traditional Chinese Medicine. Shen Q. (2012) Shanghai J Acu-Mox. Xu QJ. (2006) Journal of Chinese Physician. Zhang ZJ. (2011) Shanxi Journal of Traditional Chinese Medicine. Joos S. (2006) Scandinavian Journal of Gastroenterology. Yang C. (1999) Traditional Chinese Medicine. Ma S. (1999) World Journal of Acupuncture-Moxibustion. Ma X. (2005) Journal of Traditional Chinese Medicine. Wang Z. (2013) China Foreign Medical Treatment. Zhong Z. (2013) Chengdu University of Traditional Chinese Medicine. Hu XB. (2013) Clinical Journal of Chinese Medicine.	concealment. The methods of random allocation and allocation concealment of the other trials were not appropriate or were unclear. **Notes:** The study is a statistical evaluation of methods used for Moxibustion and acupuncture. Because of that the results are not directly valid for the key question of the guideline.

			Li WY. (2014) Information on Traditional Chinese Medicine. Ou Y. (2014) Chinese Journal of Ethnomedicine and Ethnopharmacy. Wang CY. (2014) Medical Journal of West China. Ma XW. (2014) Journal of Practical Traditional Chinese Internal Medicine. Sun B. (2015) Asia-Pacific Traditional Medicine. Wu ZY. (2015) Journal of Zhejiang Chinese Medical University. Mi Y. (2015) Mongol Journal of Traditional Chinese Medicine. Mo TM. (2015) Yunnan Journal of Traditional Chinese Medicine and Materia Medica. Huang XY. (2015) Chinese Journal ofModern Drug Application. Dong WQ. (2014) Beijing University of Chinese Medical, 2014. He ZS. (2013) Journal of Changchun University of Traditional Chinese Medicine. Wang X. (2014) Nanjing University of Chinese Medicine. Han GY. (2015) Journal of Clinical and Experimental Medicine. He J. (2015) Journal of Guangzhou University of Traditional Chinese Medicine. Quan X. (2015) Hunan Journal of Traditional Chinese Medicine. Chen K. (2015) Chinese Acupuncture&Moxibustion. Ge F. (2015) China Modern Medicine. Wei LP. (2014) Chinese Medicine Modern Distance Education of China.	

McCombie, A.M. et al. Psychotherapy for inflammatory bowel disease: a review and update. J Crohns Colitis. 7. 935 – 949. 2013 Evidence

Evidence level/ Study Types	Population	Outcomes/Results	Literature/References	Methodical Notes
Evidence level: 2 **Study type:** SR of 18 studies (6 × RCT, 1 CT, 1 report of trial, 10 × not specified) **Databases:** PsychInfo, Medline, Embase **Search period:** 2010 – 2012 (in addition all	**Intervention:** psychotherapy or experimental cognitive therapy (group based programs, hypnotherapy, cognitive behavioural approaches, relaxation, stress management techniques,	**Primary:** depression, anxiety, quality of life (QOL), relapse frequency, hospitalizations, sick-leave days, symptoms, fatigue, medication adherence, and pain measures. **Secondary:** –	Keeper L (2011) Biological research for nursing. Diaz Sibaja MA (2007) Rev Esp Enferm Dig. Shaw L (1987) Pain Jun. Wahed M (2010) Inflamm Bowel Dis. Garcia-Vega E (2004) Behav Res Ther.	**Funding Sources:** Two of the included paper reported Research support by NIH or Non-U.S. Gov't. **COI:** No author of this article has a financial conflict of interest relating to the article. **Study Quality:** Six studies reported some form of blinding.

included and excluded studies of Cochrane Review 2011 were screened) **Inclusion Criteria:** 1) involved IBD patients, 2) performed psychotherapy (i. e. not just education or self- management), 3) had control groups, 4) were published in English 5) involved more than one session of psychotherapy, 6) used quantitative psychological or disease-related outcomes, 7) were published after 1980. **Exclusion Criteria:** Abstracts and studies which were incomplete or had inadequate reporting of results.	study used social support, an individually tailored behavioural treatment, study used nurse-led counselling, and one study had problem solving therapy and solution focused therapy) Patients with UC, IBD or CD. Total number of patients: n = 924 **Comparison:** Control: treatment as usual (TAU), waitlist control (WLC) or active attention control	**Results:** Psychotherapy was found to have minimal effect on measures of anxiety, depression, QOL and disease progression although shows promise in reducing pain, fatigue, relapse rate and hospitalisation, and improving medication adherence. It may also be cost effective. **Author's Conclusion:** Psychotherapy for IBD has minimal effect on measures of anxiety, depression, QOL and disease progression. It shows promise in reducing pain, reducing fatigue, reducing relapse and hospitalisation, improving medication adherence and may be cost-effective. We suggest that targeting patients who are most likely to benefit, matching the type if psychotherapy to individual patients and careful selection of treatment goals via outcomes measures is a way to progress the field. We also recommend that computerised CBT is evaluated given its high acceptability and low cost.	Larsson K (2003) Scand J Gastroenterol. Smith GD (2002) J Adv Nurs. Grootenhuis MA (2009) Eur J Gastroenterol Hepatol. Szigethy E (2007) J Am Acad Child Adolesc Psychiatry. Langhorst J (2007) Scand J Gastroenterol. Jantschek G (1998) Scand J Gastroenterol. Oliveira S (2007) Inflamm Bowel Dis. Deter H-C (2007) Inflamm Bowel Dis. Keefer L (2011) Behav Res Ther. Boye B (2011) Inflamm Bowel Dis. Hommel KA (2012) Eur J Gastroenterol Hepatol. Hommel KA (2011) J Pediatr Gastroenterol Nutr. Vogelaar L (2011) J Crohns Colitis. Keefer L (2012) Inflamm Bowel Dis.	Dropout rates ranged from 0 % at post- intervention to 50 %. Six studies did not mention standardization of treatment, nine studies used some form of standardization of treatment, and four had the same therapist deliver the therapy to all patients. **Heterogeneity:** n.s. **Publication Bias:** n.s. **Notes:** –

AG 6: Welche komplementärmedizinischen Verfahren sind effektiv zur Behandlung der CU?

Bewertungsvorlage:
OXFORD Appraisal Sheet: RCT

Kamali, M et al. Efficacy of the Punica granatum peels aqueous extract for symptom management in ulcerative colitis patients. A randomized, placebo-controlled, clinical trial. Complementary therapies in clinical practice. 21. 141 – 146. 2015

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 2 Study type: RCT Number of Patient: 78 patients were randomized. For analysis 29 patients were included in the P.granatum group and 33 patients in the control group. **Recruitung Phase:** January and June 2014. **Inclusion Criteria:** a) age between 18 and 65 years, b) diagnosis of UC by a gastroenterologist based on clinical symptoms, endoscopic appearance, and pathologic studies, c) Lichtiger Colitis Activity Index (LCAI) score of 4 – 11 indicating moderate disease activity d) willingness to participate **Exclusion Criteria:**	**Intervention:** aqueous extract of the P. granatum peel (each 8 cc of the syrup contained 6 g of the dry peel to be consumed daily for four weeks). **Comparison:** Placebo was prepared based on USP simple syrup formula adding approved additives (Amaranth) to look and smell the same as the P. granatum syrup.	**Primary:** changes in LCAI score after treatment. **Secondary:** Change in each of the symptoms included in the LCAI and the treatment side effects. **Results:** LCAI score: similarly reduced in both the P. granatum (1.68 ± 3.85, P = 0.019) and placebo groups (1.39 ± 2.41, P ¼ 0.002). Clinical response: higher with P. granatum compared with placebo at week 4 (41.4 % vs. 18.2 %, P = 0.055), but not at week 10 (48.3 % vs. 36.4 %, P = 0.441). Side effects: urticaria in 2 (6.8 %) and 2 (6.4 %), nausea in 2 (6.8 %) and 1 (3.2 %), and increased appetite in 2 (6.4 %) and 3 (9.6 %) of the P. granatum and placebo groups respectively. **Author's Conclusion:** The P. granatum peel extract seems effective in complementary management of UC. Further studies in a larger sample of patients are warranted.	**Funding Sources:** This study was derived from a thesis for PhD in Traditional Medicine in the Shahid Beheshti University of Medical Sciences [grant number 155, approval date Oct. 21 2013]. **COI:** None. **Randomization:** Randomization was done using computer generated random numbers. **Blinding:** The P. granatum and placebo syrup were packed and alphabetically labeled in the same opaque and sealed bottles. Attending physician, patients, principal investigators, and data analyzer were blinded to the study arms. A co-investigator who was not involved in patients' recruitment or allocation or in outcome assessment was

a) previous history of allergic response or intolerance to pomegranate compounds, b) opium addiction, c) consuming 15 mg or higher dosage of prednisolone per day, cyclosporine, or anti-TNF agents (e. g. infliximab) d) pregnant women. e) Patients with no appropriate treatment compliance and those experiencing disease flare or severe side effects were excluded from the trial.			aware of the drug codes and cleared it after data analysis. **Dropout Rate/ITT-Analysis:** Sample sizewas determined considering type I and II error rates of 5 % and 20 %, respectively. Minimum detectable effect size (i. e. D of clinical response) was considered to be of 30 % based on a similar herbal medicine trial in UC patients. Sample size was then calculated as 39 patients in each study group after about 20 % dropout rate was considered. During the 10-week study duration 16 patients dropped out of the study. **Notes:** Oxford LoE for validating cohort study.

Sharma, P. et al. Effect of Yoga-Based Intervention in Patients with Inflammatory Bowel Disease. Int J Yoga Therap. 25. 101 – 112. 2015

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 2 **Study type:** RCT **Number of Patient:** 100 patients between 16 – 60 years who were in the clinical remission phase of the disease, were randomized. 60 patients with CU wer randomized (30 for each group: analyzed yoga n = 26, control n = 25 patients) **Recruitung Phase:** 2004 and 2008 **Inclusion Criteria:** (a) one or two stools a day without blood, (b) no fever, (c) no tachy-cardia, (d) hemoglobin normal or returning towards normal, (e) erythrocyte sedimentation rate (ESR) normal or returning towards normal. Patients with a CDAI score < 150 were considered in remission **Exclusion Criteria:** (a) IBD patients with other chronic diseases like diabetes mellitus, hypertension, or cardiovascular diseases, (b) any condition known to affect the cardiovascular autonomic functions such as chronic alcoholism or smoking, (c) patients who have undergone any surgical intervention for IBD, (d) pregnant women, (e) patients on any drug regime affecting autonomic functions, (f) patients on psychiatric medication (g) patients who have practiced yoga within at least one year preceding the study.	**Intervention:** the yoga group (yoga intervention (8 weeks) plus standard medical therapy): physical postures, pranayama, and meditation; 1- hour/day in addition to standard medical therapy (UC, n = 30; CD, n = 20). Standard medical therapy: mesalamines and azathioprine, along with multivitamins and calcium supplements. **Comparison:** control group (standard medical therapy alone): UC, n = 30; CD n = 20.	**Primary:** cardiovascular autonomic functions, serum eosinophilic cationic protein, interleukin- 2 soluble receptors, Speilberger's State Trait Anxiety Inventory (STAI) scores, and clinical symptoms **Secondary:** – **Results:** Fewer UC patients reported arthralgia. The number of patients reporting intestinal colic pain in the control group was higher. State and trait anxiety levels were significantly reduced in patients with UC (state yoga: 38.88 ± 8.85 to 32.8 ± 8.21 (p = 0.01 control: 39.73 ± 8.58 to 39 ± 9.05 p = 0.59) and trait anxiety (Yoga 49.48 ± 8.7 to 41.24 ± 8.22 (p = 0.001) and Control 44 ± 7.88 to 42.26 ± 8.49 p = 0.30) No significant changes were observed in cardiovascular autonomic functions, eosinophilic cationic proteins, or interleukin-2 soluble receptors. **Author's Conclusion:** In IBD, treatment goals are usually directed towards the management of digestive and systemic symptoms. Outcome and follow-up measures are typically based on clinical symptoms, laboratory findings, and endoscopic and histological features. However, since these objective measures may not necessarily correspond with patients' subjective experience of illness and health outcomes, current trends point towards improving general well-being and to reducing the disease associated concerns. This study suggests that medical treatment plus yoga intervention is more effective than medical treatment alone in reducing the anxiety in patients with UC.	**Funding Sources:** Central Council for Research in Yoga and Naturopathy (CCRYN), New Delhi, India. **COI:** The authors declare that they have no competing interests. **Randomization:** Group assignment was determined by a randomization scheme devised from computer- generated random number tables. The tables were prepared by other researchers who were not involved in the study. The randomization schedule was concealed in sequentially numbered, sealed opaque envelopes. Participants were randomized by the research assistant. **Blinding:** – **Dropout Rate/ITT-Analysis:** The patient dropout rate was 10 % and 15 % for UC and CD, respectively. The dropout rate was not significantly different between the groups and was also not related to any adverse events related to the intervention. **Notes:** –

Langhorst, J et al. Randomised clinical trial: a herbal preparation of myrrh, chamomile and coffee charcoal compared with mesalazine in maintaining remission in ulcerative colitis–a double-blind, double-dummy study. Alimentary pharmacology & therapeutics. 38. 490 – 500. 2013

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 2 **Study type:** Randomised, double- blind, double-dummy, active-controlled trial; multicentric (2 German centers) **Number of Patient:** 97 **Recruitung Phase:** 06.2008 – 07.2010. **Inclusion Criteria:** Diagnosed UC, verified by the defining symptoms (rectal bleeding, diarrhoea), colonoscopy and histopathology. All included participants had to be aged ≥ 18 and ≤ 75 years and in self-reported clinical remission for at least 7 days and at most 12 months prior to the beginning of the study reported retrospectively at the time point of the screening visit. **Exclusion Criteria:** Clinically active disease (CAI > 4) Rachmilewitz infectious or chronic active colitis, the current use of antibiotics, Escherichia coli Nissle or ispaghula (Plantago ovata), a treatment within the last 3 months with biologicals or other immunosuppressive drugs (azathioprine, methotrexate a.o.), complete colectomy, relevant comorbidity or pregnancy. Corticosteroids had to be discontinued at least 7 days prior to the beginning of the study.	**Intervention:** Herbal treatment: oral preparation of 100 mg myrrh 4*3 tablets per day for 12 months, 70 mg chamomile extract and 50 mg coffee charcoal (MYRRHINIL- INTEST; Repha GmbH, Hannover, Germany). It is registered as a traditional medicinal product and produced by a contract manufacturer strictly in compliance with GMP (Good Manufacturing Practice). +Placebo Mesalazine 3*1 tablets per day for 12 months. **Comparison:** Mesalazine, consisting of eudragit L coated 5-aminosalicylic acid; 3*1 tablets per day for 12 months. (Salofalk 500 mg; Dr Falk Pharma GmbH, Freiburg, Germany). +Placebo herbal treatment 4*3 tablets per day for 12 months,	**Primary:** *Non-inferiority:* of the herbal preparation with regard to clinical disease activity evaluated by the Clinical Colitis Activity Index (CAI) of Rachmilewitz. CAI was assessed at baseline, 1,3,6,9,12 months and in case patients reported flares. A score of ≤ 4 indicated remission. Active disease was defined with a score of > 4. Non-inferiority test is equivalent to a noncentral t-test on the level a = 0.05 resp. a = 0.025 that the difference in the expected mean values of CAI averaged over the 6 visits between herbal treatment and mesalazine is less than 1. **Secondary:** *Relapse rate, relapse free time, safety and faecal biomarkers:* Lactoferrin (Lf; > 7.25 µg/g for elevated), Calprotectin (Cal; > 50 µg/g for elevated) and PMN-Elastase (PMN-e; > 0.062 µg/g for elevated). Further outcome criteria included mucosal inflammation activity using the Comprehensive Activity Index. **Results:** Mean CAI demonstrated no significant difference between the two treatment groups in the intention-to-treat (P = 0.121) or per- protocol (P = 0.251) analysis. Relapse rates in total were 22/49 patients (45 %) in the mesalazine treatment group and 25/47 patients (53 %) in the herbal treatment group (P = 0.540). Safety profile and tolerability were good and no significant differences were shown in relapse-free time, endoscopy and faecal biomarkers. **Author's Conclusion:** The herbal preparation of myrrh, chamomile extract and coffee charcoal is well tolerated and shows a good safety profile. We found first evidence for a potential efficacy non-inferior to the gold standard therapy mesalazine, which merits further study of its clinical usefulness in maintenance therapy of patients with ulcerative colitis.	**Funding Sources:** This study was funded in full by REPHA GmbH Biologische Arzneimittel, Hannover, Germany. **COI:** J. Langhorst has served as a speaker for Repha GmbH, Techlab Inc, Falk Foundation and received research funding from Techlab Inc. U. Albrecht has served as a consultant and an advisory board member for Repha Gmbh. Rainer Stange has served as a consultant for Steigerwald Arzneimittel GmbH, mediconomics GmbH and Klosterfrau Vertriebsgesellschaft mbH and has received research funding from Repha and IFAG Basel AG. A. Michalsen has served as consultant for Heel, Hevert, Pascoe, Steigerwald and for Repha, Casella as advisory board member. G. Dobos has served as a speaker for Schwabe GmbH, Roche GmbH and received research funding from Schwabe GmbH. Special thanks to Mrs Annette Tengelmann, Mrs. Anna Hofstetter and Mrs Miriam Mohr for their contribution to the study. **Randomization:** "Randomisation was carried out in concealed allocation on a computer-generated sequence in a double-blind manner in blocks of four patients using 1:1 allocation to the two treatment groups. Only complete blocks of ran- dom numbers were used for each centre. If patients were eligible for study entry, they were assigned to random numbers (= treatment numbers) in ascending order within each centre according to the chronological order of their randomisation and were given the corresponding study medication." **Blinding:** Double blind study. **Dropout Rate/ITT-Analysis:** "All analyses and the subgroup analyses, except for the passage 'per protocol', were performed in the ITT population." One participant who was randomized was not included in the ITT analysis, because he was only treatment compliant for 7 days. **Notes:** ITT does not contain all randomized participants.

Sandborn, Wj et al. Andrographis paniculata extract (HMPL-004) for active ulcerative colitis. The American journal of gastroenterology. 108. 90 – 98. 2013

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 2 **Study type:** Multicenter, randomized, double- blind, placebo-controlled trial conducted in 52 centers in 5 countries (USA, Germany, Romania, Ukraine, Canada). **Number of Patient:** 224. **Recruitung Phase:** 02.2008 – 10.2009. **Inclusion Criteria:** Age: ≥ least 18 years; confirmed diagnosis of ulcerative colitis. Patients had a Mayo Score of 4 – 10 points and mildly to moderately active disease on sigmoidoscopy (endoscopic subscore of at least 1) while receiving either oral mesalamine (or equivalent medications sulfasalazine, balsalazide, and olsalazine) for at least 4 weeks or no medical therapy. **Exclusion Criteria:** Patients with Crohn's disease or indeterminate colitis, severe ulcerative colitis (Mayo Score of 11 or 12 points, toxic mega- colon, toxic colitis), previous colonic surgery or probable requirement for intestinal surgery within 12 weeks, enteric infec- tion within 2 weeks, a history of tuberculosis, a positive chest X-ray or tuberculin protein-purified derivative skin test, active infection with hepatitis B or any infection with hepatitis C, infection with human immunodeficiency virus, cancer within 5 years, inadequate bone marrow, hepatic, or renal function, a history of alcohol or drug abuse that would interfere with the study, significant concurrent medical diseases, allergy to plants in the Acanthacea family, and women who were pregnant or breast-feeding were not eligible. Patients receiving oral or rectal steroids within 1 month, rectal mesalamine within 1 week, antibiotics within 2 weeks, or azathioprine, 6- mercaptopurine, anti- tumor necrosis factor agents, or immuno-suppressive therapy within 6 weeks were also excluded.	**Intervention:** Oral capsules containing Andrographis paniculata ethanol extract (HMPL-004; Hutchison MediPharma Ltd., Shanghai, China) at doses of 1200 mg or 1800 mg for 8 weeks in three divided doses. Oral mesalamine was continued at a stable dose. **Comparison:** Placebo, administered in three divided doses. Patients were treated for 8 weeks and followed through week 12. Oral mesalamine was continued at a stable dose.	**Primary:** *Clinical response at week 8*. A colonoscopy or flexible sigmoidoscopy was performed and the Mayo Score was determined at weeks 0 and 8. Clinical response was defined as a decrease from baseline in the total Mayo Score by at least 3 points and at least 30 % with an accompanying decrease in rectal bleeding subscore of at least 1 point or a absolute rectal bleeding subscore of 0 or 1 point) **Secondary:** *clinical remission at week 8, Mucosal healing at week 8, time to partial Mayo Score response* (defined as the time point at weeks 2, 4, 6, or 8 at which there was a decrease from baseline in the partial Mayo Score by at least 2 points); *change from baseline in the partial Mayo Score at weeks 2, 4, 6, or 8; and the mean change from baseline in the total Mayo Score at week 8*; Safety assessments on *adverse events* were conducted through week 12. Clinical remission was defined as a total Mayo Score of 2 points or lower, with no individual subscore exceeding 1 point (12,13). Mucosal healing was defined as a decrease from baseline in the endoscopy subscore by at least 1 point and an absolute endoscopy subscore of 0 or 1 point. Adverse events and concomitant medications were followed through week 12. **Results: Primary:** *Clinical response:* 45 and 60 % of patients receiving A. paniculata 1200 mg and 1800 mg daily, respectively, were in clinical response at week 8, compared with 40 % of those who received placebo (P = 0.5924 for 1200 mg vs. placebo and P = 0.0183 for 1800 mg vs. placebo). **Secondary:** *Clinical remission*: 34 and 38 % of patients receiving A. paniculata 1200 mg and 1800 mg daily, respectively, were in clinical remission at week 8, compared with 25 % of those who received placebo (P = 0.2582 for 1200 mg vs. placebo and P = 0.1011 for 1800 mg vs. placebo). *Adverse events:* developed in 60 and 53 % of patients in the A. paniculata 1200 mg and 1800 mg daily groups, respectively, and 60 % in the placebo group. **Author's Conclusion:** Patients with mildly to moderately active ulcerative colitis treated with A. paniculata extract (HMPL-004) at a dose of 1800 mg daily were more likely to achieve clinical response than those receiving placebo.	**Funding Sources:** This work was supported by a research grant from Hutchison Medipharma Ltd., Shanghai, China. **COI:** Dr Sandborn reports having received consulting fees from Abbott Laboratories, ActoGeniX NV, AGI erapeutics, Inc., Alba erapeutics Corporation, Albireo, Alfa Wasserman, Amgen, AM-Pharma BV, Anaphore, Astellas Pharma, Athersys, Inc., Atlantic Healthcare Limited, Axcan Pharma (now Aptalis), BioBalance Corporation, Boehringer-Ingelheim Inc, Bristol Meyers Squibb, Celegene, Celek Pharmaceuticals, Cellerix SL, Cerimon Pharmaceuticals, ChemoCentryx, CoMentis, Cosmo Technologies, Coronado Biosciences, Cytokine Pharmasciences, Eagle Pharmaceuticals, Eisai Medical Research Inc., Elan Pharmaceuticals, EnGene, Inc., Eli Lilly, Enteromedics, Exagen Diagnostics, Inc., Ferring Pharmaceuticals, Flexion erapeutics, Inc., Funxional erapeutics Limited, Genzyme Corporation, Genentech (now Roche), Gilead Sciences, Given Imaging, Glaxo Smith Kline, Human Genome Sciences, Ironwood Pharmaceuticals (previously Microbia Inc.), Janssen (previously Centocor), KaloBios Pharmaceuticals, Inc., Lexicon Pharmaceuticals, Lycera Corporation, Meda Pharmaceuticals (previously Alaven Pharmaceuticals), Merck Research Laboratories, MerckSerono, Millennium Pharmaceuticals (subsequently merged with Takeda), Nisshin Kyorin Pharmaceuticals Co., Ltd., Novo Nordisk A/S, NPS Pharmaceuticals, Optimer Pharmaceuticals, Orexigen Therapeutics, Inc., PDL Biopharma, Pfizer, Procter and Gamble, Prometheus Laboratories, ProtAb Limited, Purgenesis Technologies, Inc., Receptos, Relypsa, Inc., Salient Pharmaceuticals, Salix Pharmaceuticals, Inc., Santarus, Schering Plough Corporation (acquired by Merck), Shire Pharmaceuticals, Sigmoid Pharma Limited, Sirtris Pharmaceuticals, Inc. (a GSK company), S.L.A. Pharma (UK) Limited, Targacept, Teva Pharmaceuticals, Therakos, Tillotts Pharma AG (acquired by Zeria Pharmaceutical Co., Ltd.), TxCell SA, UCB Pharma, Viamet Pharmaceuticals, Vas- cular Biogenics Limited (VBL), Warner Chilcott UK Limited, Wyeth (now P zer). He

			has received lecture fees from Abbott Laboratories, Bristol Meyers Squibb, and Janssen (previously Centocor). He has received research support from Abbott Laboratories, Bristol Meyers Squibb, Genentech, Glaxo Smith Kline, Janssen (previously Cento- cor), Millennium Pharmaceuticals (now Takeda), Novartis, P zer, Procter and Gamble Pharmaceuticals, Shire Pharmaceuticals, and UCB Pharma. Dr Targan reports having received consulting fees from Amgen, Biogen, Esai, GSK, Hutchison Medipharma, Lycera, Merck, Prometheus, Symbiotix, Takeda Pharmaceutical and Zyngenia. In addition, he reports having received research and meeting/ travel support from Hutchison Medipharma. He also reports having received a grant for researching the mechanism of action for the drug published in this paper from Hutchison Medipharma. Dr Byers reports having received the following from Hutchison Medipharma: support for travel to meetings for the study and other purposes, receiving fees for review activity related to data monitoring and anal- ysis, and for writing and reviewing the manuscript. Mr. Rutty reports having received the following from Hutchison Medipharma: support for travel to meetings for the study and other purposes, receiving fees for review activity related to data monitoring and analysis, and for writing and reviewing the manuscript. In addition, he reports Board membership for Steba Biotech SA and reports consulting for the following companies: Schering Corporation, Roche, Methylgene, Steba Biotech SA, Aderans Research Institute Inc., Stem Cell eraputics, Genentech, Pearly erapeutics, Sundise Chinese Medicine Technol- ogy Development Corp., Endocyte, Inc, and Generon Corporation Ltd. Mr Rutty is an employee of Everest Clinical Research Services Inc. Dr Tang reports being an employee of Hutchison Medipharma at the time of the clinical trial described herein and during the drafting of this manuscript. He is currently an employee of Generon (Shanghai). Dr Mu reports being an employee of Hutchison Medipharma. Dr Zhang reports being an employee of Hutchison Medipharma. **Randomization:** "Randomization was performed centrally using a block randomization schedule stratified by concurrent mesalamine

			use (yes or no) and country/geographic region (North East USA, Mid-East USA, South East USA, Western USA, Canada, Ukraine, and Romania)." **Blinding:** Double blind study, no description of allocation concealment. **Dropout Rate/ITT-Analysis:** Missing data were handled using a "worst case" intention- to-treat analysis in which patients with any missing component of the Mayo Score were considered not to be in clinical response, clinical remission, or to have mucosal healing. **Notes:** ITT analysis does not include all patients that were randomized (one person was incorrectly randomized).

Gong, Y et al. Efficacy and safety of Fufangkushen colon-coated capsule in the treatment of ulcerative colitis compared with mesalazine: A double-blinded and randomized study. [German]. Deutsche Zeitschrift fur Akupunktur. 57. 20 – 21. 2014

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 3 **Study type:** Double-blinded, randomized clinical trial, multicentric 13 centers in China. **Number of Patient:** 320 **Recruitung Phase:** 2007 – 2009 **Inclusion Criteria:** Patients who were 18 – 65 years of age at the time of informed consent; who had active UC defined by a Mayo score of 6 – 12 points; and who meet the Chinese pattern diagnosis of damp-heat accumulation interior. The damp-heat accumulation interior pattern diagnosis can be identified based on the co-existence of 3 major symptoms (diarrhea, mucous or bloody purulent stools, abdominal pain) and at least 2 secondary symptoms (tenesmus, burning pain in anus, fever, anorexia, dry or bitter mouth, foul stools). **Exclusion Criteria:** patients with quiescent UC; patients with other severe diseases; female patients in pregnancy or lactation and male patients with desire for procreation; patients who showed allergic reaction to the drug; who had higher blood creatinine level, or blood alanine transaminase level higher than double of normal; who took any other investigational drugs within 3 months.	**Intervention:** Fufangkushen colon-coated capsule (FCC, 0.4 g/capsule, supplied by Zhonghui Pharmaceutical, Beijing, China. Patch No. 20 070 301), and placebos prepared identical in color, taste and consistency to the intervention drug (supplied by Zhonghui Pharmaceutical, Beijing, China). FCC is composed of extracts of Chinese herbal medicine Radix Sophorae Flavescentis (Kushen), Radix Sanguisorbae (Diyu), Indigo Naturalis (Qingdai), Bletilla hyacinthina reichb (Baiji), Radix Glycyrrhizae (Gancao). All the extracts were coated in a capsule which ensures the medicine to be released in the colon. **Comparison:** Huidi mesalazine tablet (HD, mesalazine enteric-coated tablets, 0.25 g/tablet, supplied by Luling Pharmaceutical, Jiamusi, China. Patch No. 071 006), and placebos prepared	**Primary:** Patients were evaluated at weeks 0 and 8. The Mayo score was determined at weeks 0, 8. **Primary outcome** *Efficacy: Clinical response* was defined as a decrease from baseline in the total Mayo score of at least 3 points and at least 30 %, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or absolute subscore for rectal bleeding of 0 or 1. **Secondary: Secondary outcome** : *Efficacy: Clinical remission* was defined as a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point. *Efficacy: Mucosal healing* was defined as absolute subscore for endoscopy of 0 or 1. *Safety outcomes:* are not described in the methods; results section lists the incidence of adverse events. **Results: Primary:** *Efficacy Clinical response:* At the 8th week, 72.50 % of patients in FCC group (170 of 234) and 65.00 % of patients in HD group(52 of 80) had achieved a clinical response with no statistically significant difference (P> 0.05). *Efficacy Clinical remission* The proportions of patients who had a clinical remission was similar (41.50 % in FCC group, 41.25 % in HD group, P> 0.05) *Efficacy Mucosal healing:* The rate at week 8 in the two groups was similar and also without significant difference (55.13 % in FCC group, 55.00 % in HD group, P> 0.05). Mayo scores at week 8 showed no statistically significant difference between the two groups *Safety:* No significant differences were observed between the safety profiles of the 2 groups (P> 0.05). No severe AEs were reported in either group. The latent class analysis indicated that FCC was superior applicable for the left hemicolon involved patients than HD. **Author's Conclusion:** FCC has a similar effect and safety in the treatment of active UC with TCM damp-heat accumulation interior pattern at week 8 compared compared with HD, a mesalamine enteric-coated tablets, in achieving clinical response	**Funding Sources:** This study was supported jointly by the National Eleventh Five Year Support Project of China (2006BAI04A10) and National ScienceFoundation of China (No. 30 902 003). **COI:** n.a. **Randomization:** All eligible patients were randomly allocated at a 3:1 ratio into two groups. 240 patients accepted FCC, 80 accepted HD treatment. The central randomization system was adopted for the patient allocation, and the randomization code was sealed until the blind was removed. **Blinding:** Double blind study. **Dropout Rate/ITT-Analysis:** "All efficacy analyses used intention-to-treat methods." The exact number in these analyses is not provided, not even in the prisma charts **Notes:** Inclusion criteria for patients are not necessarily compatible with conventional inclusion criteria "*patients .. who meet the Chinese pattern diagnosis of damp-heat accumulation interior. The damp-heat accumulation interior pattern diagnosis can be identified based on the co-existence of 3 major symptoms (diarrhea, mucous or bloody purulent stools, abdominal pain) and at least 2 secondary symptoms (tenesmus, burning pain in anus, fever, anorexia, dry or bitter mouth, foul stools)*" Only the names of the ingredients in the TCM drug are known, not their dosage, which affects the reproducibility of the experiment. Unequal allocation TCM:5-ASA 3:1 brings up questions

	identical in color, taste and consistency to the comparison drug (supplied by Zhonghui Pharmaceutical, Beijing, China).	and remission, mucosal healing. In addition, FCC is superior to HD in treating patients with UC as the inflamed area was the left hemicolon.	of the rationale and internal validity of the study. Unclear how many participants were included in the ITT analysis set. Randomization sequence not specified. No mention of conflicts of interest. Subgroup analysis not part of the hypothesis and appears to be a post hoc analysis. The 5-ASA group of patients with left- sided colitis might also lack statistical power (n = 26).

Kyaw, Mh et al. A prospective, randomized, controlled, exploratory study of comprehensive dietary advice in ulcerative colitis: impact on disease activity and quality of life. European journal of gastroenterology & hepatology. 26. 910 – 917. 2014

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 3 **Study type:** Prospective randomized controlled study, non blinded. **Number of Patient:** 130 **Recruitung Phase:** n.a. **Inclusion Criteria:** Patients aged 18 – 80 years with a confirmed diagnosis of UC on the gastroenterology outpatient registers of Leicester General Hospital and Leicester Royal Infirmary, UK, were eligible for inclusion. **Exclusion Criteria:** Patients who were unwilling or unable to provide informed consent were excluded. Potential participants were approached either by letter or in person when attending clinic appointments. This was an exploratory study, as recommended by the Medical Research Council guidelines.	**Intervention:** Participants who were assigned to the intervention group were provided dietary guidelines DMF in UC in the form of an educational booklet 'Diet and Ulcerative Colitis' (originally sponsored by an educational grant from Procter & Gamble Pharmaceuticals). This booklet was developed and published in 2007 with an aim to translate research-based dietary knowledge into practical dietary guidelines. The booklet is now freely distributed by NHS IBD services and published by Warner Chilcott Pharmaceuticals. **Comparison:** Patients in the control group were given 'Healthy Eating for a Healthy Leicestershire' and assigned to follow their usual diet. This standard booklet on healthy eating, which was normally used to provide dietary advice to the general public, was published by the Leicestershire Nutrition and Dietetic service.	**Primary:** The simple clinical colitis activity index and the UK inflammatory bowel disesase questionnaire (IBDQ). **Secondary:** n.a. **Results:** Overall, 112 patients completed the study. Study participants were asked to complete the IBDQ and SCCAI together with the Food Frequency Questionnaire at 0, 6 and 24 weeks. At 24 weeks, there was a mean reduction in the Simple Clinical Colitis Activity Index score in the intervention group compared with an increase in the score in the control group [−1.304 (P = 0.0108) vs. 0.875 (P = 0.0249)]. There was a mean increase in the IBDQ score in the intervention group compared with a reduction in the score in the control group [7.17 (P = 0.126) vs. −3.44 (P = 0.205)]. A total of 69 % of patients in the intervention group found the dietary advice significantly or moderately helpful. **Author's Conclusion:** The study suggests that there is likely to be a link between the dietary advice provided and symptomatic improvement. The effect of diet may not occur through the addition or the elimination of single nutrients; rather, each food consumed combines many nutrients that allow for a synergistic or an antagonistic action when present in a certain composition.	**Funding Sources:** This study was funded by an educational grant from Warner Chilcott UK Ltd through the charity GEAR (Gastrointestinal Education And Research). **COI:** There are no conflicts of interest. **Randomization:** A computer-generated randomization schedule produced by SPSS 18.0 (IBM, Chicago, Illinois, USA) was used to assign each patient to an intervention or a control arm. **Blinding:** No blinding **Dropout Rate/ITT- Analysis:** There were 10 and 8 dropouts out of 71 and 59 for Intervention and Control groups. No ITT analysis was performed. "Because of lack of complete data for relevant outcome measures in patients withdrawn from study, a strict intention-to-treat analysis was not feasible." **Notes:** ITT analysis was not performed and strictly speaking the 18 dropouts were not taken into account. Outcomes were patient – reported and subjective, therefor they are especially likely to be influenced by the lack of blinding. Inclusion criteria do not specify a UC severity or activity state.

Tang, T et al. Randomised clinical trial: herbal extract HMPL-004 in active ulcerative colitis – a double-blind comparison with sustained release mesalazine. Alimentary pharmacology & therapeutics. 33. 194 – 202. 2011

Population	Intervention	Outcomes/Results	Methodical Notes
Evidence level: 3 **Study type:** Double-blind double-dummy randomized trial. Multicentric	**Intervention:** HMPL-004 (Hutchison Medipharma Ltd., Shanghai,	**Primary:** Clinical symptoms were assessed using the Chinese Gastro- enterological Association (CGA), 200 113 Standard for Diagnosis of UC Symptom Score Paradigm. Mucosal healing was	**Funding Sources:** This study was funded in full by Hutchison Medipharma, Ltd. The preparation of this paper was funded in full by Hutchi-

Number of Patient: 125
Recruitung Phase: 11.2005 – 11.2006
Inclusion Criteria: Male or female patients, 18 – 65 years of age, with a diagnosis of mildly to moderately active UC confirmed by colonoscopy within 1 week of study entry. Mild-to-moderately active UC was defined as chronic persistent or relapsing clinical symptoms of bloody stool, abdominal pain and distension.
Exclusion Criteria: Patients were excluded from the study if they were pregnant or lactating, had stools positive for bacterial pathogens, renal or hepatic disease, a history of asthma, a bleeding or coagulation disorder, severe UC, or severe complications of UC, Crohn's disease, cancer, a history of allergy or hypersensitivity to aminosalicylates or any component of the HMPL-004 products, if they had received any medication for UC within 1 week of study, including sulfasalazine, mesalazine, steroids, and Chinese herbal medicines, or if they had participated in any clini- cal study within 3 months. During study participation patients were prohibited from concomitant medications for UC.

China) 400 mg t.d.s., 1200 mg/day. The study material is water-soluble, formulated in single-dose level hard gelatin capsules each containing 1200 mg Andrographis paniculata extract (APE), which was manufactured under current Good Manufacturing Practices (cGMP) for 8 weeks + Mesalazine placebo
Comparison: Mesalazine Slow release granules (Etiasa, Ethypharm Industries, France, same as Pentasa) 1500 mg t. d.s., 4500 mg/day for 8 weeks + HMPL-004 placebo.

evaluated by colonoscopy and histopathology by biopsy at baseline and at 8 weeks. Mucosal healing was scored using the CGA colonoscopy paradigm and histopathology was scored using the CGA histopathological paradigm. Colonoscopy scores at baseline were compared with those obtained at the completion of the 8-week study. There were two primary efficacy endpoints, both based on the clinical response. The 'general evaluation' was calculated by the percentage of the reduction of sum scores after completion of study treatment compared with the sum scores at the baseline. The 'clinical evaluation' was judged by the percentage of patients attaining remission, partial remission, or improvement at week 8. Remission meant all symptoms disappeared, partial remission meant reduction of 50 % of symptoms, and improvement meant more than 25 % reduction in symptoms.
Secondary: Secondary endpoints were based on colonoscopy findings. The first was the percentage of patients showing remission (no inflammation), partial remission (inflammation reduced by two grades) or improvement (inflammation reduced by one grade) in the mucosal appearance, and the second was the percentage of patients who showed histological improvement on biopsy.
Results: Clinical remission and response were seen in 21 % and 76 % of HMPL-004-treated patients, and 16 % and 82 % of mesalazine-treated patients. By colonoscopy, remission and response were seen in 28 % and 74 % of HMPL-004-treated patients and 24 % and 71 % of mesalazine-treated patients, respectively. There was no significant difference between the two treatment groups.
Author's Conclusion: In conclusion, in this Phase II study, HMPL-004 had efficacy similar to slow release mesalazine and was well tolerated in patients with mildly to moderately active UC.

son Medipharma, Ltd. Initial data analyses were undertaken by Tom Tang, who is an employee of Hutchison Medipharma Ltd. and Zhao-Shen Li, who is an employee of Changhi Hospital, Second Military Medical University and received funding from Hutchison Medipharma, Ltd. Secondary, efficacy analysis was undertaken by Stephan R. Targan, an employee of Cedars Sinai Medical Center, William J. Sandborn, an employee of Mayo Clinic, Tom Tang, an employee of Hutchison Medipharma Ltd., and Vera S. Byers, an employee of Immunology Inc. and received funding from Hutchison Medipharma, Ltd. Writing support was provided by Vera S. Byers, funded by Hutchi- son Medipharma, Ltd.
COI: William J. Sandborn is a consultant for both Hutchison Medipharma and Salix Pharmaceuticals, and has served as a consultant for and received research funding from Procter & Gamble Pharmaceuticals, Inc. and Shire Pharmaceuticals. Dr. Sandborn is an employee of University of California San Diego. Stephan R. Targan is a consultant for Hutchison Medipharma, Prometheus RxDx, Inc., Procter & Gamble, Elan, Wyeth, Amgen, and Takeda Pharmaceutical and is on the Board of Directors for Prometheus RxDx, Inc. Dr Targan is an employee of Cedars Sinai Medical Center, Los Angeles, California. Dr Targan owns stock in Prometheus RxDx, Inc. Stephan R. Targan et al. own patent US 7,662,569, B2, Methods of assessing Crohn's Disease patient phenotype by 12 serological response.
Randomization: No description of the randomization sequence. "Eligible patients were randomised (in a 1:1 ratio) to receive either HMPL-004 (Hutchison Medipharma Ltd., Shanghai, China) 400 mg t.d.s., 1200 mg/day or mesalazine SR Granules (Etiasa, Ethypharm Industries, France, same as Pentasa) 1500 mg t.d.s., 4500 mg/day in a blinded double-dummy fashion."
Blinding: Double-blind study.
Dropout Rate/ITT-Analysis: Not all patients who were randomized were included in the ITT analysis. "All analyses were conducted in the intent- to-treat (ITT) population. The ITT population included all patients who were randomised and took one or more doses of study medication."
Notes: "The baseline characteristics were similar in the two treat-

			ment groups." No tests were performed to make certain this is the case. This was a double blind double dummy study, so it is likely. But there is no description of allocation concealment. Not all patients who were randomized were included in the ITT analysis. "All analyses were conducted in the intent-to-treat (ITT) population. Grading of the UC severity and all outcomes were performed using the Chinese Gastroenterologic Association scores, which differ from more established scoring systems (such as MAYO), which has an influence on the comparability of the results.

Anhang D – Literaturrecherche und Evidenztabellen AG 6

Literaturrecherche

Cochrane Suche 20.07.2016

#1
acupuncture or "acupuncture therapy" or acupressure or tcm or "Chinese medicine" or "Chinese herbs" or Ayurveda or "ayurvedic medicine" or kampo:ti, ab, kw (Word variations have been searched)
#2
MeSH descriptor: [Acupuncture] explode all trees
#3
MeSH descriptor: [Acupuncture Therapy] explode all trees
#4
MeSH descriptor: [Medicine, Chinese Traditional] explode all trees
#5
MeSH descriptor: [Drugs, Chinese Herbal] explode all trees
#6
MeSH descriptor: [Medicine, Ayurvedic] explode all trees
#7
mindfulness or relaxation or mbsr or "breathing exercise" or movement or "movement therapy" or "autogenic training" or yoga or "tai ji" or "tai chi" or qigong or "qi gong" or hypnosis or hypnotherapy or meditation or aromatherapy or imagery:ti,ab,kw (Word variations have been searched)
#8
MeSH descriptor: [Mindfulness] explode all trees
#9
MeSH descriptor: [Relaxation] explode all trees
#10
MeSH descriptor: [Movement] explode all trees
#11
MeSH descriptor: [Autogenic Training] explode all trees
#12
MeSH descriptor: [Yoga] explode all trees
#13
MeSH descriptor: [Tai Ji] explode all trees
#
MeSH descriptor: [Qigong] explode all trees
#16
MeSH descriptor: [Hypnosis] explode all trees
#17
MeSH descriptor: [Aromatherapy] explode all trees
#18
MeSH descriptor: [Imagery (Psychotherapy)] explode all trees
#19
MeSH descriptor: [Meditation] explode all trees
#20
exercise or hydrotherapy or "hydro therapy" or "photo therapy" or phototherapy or "light therapy" or chronotherapy or "chrono therapy" or biofeedback or warming or massage or homeopathy or homoeopathy:ti,ab,kw (Word variations have been searched)
#21
MeSH descriptor: [Exercise] explode all trees
#22
MeSH descriptor: [Breathing Exercises] explode all trees
#23
MeSH descriptor: [Hydrotherapy] explode all trees
#24
MeSH descriptor: [Phototherapy] explode all trees
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MeSH descriptor: [Chronotherapy] explode all trees
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MeSH descriptor: [Biofeedback, Psychology] explode all trees
#27
MeSH descriptor: [Massage] explode all trees
#28
MeSH descriptor: [Homeopathy] explode all trees
#29
phytotherapy or "phyto therapy" or phytochemicals or herbs or "herbal medicine" or valerian or hop or kava or "kava kava" or passiflora or passionflower or vitamins or nutrition or "nutritional supplements" or "dietary supplements":ti,ab,kw (Word variations have been searched)
#30
MeSH descriptor: [Phytotherapy] explode all trees

#31
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#32
MeSH descriptor: [Herbal Medicine] explode all trees
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MeSH descriptor: [Valerian] explode all trees
#34
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MeSH descriptor: [Passiflora] explode all trees
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MeSH descriptor: [Vitamins] explode all trees
#37
MeSH descriptor: [Dietary Supplements] explode all trees
#38
“Complementary therapies” or “alternative therapies” or “complementary and alternative therapies” or CAM or naturopathy:ti,ab,kw (Word variations have been searched)
#39
MeSH descriptor: [Complementary Therapies] explode all trees
#41
MeSH descriptor: [Naturopathy] explode all trees
#42
Enter terms for search #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39
#43
“ulcerative colitis” or " “inflammatory bowel disease*” or UC:ti,ab,kw
#44
MeSH descriptor: [ulcerative colitis] explode all trees
#45
MeSH descriptor: [inflammatory bowel disease] explode all trees
#45
Enter terms for searc#43 or #44 or #45
#46
Enter terms for searc#45 and #42

Psychinfo Suche 20.07.2016

1	acupuncture.ab. or acupuncture.ti. or acupuncture.id. or acupuncture.sh.
2	acupressure.ab. or acupressure.ti. or acupressure.id. or acupressure.sh.
3	acupuncture therapy.ab. or acupuncture therapy.ti. or acupuncture therapy.id. or acupuncture therapy.sh.
4	tcm.ab. or tcm.ti. or tcm.id. or tcm.sh.
5	chinese medicine.ab. or chinese medicine.ti. or chinese medicine.id. or chinese medicine.sh.
6	chinese herbs.ab. or chinese herbs.ti. or chinese herbs.id. or chinese herbs.sh.
7	ayurveda.ab. or ayurveda.ti. or ayurveda.id. or ayurveda.sh. or ayurvedic medicine.ab. or ayurvedic medicine.ti. or ayurvedic medicine.id. or ayurvedic medicine.sh. or kampo.ab. or kampo.ti. or kampo.id. or kampo.sh.
8	1 or 2 or 3 or 4 or 5 or 6
9	mindfulness.ab. or mindfulness.ti. or mindfulness.id. or mindfulness.sh. or relaxation.ab. or relaxation.ti. or relaxation.id. or relaxation.sh. or relaxation therapy.ab. or relaxation therapy.ti. or relaxation therapy.id. or relaxation therapy.sh.
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11	movement.ab. or movement.ti. or movement.id. or movement.sh. or movement therapy.ab. or movement therapy.ti. or movement therapy.id. or movement therapy.sh. or autogenic training.ab. or autogenic training.ti. or autogenic training.id. or autogenic training.sh.
12	yoga.ab. or yoga.ti. or yoga.id. or yoga.sh. or taiji.ab. or taiji.ti. or taiji.id. or taiji.sh. or tai chi.ab. or tai chi.ti. or tai chi.id. or tai chi.sh.
13	qi gong.ab. or qi gong.ti. or qi gong.id. or qi gong.sh. or qigong.ab. or qigong.ti. or qigong.id. or qigong.sh. or meditation.ab. or meditation.ti. or meditation.id. or meditation.sh.
14	hypnotherapy.ab. or hypnotherapy.ti. or hypnotherapy.id. or hypnotherapy.sh. or hypnosis.ab. or hypnosis.ti. or hypnosis.id. or hypnosis.sh. or imagery.ab. or imagery.ti. or imagery.id. or imagery.sh.
15	aromatherapy.ab. or aromatherapy.ti. or aromatherapy.id. or aromatherapy.sh. or aroma therapy.ab. or aroma therapy.ti. or aroma therapy.id. or aroma therapy.sh. or exercise.ab. or exercise.ti. or exercise.id. or exercise.sh.
16	hydrotherapy.ab. or hydrotherapy.ti. or hydrotherapy.id. or hydrotherapy.sh. or hydro therapy.ab. or hydro therapy.ti. or hydro therapy.id. or hydro therapy.sh. or photo therapy.ab. or photo therapy.ti. or photo therapy.id. or photo therapy.sh. or phototherapy.ab. or phototherapy.ti. or phototherapy.id. or phototherapy.sh.
17	light therapy.ab. or light therapy.ti. or light therapy.id. or light therapy.sh. or lighttherapy.ab. or lighttherapy.ti. or lighttherapy.id. or lighttherapy.sh. or chronotherapy.ab. or chronotherapy.ti. or chronotherapy.id. or chronotherapy.sh. or chrono therapy.ab. or chrono therapy.ti. or chrono therapy.id. or chrono therapy.sh.
18	biofeedback.ab. or biofeedback.ti. or biofeedback.id. or biofeedback.sh. or warming.ab. or warming.ti. or warming.id. or warming.sh. or homeopathy.ab. or homeopathy.ti. or homeopathy.id. or homeopathy.sh. or homoeopathy.ab. or homoeopathy.ti. or homoeopathy.id. or homoeopathy.sh.

19	massage.ab. or massage.ti. or massage.id. or massage.sh. or phyto therapy.ab. or phyto therapy.ti. or phyto therapy.id. or phyto therapy.sh. or phytotherapy.ab. or phytotherapy.ti. or phytotherapy.id. or phytotherapy.sh. or phytochemicals.ab. or phytochemicals.ti. or phytochemicals.id. or phytochemicals.sh.
20	herbs.ab. or herbs.ti. or herbs.id. or herbs.sh. or herbal medicine.ab. or herbal medicine.ti. or herbal medicine.id. or herbal medicine.sh. or valerian.ab. or valerian.ti. or valerian.id. or valerian.sh. or hop.ab. or hop.ti. or hop.id. or hop.sh.
21	kava.ab. or kava.ti. or kava.id. or kava.sh. or kava kava.ab. or kava kava.ti. or kava kava.id. or kava kava.sh. or passiflora.ab. or passiflora.ti. or passiflora.id. or passiflora.sh. or passionflower.ab. or passionflower.ti. or passionflower.id. or passionflower.sh.
22	vitamins.ab. or vitamins.ti. or vitamins.id. or vitamins.sh. or nutrition.ab. or nutrition.ti. or nutrition.id. or nutrition.sh. or nutritional supplements.ab. or nutritional supplements.ti. or nutritional supplements.id. or nutritional supplements.sh. or dietary supplements.ab. or dietary supplements.ti. or dietary supplements.id. or dietary supplements.sh.
23	complementary therapies.ab. or complementary therapies.ti. or complementary therapies.id. or complementary therapies.sh. or alternative therapies.ab. or alternative therapies.ti. or alternative therapies.id. or alternative therapies.sh. or “complementary and alternative therapies”.ab. or “complementary and alternative therapies”.ti. or “complementary and alternative therapies”.id. or “complementary and alternative therapies”.sh. or cam.ab. or cam.ti. or cam.id. or cam.sh.
24	naturopathy.ab. or naturopathy.ti. or naturopathy.id. or naturopathy.sh.
25	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26	“ulcerative colitis”.ab. or “ulcerative colitis”.ti. or “ulcerative colitis”.id. or “ulcerative colitis”.sh. or “inflammatory bowel diseases”.ab. or “inflammatory bowel diseases”.ti. or “inflammatory bowel diseases”.id. or “inflammatory bowel diseases”.sh. or UC**.ti. OR** UC**.ab. OR** UC**.sh. OR** UC**.id.**
27	randomized controlled trial.af. or randomized controlled trial.pt. or controlled clinical trial.af. or controlled clinical trial.pt. or double blind.af. or single blind.af. or placebo.af. or random$.af. or systematic review.af. or systematic review.dt. or literature review.af. or literature review.dt. or meta-analysis.af. or meta-analysis.dt.
28	25 and 26 and 27

Pubmed Suche 20.07.2016

Search	Query
#11	Search **(#9 NOT #10)**
#10	Search **((animals[mh] NOT humans[mh]))**
#9	Search **(#6 AND #7 AND #8)**
#8	Search **(#1 or #2 or #3 or #4 or #5)**
#7	Search **(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Systematic Review[pt] OR Systematic Review[tiab] OR Systematic Review[sh] OR Meta-Analysis[pt] OR Meta-Analysis[tiab] OR Meta-Analysis[sh] OR Cochrane Database Syst Rev[Journal])**
#6	Search **(**“ulcerative colitis**”[MeSH] OR “**ulcerative colitis**”[Title/Abstract] OR “UC”[Title/Abstract])**
#5	Search **("complementary therapies"[MeSH Terms] OR ("complementary"[Tiab] AND "therapies"[Tiab]) OR "complementary therapies"[Tiab] OR ("complementary"[Tiab] AND "medicine"[Tiab]) OR "complementary medicine"[Tiab]) OR ("complementary therapies"[MeSH Terms] OR ("complementary"[Tiab] AND "therapies"[Tiab]) OR "complementary therapies"[Tiab] OR ("alternative"[Tiab] AND "medicine"[Tiab]) OR "alternative medicine"[Tiab]) OR ("complementary"[Tiab] AND "and"[Tiab] AND "alternative"[Tiab] AND "medicine"[Tiab]) OR "complementary and alternative medicine"[Tiab] OR ("complementary"[Tiab] AND "and"[Tiab] AND "alternative"[Tiab] AND "medicine"[Tiab]) OR "complementary and alternative medicine"[Tiab]) OR ("naturopathy"[MeSH Terms] OR "naturopathy"[Tiab])**
#4	Search **("phytotherapy"[MeSH Terms] OR "phytotherapy"[tiab]) OR ("phytochemicals"[MeSH Terms] OR "phytochemicals"[tiab]) OR herbs[tiab] OR ("herbal medicine"[MeSH Terms] OR ("herbal"[tiab] AND "medicine"[tiab]) OR "herbal medicine"[tiab]) OR ("valerian"[MeSH Terms] OR "valerian"[tiab]) OR hop[tiab] OR ("kava"[MeSH Terms] OR "kava"[tiab] OR ("kava"[tiab] AND "kava"[tiab]) OR "kava kava"[tiab]) OR balm[tiab] OR ("passiflora"[MeSH Terms] OR "passiflora"[tiab] OR "passionflower"[tiab]) OR ("vitamins"[Pharmacological Action] OR "vitamins"[MeSH Terms] OR "vitamins"[tiab]) OR ("nutritional status"[MeSH Terms] OR ("nutritional"[tiab] AND "status"[tiab]) OR "nutritional status"[tiab] OR "nutrition"[tiab] OR "nutritional sciences"[MeSH Terms] OR ("nutritional"[tiab] AND "sciences"[tiab]) OR "nutritional sciences"[tiab]) OR supplements[tiab] OR ("dietary supplements"[MeSH Terms] OR ("dietary"[tiab] AND "supplements"[tiab]) OR "dietary supplements"[tiab] OR "supplementation"[tiab]) OR ("dietary supplements"[MeSH Terms] OR ("dietary"[tiab] AND "supplements"[tiab]) OR "dietary supplements"[tiab] OR ("nutritional"[tiab] AND "supplement"[tiab]) OR "nutritional supplement"[tiab] balm[tiab] OR ("passiflora"[MeSH Terms] OR "passiflora"[tiab]) OR ("curcumin"[MeSH Terms] OR "curcumin "[tiab]) OR ("Boswellia serrata"[MeSH Terms] OR " Boswellia serrata"[tiab]) OR**

Search	Query
	("aloe vera"[MeSH Terms] OR "aloe vera"[tiab]) OR ("glycyrrhiza"[MeSH Terms] OR " glycyrrhiza"[tiab]) OR ("belladonna"[MeSH Terms] OR " belladonna"[tiab]) OR ("frankincense"[MeSH Terms] OR " frankincense"[tiab]) ("calendula"[MeSH Terms] OR "calendula"[tiab]) OR ("Tormentill"[MeSH Terms] OR "Tormentill"[tiab]) OR ("helminths"[MeSH Terms] OR " helminths "[tiab])OR ("caraway"[MeSH Terms] OR "caraway"[tiab]) OR ("myrrh"[MeSH Terms] OR "myrhh"[tiab]) OR ("turmeric"[MeSH Terms] OR "turmeric"[tiab]) OR ("plantago ovata"[MeSH Terms] OR " plantago ovata"[tiab]) OR ("ginger"[MeSH Terms] OR "ginger"[tiab]) OR ("Trichuris suis ovata"[MeSH Terms] OR " Trichuris suis ovata"[tiab]) OR ("passionflower"[tiab]))
#3	Search **("exercise"[MeSH Terms] OR "exercise"[tiab]) OR ("movement"[MeSH Terms] OR "movement"[tiab]) OR ("hydrotherapy"[MeSH Terms] OR "hydrotherapy"[tiab]) OR ("phototherapy"[MeSH Terms] OR "phototherapy"[tiab] OR ("light"[tiab] AND "therapy"[tiab]) OR "light therapy"[tiab]) OR ("chronotherapy"[MeSH Terms] OR "chronotherapy"[tiab]) OR ("biofeedback, psychology"[MeSH Terms] OR ("biofeedback"[tiab] AND "psychology"[tiab]) OR "psychology biofeedback"[tiab] OR "biofeedback"[tiab]) OR ("lifestyle modification"[MeSH Terms] OR "lifestyle modification"[tiab]) OR warming[tiab] OR ("massage"[MeSH Terms] OR "massage"[tiab]) OR ("homoeopathy"[tiab] OR "homeopathy"[MeSH Terms] OR "homeopathy"[tiab])**
#2	Search **("mindfulness"[MeSH Terms] OR "mindfulness"[tiab]) OR ("relaxation"[MeSH Terms] OR "relaxation"[tiab]) OR pmr[tiab] OR mbsr[tiab] OR ("breathing exercises"[MeSH Terms] OR ("breathing"[tiab] AND "exercises"[tiab]) OR "breathing exercises"[tiab] OR ("breathing"[tiab] AND "exercise"[tiab]) OR "breathing exercise"[tiab]) OR (("movement"[MeSH Terms] OR "movement"[tiab]) AND ("therapy"[Subheading] OR "therapy"[tiab] OR "therapeutics"[MeSH Terms] OR "therapeutics"[tiab])) OR ("autogenic training"[MeSH Terms] OR ("autogenic"[tiab] AND "training"[tiab]) OR "autogenic training"[tiab]) OR ("yoga"[MeSH Terms] OR "yoga"[tiab]) OR ("tai ji"[MeSH Terms] OR ("tai"[tiab] AND "ji"[tiab]) OR "tai ji"[tiab]) OR ("tai ji"[MeSH Terms] OR ("tai"[tiab] AND "ji"[tiab]) OR "tai ji"[tiab] OR ("tai"[tiab] AND "chi"[tiab]) OR "tai chi"[tiab]) OR ("qigong"[MeSH Terms] OR "qigong"[tiab]) OR ("qigong"[MeSH Terms] OR "qigong"[tiab] OR ("qi"[tiab] AND "gong"[tiab]) OR "qi gong"[tiab]) OR ("hypnosis"[MeSH Terms] OR "hypnosis"[tiab]) OR ("hypnosis"[MeSH Terms] OR "hypnosis"[tiab] OR "hypnotherapy"[tiab]) OR ("meditation"[MeSH Terms] OR "meditation"[tiab]) OR ("aromatherapy"[MeSH Terms] OR "aromatherapy"[tiab] OR ("aroma"[tiab] AND "therapy"[tiab]) OR "aroma therapy"[tiab]) OR ("imagery (psychotherapy)"[MeSH Terms] OR ("imagery"[tiab] AND "(psychotherapy)"[tiab]) OR "imagery (psychotherapy)"[tiab] OR "imagery"[tiab])**
#1	Search **("acupuncture"[MeSH Terms] OR "acupuncture"[tiab] OR "acupuncture therapy"[MeSH Terms] OR ("acupuncture"[tiab] AND "therapy"[tiab]) OR "acupuncture therapy"[tiab]) OR ("acupressure"[MeSH Terms] OR "acupressure"[tiab]) OR "tcm"[tiab] OR ("chinese"[tiab] AND "medicine"[tiab]) OR "chinese medicine"[tiab] OR (("asian continental ancestry group"[MeSH Terms] OR ("asian"[tiab] AND "continental"[tiab] AND "ancestry"[tiab] AND "group"[tiab]) OR "chinese"[tiab]) AND herbs[tiab]) OR ("medicine, ayurvedic"[MeSH Terms] OR ("medicine"[tiab] AND "ayurvedic"[tiab]) OR "ayurvedic medicine"[tiab] OR "ayurveda"[tiab]) OR ("medicine, kampo"[MeSH Terms] OR ("medicine"[tiab] AND "kampo"[tiab]) OR "kampo medicine"[tiab] OR "kampo"[tiab])**

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- History Search Identifier 16
  History Search Terms ((TITLE-ABS-KEY ("randomized controlled trial") OR TITLE-ABS-KEY ("controlled trial") OR TITLE-ABS-KEY (placebo) OR TITLE-ABS-KEY ("single blind") OR TITLE-ABS-KEY ("double blind") OR TITLE-ABS-KEY ("systematic review") OR TITLE-ABS-KEY ("literature review") OR TITLE-ABS-KEY ("Meta-Analysis") OR TITLE-ABS-KEY ("meta analysis")) AND DOCTYPE (ar OR re)) AND (TITLE-ABS-KEY (**"ulcerative colitis" OR "inflammatory bowel diseases" OR "UC"**) AND DOCTYPE (ar OR re)) AND ((TITLE-ABS-KEY (acupuncture OR "acupuncture therapy" OR acupressure OR tcm OR "Chinese medicine" OR "Chinese herbs" OR ayurveda OR "ayurvedic medicine" OR kampo) AND DOCTYPE (ar OR re)) OR (TITLE-ABS-KEY (mindfulness OR relaxation OR mbsr OR "breathing exercise" OR movement OR "movement therapy" OR "autogenic training" OR yoga OR "tai ji" OR "tai chi" OR qigong OR "qi gong" OR hypnosis OR hypnotherapy OR meditation OR aroma-therapy OR imagery) AND DOCTYPE (ar OR re)) OR (TITLE-ABS-KEY (exercise OR hydrotherapy OR phototherapy OR "photo therapy" OR "light therapy" OR chronotherapy OR "chrono therapy" OR biofeedback OR warming OR massage OR homeopathy OR homoeopathy) AND DOCTYPE (ar OR re)) OR (TITLE-ABS-KEY ("Complementary therapies" OR "alternative therapies" OR "complementary and alternative therapies" OR cam OR naturopathy) AND DOCTYPE (ar OR re)) OR (TITLE-ABS-KEY (phytotherapy OR "phyto therapy" OR phytochemicals OR herbs OR "herbal medicine" OR valerian OR hop OR kava OR "kava kava" OR passiflora OR passionflower OR vitamins OR nutrition OR "nutritional supplements" OR "dietary supplements") AND DOCTYPE (ar OR re)))
- History Search Identifier 13
  History Search Terms (TITLE-ABS-KEY (acupuncture OR "acupuncture therapy" OR acupressure OR tcm OR "Chinese medicine" OR "Chinese herbs" OR ayurveda OR "ayurvedic medicine" OR kampo) AND DOCTYPE (ar OR re)) OR (TITLE-ABS-KEY (mindfulness OR relaxation OR mbsr OR "breathing exercise" OR movement OR "movement therapy" OR "autogenic training" OR yoga OR "tai ji" OR "tai

chi" OR qigong OR "qi gong" OR hypnosis OR hypnotherapyORmeditationORaromatherapyORimagery)ANDDOCTYPE (ar OR re)) OR (TITLE-ABS-KEY (exercise OR hydrotherapy OR phototherapy OR "photo therapy" OR "light therapy" OR chronotherapy OR "chrono therapy" OR biofeedback OR warming OR massage OR homeopathy OR homoeopathy) AND DOCTYPE (ar OR re)) OR (TITLE-ABS-KEY ("Complementary therapies" OR "alternative therapies" OR "complementary and alternative therapies" OR cam OR naturopathy) AND DOCTYPE (ar OR re)) OR (TITLE-ABS-KEY (phytotherapy OR "phyto therapy" OR phytochemicals OR herbs OR "herbal medicine" OR valerian OR hop OR kava OR "kava kava" OR passiflora OR passionflower OR vitamins OR nutrition OR "nutritional supplements" OR "dietary supplements") AND DOCTYPE (ar OR re))

- History Search Identifier 12
  History Search Terms TITLE-ABS-KEY ("Complementary therapies" OR "alternative therapies" OR "complementary and alternative therapies" OR cam OR naturopathy) AND DOCTYPE (ar OR re)
- History Search Identifier 11
  History Search Terms TITLE-ABS-KEY (phytotherapy OR "phyto therapy" OR phytochemicals OR herbs OR "herbal medicine" OR valerian OR hop OR kava OR "kava kava" OR passiflora OR passionflower OR vitamins OR nutrition OR "nutritional supplements" OR "dietary supplements") AND DOCTYPE (ar OR re)
- 10
  TITLE-ABS-KEY (exercise OR hydrotherapy OR phototherapy OR "photo therapy" OR "light therapy" OR chronotherapy OR "chrono therapy" OR biofeedback OR warming OR massage OR homeopathy OR homoeopathy) AND DOCTYPE (ar OR re)
- 9
  TITLE-ABS-KEY(mindfulness or relaxation or mbsr or "breathing exercise" or movement or "movement therapy" or "autogenic training" or yoga or "tai ji" or "tai chi" or qigong or "qi gong" or hypnosis or hypnotherapy or meditation or aromatherapy or imagery) AND DOCTYPE(ar OR re)
- 8
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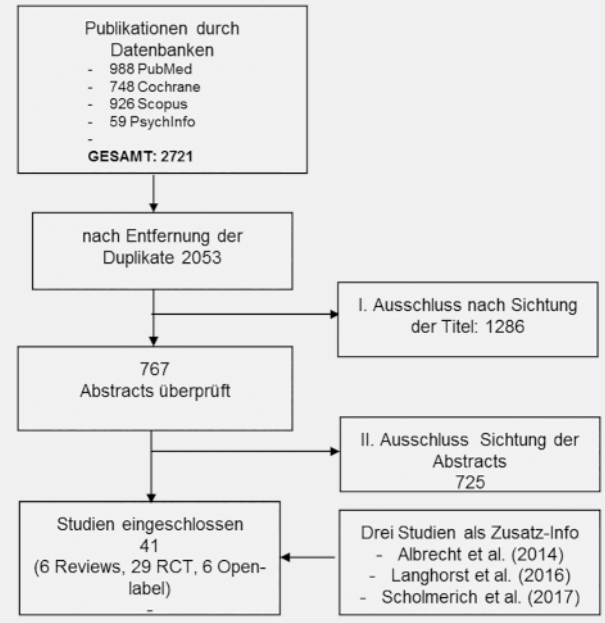
- 7
- 17
- History Search Terms TITLE-ABS-KEY ("ulcerative colitis" OR "inflammatory bowel diseases" OR "UC") AND DOCTYPE (ar OR re)
- 6
  (TITLE-ABS-KEY("randomized controlled trial") OR TITLE-ABS-KEY("controlled trial") OR TITLE-ABS-KEY(placebo) OR TITLE-ABS-KEY("single blind") OR TIT-ABS-KEY("double blind") OR TITLE-ABS-KEY("systematic review") OR TITLE-ABS-KEY("literature review") OR TITLE-ABS-KEY("Meta-Analysis") OR TITLE-ABS-KEY("meta analysis")) AND DOCTYPE(ar OR re)

Flow-Chart



EVIDENZTABELLE

▶ **Tab. 1** Characteristics of included primary studies on CAM

Author	No of subjects, no of groups	Study type	Intervention	Control	Results
Singla et al. (2014)	45, 2 groups	RCT	Standardized *curcumin* preparation enema (NCB-02) + oral 5-ASA	Placebo + oral 5-ASA	▪ N.s.: Disease activity (UCDAI), remission rate (UCDAI < 3) and endoscopic disease activity
Hanai et al. (2006)	89, 2 groups	RCT	*Curcumin* + sulfasalazine or mesalamine; 2 g/day	Placebo + sulfasalazine or mesalamine	▪ Sign. improvements in favor of curcumin: CAI, endoscopic index and recurrence rate ▪ No serious adverse events
Lang et al. (2015)	50, 2 groups	RCT	Oral capsules of *curcumin*; 2 × 3 g/day	Placebo	▪ Sign. in favor of curcumin*:* clinical remission (SCCAI), clinical improvement (SCCAI), endoscopic remission ▪ 3 serious adverse events (n.s. between the groups)
Langmead et al. (2004)	44, 2 groups	RCT	*Aloe vera gel;* 2 × 100/day	Placebo	▪ Sign. in favor of aloe vera: disease activity (SCCAI) and histologic results ▪ Sign. in favor of placebo: IBDQ ▪ N.s.: remission, physician´s global assessment, sigmoidoscopic examination, laboratory testings ▪ No serious adverse events
Tang et al. (2011)	120, 2 groups	RCT	*Andrographis paniculata* (HMPL- 2004); 3 × 400 mg/day	Mesalamine	▪ Sig. improvements in both groups: Clinical efficacy (DAI), endoscopic efficacy, histologic efficacy
Sandborn et al. (2013)	224, 3 groups	RCT	*Andrographis paniculata* extract (HMPL-004) + mesalamine; 3 × 1200 mg or 1800 mg/day	Placebo + mesalamine	▪ Sig. differences in favor of HMPL: Clinical response ▪ N.s.: Clinical remission, mucosal healing, MAYO score
Kamali et al. (2015)		RCT	*Punica granatum peel extract;* 6 g/day	Placebo	▪ Sign. Reduction in both groups: Lichtiger Colitis Activity Index ▪ Clinical response higher in favor of Punica granatum at week 4 but not 10
Ben-Arye et al. (2002)	24, 2 groups	RCT	*Wheat grass (WG) juice;* 100 ml/day	Placebo	▪ Sig. differences in favor of WG: DAI, rectal bleeding, physician global assessment, patients' retrospective evaluation, and abdominal pain ▪ N.s.: Stool frequency, sigmoidoscopic score, mucus, abdominal bloating, number of bowel movements ▪ No serious adverse events
Tong et al. (2010)	126, 3 groups	RCT	*Sophora colon soluble capsules;* 18 or 12 × 960 mg/day	Mesalamine	▪ N.s.: Clinical efficacy, fibrocolonoscopic examination, stool sample
Biedermann et al. (2013)	13, 1 group	Open pilot trial	*Bilberry (Vaccinium myrtillus)* preparation*;* 4 × 40 g/day with an average anthocyanin dose of 840 mg/day	-	▪ 63.4 % achieved remission (CAI) ▪ Response rate (CAI) was 90.9 % ▪ Sign. changes in favor of bilberry in Mayo score, Short Inflammatory Bowel ▪ Disease Questionnaire, and fecal calprotectin ▪ N.s.: acute inflammatory activity as defined by biopsy, serum markers (CRP, leukocytes, neutrophil granulocytes, and thrombocytes), electrolytes, markers of renal and liver function
Patel et al. (2013)	50, 1 group	Non-randomized observational clinical study	Oral administration of herbal drugs (*Holarrhena antidysenterica, Ficus glomerata,*	-	▪ Reduction of: frequency of bowl-movements, blood presence in stool, requirement of conventional standard drugs, symptoms (abdominal pain, weakness and weight loss)

▶ **Tab. 1** (Fortsetzung)

Author	No of subjects, no of groups	Study type	Intervention	Control	Results
			Cyperus rotundus, *Mesua ferrea* and *Symplocos racemosa*) + recto-colonic administration of Ficus glomerata and Ayurvedic dietary advice		▪ Improvement in haemoglobin, erythrocyte sedimentation rate, erythrocytes and pus cells in stool ▪ No serious adverse events
Huber et al. (2007)	16, 1 group	Open-label, dose-escalating study	*Tormentil extracts;* 1200, 1800, 2400 and 3000 mg/day	-	▪ CAI and C-reactive protein improved during therapy with 2400 mg tormentil/day ▪ Neither undegraded nor metabolized tannins could be detected in patient sera
Langhorst et al. (2013)	97, 2 groups	RCT	4 tablets *Myrrhinil intest®* (100 mg myrrh,70 mg chamomile extract and 50 mg coffee charcoal) /3 times a day + 1 tablet placebo/3 times a day	Mesalamine	▪ N.s.: Clinical Colitis Index (CAI), modified CAI, endoscopic index, fecal markers, laboratory measures (CRP, white blood cells, hemoglobin) ▪ 10 (Myrrhinil) vs. 8 (mesalamine) serious adverse events, no causal relation to therapy
Fernandez-Banares et al. (1999)	102, 3 groups	RCT	*Plantago ovata seeds (Psyllium);* 20 g/day	Mesalamine or Plantago ovata seeds + mesalamine	▪ Sign. improvements in favor of psyllium: increase in butyrate concentrations ▪ N.s.: maintenance of remission ▪ No serious adverse events
Rastegar-panah et al. (2015)	80, 2 groups	RCT	Oral *silymarin*; 140 mg/day	Placebo	▪ Sign. improvements in favor of silymarin: Hemoglobin, erythrocyte sedimentation rate increase in butyrate concentrations, and disease activity (DAI) ▪ Not reported: Symptoms (abdominal pain, diarrhea, fatigue, anorexia, joint or eye complications)
Gupta, 1997	42, 2 groups	Verum-controlled Open-label	Boswellia serrata gum resin 3 × 350 mg daily for 6 weeks	Sulfasalazine	▪ N.s.: Remission, abdominal pain, sigmoidoscopic examination. rectal biopsy, stool sample, grading of colitis, body weight, laboratory testing
Gupta, 2001	30, 2 groups;	Verum-controlled Open-label	Boswellia serrata gum resin 3 × 350 mg daily for 6 weeks	Sulfasalazine	▪ N.s.: Remission, abdominal pain, sigmoidoscopic examination. rectal biopsy, stool sample, grading of colitis, body weight, laboratory testing
Greenfield, 1992	43, 3 groups	RCT	Super evening primrose oil (SEPO), 12 × 250 mg daily for 1 month, 6 × 250 mg for 5 months; dietary fish oil	Olive oil	▪ N.s.: Stool frequency, rectal bleeding, relapse, sigmoidoscopic score, histology, laboratory ▪ Sign. in favor of SEPO: stool consistency
Elsenbruch et al. (2005)	60, 2 groups	RCT	*Life style modification*; 6 h, 1 day a week for 10 weeks	Waiting list control group [WL]; usual care	▪ Sig. improvement in SF-36 Mental Health Scale, Psychological Health Sum Score and IBDQ Bowel Symptoms Scale after 10 weeks in MBSR compared with WL ▪ N.s.: Perceived stress, CAI, laboratory lymphocytes, TNF-α, catecholamine, cortisol, prolactin, growth hormones
Langhorst et al. (2007)	60, 2 groups	RCT	*Life style modification*; 6 h, 1 day a week for 10 weeks	WL; usual care	▪ Sig. improvement in SF-36 physical functioning after 3 months compared with WL ▪ Sig. reduction of Psychological distress – anxiety after 3 months in compared with WL ▪ N.s.: CAI, medication change
Berill et al. (2014)	66, 2 groups	RCT	*Multi-convergent Therapy*; 6 × 40-min sessions over 16 weeks	Standard care	▪ N.s.: IBDQ, relapse, medication escalations, perceived stress, coping, irritable bowel symptoms
Jedel et al. (2014)	55, 2 groups	RCT	*Mindfulness-Based*	Attention control once weekly	▪ IBDQ: Sig. group difference in bowel subscale and systemic subscale

▶ **Tab. 1** (Fortsetzung)

Author	No of subjects, no of groups	Study type	Intervention	Control	Results
			Stress Reduction; 2.5 hours, once weekly + 45 min/ day homework for 8 weeks	+ homework for 8 weeks	▪ N.s.: Disease status, inflammatory markers, time to flare-up. severity of flare-up, markers of stress, perceived stress, depression, anxiety, mindfulness, perceived health competence
Mizrahi et al. (2012)	56, 2 groups	RCT	Relaxation training, 3 sessions and CD for home practice	Waiting control group, usual care	▪ Sign. improvement in relax group but not WC: Pain, anxiety, QOL, depression, mood, stress
Shaw et al. (1987)	40, 2 groups	RCT	*Relaxation* 75 min weekly for 6 weeks	Attention control	▪ Sign. improvement in favor of relax group: frequency of a pain episode, intensity of present pain amount of pain relief experienced ▪ N.s.: duration of a pain episode ▪ Unclear: McGill Pain Questionnaire, The Pain and Distress Scale
Gerbarg et al. (2015)	29, 2 groups	RCT (Pilot)	*Breath–Body–Mind Workshop (BBMW)*	Educational seminar	▪ N.s.: Anxiety, depression, disease acceptance, illness perception ▪ Unclear: Inflammatory biomarkers, physiological measures ▪ Sign in favor of BBMW: Perceived Disability, perceived stress
Klare et al. (2015)	30, 2 groups (UC and CD)	RCT (Pilot)	Moderate-intensity *running* thrice a week for 10 weeks	control group (not prescribed any exercise)	▪ N.s.: total IBDQ, disease activity, body weight, inflammation parameters ▪ Sign. changes only in IBDQ social sub-scale ▪ No adverse events
Sharma et al. (2015)	100, 2 groups (60 with UC, 40 with CD)	RCT (Pilot)	Supervised *Yoga* daily for 60 minutes for one week & at home for an additional seven weeks + standard medical therapy	standard medical therapy	▪ N.s.: Autonomic tone and autonomic reactivity, immune markers, clinical symptoms evaluation after one month ▪ Sign. reduced levels of state and trait anxiety ▪ Clinical symptoms evaluation after two months: fewer participants reported arthralgia in the yoga group. More patients in the control group reported intestinal colicky pain
Cramer et al. (2017)	77, 2 groups	RCT	*Yoga*	Self-care	▪ Sign. in favor of yoga: SF36 Physical and mental component summary, anxiety, depression, positive affect, perceived stress, self-efficacy ▪ N.s.: Negative affect, body awareness, body responsiveness, laboratory parameters
Joos et al. (2006)	29, 2 groups	RCT	Acupuncture + moxibustion; 10 sessions in 5 weeks	Control group [CG]; Acupuncture at non-acupuncture points; 10 sessions in 5 weeks	▪ CAI. Sig. decrease after 5 weeks in TCM compared with CG ▪ Quality of life: Sig. increases after 5, 16 weeks in TCM and CG compared with baseline ▪ General well-being: Sig. increases after 5 weeks in TCM and CG compared with baseline ▪ N.s: Serum markers of inflammation
Thomas et al. (1995)	80, 2 groups	RCT	*Nicotine patches* + standard medical therapy for 26 weeks	Placebo + standard medical therapy	▪ N.s.: number of relapses between the groups, severity of relapse between the groups, blood pressure, heart rate, or any hematologic or biochemical measurements ▪ In both groups, the sigmoidoscopic and histologic grades worsened ▪ More side effects reported in the nicotine group

▶ **Tab. 1** (Fortsetzung)

Author	No of subjects, no of groups	Study type	Intervention	Control	Results
Thomas et al. (1996)	61, 2 groups	RCT	*Nicotine patches* for 6 weeks	Prednisolone	▪ N.s.: sigmoidoscopic remission, St Mark's score, global clinical grade, blood in the stool, abdominal pain, and sigmoidoscopic score ▪ Sigmoidoscopic score in favor of prednisolone ▪ Higher dropout rates and more side effects in the nicotine group
Sandborn et al (1997)	64, 2 groups	RCT	*Nicotine patches* + standard medical therapy for 4 weeks	Placebo + standard medical therapy	▪ Sign.: DAI overall, stool frequency, sigmoidoscopic findings, and physician global assessment in favor of nicotine group ▪ N.s.: histologic disease activity, rectal bleeding, clinical remission ▪ More adverse reactions in nicotine group
Pullan et al. (1994)	77, 2 groups	RCT	*Nicotine patches* + standard medical therapy for 6 weeks	Placebo + standard medical therapy	▪ N.s.: stool consistency, presence of blood or mucus, general well-being, sigmoidoscopy, ▪ Sign. in favor of nicotine: global clinical assessement, stool frequency, abdominal pain, fecal urgency, histologic score ▪ More frequent and severe adverse events in nicotine group
Pagoldh et al. (2013)	18, 2 groups	Prospective randomized open-label study	*Hyperbaric oxygen treatment chamber (HBOT)* 90 min/session, 5 days/week, for 6 consecutive weeks + standard care	Standard care	▪ N.s.: Mayo score, laboratory tests and fecal weight, HRQOL, avoidance of colectomy and evaluation of HBOT safety
Summers et al. (2005)	54, 2 groups	RCT	Trichuris suis ova; 2500x at 2- week intervals for 12 weeks	Placebo	▪ N.s.: Remission, laboratory testings ▪ Sign.: UCDAI, Clinical Colitis Activity Index in favor of trichuris ▪ Stool examination Negative for ova and parasites

Note. RCT = randomized controlled trial; n.s. = not significant; sign. = significant; CG = control group; SF-36 = Short Form (36) Health Survey; IBDQ = inflammatory bowel disease questionaire; UCDAI = Ulcerative Colitis Disease Activity Index; DAI = disease activity index; CAI = Clinical Colitis Activity Index; TCM = traditional chinese medicine.

Anhang E: Übersichtstabelle zur Evidenzgrundlage der Schlüsselfragen

Nr.	Empfehlung	Experten-konsens	Leitlinien-adaptation[1]	DGVS 2011	De-Novo-Recherche
AG1	**Diagnostik**				
2.1	Eine Klassifikation bezüglich der Ausdehnung der Erkrankung soll erfolgen. Es soll eine endoskopische Einteilung in die Proktitis (begrenzt auf das Rektum), die Linksseitenkolitis (Ausdehnung bis zur linken Flexur) und die ausgedehnte Kolitis erfolgen.	x			
2.2	Das gleichzeitige Vorliegen einer PSC soll dokumentiert werden, da dies die endoskopische Überwachungsstrategie beeinflusst.	x			
2.3	Die Anamnese sollte eine detaillierte Erfragung über Art und Beginn der Symptome, eine kürzliche Reiseanamnese, Nahrungsmittelunverträglichkeiten, Kontakte mit infektiösen Durchfallerkrankungen, Impfstatus, Raucheranamnese, Familienanamnese und die Medikamentenanamnese (insbesondere auch bzgl. Antibiotika und nichtsteroidaler Antirheumatika) beinhalten. Weiterhin sollte die Anamnese Fragen bzgl. extraintestinaler Manifestationen (Mund, Haut, Augen und/oder Gelenke) sowie nach perianalen Abszessen, Fisteln und Analfissuren beinhalten.	x			
2.4	Bei Erstdiagnose und bei Auftreten spezifischer Symptome sollen eine komplette körperliche Untersuchung inklusive einer oralen und perianalen Inspektion und die Beachtung eventuell vorliegender extraintestinaler Manifestationen erfolgen. Eine rektale Untersuchung soll spätestens im Rahmen der Koloskopie durchgeführt.	x			
2.5	Bei Kindern und Jugendlichen sollen zusätzlich die Entwicklung von Gewicht, Länge und das Pubertätsstadium bei Erstdiagnose und regelmäßig im Krankheitsverlauf erfasst werden.	x			
2.6	Die Diagnose einer Colitis ulcerosa soll auf dem Boden einer Kombination von Anamnese, klinischer Untersuchung und typischen laborchemischen, sonographischen, endoskopischen und histologischen Befunden gestellt werden.	x			
2.7	Bei Zweifel bzgl. der Diagnose sollte die Endoskopie inklusive HistologieGewinnung im Intervall (z. B. nach 3 – 6 Monaten) wiederholt werden.		x		
2.8	Die initiale Labordiagnostik sollte neben dem Blutbild mindestens folgende Parameter enthalten: Entzündungsstatus, Eisenhaushalt Nierenfunktion, Transaminasen und Cholestaseparameter.		x		
2.9	Für die begleitende laborchemische Diagnostik eines Ansprechens auf die Therapie können CRP und / oder sowie fäkale Neutrophilenmarker als laborchemische Verlaufsparameter herangezogen werden.			x	
2.10a	Eine intestinale Infektion sollte bei Erstdiagnostik und bei einer Schubsymptomatik im Verlauf ausgeschlossen werden.		x		
b	Bei der Erstdiagnostik sollte eine mikrobiologische StuhlDiagnostik auf bakterielle infektiöse Erreger inklusive Clostridium difficileToxin erfolgen.		x		
c	Bei Patienten mit entsprechender Reiseanamnese sollte eine ergänzende Diagnostik bzgl. landestypischer Erreger durchgeführt werden.		x		
2.11	Bei etablierter Colitis ulcerosa soll bei schwerem Schub und bei therapierefraktärem Verlauf bzw. vor Intensivierung einer immunsuppressiven Therapie eine mikrobiologische Diagnostik inklusive Untersuchungen auf Clostridium difficileToxin und Cytomegalievirus erfolgen.		x		
2.12	Die quantitative Bestimmung von fäkalen Neutrophilenmarkern (z. B. Calprotectin) sollte in der klinischen Differentialdiagnostik zur Abgrenzung der Beschwerden gegenüber einer (funktionellen) Reizdarmsymptomatik genutzt werden.				x

Nr.	Empfehlung	Experten-konsens	Leitlinien-adaptation[1]	DGVS 2011	De-Novo-Recherche
2.13	Zur Verlaufsdiagnostik bei etablierter Colitis ulcerosa sollte die quantitative Bestimmung von fäkalen Neutrophilenmarkern im Stuhl herangezogen werden.			x	x
2.14	Bei Verdacht auf Colitis ulcerosa sollte eine Ileokoloskopie mit Biopsien aus dem term. Ileum und allen Kolonsegmenten unter Einschluss des Rektums (zumindest zwei Biopsien/Segment; Einsendung in getrennten Probengefäßen) unter Einschluss des Rektums (Einsendung in getrennten Probengefäßen) erfolgen, um die Diagnose zu stellen und die Ausdehnung der Erkrankung festzustellen.		x		
2.15 a	Eine routinemäßige Koloskopie sollte bei Patienten mit Colitis ulcerosa in der Remission bis zum Beginn der Karzinomüberwachung nicht erfolgen.	x			
2.15 b	Eine erneute endoskopische Diagnostik in der klinischen Remission kann zur Beurteilung des Therapieansprechens und unter Immunsuppression oder biologischer Therapie unter dem Aspekt einer Therapiedeeskalation erwogen werden.	x			
2.16	Eine endoskopische Evaluation kann bei therapierefraktären Verläufen zur Bestätigung der Aktivität der Erkrankung und zum Ausschluss von infektiösen oder anderen Komplikationen durchgeführt werden.	x			
2.17	Bei nicht eindeutig zu klassifizierender Kolitis sollte eine Diagnostik des oberen Gastrointestinaltraktes mittels Ösophagogastroduodenoskopie (mit Biopsien) und des mittleren Gastrointestinaltraktes mittels MRT des Dünndarms und/oder abdomineller Sonographie durchgeführt werden (Evidenzgrad IV, Empfehlungsgrad B).	x			
2.18	Die hochauflösende abdominelle Sonografie sollte Bestandteil der Diagnostik bei der Erstdiagnose und in der Verlaufsdiagnostik sowie beim schweren akuten Schub zur Erfassung von Komplikationen sein.			x	
2.19	Da das Vorliegen einer Kolonstenose bei Colitis ulcerosa malignitätsverdächtig ist, sollte eine ausgiebige Biopsieentnahme aus dem Bereich der Stenose erfolgen und zusätzlich eine bildgebende Diagnostik (z. B. CT, MRT) erfolgen. Bei unklarer Dignität einer Kolonstenose soll die Entscheidung zur Operation großzügig gestellt werden.		x	x	
2.20	Die Diagnose einer Colitis ulcerosa sollte bei Kindern bei Vorliegen von chronischen (> 4 Wochen) oder rezidivierenden (> 2 Episoden innerhalb von 6 Monaten) blutigen Durchfällen nach Ausschluss einer infektiösen Genese in Betracht gezogen werden.			x	
2.21	Die initiale Diagnostik bei Kindern und Jugendlichen mit Verdacht auf eine chronisch entzündliche Darmerkrankung soll eine Ileokoloskopie mit Entnahme von Stufenbiopsien aus dem term. Ileum und allen Kolonsegmenten beinhalten. Im gleichen Untersuchungsgang sollte eine Ösophagogastroduodenoskopie mit Entnahme von Stufenbiopsien erfolgen.			x	
2.22	Histopathologische Kriterien, die bei der Beurteilung von Biopsien zur Diagnose einer Colitis ulcerosa herangezogen werden sollten, sind: ▪ diffuse panmukosale chronische Entzündung (Lymphozyten und Plasmazellen) in Kombination mit einer Störung der Kryptenarchitektur/ Kryptenatrophie, ▪ Plasmozytose im basalen Schleimhautstroma ▪ PanethzellMetaplasien distal der rechten Kolonflexur ▪ Reduktion der Anzahl von Becherzellen bzw. des Muzingehalts der Einzelzelle, ▪ kontinuierliche Verteilung der entzündlichen und strukturellen Schleimhautveränderungen, abnehmender Gradient von distal nach proximal.		x		

Nr.	Empfehlung	Experten-konsens	Leitlinien-adaptation[1]	DGVS 2011	De-Novo-Recherche
2.23	Abweichende morphologische Befundmuster können bei der Colitis ulcerosa vorkommen und sollen speziell bei pädiatrischen Patienten berücksichtigt werden.		x	x	
2.24	Der Pathologiebefund sollte eine Aussage zur histologischen Entzündungsaktivität enthalten.	x			
2.25	Die Diagnose von intraepithelialen Neoplasien/Dysplasien bei der Colitis ulcerosa soll nach den jeweils gültigen Kriterien der WHO erfolgen IEN/Dysplasien sollen histopathologisch graduiert werden in niedrigradig, hochgradig oder unklar (indefinite).	x			
2.26	Bei histologischer Diagnose jeder IEN/Dysplasie sollte der Prozess einer kompetenten (dokumentierten) pathologischen Zweitmeinung im Sinn eines VierAugenPrinzips sichergestellt sein.			x	
2.27	Im Falle einer sichtbaren Läsion mit IEN/Dysplasie sollte eine Differenzierung durch den Endoskopiker der CEDassoziierten Neoplasien in polypoide oder nicht polypoide Läsionen erfolgen, jeweils mit Angabe des IEN/Dysplasiegrades (LGIEN oder HGIEN), da diese Aussage von therapeutischer Bedeutung ist.			x	
2.28	Da die kolitisassoziierte Kolonkarzinommortalität durch eine endoskopische Überwachung gesenkt werden kann, sollten angepasst an eine Risikostratifizierung Überwachungskoloskopien erfolgen.				x
2.29	Zur Festlegung der Überwachungsstrategie sollten bei allen CU-Patienten unabhängig von der Krankheitsaktivität eine Kontrollkoloskopie mit Entnahme von zumindest zwei Biopsien aus jedem Kolonsegment zusätzlich zu gezielten Biopsien zur Erfassung des Befallmusters 68 Jahre nach Beginn der Symptomatik/Diagnosestellung erfolgen.			x	
2.30	Wenn die Krankheitsaktivität auf das Rektum ohne Nachweis einer vorherigen oder aktuellen endoskopischen und / oder mikroskopischen Entzündung proximal zum Rektum beschränkt ist, sollte die Einbeziehung in ein regelmäßiges Überwachungskoloskopie-Programm nicht erfolgen. Zur Kontrolle und um eine Ausdehnung der Colitis ulcerosa nicht zu übersehen, kann alle 5 Jahre eine Koloskopie-Kontrolle sinnvoll sein.	x			
2.31	Bei Patienten mit Befall über das Rektum hinaus sollen regelmäßige Überwachungskoloskopien ab dem 8. Erkrankungsjahr durchgeführt werden. Die Überwachungsstrategie sollte individuell abgestimmt werden und eine Risikostratifizierung berücksichtigen. Dabei sollte sich das Intervall nach einer Risikostratifizierung richten. Nach dieser Risikostratifizierung sollte bei Patienten mit einem hohen Risiko (Stenose, IEN innerhalb der letzten 5 Jahre, ausgedehnte Kolitis mit starker Entzündung oder erstgradigem Verwandten mit KRK < 50 J.) jährlich und Patienten mit einem intermediären Risiko (Kolitis mit milder oder mäßiger Entzündung, viele Pseudopolypen, erstgradiger Verwandter mit KRK ≥ 50 J.) alle 13 Jahre und Patienten mit einem niedrigen Risiko (es liegen keine der genannten Faktoren vor) alle 4 Jahre eine Überwachungskoloskopie durchgeführt werden.	x			
2.32	Wenn gleichzeitig eine PSC besteht, sollten die Überwachungskoloskopien unabhängig von der Krankheitsaktivität und Ausdehnung der CU ab dem Zeitpunkt der PSCDiagnosestellung jährlich erfolgen.		x		
2.33	Die Überwachungskoloskopie mit Biopsieentnahme sollte möglichst in der Remissionsphase durchgeführt werden, da die histomorphologische Abgrenzung von entzündlichen gegenüber neoplastischen Veränderungen sonst schwierig sein kann.		x		
2.34	Gezielte Biopsien sollten aus allen endoskopisch suspekten Läsionen entnommen werden. Die Überwachungskoloskopie sollte in einem sauberen Darm mit ausreichender Rückzugzeit erfolgen.			x	

Nr.	Empfehlung	Experten-konsens	Leitlinien-adaptation[1]	DGVS 2011	De-Novo-Recherche
2.35	Die Überwachungskoloskopie sollte als Chromoendoskopie mit gezielten Biopsien ohne zusätzliche zufällige Biopsien als Überwachungsverfahren der Wahl durchgeführt werden. Alternativ kann eine hochauflösende WeißlichtEndoskopie (HDWLE) mit gezielten Biopsien jeder sichtbaren Läsion ohne zusätzliche zufällige Biopsien mit besonderer Sorgfalt und entsprechender Rückzugszeit durchgeführt werden. Falls die HDWLE Endoskopie nicht zur Verfügung steht, sollen zusätzlich ungezielte Stufenbiopsien entnommen werden.		x		x
2.36	Der Stellenwert der hochauflösenden virtuellen Chromoendoskopie (NBI, FICE, iScan) in Kombination mit gezielten Biopsien ohne zufällige Biopsien ist nicht ausreichend definiert und sollte deshalb nicht als alleinige Strategie verfolgt werden.			x	x
2.37	Bei Vorliegen einer fraglichen IEN/Dysplasie sollte eine endoskopische Kontrolle ggf. nach Intensivierung der antiinflammatorischen Therapie innerhalb von 36 Monaten durchgeführt werden.			x	
2.38	Bei dem Nachweis einer endoskopisch nicht resektablen Läsion mit IEN/Dysplasie oder eines Adenokarzinoms (B) soll wegen der hohen Assoziation mit einem metachronen oder synchronen Karzinom eine Proktokolektomie erfolgen.			x	
2.39	Bei endoskopisch komplett resezierten polypoiden Läsionen mit Dysplasie/IEN ohne weitere Dysplasien im übrigen Kolon kann als Überwachungsstrategie die Koloskopie in jährlichen Abständen empfohlen werden.	x			
2.40	Nach der kompletten endoskopischen Resektion von nicht-polypoiden Läsionen mit Dysplasie/IEN ohne weitere Dysplasien im übrigen Kolon sollte die endoskopische Überwachung in jährlichen Abständen durchgeführt werden.	x			
2.41	Falls durch Zweitbefundung histologisch bestätigte IEN/Dysplasien aus endoskopisch unauffälligen Arealen detektiert werden, sollte eine erneute endoskopische Abklärung primär durch Chromoendoskopie mit hochauflösender WeißlichtEndoskopie (HDWLE) durch einen in der Überwachungskoloskopie erfahrenen Untersucher erfolgen.	x			
2.42	Falls IEN/Dysplasien aus endoskopisch unauffälligen Arealen detektiert werden, sollte eine endoskopische und bioptische Kontrolle durchgeführt werden. Bei bestätigten niedriggradigen IEN sollte eine erneute endoskopisch/bioptische Kontrolle innerhalb von 3 – 6 Monaten durchgeführt werden. Alternativ kann auch eine Proktokolektomie mit dem Patienten diskutiert werden. Bei bestätigten hochgradigen IEN soll eine Empfehlung zur Proktokolektomie gegeben werden.	x			
2.43	Polypen mit Dysplasien, die sich proximal zu den Segmenten mit anamnestisch maximaler makroskopischer oder histologischer CU-Beteiligung ergeben, werden als sporadische Adenome betrachtet und sollten bei endoskopischer Resektabilität entsprechend behandelt werden.	x			
2.44	Beim zusätzlichen Nachweis einer PSC kann zur Prophylaxe eines Colitisassoziierten Karzinoms Ursodesoxycholsäure eingesetzt werden.			x	
AG 2 + 3	**Behandlung der aktiven Erkrankung inkl. Remissionserhaltung**				
3.0	Das primäre Ziel der Colitis ulcerosa Therapie ist das rasche Erreichen einer klinischen Remission und die Bewahrung einer langfristigen steroidfreien klinischen und endoskopischen Remission.	x			
3.1	Vor Einleitung einer antientzündlichen Therapie sollte eine Entzündungsaktivität objektiv nachgewiesen werden.	x			
3.2	Bei allen Patienten sollte nach erfolgreicher Schubtherapie eine langfristige Remissionserhaltungstherapie durchgeführt werden.	x			

Nr.	Empfehlung	Experten-konsens	Leitlinien-adaptation[1]	DGVS 2011	De-Novo-Recherche
3.3	Die Wahl und die Dauer der geeigneten Schub und Erhaltungstherapie hängt von der Erkrankungsausbreitung, dem Erkrankungsverlauf (Häufigkeit und Schweregrad der Erkrankungsschübe), Ansprechen und Nebenwirkungen auf vorangegangene Therapien, Schweregrad des letzten Erkrankungsschubes, der remissionsinduzierenden Medikation, der Sicherheit der remissionserhaltenden Therapie und dem Potential einer Dysplasie und Krebsprävention ab.	x			
3.4	Die medikamentösen Therapiemöglichkeiten und -risiken sollten gegen eine operative Therapie abgewogen werden.	x			
3.5	Eine leichte bis mäßig aktive Proktitis soll zunächst mit Mesalazin ≥ 1000 mg/d als Suppositorium einmal täglich behandelt werden.		x		x
3.5a	Mesalazinschaum und Mesalazineinläufe stellen eine äquivalente therapeutische Alternative dar.				x
3.6	Bei Versagen der Monotherapie sollte die rektale Mesalazin Anwendung entweder mit topischen Steroiden oder mit einer oralen Gabe von Mesalazin freisetzenden Präparaten kombiniert werden.		x		
3.7	Eine leichte bis mäßig schwere linksseitige CU sollte initial mit rektalem Mesalazin in Form von Einläufen oder Schäumen (≥ 1 g/d) in Kombination mit oralen Mesalazin freisetzenden Präparaten (≥ 3 g/d) behandelt werden.		x		
3.8	Die rektale Anwendung von Mesalazin-Einläufen oder Schäumen (≥ 1 g/d) soll der topischen Steroidtherapie vorgezogen werden.			x	x
3.9	Bei oraler Gabe von Mesalazin freisetzenden Präparaten sollte die einmal tägliche Gabe vorgezogen werden.		x		
3.10	Eine systemische Steroidtherapie (0,5 – 1 mg/kg KG/d Prednisolonäquivalent) soll begonnen werden, wenn die Symptome der CU nicht auf die unter 4.4. – 4.6. genannte Therapie ansprechen. Budesonid MMX 9 mg/d kann bei leichter bis mäßig aktiver linksseitiger CU bei unzureichendem Ansprechen oder einer Unverträglichkeit von 5-Aminosalizylaten freisetzenden Präparaten eingesetzt werden.			x	x
3.11	Bei ausgedehntem Befall soll eine leicht bis mäßig schwere CU zunächst mit einem oralen Mesalazin freisetzenden Präparat in einer Dosierung ≥ 3 g/d in Kombination mit Mesalazineinläufen oder –schäumen behandelt werden.			x	
3.12	Eine systemische Steroidtherapie (0,5 – 1 mg/kg KG/d Prednisolonäquivalent) soll begonnen werden, wenn die Symptome der CU nicht auf die unter 4.4 – 4.6 und 4.8 – 4.9 genannten Therapien ansprechen oder bereits bei Diagnosestellung eine schwere Form der Kolitis vorliegt.			x	
3.13	Aminosalizylate sollen primär als remissionserhaltende Therapie eingesetzt werden, wenn ein Ansprechen auf Aminosalizylate oder Steroide besteht.		x		
3.14	Der Weg der Applikation von Aminosalizylaten soll sich nach dem Befallsmuster der Erkrankung richten. Die Proktitis und die linksseitige Colitis sollten primär rektal therapiert werden.			x	
3.15	Eine Kombination von oralen und rektalen Aminosalizylaten soll als Zweitlinien- Erhaltungstherapie verwendet werden.		x		
3.16	Zur Remissionserhaltung **sollen** Dosierungen der Aminosalizylate verwendet werden, für die klinische Wirksamkeit nachgewiesen wurde (siehe Tabelle) [EL1, Empfehlungsgrad A].			x	
	Es **soll** bevorzugt eine tägliche Einmalgabe verabreicht werden [EL2, Empfehlungsgrad A].		x		
	Angesichts des Nebenwirkungsprofils bei vergleichbarer Effizienz **sollte** Mesalazin der Vorzug gegenüber SASP gegeben werden (EL2, Empfehlungsgrad B).		x		

Nr.	Empfehlung	Experten-konsens	Leitlinien-adaptation[1]	DGVS 2011	De-Novo-Recherche
3.17	Eine remissionserhaltende Therapie mit Aminosalizylaten sollte bei Effektivität mindestens 2 Jahre durchgeführt werden		x		
3.18	Eine Langzeittherapie mit 5-ASA sollte den CU-Patienten unter dem Aspekt der Karzinomprävention angeboten werden.		x		
3.19	Bei erneuten Schüben soll die remissionserhaltende Therapie eskaliert werden.			x	
3.20	Möglichkeiten zur stufenweisen remissionserhaltenden Therapieeskalation sind eine Dosiseskalation einer oralen/ rektalen Kombinationstherapie mit Aminosalizylaten, eine Therapie mit Thiopurinen, eine anti-TNF Therapie oder eine Therapie mit Vedolizumab.			x	x
3.21	Kortikosteroide sollen zur Remissionserhaltung nicht eingesetzt werden.		x	x	
3.22	Patienten mit einem schweren akuten Schub einer Colitis ulcerosa sollten stationär behandelt werden. Die Behandlung sollte in enger Zusammenarbeit in einem interdisziplinären Team incl. eines erfahrenen Abdominalchirurgen erfolgen.		x		
3.23	Ein schwer verlaufender Schub einer Colitis ulcerosa soll mit einer systemischen Steroidtherapie (z. B. 1 mg/kg KG Prednisolonäquivalent pro Tag) behandelt werden.			x	
3.24	Patienten mit einem schweren akuten Schub sollten eine Thromboseprophylaxe erhalten.		x		
3.25	Zur Beurteilung des Ansprechens der systemischen Steroidtherapie sollten das klinische Bild und objektivierbare Parameter (z. B. Stuhlfrequenz, Blutbeimengungen im Stuhl, Hb-Wert, Ultraschallbefund, Endoskopiebefund, CRP, Blutbild, Neutrophilenmarker) herangezogen werden.			x	
3.26	Patienten mit einer Colitis ulcerosa mit mittelschwerer bis schwerer Krankheitsaktivität, welche unzureichend auf die Behandlung mit systemischen Steroiden ansprechen bzw. bei denen Kontraindikationen oder Intoleranz vorliegen, sollen mit anti-TNF Antikörpern oder Ciclosporin A (oder Tacrolimus behandelt werden. Im Falle von Infliximab sollte vorzugsweise eine Kombinationstherapie mit einem Thiopurin eingesetzt werden. Bei der Therapieentscheidung sollte eine Proktokolektomie mit in Erwägung gezogen werden.		x		
3.27	Patienten mit einer Colitis ulcerosa mit fulminanter Krankheitsaktivität, welche refraktär auf die Behandlung mit intravenösen Steroiden sind, sollten mit Infliximab (vorzugsweise als Kombinationstherapie mit einem Thiopurin) (Evidenzgrad 2, Empfehlungsgrad B) oder mit Ciclosporin A (Evidenzgrad 1, Empfehlungsgrad B) oder Tacrolimus (Evidenzgrad 2, Empfehlungsgrad B) behandelt werden. Eine Proktokolektomie sollte mit in Erwägung gezogen werden (Evidenzgrad 5, Empfehlungsgrad B). Starker Konsens		x		
3.28	Tritt unter oben genannter Therapie eine klinische Zustandsverschlechterung ein, sollte eine Proktokolektomie durchgeführt werden. Die Proktokolektomie kann ebenso indiziert sein, wenn nach 4 – 7 Tagen keine Verbesserung des klinischen Zustands eintritt.		x		x
3.29	Nach Ansprechen auf eine Therapie mit Calcineurininhibitoren kann eine Therapie mit Azathioprin/Mercaptopurin (EG …) oder Vedolizumab EG…) eingeleitet werden (EL korrigieren, Empfehlungsgrad B für Calcineurininhibitoren und EL korrigieren, Empfehlungsgrad A für Vedolizumab), bei Ansprechen auf eine Therapie mit Anti-TNF-Antikörpern sollen diese Therapie zur Remissionserhaltung fortgesetzt werden (EL2, Empfehlungsgrad A).		x	x	x
3.30	Patienten mit einer steroidabhängigen Colitis ulcerosa sollten mit einem Thiopurin (EL 2) oder TNF-Antikörpern (EL 1) (im Falle von Infliximab ggf. kombiniert mit einem Thiopurin [EL 2]) oder mit Vedolizumab (EL 2) behandelt werden.		x		x

Nr.	Empfehlung	Experten-konsens	Leitlinien-adaptation[1]	DGVS 2011	De-Novo-Recherche
3.31	Patienten mit leichter bis mittelschwerer Colitis ulcerosa, die nicht ausreichend auf eine Therapie mit Thiopurinen ansprechen, sollten mit TNF-Antikörpern (EL 1) (im Falle von Infliximab ggf. in Kombination mit Thiopurinen (EL 2) oder mit Vedolizumab (EL 2) behandelt werden.		x		
3.32	Patienten mit primärem Versagen auf eine Therapie mit TNF-Antikörpern sollten mit Vedolizumab (EL 2) oder Calcineurininhibitoren (EL 3) behandelt werden. Patienten mit mittelschwerer Colitis ulcerosa mit sekundärem Versagen auf eine Therapie mit TNF-Antikörpern, sollten mit alternativen TNF-Antikörpern oder Vedolizumab oder Calcineurininhibitoren behandelt werden. Eine Proktokolektomie sollte in Erwägung gezogen werden.		x		
3.33	Nach Erreichen einer Remission sollte eine remissionserhaltende Therapie mit Thiopurinen bei Patienten mit milder bis moderater Erkrankungsaktivität eingesetzt werden, wenn frühe oder gehäufte Schübe unter einer optimal dosierten Therapie mit Aminosalizylaten auftreten oder eine Unverträglichkeit gegen Aminosalizylaten besteht, wenn ein steroidabhängiger Erkrankungsverlauf besteht oder wenn ein Ansprechen auf eine remissionsinduzierende Therapie mit Ciclosporin oder Tacrolimus besteht.				x
3.34	Bei Patienten, die auf eine remissionsinduzierende Therapie mit TNF-Antikörpern ansprechen, ist eine remissionserhaltende Therapie mit TNF-Antikörpern mit oder ohne Thiopurinen sinnvoll [EL1]. Bei Patienten, die auf eine Induktionstherapie mit Vedolizumab ansprechen, ist eine Remissionserhaltung mit Vedolizumab sinnvoll [EL2].		x		x
3.35	Methotrexat, Ciclosporin und Tacrolimus sollten zur Remissionserhaltung der Colitis ulcerosa nur in Ausnahmesituationen eingesetzt werden.			x	
3.36	Aufgrund fehlender Evidenz kann keine Empfehlung zur Dauer einer Remissionserhaltung mit Thiopurinen, TNF-Antikörpern und Vedolizumab gemacht werden. Eine langfristige Fortsetzung der Remissionserhaltung wird aber häufig notwendig sein.	x			
3.37	Der apathogene Escherichia coli Stamm Nissle 1917 kann in begründeten Fällen als Alternative zu Aminosalizylaten eingesetzt werden.				x
3.38	Ein therapeutisches Drug-Monitoring kann unter einer Therapie mit Thiopurinen, TNF-Antikörpern und Vedolizumab durchgeführt werden, wenn dadurch eine klinische Entscheidung unterstützt wird. Unter einer Therapie mit Calcineurin-Inhibitoren sollen regelmäßig Spiegelbestimmungen durchgeführt werden.	x			
4.1	Bei einer Kombinationstherapie aus mehreren immunsuppressiv wirkenden Medikamenten steigt das Risiko mit Hinzunahme jedes weiteren Medikaments deutlich an. Ältere Patienten, Patienten mit Komorbiditäten, Patienten mit stattgehabten schweren Infektionskrankheiten und Patienten mit Mangelernährung sind durch Infektionen besonders gefährdet.	x			
4.2	Bei Erstdiagnose bzw. spätestens vor Beginn einer immunsuppressiven Therapie sollte bei allen Patienten ein Infektionsscreening auf Hepatitis B, Tuberkulose und EBV durchgeführt werden. Vor Einleitung einer Therapie mit Biologika ist das Tuberkulose-Screening zu aktualisieren.				RKI
4.3	Vor Beginn einer immunsuppressiven oder immunmodulatorischen Therapie bei Colitis ulcerosa sollte eine gezielte Anamnese, eine Röntgenaufnahme der Lunge und ein Interferon-gamma-Release-Assay (IGRA) erfolgen, um eine aktive oder latente Tuberkulose-Infektion auszuschließen.			x	

Nr.	Empfehlung	Experten-konsens	Leitlinien-adaptation[1]	DGVS 2011	De-Novo-Recherche
4.4	Bei Erstdiagnose, spätestens aber vor Einleitung einer immunsuppressiven Therapie, sollte der Impfstatus überprüft und ggf. aktualisiert werden. Nicht-Lebendimpfungen unter immunsuppressiver Therapie gelten als sicher, während Lebendimpfungen kontraindiziert sind. Vor diesem Hintergrund sollten insbesondere Impfungen gegen Pneumokokken und gegen Hepatitis B sowie gegen Influenza und die pandemische Grippe in Analogie zu den Empfehlungen des RKI zu „Impfungen bei Immunsuppression“ durchgeführt werden.				x
4.5	Bei bekannter Colitis ulcerosa sollte bei schwerem akutem Schub, atypischer Symptomatik, therapierefraktärem Verlauf und vor Intensivierung einer immunsuppressiven Therapie eine mikrobiologische Diagnostik inklusive Untersuchungen auf Clostridium difficile erfolgen.			x	
4.6	Die Diagnostik auf eine Clostridium difficile Infektion sollte zeitnah durch ein sensitives Verfahren erfolgen.	x			
4.7	In Abhängigkeit von der Schwere des Krankheitsbilds werden für die spezifische Primärtherapie der CDI folgende Empfehlungen gegeben: ▪ Bei leichter bis moderater Krankheitsausprägung und in Abwesenheit von Risikofaktoren für einen schweren Verlauf kann die Therapie mit Metronidazol 3 × 400 mg/ Tag p. o. für mindestens 10 Tage erfolgen. ▪ Bei schwerer Krankheitsausprägung oder bei Vorliegen von Prädiktoren für einen schweren Verlauf sollte die Therapie mit Vancomycin 4 × 125 – 250 mg/Tag p. o. für mindestens 10 Tage erfolgen. ▪ BeimRezidiv und zusätzlichem Vorliegen von Risikofaktoren für Komplikationen (Immunsuppression, Komorbidität, Notwendigkeit einer zusätzlichen Antibiotikatherapie) kann der Einsatz von Fidaxomicin 2 × 200 mg/Tag p. o. erwogen werden. ▪ Bei rezidivierender oder therapierefraktärer Clostridium difficile-Infektion kann ein fäkaler Mikrobiom-Transfer durchgeführt werden.	x			
4.8	EBV-seronegative erwachsene Patienten sollten möglichst nicht mit Thiopurinen behandelt werden. Die Therapieentscheidung bei Kindern stellt eine Sondersituation dar und erfordert eine Risikoabwägung.	X			
4.9	Bei einer EBV-(Re-)Infektion sollte eine immunsuppressive/ immunmodulierende Therapie pausiert werden.	x			
4.10	Bei einer EBV-assoziierten lymphoproliferativen Erkrankung sollte die immunmodulatorische Therapie mit Azathioprin beendet werden.	x			
4.11	Bei Patienten mit einem unzureichenden Ansprechen auf eine medikamentöse Therapie, insbesondere eine systemische Steroidtherapie, sollte eine geeignete Diagnostik einer CMV-Neuinfektion oder Reaktivierung durchgeführt werden.	x			
4.12	Zur Diagnostik sollte ein immunhistochemischer CMV-Nachweis aus endoskopisch gewonnen Proben und/oder ein molekularbiologischer Nachweis aus Gewebeproben oder ein molekularbiologischer Nachweis aus Vollblut erfolgen.				x
4.13	Der alleinige CMV-Nachweis sollte keine Therapie begründen. Die Therapieindikation kann sich aus dem klinischen Kontext ergeben. Die Akuttherapie sollte für mindestens 14 Tage durchgeführt werden.				x
4.14	Bei klinisch schwerwiegendem Verlauf einer CMV-Krankheit, insbesondere schwerer CMV-Colitis, Meningoenzephalitis, Pneumonitis oder Hepatitis, sollte die begleitende Immunsuppression zumindest bis zur virustatisch induzierten Restitutio pausiert werden. Bei alleiniger intestinaler Symptomatik eines CU-Schubes mit CMV-Nachweis kann die Immunsuppression fortgeführt oder modifiziert werden.				x

Nr.	Empfehlung	Experten-konsens	Leitlinien-adaptation[1]	DGVS 2011	De-Novo-Recherche
4.15	Bei nachgewiesener CMV-Erkrankung sollte bei Wiedereinführung bzw. Fortführung oder Intensivierung der immunsuppressiven Therapie eine Rezidivprophylaxe durchgeführt werden. Diese Therapie schließt sich der Akuttherapie an (s. oben) und sollte für 4 – 8 Wochen durchgeführt werden.	x			
4.16	Bei aktiver VZV-Infektion sollte eine Immunsuppression nicht begonnen werden.	x			
4.17	Bei florider VZV-Infektion während einer immunsuppressiven Therapie sollte unverzüglich eine Therapie erfolgen. Falls möglich sollte die immunsuppressive Therapie unterbrochen werden.	x			
4.18	Bei Nachweis einer latenten Tuberkulose (LBTI) (Interferongamma-release-Assay IGRA) soll eine chemopräventive Therapie mit Isoniazid nach RKI-Empfehlungen durchgeführt werden. Eine immunsuppressive Therapie sollte frühestens 4 Wochen nach Start der Chemoprävention begonnen werden.	x			
4.19	Bei Nachweis einer aktiven Tuberkulose ist eine Kombinationstherapie gemäß den RKI-Empfehlungen einzuleiten. Eine immunsuppressive Therapie, insbesondere eine anti-TNF-Therapie sollte – bei stets strenger Indikationsstellung – idealerweise erst nach Beendigung der Tuberkulose-Therapie durchgeführt werden.	x			
4.20	Eine Vakzinierung mit Lebendimpfstoffen (Rotavirus) soll bei Neugeborenen, deren Mütter in der Schwangerschaft mit TNF-AK behandelt wurden, für mindestens 9 Monate nicht durchgeführt werden.	x			
AG 5	**Chirurgie**				
5.1.1	Als Standardoperation sollte eine restaurative Proktokolektomie durchgeführt werden.			x	
5.1.2	Die restaurative Proktokolektomie sollte in der Regel mit protektivem Ileostoma erfolgen, eine einzeitige Operation sollte nur selektionierten Einzelfällen erfolgen.				x
5.1.3	Der J-Pouch sollte die Pouchkonstruktion der Wahl sein, da er am einfachsten anzulegen ist und im Langzeitverlauf eine vergleichbare Funktion aufweist wie andere Konstruktionen.				x
5.1.4	Die freie oder gedeckte Perforation soll als Notfallindikation operiert werden.			x	x
5.1.5	Bei einer therapierefraktären Blutung sollte bei fortgesetzter Transfusionspflichtigkeit dringlich operiert werden.				x
5.1.6	Patienten mit einem medikamentös therapierefraktären fulminanten Schub sollten dringlich operiert werden.			x	
5.1.7	Ein trotz Einsatz von Immunsuppressiva und/ oder Biologika therapierefraktärer Verlauf sollte operiert			x	x
5.1.8	Bei Patienten mit CU und Kolonstenose, deren Dignität durch weitere diagnostische Maßnahmen nicht sicher geklärt werden kann, sollte operiert werden.			x	
5.1.9	Eine elektive Operation kann bei Patientenwunsch erfolgen. Dabei sind die Risiken der konservativen Behandlungsstrategien gegen die Risiken einer Operation abzuwägen.			x	
5.1.10	Kinder und Jugendliche mit aktiver Colitis und Wachstumsstörungen trotz adäquater Therapie sollten nach Konsultation eines Kindergastroenterologen und Ausschluss anderer Ursachen proktokolektomiert werden mit pouchanaler Anastomose.			x	
5.1.11	Bei erhöhtem perioperativem Risiko, unter Berücksichtigung der perioperativen Medikation, sollte die Proktokolektomie dreizeitig operiert werden.			x	

Nr.	Empfehlung	Experten-konsens	Leitlinien-adaptation[1]	DGVS 2011	De-Novo-Recherche
5.1.12	Bei Mangelernährung (hohes metabolisches Risiko) sollte vor elektiver Operation präoperativ eine gezielte Ernährungstherapie für mindestens 7 Tage erfolgen.			x	
5.1.13	Bei der dreizeitigen Proktokolektomie sollte die Kolektomie bis zum rektosigmoidalen Übergang erfolgen.	X			
5.1.14	Die Rektumresektion sollte bei benigner Operationsindikation, wenn technisch möglich, darmnah (mesorektumerhaltend) erfolgen, weil dadurch die Komplikationsrate einschließlich Nervenverletzungen verringert werden kann.				x
5.1.15	Bei der ileoanalen Pouchanlage sollte die belassene Rektummukosa nicht länger als 2 cm sein.	x			
5.1.16	Unter der Indikation einer intraepithelialen Neoplasie oder eines manifesten Karzinoms im Rektum sollte eine komplette Mukosektomie mit Anastomose an der Linea dentata durchgeführt werden.			x	
5.1.17	Pouchchirurgie sollte nur in dafür spezialisierten Zentren durchgeführt werden.			x	
5.1.18	Patienten mit einer chronischen Pouchitis oder nach Colitis-ulcerosa-assoziiertem Karzinom oder intraepithelialer Neoplasie sollten jährlich endoskopisch überwacht werden.			x	
5.1.19	Die Kolektomie mit ileorektaler Anastomose sollte nur für ausgewählte Konstellationen wie z. B. bei Kinderwunsch empfohlen werden.			x	
5.1.20	Das kontinente Ileostoma nach Kock kann als mögliche Alternative für besondere Fälle angeboten werden.			x	
b	Es sollte in dafür spezialisierten Zentren durchgeführt werden.	x			
5.1.21	Bei belassenem Rektum unter ileorektaler Anastomose oder bei endständigem Ileostoma mit Rektumblindverschluss nach Hartmann sollte das Intervall der endoskopischen Kontrolle entsprechend der initialen OP-Indikation gewählt werden. Die Durchführung sollte der Empfehlung der allgemeinen koloskopischen Nachsorge bei C. entsprechen.			x	
5.1.22	In der elektiven Situation ist die laparoskopische restaurative Proktokolektomie der offenen Operation mindestens gleichwertig, in einigen Punkten überlegen. Bei Frauen mit Kinderwunsch sollte bevorzugt minimal invasiv operiert werden [Evidenzgrad: III].				x
5.1.23	Bei Colitis indeterminata ohne anorektales Fistelleiden und entsprechender Operationsindikation kann eine restaurative Proktokolektomie unter Aufklärung mit den damit verbundenen Risiken dem Patienten angeboten werden.			x	
5.2.1	Die Diagnose Pouchitis sollte unter der Berücksichtigung der Parameter Klinik, Endoskopie und Histologie erfolgen.		x		
5.2.2	Bei einer chronischen Pouchitis sollte ein M. Crohn, eine chirurgische Komplikation oder eine Infektion ausgeschlossen werden.	x			
5.2.3	Als Primärtherapie der akuten Pouchitis sollen Ciprofloxacin oder Metronidazol eingesetzt werden.				x
b	Bei Versagen der Monotherapie kann auch eine Kombination eingesetzt werden.		x		
c	Antibiotika-refraktäre Verlaufsformen sollten mit oralem oder lokalem Budesonid behandelt werden.		x		
d	Weitere Therapieoptionen sind unter anderem Infliximab, Adalimumab, Vedolizumab, Rifaximin, E. coli Nissle oder Calcineurininhibitoren.	x			
5.2.4	Bei einer häufig rekurrierenden oder einer chronischen Pouchitis sollte intermittierend eine Monotherapie oder eine kombinierte antibiotische Therapie mit Ciprofloxacin und/oder Metronidazol eingesetzt werden.		x		

Nr.	Empfehlung	Experten-konsens	Leitlinien-adaptation[1]	DGVS 2011	De-Novo-Recherche
b	Antibiotika-refraktäre Verlaufsformen sollten mit oralem oder lokalem Budesonid behandelt werden.		x		
c	Weitere Therapieoptionen sind unter anderem Infliximab, Adalimumab, Vedolizumab, Rifaximin, E. coli Nissle oder Calcineurininhibitoren.		x		
5.2.5	Zu VSL#3 liegen ältere Studien vor, die eine Wirksamkeit gezeigt haben. Derzeitig ist dieses Präparat aber nicht in der ursprünglichen Zusammensetzung verfügbar.	x			
5.2.6	Bei Vorliegen von Risikofaktoren sollten jährlich eine endoskopische Kontrolluntersuchung erfolgen. Andernfalls sollte bei Beschwerden oder spätestens alle 2 Jahre eine Pouchoskopie erfolgen.	x			
5.2.7	Bei einer Cuffitis sollte initial ein Therapieversuch mit topischer 5ASA Applikation durchgeführt werden.		x		
b	Bei therapierefraktärer Entzündung kann eine endoskopische Mukosektomie oder Rest-Proktektomie erwogen werden.	x			
5.2.8	Patienten mit einem irritablen Pouchsyndrom können wie Patienten mit RDS behandelt werden. Es sollten alternative Ursachen in Erwägung gezogen werden.	x			
AG 6	**Komplementäre Verfahren**				
6.1.1	Mit Ausnahme des Stillen gibt es keine Ernährungsfaktoren, die zur Risikominderung für ein CU empfohlen werden könnten. Die Stilldauer sollte mindestens 6 Monate betragen.				x
6.1.2	Patienten mit CU haben ein erhöhtes Risiko für eine Mangelernährung. Sie sollten daher zum Zeitpunkt der Erstdiagnose und im weiteren Krankheitsverlauf auf das Vorliegen einer Mangelernährung untersucht werden.				x
6.1.3	Bei Patienten mit CU besteht ein erhöhtes Risiko für einen Mikronährstoffmangel. Sie sollten daher initial und im weiteren Krankheitsverlauf, wenn klinische Zeichen oder erhöhte Risiken für einen Mangel vorliegen, auf das Vorliegen eines Mangels an Mikronährstoffen untersucht werden.				x
6.1.4	Eine spezielle enterale Ernährungstherapie und/oder ausschließliche parenterale Ernährung sollte als primäre Therapie zur Remissionsinduktion bei Colitis ulcerosa nicht durchgeführt werden.	x			
6.1.5	Eine spezielle Diät oder Ernährungstherapie zur Remissionserhaltung sollte nicht empfohlen werden.	x			
6.1.6	Ein isolierter Mikronährstoffmangel sollte durch entsprechende orale oder parenterale Supplemente behandelt werden. Eine generelle Vitamin- oder Spurenelementsubstitution ist bei CU nicht sinnvoll.	x			
6.1.7	Präoperativ sollte bei schwerer Mangelernährung (vor elektiver Operation präoperativ eine gezielte Ernährungstherapie für mindestens 7 Tage erfolgen.	x			
6.1.8	CU Patienten mit high output Jejuno- oder Ileostomie sollten engmaschig im Hinblick auf Wasser- und Elektrolytbilanz überwacht werden.	x			
6.1.9	Patienten mit Pouch sollten regelmäßig auf das Vorliegen eines Vitamin D-, B_{12}-, und Eisenmangels untersucht werden.	x			
6.2.1	Alternativtherapien anstatt einer evidenzgesicherten Therapie sollen abgelehnt werden.	x			
6.2.2	Die Beurteilung naturheilkundlicher und komplementärmedizinischer Verfahren soll nach Kriterien einer evidenzbasierten Medizin erfolgen.	X			
6.2.3	Patient/inn/en sollen über die Anwendung komplementärer Heilmethoden befragt werden. Der behandelnde Arzt soll mit ihnen über ihre Gründe für die Anwendung komplementär-medizinischer Verfahren zu sprechen.	x			

Nr.	Empfehlung	Experten-konsens	Leitlinien-adaptation[1]	DGVS 2011	De-Novo-Recherche
6.2.4	Aufgrund des hohen Anteils an Patienten, die komplementärmedizinische Therapien anwenden, sollten Ärzte sich über diese Verfahren informieren.	x			
6.2.5	Achtsamkeitsbasierte Verfahren zur Stressreduktion können komplementär zur Verbesserung der Lebensqualität eingesetzt werden.				x
6.2.6	Yoga kann komplementär (zur Verbesserung der Lebensqualität) eingesetzt werden.				x
6.2.7	Akupunktur kann im leicht bis moderatem Schub komplementär in der Therapie eingesetzt werden.				x
6.2.8	Plantago Ovata kann komplementär in der remissionserhaltenden Behandlung eingesetzt werden.				x
6.2.9	Für die Therapie mit Curcumin komplementär zu einem Aminosalicylat liegen Studien mit positiven Ergebnissen in der Remissionsinduktion sowie in der Remissionserhaltung vor. Curcumin steht in Deutschland nicht als Arzneimittel zur Verfügung.				x
6.2.10	Die Kombination von Myrrhe, Kamilleblütenextrakt und Kaffeekohle kann komplementär in der remissionserhaltenden Behandlung eingesetzt werden.				x
6.2.11	Weitere unkonventionelle Verfahren können aufgrund der unzureichenden Datenlage nicht empfohlen werden.	x			

[1] Siehe Anlage Leitlinienadaptation.

Anhang F: Interessenkonflikt-Erklärungen – Tabellarische Zusammenfassung

1. Berater- bzw. Gutachtertätigkeit oder bezahlte Mitarbeit in einem wissenschaftlichen Beirat eines Unternehmens der Gesundheitswirtschaft (z. B. Arzneimittelindustrie, Medizinproduktindustrie), eines kommerziell orientierten Auftragsinstituts oder einer Versicherung
2. Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften im Auftrag eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung
3. Finanzielle Zuwendungen (Drittmittel) für Forschungsvorhaben oder direkte Finanzierung von Mitarbeitern der Einrichtung von Seiten eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung
4. Eigentümerinteresse an Arzneimitteln/Medizinprodukten (z. B. Patent, Urheberrecht, Verkaufslizenz)
5. Besitz von Geschäftsanteilen, Aktien, Fonds mit Beteiligung von Unternehmen der Gesundheitswirtschaft
6. Persönliche Beziehungen zu einem Vertretungsberechtigten eines Unternehmens der Gesundheitswirtschaft
7. Mitglied von in Zusammenhang mit der Leitlinienentwicklung relevanten Fachgesellschaften/ Berufsverbänden, Mandatsträger im Rahmen der Leitlinienentwicklung
8. Politische, akademische (z. B. Zugehörigkeit zu bestimmten „Schulen“), wissenschaftliche oder persönliche Interessen, die mögliche Konflikte begründen könnten
9. Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre

	Andus, Tilo	**Atreya, Raja**	**Autschbach, Frank**	**Bachmann, Oliver**
1	nein	ja: Beratertätigkeit bei folgenden Firmen: AbbVie, Ferring, InDex Pharmaceuticals, Janssen-Cilag, Philogen, Stelic Institute, Takeda Pharma.	nein	ja: Advisory-Boards: Astellas, Janssen, biogen, Takeda, Pfizer
2	ja: Vortragshonorare	ja: Vortragstätigkeit im Auftrag folgender Firmen: AbbVie, Falk Pharma, Janssen-Cilag, MSD, Takeda Pharma.	nein	ja: Vortragshonorare: Abbvie, Falk, Immundiagnostik, Janssen, MSD, Takeda Bezahlte Autorenschaften: BMS, Takeda
3	nein	ja: Drittmittel für Forschungsvorhaben: AbbVie, Takeda Pharma.	nein	nein
4	nein	nein	nein	nein
5	nein	nein	nein	nein
6	nein	nein	nein	nein
7	ja: Mitglied DGVS	nein	ja: Mandatsträger der Deutschen Gesellschaft für Pathologie für die S3-Leitlinie Colitis ulcerosa	ja: DGVS-Mitglied
8	nein	nein	nein	nein
9	Stadt Stuttgart	Med. Klinik 1 Uniklink Erlangen	SLK-Kliniken Heilbronn GmbH	Medizinische Hochschule Hannover (Land Niedersachsen)
	Baretton, Gustavo	**Baumgart, Daniel**	**Bettenworth, Dominik**	**Bläker, Michael**
1	ja: Beratertätigkeit/Advisory Boards: Fa. Roche, Fa. Astra-Zeneca, Fa. Pfizer	ja: Wissenschaftliche Beratungstätigkeit (kein Beirat) für AbbVie, Merck (MSD), Takeda, Ferring, Genentech (Roche Group), Pfizer, BMS, Janssen, Dr. Falk, Biogen, Foreward Pharma, Tigenix	ja: Beratertägikeiten für Takeda, Abbvie und Janssen.	ja: Advisory Board: MSD, Takeda
2	ja: Vortragshonorare: Fa. Roche, Fa. Astra-Zeneca, Fa. Pfizer Schulungstätigkeit: Fa. Roche Reisekosten: Fa. Roche	ja: Wissenschaftliche Vorträge auf Tagungen von wissenschaftlichen Fachgesellschaften für AbbVie, Merck (MSD), Pfizer, BMS, Takeda, Ferring, Genentech (Roche Group), Janssen, Dr. Falk, Biogen, Recordati, Tigenix	ja: Vortrags- und Schulungstätigkeiten für MSD, Abbvie, Falk, Takeda.	ja: AbbVie, Falk, Ferring, Janssen, MSD, Olympus, Takeda
3	nein	ja: Uneingeschränkte, extern begutachtete Fördermittel für grundlagenwissenschaftliche und klinische Forschung von Hitachi, AbbVie, Shire und Janssen.	nein	nein

4	nein	nein	nein	nein
5	nein	nein	nein	nein
6	nein	nein	nein	nein
7	ja: Deutsche Ges. für Pathologie e. V. Bundesverband Dtsch. Pathologen	ja: Mitglied von DGVS, ECCO, AGA, ASGE, DHV, Cochrane Collaboration.	ja: Mitglied des Young-ECCO Komitee der europäischen Crohn und Colitis Organisation (ECCO).	ja: DGVS, AGA
8	nein	nein	nein	nein
9	Universitätsklinikum „Carl Gustav Carus“/Med. Fakultät, TU Dresden	Charité	Universitätsklini-kum Münster seit 10 Jahren	Selbständig
	Bokemeyer, Bernd	**Buderus, Stephan**	**Büning, Jürgen**	**Dignaß, Axel**
1	ja: Consulting Fee: Abbvie, MSD, Shire, Ferring, UCB, Hospira, Takeda, Movetis, Shield Therapeutics, Pfizer, Biogen, Janssen, Hexal, Cellgene	ja: Mitglied des Milupa – Gutachtergremium „Säuglings- und Kleinkindernährung“ Medizinisch wissenschaftliche Experten-Stellungnahme zum aktuellen Stand der Wissenschaft (September 2015) bezüglich des diätetischen Managements von Säuglingskoliken mit übermäßigem Schreien bei gestillten Säuglingen mit Lactobacillus reuteri (DSM 17 938) (Auftraggeber Firma Infectopharm) Medizinisch-wissenschaftliche Beratung der Fimra Hipp bei der Erstellung der Fachinformation zum Produkt ORS 200 (orale Rehydratiationslösung) und zur Informationskarte „Beratung kompakt“ –Leitliniengerechtes Vorgehen zur oralen Rehydration bei akuter Gastroenteritis im Kindesalter Empfehlungen der ESPGHAN (2014)und GPGE (2008)2	ja: Adv. Board: fa. Janssen, Fa. Takeda, Fa. MSD	ja: Ferring, MSD, Abbvie, Takeda, Janssen Cilag, Mundipharma, Pfizer, Boehringer Ingelheim, Hexal, Otsuka, Vifor, Pharmacosmos; Roche, Allergosan, Celgene
2	ja: Speaking and Teaching: Abbvie, Ferring, MSD, Merckle, Falk, HLR, UCB, Shield Therapeutics, Pfizer, Celltrion, Takeda, Janssen, Mundipharma	ja: Sonderheft „consilium pädiatrie“ Der übermäßig schreiende Säugling 1/2014 Wissenschaftliche Vortragstätigkeit zu pädiatrisch-gastroenterologischen Themen wie nicht-IGe-vermittelte Nahrungsmittelallergie, bauchschmerzen, Obstipation, CED, Ernährung und Erhnährungstherapie mit Honorierung durch AbbVie, Falk-Foundation, Hipp, Infectopharm, MSD, NNI, Norgine, Nutricia	ja: Vorträge: Fa. Takeda, Fa. Abbvie; CED Service GmbH; Falk Foundation	ja: Ferring, Falk Foundation, MSD, Abbvie, Takeda, Janssen Cilag, Tillots, Otsuka, Vifor, Immundiagnostik, Pharmacosmos, Allergosan; Medice
3	ja: Grant/Research: Abbvie, Ferring, UCB, Janssen, Takeda	nein	nein	nein
4	nein	nein	nein	nein
5	nein	nein	nein	nein
6	nein	nein	nein	nein
7	ja: bng, Kompetenznetz Darmerkrankungen, DGVS	ja: GPGE, DGKJ, ESPGHAN, ECCO, DGE-BV	ja: DGVS	ja: DGVS, ECCO, UEG, Chair Guideline Task Force
8	nein	nein	nein	nein
9	Selbstständig tätig in „Gastroenterologische Gemeinschaftspraxis Minden“ seit 1988 bis heute	GFO-Kliniken Bonn, St. Marien-Hospital	Universitätsklinikum Schleswig-Holstein	Agaplesion Markus Krankenhaus Wilhelm-Epstein-Str. 4 60431 Frankfurt

	Ehehalt, Robert	Fellermann, Klaus	Fichtner-Feigl, Stefan	Goetz, Martin
1	ja: MSD, Abbvie, Ferring, Takeda, Janssen, Pfizer	ja: Falkpharma	Nein	ja: Takeda, NPS (jetzt Shire), MSD, Pentax, Boston-Scientific
2	ja: Falk, Abbvie, MSD, Shield, Ferring, Norgine, Ardeypharm, Takeda, Janssen, Vifor, Pfizer, Mundipharma	ja: Falkfoundation, Abbvie, MSD, Takeda, Medac	Nein	ja: Cook, Boston-Scientific, Pentax, MSD, AbbVie, NPS, Falk Foundation Autorenschaften: Elsevier, Springer, Schattauer
3	nein	ja: Studienschwester wird über Studiengelder finanziert.	Nein	ja: Cook: Mukosale Heilung
4	nein	nein	Nein	ja: laufendes Verfahren
5	nein	nein	Nein	nein
6	nein	nein	Nein	nein
7	ja: BNG, Kompetenznetz Darmerkrankungen, DCCV, DGVS, SWDGG, ECCO, AGA	ja: Mitglied DGVS, DGIM, DEGUM	Nein	ja: DGVS AG Endoskopische Forschung der DGVS Beirat Sektion Endoskopie der DGVS Beirat DGE-BV
8	nein	nein	Nein	nein
9	selbständig	UKSH Campus Lübeck Bundesland SH	Uniklinikum Freiburg Hugstetter Str. 55 79 106 Freiburg	Universitätsklinikum Tübingen st. >3 Jahren
	Gross, Cordula	**Hartmann, Franz**	**Häuser, Winfried**	**Helwig, Ulf**
1	nein	ja: advisory board Takeda, AbbVie, Recordati	nein	ja: Wissenschaftlicher Beirat bei AbbVie Beratung und Mitwirkung der der Studien EPIC, TRUST CD und TRUST UC
2	nein	ja: Vortrags- u. Schulungstätigkeit für AbbVie, Takeda, Janssen, Falk Foundation, Recordati	nein	ja: Vortragshonorare erhalten von AbbVie, Vifor, MSD, Pfizer, Mundipharma, Shield, Ferring, Falk, Takeda
3	nein	nein	nein	nein
4	nein	nein	nein	nein
5	nein	nein	ja: Ich besitze einige Mischfonds, die Aktien von Unternehmen der Gesundheitswirtschaft enthalten können. Ich wähle die Mischfonds nicht unter dem Kriterium des Vorhandenseins von Aktien von Unternehmen der Gesundheitswirtschaft aus und überprüfe auch die Zusammensetzung der Fonds nicht regelmäßig.	nein
6	nein	nein	nein	nein
7	nein	ja: DGVS, AGA, Mitteldeutsche Gastroenterologen Gesellschaft, Deutsche Gesellschaft für Coloproktologie, BVGD	ja: DGVS; Deutsche Schmerzgesellschaft; Deutsche Gesellschaft für Psychosomatische Medizin und Psychotherapie	ja: MItgliedschaft: DGVS, BDI, BNG, DGIM, BNFI
8	nein	nein	nein	nein
9	geringfügig beschäftigt bei SQL Projekt AG Dresden	MVZ Agaplesion Frankfurt St. Marienkrankenhaus Frankfurt	Klinikum Saarbrücken MVZ Schmerzmedizin und seelische Gesundheit Saarbrücken St. Johann	selbstständig

	Herrlinger, Klaus	In der Smitten, Susanne	Kaltz, Birgit	Keller, Klaus-Michael
1	ja: Lokales Advisory Board der Firma Janssen mit kritischer Auseinandersetzung bzgl. Effektivität, Toxizität und Preis von Ustekinumab zur Behandlung des Morbus Crohn.	nein	nein	ja: Beratung von Fa. Infectopharm bezüglich der LGG-Studie (DIALAGG) bei Gastroenteritis und bezügl. LGG-Studie (PADLAGG) zur Prävention von antibiotikaassoziierten Durchfällen bei Kleinkindern
2	ja: Honorare für diverse Vorträge oder Moderatorentätigkeiten auf unabhängigen wissenschaftlichen Symposien. Niemals hat aber eine Einflussnahme bzgl. der Inhalte meiner Vorträge stattgefunden. Ich habe niemals Vorlagen oder vorgefertigte Darstellungen einer Firma verwendet. Entwicklung einer Diaserie zur Therapie der CED für die Firma Janssen für interne Schulungszwecke.Entwicklung von produktneutralen Schulungsmaterialien (Broschüren) für Ärzte und Patienten zusammen mit der Firma Falk. Jeweils keinerlei inhaltliche Einflussnahme der Firmen.	nein	nein	ja: Vortragshonorare bei Ärztlichen Fortbildungen Fa. Abbott, Danone, Falk, Essex, Hipp, Humana, Infectopharm, Nestle, Nutricia, Phadia
3	nein	nein	nein	ja: Vortragshonorare bei Ärztl. Fortbildungen und Studiensupport (Fa. Infectopharm. Lactobac. GG bei Durchfall und LGG zur Prophylaxe von ATB-assoziierten Durchfällen) und Fa. Euroimmun (Studie zur Serodiagnostik der Zöliakie)
4	nein	nein	nein	nein
5	nein	nein	nein	nein
6	nein	nein	nein	nein
7	ja: Mitglied in der DGVS	nein	ja: Mitglied und Mandatsträger der DCCV	ja: Mitglied Gesellsch. PÃ¤d. Gastro und ErnÃ¤hrung (GPGE), Europ. Society for Ped. Gastro hepatol Nutr (ESPGHAN). DGVS, Dt. Gesellsch Kinder- ud JUgendmedizin (DGKJ), Berufsverband Kinder- und JugendÃ¤rzte (BVKJ)
8	nein	nein	nein	nein
9	Asklepios Kliniken Hamburg	Deutsches Zentrum für Hochschul- und Wissenschaftsforschung (DZHW GmbH) Lange Laube 12 30 159 Hannover	Armbruster Engineering GmbH Co KG, Bremen	DKD Helios Klinik Wiesbaden
	Kienle, Peter	**Koletzko, Sibylle**	**Kroesen, Anton-J.**	**Kruis, Wolfgang**
1	ja: Beratertätigkeit für Aesculap, Ethicon, Takeda	ja: Abbvie, Danone, Janssen, Merck, MSD; Nestle Nutrition, Boehringer Ingelheim, Biocodex, Shire	nein	nein
2	ja: Vorträge, Schulungen für Aesculap, Ethicon, MSD, Abbvie, Takeda	ja: Abbvie, Danone, Hipp, Menarini, MSD, Nestle, R-Biopharm, Mead Johnen	ja: Vortragshonorare Fa. Falk, Fa. Abwies, Fa. Roche	ja: Dr Falk Pharma Ferring Deutschland Abbott Deutschland Ardeypharm Deutschland Allergosan Österreich

3	nein	ja: Nestle Nutrition, Mead Johnson, BioGaia,	nein	nein
4	nein	nein	nein	nein
5	nein	nein	nein	nein
6	nein	nein	nein	nein
7	nein	ja: GPGE, ESPGHAN	ja: Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie	nein
8	nein	nein	nein	nein
9	Universitätsmedizin Mannheim	Klinikum der Ludwig Maximilians Universtität München	Krankenhaus Porz am Rhein, Urbascher Weg 19; 51149 Köln	Evangelische Krankenhaus Kalk gGmbH
	Kucharzik, Torsten	**Kühbacher, Tanja**	**Langhorst, Jost**	**Leifeld, Ludger**
1	ja: Beratertätigkeit für folgende Firmen: Abbvie, Biogen, Hospira, Mundipharma, Dr. Falk Pharma GmbH, Janssen, MSD Sharp & Dome GmbH, Novartis, Takeda Pharma GmbH, Wolff Pharma	ja: Adboard für MSD, Takeda, Mundipharma, Janssen, Arena	ja: Medizinverlage Stuttgart; Steigerwald Arzneimittelwerke GmbH; Repha GmbH; CGC Gesundheitsconsulting, Ferring Arzneimittel GmbH	nein
2	ja: Abbvie, Dr. Falk Pharma GmbH, Ferring Arzneimittel GmbH, MSD Sharp & Dome GmbH, Takeda Pharma GmbH	ja: Abbvie, Takeda, MSD, Ferring, Falk, Allmiral, Janssen, Arena, Shire	ja: Falk Foundation; MSD Sharp&Dohme GmbH; Repha GmbH biologische Arzneimittel; Ardeypharm GmbH; Celgene GmbH	ja: Vortragshonorare und Reisekostenübernahme von Falk, Abbvie, MSD, Fujinon
3	nein	nein	ja: Steigerwald Arzneimittelwerke GmbH, Falk Foundation; Tech-Lab, Dr. Willmar Schwabe; Repha GmbH biologische Arzneimittel	ja: Übernahme von partiellen Kosten der Studie Detect dysplasia durch Olympus, überwiegend jedoch durch ein Stipendium der DCCV
4	nein	nein	nein	nein
5	nein	nein	nein	nein
6	nein	nein	nein	nein
7	ja: DGVS, NDGG, DGIM, ECCO, AGA	nein	ja: Leitlinienbeauftragter der Gesellschaft für Phytotherapie und der Deutschen Gesellschaft für Naturheilkunde, Deutsche Gesellschaft für Gastroenterologie, Deutsche Schmerzgesellschaft, Deutsches Kollegium für Psychosomatische Medizin	ja: wissenschaftlicher Beirat: DGVS, NDGG, ALGK, DCCV
8	nein	nein	ja: Leitlinienbeauftragter der Gesellschaft für Phytotherapie und der Deutschen Gesellschaft für Naturheilkunde, Deutsche Gesellschaft für Gastroenterologie, Deutsche Schmerzgesellschaft, Deutsches Kollegium für Psychosomatische Medizin	nein
9	Klinikum Lüneburg	UKSH und CAU zu Kiel	Kliniken Essen-Mitte Knappschafts Krankenhaus Am Deimelsberg 34a 45 276 Essen	St Bernward Krankenhaus, Hildesheim
	Lügering, Andreas	**Maaser, Christian**	**Matthes, Harald**	**Moog, Gero**
1	ja: Beratertätigkeit für Abbie, Janssen, MSD, Takeda	ja: Beratertätigkeit Abbvie, MSD, Takeda, Janssen	ja: Verwaltungsratsmitglied der Weleda AG Schweiz	nein
2	ja: Vortragstätigkeit für für Abbie, Falk, Ferring, Janssen, MSD, Takeda	ja: Falk, Abbvie, Janssen, Takeda	ja: Vortragstätigkeit für Ardeypharm, Weleda und Falk-Foundation.	nein
3	nein	ja: Abbvie	nein	nein
4	nein	nein	nein	nein

5	nein	nein	nein	nein
6	nein	nein	nein	nein
7	nein	nein	nein	nein
8	nein	nein	nein	nein
9	MVZ Portlal10, Albersloher Weg 10, 48151 Münster	Klinikum und MVZ am Klinikum Lüneburg	Gemeinschaftskrankenhaus Havelhöhe, Kladower Damm 221 14089 Berlin	nein
	Ockenga, Johann	**Pace, Andrea**	**Reinshagen, Max**	**Rogler, Gerhard**
1	ja: Fresenius Kabi GmbH, Advisory Board zum Studiendesign einer parenteralen Ernährung bei ontologischen Patienten	nein	ja: AbbVie, Takeda, Janssen, Boehringer, MSD, Recordati	ja: Gerhard Rogler war beratend für Abbot, Abbvie, Augurix, Boehringer, Calypso, FALK, Ferring, Fisher, Genentech, Essex/MSD, Novartis, Pfizer, Phadia, Roche, UCB, Takeda, Tillots, Vifor, Vital Solutions und Zeller tätig;
2	ja: Honorare für Vorträge von: Abbvie, Abbott, Bayer, Baxter, Braun, Bristal Myer Squibs, Fresenius, GHD, Nutricia, Roche, GILEAD	ja: Vortragshonorare: Abbvie, MSD, Janssen, Takeda, Falk, Advisory Board regional: Takeda, Janssen, MSD	ja: AbbVie, Takeda, Janssen, Boehringer, MSD, Bristol-Myers, Falk-foundation	ja: Gerhard Rogler erhielt Vortragshonorare von Astra Zeneca, Abbott, Abbvie, FALK, MSD, Phadia, Tillots, UCB, und Vifor;
3	nein	nein	nein	ja: Gerhard Rogler erhielt Forschungsunterstützung von Abbot, Abbvie, Ardeypharm, Augurix, Calypso, Essex/MSD, FALK, Flamentera, Novartis, Roche, Takeda, Tillots, UCB und Zeller.
4	nein	nein	nein	nein
5	nein	nein	nein	ja: Pharmabiome AG, Zürich
6	nein	nein	nein	nein
7	ja: Mitglied der DGVS, DGEM, Präsident der DGEM, Beirat Gastro Liga	ja: DGVS-Mitglied	ja: DGVS, BVGD	ja: DGVS, SGG, ECCO, IOIBD
8	nein	nein	nein	ja: Bündnis 90/ Die Grünen
9	Gesundheit Nord GmbH, Klinikum Bremen Mitte	FEK Neumünster	Klinikum Braunschweig	Universität Zürich Universitäts-Spital Zürich
	Schreiber, Stefan	**Siegmund, Britta**	**Stallmach, Andreas**	**Stange, Eduard F.**
1	ja: Advisory Boards für AbbVie, Celltrion, Falk Pharma, Ferring Arzneimittel, Janssen, MSD, Pfizer, Takeda	ja: Abbvie, Falk, Janssen, MSD, Takeda –> alle Honorare gingen auf ein allgemeines Konto der Charité	ja: Abbvie, Astellas, Biogen, CSL Behring, Janssen, MSD, Norgine, Pfizer Pharma, Roche, Shield Therapeutics, Shire, Summit Therapeutics, Steigerwald, Takeda	ja: MSD, Takeda, Janssen Advisory Board
2	ja: Vorträge für für AbbVie, Celltrion, Falk Pharma, Janssen, MSD, Pfizer, Takeda	ja: Abbvie, Falk, Ferring, Janssen, MSD, Merck, Pfizer, Takeda –> alle Honorare gingen auf ein allgemeines Konto der Charité	ja: Abbvie, Astellas, Falk Foundation, Janssen, Mundipharma, MSD, Recordati Pharma, Takeda	ja: Honorare für VortrÃ¤ge von Falk, Abbvie, MSD, Ferring, Ardeypharm, Takeda, Janssen
3	nein	ja: Hospira/Pfizer –> Gelder gingen auf ein allgemeines Konto der Charité	nein	nein
4	nein	nein	nein	nein
5	ja: Aktienbesitz	nein	nein	nein
6	nein	nein	nein	nein
7	ja: DGVS Mitgliedschaft, ECCO Mitgliedschaft, Vorstand Kompetenznetz CED	ja: DGIM Vorstandsmitglied DGVS ECCO member	ja: DGVS, DGIM	ja: DGVS, DCCV,

8	nein	nein	nein	nein
9	Universitätsklinikum Schleswig-Hosltein (UKSH) Christian-Albrechts-Universität zu Kiel (CAU)	Charité – Universitätsmedizin Berlin	Universitätklinikum Jena	Universitätsklinik Tübingen untenstehende Adresse lässt sich nicht ändern. Korrekt: Hapoldstr. 71a, 70469 Stuttgart
	Stein, Jürgen	**Sturm, Andreas**	**Teich, Niels**	**Lynen Jansen, Petra**
1	ja: Fresenius-Kabi, Immundiagnostik, MSD, Pharmacosmos, Takeda, Vifor	ja: Advisory Board: Jansen, MSD, Takeda, AbbVie	ja: Wissenschaftlicher Berater der Firmen MSD, Jannsen und Takeda	nein
2	ja: Abbott, Falk, Fresenius-Kabi, Immundiagnostik, MSD, Pharmacosmos, Shire, Takeda, Vifor	ja: Jansen, MSD, Takeda, AbbVie, Falk	ja: Honorare für Vortrags- und/oder Schulungstätigkeiten für AbbVie, MSD, Takeda, Vifor, Ferring, Falk, Recordati	nein
3	ja: Immundiagnostik, Vifor	nein	ja: Finanzielle Zuwendungen (Drittmittel) für Forschungsvorhaben von der Firma Ferring.	nein
4	nein	nein	nein	nein
5	nein	nein	nein	nein
6	nein	nein	nein	nein
7	ja: DGVS, DÂ´GEM, DGIM	ja: ECCO, UEG, DGVS	ja: Mitglied der DGVS, des KN CED und des BNG	nein
8	nein	nein	nein	nein
9	DGD Kliniken Frankfurt-Sachsenhausen	DRK Kliniken Berlin	selbständig	DGVS
	Veltkamp, Claudia	**Klose, Petra**	**Hartmann, Petra**	**Esters, Philip**
1	nein	nein	nein	nein
2	nein	nein	nein	ja: Vortrag Mundipharma, allgemeine Aspekte CED, 2015
3	nein	nein	nein	nein
4	nein	nein	nein	nein
5	nein	nein	nein	nein
6	nein	nein	nein	nein
7	ja: Mitglied DGVS	ja: Deutsche Gesellschaft für Naturheilkunde Gesellschaft für Phytotherapie	nein	nein
8	nein	nein	nein	nein
9	Stadtmission Heidelberg	Kliniken Essen-Mitte Innere Medizin Am Deimelsberg 34a 45276 Essen	Gastroenterologische Gemeinschaftspraxis Minden – PD Dr. Bernd Bokemeyer und Kollegen Uferstr. 3 32423 Minden	Agaplesion Markus Krankenhaus, Medizinische Klinik I, Wilhelm Epstein Straße 4, 60431 Frankfurt am Main
	Klaus, Jochen	**Zemke, Jennifer**	**Kanbach, Inken**	**Kannengießer, Klaus**
1	ja: Berater- bzw. Gutachtertätigkeit oder bezahlte Mitarbeit in einem wissenschaftlichen Beirat für MSD, Takeda, Celltrion, Jansen, Shield, Pfizer	nein	nein	nein
2	ja: Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften im Auftrag von Abbvie, Falk, MSD, Takeda, Jansen, Shield, Recordati	ja: Vortragshonorare für AbbVie, MSD, Takeda, Mundipharma	nein	ja: Vortragstätigkeiten zum Thema Darmsonographie für Abbvie Vortragstätigkeit Ultraschallworkshop im Auftrag der CED Service GmbH/Kompetenznetz Darmerkrankungen
3	nein	nein	nein	nein
4	nein	nein	nein	nein
5	nein	nein	nein	nein

6	nein	nein	nein	nein
7	nein	ja: FA-CED Vorstandsmitglied	nein	ja: DGVS, AGA, BDI
8	nein	nein	nein	nein
9	Universitätsklinik Ulm, Ulm	Gastroenterologische Gemeinschaftspraxis Herne Dres. Felten, Hinz, Mittrop, von der Ohe, Wallner Wiescherstr. 20, 44623 Herne	derzeit: Studentin	Städtisches Klinikum Lüneburg Klinik für Allgemeine Innere Medizin und Gastroenterologie Bögelstraße 1 21 339 Lüneburg
	Rijcken, Emile			
1	ja: St. 12/2015: Development of a Simulation for Laparoscopic Treatment of Inguinal Hernia. 3D-Systems – Simbionix Ltd., Golan House, Airport City, Israel			
2	ja: Organisation eines OP-Workshops Chirurgie des oberen und unteren Gastrointestinal-Traktes – Anastomosen-Techniken am 23.–24.11.2015 und 23.–24.11.2016, IRCAD, Strasbourg, Frankreich in Zusammenarbeit mit Medtronic Deutschland GmbH Organisation des Sympsoiums „CED-Interdisziplinär. Interaktiver Workshop Gastroenterologie Viszeralchirurgie“, Münster, 24.08.2016 in Zusammenarbeit mit Abbvie Kursleiter, Referent und Tutor, Basiskurs Laparoskopische Chirurgie, Aesculap Akademie, Bochum, 16.–18.02.2016 und 06 – 09.02.2017			
3	nein			
4	nein			
5	nein			
6	nein			
7	nein			
8	nein			
9	Universitätsklinikum Münster (UKM) Klinik für Allgemein- und Viszeralchirurgie Albert-Schweitzer-Campus 1, Geb. W1 48149 Münster			