Literatursammlung:

AG 1 Diagnostik-Frage 1

Inhalt: 2 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Colombel, J. F. 2018	2	A multicentre, randomised, open-label, active-controlled, two-group, phase 3, efficacy and safety trial.
D'Haens, G. 2018	3	A proof-of-concept randomized double-blind controlled study.

OXFORD (2011) Appraisal Sheet: RCT: 2 Bewertung(en)

Colombel, J. F. et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. Lancet. 390. 2779-2789. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: A multicentre, randomised, open-label, active-controlled, two-group, phase 3, efficacy and safety trial. Number of Patient: 244 patients Recruitung Phase: Feb 11, 2011 until Nov 3, 2016 Inclusion Criteria: Adult patients were enrolled in the study, age 18–75 years, with Crohn's disease at baseline and a diagnosis of ileal, colonic (including rectal), or ileocolonic Crohn's disease (as confirmed by endoscopy not >6 years before baseline). Key inclusion criteria were: (1) moderate to severe Crohn's disease at baseline, defined as Crohn's Disease Activity Index (CDAI)9scores of 220–450 for patients not receiving prednisone at baseline, 200–450 for patients receiving 20 mg prednisone (or less) for 7 days or more before baseline, and >150–450 for patients	Intervention: In both groups, treatment was escalated in a stepwise manner, from no treatment, to adalimumab induction followed by adalimumab every other week, adalimumab every week, and lastly to both weekly adalimumab and daily azathioprine. This escalation was based on meeting treatment failure criteria.	Primary: The primary endpoint of the study was the proportion of patients with mucosal healing, defined as a CDEIS of less than 4 and no deep ulcers 48 weeks after randomisation. Secondary: (1) deep remission (CDAI <150, CDEIS <4 and no deep ulcers, absence of draining fistula, discontinuation of corticosteroids for ≥8 weeks); (2) biological remission (FC <250 µg/g, CRP <5 mg/L, and CDEIS <4); (3) CDEIS of less than 4; (4) overall CDEIS of less than 4 plus CDEIS of less than 4 in every segment; (5) complete endoscopic remission (CDEIS=0); and(6) endoscopic response (CDEIS decrease of >5 points) Results: The study's primary endpoint of mucosal healing (CDEIS <4) and no deep ulcers at 48 weeks after randomisation was met in 56 (46%) patients in the tight control group compared with 37 (30%) patients in the clinical management group, with a CMH-adjusted risk difference of 16·1% (95% CI 3·9 to 28·3; p=0·010). A higher proportion of patients in the tight control group achieved the following key secondary endpoints 48 weeks after randomisation than in the clinical management group: deep remission, with a CMH-adjusted risk difference of 14·5% (2·9 to 26·0; p=0·014); biological remission, with a CMH-adjusted risk difference of 14·5% (4·1 to 25·0; p=0·006); and an overall CDEIS of less than 4, with a CMH-adjusted risk difference of 16·1% (3·9 to 28·3; p=0·010). No significant differences were observed between the groups regarding the proportion of patients with an overall CDEIS of less than 4 plus a CDEIS of less than 4 in every segment (CMH-

receiving more than 20 mg prednisone for 7 days or more before baseline; (2) active endoscopic disease, defined as a total Crohn's Disease Endoscopic Index of Severity (CDEIS) of more than 6 and a sum of CDEIS subscores of more than 6 in one or more segments with ulcers; and (3) CRP of 5 mg/L or more, FC of 250 µg/g or more, or both. **Exclusion Criteria: Exclusion criteria were previous or current use of biologics or immunomodulators, more than two previous courses of corticosteroids, or current use of corticosteroids for more than 3 months before screening. Patients with any fibrotic stricture (passable or non-passable and regardless of symptoms), draining perianal fistulas, or non-perianal fistulas were excluded.**	**Comparison: Two treatment algorithms: tight control and clinical management.**	**adjusted risk difference of 5·9% [95% CI –5·2 to 17·0]; p=0·299), complete endoscopic remission (1·7% [–7·9 to 11·3]; p=0·728), or endoscopic response (11·5% [–0·8 to 23·9]; p=0·067;). A significantly higher proportion of patients achieved steroid-free remission in the tight control group than the clinical management group and clinical remission (CDAI <150) at 11, 23, 35, and 48 weeks after randomisation. A significantly greater mean change from baseline in CDAI was observed in the tight control group than in the clinical management group at 11, 35, and 48 weeks. The mean change from baseline in CRP concentration was not significantly different between tight control and clinical management.** **Author's Conclusion: CALM is the first study to show that timely escalation with an anti-tumour necrosis factor therapy on the basis of clinical symptoms combined with biomarkers in patients with early Crohn's disease results in better clinical and endoscopic outcomes than symptom-driven decisions alone.**

Methodical Notes

Funding Sources: Funding AbbVie

COI: J-FC reports personal fees from AbbVie, Amgen, Boehringer Ingelheim, Celgene Corporation, Celltrion, Eli Lilly, Enterome, Ferring Pharmaceuticals, Genentech, Janssen, MedImmune, Merck & Co, Pfizer, Protagonist Therapeutics, PPM Services, Second Genome, Seres Therapeutics, Shire, Takeda, Theradiag, Intestinal Biotech Development, and Genfit outside the submitted work; and grants from AbbVie, Janssen, and Takeda outside the submitted work. RP reports grants and personal fees from AbbVie outside the submitted work. PB reports personal fees
Articles2788www.thelancet.comVol 390 December 23/30, 2017from AbbVie, Takeda, Vifor Pharma, Hospira, Jannsen, Roche, Pfizer, Dr Falk Benelux, and Mundipharma; and reports grants from AbbVie, outside the submitted work. FB reports personal fees from Abbvie, MSD, Ferring Pharmaceuticals, Janssen, Takeda, Pfizer/Hospira, and Mundipharma outside the submitted work; and reports grants from AbbVie, Chiesi Farmaceutici, Ipsen, and Roche outside the submitted work. TV reports fees from advisory board membership of Hospira, Takeda, and Pfizer; and reports personal fees from Takeda outside the submitted work. GN reports personal fees from AbbVie, MSD, Takeda, Ferring Pharmaceuticals, Vifor Pharma, and Merck & Co outside the submitted work. AA reports personal fees from AbbVie, AstraZeneca, Biogen, Celltrion, Chiesi, Ferring Pharmaceuticals, Hospira, Janssen, Eli Lilly, MSD, Mitsubishi-Tanabe Pharma, Mundipharma, Nikkiso, Pfizer, Samsung, Sofar, Takeda, TiGenix, and Zambon outside the submitted work; and reports grants from MSD outside the submitted work. XH reports personal fees from AbbVie, Fresenius Kabi, Nutricia, MSD, Takeda, Vifor, Janssen, Arard, Laboratoires Mayoli-Spindler, Nestlé-Nutrition, and Ferring Pharmaceuticals outside the submitted work. ST reports personal fees from AbbVie, Centocor, Schering-Plough, Bristol-Myers Squibb, Chemocentryx, Cosmo Technologies, Elan Pharma International, Genentech, Giuliani Pharma, Merck & Co, Takeda, Otsuka Pharmaceutical, PDL Biopharma, Pfizer, Shire, Glenmark Pharmaceuticals, Warner Chilcott, Proximagen, VHsquared, TopiVert, Ferring Pharmaceuticals, Celgene, GlaxoSmithKline, Amgen, Biogen, Enterome, UCB Pharma, Boehringer Ingelheim, Grünenthal, Sigmoid Pharma, Oxford University Hospitals, University of Oxford, Santarus Inc, Tillotts Pharma, Procter & Gamble, Vifor, Given Imaging, Sanofi, Wiley Blackwell, Elsevier, Oxford University Press, Abbott Laboratories, and UEG outside the submitted work; reports grants from AbbVie, Schering-Plough, Takeda, Eli Lilly, Warner Chilcott, UCB Pharma, Ferring Pharmaceuticals, MSD, Procter & Gamble, IOIBD, Vifor, and Norman Collisson Foundation outside the submitted work; and institutional support for educationfrom IBD2020, Crohns Colitis Cure, Schering-Plough, Takeda, Synthon, Eli Lilly, Celgene, GlaxoSmithKline, Janssen, Grunenthal, Ferring Pharmaceuticals, MSD, Procter & Gamble, Vifor, ICHOM, and Warner Chilcott outside the submitted work. SD reports personal fees from AbbVie, Actelion Pharmaceuticals, Alfa Wasserman, AstraZeneca, Cellerix, Cosmo Pharmaceuticals, Ferring Pharmaceuticals, Genentech, Grunenthal, Johnson & Johnson, Millennium Pharmaceuticals, Merck & Co, Novo Nordisk, Nycomed, Pfizer, Pharmacosmos, Schering-Plough, Salix, Takeda, UCB Pharma, and Vifor outside the

submitted work. WR reports personal fees from Abbott Laboratories, AbbVie, AESCA, Aptalis, Astellas Pharma, Janssen, Celltrion, Danone Austria, Elan, Falk Pharma GmbH, Ferring Pharmaceuticals, Immundiagnostik, Mitsubishi Tanabe Pharma, MSD, Otsuka Pharmaceutical, PDL, Pharmacosmos, PLS Educational, Schering-Plough, Shire, Takeda, Therakos, Vifor, Yakult, Amgen, AM-Pharma, AstraZeneca, Avaxia Biologics, Roland Berger GmBH, Bioclinica, Biogen IDEC, Boehringer Ingelheim, Bristol-Myers Squibb, Cellerix, Chemocentryx, Celgene, Covance, Ernst & Young, Galapagos NV, Genentech, Gilead Sciences, Grünenthal, ICON, InDex Pharmaceuticals, Inova, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, LivaNova, Mallinckrodt Pharmaceuticals, MedImmune, Millennium Pharmaceuticals, Nestle, Novartis, Ocera Therapeutics, Parexel, Philip Morris Institute, Pfizer, Procter & Gamble, Prometheus, Provention Bio, Robarts Clinical Trials, Sandoz, Second Genome, SetPoint Medical, Sigmoid, TiGenix, UCB Pharma, Zealand Pharma, Zyngenia, and 4SC outside the submitted work; and grants from AbbVie, AESCA, Centocor, Falk Pharma GmbH, Immundiagnostik, and MSD outside the submitted work. WJS reports personal fees from AbbVie (during the conduct of the study and outside the submitted work), and from Prometheus Laboratories, Boehringer Ingelheim, Takeda, Atlantic Pharmaceuticals, Janssen, Bristol-Myers Squibb, Genentech, Nutrition Science Partners, Kyowa Hakko Kirin Pharma, Millennium Pharmaceuticals, Celgene Cellular Therapeutics, Santarus, Salix Pharmaceuticals, Catabasis Pharmaceuticals, Vertex Pharmaceuticals, Warner Chilcott, Gilead Sciences, Cosmo Pharmaceuticals, Ferring Pharmaceuticals, Sigmoid Biotechnologies, Tillotts Pharma, AM-Pharma BV, Dr August Wolff, Avaxia Biologics, Zyngenia, Ironwood Pharmaceuticals, InDex Pharmaceuticals, Nestlé, Lexicon Pharmaceuticals, UCB Pharma, Orexigen Therapeutics, Luitpold Pharmaceuticals, Baxter Healthcare, Ferring Research Institute, Amgen, Novo Nordisk, Mesoblast, Shire, Ardelyx, Actavis, Seattle Genetics, MedImmune (AstraZeneca), ActoGeniX NV, Lipid Therapeutics, Eisai, Qu Biologics, Toray Industries, Teva Pharmaceutical Industries, Eli Lilly, Chiasma, TiGenix, Adheron Therapeutics, Immune Pharmaceuticals, Celgene, Arena Pharmaceuticals, Ambrx, Akros Pharma, Vascular Biogenics, Theradiag, Forward Pharma, Regeneron, Galapagos NV, Seres Therapeutics, Ritter Pharmaceuticals, Theravance Biopharma, Palatin Technologies, Biogen, and Western University (owner of Robarts Clinical Trials) outside the submitted work; reports grants from AbbVie (during the conduct of the study, and outside the submitted work), Prometheus Laboratories, Boehringer Ingelheim, Takeda, Atlantic Pharmaceuticals, Janssen, Bristol-Myers Squibb, Genentech, and Nutrition Science Partners; reports non-financial support from AbbVie; and reports patents for use of topical azathioprine to treat inflammatory bowel disorders (US 5691343), topical formulations of azathioprine to treat inflammatory bowel disorders (US 5905081), colonic delivery of nicotine to treat inflammatory bowel disease (South African patent 97/1020; US 5846983, 5889028, and 6166044; Mexico patent 209636; Europe patents 0954337 and 893998; Hong Kong patent HK1019043; China patent ZL97192177; Czech patent 293616; Canada patent 2246235), the use of azathioprine to treat Crohn's disease (US 5733915), azathioprine compositions for colonic administration (New Zealand patent 306062; Singapore patent 45647; Australia patent 707168; Czech patent 290428), intestinal absorption of nicotine to treat nicotine responsive conditions (Australia patent 718052; US 6238689), the use of topical azathioprine and thioguanine to treat colorectal adenomas (US 6166024), enema and enterically-coated oral dosage forms of azathioprine (US 6432967), a pharmaceutical composition for the treatment of inflammatory bowel disease (US 7341741), and intestinal absorption of nicotine to treat nicotine responsive conditions (Canada patent CA2260909), and for obesity treatment and device (US 7803195 B2) that is licensed to Enteromedics. PR reports personal fees from AbbVie, Bristol-Myers Squibb, Johnson & Johnson, Merck & Co, Takeda, UCB Pharma, Genentech, Tillotts Pharma, Pfizer, Celgene, Amgen, AstraZeneca, Robarts, outside the submitted work; and reports grants from AbbVie, Johnson & Johnson, UCB Pharma, and MSD outside the submitted work. DH reports grants and personal fees from AbbVie, AstraZeneca, Janssen, MSD, Bristol Myers Squibb, Cellerix, Centocor, Chemocentryx, ELAN, Falk Pharma GmbH, Ferring Pharmaceuticals, Genentech, Giuliani Pharma, IBM, Johnson & Johnson, Leo Pharma, Otsuka Pharmaceutical, Novimmune, PDL BioPharma, Philips, Procter & Gamble, Roche, Schering-Plough, Merck Serono, Tramedico, and UCB Pharma outside the submitted work; and reports grants from MSD, Centocor, Chemocentryx, Genentech, Novimmune, PDL BioPharma, Schering-Plough, Cytokine PharmaSciences, AM-Pharma, Vivify Health, Takeda, and Gilead outside the submitted work. SS reports personal fees AbbVie, Allergen, Biogen, Boehringer Ingelheim, Celltrion, Falk Pharma GmbH, Ferring Pharmaceuticals, Genentech, GlaxoSmithKline, MSD, Pfizer, Roche, Sandoz, Shire, and Takeda outside the submitted work. EN, BH, QZ, PM, JP, KW, AMR, and RBT report personal fees from AbbVie outside the submitted work; were AbbVie employees during writing of submitted work; and own AbbVie stock, options, or both. GD'H reports personal fees from AbbVie, Ablynx, Boehringer-Ingelheim, Celgene, Celltrion, and Galapagos NV outside the submitted work; and reports grants from AbbVie and Covidien outside the submitted work. ML and AD declare no competing interests.

Randomization: 1:1 ratio. The patient number and group of each stratum were assigned by a central randomisation schedule generated by AbbVie (Chicago, IL, USA) using WebRando software for randomisation and ClinPhone, an interactive voice and web response system for patient allocation. The subject randomisation schedule was generated by a designated person in the AbbVie statistics department, who was not involved in the rest of the study. The investigators and patients were masked to patient allocation and post-screening FC and CRP results, but treatments were open label.

Blinding: no

Dropout Rate/ITT-Analysis: 11 were enrolled but not randomly assigned, 61 patients did not complete the study.

Notes:
In Hinblick auf PICO Limitation: nicht alle Patienten bei Einschluss bzw. Randomisation in Remission.

D'Haens, G. et al. Increasing Infliximab Dose Based on Symptoms, Biomarkers, and Serum Drug Concentrations Does Not Increase Clinical, Endoscopic, and Corticosteroid-Free Remission in Patients With Active Luminal Crohn's Disease. Gastroenterology. 154. 1343-1351.e1. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 **Study type: A proof-of-concept randomized double-blind controlled study.** **Number of Patient: 122 biologic-naïve adult patients with active CD.** **Recruitung Phase: July 2012 through September 2015** **Inclusion Criteria: Patients recruited were adults with active luminal CD naive to biologics with an indication to start anti-TNF therapy in accordance with national guidelines and reimbursement criteria. Disease activity was confirmed by a Crohn's disease activity index (CDAI) >220 with objective signs of active inflammation (high-sensitivity CRP >5 mg/L and/or fecal calprotectin >250 µg/g) and visible ulcers at baseline ileocolonoscopy.** **Exclusion Criteria: Patients with an imminent need for surgery, critical gastrointestinal stricture and obstructive symptoms, using corticosteroid therapy at doses >40 mg/d prednisolone or equivalent, active systemic infection, evidence of tuberculosis, usual contraindications to anti-TNF or immunosuppressants, or**	**Intervention: IFX was given intravenously at 5 mg/kg at weeks 0, 2, and 6 to all patients. Patients were randomized 1:1:1 at inclusion into 3 double-blind IFX maintenance regimens, administered every 8 weeks from week 14 to week 54 (end of the study period) as follows: IFX dose increase by increments of 2.5 mg/kg, maximally 2 times to a maximum dose of 10 mg/kg (DIS1) according to a prespecified algorithm (outlined later in this article), IFX dose increase by increments of 5 mg/kg, maximally 1 time, to a maximum dose of 10 mg/kg (DIS2) according to the same prespecified algorithm** **Comparison: IFX dose increase by 5 to 10 mg/kg if patients had a CDAI >220 at the current visit or a CDAI between 150 and 220 in the 2 weeks before the current visit in line with the registered label of IFX**	**Primary: The primary endpoint of the study was corticosteroid-free remission (CDAI <150) at all visits between week 22 and 54 associated with the absence of ulcers at week 54 and no surgery for bowel resection or abscess and no new fistula.** **Secondary: Prespecified secondary endpoints were the proportion of patients with no ulcers at weeks 12 and 54, clinical remission (CDAI <150) at each visit, sustained remission from week 14 onward, endoscopic remission (CDEIS <3) at weeks 12 and 54, endoscopic response (decrease of CDEIS score of atleast 50%) at weeks 12 and 54, IFX dose increase during the study period, IFX TL >3 µg/mL between weeks 14 and 54, adverse events, total use of infliximab, need for resection, and new fistula or abscesses.** **Results: The primary endpoint (CDAI <150) between week 22 and 54 off glucocorticosteroids, without new fistula and surgery and without ulcers at the week 54 ileocolonoscopywas reached in 15 (33%) of 45, 10 (27%) of 37, and 16 (40%) of 40 patients in the DIS1, DIS2, and the control group, respectively (P= .50).** **At week 12, 16 (36%), 6 (16%), and 16 (40%) patients had no ulcerations on endoscopy in the DIS1, DIS2, and control groups (P= .054); by week 54, these proportions increased to 19 (42%), 20 (54%), and 20 (50%) patients, respectively (P=.56). Endoscopic remission (CDEIS <3) was attained in 26 (58%), 13 (35%), and 15 (37.5%) patients in DIS1, DIS2, and the control group by week 12 (P = .070) and in 23 (51%), 19 (51%), and 21 (53%) patients by week 54 (P= 1.00) .Significant endoscopic improvement (CDEIS reduction >50%) was observed in 32 (71%), 24 (65%), and 26 (65%) patients by week 12 (P= .88), and in 28 (62%), 23 (62%), and 23 (57.5%) patients by week 54 (P= .89).** **A sustained IFX serum concentration >3 µg/mL between week 12 and 54 was observed in 21 (47%), 17 (46%), and 24 (60%) of the patients in DIS1, DIS2, and the**

other serious concomitant diseases were excluded.		**control group, respectively (P= .38). The mean concentrations in patients continuously above the 3 µg/mL cutoff was 7.8 ± 2.9 µg/mL, 9.3 ± 5.2 µg/mL, and 9.7 ± 4.5 µg/mL in DIS1, DIS2, and the control group, respectively, vs3.6 ± 2.1 µg/mL, 4.3 ± 2.3 µg/mL, and 3.4 ± 2.3 µg/mL in patients not meeting that success criterion.Antibodies to IFX were measured at the end of the trial and were detected in 10 (22%), 6 (16%), and 5 (12.5%) patients in the DIS1, DIS2, and control groups.** **Author's Conclusion: In a prospective randomizedexploratory trial of patients with active CD, we found increasing dose of infliximab based on a combination of symptoms, biomarkers, andserum drug concentrations does not lead to corticosteroid-free clinical remission in a larger proportion of patients than increasing dose based on symptoms alone.**

Methodical Notes

Funding Sources: This investigator-initiated trial was financially supported by Merck Sharp Dome and Janssen, which also provided the IFX study drug. Buhlmann Laboratories, Switzerland, kindly provided materials for Quantum Blue rapid measurements of fecal calprotectin. Prometheus Laboratories, San Diego, CA, performed the measurements of anti-infliximab antibodies at the end of the trial.

COI: Geert D'Haens declares grant support from Abbvie, Jansen, Merck Sharp Domem, and Pfizer; has served as advisor for Abbvie, Johnson andJohnson, Merck Sharp Dome, Mundipharma, Pfizer, Prometheus Laboratories/ Nestle, and Sandoz; and received speaker fees from Abbvie, Johnson and Johnson, Merck Sharp Dome, Mundipharma, and Pfizer. Severine Vermeire reports grant support from Abbvie, MSD, Takeda, and Pfizer; lecture fees from Abbie, MSD, Takeda, Ferring, Falk Pharma, Hospira, and Tillotts; and consultancy fees from Abbvie, MSD, Takeda, Ferring, Genentech/Roche, Shire, Pfizer, Galapagos, Mundipharma, Hospira, Celgene, Second Genome, and Janssen. Filip Baert reports research grants from Abbvie, Chiesi, Ipsen, MSD, and Roche;and speaker's and consultancy fees from Abbvie, Falk, Ferring, Janssen, Mundipharma, MSD, Pfizer, Takeda, and Vifor. Anthony Buisson declares consulting fees for Abbvie, Hospira, and Takeda; and lecture fees from Abbvie, Hospira, Takeda, MSD, Vifor Pharma, Sanofi-Aventis, and Ferring. Janneke vander Woude received grants from Abbvie, Jansen, Pfizer, Tramedico, and Falk; and speakers and consultancy fees from Abbvie, Falk, Ferring, Janssen, Mundipharma, MSD, Pfizer, Takeda, and Vifor. Edouard Louis has received fees from MSD, Abbvie, Takeda, Ferring, MSD, Chiesi, Mitsubishi Pharma, Hospira, Janssen, and Takeda; and is on the advisory board of Abbvie, Ferring, MSD, Takeda, Hospira, Mitsubishi Pharma, Celltrion, and Prometheus. Matthieu Allez received fees from Abbvie, MSD, Janssen, Takeda, Ferring, Mayoli, UCB, Novartis, Genentech,Pfizer, Novo Nordisk, and Falk. Alexandre Aubourg reports consultancy fees from MSD, Abbvie, and Takeda. Bas Oldenburg reports grants from MSD, Abbvie, Takeda, Cablon, Ferring, and Falk. Ann Gils has served as a speaker for MSD, Janssen Biologicals, Pfizer, Takeda, and Abbvie, and as a consultant for UCB; and has received Investigator-Initiated Research Grants from Pfizer. Guy Lambrecht, Peter Bossuyt, Benjamin Pariente, Yoram Bouhnik, Jerome Filippi, Philippe Van Hootegem, Jacques Moreau, Denis Franchimont, Martine De Vos, Fazia Mana, Laurent Peyrin-Biroulet, Hedia Brixi, Philip Caenepeel, MariekePierik, Sylvie Chevret, and David Laharie declare no competing interest in the presentstudy. KU Leuven licensed the infliximab, adalimumab, and vedolizumab ELISA to apDia and R-Biopharm and the use of monoclonal antibodies mAb-IFX6B7 and mAb-ADM6A10 in the lateral flow assay to R-Biopharm.

Randomization: Randomization at week 0 was centrally performed online (ClinInfo, Lyon, France), balanced by permutation blocks the size of which was not disclosed to investigators, and stratified by center, and previous use of azathioprine, 6-mercaptopurine, or methotrexate.

Blinding:

Dropout Rate/ITT-Analysis: Thirty-five (29%) of the patients dropped out of the trial before week 54: 13 (29%) of 45 in DIS1, 8 (22%) of 37 in DIS2, and 14 (35%) of 40 in the control group, after a median of 2.9, 4.6, and 5.8

months, respectively.

Notes:
In Hinblick auf PICO: Outcome nicht Zeit bis zur Therapieintensivierung, sondern steroid-freie Remission; Andere Faktoren (erhöhtes CRP, niedriger IFX-Spiegel) weitere mögliche Faktoren für Dosisanpassung. Patienten bei Studieneinschluss nicht in Remission. Insgesamt Studie zur Beantwortung der PICO-Frage nur sehr bedingt geeignet.

Literatursammlung:

AG 1 Diagnostik-Frage 2

Inhalt: 5 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Assa, A. 2019	2	Nonblinded, randomized controlled trial.
D'Haens, G. 2018	2	A proof-of-concept randomized double-blind controlled study.
Papamichael, K. 2017	3	multicenter, retrospective study
Papamichael, K. 2019	3	A multicentre retrospective cohort study.
Vande Casteele, N. 2015	2	Randomized controlled trial

OXFORD (2011) Appraisal Sheet: RCT: 5 Bewertung(en)

Assa, A. et al. Proactive Monitoring of Adalimumab Trough Concentration Associated With Increased Clinical Remission in Children With Crohn's Disease Compared With Reactive Monitoring. Gastroenterology. 157. 985-996.e2. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: Nonblinded, randomized controlled trial. Number of Patient: 78 children with CD. Recruitung Phase: July 2015 through December 201 Inclusion Criteria: Patients recruited were biologic-naïve children (6–17years) with luminal CD who had responded to standard ADL induction at weeks 0 and 2, as indicated at week 4 by a reduction of Pediatric Crohn's Disease Activity Index (PCDAI) of at least 15 points from ADL initiation, or clinical remission(PCDAI<10 points). Exclusion Criteria: Patients were excluded in cases of prior exposure to anti-TNFa agents; current or previous bowel perforation; small bowel obstruction within the last 3 months; fixed non inflammatory stricture (thickened bowel wall with minimal or	Intervention: In group 1 (proactive group), patients were assessed during each visit for clinical and biologic disease activity, while treating physicians were also informed of ADL TC for all patients within 2 weeks of sampling. ADL treatment was intensified based on plasmatic TC only, meaning that patients with ADL TC<5mg/mL were intensified regardless of disease activity (PCDAI, CRP, and calprotectin). Comparison: In group 2 (reactive group), patients were also assessed during each visit for clinical and biologic disease activity, but physicians were informed of the TC only in cases of clinical or biologic LOR, with subsequent intensification of ADL treatment only in patients with LOR and TC<5mg/mL, meaning that patients with LOR (either clinical and/or biologic) were intensified only if ADL TC was <5mg/mL. Patients in clinical and biologic remission were	Primary: The primary endpoint of the study was sustained corticosteroid-free clinical remission (PCDAI<10 points) at all visits from weeks 8 to 72. Secondary: Secondary outcomes included corticosteroid-free clinical remission on ADL at weeks 48 and72; sustained biologic remission (defined by CRP <0.5 mg/dL and fecal calprotectin<150mg/g) from week 8 to 72, and at weeks 48 and 72; ADL discontinuation rate at 72 weeks; treatment modification rate during the study period; number of ADL TC measurements <5mg/mL between weeks 8 to 72; and cumulative dose of ADL and adverse events; Results: The primary endpoint was reached in 31 (82%) of 38 and 19 (48%) of 40 in the

no enhancement oncross-sectional imaging); complicated or draining perianal fis-tula; previous malignancy; sepsis or active bacterial infection; previous surgical resection of the bowel, diagnosis of IBD-unclassified; or infection (actively tested in all patients) with hepatitis B, hepatitis C, tuberculosis or Clostridium difficile.	**not intensified and their physicians were not informed of their TC**	**proactive and reactive groups, respectively,P=.002.** **Author's Conclusion: Proactive monitoring of adalimumab trough concentrations and adjustment of doses and intervals resulted in significantly higher rates corticosteroid-free clinical remission than reactive monitoring (measuring trough concentration after loss of response.**

Methodical Notes

Funding Sources: The study was supported by an unrestricted educational grant by AbbVie Pharmaceutical.

COI: Amit Assa: Consultation and lectures fees from AbbVie; and research grants from AbbVie and Janssen. Dan Turner: Consultation fees, research grants, royalties, or honorarium from Janssen, Pfizer, Ferring, AbbVie, Takeda, Biogen, Neopharm, Uniliver, Atlantic Health, Shire, Celgene, Lilly, and Roche. Batia Weiss: Consultationfees from Janssen, and lecture fees from AbbVie. Ron Shaoul: Consultation and lecture fees from AbbVie and Janssen, and research grant from Janssen. Raanan Shamir: Research grant from AbbVie. The remaining authors disclose no conflicts

Randomization: Randomization and coding were performed by a dedicated clinical trial assistant at the Schneider Children's Medical Center for all centers in blocks of 4 (1:1 ratiostratified by immunomodulators use and medical center).

Blinding: No blinding.

Dropout Rate/ITT-Analysis: Treatment termination in 5 (13%) in proactive group, 8 (20%) reactive group, respectively.

Notes:
In Hinblick auf PICO: Outcome nicht Zeit bis zum Remissionsverlust, sondern Steroid-freie Remission.

D'Haens, G. et al. Increasing Infliximab Dose Based on Symptoms, Biomarkers, and Serum Drug Concentrations Does Not Increase Clinical, Endoscopic, and Corticosteroid-Free Remission in Patients With Active Luminal Crohn's Disease. Gastroenterology. 154. 1343-1351.e1. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type: A proof-of-concept randomized double-blind controlled study.** **Number of Patient: 122 biologic-naïve adult patients with active CD.** **Recruitung Phase: July 2012 through September 2015** **Inclusion Criteria: Patients recruited were adults with active luminal CD naive to**	**Intervention: IFX was given intravenously at 5 mg/kg at weeks 0, 2, and 6 to all patients. Patients were randomized 1:1:1 at inclusion into 3 double-blind IFX maintenance regimens, administered every 8 weeks from week 14 to week 54 (end of the study period) as follows: IFX dose increase by increments of 2.5 mg/kg, maximally 2 times to a maximum dose of 10 mg/kg (DIS1) according to a prespecified algorithm, IFX dose increase by increments of 5 mg/kg, maximally 1 time, to a maximum dose of 10 mg/kg (DIS2) according to the same prespecified algorithm**	**Primary: The primary endpoint of the study was corticosteroid-free remission (CDAI <150) at all visits between week 22 and 54 associated with the absence of ulcers at week 54 and no surgery for bowel resection or abscess and no new fistula.** **Secondary: Prespecified secondary endpoints were the proportion of patients with no ulcers at weeks 12 and 54, clinical remission (CDAI <150) at each visit, sustained remission from week 14 onward, endoscopic remission (CDEIS <3) at weeks 12 and 54, endoscopic response (decrease of CDEIS score of atleast 50%) at weeks 12 and 54, IFX dose increase during the study period, IFX TL >3 µg/mL between weeks 14 and 54, adverse events, total use of**

biologics with an indication to start anti-TNF therapy in accordance with national guidelines and reimbursement criteria. Disease activity was confirmed by a Crohn's disease activity index (CDAI) >220 with objective signs of active inflammation (high-sensitivity CRP >5 mg/L and/or fecal calprotectin >250 µg/g) and visible ulcers at baseline ileocolonoscopy. Exclusion Criteria: Patients with an imminent need for surgery, critical gastrointestinal stricture and obstructive symptoms, using corticosteroid therapy at doses >40 mg/d prednisolone or equivalent, active systemic infection, evidence of tuberculosis, usual contraindications to anti-TNF or immunosuppressants, or other serious concomitant diseases were excluded.	Comparison: IFX dose increase by 5 to 10 mg/kg if patients had a CDAI >220 at the current visit or a CDAI between 150 and 220 in the 2 weeks before the current visit in line with the registered label of IFX.	infliximab, need for resection, and new fistula or abscesses. Results: The primary endpoint (CDAI <150) between week 22 and 54 off glucocorticosteroids, without new fistula and surgery and without ulcers at the week 54 ileocolonoscopy was reached in 15 (33%) of 45, 10 (27%) of 37, and 16 (40%) of 40 patients in the DIS1, DIS2, and the control group, respectively (P= .50). At week 12, 16 (36%), 6 (16%), and 16 (40%) patients had no ulcerations on endoscopy in the DIS1, DIS2, and control groups (P= .054); by week 54, these proportions increased to 19 (42%), 20 (54%), and 20 (50%) patients, respectively (P=.56). Endoscopic remission (CDEIS <3) was attained in 26 (58%), 13 (35%), and 15 (37.5%) patients in DIS1, DIS2, and the control group by week 12 (P = .070) and in 23 (51%), 19 (51%), and 21 (53%) patients by week 54 (P= 1.00) .Significant endoscopic improvement (CDEIS reduction >50%) was observed in 32 (71%), 24 (65%), and 26 (65%) patients by week 12 (P= .88), and in 28 (62%), 23 (62%), and 23 (57.5%) patients by week 54 (P= .89). A sustained IFX serum concentration >3 µg/mL between week 12 and 54 was observed in 21 (47%), 17 (46%), and 24 (60%) of the patients in DIS1, DIS2, and the control group, respectively (P= .38). The mean concentrations in patients continuously above the 3 µg/mL cutoff was 7.8 ± 2.9 µg/mL, 9.3 ± 5.2 µg/mL, and 9.7 ± 4.5 µg/mL in DIS1, DIS2, and the control group, respectively, vs3.6 ± 2.1 µg/mL, 4.3 ± 2.3 µg/mL, and 3.4 ± 2.3 µg/mL in patients not meeting that success criterion. Antibodies to IFX were measured at the end of the trial and were detected in 10 (22%), 6 (16%), and 5 (12.5%) patients in the DIS1, DIS2, and control groups. Author's Conclusion: Increasing dose of infliximab based on a combination of symptoms, biomarkers, and serum drug concentrations does not lead to corticosteroid-free clinical remission in a larger proportion of patients than increasing dose based on symptoms alone.

Methodical Notes

Funding Sources: This investigator-initiated trial was financially supported by Merck Sharp Dome and Janssen, which also provided the IFX study drug. Buhlmann Laboratories, Switzerland, kindly provided materials for Quantum Blue rapid. measurements of fecal calprotectin. Prometheus Laboratories, San Diego, CA, performed the measurements of anti-infliximab antibodies at the end of the trial.

COI: Geert D'Haens declares grant support from Abbvie, Jansen, Merck Sharp Domem, and Pfizer; has served as advisor for Abbvie, Johnson andJohnson, Merck Sharp Dome, Mundipharma, Pfizer, Prometheus Laboratories/ Nestle, and Sandoz; and received speaker fees from Abbvie, Johnson and Johnson, Merck Sharp Dome, Mundipharma, and Pfizer. Severine Vermeire reports grant support from Abbvie, MSD, Takeda, and Pfizer; lecture fees from Abbie, MSD, Takeda, Ferring, Falk Pharma, Hospira, and Tillotts; and consultancy fees

from Abbvie, MSD, Takeda, Ferring, Genentech/Roche, Shire, Pfizer, Galapagos, Mundipharma, Hospira, Celgene, Second Genome, and Janssen. Filip Baert reports research grants from Abbvie, Chiesi, Ipsen, MSD, and Roche;and speaker's and consultancy fees from Abbvie, Falk, Ferring, Janssen, Mundipharma, MSD, Pfizer, Takeda, and Vifor. Anthony Buisson declares consulting fees for Abbvie, Hospira, and Takeda; and lecture fees from Abbvie, Hospira, Takeda, MSD, Vifor Pharma, Sanofi-Aventis, and Ferring. Janneke vander Woude received grants from Abbvie, Jansen, Pfizer, Tramedico, and Falk; and speakers and consultancy fees from Abbvie, Falk, Ferring, Janssen, Mundipharma, MSD, Pfizer, Takeda, and Vifor. Edouard Louis has received fees from MSD, Abbvie, Takeda, Ferring, MSD, Chiesi, Mitsubishi Pharma, Hospira, Janssen, and Takeda; and is on the advisory board of Abbvie, Ferring, MSD, Takeda, Hospira, Mitsubishi Pharma, Celltrion, and Prometheus. Matthieu Allez received fees from Abbvie, MSD, Janssen, Takeda, Ferring, Mayoli, UCB, Novartis, Genentech,Pfizer, Novo Nordisk, and Falk. Alexandre Aubourg reports consultancy fees from MSD, Abbvie, and Takeda. Bas Oldenburg reports grants from MSD, Abbvie, Takeda, Cablon, Ferring, and Falk. Ann Gils has served as a speaker for MSD, Janssen Biologicals, Pfizer, Takeda, and Abbvie, and as a consultant for UCB; and has received Investigator-Initiated Research Grants from Pfizer. Guy Lambrecht, Peter Bossuyt, Benjamin Pariente, Yoram Bouhnik, Jerome Filippi, Philippe Van Hootegem, Jacques Moreau, Denis Franchimont, Martine De Vos, Fazia Mana, Laurent Peyrin-Biroulet, Hedia Brixi, Philip Caenepeel, MariekePierik, Sylvie Chevret, and David Laharie declare no competing interest in the presentstudy. KU Leuven licensed the infliximab, adalimumab, and vedolizumab ELISA to apDia and R-Biopharm and the use of monoclonal antibodies mAb-IFX6B7 and mAb-ADM6A10 in the lateral flow assay to R-Biopharm.

Randomization: Randomization at week 0 was centrally performed online (ClinInfo, Lyon, France), balanced by permutation blocks the size of which was not disclosed to investigators, and stratified by center, and previous use of azathioprine, 6-mercaptopurine, or methotrexate.

Blinding: Serum samples for IFX concentrations were shipped to and measured at a single laboratory (KU Leuven, Leuven, Belgium) and the results were entered in the same CRF but remained invisible for the sites.

Dropout Rate/ITT-Analysis: Thirty-five (29%) of the patients dropped out of the trial before week 54: 13 (29%) of 45 in DIS1, 8 (22%) of 37 in DIS2, and 14 (35%) of 40 in the control group, after a median of 2.9, 4.6, and 5.8 months, respectively.

Notes:
In Hinblick auf PICO: Outcome nicht Zeit bis zum Remissionsverlust, sondern steroid-freie Remission. Andere Faktoren (erhöhtes CRP, niedriger IFX-Spiegel) weitere mögliche Faktoren für Dosisanpassung.

Papamichael, K. et al. Improved Long-term Outcomes of Patients With Inflammatory Bowel Disease Receiving Proactive Compared With Reactive Monitoring of Serum Concentrations of Infliximab. Clin Gastroenterol Hepatol. 15. 1580-1588.e3. 2017

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 **Study type: multicenter, retrospective study** **Number of Patient: 264 patients** **Recruitung Phase: September 2006 to January 2015** **Inclusion Criteria: Consecutive IBD patients who responded to infliximab induction therapy and subsequently received maintenance therapy and underwent either proactive or reactive TDM, based on the first infliximab concentration or antibodies to infliximab (ATI) measurement.**	**Intervention: Proactive drug monitoring.** **Comparison: Reactive drug monitoring.**	**Primary: Time to treatment failure.** **Secondary: Time to first IBD-related surgery or hospitalization, serious infusion reaction, and detection of antibodies to infliximab.** **Results: In the entire cohort, 105 patients had a treatment failure during follow-up. Among patients who underwent proactive TDM, only 17 (13%) had a treatment failure, in contrast with 88 (66%) patients in the reactive TDM group. Multiple Cox regression analysis independently associated proactive drug monitoring, compared with reactive monitoring, with reduced risk for treatment failure (hazard ratio [HR],0.16; 95% confidence interval [CI], 0.09–0.27;P<.001 multiple cox regression analysis independently associated proactive drug monitoring with reactive reduced risk for ibd-related surgery ci hospitalization to infliximab and serious infusion reaction>**

Exclusion Criteria: Patients were excluded if they underwent TDM only during the induction phase, subsequent proactive after first reactive TDM, total colectomy with an ileal pouch-anal anastomosis or a terminal ostomy prior to infliximab TDM initiation, had no follow-up visit after the initiation of infliximab TDM, or had a long drug holiday during infliximab maintenance therapy.		**Author's Conclusion: Proactive monitoring was associated with better clinical outcomes, including greater drug durability, less need for IBD-related surgery or hospitalization, and lower risk of antibodies to infliximab or serious infusion reactions**

Methodical Notes

Funding Sources: Konstantinos Papamichael received a fellowship grant from the Hellenic Groupfor the Study of IBD.

COI: Byron P. Vaughn receives research support from Takeda and Genentech and has received compensation from Janssen and AbbVie for speaking and advisory boards. Mark T. Osterman received consultancy fees from Janssen, AbbVie, UCB, Takeda, Pfizer, and Lycera, and received research grant support from UCB. Adam S. Cheifetz received consultancy fees from AbbVie, Janssen, UCB, Takeda, Prometheus, and Pfizer. The remaining authors disclose no conflicts of interest.

Randomization: No randomization, retrospective study.

Blinding: No blinding, retrospective study.

Dropout Rate/ITT-Analysis: No dropouts.

Notes:

Papamichael, K. et al. Proactive Therapeutic Drug Monitoring of Adalimumab Is Associated With Better Long-term Outcomes Compared With Standard of Care in Patients With Inflammatory Bowel Disease. J Crohns Colitis. 13. 976-981. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 **Study type: A multicentre retrospective cohort study.** **Number of Patient: 382 patients.** **Recruitung Phase: June 2006 to December 2015.** **Inclusion Criteria: Patients with IBD who received maintenance adalimumab therapy were eligible for the study and were followed until July 2016.** **Exclusion Criteria: Patients with early [≤8 weeks] failure, defined as drug discontinuation for either primary non-response or serious adverse event [SAE], and those with a previous total colectomy with an ileal pouch-anal anastomosis or ileostomy.**	**Intervention: Proactive TDM.** **Comparison: Reactive TDM.**	**Primary: Time to treatment failure.** **Secondary: The need for an IBD-related surgery.** **Results: At the end of follow-up, nine [17%] patients with at least one proactive TDM had treatment failure [SLR, n = 8; SAE, n = 1] in contrast to 119 [36%] receiving standard of care [SLR, n = 91; SAE, n = 28], 31 with reactive TDM alone [SLR, n = 27; SAE, n = 4]. Multiple Cox regression analyses showed that at least one proactive TDM was independently associated with a reduced risk for treatment failure (hazard ratio [HR]: 0.4; 95% confidence interval [CI]: 0.2–0.9; p = 0.022).** **Author's Conclusion: At the end of follow-up, one patient [2%] with at least one proactive TDM had an IBD-related surgery in contrast to 28 [9%] with standard of care [nine patients with reactive TDM alone]. There was a trend towards a lower cumulative probability of IBD-related surgery in patients with at least one proactive adalimumab testing compared with standard of care.**

Methodical Notes

Funding Sources: KP is supported by Ruth L. Kirschstein NRSA Institutional Research Training Grant 5T32DK007760-18.

COI: ASC: received consultancy fees from AbbVie, Janssen, Takeda, Ferring, Miraca, AMAG, Arena, Samsung, and Pfizer, and research support from Miraca; BPV: receives research support from Takeda, Genentech, and Celgene and has received compensation from Janssen and AbbVie for speaking and advisory boards; the remaining authors disclose no conflict of interest.

Randomization: No Randomization.

Blinding: No Blinding.

Dropout Rate/ITT-Analysis: No Dropouts.

Notes:
Retrospective analysis.

Vande Casteele, N. et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. Gastroenterology. 148. 1320-9.e3. 2015

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type: Randomized controlled trial** **Number of Patient: 263 Patienten** **Recruitung Phase: August 2011 to April 2013.** **Inclusion Criteria: Eligibility criteria included age of at least 18 years and adiagnosis of moderate-to severe CD or UC confirmed by endoscopy and histology. Patients needed to be treated with maintenance infliximab therapy for at least 14 weeks and needed to be in stable clinical response.** **Exclusion Criteria: Patients who were on a nonstandard higher dosing regimen because of secondary loss of response to infliximab therapy at the time of screening were ineligible and patients with**	**Intervention: All patients were first dose optimized to have an infliximab TC within the in-terval of 3–7mg/mL (optimization phase) according to the TAXIT algorithm. Patients who successfully achieved an infliximab TC within the optimal interval were then assigned to infliximab dosing based on clinical symptoms and C-reactive protein (CRP), or to continue dosing based on infliximab TC (maintenance phase). In the concentration-based dosing group, individual infliximab TCs were evaluated at each infusion and the dosing regimen was changed for the next infusion according to the TAXIT algorithm to keep patients within the optimal infliximab TC interval.** **Comparison: In the clinically based dosing group, dosing of infliximab was guided based on symptoms and CRP (recorded at each infusion) according to standard clinical practice criteria.**	**Primary: Primary end point was defined as the proportion of patientsin each group in clinical and biological remission at year 1 after optimization.** **Secondary: Secondary end points were durable remission, relapse (defined as the need for infliximab dose escalation, ie, interval decrease and/or dose increase, the addition of steroids, or switch to another anti-inflammatory agent as decided by the treating physician), infliximab TC within the optimal interval, ATI positivity, total cost of infliximab treatment, and quality adjusted life years (QALY).** **Results: The randomized maintenance phase did not show an additional benefit to continue concentration-based dose adjustments over clinically based dose adjustments.** **Author's Conclusion: Targeting patients' infliximab TCs to 3–7mg/mL results in a more efficient use of the drug. After dose optimization, continued concentration-based dosing was not superior to clinically based dosing for**

ATI>8mg/mL equivalents.		**achieving remission after 1 year, but was associated with fewer flares during the course of treatment.**

Methodical Notes

Funding Sources: The study was funded in part by the Research Foundation–Flanders (FWO),Belgium; grant number G061712 and Niels Vande Casteele is a Postdoctoral Fellow of the Research Foundation–Flanders (FWO), Belgium; grant number 1260714N. There was no external funding source that had an involvement on any aspect pertinent to the study.

COI: Niels Vande Casteele reports consultancy fees from MSD, Janssen Biologics, UCB, and speaker's fees from Abbvie, outside the submitted work. Marc Ferrante reports consultancy fees from Abbvie, Merck, Janssen Biologics, grants from Janssen Biologics, and speaker's fees from Merck, Tillots, Ferring, Abbvie, outside the submitted work. Gert Van Assche reports consultancy fees from Zealand Pharma, Shire, Abbott/Abbvie, Novartis, MSD, Janssen, BMS, Ferring, Chiesi, Takeda, grants from MSD, Abbott/Abbvie, Zealand Pharma, and speaker's fees from Janssen, Abbott/Abbvie, Ferring, Aptalis, Ferring, MSD, outside the submitted work; Vera Ballet has nothing to disclose; Griet Compernolle has nothing to disclose. Paul Rutgeerts reports consultancy fees from Amgen, Merck, UCB Pharma, Genentech, BMS, Abbvie, Janssen Biologics, Millennium, Neovacs, Actogenics, Prometheus Laboratories, Inc.,grants from UCB Pharma, Abbvie, Janssen Biologics, Merck, Prometheus Laboratories, Inc., and speaker's fees from Abbvie, Merck, outside the submitted work. Ann Gils reports grants from Pfizer, and speaker's fees from MSD, Janssen Biologicals, Pfizer, outside the submitted work. Séverine Vermeire reports consultancy fees from Takeda, Roche/Genentech, Merck, Centocor, Abbvie, UCB, Pfizer, Ferring, grants from Centocor, Abbvie,Merck, and speaker's fees from Merck, Abbvie, Takeda, Pfizer, Ferring, Falk, Centocor, outside the submitted work. The remaining authors disclose no conflicts.

Randomization: Randomization was performed by one person (VB) not in charge of the clinical care of patients using a computer-generated randomization schedule, with random block sizes.

Blinding: Both patients and treating physicians were blinded to individual infliximab trough and ATI concentrations.

Dropout Rate/ITT-Analysis: In total, 25 out of 251 randomized patients did not complete the study (10%).

Notes:
In Hinblick auf PICO: Endpunkt in dieser Studie nicht Zeit bis zum Remissionsverlust, sondern Anteil der Patienten in Remission.

Literatursammlung:

AG 2 akuter Schub-Frage 1

Inhalt: 30 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Abiko, Y. 2014	5	
Allegretti, J. R. 2017	3	retrospective observational
Ankersen, D. V. 2019	2	RCT
Assa, A. 2019	2	Nonblinded, randomized controlled trial.
Baert, F. 2016	4	prospektive obernational
Bek, S. 2016	1	sytematic review
Boube, M. 2020	2	RCT
Brand, E. C. 2019	1	systemaitc review
Colombel, J. F. 2018	2	A multicentre, randomised, open-label, active-controlled, two-group, pha
Cornillie, F. 2014	3	post hoc analysis of RCT
D'Haens, G. 2018	2	A proof-of-concept randomized double-blind controlled study.
Di Ruscio, M. 2017	1	systematic review, meta analysis
Gutiérrez, A. 2016	3	prospektive observational
Kopylov, U. 2016	1	systematic review, metaanalysis
Levesque, B. G. 2014	3	yes
Lin, J. F. 2014	1	metaanalysis
Louis, E. 2012	3	prospective multicenter cohort study
Mao, R. 2012	1	systematic review, meta analysis
Meuwis, M. A. 2013	3	prospective cohort trial
Molander, P. 2015	3	Prospective multicenter study
Mosli, M. H. 2015	1	Systematic Review and Meta-Analysis
Peyrin-Biroulet, L. 2014	3	RCT, but not primary endpoint.
Qiu, Y. 2015	1	Meta-analysis of Prospective Studies
Reinisch, W. 2020	3	post-hoc analysis of RCT
Reinisch, W. 2012	1	post-hoc analysis of RCT
Tham, Y. S. 2018	2	systematic review, meta-analysis

Waljee, A. K. 2019	**1**	**cohort study**
Wright, E. K. 2016	**3**	**prospective, randomized controlled trial**
Wright, E. K. 2015	**3**	**Subgroup analysis (POCER)**
Zhuge, Y. 2016	**1**	**meta-analysis**

OXFORD (2011) Appraisal Sheet: Systematic Reviews: 10 Bewertung(en)

Bek, S. et al. Systematic review: genetic biomarkers associated with anti-TNF treatment response in Aliment Pharmacol Ther. 44. 554-67. 2016

Evidence level/Study Types	P - I - C	Outcomes/Results	Lite
Evidence level: 1 **Study type: sytematic review** **Databases: Pubmed** **Search period: October 2015** **Inclusion Criteria:** **three individual searches were performed in PubMed using various alternative search terms for (i) "anti-TNF** **three individual searches were performed in PubMed using various alternative search terms for (i) "anti-TNF treatment", (ii) "genetic variation", and (iii) "autoimmune disease", respectively. Subsequently, studies appearing in all of the three searches were identified resulting in 572 abstracts (latest search date: 27 October 2015). Figure 1 shows the search strategy and a full list of search terms is shown in Table S1. All studies suggesting that they pre-sented original data on polymorphisms and anti-TNF treatment response were retrieved (138 articles) and reviewed by three independent authors (SB, JVN, VA)** **Exclusion Criteria: Studies were excluded due to small numbers of study par- ticipants for treatment evaluation (less than 100 cases), missing data, not reporting original data and not report- ing data on anti-TNF response (78 studies).**	**Population: A systematic review and meta-analysis were carried out according to the guidelines of 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) statement.23 To identify the relevant primary literature three individual searches were performed in PubMed using various alternative search terms for (i) "anti-TNF treatment", (ii) "genetic variation", and (iii) "autoimmune disease", respectively. Subsequently, studies appearing in all of the three searches were identified resulting in 572 abstracts (latest search date: 27 October 2015).**	**Primary: To identify polymorphisms and candidate genes from the literature that are associated with anti-tumour necrosis factor (TNF) treatment response in patients with inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis.** **Secondary: -** **Results: A functional polymorphism in FCGR3A was significantly associated with anti-TNF treatment response among CD patients using biological response criterion (decrease in C-reactive protein, levels). Meta-analyses showed that polymorphisms in TLR2 (rs3804099, OR (95% CI) = 2.17 (1.35–3.47)], rs11938228 [OR = 0.64 (0.43–0.96)], TLR4 (rs5030728) [OR = 3.18 (1.63–6.21)], TLR9**	**27 c** **Sys bio TNF infl Bek Fra And Alir Sep 10.1 15. PMI Rev** **2 Cite** **Trea dise me Kim Cho Arc Mar 10.1 202 PMI** **3 Cite** **Pro Sel Res Pat Dis up. Bra Pat Mac (Se Cro Col**

		Figure 1 shows the search strategy and a full list of search terms is shown in Table S1. All studies suggesting that they presented original data on polymorphisms and anti-TNF treatment response were retrieved (138 articles) and reviewed by three independent authors (SB, JVN, VA). Studies were excluded due to small numbers of study participants for treatment evaluation (less than 100 cases), missing data, not reporting original data and not reporting data on anti-TNF response (78 studies). In total, 60 studies reported on genetic markers and anti-TNF response in autoimmune diseases whereof 15 reported on IBD (and the others on ankylosing arthritis, psoriasis and rheumatoid arthritis). No further studies were identified by searching the literature list of the retrieved articles.	(rs352139) [OR = 0.43 (0.21–0.88)], TNFRSF1A (rs4149570) [OR = 2.06 (1.02–4.17)], IFNG (rs2430561) [OR = 1.66 (1.05–2.63)], IL6 (rs10499563) [OR = 1.65 (1.04–2.63)] and IL1B (rs4848306) [OR = 1.88 (1.05–3.35)] were significantly associated with response among IBD patients using clinical response criteria. A positive predictive value of 0.96 was achieved by combining five genetic markers in an explorative analysis. Author's Conclusion: There are no genetic markers currently available which are adequately predictive of anti-TNF response for use in the clinic. Genetic markers bear the advantage that they do not change over time. Therefore, hypothesis-free approaches, testing a large number of polymorphisms in large, well-characterised cohorts, are required in order to identify genetic profiles with larger effect sizes, which could be employed as biomarkers for treatment selection in clinical settings.	Clir 15;1 10.1 PMI 4 Cite Pre Res Infl Priv GL, L. J C doi PMI Rev 5 Cite Per Mor Infl Pha Dru Di F Fro 8;11 10.3 eCo PMI Rev 6 Cite IL6 ass dis res infl Gor de Alc Wes EMV Int Feb 10.1 202 PMI 7 Cite Ass Fac Pol G/T the Pre Car in a

		Intervention: none **Comparison:** Biomarkers		**Bou Jou Ket Bio 24;2 10.1 202 PMI 8 Cite Per Hyp Pre Atr Fro 2;7: 10.3 eCo PMI Rev 9 Cite Is I and Ass Res Cro Wal Plu Zak Kre Zyw M, Skr Fro 14;1 10.3 eCo PMI 10 Cite Ger to Infl Sal Gut Gal Álv Coc Oji Jim Vay Bos Gon Bla Eiz Mer M, I Int**

				doi PMI Pag 11 Cite The Mic Ger Infli Infl Dov The Kol Gaz Mic 20;8 10.3 PMI 12 Cite Pre cou infl witl IBD mul stu Zha Lar JB, BM 25; 10.1 PMI 13 Cite Ider Met Clir Mor Gor Sar P, E Clir Oct 10.1 PMI 14 Cite Car imp infl Wa RJE Pha Oct 10.1

				201 PMI Rev 15 Cite Pre witl The Vos RK, Wo 7;25 10.3 PMI Rev 16 Cite Mol Bov in C Lee Cel 10.3 PMI Rev 17 Cite Pre Tun Res Sys Ont Gol Cel 10.3 PMI 18 Cite Imp Env and Infl Zha Dig 176 056 PMI 19 Cite Ger Bov Pat Par Cel 10.3

				PMI Rev 20 Cite Ulc D'H Par Dru doi PMI Rev Pag 21 Cite Ger acti IL23 ass ank Soc PS, And RB, Het And BM 12;1 018 PMI 22 Cite Oliv oxy imb res Ser Mel Bia Rec doi Epu PMI 23 Cite Imp and out chr pro stu per Chr And Sør Hvi H, SG,

				Knu Dah GL, Bra Ste A, E J, E Mur Hol V. BM doi PMI 24 Cite Sys ana TNF rhe Bek Soc V. Pha Oct 10.1 13. PMI Rev 25 Cite A Trea Rec Infl Mul Pro Per And SB, Byg Wie Villa J, Bro Nie AB, Fær Ste A, E J, H Wer Nut doi PMI 26 Cite Pot Trea Dru

			Dis And BL. Nut 10.3 PMI Rev 27 Cite Pro the inte app Hal Yau Wil Nar Jan 10.1 15. PMI Rev 28 Cite Ger of coli wer to a Bar Ped Tur Ras TB, Vog Pha Jan 10.1 31. PMI

Methodical Notes

Funding Sources: none

COI: declared

Study Quality: drop-out indicated
study quality not addressed

Heterogeneity: Forest pmts of significant associations provided

Publication Bias: not addressed

Notes:

Brand, E. C. et al. Systematic Review and External Validation of Prediction Models Based on Symptoms a Endoscopic Activity in Crohn's Disease. Clin Gastroenterol Hepatol. . . 2019

Evidence level/Study Types	P - I - C	Outcomes/Results
Evidence level: 1 **Study type: systemaitc review** **Databases: Pubmed Cochrane** **Search period: feb 14 2018** **Inclusion Criteria: explained** **We included articles based on the following eligibility criteria: (1) full-text articles published in peer-reviewed journals; (2) no language restrictions; (3) a cross-sectional study design (ie, the developed model must predict the endoscopic outcome at the same moment in time); (4) studies exclusively aimed at adult Crohn's disease patients, or, if both ulcerative colitis and Crohn's disease patients were studied, enabling the extraction of data for Crohn's disease alone; (5) description of the prediction/diagnostic model, risk score, noninvasive index, clinical decision rule, or equivalent for the outcome ileocolonic We included articles based on the following eligibility criteria: (1) full-text articles published in peer-reviewed journals; (2) no language restrictions; (3) a cross-sectional study design (ie, the developed model must predict the endoscopic outcome at the same moment in time); (4) studies exclusively aimed at adult Crohn's disease patients, or, if both ulcerative colitis and Crohn's disease patients were studied, enabling the extraction of data for Crohn's disease alone; (5) description of the prediction/diagnostic model, risk score, noninvasive index, clinical decision rule, or equivalent for the outcome ileocolonic** **Exclusion Criteria: explained**	**Population: defined** **Intervention: clear** **Comparison: clear**	**Primary: Biomarker for detection of CD activity** **Secondary: -** **Results: We screened 5303 articles and identified models (from 21 studies) for our analysis. Sev models could be validated externally; in the AILORIX data set, these models identified patie with endoscopic activity with AUROC values rang from 0.61 (95% CI, 0.51-0.70) to 0.81 (95% CI, 0. 0.86). In this data set, the AUROC value for concentration was 0.79 (95% CI, 0.74-0.85) and AUROC value for CRP level was 0.72 (95% CI, 0. 0.77). The AUROC values for the validation in the U data set were similar. In the TAILORIX and/or U data set, 4 of the 7 models, as weil as the FC a CRP assays, were able to identify patients w endoscopic activity with positive predictive values 90% or more. Two of the 7 models (but not the FC CRP values) identified patients without endosco activity with a negative predictive value (NPV) of 9 or mure, leading to correct prediction of endosco healing in 3.2% to 11.3% of all patients. For examp applying the Herranz-Bachiller model (1 of 7 mode at a NPV of 92.1 % and a positive predictive value 91.9% correctly identified 35.7% of all patients whom ileocolonoscopy could be avoided expected endoscopic activity or healing incorrectly identified 3.2% of all patients. M ileocolonoscopies (66.5% in TAILORIX and 72.6% the UAI of all ileocolonoscopies) could be avoic correctly based on concentrations of FC of 100 µ or less and 250 µg/g or higher. However, using t range of FC concentrations to identify patients w do not require ileocolonoscopy caused 18.7% of patients in the TAILORIX cohort and 19.8% of patients in the UAI cohort to be predicted incorrec to have endoscopic activity or healing.** **Author's Conclusion: endoscopy stays the g standard**

Methodical Notes

Funding Sources: Medical university

COI: decalred

Study Quality: not addressed

Heterogeneity: low, not specifically addressed

Publication Bias:
Critical Appraisal. The risk of bias and applicability of the included studies was assessed independently by 2 auth on the Prediction model Risk Of Bias ASsessment Tool (PROBAST).1 7 Publications were assessed for risk o selection, predictors, outcome, and analyses) and for applicability in

Notes:

Di Ruscio, M. et al. Surrogate Fecal Biomarkers in Inflammatory Bowel Disease: Rivals or Complementary Inflamm Bowel Dis. 24. 78-92. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type: systematic review, meta analysis** **Databases: Medline and the Cochrane Library** **Search period: April 2017** **Inclusion Criteria: A systematic electronic search of the English literature up to April 2017 was performed using Medline (EBSCO host) and the Cochrane Library. The search strategy used a combination of Medical Subject (MeSH) headings and key words as follows: "inflammatory bowel disease," "Crohn's disease," "ulcerative colitis," "fecal markers," "fecal biomarkers," "S100A12," "high mobility group box 1," "neopterin, polymorphonuclear neutrophil elastase," "fecal hemoglobin," "alpha1-antitrypsin,"**	**Population: ok** **Intervention: none** **Comparison: ok**	**Primary: Fecal calprotectin, comparisons?** **Secondary: none** **Results: Out of 1023 citations, 125 eligible studies were identified. Data were grouped according to each fecal marker including S100A12, high-mobility group box 1, neopterin, polymorphonuclear neutrophil elastase, fecal hemoglobin, alpha1-antitrypsin, human neutrophil peptides, neutrophil gelatinase-associated lipocalin, chitinase 3-like-1, matrix metalloproteinase 9, lysozyme, M2-pyruvate kinase, myeloperoxidase, fecal eosinophil proteins, human beta-defensin-2, and beta-glucuronidase. Some of these markers showed a high sensitivity and specificity and correlated with disease activity, response to therapy, and mucosal healing. Furthermore, they showed a potential utility in the prediction of clinical relapse.** **Author's Conclusion: Several fecal biomarkers have the potential to become useful tools complementing FC in IBD diagnosis and monitoring. However, wide variability in their accuracy in assessment of intestinal inflammation suggests the need for further studies.**	**Surrogate Fecal Biomarkers in Inflamm Complementary Tools of Fecal Calprotec Di Ruscio M, Vernia F, Ciccone A, Frieri G Inflamm Bowel Dis. 2017 Dec 19;24(1):78 PMID: 29272479 Review.** **2** **Cite Share** **The Usefulness of Serum Vitamin D Le Activity and Response to Biologics. Valvano M, Magistroni M, Mancusi A, D'A Vernia F, Viscido A, Necozione S, Latella Nutrients. 2021 Jan 22;13(2):323. doi: 10. PMID: 33499406 Free PMC article.** **3** **Cite Share** **The Intestinal Barrier and Current Techn Permeability. Schoultz I, Keita ÅV. Cells. 2020 Aug 17;9(8):1909. doi: 10.339 PMID: 32824536 Free PMC article. Review** **4** **Cite Share** **Paneth Cell-Derived Lysozyme Defines Microbiota and the Inflammatory Tone of Yu S, Balasubramanian I, Laubitz D, To Flores J, Singh R, Liu Y, Macazana C, Zh Midura-Kiela MT, Wang D, Yap GS, Fe Häggblom MM, Zhang L, Douard V, Verzi Immunity. 2020 Aug 10.1016/j.immuni.2020.07.010. PMID: 32814028** **5** **Cite Share** **S100A12 in Digestive Diseases and Healt Carvalho A, Lu J, Francis JD, Moore RE, SD, Johnson JG, Damo SM, Gaddy JA. Gastroenterol Res Pract. 2020 10.1155/2020/2868373. eCollection 2020.**

“human neutrophil peptides,” “neutrophil gelatinase-associated lipocalin,” “chitinase 3-like-1,” “matrix metalloproteinase 9,” “lysozyme,”” M2-pyruvate kinase,” “myeloperoxidase,” “fecal eosinophil proteins,” “human beta-defensin-2,” and “beta-glucuronidase.” Four authors (M.D.R., F.V., A.C., and G.L.) screened the abstracts and identified relevant articles. Additional studies were identified via a manual review of the reference list of the identified studies and review articles. Any discrepancy was resolved by consensus, referring back to the original article. Out of 1023 citations, 125 eligible studies were identified. Data have been grouped according to each fecal marker. Exclusion Criteria: Only papers written in English that analyzed human stool samples were included. In vitro studies, animal studies, studies on blood/serum samples, and studies analyzing FC or FL alone were excluded.			PMID: 32184815 Free PMC article. Review 6 Cite Share Differential gene expression and gene-s monolayers during a 30-day timeline with Robinson JM, Turkington S, Abey SA, Ke Tissue Barriers. 20 10.1080/21688370.2019.1651597. Epub 20 PMID: 31438773 Free PMC article. 7 Cite Share Eosinophils in the gastrointestinal pathogenesis of major colorectal disorde Loktionov A. World J Gastroenterol. 2019 J 10.3748/wjg.v25.i27.3503. PMID: 31367153 Free PMC article. Review 8 Cite Share Systematic review: outcomes and advers in Crohn's disease. Catt H, Hughes D, Kirkham JJ, Bodger K Aliment Pharmacol Ther. 2019 Apr;49(8) Epub 2019 Mar 3. PMID: 30828852 Free PMC article. 9 Cite Share Faecal Calprotectin. Pathirana WGW, Chubb SP, Gillett MJ, Va Clin Biochem Rev. 2018 Aug;39(3):77-90. PMID: 30828114 Free PMC article. Review 10 Cite Share Role of indoleamine 2,3-dioxygenase in tract. Acovic A, Gazdic M, Jovicic N, Harrell Volarevic V. Therap Adv Gastroenterol. 2018 De 10.1177/1756284818815334. eCollection 2 PMID: 30574192 Free PMC article. Review Page 2 11 Cite Share Redefining the Practical Utility of Bloo Inflammatory Bowel Diseases. Ostrowski J, Dabrowska M, Lazowska I, A, Kulecka M, Karczmarski J, Ambrozkie Zeber-Lubecka N, Kierkus J, Socha P, L B, Bak-Drabik K, Walkowiak J, Radwan Korczowski B, Starzynska T, Mikula M. J Crohns Colitis. 2019 Apr 26;13(5):626-6 PMID: 30541017 Free PMC article.	

			12 **Cite Share** **Indoleamine 2,3-dioxygenase-dependent maintains mucosal healing in ulcerative** **Acovic A, Simovic Markovic B, Gazdi Gajovic N, Jovanovic M, Zdravkovic N, K C, Dolicanin Z, Djonov V, Arsenijevic N, L** **Therap Adv Gastroenterol. 2018 Aug 10.1177/1756284818793558. eCollection 2** **PMID: 30159037 Free PMC article.** **13** **Cite Share** **Diagnostic Markers for Nonspecific Infla** **Derkacz A, Olczyk P, Komosinska-Vasse** **Dis Markers. 2018 Jun 11;2018:74519 eCollection 2018.** **PMID: 29991970 Free PMC article. Review** **14** **Cite Share** **Emerging concepts in non-invasive mon** **Marlicz W, Skonieczna-Żydecka K, Dabc A.** **Therap Adv Gastroenterol. 2018 Apr 10.1177/1756284818769076. eCollection 2** **PMID: 29707039 Free PMC article. Review**

Methodical Notes

Funding Sources: none

COI: none

Study Quality: OK, not specifically addressed

Heterogeneity: low, not specifically addressed

Publication Bias: not addressed

Notes:

Kopylov, U. et al. Fecal calprotectin for the prediction of small-bowel Crohn's disease by capsule endosc meta-analysis. Eur J Gastroenterol Hepatol. 28. 1137-44. 2016

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type: systematic review, metaanalysis** **Databases: pub/Embase** **Search period: 1/200 to 11/2015** **Inclusion Criteria: To**	**Population: defined** **Intervention: The diagnostic accuracy [sensitivity, specificity, diagnostic odds ratio (DOR)] of FC for diagnosis of SBCD or evidence of active inflammation in the small-bowel in**	**Primary: The aim of the current study was to assess the diagnostic accuracy of calprotectin for the prediction of active small-bowel disease on capsule endoscopy by performing a diagnostic test meta-analysis** **Secondary: -** **Results: Seven studies (463 patients) were entered into the final analysis. The**	**Fecal calprotectin for Crohn's disease by ca review and meta-analy** **Kopylov U, Yung DE, Horin S, Plevris JN, Eli** **Eur J Gastroenterol H doi: 10.1097/MEG.0000** **PMID: 27415156 Review** **2** **Cite Share**

capture as many articles and abstracts as possible, a broad search strategy was used by combining the terms 'capsule endoscopy' and 'calprotectin'. The search was performed with no limitations. The pool was supplemented with a hand search of relevant abstracts from major gastroenterological meetings. For a study to be included in this meta-analysis, the following predefined inclusion criteria had to be fulfilled: randomizedcontrolled trials, open-label prospective, observational studies, and case–control studies of FC and CE in patients undergoing evaluation for suspected CD or reassessment of CD activity. For studies with multiple indications for CE examination, only results pertaining to suspected CD or CD reassessment were considered for inclusion in our study. Studies addressing patients undergoing evaluation for obscure GI bleeding or suspected small bowel malignancy were excluded. Only studies including more than 30 patients were eventually included. Exclusion Criteria: shown	established CD was evaluated. The diagnosis of active SBCD was made in accordance to the criteria used in the original publications. We evaluated three FC level cut-offs as per availability of reports in the included studies: 50, 100, and 200 µg/g. Comparison: prediction	DOR was significant for all the evaluated FC cutoffs (50 µg/g: sensitivity 0.83, specificity 0.53, DOR-5.64; 100 µg/g: sensitivity 0.68, specificity 0.71, DOR-5.01; 200 µg/g: sensitivity 0.42, specificity 0.94, DOR-13.64). On sensitivity analyses, when only studies addressing suspected Crohn's or retrospective studies were included, the results did not change significantly. For studies including patients with suspected CD only, the overall accuracy for FC cut-off 50 µg/g was further increased (sensitivity 0.89, specificity 0.55, DOR-10.3), with a negative predictive value of 91.8%. Author's Conclusion: Fecal calprotectin has a significant diagnostic accuracy for the detection of small-bowel CD. Our results suggest that in patients with suspected CD with calprotectin < 50 µg/g, the likelihood of positive diagnosis is very low.	Capsule endoscopy i when and how. Hilmi I, Kobayashi T. Intest Res. 202 10.5217/ir.2019.09165. PMID: 32623876 Free P 3 Cite Share A Light-Weight Pra Detection and Trait Re Leng L, Yang Z, Kim C, Sensors (Basel). 2 10.3390/s20092644. PMID: 32384651 Free P 4 Cite Share A novel PillCam Crohr for quantification of m disease. Eliakim R, Yablecovitc E, Carter D, Selinge Kopylov U. United European Gas 551. doi: 10.1177/205(12. PMID: 32213037 Free P 5 Cite Share Comparison of the use with magnetic resonan inflammatory bowel dis Hijaz NM, Attard TM, C CA. World J Gastroentero doi: 10.3748/wjg.v25.i2 PMID: 31391775 Free P 6 Cite Share Should We Divide Dominant and Isolated Dulai PS, Singh S, V Rivera-Nieves J, Erns Chang JT, Sandborn W Clin Gastroenterol Hep doi: 10.1016/j.cgh.2019 PMID: 31009791 Free P 7 Cite Share Association Between Progression of Crohn's Kennedy NA, Jones G ID, Lees CW. Clin Gastroenterol H 2276.e4. doi: 10.1016/j. 14.

PMID: 30772585 Free P

8
Cite Share

Proteomic Evaluation
of the Gastrointestina
Irradiation Model.
Huang W, Yu J, Jones
Tudor G, Booth C, Mac
Health Phys. 20
10.1097/HP.0000000000
PMID: 30624357 Free P

9
Cite Share

Usefulness of fecal
antibody testing in ad
bowel diseases: a pros
Nakamura S, Imaeda
Matsuura M, Oka H,
Watanabe K, Nakase H
Intest Res. 201
10.5217/ir.2018.00027.
PMID: 30301337 Free P

10
Cite Share

From bench to be
inflammatory bowel dis
Mumolo MG, Bertani L
G, Albano E, Tapete G,
World J Gastroentero
doi: 10.3748/wjg.v24.i3
PMID: 30197475 Free P
Page 2

11
Cite Share

Fecal calprotectin fo
endoscopic recurrenc
review and meta-analy
Tham YS, Yung DE, Fa
Eliakim R, Koulaouzidi
Therap Adv
8;11:175628481878557
10.1177/175628481878
PMID: 30034529 Free P

12
Cite Share

Small bowel imaging in
Gauci J, Sammut L, Sc
Cortis K, Ellul P.
Ann Gastroenterol. 2
10.20524/aog.2018.026
PMID: 29991884 Free P

13
Cite Share

Emerging concepts
Crohn's disease.
Marlicz W, Skoniec
Łoniewski I, Koulaouzi
Therap Adv G
18;11:17562848187690
10.1177/175628481876
PMID: 29707039 Free P

14
Cite Share

A review of magnetic
indices for quantif
inflammation.
Rozendorn N, Amitai
Klang E.
Therap Adv G
13;11:17562848187659
10.1177/175628481876
PMID: 29686731 Free P

15
Cite Share

The role of inflamma
inflammatory bowel di
Kiely CJ, Pavli P, O'Bri
Gut Microbes. 201
10.1080/19490976.2018
PMID: 29543557 Free P

16
Cite Share

The Lewis score or t
disease activity inde
assessment of sm
established Crohn's di
Yablecovitch D, Lahat
B, Ben-Horin S, Eliakim
Therap Adv G
14;11:1756283X177477
10.1177/1756283X1774
PMID: 29399042 Free P

17
Cite Share

Validation of Neutrop
Detect Mucosal Infla
Disease.
Minar P, Jackson K, T
Denson LA.
Inflamm Bowel Dis. 2
10.1093/ibd/izx022.
PMID: 29272485 Free P

18
Cite Share

Balloon-Assisted E
Endoscopy in Susp
Disease.
Yen HH, Chang CW, Ch

			Clin Endosc. 20 10.5946/ce.2017.142. E PMID: 29017295 Free P 19 Cite Share The impact of panent management of Crohn Eliakim R. Therap Adv Gastroente 10.1177/1756283X1772 PMID: 28932274 Free P 20 Cite Share Fecal occult blood tes bowel pathology dete systematic review and Yung DE, Vijayan S, Koulaouzidis A. Ann Gastroenterol 10.20524/aog.2017.012 PMID: 28243039 Free P Page 3 21 Cite Share Capsule endoscopy fo Crohn's disease: a co status. Jensen MD, Brodersen Ann Gastroenterol 10.20524/aog.2016.011 PMID: 28243037

Methodical Notes

Funding Sources: none

COI: none

Study Quality: The diagnostic accuracy [sensitivity, specificity, diagnostic odds ratio (DOR)] of FC for diagnosis inflammation in the small-bowel in estab- lished CD was evaluated. The diagnosis of active SBCD was made in a the original publications. We evaluated three FC level cut-offs as per availability of reports in the included studies: Quality assessment of diagnostic accuracy studies (QUADAS) 2 results for the studies included.

Heterogeneity: high
The I2 statistic was used and a value of more than 50% was used as a cut- off for significant heterogeneity. Bec between the studies included, the DerSimoian–Laird random-effects model was applied. Sensitivity analysis usi (defined as trials that were both blinded and published as full manuscripts) was carried out for comparisons wit Methodological quality of the included studies was evaluated using the quality assessment of diagnostic accuracy Analyses were carried out using STATA 12 (StataCorp, College Station, Texas, USA) and RevMan 5.3 (Cochrane co packages.

Publication Bias: not addressed

Notes:

Lin, J. F. et al. Meta-analysis: fecal calprotectin for assessment of inflammatory bowel disease activity. In 2014

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: metaanalysis Databases: databases Medline, Web of Science, Cochrane Library, and EMBASE Search period: december 2013 Inclusion Criteria: if it met the inclusion criteria as follows: (1) the study evaluated FC for monitoring IBD activity; (2) an endoscopic scoring system was used as reference standard to assess inflammatory activity; (3) the study provided sufficient details to construct a 2-by-2 table. Studies were excluded if conducted in pediatric patients with IBD. Exclusion Criteria: -	Population: defined Intervention: measurement calproetctin Comparison: disease activity	Primary: The aim of our study was to evaluate the diagnostic accuracy of FC for differentiating between patients with active IBD and those in remission. Secondary: - Results: We included 13 studies (744 patients with UC and 727 with CD) in the final analysis. The area under the curve values were 0.89 (95% confidence interval, 0.86–0.92), 0.93 (0.89–0.97), and 0.88 (0.83–0.93) in the IBD, UC, and CD groups, respectively. For the IBD group at a cutoff value of 50 mg/g, the pooled sensitivity was 0.92 (0.90–0.94) and specificity 0.60 (0.52–0.67). For a cutoff value at 100 mg/g, the pooled sensitivity was 0.84 (0.80–0.88) and specificity was 0.66 (0.59–0.73). For a cutoff value at 250 mg/g, the pooled sensitivity was 0.80 (0.76–0.84) and specificity was 0.82 (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	Cite Share Meta-analysis: fecal calprotectin for asse disease activity. Lin JF, Chen JM, Zuo JH, Yu A, Xiao ZJ, Den Inflamm Bowel Dis. 2014 10.1097/MIB.0000000000000057. PMID: 24983982 2 Cite Share Factors Associated with Poor Quality of Patients with Inflammatory Bowel Disease: A Nazarian A, Bishay K, Gholami R, Scaffid Griller N, Satchwell JB, Baker JP, Grover SC J Can Assoc Gastroenterol. 202(10.1093/jcag/gwaa014. eCollection 2021 Apr PMID: 33855267 Free PMC article. 3 Cite Share Assessment of fecal calprotectin and feca markers for soil-transmitted helminth attril case-control substudy conducted in Côte Island, Tanzania. Patel C, Keller L, Welsche S, Hattendorf J Coulibaly JT, Hürlimann E, Keiser J. EClinicalMedicine. 2021 Jan 10.1016/j.eclinm.2021.100724. eCollection 2(PMID: 33554091 Free PMC article. 4 Cite Share Increased Fecal Calprotectin Is Associate Symptoms and Quality of Life Scores in Chi Beaufils F, Mas E, Mittaine M, Addra M, Fa Galode F, Lamireau T, Bui S, Enaud R. J Clin Med. 2020 Dec 17;9(12):4080. doi: 10.3 PMID: 33348735 Free PMC article. 5 Cite Share A Pilot Study Evaluating Novel Urinary Bion Ho SS, Wall C, Gearry RB, Keenan J, Day AS Inflamm Intest Dis. 2020 Nov;5(4):212-220 2020 Oct 14. PMID: 33313074 Free PMC article. 6 Cite Share First United Arab Emirates consensus on inflammatory bowel diseases: A 2020 Delph Alkhatry M, Al-Rifai A, Annese V, Georgop AM, Koutoubi Z, Nathwani R, Taha MS, Limc World J Gastroenterol. 2020 No 10.3748/wjg.v26.i43.6710.

PMID: 33268959 Free PMC article. Review.

7
Cite Share

COVID-19 Pandemic: Which IBD Patients
Scoped Now, Who Can Wait, and how to Re
Ng SC, Mak JWY, Hitz L, Chowers Y, Bernste
J Crohns Colitis. 2020 Oct 21;14(S
10.1093/ecco-jcc/jjaa128.
PMID: 33085973 Free PMC article.

8
Cite Share

Biomarkers of Crohn's Disease to Supp
Therapeutic Interventions.
Porter AC, Aubrecht J, Birch C, Braun J,
Hinton R, Hoffmann SC, Honig G, Linggi B,
Inflamm Bowel Dis. 2020 Sep 18;26(10):149
PMID: 32840322

9
Cite Share

Normal fecal calprotectin levels in healthy c
and decrease with age.
Velasco Rodríguez-Belvís M, Viada Bris JF,
A, Asensio Antón J, Domínguez Ortega G, M
Paediatr Child Health. 2020 Aug;25(5):28
Epub 2019 Jun 17.
PMID: 32765164

10
Cite Share

Analytical and clinical performance of t
calprotectin immunoassay from DiaSorin in
Vicente-Steijn R, Jansen JM, Bisheshar R, H
Pract Lab Med. 2020 Jun 24;21:e00175. d
eCollection 2020 Aug.
PMID: 32637525 Free PMC article.
Page 2

11
Cite Share

Comparison of 18F-FDG PET-MR and fecal l
disease activity in patients with ulcerative c
Li Y, Khamou M, Schaarschmidt BM, Umut
Haubold J, Koch AK, Bruckmann NM, Saw
Langhorst J.
Br J Radiol. 2020 Aug;93(1112):20200167.
2020 Jun 24.
PMID: 32579403 Clinical Trial.

12
Cite Share

Ranking microbiome variance in inflamm
longitudinal intercontinental study.
Clooney AG, Eckenberger J, Laserna-Mend
Vagianos K, Sargent M, Ryan FJ, Mora
Targownik LE, Bernstein CN, Shanahan F, C
Gut. 2021 Mar;70(3):499-510. doi: 10.1136/gu

14.
PMID: 32536605 Free PMC article.

13
Cite Share

Microbiota changes induced by microen
patients with inflammatory bowel disease.
Facchin S, Vitulo N, Calgaro M, Buda A,
Lorenzon G, Marinelli C, D'Incà R, Sturniolo
Neurogastroenterol Motil. 2020 Oct;32(10):
Epub 2020 May 31.
PMID: 32476236 Free PMC article.

14
Cite Share

MicroRNA-320a Monitors Intestinal Dise
Inflammatory Bowel Disease.
Cordes F, Demmig C, Bokemeyer A, Brückn
Tepasse P, Schmidt HH, Schmidt MA, Cicho
Clin Transl Gastroenterol. 202
10.14309/ctg.0000000000000134.
PMID: 32352717 Free PMC article.

15
Cite Share

Endoscopy in inflammatory bowel diseases
and post-pandemic period.
Iacucci M, Cannatelli R, Labarile N, Mac
Kochhar GS, Ghosh S, Shen B.
Lancet Gastroenterol Hepatol. 2020 Jun;5
1253(20)30119-9. Epub 2020 Apr 16.
PMID: 32305075 Free PMC article. Review.

16
Cite Share

Point-of-care gastrointestinal ultrasound in
accurate alternative for disease monitoring.
Sathananthan D, Rajagopalan A, Van De Ve
Bryant RV.
JGH Open. 2019 Oct 9;4(2):273-279. doi:
2020 Apr.
PMID: 32280777 Free PMC article.

17
Cite Share

Measuring Vitamin D Status in Chronic Inf
Chronic Inflammation Affect the Reliabili
Patients with IBD?
Aksan A, Tugal D, Hein N, Boettger K, Caic
Armbruster FP, Stein J.
J Clin Med. 2020 Feb 17;9(2):547. doi: 10.33
PMID: 32079317 Free PMC article.

18
Cite Share

Targeting Mucosal Healing in Crohn's Disea
Picco MF, Farraye FA.
Gastroenterol Hepatol (N Y). 2019 Oct;15(10
PMID: 31802977 Free PMC article.

19
Cite Share

Can the CalproQuest predict a positive C diagnostic study.
Chmiel C, Senn O, Hasler S, Rosemann T, Scherz N, Sulz MC, Vavricka S.
PLoS One. 2019 Nov 21;14(11):e0224961. do eCollection 2019.
PMID: 31751360 Free PMC article. Clinical T

20
Cite Share

Impact of faecal calprotectin measuremen patients with Crohn's disease and ulcerative Bathe AL, Mavropoulou E, Mechie NC, Pet Amanzada A.
PLoS One. 2019 Oct 24;14(10):e0223893. do eCollection 2019.
PMID: 31647834

Diagnostic accuracy of fecal calprotecti colorectal cancer: A meta-analysis.
Ye X, Huai J, Ding J.
Turk J Gastroenterol. 2018 Jul;29(4):397-405
PMID: 30249553 Free PMC article.

32
Cite Share

The Management of Inflammatory Bowe Evidence and Future Perspectives.
Arnott I, Rogler G, Halfvarson J.
Inflamm Intest Dis. 2018 Jul;2(4):189-199. do Jun 26.
PMID: 30221146 Free PMC article. Review.

33
Cite Share

From bench to bedside: Fecal calprotectin clinical setting.
Mumolo MG, Bertani L, Ceccarelli L, Laino G Costa F.
World J Gastroenterol. 2018 Se 10.3748/wjg.v24.i33.3681.
PMID: 30197475 Free PMC article. Review.

34
Cite Share

Faecal calprotectin level for assessing end future clinical course in patients with mo undergoing granulomonocytapheresis: a pr Shimoyama T, Yamamoto T, Umegae S, Mats BMC Gastroenterol. 2018 Aug 1;18(1):120. d PMID: 30068300 Free PMC article.

35
Cite Share

Fecal calprotectin for detection of postope Crohn's disease: systematic review and me

Tham YS, Yung DE, Fay S, Yamamot
Koulaouzidis A, Kopylov U.
Therap Adv Gastroenterol. 2018 Jul
10.1177/1756284818785571. eCollection 201
PMID: 30034529 Free PMC article.

36
Cite Share

Diagnostic Markers for Nonspecific Inflamm
Derkacz A, Olczyk P, Komosinska-Vassev K
Dis Markers. 2018 Jun 11;2018:74519
eCollection 2018.
PMID: 29991970 Free PMC article. Review.

37
Cite Share

Methotrexate Is Not Superior to Placeb
Response or Remission in Ulcerative Colitis
Herfarth H, Barnes EL, Valentine JF, Hans
Jackson S, Osterman MT, Anton K, Ivanova
RS, Abraham B, Cross RK, Dryden G, Fisch
R, Polyak S, Saha S, Williams E, Yajnik V,
Clinical Research Alliance of the Crohn's ar
Gastroenterology. 2018 Oct;
10.1053/j.gastro.2018.06.046. Epub 2018 Jur
PMID: 29964043 Free PMC article. Clinical T

38
Cite Share

Andecaliximab [Anti-matrix Metalloprotei
Ulcerative Colitis: A Randomised, Double-B
2/3 Study in Patients With Moderate to Seve
Sandborn WJ, Bhandari BR, Randall C, Y
Wendt E, Chai H, McKevitt M, Zhao S, Sundy
J Crohns Colitis. 2018 Aug 29;12(9):1021-10
PMID: 29767728 Free PMC article. Clinical T

39
Cite Share

Aberrant MRP14 expression in thyroid folli
secretion through the IL-1β/MAPK pathway
Luo X, Zheng T, Mao C, Dong X, Mou X, Xu C
Endocr Connect. 2018 Jun;7(6):850-858. doi
May 15.
PMID: 29764904 Free PMC article.

40
Cite Share

Practical guidance on the use of faecal calp
Brookes MJ, Whitehead S, Gaya DR, Hawthe
Frontline Gastroenterol. 2018 Apr;9(2):87
100762. Epub 2017 Feb 22.
PMID: 29588834 Free PMC article. Review.

The role of inflammation in temporal sh
disease mucosal microbiome.
Kiely CJ, Pavli P, O'Brien CL.
Gut Microbes. 2018 Nov 2;9(6):477-485. doi:
Epub 2018 Sep 5.

PMID: 29543557 Free PMC article.

42
Cite Share

Endoscopic score vs. fecal biomarkers fo
with ulcerative colitis after clinical remissio
Yamamoto T, Shimoyama T, Umegae S, Mats
Clin Transl Gastroenterol. 2018 Feb 20;9(
0006-7.
PMID: 29491393 Free PMC article.

43
Cite Share

Factors affecting clinical decision-making
and the role of point-of-care calprotectin.
Derwa Y, Williams CJM, Sood R, Mumtaz S,
PJ, Ford AC, Gracie DJ.
Therap Adv Gastroenterol. 2018 Jan
10.1177/1756283X17744739. eCollection 201
PMID: 29383026 Free PMC article.

44
Cite Share

Urinary potassium is a potential biomarker
colitis and displays in vitro immunotolerant
Goyal S, Rampal R, Kedia S, Mahajan S, Bo
AK, Wari MN, Makharia G, Awasthi A, Ahuja
Sci Rep. 2017 Dec 22;7(1):18068. doi: 10.103
PMID: 29273710 Free PMC article.

45
Cite Share

Fecal Calprotectin for predicting Relapse
Crohn's Disease: A Meta-analysis.
Zhuge Y, Huang QP, Li Q, Wang JS.
Euroasian J Hepatogastroenterol. 2016 Jul-
journals-10018-1182. Epub 2016 Dec 1.
PMID: 29201742 Free PMC article.

46
Cite Share

Detection of calprotectin in inflammatory b
levels and immunohistochemical localizatio
Fukunaga S, Kuwaki K, Mitsuyama K, Takec
Yamauchi R, Mori A, Kakuma T, Tsuruta O, T
Int J Mol Med. 2018 Jan;41(1):107-118. do
2017 Nov 7.
PMID: 29115397 Free PMC article.

47
Cite Share

Faecal biomarkers for screening small bow
Crohn's disease: a prospective study.
Shimoyama T, Yamamoto T, Umegae S, Mats
Therap Adv Gastroenterol. 2017
10.1177/1756283X17717683. Epub 2017 Jul 4
PMID: 28835772 Free PMC article.

48

Cite Share

Compliance with the faecal calprotectin te bowel disease.
Maréchal C, Aimone-Gastin I, Baumann Peyrin-Biroulet L.
United European Gastroenterol J. 10.1177/2050640616686517. Epub 2017 Feb
PMID: 28815034 Free PMC article.

49
Cite Share

Selecting children with suspected infl endoscopy with the calgranulin C or calpro CACATU study.
Heida A, Van de Vijver E, Muller Kobold A, v
BMJ Open. 2017 May 29;7(5):e015636. doi: 1
PMID: 28554936 Free PMC article.

50
Cite Share

Clinical Utility of Fecal Calprotectin Monit with Inflammatory Bowel Disease: A Sy Guide.
Heida A, Park KT, van Rheenen PF.
Inflamm Bowel Dis. 2017 10.1097/MIB.0000000000001082.
PMID: 28511198 Free PMC article. Review.

Comparison of Fecal Calprotectin Meth Pediatric Inflammatory Bowel Disease.
Kittanakom S, Shajib MS, Garvie K, Turner R, Chetty VT, Macri J, Khan WI.
Can J Gastroenterol Hepatol. 2017;2017:145 Epub 2017 Apr 16.
PMID: 28491862 Free PMC article.

52
Cite Share

High-fat diet induced leptin and Wnt ex pathway analysis of mouse colonic tissue a
Penrose HM, Heller S, Cable C, Nakhou Crawford SE, Savkovic SD.
Carcinogenesis. 2017 Mar 1;38(3):302-311. d
PMID: 28426873 Free PMC article.

53
Cite Share

Update on clinical and research applic gastrointestinal diseases.
Siddiqui I, Majid H, Abid S.
World J Gastrointest Pharmacol Ther. 10.4292/wjgpt.v8.i1.39.
PMID: 28217373 Free PMC article. Review.

54
Cite Share

Treat to Target in Inflammatory Bowel D Literature.
Darr U, Khan N.

Curr Treat Options Gastroenterol. 10.1007/s11938-017-0130-6.
PMID: 28161818 Review.

55
Cite Share

Utility of Biomarkers in the Management of
Kochhar G, Lashner B.
Curr Treat Options Gastroenterol. 10.1007/s11938-017-0129-z.
PMID: 28138859 Review.

56
Cite Share

Inter- and intraobserver agreement in com
in inflammatory bowel disease.
Horvat N, Tavares CC, Andrade AR, Cabral
Ueda SK, Leite AZ, Sipahi AM, Rocha MS.
World J Gastroenterol. 2016 Dec
10.3748/wjg.v22.i45.10002.
PMID: 28018107 Free PMC article.

57
Cite Share

The Utility of Infliximab Therapeutic Drug
Inflammatory Bowel Disease and Conce
Retrospective Analysis of a Real-World Exp
Mitchell RA, Shuster C, Shahidi N, Galorpo
Enns RA, Bressler B.
Can J Gastroenterol Hepatol. 2016;2016:520
Epub 2016 Nov 10.
PMID: 27957480 Free PMC article.

58
Cite Share

The Utility of Fecal Calprotectin in the Rea
with Inflammatory Bowel Disease.
Abej E, El-Matary W, Singh H, Bernstein CN.
Can J Gastroenterol Hepatol. 2016;2016:248
Epub 2016 Sep 28.
PMID: 27774443 Free PMC article.

59
Cite Share

New Biomarkers for Diagnosing Inflar
Assessing Treatment Outcomes.
Barnes EL, Burakoff R.
Inflamm Bowel Dis. 2016
10.1097/MIB.0000000000000903.
PMID: 27763951 Free PMC article. Review.

60
Cite Share

Evaluation of Serum S100A8/S100A9 Leve
Thyroid Diseases.
Korkmaz H, Tabur S, Savaş E, Özkaya M, Ak
Balkan Med J. 2016 Sep;33(5):547-551. doi:
Epub 2016 Sep 1.
PMID: 27761284 Free PMC article.

Biomarkers in Search of Precision Medicine
Boyapati RK, Kalla R, Satsangi J, Ho GT.
Am J Gastroenterol. 2016 Dec;111(12):1682
Epub 2016 Sep 27.
PMID: 27670602 Review.

62
Cite Share

Soluble ST2 is a sensitive clinical marker of
Díaz-Jiménez D, De la Fuente M, Dubois-Ca
J, Pérez T, González MJ, Simian D, Hermosc
BMC Gastroenterol. 2016 Aug 26;16(1):103.
PMID: 27565556 Free PMC article.

63
Cite Share

Clinical outcomes at 12 months and risk o
patients with an intermediate raised fecal ca
McFarlane M, Chambers S, Malik A, Lee B
Arasaradnam R.
BMJ Open. 2016 Jun 6;6(6):e011041. doi: 10
PMID: 27266773 Free PMC article.

64
Cite Share

Characteristics, Treatment, and Long-Ter
Involvement in Behcet's Syndrome: A S
Study From a Dedicated Multidisciplinary C
Hatemi I, Esatoglu SN, Hatemi G, Erzin Y, Ya
Medicine (Baltimore). 2016
10.1097/MD.0000000000003348.
PMID: 27100417 Free PMC article.

65
Cite Share

Poor Correlation Between Clinical Di
Inflammation, and the Role of Psychologic
Bowel Disease.
Gracie DJ, Williams CJ, Sood R, Mumtaz S,
Am J Gastroenterol. 2016 Apr;111(4):541-5
2016 Mar 22.
PMID: 27002800 Free article.

66
Cite Share

Gut mucosal DAMPs in IBD: from mechanis
Boyapati RK, Rossi AG, Satsangi J, Ho GT.
Mucosal Immunol. 2016 May;9(3):567-82. do
Mar 2.
PMID: 26931062 Review.

67
Cite Share

Fecal calprotectin: its scope and utility in t
bowel disease.
Ikhtaire S, Shajib MS, Reinisch W, Khan WI.
J Gastroenterol. 2016 May;51(5):434-46.

Epub 2016 Feb 20.
PMID: 26897740 Review.

68
Cite Share

Diagnosis and management of functional s
disease in remission.
Teruel C, Garrido E, Mesonero F.
World J Gastrointest Pharmacol Ther.
10.4292/wjgpt.v7.i1.78.
PMID: 26855814 Free PMC article. Review.

69
Cite Share

Gut inflammation and microbiome in spond
Kabeerdoss J, Sandhya P, Danda D.
Rheumatol Int. 2016 Apr;36(4):457-68. doi:
2015 Dec 30.
PMID: 26719306 Review.

70
Cite Share

Rapid fecal calprotectin testing to assess fo
inflammatory bowel disease: A diagnostic c
Kwapisz L, Mosli M, Chande N, Yan B, B
Barnett W, Bax K, Ponich T, Howard J, Tirole
Saudi J Gastroenterol. 2015 Nov-Dec;
3767.170948.
PMID: 26655130 Free PMC article.

Use of blood based biomarkers in the eva
ulcerative colitis.
Barnes EL, Liew CC, Chao S, Burakoff R.
World J Gastrointest Endosc. 2015
10.4253/wjge.v7.i17.1233.
PMID: 26634038 Free PMC article.

72
Cite Share

Small Intestinal Bacterial Overgrowth
Inflammation in the Irritable Bowel Syndrom
David L, Babin A, Picos A, Dumitrascu DL.
Clujul Med. 2014;87(3):163-5. doi: 10.15386/
PMID: 26528017 Free PMC article.

73
Cite Share

Inflammation, Antibiotics, and Diet as Env
Microbiome in Pediatric Crohn's Disease.
Lewis JD, Chen EZ, Baldassano RN, Otley A
K, Bailey A, Friedman ES, Hoffmann C, Alb
Gilroy E, Nessel L, Grant A, Chehoud C, Li H
Cell Host Microbe. 2015 O
10.1016/j.chom.2015.09.008.
PMID: 26468751 Free PMC article.

74
Cite Share

Trimethylamine-N-oxide: A Novel Bioma

Inflammatory Bowel Disease.
Wilson A, Teft WA, Morse BL, Choi YH, Woo
Tirona RG, Kim RB.
Dig Dis Sci. 2015 Dec;60(12):3620-30. doi: 1
2015 Jul 10.
PMID: 26160437

75
Cite Share

Clinicians' guide to the use of fecal calpr
disease activity in inflammatory bowel disea
Bressler B, Panaccione R, Fedorak RN, Seic
Can J Gastroenterol Hepatol. 2
10.1155/2015/852723. Epub 2015 Jun 30.
PMID: 26125109 Free PMC article. Review.

76
Cite Share

The Relationship Among Perceived Stress,
Persons With Inflammatory Bowel Disease.
Targownik LE, Sexton KA, Bernstein MT, B
Graff LA.
Am J Gastroenterol. 2015 Jul;110(7
10.1038/ajg.2015.147. Epub 2015 Jun 16.
PMID: 26077178

77
Cite Share

C-Reactive Protein, Fecal Calprotectin, and
of Endoscopic Activity in Symptomatic
Patients: A Systematic Review and Meta-An
Mosli MH, Zou G, Garg SK, Feagan SG, Mac
WJ, Feagan BG.
Am J Gastroenterol. 2015 Jun;110
10.1038/ajg.2015.120. Epub 2015 May 12.
PMID: 25964225 Review.

78
Cite Share

VAlidation of an 8-item-questionnaire predi
tEst and Real-life implemenTation in prim
delay in inflammatory bowel disease (ALE
diagnostic study.
Hasler S, Zahnd N, Müller S, Vavricka S, Rog
BMJ Open. 2015 Mar 10;5(3):e007306. doi: 1
PMID: 25757949 Free PMC article. Clinical T

79
Cite Share

Flow cytometry detection of vitamin D rec
treatment in Crohn's disease.
Bendix M, Dige A, Deleuran B, Dahlerup
Husted LB, Harsløf T, Langdahl B, Agnholt J
Clin Exp Immunol. 2015 Jul;181(1):19-28. d
May 5.
PMID: 25707738 Free PMC article.

80
Cite Share

			The clinical value of faecal calprotectin a postoperative Crohn's disease. **Yamamoto T.** **United European Gastroenterol J. 10.1177/2050640614558106.** **PMID: 25653853 Free PMC article. Review.** **No association between serum adenosine activity in Crohn's disease.** **Sajjadi M, Gholamrezaei A, Daryani NE.** **Dig Dis Sci. 2015 Jun;60(6):1755-60. doi: 1 2015 Feb 5.** **PMID: 25652144** **82** **Cite Share** **Accuracy of Rapid Fecal Calprotectin Te Bowel Diseases Under Treatment with TNFo** **Tursi A, Elisei W, Picchio M, Giorgetti G, Bra** **Dig Dis Sci. 2015 May;60(5):1406-13. doi: 1 2014 Dec 2.** **PMID: 25445163**

Methodical Notes

Funding Sources: none

COI: none

Study Quality: Study quality was assessed using the QUADAS (QUality Assessment of studies of Diagnostic A reviews) tool. Each item should be answered "yes,"
"no," or "unclear." We chose all of the 11 items and followed the guidelines for scoring each of them included i using scales yielding a summary score because the interpretation of the summary score was problematic and pot evaluated the checklist ndependently. Disagreements were resolved by consensus.

During quality assessment, data extraction, and analysis process, we encountered many obstacles, highlighting t current studies. It is hoped that more widespread multicenter large samples and implementation of the Standards Accuracy studies will enable readers to directly extract desired information. These can be emphasized as factors improved in future studies in the area.

Heterogeneity: high

The heterogeneity was detected by a chi-square
test or Q-statistic and Higgins I-squared statistic (I2). A P value of
less than 0.1 was considered statistically significant heterogeneity
for the chi-square or Q-statistics. The percentage of I2 represented
the degree of heterogeneity. I2 percentages of 25%, 50%, and 75%
indicated a low, moderate, and high degree of heterogeneity,
The source of heterogeneity was explored using threshold analysis, meta-regression, and sensitivity analysis. Me included pretest probability, blinded design, and sample size. Sensitivity analysis was under- taken to asses probability (pretest probability more than overall average pretest probability) and small sample studies (sample siz

Publication Bias: Publication bias was assessed using Deeks' test. P , 0.05 was considered to indicate statistically Although the funnel plot of publication bias showed some asymmetry due to the limited number of studies, the D nonsignificant value (P ¼ 0.425), indicating no publication bias among the included studies.

Notes:

Mao, R. et al. Fecal calprotectin in predicting relapse of inflammatory bowel diseases: a meta-analysis of Bowel Dis. 18. 1894-9. 2012

Evidence level/Study Types	P - I - C	Outcomes/Results	Li

Evidence level: 1 **Study type: systematic review, meta analysis** **Databases: Medline, Web of Science, Cochrane Library, and EMBASE databases** **Search period: up to August 2011** **Inclusion Criteria: A study was included when meeting the criteria as fol- lows: 1) prospective studies about using FC in predicting IBD relapse; 2) FC level for predicting IBD relapse was measured at remission; 3) estimates of diagnostic accuracy (such as sen- sitivity or specificity); 4) the identification of relapse is based on clinical activity indices or endoscopic findings; and 5) stud- ies were conducted in human, nonpediatric populations.** **Exclusion Criteria: -**	**Population: IBD** **Intervention: measurement fecal calprotectin** **Comparison: FC predictive capacity in IBD relapse**	**Primary: We aimed to perform a meta- analysis of the predictive capacity of FC in IBD relapse.** **Secondary: -** **Results: A total of 672 IBD patients (318 UC and 354 CD) from six different studies were analyzed. The pooled sensitivity and specificity of FC to predict relapse of quiescent IBD was 78% (95% confidence interval [CI]: 72–83) and 73% (95% CI: 68–77), respectively. The area under the summary receiver-operating characteristic (sROC) curve was 0.83 and the diagnostic odds ratio was 10.31 (95% CI: 5.05–21.06). The capacity of FC to predict relapse was comparable between UC and CD. In CD patients the predictive value of FC in isolated small bowel CD was not assessed due to insufficiency of available data. Compared with all enrolled CD patients, FC appeared to be more accurate in ileocolonic and colonic CD.** **Author's Conclusion: As a simple and noninvasive marker, FC is useful to predict relapse in quiescent IBD patients.**	**76** **Fe re di pr M H In O 10 11 Pl** **2 Ci** **Sy Pe In G C J Ja 10 20 Pl** **3 Ci** **Se st bo K B J, Se do Pl** **4 Ci** **Fe pr ar st in Pa Er Th D 10 eC Pl** **5 Ci** **G Bi in Li L,**

				Fr 17 10 eC Pl Re **6 Ci** **Th Fa Pa In Pr Di Hi In Ne 10 Se Pl** **7 Ci** **Sy ar im w co in De Ki Pa Al Ja 10 28 Pl Re** **8 Ci** **Ca bo Kl Ka Va Cl 56 10 20 Pl Re** **9 Ci** **Sa in re Fe JY**

				Cl Cl 20 10 Pl 10 Ci M In Pa Di Co A, No Hl Bo Cl M 10 Pl Cr Ro Ar A, Da Na 2; 01 Pl 12 Ci Cl M Fi To St Ta R, Cl Cl Ko EV M Ro Cl J Do 10 So Pl Ro 13 Ci Fe Is Bi In

			Al Ru C, J 20 10 Pl 14 Ci Ca in in W Ra Pl O 10 20 Pl Re 15 Ci Ca G G Lu Pa Br Jl Be Ha Le M S, Sc Be J Ac 10 Ju Pl 16 Ci Sy Ar Su Re Co Li M 28 10 20 Pl Re 17 Ci

				C m re di Fe Ju W 14 10 Pl **18 Ci** **U sp to w Ba D, L, Se Pl 14 10 eC Pl Cl** **19 Ci** **Fa Pa M Cl Au Pl Re** **20 Ci** **Fa Re M Th Pa Di Bu Le Rh J 14 10 Pl** **Ex ca m di Re P, F. U**

				20 **10** **20** **Pl** **Re** **22** **Ci** **Fr** **ca** **bo** **M** **L,** **Ta** **W** **7;** **10** **Pl** **Re** **23** **Ci** **Fa** **as** **pr** **pa** **ul** **gr** **pr** **Sl** **Ur** **Bl** **1;** **01** **Pl** **24** **Ci** **Lo** **In** **De** **Di** **Ka** **Be** **In** **M** **10** **21** **Pl** **25** **Ci** **Di** **Ne** **Di** **De** **Va** **Di** **11** **10** **20**

				Pl **R** **26** **Ci** **Er** **bi** **in** **af** **m** **Ya** **U** **Cl** **Fe** **10** **Pl** **27** **Ci** **G** **Bi** **In** **Di** **R** **Zl** **Li** **A** **Cl** **H** **m** **30** **10** **e** **Pl** **28** **Ci** **Th** **Pr** **In** **G** **Le** **Fr** **do** **e** **Pl** **R** **29** **Ci** **Pr** **O** **In** **Pa** **W** **Zl** **G** **R** **In** **19** **10**

				Pl 3(Ci Fe R w ar Zl JS Eu 2(1(E Pl Fe a ou he in K K M J, Pa W 7; 1(Pl 32 Ci Va th m di Tu G Fr Ju 1(E Pl 33 Ci M ou le bi Tu Fr Ju 1(E Pl 34 Ci C

				ca **in** **M** **Ba** **G** **Ur** **20** **10** **20** **Pl** **35** **Ci** **Ca** **Ar** **Cl** **Pa** **In** **Pl** **Es** **M** **Co** **P,** **G** **Vi** **Ca** **Lo** **Fa** **Pe** **(G** **El** **13** **10** **20** **Pl** **36** **Ci** **In** **In** **Ta** **M** **Di** **20** **46** **Pl** **37** **Ci** **Cl** **Ca** **As** **In** **Sy** **G** **He** **In** **Ju** **10** **Pl** **Re**

				38 Ci C M Pe Di Ki K Is Kl C 20 10 A Pl 39 Ci Se re pa di Ye S. M M 10 Pl 40 Ci U ap ga Si W Th 10 Pl A ev as M Cl 53 10 Ep Pl Cl 42 Ci Cl as ul ev M W 14

				10 Pl Re 43 Ci Th th Pa Di Al Be Ca 20 10 Se Pl 44 Ci Fa af ro of Di M Ku Bl 7; 01 Pl Re 45 Ci Fo ca in Re A, Sa R, W 28 10 Pl 46 Ci In in cl Zh Li Ni M Se 10 Pl 47

				Ci **As** **Ca** **bo** **Ca** **M** **Ko** **No** **Na** **Jo** **Th** **El** **Di** **40** **7.** **Pl** **48** **Ci** **Ut** **pr** **in** **M** **J** **Ju** **10** **20** **Pl** **49** **Ci** **En** **Dy** **Sy** **J** **Ju** **10** **Pl** **Re** **50** **Ci** **Fe** **ut** **in** **Ik** **Kl** **J** **M** **10** **20** **Pl** **Di** **fu** **in** **re** **Te** **W** **Th** **10**

				Pl Re 52 Ci He in pa Li Be W 21 10 Pl Re 53 Ci O IB w Be Bl 18 01 Pl Re 54 Ci Di in Cl W 28 10 Pl Re 55 Ci Cl fe m in Br Fe Ca O 10 Ju Pl Re 56 Ci M In Cl Di

				ar Th Ji M Ju 10 Pl 57 Ci Co Ca th Pr Re Ul Ya Ba Ar Ju 10 Ap Pl 58 Ci Fe in be Al Ca Ap 10 Pl Re 59 Ci Fe To in Pa He Sa M Ira Fe 10 20 Pl 60 Ci Pl ba in at pr co La Is

				K **U** **2** **1** **P** **T** **c** **m** **C** **Y** **U** **2** **1** **P** **R** **6** **C** **T** **m** **d** **L** **T** **J** **1** **P** **R** **6** **C** **A** **C** **In** **U** **A** **T** **G** **D** **1** **x.** **P** **6** **C** **F** **a** **m** **p** **B** **L** **D** **d** **E** **P** **6** **C** **T** **in** **a**

				di di Va Le Si O Ru W G 10 20 Pl Cl 66 Ci Bi di Fe Di do 20 Pl Re 67 Ci Fa as ac re Cr re st Ya Ur Ur 20 10 Pl 68 Ci In m ac st va R. Bl 23 14 Pl 69 Ci M Cr av D' Cl

				20 10 20 Pl Re 70 Ci Bi in M Ry Pr 83 Ep Pl Ci M re pa co Os Li W Br Di Cl Ne 10 20 Pl Cl 72 Ci M po de He Cl 11 10 20 Pl Re 73 Ci Fa sy tir pr rh Au Ba Re Au 6; Pl

			74 Ci Ta pe Cl Ra Ap 10 Ap Pl 75 Ci Ut ar bo Su W 14 10 Pl 76 Ci En cr un Ko Tr Ju 10 Ep Pl Re 77 Ci Co ta ul Sa Cl O 10 20 Pl

Methodical Notes

Funding Sources: none declared

COI: not declared

Study Quality: Forest plots of the pooled sensitivity and specificity are shown in Figure 1. The sensitivity sensitivity 0.78, 95% CI: 0.72–0.83), while specificity ranged from 0.62–0.91 (pooled specificity 0.73, 95% CI: 0.68–0 2.09– 3.78), NLR was 0.31 (95% CI: 0.2–0.47), and DOR was 10.31 (95% CI: 5.05–21.06). Chi-square values for sensit DOR were 11.75 (P ¼ 0.038), 16.68, (P ¼ 0.005), 12.95 (P ¼ 0.024), 10.93, (P ¼ 0.0529), and 13.82 (P ¼ 0.016), respect significant heterogeneity across studies regarding sensitivity, PLR, NLR, and DOR, except for NLR.

Heterogeneity: As shown in Table 1, three publications had higher QUADAS scores (

Publication Bias: The Egger test showed that the potential publication bias was significant (P < 0.05).

Notes:

Mosli, M. H. et al. C-Reactive Protein, Fecal Calprotectin, and Stool Lactoferrin for Detection of Endosc Inflammatory Bowel Disease Patients: A Systematic Review and Meta-Analysis. Am J Gastroenterol. 110. 8

Evidence level/Study Types	P - I - C	Outcomes/Results
Evidence level: 1 **Study type: Systematic Review and Meta-Analysis** **Databases: MEDLINE and EMBASE using Ovid SP, the Cochrane Library, and the ISI Web of Knowledge** **Search period: 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 in patients with previously diagnosed UC or CD presenting with symptoms suggestive of endoscopically active disease were included. The search included all studies regardless of publication status or language. Study participants were pediatric or adult patients, of any age, previously diagnosed with UC or CD, with symptoms suggestive of endoscopic active disease, in which the presence or absence of active disease was confirmed by endoscopy. Studies that included healthy volunteers or patients with IBS as controls were also evaluated.** **Exclusion Criteria: see inclusion**	**Population: UC, CD and controls** **Intervention: measurement of fecal markers** **Comparison: time to flare**	**Primary: The o evaluate the diagnos reactive protein calprotectin (FC), an (SL) for assessr scopically defined c IBD.** **Secondary: -** **Results: Nineteen patients) were elig sensitivity and spe for CRP, FC, and S confidence interval (0.92 (95% CI 0.72–0 0.84–0.90) and 0.73 (and 0.82 (95% CI 0. (95% CI 0.62–0.89), was more sensitive diseases and was ulcerative colitis disease.** **Author's Conclusion FC, and SL are us their value in ma patients must be specific clinical cont**

Methodical Notes

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) (CON—105529) and the CIHR Institutes of Nutrition, Metabolism and Diabetes (INMD), and Infection and Immunity Health and Long-Term Care (HLTC3968FL-2010-2235).

COI: declared

Study Quality: flow chart shown

Heterogeneity: sensitivity, specificity, PPV, NPV provided

Publication Bias: Publication bias. No statistically significant risk of publication bias was observed f coefficient=−19.34, P=0.117; 95% CI: −44.96 to 6.27, FC: coefficient=−9.712078, P=0.085; 95% CI: −20.86 to 1.43, and 95% CI: −63.49 to 21.81)

Notes:

Qiu, Y. et al. Fecal calprotectin for evaluating postoperative recurrence of Crohn's disease: a meta-an Inflamm Bowel Dis. 21. 315-22. 2015

Evidence level/Study Types	P - I - C	Outcomes/Results
Evidence level: 1 **Study type: Meta-analysis of Prospective Studies** **Databases: PubMed, EMBASE, Web of Science, and the Cochrane Central Register of Controlled Trials** **Search period: 1966 to March 2014** **Inclusion Criteria: (1) studies in which FC was used to investigate suspected POR in CD, (2) raw data (for true-positive, false-positive, false-negative, and true-negative re-sults) that could be extracted or calculated from data in the original published study, and (3) studies that applied histopathological or ileocolonoscopic assessment as the reference standard.** **Exclusion Criteria: Studies were excluded if the crude rates of postoper- ative relapse or remission were not reported**	**Population: CD patients postoperative with endoscopy** **Intervention: surgery and endoscopy** **Comparison: postoperative recurrence dependent on calprotectin**	**Primary: Using meta-analysis, we aimed to evaluate the utility of FC as a noninvasive marker of recurrence in patients with CD who had undergone previous surgical resection** **Secondary: -** **Results: Ten articles met the inclusion criteria, and methodological quality was determined in detail for each study. The 10 studies presented FC levels in 613 postoperative CD patients. The pooled sensitivity and specificity values for assessing suspected endoscopic recurrence were 0.82 (95% confidence interval (CI), 0.73–0.89, 8 studies, n ¼ 391) and 0.61 (95% CI, 0.51–0.71), respectively. The overall positive and negative likelihood ratios were 2.11 (95% CI, 1.68–2.66) and 0.29 (95% CI, 0.197–0.44), respectively. The pooled sensitivity and specificity values for evaluating clinical relapse were 0.59 (95% CI, 0.47–0.71; 3 studies, n ¼ 183) and 0.88 (95% CI, 0.80–0.93), respectively. The overall positive and negative likelihood ratios were 5.10 and 0.47, respectively.** **Author's Conclusion: As a simple and noninvasive marker, FC is useful in evaluating recurrence of postoperative patients with CD**

Methodical Notes

Funding Sources: not shown

COI: none declared

Study Quality: selection flow shown

Heterogeneity: sensitivity, specificity calculated

Publication Bias: QUADAS-2 Risk of Bias Assessment performed and low

Notes:

Tham, Y. S. et al. Fecal calprotectin for detection of postoperative endoscopic recurrence in Crohn's di meta-analysis. Therap Adv Gastroenterol. 11. 1756284818785571. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type: systematic**	**Population: Crohns disease after**	**Primary: recurrence of disease** **Secondary: -**	**Global Studies of Using Fecal Bio Inflammatory Bowel Disease. Liu F, Lee SA, Riordan SM, Zhang**

review, meta-analysis Databases: A comprehensive literature search was conducted on 22 July 2017 using both PubMed and Embase databases. Search period: A comprehensive literature search was conducted on 22 July 2017 using both PubMed and Embase databases. Inclusion Criteria: (1) studies evaluating postoperative CD patients using both ileocolonoscopy and FC; (2) adult patients only; (3) studies that utilized RS for definition of endoscopic recurrence; (4) studies including at least 15 patients; (5) those published in full form in peer-reviewed literature. Exclusion Criteria: -	ICR Intervention: calprotectin Comparison: calprotectin, endoscopy	Results: A total of 54 studies were retrieved; 9 studies were eligible for analysis. Diagnostic accuracy was calculated for FC values of 50, 100, 150 and 200 µg/g. A significant threshold effect was observed for all FC values. The optimal diagnostic accuracy was obtained for FC value of 150 µg/g, with a pooled sensitivity of 70% [95% confidence interval (CI) 59–81%], specificity 69% (95% CI 61–77%), and DOR 5.92 (95% CI 2.61–12.17). The area under the SROC curve was 0.73. Author's Conclusion: FC is an accurate surrogate marker of postoperative endoscopic recurrence in CD patients. The FC cut-off 150 µg/g appears to have the best overall accuracy. Serial FC evaluations may eliminate or defer the need for colonoscopic evaluation in up to 70% of postoperative CD patients.	Front Med (Lausanne). 20 10.3389/fmed.2020.580803. eColle PMID: 33392214 Free PMC article. Ustekinumab Inhibits T Follicula Patients With Crohn's Disease. Globig AM, Sommer NP, Wild K, AK, Schulte LA, Schreiner R, Re Hofmann M, Thimme R, Boettler T, Cell Mol Gastroenterol He 10.1016/j.jcmgh.2020.07.005. Epub PMID: 32679193

Methodical Notes

Funding Sources: none

COI: declared

Study Quality: Data extraction and quality control were per- formed independently by two reviewers (YST, SF). A by consen- sus and involvement of the senior authors. Where additional data were required, the corresponding a contacted by email in an attempt to obtain the necessary data.

Heterogeneity: The I2 statistic was used to quantify heterogeneity between the included studies.
low

Publication Bias: Risk of bias and overall quality of the included studies was assessed using the quality ass studies (QUADAS)-2 scale.36 Statistical analyses in this study were car- ried out using the meta4diag,37 mad version 3.4.2.

Notes:

Zhuge, Y. et al. Fecal Calprotectin for predicting Relapse and Activity in Patients with Crohn's Disease: Hepatogastroenterol. 6. 116-124. 2016

Evidence level/Study Types	P - I - C	Outcomes/Results

Evidence level: 1 **Study type: meta-analysis** **Databases: Medline (PubMed), the Cochrane central register of controlled trials, EMBASE, PubMed, EMBASE, the Cochrane Database of Systematic Reviews, and DARE** **Search period: from 1966 to August 2014:** **Inclusion Criteria: Clinical studies that described the predictive roles of FC in monitoring activity or relapse of CD were eligible for inclusion. Other criteria for inclusion included studies with adult populations, articles written in English, and evaluating relationship between FC and CD.** **Exclusion Criteria: Studies not written in English, animal studies, studies without proper control setting, absence of abstract, insufficient data, or those focusing on quality of life were excluded.**	**Population: CD** **Intervention: calprotectin measurement** **Comparison: prediction of flare**	**Primary: We aimed to perform a meta-analysis of the prec fecal calprotectin (FC) in activity and relapse of Crohn's disea** **Secondary: -** **Results: A total of 1,252 CD patients from 18 different studi The pooled sensitivity and specificity of FC at a cutoff va predict activity of CD were 0.91 [95% confidence interval (C 0.47 (95% CI: 0.35–0.59) respectively. The pooled sensitivity FC at a cutoff value of larger than 150 μg/g to monitor relaps (95% CI: 0.67–0.82) and 0.71 (95% CI: 0.66–0.76) respectivel the summary receiver operating characteristic (SROC) detecting CD activity was 0.78 (50 μg/g), 0.88 (100 μg/g), 0.8 the diagnostic odds ratio (DOR) was 10.21 (50 μg/g), 10.20 (>150 μg/g) respectively.** **Author's Conclusion: As a simple and noninvasive marke predict the activity and relapse in CD patients, and the capaci CD activity was superior to its application in monitoring relap**

Methodical Notes

Funding Sources: none

COI: none

Study Quality: shown

Heterogeneity: Reference-positive patients/ total subjects were used to calculate the pretest probabil- ity of CD. FC in a certain study were extracted or calculated using appropriate contingency tables. If there were potential p studies with sensitivities or speci- ficities of 100%, then a value of 0.5 was added to all cells of trials that containe negative likelihood were determined as functions of these summary estimates; the derived estimates of sensit variances were also used to construct a summary receiver operating characteristic (SROC) curve.18 The area unde alternative global measure of test performance.18 Diagnostic odds ratio (DOR) and the area under the SROC evaluate the diagnostic performance of FC in patients with CD.

Publication Bias: Though we tried to avoid any possible bias, there are still several limitations in our meta-analysi present study had relatively high heterogeneity and bias of publication. The sources of heterogeneity and public populations, disease duration, treatment regimen, time of measuring FC, and cutoff value of FC. Second, the sar significantly. The pooled results were probably compromised due to the small number of eligible studies. Thir similar in most included studies, but the application of various scoring systems to assess CD activity was a pro scoring method should be established to minimize variation and provide a better accuracy. Last, a few studies fa information of interest.

Notes:

OXFORD (2011) Appraisal Sheet: RCT: 6 Bewertung(en)

Ankersen, D. V. et al. Individualized home-monitoring of disease activity in adult patients with inflamr recommended in clinical practice: A randomized-clinical trial. World J Gastroenterol. 25. 6158-6171. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type: RCT** **Number of Patient: 102** **Recruitung Phase: July 2015 to July 25 2016** **Inclusion Criteria: yes** **Exclusion Criteria: yes**	**Intervention: different monitoring** **Comparison: monitoring**	**Primary: Adult IBD patients were consecutively randomized to interventions (3M vs OD). Both intervention arms were screenin activity, quality of life and fatigue and were measuring medical c the constant care web-application according to the screening in 3M. Disease activity was assessed using home measured fecal and a disease activity score.** **Secondary: -** **Results: In total, 102 patients were randomized (n = 52/50 3M/O patients completed the 1-year study (n = 43 3M; n = 45 OD). No c two screening procedures could be found regarding medical co 0.58), fatigue (P = 0.86), quality of life (P = 0.17), mean time spen > 0.32), overall FC relapse rates (P = 0.49), FC disease courses relapse (P = 0.69) and remission (P = 0.88) during 1 year. Mediar (interquartile range) numbers of FC home-monitoring test-kits u were significantly different, 3M: 6.0 (5.0-8.0) and OD: 4.0 (2.0-9.0** **Author's Conclusion: The two eHealth screening procedures relapse and bringing about remission. However, the OD group used few per patient. Individualized screening procedures can be recomm adult IBD patients in clinical web-practice.**

Methodical Notes

Funding Sources: Calpro AS; Crohn Colitis patient society Denmark; and North Zealand University Hospital and Ferring Pharmaceuticals.

COI: decalred

Randomization: yes

Blinding: yes

Dropout Rate/ITT-Analysis: yes,

Notes:

Assa, A. et al. Proactive Monitoring of Adalimumab Trough Concentration Associated With Increased C With Crohn's Disease Compared With Reactive Monitoring. Gastroenterology. 157. 985-996.e2. 2019

Population	Intervention - Comparison	Outcom
Evidence level: 2 **Study type: Nonblinded, randomized controlled trial.** **Number of Patient: 78 children with CD.** **Recruitung Phase: July 2015 through December 201** **Inclusion Criteria: Patients recruited were biologic-naïve children (6–17years) with luminal CD who had responded to standard ADL induction at weeks 0 and 2, as indicated at week 4 by a reduction of Pediatric Crohn's Disease Activity Index (PCDAI) of**	**Intervention: In group 1 (proactive group), patients were assessed during each visit for clinical and biologic disease activity, while treating physicians were also informed of ADL TC for all patients within 2 weeks of sampling. ADL treatment was intensified based on plasmatic TC only, meaning that patients with ADL TC<5mg/mL were intensified regardless of disease activity (PCDAI, CRP, and calprotectin).** **Comparison: In group 2 (reactive group), patients were also assessed during each visit for clinical and biologic disease activity, but**	**Primary: study wa clinical all visits** **Seconda included remissio sustaine CRP calprote and at disconti**

at least 15 points from ADL initiation, or clinical remission(PCDAI<10 points). Exclusion Criteria: Patients were excluded in cases of prior exposure to anti-TNFa agents; current or previous bowel perforation; small bowel obstruction within the last 3 months; fixed non inflammatory stricture (thickened bowel wall with minimal or no enhancement oncross-sectional imaging); complicated or draining perianal fis-tula; previous malignancy; sepsis or active bacterial infection; previous surgical resection of the bowel, diagnosis of IBD-unclassified; or infection (actively tested in all patients) with hepatitis B, hepatitis C, tuberculosis or Clostridium difficile.	physicians were informed of the TC only in cases of clinical or biologic LOR, with subsequent intensification of ADL treatment only in patients with LOR and TC<5mg/mL, meaning that patients with LOR (either clinical and/or biologic) were intensified only if ADL TC was <5mg/mL. Patients in clinical and biologic remission were not intensified and their physicians were not informed of their TC	treatmen study p measure 8 to 72; a adverse Results: reached 40 in the respectiv Author's monitori concentr and inte higher r remissio (measuri loss of r

Methodical Notes

Funding Sources: The study was supported by an unrestricted educational grant by AbbVie Pharmaceutical.

COI: Amit Assa: Consultation and lectures fees from AbbVie; and research grants from AbbVie and Janssen. research grants, royalties, or honorarium from Janssen, Pfizer, Ferring, AbbVie, Takeda, Biogen, Neopharm, Celgene, Lilly, and Roche. Batia Weiss: Consultationfees from Janssen, and lecture fees from AbbVie. Ron Shaou from AbbVie and Janssen, and research grant from Janssen. Raanan Shamir: Research grant from AbbVie. The conflicts

Randomization: Randomization and coding were performed by a dedicated clinical trial assistant at the Schneider centers in blocks of 4 (1:1 ratiostratified by immunomodulators use and medical center).

Blinding: No blinding.

Dropout Rate/ITT-Analysis: Treatment termination in 5 (13%) in proactive group, 8 (20%) reactive group, respective

Notes:
In Hinblick auf PICO: Outcome nicht Zeit bis zum Remissionsverlust, sondern Steroid-freie Remission.

Boube, M. et al. Variation of faecal calprotectin level within the first three months after bowel resectio postoperative recurrence in Crohn's disease. Dig Liver Dis. . . 2020

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: RCT Number of Patient: 48 Recruitung Phase: November 2014 to September 2017	Intervention: yes Comparison: yes	Primary: The primary endpoint was endoscopic POR at 6 months defined by an endo Secondary: - Results: Among the 48 patients included, there was no significant difference of me 0.15), M1 (p = 0.44) and M3 (p = 0.28) between patients with or without endoscopic the first 3 months after surgery was significantly different between the patients w 0.021). The median variation between Fcal level at baseline and M3 (Fcal M3–M0) wa with endoscopic POR compared to those without POR (p = 0.01). Fcal M3–M0 > performances to predict endo- scopic POR at M6 (AUC = 0.73, sensitivity = 64.7%[41. 96.3], negative predic- tive value = 77.8%[57.5–91.4] and positive predictive value = 78 Author's Conclusion: Fcal variation within the first three months after ileocolonic res of early endoscopic POR in CD patients.

Inclusion Criteria: OK **Exclusion Criteria: OK**		

Methodical Notes

Funding Sources: PHRC inter-régional, Association François Aupetit, 3i Nature, CHU Clermont-Ferrand.

COI: None declared

Randomization: yes

Blinding: yes

Dropout Rate/ITT-Analysis: yes

Notes:

Colombel, J. F. et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randon Lancet. 390. 2779-2789. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type: A multicentre, randomised, open-label, active-controlled, two-group, phase 3, efficacy and safety trial.** **Number of Patient: 244 patients** **Recruitung Phase: Feb 11, 2011 until Nov 3, 2016** **Inclusion Criteria: Adult patients were enrolled in the study, age 18–75 years, with Crohn's disease at baseline and a diagnosis of ileal, colonic (including rectal), or ileocolonic Crohn's disease (as confirmed by endoscopy not >6 years before baseline). Key inclusion criteria were: (1) moderate to severe Crohn's disease at baseline, defined as Crohn's Disease Activity Index (CDAI)9scores of 220–450 for patients not receiving prednisone at baseline, 200–450 for patients receiving 20 mg prednisone (or less) for 7 days or more before baseline, and >150–450 for patients receiving more than 20 mg prednisone for 7 days or more before baseline; (2) active endoscopic disease, defined as a total Crohn's Disease Endoscopic Index of Severity (CDEIS) of more than 6 and a sum of CDEIS subscores of more than 6 in one or more segments with ulcers; and (3) CRP of 5 mg/L or more, FC of 250 µg/g or more, or both.**	**Intervention: In both groups, treatment was escalated in a stepwise manner, from no treatment, to adalimumab induction followed by adalimumab every other week, adalimumab every week, and lastly to both weekly adalimumab and daily azathioprine. This escalation was based on meeting treatment failure criteria.** **Comparison: Two treatment**	**Primary: The primary endpoint of the study was mucosal healing, defined as a CDEIS of less than after randomisation.** **Secondary: (1) deep remission (CDAI <150, CDEIS of draining fistula, discontinuation of corticostero remission (FC <250 µg/g, CRP <5 mg/L, and CDEIS overall CDEIS of less than 4 plus CDEIS of les complete endoscopic remission (CDEIS=0); and((decrease of >5 points)** **Results: The study's primary endpoint of mucosal ulcers at 48 weeks after randomisation was met control group compared with 37 (30%) patients in with a CMH-adjusted risk difference of 16·1% (95% proportion of patients in the tight control grou secondary endpoints 48 weeks after randomisation group: deep remission, with a CMH-adjusted risk p=0·014); biological remission, with a CMH-adjuste 25·0; p=0·006); and an overall CDEIS of less tha difference of 16·1% (3·9 to 28·3; p=0·010). No signi between the groups regarding the proportion of pa less than 4 plus a CDEIS of less than 4 in eve difference of 5·9% [95% CI –5·2 to 17·0]; p=0·299), (1·7% [–7·9 to 11·3]; p=0·728), or endoscopic r p=0·067;). A significantly higher proportion of remission in the tight control group than the c clinical remission (CDAI <150) at 11, 23, 35, and 4 significantly greater mean change from baseline in control group than in the clinical management gro mean change from baseline in CRP concentration between tight control and clinical management.** **Author's Conclusion: CALM is the first study to**

Exclusion Criteria: Exclusion criteria were previous or current use of biologics or immunomodulators, more than two previous courses of corticosteroids, or current use of corticosteroids for more than 3 months before screening. Patients with any fibrotic stricture (passable or non-passable and regardless of symptoms), draining perianal fistulas, or non-perianal fistulas were excluded.	**algorithms: tight control and clinical management.**	**an anti-tumour necrosis factor therapy on the basis with biomarkers in patients with early Crohn's dise endoscopic outcomes than symptom-driven decisi**

Methodical Notes

Funding Sources: Funding AbbVie

COI: J-FC reports personal fees from AbbVie, Amgen, Boehringer Ingelheim, Celgene Corporation, Celltri Pharmaceuticals, Genentech, Janssen, MedImmune, Merck & Co, Pfizer, Protagonist Therapeutics, PPM Se Therapeutics, Shire, Takeda, Theradiag, Intestinal Biotech Development, and Genfit outside the submitted work; a and Takeda outside the submitted work. RP reports grants and personal fees from AbbVie outside the submitted w Articles2788www.thelancet.comVol 390 December 23/30, 2017from AbbVie, Takeda, Vifor Pharma, Hospira, Jannse and Mundipharma; and reports grants from AbbVie, outside the submitted work. FB reports personal fe Pharmaceuticals, Janssen, Takeda, Pfizer/Hospira, and Mundipharma outside the submitted work; and repo Farmaceutici, Ipsen, and Roche outside the submitted work. TV reports fees from advisory board membership of reports personal fees from Takeda outside the submitted work. GN reports personal fees from AbbVie, MSD, Taked Pharma, and Merck & Co outside the submitted work. AA reports personal fees from AbbVie, AstraZeneca, B Pharmaceuticals, Hospira, Janssen, Eli Lilly, MSD, Mitsubishi-Tanabe Pharma, Mundipharma, Nikkiso, Pfizer, Sams Zambon outside the submitted work; and reports grants from MSD outside the submitted work. XH reports perso Kabi, Nutricia, MSD, Takeda, Vifor, Janssen, Arard, Laboratoires Mayoli-Spindler, Nestlé-Nutrition, and Ferri submitted work. ST reports personal fees from AbbVie, Centocor, Schering-Plough, Bristol-Myers Squibb, Chem Elan Pharma International, Genentech, Giuliani Pharma, Merck & Co, Takeda, Otsuka Pharmaceutical, PDL Bio Pharmaceuticals, Warner Chilcott, Proximagen, VHsquared, TopiVert, Ferring Pharmaceuticals, Celgene, Gla Enterome, UCB Pharma, Boehringer Ingelheim, Grünenthal, Sigmoid Pharma, Oxford University Hospitals, Uni Tillotts Pharma, Procter & Gamble, Vifor, Given Imaging, Sanofi, Wiley Blackwell, Elsevier, Oxford University Pres outside the submitted work; reports grants from AbbVie, Schering-Plough, Takeda, Eli Lilly, Warner C Pharmaceuticals, MSD, Procter & Gamble, IOIBD, Vifor, and Norman Collisson Foundation outside the submitted w educationfrom IBD2020, Crohns Colitis Cure, Schering-Plough, Takeda, Synthon, Eli Lilly, Celgene, GlaxoSmithKli Pharmaceuticals, MSD, Procter & Gamble, Vifor, ICHOM, and Warner Chilcott outside the submitted work. SD rep Actelion Pharmaceuticals, Alfa Wasserman, AstraZeneca, Cellerix, Cosmo Pharmaceuticals, Ferring Pharmace Johnson & Johnson, Millennium Pharmaceuticals, Merck & Co, Novo Nordisk, Nycomed, Pfizer, Pharmacosmos, UCB Pharma, and Vifor outside the submitted work. WR reports personal fees from Abbott Laboratories, AbbVie, A Janssen, Celltrion, Danone Austria, Elan, Falk Pharma GmbH, Ferring Pharmaceuticals, Immundiagnostik, Mitsubis Pharmaceutical, PDL, Pharmacosmos, PLS Educational, Schering-Plough, Shire, Takeda, Therakos, Vifor AstraZeneca, Avaxia Biologics, Roland Berger GmBH, Bioclinica, Biogen IDEC, Boehringer Ingelheim, Chemocentryx, Celgene, Covance, Ernst & Young, Galapagos NV, Genentech, Gilead Sciences, Grünenthal, ICON Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, LivaNova, Mallinckrodt Pharmace Pharmaceuticals, Nestle, Novartis, Ocera Therapeutics, Parexel, Philip Morris Institute, Pfizer, Procter & Gamb Robarts Clinical Trials, Sandoz, Second Genome, SetPoint Medical, Sigmoid, TiGenix, UCB Pharma, Zealand Pha the submitted work; and grants from AbbVie, AESCA, Centocor, Falk Pharma GmbH, Immundiagnostik, and MSD reports personal fees from AbbVie (during the conduct of the study and outside the submitted work), and Boehringer Ingelheim, Takeda, Atlantic Pharmaceuticals, Janssen, Bristol-Myers Squibb, Genentech, Nutrition S Kirin Pharma, Millennium Pharmaceuticals, Celgene Cellular Therapeutics, Santarus, Salix Pharmaceuticals, Ca Pharmaceuticals, Warner Chilcott, Gilead Sciences, Cosmo Pharmaceuticals, Ferring Pharmaceuticals, Sigmoid E AM-Pharma BV, Dr August Wolff, Avaxia Biologics, Zyngenia, Ironwood Pharmaceuticals, InDex Pharmaceuticals, N UCB Pharma, Orexigen Therapeutics, Luitpold Pharmaceuticals, Baxter Healthcare, Ferring Research Institute, A Shire, Ardelyx, Actavis, Seattle Genetics, MedImmune (AstraZeneca), ActoGeniX NV, Lipid Therapeutics, Eisai, Qu Pharmaceutical Industries, Eli Lilly, Chiasma, TiGenix, Adheron Therapeutics, Immune Pharmaceuticals, Celgene, Akros Pharma, Vascular Biogenics, Theradiag, Forward Pharma, Regeneron, Galapagos NV, Seres Therap Theravance Biopharma, Palatin Technologies, Biogen, and Western University (owner of Robarts Clinical Tria reports grants from AbbVie (during the conduct of the study, and outside the submitted work), Prometheus Lab Takeda, Atlantic Pharmaceuticals, Janssen, Bristol-Myers Squibb, Genentech, and Nutrition Science Partners; rep AbbVie; and reports patents for use of topical azathioprine to treat inflammatory bowel disorders (US 5691343), top to treat inflammatory bowel disorders (US 5905081), colonic delivery of nicotine to treat inflammatory bowel diseas US 5846983, 5889028, and 6166044; Mexico patent 209636; Europe patents 0954337 and 893998; Hong Kong p ZL97192177; Czech patent 293616; Canada patent 2246235), the use of azathioprine to treat Crohn's dise compositions for colonic administration (New Zealand patent 306062; Singapore patent 45647; Australia patent

intestinal absorption of nicotine to treat nicotine responsive conditions (Australia patent 718052; US 6238689), the thioguanine to treat colorectal adenomas (US 6166024), enema and enterically-coated oral dosage forms o pharmaceutical composition for the treatment of inflammatory bowel disease (US 7341741), and intestinal absorp responsive conditions (Canada patent CA2260909), and for obesity treatment and device (US 7803195 B2) that reports personal fees from AbbVie, Bristol-Myers Squibb, Johnson & Johnson, Merck & Co, Takeda, UCB Phar Pfizer, Celgene, Amgen, AstraZeneca, Robarts, outside the submitted work; and reports grants from AbbVie, Joh and MSD outside the submitted work. DH reports grants and personal fees from AbbVie, AstraZeneca, Janss Cellerix, Centocor, Chemocentryx, ELAN, Falk Pharma GmbH, Ferring Pharmaceuticals, Genentech, Giuliani Pharm Pharma, Otsuka Pharmaceutical, Novimmune, PDL BioPharma, Philips, Procter & Gamble, Roche, Schering-Plough UCB Pharma outside the submitted work; and reports grants from MSD, Centocor, Chemocentryx, Genentech Schering-Plough, Cytokine PharmaSciences, AM-Pharma, Vivify Health, Takeda, and Gilead outside the submitted AbbVie, Allergen, Biogen, Boehringer Ingelheim, Celltrion, Falk Pharma GmbH, Ferring Pharmaceuticals, Genentec Roche, Sandoz, Shire, and Takeda outside the submitted work. EN, BH, QZ, PM, JP, KW, AMR, and RBT report pe the submitted work; were AbbVie employees during writing of submitted work; and own AbbVie stock, options, or from AbbVie, Ablynx, Boehringer-Ingelheim, Celgene, Celltrion, and Galapagos NV outside the submitted work; and Covidien outside the submitted work. ML and AD declare no competing interests.

Randomization: 1:1 ratio. The patient number and group of each stratum were assigned by a central randomisatio (Chicago, IL, USA) using WebRando software for randomisation and ClinPhone, an interactive voice and we allocation. The subject randomisation schedule was generated by a designated person in the AbbVie statistics de in the rest of the study. The investigators and patients were masked to patient allocation and post-screening FC were open label.

Blinding: no

Dropout Rate/ITT-Analysis: 11 were enrolled but not randomly assigned, 61 patients did not complete the study.

Notes:
In Hinblick auf PICO Limitation: nicht alle Patienten bei Einschluss bzw. Randomisation in Remission.

D'Haens, G. et al. Increasing Infliximab Dose Based on Symptoms, Biomarkers, and Serum Drug Conc Clinical, Endoscopic, and Corticosteroid-Free Remission in Patients With Active Luminal Crohn's Disease 1351.e1. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: A proof-of-concept randomized double-blind controlled study. Number of Patient: 122 biologic-naïve adult patients with active CD. Recruitung Phase: July 2012 through September 2015 Inclusion Criteria: Patients recruited were adults with active luminal CD naive to biologics with an indication to start anti-TNF therapy in accordance with national guidelines and reimbursement criteria. Disease activity was confirmed by a Crohn's disease activity index (CDAI) >220 with objective signs of active inflammation (high-sensitivity CRP >5 mg/L and/or fecal calprotectin >250 µg/g) and visible ulcers at baseline ileocolonoscopy. Exclusion Criteria: Patients with an	Intervention: IFX was given intravenously at 5 mg/kg at weeks 0, 2, and 6 to all patients. Patients were randomized 1:1:1 at inclusion into 3 double-blind IFX maintenance regimens, administered every 8 weeks from week 14 to week 54 (end of the study period) as follows: IFX dose increase by increments of 2.5 mg/kg, maximally 2 times to a maximum dose of 10 mg/kg (DIS1) according to a prespecified algorithm, IFX dose increase by increments of 5 mg/kg, maximally 1 time, to a maximum dose of 10 mg/kg (DIS2) according to the same prespecified algorithm Comparison: IFX dose increase by 5 to 10 mg/kg if patients had a CDAI >220 at the current visit or a CDAI between 150 and 220 in the 2 weeks before the current visit in line with the registered label of IFX.	Primary: The primary corticosteroid-free remis between week 22 and 54 ulcers at week 54 and no abscess and no new fistu Secondary: Prespecified proportion of patients wit clinical remission (CDAI remission from week 14 (CDEIS <3) at weeks 12 (decrease of CDEIS score 54, IFX dose increase du µg/mL between weeks 1 use of infliximab, need f abscesses. Results: The primary week 22 and 54 off glu fistula and surgery and ileocolonoscopy was rea of 37, and 16 (40%) of 40 the control group, respec At week 12, 16 (36%), 6 (no ulcerations on endo control groups (P= .054); increased to 19 (42%), 2

imminent need for surgery, critical gastrointestinal stricture and obstructive symptoms, using corticosteroid therapy at doses >40 mg/d prednisolone or equivalent, active systemic infection, evidence of tuberculosis, usual contraindications to anti-TNF or immunosuppressants, or other serious concomitant diseases were excluded.		**respectively (P=.56). End was attained in 26 (58 patients in DIS1, DIS2, ar (P = .070) and in 23 (51%) by week 54 (P= 1 improvement (CDEIS redu (71%), 24 (65%), and 26 .88), and in 28 (62%), 23 (week 54 (P= .89).** **A sustained IFX serum c week 12 and 54 was obs 24 (60%) of the patients group, respectively (P= .3 patients continuously ab 2.9 µg/mL, 9.3 ± 5.2 µg/m DIS2, and the control g µg/mL, 4.3 ± 2.3 µg/mL, ar meeting that success cr measured at the end of t (22%), 6 (16%), and 5 (12 and control groups.** **Author's Conclusion: based on a combination serum drug concentr corticosteroid-free clini proportion of patients t symptoms alone.**

Methodical Notes

Funding Sources: This investigator-initiated trial was financially supported by Merck Sharp Dome and Janssen, wh drug. Buhlmann Laboratories, Switzerland, kindly provided materials for Quantum Blue rapid. measurements o Laboratories, San Diego, CA, performed the measurements of anti-infliximab antibodies at the end of the trial.

COI: Geert D'Haens declares grant support from Abbvie, Jansen, Merck Sharp Domem, and Pfizer; has served andJohnson, Merck Sharp Dome, Mundipharma, Pfizer, Prometheus Laboratories/ Nestle, and Sandoz; and rece Johnson and Johnson, Merck Sharp Dome, Mundipharma, and Pfizer. Severine Vermeire reports grant support Pfizer; lecture fees from Abbie, MSD, Takeda, Ferring, Falk Pharma, Hospira, and Tillotts; and consultancy fees fro Genentech/Roche, Shire, Pfizer, Galapagos, Mundipharma, Hospira, Celgene, Second Genome, and Janssen. Fili from Abbvie, Chiesi, Ipsen, MSD, and Roche;and speaker's and consultancy fees from Abbvie, Falk, Ferring, Jans Takeda, and Vifor. Anthony Buisson declares consulting fees for Abbvie, Hospira, and Takeda; and lecture fees fro Vifor Pharma, Sanofi-Aventis, and Ferring. Janneke vander Woude received grants from Abbvie, Jansen, Pfizer, Tra and consultancy fees from Abbvie, Falk, Ferring, Janssen, Mundipharma, MSD, Pfizer, Takeda, and Vifor. Edoua MSD, Abbvie, Takeda, Ferring, MSD, Chiesi, Mitsubishi Pharma, Hospira, Janssen, and Takeda; and is on the ad MSD, Takeda, Hospira, Mitsubishi Pharma, Celltrion, and Prometheus. Matthieu Allez received fees from Abbvie, Mayoli, UCB, Novartis, Genentech,Pfizer, Novo Nordisk, and Falk. Alexandre Aubourg reports consultancy fees fro Oldenburg reports grants from MSD, Abbvie, Takeda, Cablon, Ferring, and Falk. Ann Gils has served as a speake Pfizer, Takeda, and Abbvie, and as a consultant for UCB; and has received Investigator-Initiated Research Grants fr Bossuyt, Benjamin Pariente, Yoram Bouhnik, Jerome Filippi, Philippe Van Hootegem, Jacques Moreau, Denis Fra Mana, Laurent Peyrin-Biroulet, Hedia Brixi, Philip Caenepeel, MariekePierik, Sylvie Chevret, and David Laharie dec presentstudy. KU Leuven licensed the infliximab, adalimumab, and vedolizumab ELISA to apDia and R-Biopha antibodies mAb-IFX6B7 and mAb-ADM6A10 in the lateral flow assay to R-Biopharm.

Randomization: Randomization at week 0 was centrally performed online (ClinInfo, Lyon, France), balanced by which was not disclosed to investigators, and stratified by center, and previous use of azathioprine, 6-mercaptopu

Blinding: Serum samples for IFX concentrations were shipped to and measured at a single laboratory (KU Le results were entered in the same CRF but remained invisible for the sites.

Dropout Rate/ITT-Analysis: Thirty-five (29%) of the patients dropped out of the trial before week 54: 13 (29%) of 4 and 14 (35%) of 40 in the control group, after a median of 2.9, 4.6, and 5.8 months, respectively.

Notes:

In Hinblick auf PICO: Outcome nicht Zeit bis zum Remissionsverlust, sondern steroid-freie Remission. Andere Fa IFX-Spiegel) weitere mögliche Faktoren für Dosisanpassung.

Peyrin-Biroulet, L. et al. Clinical disease activity, C-reactive protein normalisation and mucosal healing in trial. Gut. 63. 88?95. 2014

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 **Study type: RCT, but not primary endpoint.** **Number of Patient: 188** **Recruitung Phase:** **Inclusion Criteria: subjects eligible for inclusion in this trial were adult CD patients with moderate-to-severe disease (CDAI >220 and <450 who have had an inadequate response to one or more conventional therapies (sulfasalazine, mesalamine, antibio-tics, budesonide or oral corticosteroids).** **9** **Exclusion Criteria: only mentioned in the primary publication of the study**	**Intervention: endoscopy** **Comparison: relationships between clinical disease activity, CRP normalisation and mucosal healing in Crohn's disease (CD**	**Primary: We investigated the relationships between normalisation and mucosal healing in Crohn's disease (CD). (primary of this study, but this one is analyzing data from the S primary aim)** **Secondary: -** **Results: 188 patients who had evaluable ileocolonoscopy with at baseline, CDAI scores and CRP values at baseline and wee of 136 patients (53%) who had a CDAI<150 at week 26 achieve patients (42%) achieved both CRP normalisation (CRP<0.8 mg in clinical remission. The positive predictive value (PPV) and n CDAI to detect mucosal healing using 150 as a cut-off respectively. The PPV and NPV of CDAI to detect mucosal using 150 as a cut-off for CDAI were 79% and 42%, respectively** **Author's Conclusion: Half the patients under azathioprine remission have endoscopic and/or CRP evidence of residual a with endoscopic and CRP normalisation have persistent clinic as scored by CDAI are not a reliable measure of the underlying**

Methodical Notes

Funding Sources: none declared

COI: declared

Randomization: in initial Sonic trial

Blinding: yes

Dropout Rate/ITT-Analysis: shown

Notes:

OXFORD (2011) Appraisal Sheet: Diagnostic Studies: 2 Bewertung(en)

Levesque, B. G. et al. A prospective cohort study to determine the relationship between serum infliximab patients with luminal Crohn's disease. Aliment Pharmacol Ther. 39. 1126-35. 2014

Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 3 **Study type: yes**	**Number of patients / samples: 327**	**Results: The mean CDAI score, which decreased 1.0 not** **correlate with the mean change in trough infliximab co**

	Reference standard: yes **Validation: yes** **Blinding: not clear** **Inclusion of clinical information: yes** **Dealing with ambiguous clinical findings: no**	**r = 0.099, P = 0.083), but was associated with the mear (r = 0.19, P < 0.001). Trough infliximab concentrations best predicted a ≥ 70 point increase in the CDAI betwe below 2.7–2.8 lg/mL best predicted CRP >5 mg/mL at t either visit decreased the proportion of patients with t levels compared with patients who were ATI negative (and 13.8% vs. 75.6% at visit 3; P < 0.001 for both comp** **Author conclusions: This prospective study confirms infliximab concentrations, inflammation and antibodies-to-infliximab. Infliximab t below 3 lg/mL may increase the likelihood of symptom inflammation**

Methodical Notes

Funding Sources: Industry

COI: declared

Notes:

Wright, E. K. et al. Measurement of fecal calprotectin improves monitoring and detection of recurrence of Gastroenterology. 148. 938-947.e1. 2015

Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 3 **Study type: Subgroup analysis (POCER)**	**Number of patients / samples: 135** **Reference standard: yes** **Validation: yes** **Blinding: no** **Inclusion of clinical information: Pocer Patients** **Dealing with ambiguous clinical findings: no**	**Results: Levels of FC were measured in 319 samples from 135 patients. T FC level decreased from 1347 mg/g before surgery at 6 months after surgery, but was higher in patient disease recurrence (based on endoscopic analysis score, i2) than in patients in remission (275 vs 72 m respectively; P < .001). Combined 6- and 18-month presence (r ¼ 0.42; P < .001) and severity (r ¼ 0.44; P < .001) of CD recurrence, but the CRP le CDAI score did not. Levels of FC greater than recurrence with 89% sensitivity and 58% specificity, and a negative predictive value (NPV) of means that colonoscopy could have been avoided patients. Six months after surgery, FC levels less th in patients in endoscopic remission predicted main remission (NPV, 79%). In patients with endoscopic at 6 months who stepped-up treatment, FC levels d from 324 mg/g at 6 months to 180 mg/g at 12 month mg/g at 18 months.** **Author conclusions: In this analysis of data from a prospective clinical trial, FC measurement has su sensitivity and NPV values to monitor for CD recurr intestinal resection. Its predictive value might be us identify patients most likely to relapse. After treatr can be used to monitor response to treatment. It predicts which patients will have c accuracy than CRP level or CDAI score.**

Methodical Notes

Funding Sources: Abbvie

COI:

Notes: prospektive Beobachtung bei POCER-STudie

OXFORD (2011) Appraisal Sheet: Prognostic Studies: 12 Bewertung(en)

Abiko, Y. et al. Serial changes of serum cytokines in Crohn's disease following treatment with adalimumab 357-62. 2014

Population	Intervention	Outcomes/Results
Evidence level: 5 **Study type:** **Number of Patient:** **Recruitung Phase:** **Inclusion Criteria:** **Exclusion Criteria:**	**Intervention:** **Comparison:**	**Primary:** **Secondary:** **Results:** **Author's Conclusion:**

Methodical Notes

Funding Sources:

COI:

Randomization:

Blinding:

Dropout Rate/ITT-Analysis:

Notes:

Allegretti, J. R. et al. Predictors of Clinical Response and Remission at 1 Year Among a Multicenter Cohort Bowel Disease Treated with Vedolizumab. Dig Dis Sci. 62. 1590-1596. 2017

Population	Intervention	Outcomes/Results
Evidence level: 3 **Study type: retrospective observational** **Number of Patient: 136** **Recruitung Phase: not indicated** **Inclusion Criteria: All patients C18 years of age who successfully completed induction therapy with VDZ and were receiving maintenance therapy for treatment of CD or UC were considered for inclusion in this study.** **Exclusion Criteria: Patients\18 years of age were excluded from this study. Any patient that experienced primary non-response to VDZ initiation was not eligible for this study. Primary non-response was defined as no clinical response to VDZ**	**Intervention: clinical data,** **Comparison: none**	**Primary: Our aim was t week 54 in inflammatory bow cohort of patients.** **Secondary: none** **Results: Among 136 t 76 (56%) demonstrated cl week 54. In univariate an concomitant initiation of immunomo 1.11–6.57), the addition 11.49, 3.16–41.75) and C 1.99–12.15) was asso clinical response or remissio**

during the initial 14-week induction period. Patients with prior history of surgery resulting in an ileal pouch anal anastomosis or permanent stoma were also excluded. No other exclusion criteria were defined.		hospitalization after VDZ induction was decreased odds of res (OR 0.22, 95% CI 0.05–0.88). addition of an immunon 2.15–32.26) remained si response or remission a Author's Conclusion: patients with IBD demonstrating pr addition of combination therapy significant predictor of week 54 in patients with

Methodical Notes

Funding Sources: none

COI: declared

Randomization: no

Blinding: no

Dropout Rate/ITT-Analysis: not shown

Notes:

Baert, F. et al. Antibodies to adalimumab are associated with future inflammation in Crohn's patients receiv therapy: a post hoc analysis of the Karmiris trial. Gut. 65. 1126-31. 2016

Population	Intervention	Outco
Evidence level: 4 **Study type: prospektive obernational** **Number of Patient:** **Recruitung Phase: 536** **Inclusion Criteria: All patients included in this study were Crohn's disease patients who were initially treated with IFX. Eight patients (6%) had no primary response. All other patients (94%) had an initial response and subsequently became intolerant to IFX (ie, having experienced an acute and/or delayed hypersensitivity reaction) or lost response (ie, worsening of clinical status as judged by the treating physician) despite dose adjustments. The present study included 148/168 (88%) patients of the Karmiris cohort, of whom serial serum samples were available for analysis of ADL concentration, ATA and different markers of**	**Intervention: trough level** **Comparison: Clinical information on treatment modalities was collected from the electronic charts of the patients. In addition to demographic data, the following were collected: disease duration, prior IFX use, concomitant use of immunomodulators (IMMs), induction scheme, need for dose escalation and reason for ADL discontinuation.**	**Prima adalim (ADL) limited perfor Karmi using assay focusi serum conce adalim inflam respo Secon Result patien media positi correl conce (p<0.0 showe 4 AD signifi**

inflammation (see below). **Exclusion Criteria: -**		**the f (HR=2 to 111 treatm preve 95% C 0.86; showe negati ADL c (p=0.0 (p=0.0 The n serum conce indep with p=0.0 ATA disco ADL (OR=3 1.039 Autho detect Risk lower ADL c on IMI ADL higher level a**

Methodical Notes

Funding Sources: none

COI: declared

Randomization: no

Blinding: no

Dropout Rate/ITT-Analysis: no

Notes:

Cornillie, F. et al. Postinduction serum infliximab trough level and decrease of C-reactive protein leve sustained response to infliximab: a retrospective analysis of the ACCENT I trial. Gut. 63. 1721-7. 2014

Population	Intervention	Outcomes/Results
Evidence level: 3 **Study type: post hoc analysis of RCT** **Number of Patient: 573** **Recruitung Phase: 2/1999 to 3/2001** **Inclusion Criteria: Patients included in this analysis were responders at week 14; all received a**	**Intervention: none** **Comparison: trough levels**	**Primary: To carry out a post Crohn's Disease Clinical Tria New Long-term Treatment R evaluate the association bet trough levels and C-reactive 14 weeks of induction treatm long-term response (Crohn's decrease ≥70 points and red baseline).**

full induction schedule of infliximab 5 mg/kg infusions given at weeks 0, 2 and 6. Exclusion Criteria: only those excluded in ACCENT I		Secondary: none Results: After induction wit (37/147) and 33% (47/144) of 14 response to infliximab 5 c administered every 8 weeks through week 54. Median we patients with and without du infliximab 5 mg/kg were 4.0 a (p=0.0331). Optimal predicto response to maintenance inf 14 trough level ≥3.5 mg/mL a (ORs (95% CI), 3.5 (1.1 to 11. respectively, in patients with (>8.0 mg/L); area under the R both predictors. A ≥3.5 mg/m serum level did not predict c 10 mg/kg maintenance inflix Author's Conclusion: Pa response to maintenance infliximab 5 postinduction trough levels sustained response. Serum ≥3.5 mg/mL and ≥60% CRP c associated with durable sus

Methodical Notes

Funding Sources: industry

COI: declared

Randomization: yes

Blinding: yes

Dropout Rate/ITT-Analysis: yes (in initial study)

Notes:

Gutiérrez, A. et al. Gut Bacterial DNA Translocation is an Independent Risk Factor of Flare at Short T Disease. Am J Gastroenterol. 111. 529-40. 2016

Population	Intervention	Outcomes/Results
Evidence level: 3 Study type: prospektive observational Number of Patient: 288 Recruitung Phase: unclear Inclusion Criteria: Consecutive patients diagnosed with Crohn’s disease and controlled	Intervention: Blood bactDNA Comparison: marker for flare	Primary: The primary endpoint was time--to--relapse as evaluated by CDAI>150 in the following 6 months. BactDNA in blood,

at three hospitals in the area of Alicante, Spain, who were in remission, as determined by CDAI<150 were included in this prospective, observational multicenter study. The diagnosis of CD was established according to standard clinical, endoscopic, histological and radiographical criteria 30. Patients treated with antibiotics in the previous 4 weeks, patients with signs of active infection and those who refuse to sign informed consent to		the NOD2 genotype and serum cytokine levels were determined at baseline. Secondary: - Results: A total of 288 patients were included. BactDN detected in 98 patients (34.0%). A variant-NOD2 genoty (39.6%). Forty patients (14%) relapsed during follow-up. Multiva bactDNA as an independent risk factor of flare (hazard ratio (HR) 8 interval (CI)). Hospitalization, surgery, switch of treatment, initiati necrosis factor (TNF) therapy, steroids initiation, and increased fecal calpr associated with bactDNA at baseline. A logistic regression anal independent and significant predictive factor of hospitalization (odds ratio (OR) 1 startup (OR 8.5 (2.7-27.1); P<0.001), and switch of treatment (OR 3.5 (1 relationship was observed between bactDNA and mucosal lesions admission. Serum pro-inflammatory cytokines were significantly increas variant-NOD2 genotype. The combination of both factors induced c higher percentage of patients on intensified anti-TNF therapy. Author's Conclusion: BactDNA is an independent risk relapse at 6 months in CD patients. BactDNA is also i increased risk of hospitalization, switch of treatment, and steroids initia

participate in the study were excluded. Twenty--five healthy controls were included in the study of NOD2 allelic variants distribution. Exclusion Criteria: not clear		

Methodical Notes

Funding Sources: Abbvie, Feder Program

COI: declared

Randomization: no

Blinding: no

Dropout Rate/ITT-Analysis: no

Notes:

Louis, E. et al. Maintenance of remission among patients with Crohn's disease on antimetabolite thera stopped. Gastroenterology. 142. 63-70 e5; quiz e31. 2012

Population	Intervention	Outcomes/Results
Evidence level: 3 Study type: prospective multicenter cohort study Number of Patient: 115 Recruitung Phase: March 2006 to December 2009 Inclusion Criteria: Eligible patients were at least 17 years of age and had received at least 1 year of therapy with scheduled infliximab and an antime- tabolite agent (azathioprine, 6-mercaptopurine, or methotrexate) for active luminal Crohn’s disease. At least 2 infusions of infliximab had to have been administered during the past 6 months. The dose of the antimetabolite agent (azathioprine Exclusion Criteria: a history of severe acute or delayed infusion reaction to infliximab, initial indication for infliximab being predominantly fistulizing perianal disease without signif- icant luminal disease, persistence of active fistulizing disease, predominant jejunal or proximal ileal lesions, an ostomy, severe extraintestinal manifestations, and pregnancy or lactation	Intervention: termination of infliximab treatment Comparison: new flare of disease over time	Primary: We assessed tl therapy was discontinu maintenance therapy wit factors associated with r Secondary: - Results: After a median 52 of the 115 patients e relapse rate was 43.9% Author's Conclusion: A with Crohn’s disease wh with infliximab and an a a relapse within 1 year af However, pa- tients witl identified using a comb markers.

Methodical Notes

Funding Sources: The GETAID received unrestricted study grants from the Association François Aupetit and the Gastroentérologie.

COI: declared

Randomization: no

Blinding: no

Dropout Rate/ITT-Analysis: yes shown

Notes:

Meuwis, M. A. et al. Serum calprotectin as a biomarker for Crohn's disease. J Crohns Colitis. 7. e678-83. 20

Population	Intervention	Outcomes/Results
Evidence level: 3 **Study type: prospective cohort trial** **Number of Patient: 115** **Recruitung Phase: 2006 to 2009** **Inclusion Criteria: Patients who were included in the study were in clinical remission with a CDAI b 150 under a combined treatment with infliximab (IFX) and anti-metabolites (azathi- oprine (N2 mg/kg), 6-mercaptopurine (N1.5 mg/kg) or meth- otrexate (N 15 mg weekly)) for at least one year and had been corticosteroid-free over the last 6 months.** **Exclusion Criteria: -**	**Intervention: stop of infliximab** **Comparison: time to relapse**	**Primary: The aim was to evaluate the value of serum Crohn's disease.** **Secondary: -** **Results: Medianserumcalpro 125,000ng/mL)inCrohndisease patients as compared witl ng/mL) in controls (P b 0.0001). Serum calprotectin wa disease (median = 19,584 ng/mL) than for inactive disea 0.0001). Serum calprotectin correlated with hsCRP (r = 0 0.4442, P b 0.0001), but not with CDEIS, on the contrary 0.5515, 0.2577 with P b 0.0001, P b 0.0001, P = 0.01 analysis, serum calprotectin used as a discrete va appeared complementary to hsCRP (N 5 mg/l) and fe predict relapse after infliximab withdrawal (P = 0.0173 3.561 and 4.120).** **Author's Conclusion: As a CD biomarker, serum calp hsCRP. It is also complementary to fecal calprotectin and after infliximab withdrawal.**

Methodical Notes

Funding Sources: Financial support for the STORI trial was provided by the SNFGE and the association François A

COI: none

Randomization: no

Blinding: no

Dropout Rate/ITT-Analysis: indicated

Notes:

Molander, P. et al. Does fecal calprotectin predict short-term relapse after stopping TNF?-blocking agents i patients in deep remission?. J Crohns Colitis. 9. 33-40. 2015

Population	Intervention	Outcomes/Results
Evidence level: 3 **Study type: Prospective multicenter study**	**Intervention: Stop of infliximab**	**Primary: This prospective multicenter study e calprotec tin (FC) concentrations after stop predict clinical or endoscopic relapse.**

Number of Patient: 52 **Recruitung Phase: 02/2010 to 06/2012** **Inclusion Criteria: Eligible patients were over 18 years of age, had established IBD diagnoses, had received TNFα-blocking mainte- nance therapy for at least 11 (median 16, range 11–78) months, and had been in corticosteroid-free remission over the previous 6 months before the inclusion. The maintenance therapy was unaltered during the prospective follow-up after discontinuation of TNFα-blocking therapy.** **Exclusion Criteria: The exclusion criteria included escalation of TNFα-blocking agents during the last six months, history of relapse after stopping TNFα-blocking agents, perianal disease with no other effective medication available, severe arthritis as a concomitant indication for TNFα-blocking therapy, and pregnancy**	**treatment** **Comparison: one cohort, comparison flare or not**	**Secondary: we evaluated the impact of histol risk** **Results: Of 52 enrolled patients, 49 (16 colitis/IBD unclassified) provided the stool sa the study group. During the followup, 15/49 (3 remained in remission. Patients relapsing s levels for a median of 94 (13–317) days before in median FC levels was seen 2 (p = 0.0014), 4 months before endoscopic relapse. Consta during the followup were highly predictive remission. Normal FC concentrations in associated with histological remission.** **Author's Conclusion: FC seems to increas clinical or endoscopic relapse, suggesting tha marker for predicting and identifying patier clinical practice.**

Methodical Notes

Funding Sources: his study was supported by grants from the Helsinki University Central Hospital Research Fu Foundation, Mary and George C. Ehrnrooth Foundation, Finnish Foundation for Gastroenterological Research, Foundation for Pediatric Research, and an unrestricted grant from Merck & Co., Inc. Finland.

COI: declared

Randomization: no

Blinding: no

Dropout Rate/ITT-Analysis: shown

Notes:

Reinisch, W. et al. Association of Biomarker Cutoffs and Endoscopic Outcomes in Crohn's Disease: A CALM Study. Inflamm Bowel Dis. . . 2020

Population	Intervention	Outcomes/Results
Evidence level: 3 **Study type: post-hoc analysis of RCT** **Number of Patient: 244** **Recruitung Phase: indicated in primary publication of CALM**	**Intervention: tight versus conventional monitoring** **Comparison: he association between endoscopic end points and biomarker cutoffs was performed using χ2 test.**	**Primary: Primary endpoint of CALM CDEIS <4 and no deep ulcers 48 weeks after sponse was defined as CDEIS decrease >5 from baseline** **The purpose of this post hoc analysis of CALM was to identify drivers of treatm association between biomarker cutoff concentrations and endoscopic end points.** **Secondary: -** **Results: The proportion of patients who achieved the primary end point CDEI significantly greater for those with FC <250 µg/g (74%; P < 0.001), with an additi association of FC <250 µg/g with improved endoscopic outcomes was independent greatest association was observed for ileocolonic disease. Fecal calprotectin <250 µg gave a sensitivity/specificity of 72%/63% and positive/negative predictive values of deep ulcers 48 weeks after randomization.**

study **Inclusion Criteria: in detail described in the original publication CALM** **Exclusion Criteria: in detail described in the original publication CALM**		**Author's ThisposthocanalysisofCALMdemonstratedthatacutoffofFC<250µg/gisausefulsurroga**

Methodical Notes

Funding Sources: Abbvie

COI: declared

Randomization: initial CALM study yes

Blinding: yes

Dropout Rate/ITT-Analysis: shown in flow chart

Notes: Posthof of RCT

Reinisch, W. et al. C-reactive protein, an indicator for maintained response or remission to infliximab in pa post-hoc analysis from ACCENT I. Aliment Pharmacol Ther. 35. 568-76. 2012

Population	Intervention	Outcomes/Results
Evidence level: 1 **Study type: post-hoc analysis of RCT** **Number of Patient: 573** **Recruitung Phase: 26.2.1999 to 15.3.2001** **Inclusion Criteria: explained in original ACCENT I publication**	**Intervention: Infliximab; CRP** **Comparison: Clinical outcome dependent on CRP**	**Primary: Serum C-reactive protein (CRP) levels at baseline and after infliximab inc assessed as predictors for maintained response or remission through 54 weeks of tr disease who responded to induction therapy.** **Secondary: -** **Results: A significant association was observed between baseline CRP levels and m percent of patients with baseline CRP ≥ 0.7 mg/dL vs. 22.0% with CRP < 0.7 mg/dL n CRP normalisa- tion during infliximab treatment (decrease from 0.5 mg/dL at basel resulted in higher probability of maintained response (P < 0.001) or remission (P = 0 were associated with main- tained response (56.6% of patients with CRP < 0.5 mg/dl 0.005). No optimal predictive CRP cut-off point was observed.** **Author's Conclusion:** **High baseline CRP levels increased the likelihood of maintained remission. Nor increased the likelihood of maintained response or remission during 1 year of infliximab**

Exclusion Criteria: explained in original ACCENT I publication		

Methodical Notes

Funding Sources: This study was funded in full by Schering-Plough, a subsidiary of Merck & Co. (Kenilworth, NJ Development, LLC (Spring House, PA, USA). Writing support was provided by Michaela Scheiner, a consultant mec an employee of the Medical Affairs Publication
Group, Janssen Biotech, Inc. Critical statistical review was provided by Yinghua Lang, an employee of Jans- ser and critical clinical review of the manuscript was provided by Freddy Cor- nillie, an employee of Medical Affair Biologics Europe.

COI: declared

Randomization: yes

Blinding: yes

Dropout Rate/ITT-Analysis: shown

Notes:

Waljee, A. K. et al. Development and Validation of Machine Learning Models in Prediction of Remission Severe Crohn Disease. JAMA Netw Open. 2. e193721. 2019

Population	Intervention	Outcomes/Results
Evidence level: 1 **Study type: cohort study** **Number of Patient: 401** **Recruitung Phase: 2011 to 2015** **Inclusion Criteria: The original clinical trial cohort had 1409 participants, 668 of whom were either randomized to placebo or lost to follow-up by week 8 of the trial and therefore excluded. The remaining 741 participants received ustekinumab at week 8. Of these, 462 participants had CRP measurements of 5 mg/L or higher at enrollment, suggesting active disease, and 61 participants were excluded for missing values. The final cohort comprised 401 participants, whose data were used for the week-8 model and sensitivity analyses (eTable in the Supplement).** **Exclusion Criteria: The baseline model excluded 30 additional patients for missing baseline laboratory tests and included 371 patients**	**Intervention: Random forest methods were used in building 2 models for predicting Crohn disease remission, with a CRP level lower than 5 mg/dL as a proxy for biological remission, beyond week 42 of ustekinumab treatment. The first model used only baseline data, and the second used data through week 8.** **Comparison: machine learning for prediction of response to ustekinumab**	**Primary: To identify patients with Crohn responders to ustekinumab before committing Randomforestmethodswereusedinbuilding2mo disease remission, with a CRP level lower biological remission, beyond week 42 of us model used only baseline data, and the second** **Secondary: -** **Results:** **Intotal,401participants,withamean(SD)ageof36 were included. The week-8 model had a mean a characteristic curve (AUROC) of 0.78 (95% CI, 27 of 55 participants (49.1%) classified as li achieved success with a CRP level lower than participants (10.8%) classified as likely to hav outcome. In the full cohort, 87 patients (21.7% 42. A prediction model using the week-6 albu of 0.76 (95% CI, 0.71-0.82). Baseline ustekinum the model's prediction performance.** **Author's Conclusion: Inpatientswithactiv laboratory data before week 8 of treatment identification of likely nonresponders to ust costly drug-level monitoring.**

Methodical Notes

Funding Sources: This study was supported by career development grant CDA 11-217 and merit review award IIR

of Veterans Affairs Health Services Research and Development Service (Dr Waljee), by grant R01 GM097117 from (Drs Higgins and Waljee), and by grant T32AR007080-38 from the University of Michigan (Dr Wallace).
Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, managem of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publicati

COI: declared

Randomization: initial trials

Blinding: initial trials

Dropout Rate/ITT-Analysis: shown

Notes:

Wright, E. K. et al. Comparison of Fecal Inflammatory Markers in Crohn's Disease. Inflamm Bowel Dis. 22. 1

Population	Intervention	Outcomes/Results
Evidence level: 3 **Study type: prospective, randomized controlled trial** **Number of Patient: 135** **Recruitung Phase: indicated in the primary publication of the POCER trial** **Inclusion Criteria: indicated in the primary publication of the POCER trialPatients may have had previous upper gut disease, but to be included in the study, no residual upper gut disease was present at the time of surgery. Patients were permitted to be on proton pump inhibitor therapy for symptomatic reflux disease. Patients were not permitted to be on aspirin or non steroidal anti-inflammatory drugs (NSAIDs) therapy and were instructed to avoid these during the study.** **Exclusion Criteria: indicated in the primary publication of the POCER trial**	**Intervention: sugery, endocopy, fecal markers** **Comparison: recurrence of disease**	**Primary: We evaluated fecal calprote S100A12 (FS) using endoscopic validatic progression of CD after intestinal resectio** **Secondary: -** **Results: FC, FL, and FS concentratior (median: 1347, 40.9, and 8.4 mg/g, postoperatively, marker concentrations d were higher in recurrent disease than rer 0.001; 5.7 versus 1.6 mg/g, P ¼ 0.007; 2.0 135 mg/g, FL . 3.4 mg/g, and FS . 1 recurrence (score $ i2) with a sensit predictive value (NPV) of 0.87, 0.66, and 0.12, and 71%, respectively. FC and FL presence and severity of endoscopic re CDAI did not.** **Author's Conclusion: FC was the optir disease activity in postoperative CD and FL offered modest sensitivity for detect S100A12 was sensitive but had low specif**

Methodical Notes

Funding Sources: AbbVie, Gutsy Group, Gandel Philanthropy, Angior Foun- dation, Crohn's Colitis Austra Endowment Fund provided research support. Bülhmann provided fCAL testing kits for Calprotectin. Techlab Lactoferrin. The National Health and Medical Research Council (NHMRC) supported E. K. Wright, M. A. Kamm, and

COI: declared

Randomization: POCER trial yes

Blinding: yes

Dropout Rate/ITT-Analysis: shown

Notes:

Literatursammlung:

AG 2 akuter Schub-Frage 3

Inhalt: 5 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
de Groof, E. J. 2019	1	randomized controlled trial
Fay, S. 2017	3	observational retrospective study
Tham, Y. S. 2018	1	systematic review, meta-analysis
Yung, D. E. 2017	1	Systematic Review and Meta-Analysis
Zarubova, K. 2017	3	prospective observational

OXFORD (2011) Appraisal Sheet: Systematic Reviews: 2 Bewertung(en)

Tham, Y. S. et al. Fecal calprotectin for detection of postoperative endoscopic recurrence in Crohn's disease: systematic review and meta-analysis. Therap Adv Gastroenterol. 11. 1756284818785571. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: systematic review, meta-analysis Databases: A comprehensive literature search was conducted on 22 July 2017 using both PubMed and Embase databases. Search period: A comprehensive literature search was conducted on 22 July 2017 using both PubMed and Embase databases. Inclusion Criteria: (1) studies evaluating postoperative CD patients using both ileocolonoscopy and FC; (2) adult patients only;	Population: Crohns disease after ICR Intervention: calprotectin Comparison: calprotectin, endoscopy	Primary: recurrence of disease Secondary: - Results: A total of 54 studies were retrieved; 9 studies were eligible for analysis. Diagnostic accuracy was calculated for FC values of 50, 100, 150 and 200 µg/g. A significant threshold effect was observed for all FC values. The optimal diagnostic accuracy was obtained for FC value of 150 µg/g, with a pooled sensitivity of 70% [95% confidence interval (CI) 59–81%], specificity 69% (95% CI 61–77%), and DOR 5.92 (95% CI 2.61–12.17). The area under the SROC curve was 0.73. Author's Conclusion: FC is an accurate surrogate marker of postoperative endoscopic recurrence in CD patients. The FC cut-off 150 µg/g appears to have the best overall accuracy. Serial	Liu F et al. Front Med (Lausanne). 2020 Dec 17;7:580803 Klobig AM et al. Cell Mol Gastroenterol Hepatol. 2021;11(1):1-12.

(3) studies that utilized RS for definition of endoscopic recurrence; (4) studies including at least 15 patients; (5) those published in full form in peer-reviewed literature. Exclusion Criteria: -		**FC evaluations may eliminate or defer the need for colonoscopic evaluation in up to 70% of postoperative CD patients.**	

Methodical Notes

Funding Sources: none

COI: declared

Study Quality: OK

Heterogeneity: The I2 statistic was used to quantify heterogeneity between the included studies. Calculations provided

Publication Bias: Risk of bias and overall quality of the included studies was assessed using the quality assessment of diagnostic accuracy studies (QUADAS)-2 scale.36 Statistical analyses in this study were carried out using the meta4diag,37 mada38 and INLA39 packages in R version 3.4.2.

A summary of the QUADAS-2 assessment is given in Table 3. The included studies were gen- erally of good quality with mostly low risk of bias.

Notes:

Yung, D. E. et al. Capsule Endoscopy, Magnetic Resonance Enterography, and Small Bowel Ultrasound for Evaluation of Postoperative Recurrence in Crohn's Disease: Systematic Review and Meta-Analysis. Inflamm Bowel Dis. 24. 93-100. 2017

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Systematic Review and Meta-Analysis Databases: PubMed and Embase databases Search period: on April 12, 2017 Inclusion Criteria: studies comparing CE, US, and MR enterography with ileocolonoscopy; • studies that included patients evaluated for postoperative endo- scopic recurrence; • studies that utilized RS for definition of endoscopic recurrence; • published in full form in peer-reviewed literature. Exclusion Criteria: Data	**Population: CD, post-operative Intervention: CE, MRE, and US with IC Comparison: CE, MRE, and US with IC for disease activity**	**Primary: The aim of our meta-analysis was to evaluate the accuracy of those modalities for detection of endoscopic recurrence in postoperative CD patients. Secondary: - Results: A total of 135 studies were retrieved; 14 studies were eligible for analysis. For CE, the pooled sensitivity was 100% (95% CI, 91%–100%), specificity was 69% (95% CI, 52%–83%), DOR was 30.8 (95% CI, 6.9–138), and AUC was 0.94. MRE had pooled sensitivity of 97% (95% CI, 89%–100%), specificity of 84% (95% CI, 62%–96%), DOR of 129.5 (95% CI, 16.4–1024.7), and AUC of 0.98. US had pooled sensitivity of 89% (95% CI, 85%–92%), specificity of 86% (95% CI, 78%–93%), DOR of 42.3 (95% CI, 18.6–96.0), and AUC 0.93. Author's Conclusion: CE, MRE, and**	**Sommer K, Wiendl M, Müller TM, Heidbreder K, Voskens C, Neurath MF, Zundler S. Front Med (Lausanne). 2021 Mar 23;8:643973. Quaresma AB, Baraúna FDSB, Teixeira FV, Saad-Hossne R, Kotze PG. J Clin Med. 2021 Feb 11;10(4):710. Hanzel J, Almradi A, Istl AC, Yang ML, Fleshner KA, Parker CE, Guizzetti L, Ma C, Singh S, Jairath V. Dig Dis Sci. 2021 Feb 26. Zanelli J, Chandrapalan S, Patel A, Arasaradnam RP. Therap Adv Gastroenterol. 2020 Aug 18;13:1756284820937089. Quaresma AB, Yamamoto T, Kotze PG.**

extraction and quality control were performed independently by 2 reviewers (OH, UK) using a predetermined spreadsheet form. Any disagreements were resolved by discussion. When 2 different techniques were evaluated for the same modality, the data were extracted separately per each modality.		**US provide accurate assessment of postoperative endoscopic recurrence in CD. These modalities should gain wider use for detection of postoperative recurrence; the prognostic value of those diagnostic findings merits evaluation in further prospective studies.**	**Therap Adv Gastroenterol. 2020 Jul 16;13:1756284820931738.**

Methodical Notes

Funding Sources: none

COI: none

Study Quality: The quality assessment of diagnostic accuracy studies (QUADAS)–2 scale was used to evaluate the quality of the included studies.13 Ileocolonoscopy was used as the "reference standard" for the "index tests" CE/MRE/US. Statistical analy- ses were conducted using Meta-DiSc 1.4 software14 (Ramon y, Cajal Hospital, Madrid, Spain).
--> general good quality

Heterogeneity: Study heterogeneity was estimated using the I2 statistic,

MRI: The included studies had low heterogeneity.
US: selection to achieve reduced heterogeneity

Publication Bias: Il but 1 study17 were of European origin. Included studies were gener- ally of good quality, with mostly a low risk of bias

Notes:

OXFORD (2011) Appraisal Sheet: RCT: 1 Bewertung(en)

de Groof, E. J. et al. Cost-effectiveness of laparoscopic ileocaecal resection versus infliximab treatment of terminal ileitis in Crohn's disease: the LIR!C Trial. Gut. 68. 1774-1780. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 1 **Study type: randomized controlled trial** **Number of Patient: 143 randomized,** **Recruitung Phase: MAy 2008 to October 2015** **Inclusion Criteria: adult patients with crohn's disease of the terminal ileum who failed >3 months of conventional**	**Intervention: a) ileocecal resection b) Infliximab** **Comparison: a) ileocecal resection b) Infliximab**	**Primary: quality of life and costs** **Secondary: costs** **Results: laparoscopic ileocaecal resection is a cost- effective treatment option compared with infliximab.** **No difference in Quality of life** **Author's Conclusion: In conclusion, this multicentre randomised trial showed that in patients with ileocaecal Crohn's disease in whom conventional therapy has failed, laparoscopic ileocaecal resection is associated with significantly more QALYs and higher IBDQ scores than infliximab at substantially lower costs. Therefore, laparoscopic ileocaecal resection is considered to be more**

immunomodulators or steroids without signs of critical strictures **Exclusion Criteria: Patients with a prior ileocaecal resection, an affected segment >40cm, abdominal abscesses or fluid collections, or an American Society of Anesthesiologists Score of III/IV were excluded**		**cost-effective as compared with infliximab treatment in this group of patients.**

Methodical Notes

Funding Sources: public

COI: declared

Randomization: yes

Blinding: no

Dropout Rate/ITT-Analysis: na

Notes:

OXFORD (2011) Appraisal Sheet: Prognostic Studies: 2 Bewertung(en)

Fay, S. et al. The Association Between Drug Levels and Endoscopic Recurrence in Postoperative Patients with Crohn's Disease Treated with Tumor Necrosis Factor Inhibitors. Inflamm Bowel Dis. 23. 1924-1929. 2017

Population	Intervention	Outcomes/Results
Evidence level: 3 **Study type: observational retrospective study** **Number of Patient: 73** **Recruitung Phase: 2009-2016** **Inclusion Criteria: The study cohort included consecutive patients with CD who underwent bowel resection with ileocolonic anastomosis resection and were treated with anti-TNF agents postoperatively.** **Exclusion Criteria: na**	**Intervention: trough levels Endoscopy** **Comparison: Endoscopic outcome in relation to anti-TNF trough level**	**Primary: The primary outcome of the study was a correlation of SER with anti-TNF trough levels.** **Secondary: -** **Results: Seventy-three consecutive patients (32-infliximab, 41-adalimumab) were included in the study. The colonoscopies were performed after a median of 15 (7–43) months after surgery and 8 (6–15) months from treatment onset. SER was demonstrated in 26/73 (35.6%) of the patients. The need for dose optimization, as well as trough infliximab levels (2.4 mg/mL [0.45–4.1] versus 1.1 (0–0.6), P ¼ 0.008) and presence of antidrug antibodies (1/18 [5.6%] versus 10/14 [71.4%], P ¼ 0.0001) were significantly associated with a risk of SER. The optimal cutoff infliximab level for prediction of SER was 1.8 mg/mL. No association between adalimumab levels and antiadalimumab antibodies was demonstrated.** **Author's Conclusion: our study demonstrates that lower IFX levels and presence of anti-IFX antibodies are associated with the likelihood of significant anastomotic inflammation in postoperative CD. It is possible that**

		relatively low IFX levels are sufficient to control anastomotic inflammation. No such association was demonstrated for ADA. Our results merit confirmation and validation in a large prospective setting

Methodical Notes

Funding Sources: not declared

COI: declared

Randomization: no

Blinding: no

Dropout Rate/ITT-Analysis: no

Notes: consecutively recruited patients

Zarubova, K. et al. Endoscopic Recurrence 6 Months After Ileocecal Resection in Children With Crohn Disease Treated With Azathioprine. J Pediatr Gastroenterol Nutr. 65. 207-211. 2017

Population	Intervention	Outcomes/Results
Evidence level: 3 **Study type: prospective observational** **Number of Patient: 21** **Recruitung Phase: October 2011 until June 2015** **Inclusion Criteria: an age of 0 to 19 years, a diagnosis of CD (according to Porto criteria and revised Porto criteria) (21), an indication of ICR (including combination with evacuation of abscess [n¼5], other ileal [n¼3] or partial (segmental) colonic resection [n¼3], strictureplasty [n¼1] or fistulectomy [n¼3]—none of the fistulas was in the perianal area), no residual disease, undergoing endoscopy/MRE before ICR, AZA monotherapy after ICR, patients and their legal representatives agreed to participate in the study, and signed informed consents.** **Exclusion Criteria: an active**	**Intervention: postoperative treatment following center standards (defined)** **Comparison: Endoscopic recurrence 6 month after ICR between treatment groups**	**Primary: Endoscopic recurrence 6 month after ICR** **Secondary: -** **Results: Among 21 included patients, 13 achieved endoscopic remission (Rutgeerts score between patients who received prior anti-TNF-a therapy and those who did not. We did not find any clinically relevant factors associated with endoscopic recurrence rate at the sixth month.** **Author's Conclusion: Prior anti-TNF-a therapy does not seem to be a strong risk factor for endoscopic recurrence within 6 months after ICR. Further studies on large sample of patients are needed to identify potential predictors of disease recurrence.**

colonic inflammation not suitable for surgery (confirmed by endoscopy before ICR), an active or previous perianal disease, change of therapy (an interruption of AZA therapy or a newly started anti-TNF-a therapy) before the first endoscopy after ICR, and a follow-up in another hospital after surgery.		

Methodical Notes

Funding Sources: public (ministry of health Czech)

COI: none

Randomization: no

Blinding: no

Dropout Rate/ITT-Analysis: n=26, shown

Notes: cohort

Literatursammlung:

AG 3 Remissionserhaltung-Frage 1

Inhalt: 17 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Auzolle, C. 2018	3	Porspektive, observational
Bakouny, Z. 2019	2	Metaanalysis
Buisson, A. 2012	2	Review of literature
Burr, N. E. 2019	1	Metaanalysis
De Cruz, P. 2015	2	RCT
De Cruz, P. 2015	2	Subgroup analysis of POCER study
Gjuladin-Hellon, T. 2019	2	Metaanalysis
Huang, H. 2018	2	Metaanalysis
Lamb, C. A. 2019	1	Consensus paper
Lopez-Sanroman, A. 2017	3	RCT (Superiority)
Mowat, C. 2016	2	RCT
Singh, S. 2015	1	Metaanalysis
Solon, J. G. 2013	2	Metaanalysis
Taxonera, C. 2019	3	RCT
Wright, E. K. 2015	3	Review
Wright, E. K. 2015	2	Subgroup analysis (POCER)
Yang, Z. 2014	2	Metaanalysis

OXFORD (2011) Appraisal Sheet: Systematic Reviews: 10 Bewertung(en)

Bakouny, Z. et al. Comparative Efficacy of Anti-TNF Therapies For The Prevention of Postoperative Recurrence of Crohn's Disease: A Systematic Review and Network Meta-Analysis of Prospective Trials. J Clin Gastroenterol. 53. 409-417. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 Study type: Metaanalysis Databases: Pubmed, Cochrane, AGA Abstract (1x), EMBASE Search period: until August 4, 2017	Population: CD patients Intervention: non Comparison: anti-TNF vs	Primary: The primary outcome was the comparison of the rates of endoscopic recurrence following surgical resection between different anti-TNF treatments Secondary: 1. Comparison of clinical recurrence rates	Aliment Pharmacol Ther. 2018;48:924–932

Inclusion Criteria: (a) patients: adults aged 18 years or above diagnosed with CD who have had surgical resection of small bowel and/or colon with complete removal of macroscopically visible disease (either as a first-time resection or repeat resection). (b) Intervention: biological anti-TNF agents including infliximab, adalimumab, certolizumab pegol, golimumab, and etanercept which had been started a maximum of 3 months after surgery. (c) Comparator: any anti-TNF or non–anti-TNF active agent, absence of intervention, or placebo. (d) Outcome: endoscopic and/or clinical recurrence of CD following surgery (with a minimum of 6 mo of follow-up), as well the rate of medication discontinuation due to adverse events. (e) Study design: prospective interventional comparative randomized/nonrandomized trials. Exclusion Criteria: Reviews, retrospective, noncomparative, or observational studies and studies investigating the treatment of CD postoperative recurrence with anti-TNF agents.	placebo or other therapies	between anti-TNF treatments. 2. Comparison of endoscopic and clinical recurrence rates between the different anti-TNF treatments and nonbiological treatments Results: We identified 9 studies, including 571 patients and 5 treatment agents, among which 2 anti-TNF drugs (adalimumab and infliximab). Compared with infliximab, our NMA yielded the following results for endoscopic recurrence: adalimumab [odds ratio (OR), 0.92; 95% confidence interval (CI), 0.18-4.75], thiopurines (OR, 4.11; 95% CI, 0.68-24.78), placebo (OR, 4.39; 95% CI, 0.70-27.68), and Mesalamine (OR, 37.84; 95% CI, 3.77-379.42). For clinical recurrence: adalimumab (OR, 1.03; 95% CI, 0.17-6.03), thiopurines (OR, 1.40; 95% CI, 0.20-10.02), placebo (OR, 1.77; 95% CI, 1.01-3.10), and mesalamine (OR, 16.54; 95% CI, 1.55-176.24). Author's Conclusion: On the basis of a NMA combining direct and indirect evidence either adalimumab or infliximab may be used in the postoperative prophylaxis of CD recurrence. There is currently a lack of evidence on the use of other anti-TNF agents in this setting.	

Methodical Notes

Funding Sources: non

COI:

Study Quality:

Heterogeneity:

Publication Bias:

Notes:
RCTs und nicht RCTs eingeschlossen

Buisson, A. et al. Review article: the natural history of postoperative Crohn's disease recurrence. Aliment Pharmacol Ther. 35. 625-33. 2012

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 Study type: Review of literature Databases:	Population: CD patients Intervention: none	Primary: RATES OF CLINICAL AND ENDOSCOPIC RECURRENCE Secondary: Identificaton of risk factors Results: In randomised controlled trials, clinical recurrence in the first year after surgery occurred in 10–	Aliment Pharmacol Ther 2012; 35: 625–633

Medline Search period: 1966 to September, 2011 Inclusion Criteria: placebo arms of RCTs Exclusion Criteria: non RCTs	Comparison: none	38% of patients, whereas endoscopic recurrence in the first year was reported in 35–85% of patients. In population-based studies, approximately half of patients experienced clinical recurrence at 10 years. In referral centres, 48–93% of the patients had endoscopic lesions (Rutgeerts' score 1) in the neoterminal ileum within 1 year after surgery, whereas 20–37% had symptoms suggestive of clinical recurrence. Three years after surgery, the endoscopic postoperative recurrence rate increased to 85–100%, and symptomatic recurrence occurred in 34–86% of patients. Smoking is the strongest risk factor for postoperative recurrence, increasing by twofold, the risk of clinical recurrence. Prior intestinal resection, penetrating behaviour, perianal disease and extensive bowel disease (>50 cm) are established risk factors for postoperative recurrence. Risk factors for postoperative recurrence remain poorly defined in population-based cohorts. Author's Conclusion: Endoscopic and clinical postoperative recurrence remains common in patients with Crohn's disease, and the identification of risk factors may allow targeted strategies to reduce this recurrence rate.	

Methodical Notes

Funding Sources: none

COI:

Study Quality: review by authors

Heterogeneity:

Publication Bias:

Notes:
epidemiologic study, risk factors, natural course of disease

Burr, N. E. et al. Systematic Review and Network Meta-Analysis of Medical Therapies to Prevent Recurrence of Post-Operative Crohn's Disease. J Crohns Colitis. 13. 693-701. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Metaanalysis Databases: Cochrane, Embase, Medline Search period: until July 2018 Inclusion Criteria: RCTs recruiting adults [age ≥ 16 years] with established CD, and with a history of intestinal resection. The intervention had to be an established drug, or a combination of established drugs, for the management of post-operative prophylaxis of CD, including 5-ASAs, antibiotics, immunomodulators, anti-TNF-α therapies, or any combination thereof, started within 3 months of surgery. The comparator could be	Population: CD Patients Intervention: none Comparison:	Primary: Endoscopic recurrence of CD at 12 months after the initial resection. Secondary: Clinical recurrence of CD at 12 months after the initial resection. Results: included 10 RCTs, containing 751 patients, in our primary analysis of endoscopic recurrence of CD at	Journal of Crohn's and Colitis, 2019, 693–701

another established drug, or placebo. **Exclusion Criteria: We excluded RCTs in which prophylactic medication was commenced after endoscopic recurrence of CD had already been established, or beyond 12 months post-surgery; trials comparing different doses of the same medication, without an alternative intervention or comparator arm; and trials in which subclinical relapse was defined based only on radiological evidence.**		**12 months. Anti-tumour necrosis factor [TNF]-α therapies were significantly better than placebo, either alone [P-score 0.98, RR 0.13; 95% CI 0.04–0.39] or in combination with 5-aminosalicylates [5-ASAs] [P-score 0.81, RR 0.30; 95% CI 0.12–0.75], or 5-nitroimidazoles [P-score 0.75, RR 0.40; 95% CI 0.23–0.69]. Combination therapy with a thiopurine and 5-nitroimidazole was also more effective than placebo [P-score 0.59, RR 0.56; 95% CI 0.40–0.80], as was thiopurine monotherapy [P-score 0.31, RR 0.84; 95% CI 0.74–0.94]. However, neither 5-nitroimidazoles nor 5-ASAs alone were superior to placebo.** **Author's Conclusion: In network meta-analysis, anti-TNF-α therapies alone, or in combination, appear to be the best medications for preventing endoscopic post-operative recurrence of CD.**	

Methodical Notes

Funding Sources: none

COI:

Study Quality: 14 RCTs

Heterogeneity: low

Publication Bias: none

Notes:
Metaanalysis of RCTs

Gjuladin-Hellon, T. et al. Azathioprine and 6-mercaptopurine for maintenance of surgically-induced remission in Crohn's disease. Cochrane Database Syst Rev. 8. Cd010233. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References

Evidence level: 2 **Study type: Metaanalysis** **Databases: MEDLINE;Embase;PubMed; Cochrane; IBD Group Specialized Register** **Search period: until 26 July 2018** **Inclusion Criteria: Randomised controlled trials which compared AZA or 6-MP agents to either a no treatment control, placebo or any other active intervention, with treatment durations of at least three months** **Exclusion Criteria: not fit inclusion**	**Population: CD patients** **Intervention: no** **Comparison: AZA vs placebo or other therapies**	**Primary: Clinical relapse** **Secondary: Endoscopic relapse; Radiologic relapse; Surgical relapse; Histologic relapse; Adverse event; Serieous adverse events, Life quality** **Results: At 12 to 36 months, 51% (109/215) of AZA/6-MP participants relapsed compared to 64% (124/193) of placebo participants (RR 0.79; 95% CI 0.67 to 0.92; 408 participants; 3 studies; I2 = 0%; moderate certainty evidence). The certainty of the evidence regarding the eNicacy of AZA or 6-MP for maintaining postoperative clinical remission compared to 5-ASA compounds was low.** **Author's Conclusion: Moderate certainty evidence suggests that AZA and 6-MP may be superior to placebo for maintenance of surgically-induced remission in participants with CD.**	**Gjuladin-Hellon T, Iheozor-Ejiofor Z, Gordon M, Akobeng AK. Azathioprine and 6-mercaptopurine for maintenance of surgically-induced remission in Crohn's disease. Cochrane Database of Systematic Reviews 2019, Issue 8**

Methodical Notes

Funding Sources: Cochrane

COI:

Study Quality: Metaanalysis

Heterogeneity:

Publication Bias:

Notes:

Huang, H. et al. A Meta-Analysis of Efficacy and Safety of Infliximab for Prevention of Postoperative Recurrence in Patients with Crohn's Disease. Biomed Res Int. 2018. 2615978. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type: Metaanalysis** **Databases: PubMed, Medline, Embase, and Web of Science** **Search period: 2000 until 6/2018** **Inclusion Criteria: RCTs mit (1) patients diagnosed with CD based on tissue biopsy and treated with Infliximab; (2) double-blind, randomized, placebo-controlled or prospective studies; and (3) the outcome measures regarding the rates of CD recurrence**	**Population: CD patients** **Intervention: none** **Comparison: IFX vs placebo or other therapies**	**Primary: efficacy and safety of Infliximab for the prevention of recurrence in patients with CD across studies. The outcomes included in the metaanalysis were the rates of endoscopic recurrence and clinical recurrence.** **Secondary:** **Results: A total of 7 prospective trials were included in our meta-analysis (N=455).** **Infliximab decreased the rates of endoscopic recurrence (RR =0.421; 95% CI 0.328 to 0.539; p<0.001), and there was a**	**BioMed Research International Volume 2018, Article ID 2615978, 10 pages**

Exclusion Criteria:		**signifcant reduction in rates of clinical recurrence in the Infiximab-treated group (RR =0.519; 95% CI 0.349 to 0.774; p=0.001). Furthermore, Infiximab treatment did not show adverse efects as other systematic therapeutic drugs, indicating that Infiximab treatment is effective and well tolerated.** **Author's Conclusion: Compared with the controls, Infiximab is a promising therapeutic agent for the management of CD patients.**	

Methodical Notes

Funding Sources: National Natural Science Foundation of China (No. 81603622) and Natural Science Foundation of Jiangsu Province of China (No. BK20161319).

COI: none

Study Quality:

Heterogeneity:

Publication Bias:

Notes:
RCTs and cohort studies

Lamb, C. A. et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 68. s1-s106. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type: Consensus paper** **Databases: Medline, Embase** **Search period: until 3/2017** **Inclusion Criteria:** **Exclusion Criteria:**	**Population: CD patients** **Intervention: A systematic review of 88247 publications and a Delphi consensus process involving 81 multidisciplinary clinicians and patients** **Comparison:**	**Primary:** **Secondary:** **Results:** **Author's Conclusion: Statement 71. We suggest that Crohn's disease patients with significant risk factors for disease recurrence following ileocolonic resection (particularly smoking) or with recurrent disease at 6months post-surgery colonoscopy may be started on thiopurines (GRADE: weak recommendation, low-quality evidence) or anti-TNF therapy (GRADE: weak recommendation, low-quality evidence. Agreement: 94.4%).** **Statement 72. We recommend that mesalazine should not be given to prevent recurrence after ileocolonic Crohn's disease resection (GRADE: strong recommendation, moderate-quality evidence. Agreement: 97.2%).** **Statement 70. We suggest that,**	**Lamb CA, et al. Gut 2019;68:s1–s106. doi:10.1136/gutjnl-2019-318484**

		following ileocolonic resection for Crohn's disease, ileocolonoscopy may be performed at 6months to assess the neoterminal ileum in order to consider treatment escalation if mucosal inflammation (Rutgeerts i2 or above) (GRADE: weak recommendation, low-quality evidence). If the anastomosis is not within reach of endoscopic examination, then cross-sectional imaging with MR enterogram may be performed (Agreement: 89.2%). Statement 69. We recommend that all patients smoking after intestinal resection for Crohn's disease should be actively encouraged to stop (GRADE: strong recommendation, moderatequality evidence. Agreement: 100%).	

Methodical Notes

Funding Sources:

COI:

Study Quality:

Heterogeneity:

Publication Bias:

Notes:
Guideline keine Literatur

Singh, S. et al. Comparative efficacy of pharmacologic interventions in preventing relapse of Crohn's disease after surgery: a systematic review and network meta-analysis. Gastroenterology. 148. 64-76.e2; quiz e14. 2015

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type: Metaanalysis** **Databases: Embase, Medline, Cochrane, Web of Science** **Search period: until 2015** **Inclusion Criteria: RCTs that metthe following inclusion criteria: (1) patients: adults (age,>18 y)with established CD, with a history of small-bowel and/orcolonic resection surgery, with removal of macroscopicallyvisible disease; (2) intervention:**	**Population: CD patients** **Intervention: Prophylactic Medication after surgery** **Comparison: Comparison of AZA, placebo, mesalamine and anti-TNF**	**Primary: Preventing clinical relapse and endoscopic relapse.** **Secondary:** **Results: We identified 21trials comprising 2006 participants comparing 7 treatmentstrategies. In a network meta-analysis, compared with placebo, mesalamine (relative risk [RR], 0.60; 95% credibleinterval [CrI], 0.37–0.88), antibiotics (RR, 0.26; 95% CrI,0.08–0.61), immunomodulator monotherapy (RR, 0.36;95% CrI, 0.17–0.63), immunomodulator with antibiotics(RR, 0.11; 95% CrI, 0.02–0.51), and anti-TNF monotherapy(RR, 0.04; 95% CrI, 0.00–0.14), but not budesonide (RR,0.93; 95% CrI, 0.40–1.84), reduced the risk of**	**Gastroenterology 2015;148:64–76**

established therapies for themanagement of postoperative prophylaxis for CD includingmesalamine, antibiotics, budesonide, immunomodulators, andanti-TNF agents, started within 3 months of surgery; (3)comparator: another active agent, placebo, or no intervention;and (4) outcome: clinical and/or endoscopic relapse with atleast 6 months of follow-up evaluation after surgery. Exclusion Criteria: (1) observational studies, (2) trials in which prophylactic medication was started after established endoscopic recurrence of CD or more than 3 months after surgery (or when timing of initiation was not reported), (3) trials comparing different doses of the same medication without an alternative intervention/comparator arm, (4) trials of medications not approved for CD therapy (eg, probiotics), and (5) studies in which subclinical relapse was defined based on imaging only, without any endoscopic documentation.		clinicalrelapse. Likewise, compared with placebo, antibiotics (RR,0.41; 95% CrI, 0.15–0.92), immunomodulator monotherapy(RR, 0.33; 95% CrI, 0.13–0.68), immunomodulator withantibiotics (RR, 0.16; 95% CrI, 0.04–0.48), and anti-TNFmonotherapy (RR, 0.01; 95% CrI, 0.00–0.05), but neithermesalamine (RR, 0.67; 95% CrI, 0.39–1.08) nor budesonide(RR, 0.86; 95% CrI, 0.61–1.22), reduced the risk of endo-scopic relapse. Anti-TNF monotherapy was the most effective pharmacologic intervention for postoperativeprophylaxis, with large effect sizes relative to all otherstrategies (clinical relapse: RR, 0.02–0.20; endoscopicrelapse: RR, 0.005–0.04). Author's Conclusion: Anti-TNF monotherapy appears to be the most effective strategy for postoperative prophylaxis for CD.	

Methodical Notes

Funding Sources: Supported by the Center for the Science of Healthcare Delivery, Mayo Clinic,and Center for Clinical and Translational Science grant UL1 TR000135 fromthe National Center for Advancing Translational Sciences, a component ofthe National Institutes of Health, as well as National Institutes of Health grantEB001981

COI:

Study Quality:

Heterogeneity:

Publication Bias: no

Notes:
older review

Solon, J. G. et al. The effect of NOD2 polymorphism on postsurgical recurrence in Crohn's disease: a systematic review and meta-analysis of available literature. Inflamm Bowel Dis. 19. 1099-105. 2013

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2	Population: CD patients	Primary:	Inflamm Bowel Dis Volume 19,

Study type: Metaanalysis **Databases: Medline, Embase, and Ovid and Cochrane** **Search period: until 5/12** **Inclusion Criteria: Studies published comparing expression of NOD2 polymorphisms with recurrence of CD after surgery** **Exclusion Criteria:**	**Intervention:** **Comparison: NOD2 polymorphism expression and recurrance**	**Secondary:** **Results: : Six cohort studies comprising 1003 patients with CD were included. A total of 340 patients (33.9%) expressed at least 1 of the 3 common NOD2 polymorphisms. The 1003 patients underwent surgical resection with 335 (33%) developing surgical recurrence. Of 340 NOD2-expressing patients, 130 (39%) required further resection, whereas 202 of 663 patients (30.5%) without the variant underwent repeat resection. NOD2 was not significantly associated with surgical recurrence (odds ratio: 1.58, 95% confidence interval: 0.97–2.57, P ¼ 0.064), most likely because of study heterogeneity (Cochran Q: 12.36, P ¼ 0.030, I2: 59.6%). The sensitivity of any mutation in predicting disease recurrence was 39.7% and specificity was 69%, with the area under the receiver operating characteristic curve being 0.64.** **Author's Conclusion: Patients with CD with a NOD2 polymorphism do not have an increased risk of surgical recurrence compared with patients without the variant. These data provide insufficient evidence to support postoperative medical prophylaxis based solely on the presence of NOD2 polymorphism.**	**Number 5, April 2013**

Methodical Notes

Funding Sources: none

COI: none

Study Quality:

Heterogeneity:

Publication Bias:

Notes:

Wright, E. K. et al. Impact of drug therapy and surgery on quality of life in Crohn's disease: a systematic review. Inflamm Bowel Dis. 21. 1187-94. 2015

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 3 **Study type: Review** **Databases: Medline(EBSCOhost) and Cochrane databases** **Search period: January 1970 to August 2013** **Inclusion Criteria: Articles on QoLand Crohn’s disease**	**Population: CD patients** **Intervention: non** **Comparison: non**	**Primary: QoL after surgery** **Secondary:** **Results: Remission seems to improve QoL, irrespective of whether it is achieved with drug therapy or surgery** **Author's Conclusion: Remission seems to improve QoL, irrespectiveof whether it is achieved with drug therapy or surgery.The effect of routine and targeted postoperative prophylaxis to prevent recurrenceof Crohn’s disease in facilitating significant and durable improve-ments in health-related QoL is not known.**	**Inflamm Bowel Dis 2015;21:1187–1194**

Exclusion Criteria:			

Methodical Notes

Funding Sources: no funding

COI:

Study Quality: only review

Heterogeneity:

Publication Bias:

Notes:
review by one author
do not answer key question!

Yang, Z. et al. A network meta-analysis on the efficacy of 5-aminosalicylates, immunomodulators and biologics for the prevention of postoperative recurrence in Crohn's disease. Int J Surg. 12. 516-22. 2014

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Study type: Metaanalysis** **Databases: PubMed** **Search period: until 5 November, 2013** **Inclusion Criteria:** **Exclusion Criteria:**	**Intervention:** **Comparison:**	**Primary:** **Secondary:** **Results: Fifteen trials involving 1507 patients were included in this analysis. Biological agents wereassociated with a large and significant reduction of both endoscopic and clinical recurrence comparedwith placebo, 5-aminosalicylates, or immunomodulators. Immunomodulators showed greater efficacy interms of endoscopic and clinical recurrence prophylaxis compared with 5-aminosalicylates or placebo,but with higher incidence of adverse events. 5-aminosalicylates were superior to placebo for prevention of clinical recurrence, without increasing the rate of side effect.** **Author's Conclusion: 5-aminosalicylates, immunomodulators, and biologics are more efficacious than placebo forpostoperative CD prevention. Biologics are found to be the most effective medications to prevent CD recurrence.**	**International Journal of Surgery Volume 12, Issue 5, May 2014, Pages 516-522**

Methodical Notes

Funding Sources: none

COI: none

Study Quality:

Heterogeneity:

Publication Bias: Evaluation of publications by 2 reviewers

Notes:
old metaanalysis

Studie sollte ggf. rausgenommen werden!!!!!!!!!!!!!!!

Evaluation of studies by 2 reviewer

OXFORD (2011) Appraisal Sheet: RCT: 5 Bewertung(en)

De Cruz, P. et al. Crohn's disease management after intestinal resection: a randomised trial. Lancet. 385. 1406-17. 2015

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type: RCT** **Number of Patient: 174** **Recruitung Phase: 2009-2011** **Inclusion Criteria: Patients with Crohn's disease undergoing intestinal resection of all macroscopic disease, with an endoscopically accessible anastomosis** **Exclusion Criteria: Patients were excluded if they had an anastomosis that was endoscopically inaccessible by standard colonoscopy; if there was persisting macroscopic abnormality after surgical resection; if they had an end stoma (ileostomy or colostomy); if they were not suitable to undergo endoscopy because of comorbidities or an unwell clinical state; if they were unable to give informed consent; if there was any suspicion of perforation of the gastrointestinal tract; or if they were pregnant.**	**Intervention: Drug therapy based on risk of recurrence Escalation of therapy dependend on clinic endoscopic outcome after 6 months** **Comparison: Colonscopy after 6 months vs no colonoscopy**	**Primary: Presence and severity of endoscopic recurrence 18 months aftersurgery** **Secondary: Clinical recurrence (CDAI>150 or 200), need for further surgery, C-reactive protein (normal ≤5 mg/L), and drug efficacy in prevention of mucosal recurrence.** **Results: At 18 months, endoscopic recurrence occurred in 60 (49%) patients in the active care group and 35 (67%) patients in the standard care group (p=0·03). Complete mucosal normality was maintained in 27 (22%) of 122 patients in the active care group versus four (8%) in the standard care group (p=0·03)** **Author's Conclusion: Treatment according to clinical risk of recurrence, with early colonoscopy and treatment step-up for recurrence, is better than conventional drug therapy alone for prevention of postoperative Crohn's disease recurrence. Selective immunesuppression, adjusted for early recurrence, rather than routine use, leads to disease control in most patients. Clinical risk factors predict recurrence, but patients at low risk also need monitoring. Early remission does not preclude the need for ongoing monitoring.**

Methodical Notes

Funding Sources: AbbVie, Gutsy Group, Gandel Philanthropy, Angior Foundation, Crohn's Colitis Australia, and the National Health and Medical Research Council.

COI:

Randomization: 2:1

Blinding: no

Dropout Rate/ITT-Analysis: 37 von 182 Pt, low dropout rate, ITT

Notes:
many aspects, study for best strategy

all patients recieved metronidazole after surger for 3 months

De Cruz, P. et al. Efficacy of thiopurines and adalimumab in preventing Crohn's disease recurrence in high-risk patients - a POCER study analysis. Aliment Pharmacol Ther. 42. 867-79. 2015

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type: Subgroup analysis of POCER study** **Number of Patient: 101** **Recruitung Phase: 2009-2011** **Inclusion Criteria: High risk Pt for recurrence after surgery, > 18y** **Exclusion Criteria: low risk pt**	**Intervention: Therapy with AZA or ADA** **Comparison: AZA vs ADA in patients with AZA-intolerance**	**Primary: Presence and severity of endoscopic recurrence 6 months after surgery.** **Secondary: Secondary outcome measures included clinical recurrence of Crohn's disease, defined as a Crohn's Disease Activity Index (CDAI) ≥200.21 Clinical remission was assessed for both scores of less than 150 or 200. Symptom recurrence was defined as any Crohn's related symptoms (irrespective of the calculated CDAI score) that either led to withdrawal, unscheduled colonoscopy or change in treatment. Other measures included need for further surgery for Crohn's disease, and C-reactive protein (CRP, normal ≤5 mg/L). An increase or decrease from baseline CDAI was not calculated as symptoms related to recent surgery could skew the baseline CDAI.** **Results: Endoscopic recurrence (Rutgeerts score i2–i4) occurred in 33 of 73 (45%) thiopurine vs. 6 of 28 (21%) adalimumab-treated patients [intentionto-treat (ITT); P = 0.028] or 24 of 62 (39%) vs. 3 of 24 (13%) respectively [per-protocol analysis (PPA); P = 0.020]. Complete mucosal endoscopic normality (Rutgeerts i0) occurred in 17/73 (23%) vs. 15/28 (54%) (ITT; P = 0.003) and in 27% vs. 63% (PPA; P = 0.002). The most advanced disease (Rutgeerts i3 and i4) occurred in 8% vs. 4% (thiopurine vs. adalimumab).** **Author's Conclusion: In Crohn's disease patients at high risk of post-operative recurrence adalimumab is superior to thiopurines in preventing early disease recurrence.**

Methodical Notes

Funding Sources: Abbvie

COI:

Randomization: no

Blinding: no

Dropout Rate/ITT-Analysis: low dropout, ITT

Notes:
comparision of AZA vs ADA (if intolerant to AZA)

all patients received metronidazole for 3 months

Lopez-Sanroman, A. et al. Adalimumab vs Azathioprine in the Prevention of Postoperative Crohn's Disease Recurrence. A GETECCU Randomised Trial. J Crohns Colitis. 11. 1293-1301. 2017

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 **Study type: RCT (Superiority)** **Number of Patient: 91** **Recruitung Phase: 2012-2015** **Inclusion Criteria: >18y, recetion of all inflamed sections** **Exclusion Criteria: Postsurgical stoma, resection for short indolent stenosis [< 10 cm], anastomosis that was inaccessible to standard endoscopy, local macroscopic disease after resection, and the usual contraindications to anti-TNFα therapy**	**Intervention: AZA or ADA** **Comparison: ADA vs AZA**	**Primary: Endoscopic recurrence at 1 year** **Secondary: Clinical remission at 1y** **Results: We recruited 91 patients [median age 35.0 years, disease duration 6.0 years, 23.8% smokers, 7.1% previous resections]. The study drugs were administered to 84 patients. Treatment was discontinued owing to adverse events in 11 patients [13.1%]. Discontinuation was significantly less frequent in the ADA [4.4%] than in the AZA group [23.2%] (dif.: 18.6% [95% CI 4.1–33.2], p = 0.011). According to the intention-to-treat analysis, therapy failed in 23/39 patients in the AZA group [59%] and 19/45 patients in the ADA group [42.2%] [p = 0.12]. In the per-protocol analysis [61 patients with centrally evaluable images], recurrence was recorded in 8/24 [33.3%] patients in the AZA and 11/37 [29.7%] in the ADA group [p = 0.76]. No statistically significant differences between the groups were found for recurrence in magnetic resonance images, biological markers of activity, surgical procedures, or hospital admissions.** **Author's Conclusion: ADA has not demonstrated a better efficacy than AZA [both associated with metronidazole] for prophylaxis of POR-CD in an unselected population, although tolerance to ADA is significantly better.**

Methodical Notes

Funding Sources: AbbVie

COI:

Randomization: yes

Blinding: yes

Dropout Rate/ITT-Analysis: low dropout , ITT

Notes:
no risk stratification, all patients were treated
all patients got metronidazole

Mowat, C. et al. Mercaptopurine versus placebo to prevent recurrence of Crohn's disease after surgical resection (TOPPIC): a multicentre, double-blind, randomised controlled trial. Lancet Gastroenterol Hepatol. 1. 273-282. 2016

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type: RCT** **Number of Patient: 240** **Recruitung Phase: 2008-2012** **Inclusion Criteria: Patients aged at least 16 years (Scotland) or 18 years (England and Wales) who had a diagnosis of Crohn's disease12 and an ileocolic or small bowel resection within the preceding 3 months were eligible for inclusion.** **Exclusion Criteria: Key exclusion criteria were residual active Crohn's disease present after surgery, known intolerance or hypersensitivity to thiopurines, known need for further surgery, strictureplasty alone, formation of a stoma, active or untreated malignancy, absent thiopurine methyltransferase activity, substantial abnormalities of liver function tests or full blood count, and pregnancy.**	**Intervention: 6-MP** **Comparison: Placebo vs 6-MP**	**Primary: CInical recurrence and need of rescue therapy** **Secondary: Endoscopic recurrence, life quality** **Results: 16 (13%) of patients in the mercaptopurine group versus 26 (23%) patients in the placebo group had a clinical recurrence of Crohn's disease and needed anti-inflammatory rescue treatment or primary surgical intervention (adjusted hazard ratio [HR] 0·54, 95% CI 0·27–1·06; p=0·07; unadjusted HR 0·53, 95% CI 0·28–0·99; p=0·046).** **In a subgroup analysis, three (10%) of 29 smokers in the mercaptopurine group and 12 (46%) of 26 in the placebo group had a clinical recurrence that needed treatment (HR 0·13, 95% CI 0·04–0·46), compared with 13 (13%) of 99 non-smokers in the mercaptopurine group and 14 (16%) of 86 in the placebo group (0·90, 0·42–1·94; pinteraction=0·018). The eff ect of mercaptopurine did not signifi cantly diff er from placebo for any of the other planned subgroup analyses (previous thiopurines, previous infl iximab or methotrexate, previous surgery, duration of disease, or age at diagnosis)** **Author's Conclusion: Mercaptopurine is eff ective in preventing postoperative clinical recurrence of Crohn's disease, but only in patients who are smokers.**

Methodical Notes

Funding Sources: Medical Research Council and National Institute of Health Research's Effi cacy and Mechanism Evaluation Programme, Scottish Government Chief Scientist Offi ce, and the National Institute of Health Research National Portfolio.

COI:

Randomization: yes

Blinding: yes

Dropout Rate/ITT-Analysis: low dropout, ITT

Notes:
no risk stratification, just in subgroups

Taxonera, C. et al. Quality of life during one year of postoperative prophylactic drug therapy after intestinal resection in Crohn's patients: Results of the APPRECIA trial. Dig Liver Dis. 51. 529-535. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 **Study type: RCT** **Number of Patient: 61** **Recruitung Phase: 2012 to January 2015** **Inclusion Criteria: Patients included in APPRECIA who received at least one dose of the study drug were eligible. The study population for HRQoL assessment were patients who completed the questionnaires and had evaluable data.** **Exclusion Criteria:**	**Intervention: ADA or AZA** **Comparison: ADA vs AZA**	**Primary: Quality of life during one year of postoperative prophylactic drug therapy after intestinal resection in Crohn's patients** **Secondary:** **Results: Six cohort studies comprising 1003 patients with CD were included. A total of 340 patients (33.9%) expressed at least 1 of the 3 common NOD2 polymorphisms. The 1003 patients underwent surgical resection with 335 (33%) developing surgical recurrence. Of 340 NOD2-expressing patients, 130 (39%) required further resection, whereas 202 of 663 patients (30.5%) without the variant underwent repeat resection. NOD2 was not significantly associated with surgical recurrence (odds ratio: 1.58, 95% confidence interval: 0.97–2.57, P ¼ 0.064), most likely because of study heterogeneity (Cochran Q: 12.36, P ¼ 0.030, I2: 59.6%). The sensitivity of any mutation in predicting disease recurrence was 39.7% and specificity was 69%, with the area under the receiver operating characteristic curve being 0.64.** **Author's Conclusion: HRQoL improved after intestinal resection in CD, irrespective of the postoperative therapy used(ADAorAZA). Outcomes in HRQoL were associated with prevention of endoscopic recurrence, since improvements in HRQoL were only significant in patients with endoscopic remission at 1 year.**

Methodical Notes

Funding Sources: Abbvie

COI:

Randomization: yes

Blinding: no

Dropout Rate/ITT-Analysis: high dropout

Notes:
no risk straification, only small patient group, high dopout

OXFORD (2011) Appraisal Sheet: Diagnostic Studies: 1 Bewertung(en)

Wright, E. K. et al. Measurement of fecal calprotectin improves monitoring and detection of recurrence of Crohn's disease after surgery. Gastroenterology. 148. 938-947.e1. 2015

Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 2 **Study type: Subgroup analysis (POCER)**	**Number of patients / samples: 135** **Reference standard: yes** **Validation: yes** **Blinding: no** **Inclusion of clinical information: Pocer Patients** **Dealing with ambiguous clinical findings: no**	**Results: Levels of FC were measured in 319 samples from 135 patients. The median FC level decreased from 1347 mg/g before surgery to 166 mg/g at 6 months after surgery, but was higher in patients with disease recurrence (based on endoscopic analysis; Rutgeerts score, i2) than in patients in remission (275 vs 72 mg/g, respectively; P < .001). Combined 6- and 18-month levels of FC correlated with the presence (r ¼ 0.42; P < .001) and severity (r ¼ 0.44; P < .001) of CD recurrence, but the CRP level and CDAI score did not. Levels of FC greater than 100 mg/g indicated endoscopic recurrence with 89% sensitivity and 58% specificity, and a negative predictive value (NPV) of 91%; this means that colonoscopy could have been avoided in 47% of patients. Six months after surgery, FC levels less than 51 mg/g in patients in endoscopic remission predicted maintenance of remission (NPV, 79%). In patients with endoscopic recurrence at 6 months who stepped-up treatment, FC levels decreased from 324 mg/g at 6 months to 180 mg/g at 12 months and 109 mg/g at 18 months.** **Author conclusions: In this analysis of data from a prospective clinical trial, FC measurement has sufficient sensitivity and NPV values to monitor for CD recurrence after intestinal resection. Its predictive value might be used to identify patients most likely to relapse. After treatment for recurrence, the FC level can be used to monitor response to treatment. It predicts which patients will have disease recurrence with greater accuracy than CRP level or CDAI score.**

Methodical Notes

Funding Sources: Abbvie

COI:

Notes: prospektive Beobachtung bei POCER-STudie

OXFORD (2011) Appraisal Sheet: Prognostic Studies: 1 Bewertung(en)

Auzolle, C. et al. Male gender, active smoking and previous intestinal resection are risk factors for post-operative endoscopic recurrence in Crohn's disease: results from a prospective cohort study.

Aliment Pharmacol Ther. 48. 924-932. 2018

Population	Intervention	Outcomes/Results
Evidence level: 3 **Study type: Porspektive, observational** **Number of Patient: 289** **Recruitung Phase: 2010-2017** **Inclusion Criteria: Age >18 years, ileal or ileocolonic CD and indication of CD-related intestinal surgery (ileocolonic resection)** **Exclusion Criteria: other operations**	**Intervention: non** **Comparison: non**	**Primary: Endoscopic recurrence Rutgeerts score ≥i2. Baseline factors associated with endoscopic recurrence were searched by univariate and multivariate regression analysis.** **Secondary:** **Results: MTwo hundred and eighty-nine CD patients were included. Endoscopy within 1 year following surgery was performed in 225 (78%) patients (104M/121F). Mean age and disease duration were 35 (12.2) and 8.8 (8.9) years respectively. Seventy (32%) patients were active smokers at surgery. One hundred and forty-two (63%) patients received at least one anti-TNF therapy before surgery. After surgery, 40 (18%) patients received thiopurines and 66 (29%) received an anti-TNF agent. Endoscopic recurrence occurred in 107 (47%) patients. In multivariate analysis, male gender (OR = 2.48 [IC 95% 1.40-4.46]), active smoking at surgery (OR = 2.65 [IC 95% 1.44-4.97]) and previous resection (OR = 3.03 [IC 95% 1.36-7.12]) were associated with a higher risk of endoscopic recurrence. Inversely, post-operative anti-TNF treatment decreased the risk of endoscopic recurrence (OR = 0.50 [IC 95% 0.25-0.96]).** **Author's Conclusion: Male gender, active smoking at surgery and previous intestinal resection are associated with a higher risk of endoscopic post-operative recurrence, while post-operative anti-TNF treatment is associated with a lower risk.**

Methodical Notes

Funding Sources: Association Francois Aupetit, Helmsley Charitable Trust, and MSD France laboratories

COI:

Randomization: none

Blinding: none

Dropout Rate/ITT-Analysis: 64 dropouts, no ITT

Notes:

Literatursammlung:

AG 3 Remissionserhaltung-Frage 2

Inhalt: 1 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Da, W. 2013	1	Systemic Review

OXFORD (2011) Appraisal Sheet: Systematic Reviews: 1 Bewertung(en)

Da, W. et al. Adalimumab for Crohn's disease after infliximab treatment failure: a systematic review. Eur J Gastroenterol Hepatol. 25. 885-91. 2013

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 **Study type: Systemic Review** **Databases: The search included PubMed, Google Scholar, and the Cochrane Library using a combination of search terms 'adalimumab AND inflix- imab AND Crohn's'.** **A total of 498 related studies were identified in the search, 10 of which were found by hand searching of reference lists (Fig. 1). Of these studies, 19 fulfilled the inclusion criteria and were reviewed in full. Seven of these studies reported only subjective measures of treatment response and were excluded. Two studies did not specify the reason(s) for discontinuation of infliximab and were also excluded. Hence, 10 studies were included in the review.** **Search period: Inception until September 2012** **Inclusion Criteria: Studies were eligible for inclusion in the review if they fulfilled the following criteria: RCTs or cohort studies of adalimumab treatment in patients with CD who had received previous infliximab treatment and experienced treatment failure (unresponsiveness, loss of response, or**	**Population: Crohn´s Disease patients** **Intervention: RCTs or cohort studies of adalimumab treatment in patients with CD who had received previous infliximab treatment and experienced treatment failure (unresponsiveness, loss of response, or intolerance/hypersensitivity)** **Comparison:**	**Primary: The major outcome measures of interest were the response and remission rates as indicated by the Crohn's Disease Activity Index (CDAI), the Harvey–Bradshaw Index (HBI), and fistula closure.** **Secondary: Secondary outcomes of interest were the rate of AEs and the rate of discontinuation because of AEs.** **Results: Luminal disease remission rates ranged from 12 to 67% during induction and 29 to 72% during maintenance therapy. Fistulizing disease remission rates ranged from 5 to 50% during induction and 27 to 68% during maintenance therapy. Luminal disease response rates ranged from** **29 to 83% during induction and 31 to 59% during maintenance therapy. Fistulizing disease response rates ranged from 15 to 44%**	

intolerance/hypersensitivity); reported efficacy results; and reported in English. **Exclusion Criteria: Studies were excluded from the review if they included only subjective measures of efficacy or did not specify the reason for discontinuation of infliximab.**		**during induction and 41 to 56% during maintenance therapy. The overall AE rate ranged from 13 to 69%. Most AEs were mild to moderate in severity. The rate of discontinuation because of AEs ranged from 0 to 14%. The findings reported in the current literature support adalimumab as an efficacious and safe treatment for CD in patients who have failed infliximab treatment.** **Author's Conclusion: In summary, the findings highlighted in this systematic review suggest that adalimumab can be efficacious and has favorable safety and tolerability for the treatment of CD in patients who have failed infliximab treatment. Patients who have failed infliximab treatment may therefore benefit from subsequent treatment with adalimumab. Further study is required to identify factors** **that may help identify patients who are most likely to respond to adalimumab treatment after failing infliximab treatment.**	

Methodical Notes

Funding Sources: Acknowledgements
No funding sources have been described.

COI: Acknowledgements
Conflicts of interest
There are no conflicts of interest.

Study Quality:

Heterogeneity:

Publication Bias:

Notes:

Literatursammlung:

AG 5 EIM, Komplikationen-Frage 1

Inhalt: 6 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Abhyankar, Anita 2015	1	Systematischer Review und Metaanalyse
Aksan, A 2017	1	Systematischer Review und Metaanalyse von RCTs.
Avni, T. 2013	1	Systematischer Review und Meta-Analyse von RCTs
Bonovas, Stefanos 2016	1	Systematic Review und Metaanalyse von RCTs
Nielsen, Ole Haagen 2015	2	Systematischer Review
Reinisch, Walter 2013	2	Individueller RCT

OXFORD (2011) Appraisal Sheet: Systematic Reviews: 5 Bewertung(en)

Abhyankar, Anita et al. Iron Replacement in Patients with Inflammatory Bowel Disease: A Systematic R 21. 1976-81. 2015

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature Referenc
Evidence level: 1 Study type: Systematischer Review und Metaanalyse Databases: MEDLINE, CINAHL, EMBASE Search period: 1966-2014 Inclusion Criteria: RCTs mit Vgl. i.v. zu p.o.-Eisen. Primäroutcome Hb-Anstieg > 2g/dl Exclusion Criteria: Review Artikel oder keine Information zu Primäroutcome oder keine CED-Patienten	Population: CED-Patienten mit Eisenmangelanämie Intervention: Eisenpräparat Comparison: i.v. oder p.o. Eisenpräparat	Primary: Hb-Anstieg > 2g/dl Secondary: Mittlere Hb-Veränderungen, mittlere Veränderung Serum-Ferritin, Therapiebeendigung wegen Nebenwirkungen. Results: Primäroutcome Hb-Anstieg >2g/dl identisch (RR 1,1) zwischen i.v. und p.o.-Eisen Hb-Anstieg um 0.6g/dl höher in iv im Vgl zu po-Gruppe (statistisch nicht signifikant) Bei Einschluss von Studien mit Behandlungsdauer >12 Wochen Vorteil iv gegenüber po Mittlererer Ferritin-Anstieg größer bei iv Therapiebeendigung wg. NW geringer bei iv im Vgl. zu po Author's Conclusion: We found no significant difference between IV and PO iron in correcting iron-deficiency anemia in patients with IBD in this metaanalysis. Patients who received IV iron had a greater rise in serum ferritin and were less likely to stop treatment due to	1. Kulnigg S, Stoinov formulation for treatr ferric carboxymaltos Gastroenterol. 2008;1 2. Gisbert JP, Gomo and management of Gastroenterol. 2008;1 3. Wells CW, Lewis hemoglobin level c inflammatory bowel d 30. [PubMed] [Google 4. Weinstock LB, Bo associated with re 2010;16:275–9. [PMC 5. Nissenson AR, W anemia in an insured 74. [PubMed] [Google 6. Stein J, Hartmann deficiency anemia in 2010;7:599–610. [Pub 7. Kulnigg S, Gascl Crohn's disease. Alin [Google Scholar] 8. Gasche C, Berstad and management of diseases. Inflamm I Scholar] 9. Lee TW, Kolber M inflammatory bowel systematic review ar

		adverse events, when compared with those who received PO iron.	**[PubMed] [Google Sc** **10. Reinisch W, Stau non-inferiority study compared with oral i J Gastroenterol. 2([Google Scholar]** **11. Lindgren S, Wikm superior to oral iron s stores in IBD patie multicentre study. S [Google Scholar]** **12. Assche G, Van Di evidence-based Cor Crohn's disease: Sp [PubMed] [Google Sc** **13. Lichtenstein GF Crohn's disease in a 464, 484. [PubMed] [(** **14. Kornbluth A, Sa adults: American Co Committee. Am J Ga [Google Scholar]** **15. Avni T, Bieber inflammatory bowel PLoS One. 2013;8: Scholar]** **16. Balshem H, Helfa 3. Rating the quality [PubMed] [Google Sc** **17. Guyatt GH, Oxma the quality of evidenc 2011;64:407–15. [Pub** **18. Stroup DF, Be observational studies analysis Of Observa JAMA. 2000;283:2008** **19. DerSimonian R, L Trials. 1986;7:177–88** **20. Higgins JPT, Tho analysis. Stat Med. 2(** **21. Egger M, Davey S detected by a simple article] [PubMed] [Gc** **22. Erichsen K, Ulvil intravenous iron suc Scand J Gastroenter(** **23. Schröder O, Mick versus oral iron sup anemia in patients v controlled, open-lab 2005;100:2503–9. [Pu** **24. Gisbert JP, Berm treatment in inflamm quality of life impr [PubMed] [Google Sc** **25. Avni T, Leibovic treatment of chroni review and meta-ana [Google Scholar]** **26. Evstatiev R, Ma controlled trial on fe inflammatory bowel 2. [PubMed] [Google**

Methodical Notes

Funding Sources: Keine Angabe

COI: Keine

Study Quality: Quality: Moderate

Heterogeneity: Wenig Heterogenität im Primäroutcome. Sekundäroutcomes mittlerer Hb-Anstieg, Ferrit Heterogenenität.

Publication Bias: Kein Publication bias

Notes:
Limitationen: Vergleich verschiedener Eisenformulierungen und unterschiedlicher Therapiedauern. Allerding Rechnung zu tragen.

Aksan, A et al. Systematic review with network meta-analysis: comparative efficacy and tolerability of treatment of iron deficiency anaemia in patients with inflammatory bowel disease. Aliment. Pharmacol.

Evidence level/Study Types	P - I - C	Outcomes/Results	Literatu
Evidence level: 1 Study type: Systematischer Review und Metaanalyse von RCTs. Databases: PUBMED, SCOPUS, Web of Science and the Cochrane Library (Cochrane Database of Sys- tematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Methodology Register) Search period: Bis Juni 2016 (kein Startdatum). Inclusion Criteria: original studies analysing the efficacy and safety of intravenous iron as monotherapy for iron deficiency anaemia in patients with IBD Exclusion Criteria: Studien in Kindern und Schwangeren.	Population: CED-Patienten mit Eisenmangelanämie Intervention: i.v. vs. po Eisen. Verschiedenen Eisenpräparate. Comparison: i.v. vs. po Eisen. Verschiedenen Eisenpräparate.	Primary: Hb-Normalisierung oder Hb-Anstieg ≥ 2g/dl Secondary: Nebenwirkungen Results: Eisen iv. gg.über po überlegen bzgl Primäroutcome Eisencarboxymaltose gg.über Eisensucrose überlegen In Netzwerk-Metaanalyse nur Eisencarboxymaltose oralem Eisen überlegen. Eisensucrose, Eisenisomaltose gegenüber p.o. Eisen mit nicht-signifikantem Vorteil. Bessere Verträglichkeit von i.v.-Eisen gegenüber oralem Eisen. Author's Conclusion: Ferric carboxymaltose was the most effective intravenous iron formulation, followed by iron sucrose. In addition, ferric carboxymaltose tended to be better tolerated.	1Portela inflamm sectiona Crossre 2Goodh and mar adults v Dis 2012 Wiley O Scholar 3Dignas consens deficien Crohn's Crossre 4Ebinge care in German 2004; 19 Wiley Science 5Werlin adolesc Gastroe Google 6Wells changes cognitiv patients Wiley O Scholar 7Nissen RW. Eco J Manag PubMed 8Stein manage IBD. Nat Crossre 9Avni T, Treatme systema e75540. Crossre 10Kulnig anaemia 2006; 24 Wiley Science 11Nielse Manage

				bowel d e963. Crossre 12Guagn bowel d World J Crossre 13Martin evaluati inflamm Hepatol Crossre 14Khalil Rampto dextran case-ma Hepatol CAS Pul 15Zimm effects African d'Ivoire. Crossre 16Jaegg adverse abundar infants. Crossre 17Lee intraven gut micr 2016; do Crossre 18Kortm Nutritior gut micr 1202– 34 Wiley Science 19Bonov versus inflamm meta-an 2016; 95 Crossre 20Avni Gafter-G preparat Clin Pro Crossre 21Pratt disease review. I Wiley Science 22Evsta randomi iron def Gastroe Crossre 23Auerb anathem 580– 8. Wiley Science 24Danie pharmac Nephrol PubMed

25Mohe
reportin
analyse
41.
Crossre
26Furuk
efficacy
generati
major d
BMJ ope
Crossre
27Caldw
compari
indirect
897– 90
Crossre
28Salan
multiple
covariat
62: 857–
Crossre
29Cipria
Concept
analysis
Crossre
30Greco
Zangrill
outcome
1757– 7
Crossre
31Doneg
C. Asse
a review
323.
Wiley O
Scholar
32Kibret
best tre
binary o
6: 451–
PubMed
33Salan
network
names,
generati
2012; 3:
Wiley O
Scholar
34Efthim
GetReal
methodo
Wiley O
Scholar
35Dias
consiste
analysis
Wiley
Science
36Higgi
Measuri
researcl
Crossre
37Mills
treatmer
complex
Crossre
38Neupa
Network
availabl

e115065
Crossre
39Wang
strategie
systema
2016; 6:
Crossre
40Cook
prophyla
meta-an
PubMed
41Mills
AA, loar
network
ed.) 201
Crossre
42Gasch
and ery
disease.
1997; 12
Crossre
43Han Y
efficacie
for aner
Korea. G
Crossre
44Garcia
intraven
inflamm
quality o
PubMed
45Gasch
Predicti
bowel d
2001; 96
Crossre
46Koutr
Mantzar
total-dos
for iron
bowel di
Crossre
47Millas
Gomollo
bowel d
treatmer
Gastroe
Crossre
48Gisbe
intraven
disease:
improve
Wiley O
Scholar
49Sobra
Sobrado
quality
experier
Gastroe
Crossre
50Beige
analysis
treatmer
Digestio
Crossre
51Gasch
treatmer
iron and
Crossre

				52Kulnig intraven inflamm (FERINJ Gastroe Crossre 53Lindg sucrose anaemia randomi study. S Crossre 54Reinis open-lab isomalto treatmer Gastroe Crossre 55Schro iron su treatmer inflamm open-lab 100: 250 Crossre 56Erichs fumarat inflamm 40: 1058 Crossre 57Goldb inflamm 6: 61– 7(Crossre 58Lee T replacer patients and met Crossre 59Kostic inflamm ahead. C Crossre 60Rogn Tarricon and otl systema randomi 177– 94. Crossre 61Ramp Hyperse for risk 2014; 99 Crossre 62Godd Guidelin anaemia Crossre 63Rimor too mu octogen Crossre 64Moret supplen absorpti depleted Crossre 65Ganzo

			Wkly 19 CAS Pul 66CHMF intraven develop product Europea http://w Google

Methodical Notes

Funding Sources: Nicht dargestellt.

COI: Declaration of personal interests: Axel U. Dignass has received consultancy fees from Abbott, MSD, Ferring, UCB, Otsuka, Roche/ Genentech, Takeda, Pharmacosmos, Holystone Biotech and Falk Foundation. Dr. Dignass has also received grants from Institut f€ur Gemeinwohl and Stiftung Leben mit Krebs as well as payment for lectures including service on speakers' bureaus from Falk Foundation, Ferring, MSD, Abbott, Otsuka, Vifor, Stiftung Leben mit Krebs, Kompetenznetz CED, Takeda and Pharmacosmos. Additionally, Dr. Dignass has received payment for manuscript preparation from Falk Foundation and payment for development of education presentations from Abbott, Pharmacosmos, Falk Foundation and Ferring. J€urgen Stein has received consultancy fees from AbbVie, Fresenius-Kabi, Immundiagnostik, MSD, Pharmacosmos, Takeda and Vifor. Dr. Stein has also received payment for lectures from Abbvie, Falk Foundation, Ferring, Immundiagnostik, MSD, Pharmacosmos, Takeda, Thermofischer and Vifor. Additionally, Dr. Stein has received payment for manuscript preparation from Abbvie, Falk Foundation and MSD. Ayseg€ul Aksan, Hatice Isık and Heinfried H. Radeke have no conflicts of interest.

Study Quality: Limitationen durch unterschiedliche Behandlungsdauer, Behandlungsintensität und unterschie

Heterogeneity: Wenig Heterogenität.

Publication Bias: Entspricht den eingeschlossenen Primärstudien

Notes:
Systematischer Review und Metaanalyse von RCTs.

Avni, T. et al. Treatment of anemia in inflammatory bowel disease--systematic review and meta-analysis

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature Refe
Evidence level: 1 **Study type: Systematischer Review und Meta-Analyse von RCTs** **Databases: MEDLINE (1/1966 to 1/2013), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, Issue 3 of March, 2013 and NLM gateway. Conference proceedings of the American Society of Gastroenterology, from 2007 onwards. We also searched clinical trials databases for ongoing and unpublished trials: http://www. controlled-trials.com,**	**Population: CED-Patienten mit Eisenmangelanämie** **Intervention: Vgl. Eisensubstitution iv vs. oral sowie Vergleiche verschiedener Eisenpräparate oral sowie unterschiedlicher i.v. Eisenpräparate gegeneinander und gegenüber Placebo.** **Comparison: Vgl. Eisensubstitution iv vs. oral sowie Vergleiche verschiedener Eisenpräparate oral sowie unterschiedlicher i.v. Eisenpräparate gegeneinander und gegenüber Placebo.**	**Primary: Hb-Anstieg um ≥2g/dl** **Secondary: Secondary outcomes included disease severity scores (Inflammatory Bowel Disease Questionnaire (IBDQ) scores [20], The Harvey-Bradshaw Simple Index scores (HBSI) [21], Crohn's Disease Activity Index (CDAI) diary card [22] and UC [23]); iron indices (ferritin concentration and transferrin saturation (TSAT), Hb levels or absolute**	**1. Gasche C (20 Hepatogastroen 2. Gasche C, L and inflammato article] [PubMed 3. Ohira Y, Edge et al. (1979) Wor to iron treatmer Scholar] 4. Wells CW, L changes in her function in infla Dis 12: 123–130. 5. Cucino C, Sor inflammatory b [PubMed] [Goog 6. Ebinger M, Le al. (2004) Cost bowel disease i Hepatol 19: 192- 7. Werlin SL,**

http://www.clinicaltrials.gov/ct and http:// clinicaltrials.nci.nih.gov. Search period: Bis 1/2013. Inclusion Criteria: RCTs mit Vergleich einer Eisenmangelanämie-Behandlung bei CED Exclusion Criteria: Nicht klar definiert		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: Überlegenheit von iv-Eisen gegenüber po Eisen (RR 1.25) bezüglich Primäroutcome Ferritin-Level ebenfalls höher bei iv. vs. po Eisen Author's Conclusion: iv iron vs. po iron with improved Hb response, no added toxicity and no negative effect on disease activity	adolescents: dia 73: 828–832. [Pu 8. Gasche C, R (1994) Anemia erythropoietin p 1930–1934. [Pub 9. Horina JH, P (1993) Treatmer recombinant hu Gastroenterolog 10. Hoffbrand A deficiency in C treatment. Br Me Scholar] 11. Taffet SL, D desensitization. Scholar] 12. Lamers CB, (1999) Azathiop inflammatory be 111–115. [PubMe 13. Fedorak RN, al. (2000) Recor patients with n Interleukin 10 I Group. Gastroe Scholar] 14. Giannadaki D, Fragkiadakis positive Coomb Gastroenterol 92 15. Kulnigg S, anaemia in Cro 1523. [PubMed] 16. Wilson A, R of anemia in inf the literature. A [Google Scholar 17. Gasche C Inflamm Bowel I Scholar] 18. Higgins JPT reviews of inter [Google Scholar 19. Schulz KF, C evidence of I associated with JAMA 273: 408– 20. Irvine EJ, Fe al. (1994) Qua therapeutic effi disease. Canadi Gastroenterolog 21. Harvey RF, disease activity. 22. Best WR, Development o Cooperative Cr 444. [PubMed] [C 23. Walmsley R simple clinical article] [PubMed 24. Lindgren S, (2009) Intravenc for correcting an randomized, co J Gastroenterol 25. Kulnigg S, S al. (2008) A nov

anemia in inflan
(FERINJECT) ra
1182–1192. [Pub
26. Wiebe N, Va
(2006) A system
methods for har
342–353. [PubM
27. Erichsen K,
(2005) Effects o
complex on ma
inflammatory b
838. [PubMed] [
28. Erichsen K,
(2005) Oral fer
patients with in
40: 1058–1065. [
29. Evstatiev R,
FERGIcor, a ran
for iron defici
Gastroenterolog
[Google Scholar
30. Gasche C, D
(1997) Intravenc
with Crohn dis
Med 126: 782–78
31. Kulnigg-Dab
et al. (2013) Iron
and Platelet A
ThromboVIT Tria
32. Schreiber S,
al. (1996) Recon
in inflammatory
[PubMed] [Goog
33. Schroder O,
et al. (2005)
supplementatio
patients with
controlled, oper
2503–2509. [Pub
34. Moore RA, C
efficacy and
(Ferinject) from
Blood Disord 11
35. Johansen KI
al. (2010) Syst
tolerance and
with erythropoie
548. [PubMed] [
36. Kotecha D, M
(2011) Erythrop
systematic revie
e822. [PubMed]
37. Lee TW, Ko
replacement the
iron deficiency
Crohns Colitis 6
38. Rozen-Zvi B
et al. (2008) Intr
treatment of ane
Am J Kidney Dis
39. Gafter-Gvili A
J, et al. (2013) Ir
of chemotherap
analysis of ran
[PubMed] [Goog
40. Avni T, Leibo
for the treatme
systematic revi
429. [PubMed] [

			41. Tonia T, Met (2012) Erythrop Cochrane Datal Scholar] 42. Marti-Carvaj D (2013) Eryt rheumatoid arth [PMC free article 43. Bennett CL, al. (2008) Venou recombinant er the treatment o [PubMed] [Goog 44. Gasche C, B (2007) Guidelin deficiency and Bowel Dis 13: 15 45. Eccles M, C (1996) North of project: method [PMC free article 46. Biancone L Castiglione F, e Crohn's diseas [Google Scholar 47. Pizzi LT, We (2006) Impact o with inflammato [PubMed] [Goog

Methodical Notes

Funding Sources: The authors have no support or funding to report

COI: The authors have declared that no competing interests exist

Study Quality: Unterschiedliche Beobachtungsdauer, Hb-Einschlusskriterien, und Erkrankungsaktivität in den

Heterogeneity: Limitierte Heterogenität bzgl Primärendpunkt. Signifikante Heterogenität bzgl. Sekundärendpur

Publication Bias: Not reported.

Notes:
Systematischer Review und Meta-Analyse von RCTs

Bonovas, Stefanos et al. Intravenous Versus Oral Iron for the Treatment of Anemia in Inflammatory B Analysis of Randomized Controlled Trials. Medicine (Baltimore). 95. e2308. 2016

Evidence level/Study Types	P - I - C	Outcomes/Results	Literatur
Evidence level: 1 **Study type:** Systematic Review und Metaanalyse von RCTs **Databases:** Medline, Embase, Scopus, and the Web of Science database. We also searched the Cochrane Central Register of Controlled Trials, the Cochrane Inflammatory Bowel Disease Group Specialized Trials Register, the WHO International Clinical Trials Registry Platform, and the ClinicalTrials.gov website for completed but unpublished studies; and recent international conference proceedings (European Crohn's and Colitis Organisation,2011–2015; Digestive Disease Week, 2010–2015; and the United European Gastroenterology Week, 2010–2014).	**Population:** Patienten mit Eisenmangelanämie bei CED **Intervention:** i.v. vs. po Eisen mit unterschiedlichen Präparaten **Comparison:** i.v. vs. po Eisen mit unterschiedlichen Präparaten	**Primary:** Hb-Anstieg um ≥ 2g/dl zum Ende des Beobachtungszeitraumes **Secondary:** Nebenwirkungen **Results:** Überlegenheit im Primäroutcome von i.v. im Vgl. zu po-Eisen (66 vs. 52%) Geringere Rate von Therapiebeendigung bei iv-Eisen vs. po Eisen **Author's Conclusion:** IV iron appears to be more effective and better	1. Fiorin in inflam ignored Ther 201 Cited He 2. Fiorin bowel d Gastroen Cited He 3. Bager deficienc bowel dis year fol 48:1286– Cited He 4. Abitbo deficienc receptor-

Search period: Start der jeweiligen Datenbank bis Juli 2015 **Inclusion Criteria: RCTs mit iv vs. po Eisensubstitution bei Eisenmangelanämie bei CED** **Exclusion Criteria: Beobachtungsstudien, Patienten ohne CED, pädiatrische Populationen.**		**tolerated than oral iron for the treatment of IBD-associated anemia**	**94:e1011** **Cited He** **5. Gisber** **diagnosi** **bowel dis** **Cited He** **6. Stein** **managen** **IBD. Nat** **Cited He** **7. Gasch** **inflamma** **Cited He** **8. Digna** **consens** **deficienc** **Crohns C** **Cited He** **9. Gomol** **diseases** **Cited He** **10. Wells** **in hemo** **function** **Bowel Di** **Cited He** **11. Ershl** **of patien** **2005; 8:6** **Cited He** **12. Lee T** **therapy i** **deficienc** **J Crohns** **Cited He** **13. Stein** **in patie** **practice** **Gastroen** **Cited He** **14. Abhy** **with infla** **meta-ana** **Cited He** **15. Dane** **versus** **inflamma** **meta-ana** **2015:** **http://ww** **ID=CRD4** **Cited He** **16. Mohe** **items fo** **PRISMA** **269.W64.** **Cited He** **17. WH** **Assessm** **WHO/UN** **Organiza** **Cited He** **18. Edwa** **definitior** **356:1255** **Cited He** **19. Higg** **Cochran** **randomis**

Cited He
20. Bonc
used for
included
addressi
250.
Cited He
21. Swee
nothing?
meta-ana
1375.
Cited He
22. Mant
analysis
Natl Can
Cited He
23. DerSi
Control C
Cited He
24. Tobia
the meta
Cited He
25. Begg
rank corr
50:1088–
Cited He
26. Egge
meta-ana
1997; 315
Cited He
27. Cochl
different
Cited He
28. Higgi
inconsist
Cited He
29. Higgi
in a meta
Cited He
30. Higg
Systemat
Collabora
www.coc
Cited He
31. Guya
emerging
strength
Cited He
32. Balsh
guideline
Epidemic
Cited He
33. R D
Environm
Foundati
project.o
Cited He
34. Schw
News 200
Cited He
35. Erich
fumarate
inflamma
40:1058–
Cited He
36. Kuln
intravenc
inflamma
(FERINJE

			Gastroen Cited He 37. Lindg sucrose anaemia randomiz Scand J Cited He 38. Reini open-lab isomalto treatmen Gastroen Cited He 39. Schr iron suc treatmen inflamma open-lab 100:2503 Cited He 40. Chas health Roundta 1005. View Full 41. Lope anaemia. [doi:10.1 Cited He 42. Niels of iron-d systemat Cited He 43. Avni in inflam meta-ana Cited He 44. Newe quantitat 21:837–8 Cited He 45. Dane patient p from the Colitis A Hepatol 2

Methodical Notes

Funding Sources: This study was funded by the Centro Ricerca e Cura delle Malattie Infiammatorie Croniche Intestinali, Istituto Clinico Humanitas. The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

COI: GF has served as a consultant and advisory board member for MSD, Takeda, AbbVie, and Janssen. LP-B has received consulting fees from Merck, Abbott, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Shire, Therakos, Pharmacosmos, Pile`ge, BMS, UCB-pharma, Hospira, Celltrion, Takeda, Biogaran, Boehringer-Ingelheim, Lilly, Pfizer, and HAC-pharma, and lecture fees from Merck, Abbott, Takeda, Janssen, Ferring, Norgine, Tillots, Vifor, Therakos, and HAC-pharma. SD has served as a speaker, consultant, and advisory board member for Schering-Plough, Abbott Laboratories, Merck, UCB-pharma, Ferring, Cellerix, Millenium Takeda, Nycomed, Pharmacosmos, Actelion, Danone, Alpha Wasserman, Genentech, Grunenthal, Pfizer, Astra Zeneca, Novo Nordisk, Cosmo Pharmaceuticals, Vifor, and Johnson & Johnson.

All other authors have no conflicts of interest to disclose.

Study Quality: Alle inkludierten Primärstudien mit high risk of bias, weil nicht verblindet. Keine Unters Unterschiedliche Behandlungszeiträume

Heterogeneity: Wenig Heterogenität.

Publication Bias: Keine Evidenz für Publication Bias.

Notes:
Systematic Review und Metaanalyse von RCTs

Nielsen, Ole Haagen et al. Management of Iron-Deficiency Anemia in Inflammatory Bowel Disease: A e963. 2015

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 Study type: Systematischer Review Databases: PubMed, EMBASE, the Cochrane Library, and the websites of WHO, FDA, and EMA covered prospective trials investigating the management of iron-deficiency anemia in IBD published since 2004. Search period: Januar 2004-März 2015 Inclusion Criteria: original prospective studies evaluating the treatment of iron-deficiency anemia (ie, normalization of Hb concentration) in IBD patients with a minimum observation time of 4 weeks were included Exclusion Criteria: reviews and	Population: CED-Patienten mit Eisenmangelanämie Intervention: Eisensubstitionen, oral und/oder iv. Comparison: Eisensubstitionen, oral und/oder iv.	Primary: Nicht formal definiert. Secondary: Hb-Anstieg, Nebenwirkungen Results: - bei milder Anämie (Hb≥10g/dl) und kurzem Follow-up (4 Wochen), Überlegenheit von iv-Eisen gegenüber po-Eisen bzgl. Anstieg des Ferritins, aber nicht des Hb - bei stärkerer Eisenmangelanämie iv-Eisen bzgl. po-Eisen in Hinblick auf Hb-Anstieg überlegen Author's Conclusion: Based on the data presented, oral iron therapy should be preferred for patients with quiescent disease stages and trivial iron deficiency anemia unless such patients are intolerant or have an inadequate response, whereas intravenous iron supplementation may be of advantage in patients with aggravated anemia or flares of IBD	1. Filmann N, Rey J, Schneeweiss S, et al. Prev in european countries: a systematic review ar Bowel Dis 2014; 20:936–945. Cited Here | View Full Text | PubMed | CrossRef 2. Fiorino G, Allocca M, Danese S. Commenta most common and ignored extra intestinal mar 228. Cited Here | View Full Text | PubMed | CrossRef 3. Kulnigg S, Gasche C. Systematic review: Pharmacol Ther 2006; 24:1507–1523. Cited Here | View Full Text | PubMed | CrossRef 4. Wilson A, Reyes E, Ofman J. Prevalence a disease: a systematic review of the literature. A Cited Here | PubMed 5. Larsen S, Bendtzen K, Nielsen OH. Extra disease: epidemiology, diagnosis, and manager Cited Here | PubMed | CrossRef 6. Goodhand JR, Kamperidis N, Rao A, et al. Pı adolescents, and adults with inflammatory bow Cited Here | View Full Text | PubMed | CrossRef 7. Bager P, Befrits R, Wikman O, et al. High anemia in inflammatory bowel disease outpatie study. Scand J Gastroenterol 2013; 48:1286–129 Cited Here | PubMed 8. Gisbert JP, Gomollon F. Common misconcep in inflammatory bowel disease. Am J Gastroent Cited Here | View Full Text | PubMed | CrossRef 9. Hoivik ML, Reinisch W, Cvancarova M, et population-based 10-year follow-up. Aliment Ph Cited Here | View Full Text | PubMed | CrossRef 10. Semrin G, Fishman DS, Bousvaros A, et a disease correlates with disease activity and m 12:1101–1106. Cited Here | View Full Text | PubMed | CrossRef 11. Weiss G, Goodnough LT. Anemia of chronic Cited Here | View Full Text | PubMed | CrossRef 12. Gasche C, Berstad A, Befrits R, et al. Guid deficiency and anemia in inflammatory bowel di Cited Here | View Full Text | PubMed | CrossRef 13. Vagianos K, Clara I, Carr R, et al. What a eating? A closer look at the dietary habits of a Parenter Enteral Nutr 2015; [Epub ahead of prin Cited Here 14. Shander A, Goodnough LT, Javidroozi Knowledge and Practice Gap. Transfus Med Rev Cited Here | PubMed | CrossRef 15. Stein J, Hartmann F, Dignass AU. Diagnos patients with IBD. Nat Rev Gastroenterol Hepato Cited Here | View Full Text | PubMed | CrossRef

nonhuman investigations		**because inflammation hampers intestinal absorption of iron.**	**16. Goldberg ND. Iron deficiency anemia in pa Gastroenterol 2013; 6:61–70.** **Cited Here** **17. Hentze MW, Muckenthaler MU, Galy B, et metabolism. Cell 2010; 142:24–38.** **Cited Here | PubMed | CrossRef** **18. Pantopoulos K, Porwal SK, Tartakoff A, et Biochemistry 2012; 51:5705–5724.** **Cited Here | PubMed | CrossRef** **19. Coad J, Conlon C. Iron deficiency in wom Opin Clin Nutr Metab Care 2011; 14:625–634.** **Cited Here | View Full Text | PubMed | CrossRef** **20. Andrews NC. Disorders of iron metabolism.** **Cited Here | View Full Text | PubMed | CrossRef** **21. Weiss G, Schett G. Anaemia in inflammato 9:205–215.** **Cited Here | View Full Text | PubMed | CrossRef** **22. Nemeth E, Tuttle MS, Powelson J, et al. He ferroportin and inducing its internalization. Scie** **Cited Here | View Full Text | PubMed | CrossRef** **23. Ganz T, Nemeth E. Hepcidin and disorders 360.** **Cited Here | PubMed | CrossRef** **24. Theurl I, Aigner E, Theurl M, et al. Regul disease and iron deficiency anemia: diagno 113:5277–5286.** **Cited Here | PubMed | CrossRef** **25. Bregman DB, Morris D, Koch TA, et al. Hepc therapy in patients with iron deficiency anemia.** **Cited Here | View Full Text | PubMed | CrossRef** **26. Ludwiczek S, Aigner E, Theurl I, et al. Cytoki monocytic cells. Blood 2003; 101:4148–4154.** **Cited Here | PubMed | CrossRef** **27. Thomas C, Thomas L. Anemia of chronic di Lab Hematol 2005; 11:14–23.** **Cited Here | PubMed | CrossRef** **28. Munoz M, Garcia-Erce JA, Remacha AF. Dis and iron overload. J Clin Pathol 2011; 64:287–29** **Cited Here | View Full Text | PubMed | CrossRef** **29. Weiss G, Gasche C. Pathogenesis and trea Haematologica 2010; 95:175–178.** **Cited Here | PubMed | CrossRef** **30. Kautz L, Jung G, Valore EV, et al. Identifica iron metabolism. Nat Genet 2014; 46:678–684.** **Cited Here | PubMed | CrossRef** **31. Peyssonnaux C, Zinkernagel AS, Schuepbac hypoxia-inducible transcription factors (HIFs). J** **Cited Here | View Full Text | PubMed | CrossRef** **32. Sonnweber T, Nachbaur D, Schroll A, et al mediated by platelet derived growth factor BB.** **Cited Here | View Full Text | PubMed | CrossRef** **33. Tanno T, Bhanu NV, Oneal PA, et al. High lev of the iron regulatory protein hepcidin. Nat Med** **Cited Here | PubMed | CrossRef** **34. Theurl I, Schroll A, Nairz M, et al. Pathwa anemia of chronic disease and iron deficienc 1769.** **Cited Here | PubMed | CrossRef** **35. Lasocki S, Baron G, Driss F, et al. Diagnost in critically ill patients with anemia. Intensive Ca** **Cited Here | View Full Text | PubMed | CrossRef** **36. Mullin GE. Micronutrients and inflammatory** **Cited Here | View Full Text | PubMed | CrossRef** **37. Hwang C, Ross V, Mahadevan U. Micronut from A to zinc. Inflamm Bowel Dis 2012; 18:196** **Cited Here | View Full Text | PubMed | CrossRef** **38. WHO, Geneva, Switzerland. Iron deficinecy guide for program http://www.who.int/nutrition/publications/en/ida**

April 29, 2015.
Cited Here
39. Gomollon F, Gisbert JP, Garcia-Erce JA. I
(re)view. Ther Adv Chronic Dis 2010; 1:67–75.
Cited Here
40. Klein HG, Spahn DR, Carson JL. Red blood
370:415–426.
Cited Here | PubMed | CrossRef
41. Goodnough LT, Bach RG. Anemia, transfus
1274.
Cited Here | View Full Text | PubMed | CrossRef
42. Villanueva C, Colomo A, Bosch A, e
gastrointestinal bleeding. N Engl J Med 2013; 3
Cited Here | View Full Text | PubMed | CrossRef
43. Taylor RW, Manganaro L, O'Brien J, et
transfusion on nosocomial infection rates in the
2254.
Cited Here | View Full Text | PubMed | CrossRef
44. Talbot TR, D'Agata EM, Brinsko V, et al.
poststernotomy surgical site infection: marker
Infect Dis 2004; 38:1378–1382.
Cited Here
45. Aubron C, Nichol A, Cooper DJ, et al. Age
patients. Ann Intensive Care 2013; 3:2.
Cited Here
46. Bihl F, Castelli D, Marincola F, et al. Trans
5:25.
Cited Here
47. Guinet F, Carniel E, Leclercq A. Transfusio
Infect Dis 2011; 53:583–591.
Cited Here | View Full Text | PubMed | CrossRef
48. Santiago P. Ferrous versus ferric oral iron f
clinical overview. Scient World J 2012; 2012:846
Cited Here
49. Fuqua BK, Vulpe CD, Anderson GJ. Intesti
26:115–119.
Cited Here | PubMed | CrossRef
50. Aspuru K, Villa C, Bermejo F, et al. Optimal r
dietary intake. Int J Gen Med 2011; 4:741–750.
Cited Here
51. Gasche C, Ahmad T, Tulassay Z, et al. Ferr
anemia in patients with inflammatory bowel dis
Inflamm Bowel Dis 2015; 21:579–588.
Cited Here | View Full Text | PubMed | CrossRef
52. Hallberg L, Ryttinger L, Solvell L. Side-effe
different iron compounds in tablet form. Acta M
Cited Here | PubMed
53. Cook JD. Diagnosis and management o
Haematol 2005; 18:319–332.
Cited Here | PubMed | CrossRef
54. de Silva AD, Tsironi E, Feakins RM, et al
inflammatory bowel disease: a prospective, c
22:1097–1105.
Cited Here | View Full Text | PubMed | CrossRef
55. Erichsen K, Milde AM, Arslan G, et al. Low
inflammation in rats with DSS-induced colitis. Ir
Cited Here | View Full Text | PubMed | CrossRef
56. Dignass AU, Gasche C, Bettenworth D, e
management of iron deficiency and anaemia i
2015; 9:211–222.
Cited Here | PubMed
57. Rizvi S, Schoen RE. Supplementation with
gastrointestinal bleeding: is oral iron getting a b
Cited Here
58. Lee TW, Kolber MR, Fedorak RN, et al. I
disease patients with iron deficiency anemia:
Colitis 2012; 6:267–275.
Cited Here | PubMed
59. Kostic AD, Xavier RJ, Gevers D. The mic

status and the future ahead. Gastroenterology 2
Cited Here | PubMed | CrossRef
60. Werner T, Wagner SJ, Martinez I, et al. Depl
prevents Crohn's disease-like ileitis. Gut 2011; 6
Cited Here | View Full Text | PubMed | CrossRef
61. FDA: Highlights of Prescription In
http://www.accessdata.fda.gov/drugsatfda_docs
2015.
Cited Here
62. EMA: New recommendations to manage
containing medicines.
curl=pages/news_and_events/news/2013/06/nev
Accessed April 29, 2015.
Cited Here
63. Rampton D, Folkersen J, Fishbane S, et a
guidance for risk minimization and managemen
Cited Here
64. Reinisch W, Staun M, Tandon RK, et al. A
intravenous iron isomaltoside 1,000 (monofer) c
IBD (PROCEED). Am J Gastroenterol 2013; 108:
Cited Here | View Full Text | PubMed | CrossRef
65. Auerbach M, Ballard H. Clinical use of intra
Hematology Am Soc Hematol Educ Program 20
Cited Here | CrossRef
66. Gomollon F, Gisbert JP. Intravenous iro
Gastroenterol 2013; 29:201–207.
Cited Here | View Full Text | PubMed | CrossRef
67. Gomollon F, Chowers Y, Danese S,
recommendations for allergic reactions to
Pharmacol Ther 2014; 39:743–744.
Cited Here | View Full Text | PubMed | CrossRef
68. Chertow GM, Mason PD, Vaage-Nilsen O, c
with parenteral iron. Nephrol Dial Transplant 20
Cited Here | View Full Text | PubMed | CrossRef
69. Khalil A, Goodhand JR, Wahed M, et al. Eff
and oral iron in inflammatory bowel disease:
Gastroenterol Hepatol 2011; 23:1029–1035.
Cited Here | View Full Text | PubMed
70. Koutroubakis IE, Oustamanolakis P, Karak
infusion of low molecular weight iron dextr
inflammatory bowel disease. Dig Dis Sci 2010; 5
Cited Here | View Full Text | PubMed | CrossRef
71. Rodgers GM, Auerbach M, Cella D, et al. Hig
clothing? J Am Soc Nephrol 2008; 19:833–834.
Cited Here
72. Schroder O, Mickisch O, Seidler U, et
supplementation for the treatment of iron defic
disease: a randomized, controlled, open-labe
100:2503–2509.
Cited Here | View Full Text | PubMed | CrossRef
73. Red Book. Pharmacy's Fundamental Refere
2010.
Cited Here
74. Esposito BP, Breuer W, Sirankapracha P,
activity and susceptibility to chelation. Blood 20
Cited Here | PubMed | CrossRef
75. Koskenkorva-Frank TS, Weiss G, Koppe
metabolism, reactive oxygen species, and react
various iron therapies to induce oxidative an
65C:1174–1194.
Cited Here | View Full Text | CrossRef
76. Beigel F, Lohr B, Laubender RP, et al. Iron s
carboxymaltose treatment in patients with infla
Cited Here | PubMed | CrossRef
77. Evstatiev R, Marteau P, Iqbal T, et al. FE
carboxymaltose for iron deficiency anemia in
2011; 141:846–853.
Cited Here | PubMed | CrossRef
78. Evstatiev R, Alexeeva O, Bokemeyer B, et

anemia in patients with inflammatory bowel d
277.
Cited Here | View Full Text | PubMed | CrossRef
79. Kulnigg S, Stoinov S, Simanenkov V, et al. A
of anemia in inflammatory bowel disease: the
controlled trial. Am J Gastroenterol 2008; 103:1
Cited Here | View Full Text | PubMed | CrossRef
80. Onken JE, Bregman DB, Harrington RA, e
study to investigate the efficacy and safety of i
iron deficiency anemia. Transfusion 2014; 54:30
Cited Here | View Full Text | PubMed
81. Gozzard D. When is high-dose intravenous
options. Drug Des Devel Ther 2011; 5:51–60.
Cited Here
82. Nordfjeld K, Andreasen H, Thomsen LL.
patients with inflammatory bowel disease. Drug
Cited Here
83. McCormack PL. Ferumoxytol: in iron de
disease. Drugs 2012; 72:2013–2022.
Cited Here | View Full Text | PubMed | CrossRef
84. Hetzel D, Strauss W, Bernard K, et al. A pha
compared with iron sucrose for the treatment o
of unsatisfactory oral iron therapy. Am J Hemat
Cited Here | View Full Text | PubMed | CrossRef
85. Schieda N. Parenteral ferumoxytol intera
report, review of the literature and advisory war
Cited Here
86. Bailie GR. Comparison of rates of reported
in the United States. Am J Health Syst Pharm 20
Cited Here | View Full Text | PubMed | CrossRef
87. Auerbach M, Ballard H, Glaspy J. Clinical u
369:1502–1504.
Cited Here | PubMed | CrossRef
88. Chertow GM, Winkelmayer WC. On the rela
answers, new questions. Am J Hematol 2010; 8
Cited Here | View Full Text | PubMed | CrossRef
89. Fishbane S, Ungureanu VD, Maesaka JK,
hemodialysis patients. Am J Kidney Dis 1996; 2
Cited Here | PubMed | CrossRef
90. Auerbach M, Coyne D, Ballard H. Intraveno
Hematol 2008; 83:580–588.
Cited Here | View Full Text | PubMed | CrossRef
91. Moher D, Liberati A, Tetzlaff J, et al. Prefe
meta-analyses: the PRISMA statement. PLoS M
Cited Here | PubMed
92. Gisbert JP, Bermejo F, Pajares R, et al. Ora
bowel disease: hematological response and qu
15:1485–1491.
Cited Here | View Full Text | PubMed | CrossRef
93. Katsanos K, Cavalier E, Ferrante M, et al.
deficiency induced by infliximab. J Crohns Coli
Cited Here
94. Lindgren S, Wikman O, Befrits R, et al. I
sulphate for correcting anaemia and restori
controlled, evaluator-blind, multicentre study. S
Cited Here | PubMed
95. Gasche C, Lomer MC, Cavill I, et al. Iron,
2004; 53:1190–1197.
Cited Here | View Full Text | PubMed | CrossRef
96. Oldenburg B, Koningsberger JC, Van Berg
bowel disease. Aliment Pharmacol Ther 2001; 1
Cited Here | View Full Text | PubMed | CrossRef
97. Theurl I, Mattle V, Seifert M, et al. Dysregulat
formation in patients with anemia of chronic dis
Cited Here | PubMed | CrossRef
98. Goddard AF, McIntyre AS, Scott BB. Gu
anaemia. British Society of Gastroenterology. G
Cited Here
99. Anker SD, Comin CJ, Filippatos G, et al. Fe

and iron deficiency. N Engl J Med 2009; 361:243
Cited Here | View Full Text | PubMed | CrossRef
100. Jankowska EA, Malyszko J, Ardehali H,
failure. Eur Heart J 2013; 34:827–834.
Cited Here | View Full Text | PubMed | CrossRef
101. Litton E, Xiao J, Ho KM. Safety and e
requirement for allogeneic blood transfusi
randomised clinical trials. BMJ 2013; 347:f4822.
Cited Here | View Full Text | PubMed | CrossRef
102. Stein J, Bager P, Befrits R, et al. Anaemia
disease: routine practice across nine Europe
25:1456–1463.
Cited Here | View Full Text | PubMed | CrossRef
103. Ganzoni AM. Intravenous iron-dextran: th
Med Wochenschr 1970; 100:301–303.
Cited Here | PubMed
104. Reinisch W, Chowers Y, Danese S, et al. TI
bowel disease: an online tool developed by th
Pharmacol Ther 2013; 38:1109–1118.
Cited Here | View Full Text | PubMed | CrossRef
105. Katsanos KH, Tatsioni A, Natsi D, et al. Re
inflammatory bowel disease and refractory ane
Colitis 2012; 6:56–61.
Cited Here | PubMed
106. Liu S, Ren J, Hong Z, et al. Efficacy of eryt
treatment of anemia in Crohn's disease: a prosp
127.
Cited Here
107. Solomon SD, Uno H, Lewis EF, et al. E
disease and type 2 diabetes. N Engl J Med 2010
Cited Here | View Full Text | PubMed | CrossRef
108. Camaschella C. Iron-deficiency anemia. N E
Cited Here | View Full Text | PubMed | CrossRef
109. Drueke TB, Parfrey PS. Summary of the K
between the (guide)line(s). Kidney Int 2012; 82:S
Cited Here | PubMed | CrossRef
110. Zitt E, Sturm G, Kronenberg F, et al. Iron s
patients: an observational study. PLoS One 201
Cited Here | PubMed | CrossRef
111. Goldsmith JR, Sartor RB. The role of diet
impacts on host immune function and health, a
49:785–798.
Cited Here | PubMed | CrossRef
112. Oustamanolakis P, Koutroubakis IE, Mess
concentrations in inflammatory bowel disease.
Cited Here | View Full Text | PubMed | CrossRef
113. Ganz T. Systemic iron homeostasis. Physio
Cited Here | PubMed | CrossRef
114. Nielsen OH, Ainsworth MA. Tumor necrosis
N Engl J Med 2013; 369:754–762.

Methodical Notes

Funding Sources: The National Danish Health Care System and Austrian Research Funds (FWF-TRP188) funded the research but had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

COI: OHN, MA, andMChave no conflicts of interest to disclose.GWhas received lecture honoraria from Vifor Pharma and Pharmacosmos.

Study Quality: Studies were heterogeneous in design (ie, inclusion criteria and iron compositions administere drugs), different enrollment populations as well as different lengths of therapy, and outcomes. Further, in s period was employed, although it is questionable whether such a short interval is always effective for the c efficacy of the oral supplementation may be underestimated compared with a full treatment period of, for exam

Heterogeneity: Heterogenes Studiendesign

Publication Bias: Keine Angaben.

Notes:
Systematischer Review von RCTs und prospektiven Studien

OXFORD (2011) Appraisal Sheet: RCT: 1 Bewertung(en)

Reinisch, Walter et al. A randomized, open-label, non-inferiority study of intravenous iron isomaltosid treatment of anemia in IBD (PROCEED). Am. J. Gastroenterol. 108. 1877-88. 2013

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type: Individueller RCT** **Number of Patient: 225 Eisenisomaltosid, 113 Eisensulfat** **Recruitung Phase: December 2009 to July 2012.** **Inclusion Criteria: Patients ≥ 18 years of age with a diagnosis of IBD and a score of** **≤ 5 on the Harvey – Bradshaw index for Crohn ' s disease (25) or a** **partial Mayo score of ≤ 6 for ulcerative colitis (26), a Hb < 12 g / dl** **(7.45 mmol / l), and a transferrin saturation (TSAT) < 20 %** **Exclusion Criteria: intolerance to** **oral iron treatment, other primary causes of anemia, hemochromatosis,** **hemosiderosis, hypersensitivity to IV iron complexes** **or iron sulfate, a history of multiple allergies, active intestinal** **tuberculosis / amoebic infections, liver cirrhosis, active hepatitis,** **acute infections, rheumatoid arthritis along with symptoms or** **signs of active joint infl ammation, untreated vitamin B 12 / folate** **defi ciency, pregnant or nursing women, and patients with extensive** **active bleeding necessitating blood transfusion or with** **planned elective surgery during the study**	**Intervention: Eisenbedarf nach Ganzoni-Formel berechnet. Dann:** **- Gruppe A1: 1000mg Eisenisomaltosid i.v. pro Woche bis zum errechneten Bedarf** **- Gruppe A2: 500mg Eisenisomaltosid i.v. pro Woche bis zum errechneten Bedarf** **Comparison: 200mg Eisensulfat täglich für 8 Wochen**	**Primary: Hb-Veränderung im Vgl. '** **Secondary: Th e secondary end p** **in Hb concentration from baseline** **concentrations of s- ferritin and TS** **number of patients who discontinu** **response or intolerance of investig** **QoL score from baseline to weeks** **Infl ammatory Bowel Disease Ques** **(adverse events (AEs), vital signs,** **and other safety hematology and b** **Results: Überlegenheit von Eisen** **den primären Endpunkt, mit Sign** **full analysis set (p=0.04)** **Eisenisomaltosid überlegen be** **Transferrinsättigungsanstieg höhe** **Keine Gruppenunterschiede in der** **Keine Gruppenunterschiede bzgl.** **Prädiktoren besserer Wirksamkei** **und höherer Eisenbedarf** **Author's Conclusion: We cou** **isomaltoside 1,000 compared with** **this study. Based on the dose –** **compound, we suggest** **that the true iron demand of IV iro** **our study.** **Alternative calculations including** **stores in patients** **with IBD.**

Methodical Notes

Funding Sources: Th e study was funded by Pharmacosmos A / S.
Pharmacosmos A / S was responsible for setup of the study, collection, analyses, and interpretation of the data, and in the writing of
the report.

COI: Lars L. Th omsen is employed by
Pharmacosmos A / S, and the investigators / institutions received a fee per patients.

Randomization: Permuted block randomization was used to assign patients in a

1:1:1 ratio to receive either treatment A1 (weekly infusion of up to 1,000 mg iron isomaltoside 1,000 until reaching cumulative dosage), A2 (weekly 500 mg bolus injections of iron isomaltoside 1,000 until reaching cumulative dosage), or B (200 mg oral iron sulfate daily for 8 weeks). Th e block size was 6.
Th e randomization list was prepared centrally by a Contract Research Organization, Max Neeman International Data Management Centre, using a validated computer program (Statistical Analysis Soft ware (SAS) 9.1.3, SAS Institute Inc, Cary, NC) PROC PLAN procedure). Th e randomization was stratifi ed by whether the patient had received IV iron treatment in the past or not.

Blinding: Kein Blinding

Dropout Rate/ITT-Analysis: Dropout-Rate 9-16% pro Gruppe. ITT und PP-Analyse durchgeführt

Notes:
Individueller RCT

Literatursammlung:

AG 7 Ernährung, Psycho, Komplementär-Frage 1

Inhalt: 10 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Bennebroek Evertsz', Floor 2017	2	RCT
Berrill, James W 2014	2	RCT
Keerthy, Divya 2016	3	RCT
Levy, Rona L 2016	2	RCT
Mikocka-Walus, Antonina 2017	2	RCT
Mikocka-Walus, Antonina 2015	2	RCT
Stapersma, Luuk 2018	2	RCT
Szigethy, Eva 2015	3	Randomised controled ? trial
Vogelaar, Lauran 2014	2	RCT
Wynne, Brona 2019	2	RCT

OXFORD (2011) Appraisal Sheet: RCT: 10 Bewertung(en)

Bennebroek Evertsz', Floor et al. Effectiveness of cognitive-behavioral therapy on quality of life, anxiety, and depressive symptoms among patients with inflammatory bowel disease: A multicenter randomized controlled trial. J Consult Clin Psychol. 85. 918-925. 2017

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: RCT Number of Patient: 118 Recruitung Phase: Inclusion Criteria: (a) Diagnose von Morbus Crohn (CD) oder Colitis ulcerosa (UC) (b) Alter über 18 Jahre (c) Punktzahl von 23 auf der Subskala für psychische Gesundheit der Medical Outcomes Study Short Form 36 Health Survey (d) körperliche und geistige Fähigkeit, an acht wöchentlichen	Intervention: 8 wöchige kognitiv-verhaltenstherapeutische Therapie Comparison: Wartekontrollgruppe	Primary: Inflammatory Bowel Disease Questionnaire [IBDQ] Secondary: Hospital Anxiety and Depression Scale–Depression Subscale [HADS-D] Center for Epidemiologic Studies Depression Scale [CES-D]) anxiety (HADS–Anxiety Subscale [HADS-A]) generic QoL (SF-36) Results: Die CBT hatte eine positive Wirkung auf die krankheitsspezifische Lebensqualität, Depression, Angstzustände und die allgemeine Lebensqualität. Author's Conclusion: IBD-spezifische CBT ist wirksam bei der Verbesserung der Lebensqualität und bei der Verringerung von Angst und Depression bei IBD-Patienten mit schlechter Lebensqualität. Kliniker sollten ein Screening auf schlechte geistige Lebensqualität einbeziehen und erwägen, CBT anzubieten.

Sitzungen teilzunehmen (e) Beherrschung der niederländischen Sprache **Exclusion Criteria: (a) aktuelle Psychotherapie (b) schwere andere psychiatrische Störungen (z.B. Drogenmissbrauch, bipolare Störungen oder Psychosen)**		

Methodical Notes

Funding Sources: keine Angabe

COI: keine Angabe

Randomization: TENALEA Clinical Trial Data Management System software (http:// www.formsvision.com)

Blinding: keine Angabe (Wartekontrollgruppe?)

Dropout Rate/ITT-Analysis: 10 Patienten in der Interventions-, 12 in der Wartekontrollgruppe

Notes:

Berrill, James W et al. Mindfulness-based therapy for inflammatory bowel disease patients with functional abdominal symptoms or high perceived stress levels. J Crohns Colitis. 8. 945-55. 2014

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type: RCT** **Number of Patient: 66** **Recruitung Phase: gastroenterology clinics at the University Hospital Llandough and the University Hospital of Wales, Cardiff, United Kingdom between February 2011 and May 2012** **Inclusion Criteria: 1. age 18–65 years 2. diagnosis of UC or CD that was in remission based on a clinical index score and a C-reactive protein level b 10 mg/l 3. presence of IBS-type symptoms or a high perceived stress level**	**Intervention: Multi-convergent therapy (MCT) for 16 weeks** **Comparison: waiting list control group**	**Primary: Inflammatory Bowel Disease Questionnaire (IBDQ)** **Secondary: - descriptive analysis of the acceptability and feasibility of administering MCT to an IBD population** **- the effect of MCT on disease activity** **- levels of perceived stress and coping mechanisms** **Separate exploratory sub-group analyses were performed on those patients with FC b 150 µg/g at baseline, those recruited with IBS-type symptoms at baseline, and those recruited with a high perceived stress level at baseline.** **Results: A higher mean IBDQ score was observed in the active group compared to controls at the 4-month assessment, but this was not statistically significant nor did it reached the predefined clinically significant difference of 20. In patients with IBS-type symptoms at baseline there was a significantly higher mean IBDQ score in the active group compared to controls.** **Author's Conclusion: IBS-type symptoms in patients with IBD represent a potential therapeutic target to improve quality of life. This study suggests that MCT may be useful in the management of these symptoms but larger studies are required to confirm this.**

Exclusion Criteria: 1. pregnancy 2. presence of ileostomy or colostomy 3. previous colectomy 4. change in IBD medication (including use of steroids) within 3 months of study entry 5. change in psychotropic medication within 3 months of study entry 6. diagnosis of cognitive impairment 7. previous psychological therapy		

Methodical Notes

Funding Sources: The South East Wales Trials Unit is funded by the National Institute for Social Care and Health Research (NISCHR)

COI: No

Randomization: YES

Blinding: NO

Dropout Rate/ITT-Analysis: 7 by 4 months-follow-up

Notes:

Keerthy, Divya et al. Effect of Psychotherapy on Health Care Utilization in Children With Inflammatory Bowel Disease and Depression. J. Pediatr. Gastroenterol. Nutr. 63. 658-664. 2016

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 **Study type: RCT** **Number of Patient: 70** **Recruitung Phase: Pediatric GI clinics and inpatient units at Children's Hospital of Pittsburgh of UPMC and Boston Children's Hospital** **Inclusion Criteria: - major or minor depression by DSM-IV-TR criteria** **Exclusion Criteria: - current or past history of eating disorder requiring hospitalization**	**Intervention: One year of psychotherapy** **Comparison: healthcare utilization 12-months prior to psychotherapy compared to the 12 month following the conclusion of psychotherapy**	**Primary: - frequency of hospitalization** **Secondary: - inpatient hospital days - outpatient gastrointestinal visits - number of emergency room visits - radiological exams - endoscopies** **Results: All study measures of healthcare utilization were significantly reduced after psychotherapy (p <0.01) – including gastrointestinal-related hospitalization frequency, inpatient days, outpatient visit, emergency room visits, radiological exams, and endoscopies.** **Author's Conclusion: Psychotherapy for comorbid depression in pediatric patients with IBD is associated with decreased GI-related healthcare utilization.**

- bipolar disorder or psychotic disorder according to DSM-IV TR criteria - antidepressant medications within one month of study entry - major depressive episode requiring psychiatric hospitalization within three months of study entry - suicide attempt within one month of study entry - history of substance abuse or dependence within one month of study entry and/or current psychotherapy		

Methodical Notes

Funding Sources: This research was funded by the National Institute of Mental Health (R01 MH07777), the NIH Director's Innovator Award (1DP2OD001210), NIMH training grant (R25MH054318), and the Crohn's & Colitis Foundation of America Research Fellowship Award #3590.

COI: A.B. has received consulting fees from Millenium, Dyax, Cubist, and Nutricia, lecture fees from Merck, and royalties from UpToDate. D.R.D. has received royalties from American Psychiatric Publishing Inc. E.M.S. is a paid advisor for Merck, Abbvie, and iHope Networks Inc has received payment for expert testimony in a malpractice case, has received payment from Imedex for speaking at a CCFA meeting, and receives royalties as book editor from American Psychiatric Publishing Inc.

Randomization: yes

Blinding: no

Dropout Rate/ITT-Analysis: 147 were not included in this analysis because 86 were diagnosed less than 1 year before enrollment and 61 were followed less than 1 year after enrollment.

Notes:

Levy, Rona L et al. Effects of a Cognitive Behavioral Therapy Intervention Trial to Improve Disease Outcomes in Children with Inflammatory Bowel Disease. Inflamm. Bowel Dis. 22. 2134-48. 2016

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: RCT Number of Patient: 185 Recruitung Phase: Pediatric GI clinics at Seattle Children's Hospital and Mary Bridge Children's Hospital in Tacoma, WA. Inclusion Criteria: (1) child aged 8 to 17 years	Intervention: (1) cognitive behavioral therapy condition Comparison: (2) an education support condition designed to control for time and attention.	Primary: - quality of life - number of missed school days due to CD or UC Secondary: - Parent report only - Child report only - Parent and Child Report - Physician Report - anxiety or depression Results: There was a significant overall treatment effect for school absences due to Crohn's disease or ulcerative colitis (P , 0.05) at 6 months after treatment. There was also a significant overall effect after treatment for child-reported quality of life (P , 0.05), parent-reported increases in adaptive child coping (P , 0.001), and reductions in parents' maladaptive responses to children's symptoms (P , 0.05). Author's Conclusion: This trial suggests that a brief cognitive

(2) child received a diagnosis of Crohn's or UC and was at least 3 months after diagnosis (3) child lived with the participat- ing parent or caregiver for at least the last 3 months (4) child and parent were willing and able to complete the questionnaires and agreed to participate in the intervention and follow-up evalua- tions (5) child was medically approved to engage in normal activities (e.g., attend school, extracurricular activities). Exclusion Criteria: (1) a chronic disease other than IBD (e.g., pancreatitis, diabetes, epilepsy) (2) major surgery within the past year unrelated to IBD (3) developmental disabilities requiring full-time special education or impairing ability to communicate (4) non-English speaking		**behavioral intervention for children with inflammatory bowel disease and their parents can result in improved child functioning and quality of life, and for some children may decrease disease activity.**

Methodical Notes

Funding Sources: Supported by a grant from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (award number R01HD050345 to R. L. Levy).

COI: NO

Randomization: Yes

Blinding: Yes

Dropout Rate/ITT-Analysis: 16

Notes:

Mikocka-Walus, Antonina et al. Cognitive-Behavioural Therapy for Inflammatory Bowel Disease: 24-Month Data from a Randomised Controlled Trial. Int J Behav Med. 24. 127-135. 2017

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: RCT	**Intervention: cognitive-behavioural therapy (CBT) over**	**Primary: remission at 24 months (established using the CDAI) Secondary: - subjective view of IBD activity**

Number of Patient: 176 **Recruitung Phase: Two gastroenterology clinics in Australia** **Inclusion Criteria: - established diagnosis of IBD** **- in clinical remission or had mild symptoms only for at least 3 months** **- aged 18 years or over** **- competence to consent** **Exclusion Criteria: - mental illness (e.g. psychosis, schizophrenia or any other serious mental disorder requiring one-to-one therapy which could not be offered as part of the trial)** **- receiving psychotherapy**	**10 weeks face to face or online AND standard care for IBD** **Comparison: standard care for IBD**	**measured by a question How well con- trolled is your IBD** **- disease activity measured on the blood parameters: C-reactive protein (CRP), haemoglobin (Hb), platelet, white cell count (WCC)** **- quality of life as measured on the Short Form 36 Health Status Questionnaire (SF-36)** **- mental health status (anxiety and depression as measured on the HADS and the State-Trait Anxiety Inventory (STAI)** **- stress measured on the Revised Social Readjustment Rating Scale (RSRRS)and coping as measured on the Brief COPE and the IBD Stages of Change Coping Questionnaire (IBDSCCQ)** **at 24 months** **Results: CBT did not significantly influence disease activity as measured by disease activity indices at 24 months** **Author's Conclusion: We conclude that CBT does not influ- ence the course of IBD over 24 months. Given the high rate of attrition, particularly in the CBT group, future trials should consider a personalised approach to psychotherapy, perhaps combining online and one-to-one therapist time.**

Methodical Notes

Funding Sources: The study received additionally unsolicited funding from Abbott Australia, MSD Australia and Janssen. Support was also provided by untied research funding held in the Department of Gastroenterology and Hepatology at the RAH and from JMA's personal research fund earned from consulting work for pharma and educational lectures. Study sponsors had no involvement in the study design, in the collection, analysis and interpretation of data, in the writing of the man- uscript or in the decision to submit the manuscript for publication.

COI: NO

Randomization: Yes

Blinding: No

Dropout Rate/ITT-Analysis: 101

Notes:

Mikocka-Walus, Antonina et al. Cognitive-behavioural therapy has no effect on disease activity but improves quality of life in subgroups of patients with inflammatory bowel disease: a pilot randomised controlled trial. BMC Gastroenterol. 15. 54. 2015

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type: RCT** **Number of Patient: 174** **Recruitung Phase: Participants were recruited from two Gastroenterology Clinics in Australia, together serving approximately 2,000 IBD patients.** **Inclusion Criteria: Patients had to meet ALL of the following criteria: 1). a**	**Intervention: CBT was a 10-week group program designed specifically for this patient population by senior clinical psycholo- gists working at the hospital Clinical Psychology Unit (not study investigators).** **The CBT program (2**	**Primary: IBD remission at 12 months since baseline** **Secondary: mental health status and quality of life (QoL)** **Results: Participants were 174 patients with IBD (90 +CBT, 84 SC). There was no difference in remission rates between groups, with similar numbers flaring at 12 months. Groups did not differ in anxiety, depression or coping at 6 or 12 months (p >0.05). When only**

clinically established diagnosis of IBD (according to usual clinical practice by combination of clinical, radiologic, endoscopic and histologic grounds in a tertiary care IBD centre); 2). current clinical remission or mild symptoms only for at least 3 months as evidenced by disease activity index, notes review, blood results and report from their treating gastroenterologist, if necessary (complete loss of GI symptoms in IBD is uncommon even during endoscopic remission); 3). sufficient English to understand, answer questionnaires and participate in therapy; 4). 18 years old or older; 5). competence to consent; 6). willingness to complete CBT sessions. Exclusion Criteria: Patients were excluded if they met ANY of the following: 1). serious mental illness (e.g. psychosis, schizophrenia) or alcohol/substance dependence as diagnosed by the Clinical Psychologist; 2). currently undergoing psychotherapy; 3). significant cognitive impairment. Antidepressants were not an exclusion as antidepressants are commonly used in IBD not necessarily to treat anxiety or depression but rather, in a similar fashion they are used in functional gut disorders, to manage pain and abdominal discomfort and thus may be considered usual care.	hours each week) consisted of: 1) Education about IBD and CBT; 2) Stress and relaxation; 3) Automatic thoughts and cognitive distortions; 4) Cognitive restructuring; 5) Exposure and overcoming avoidance; 6) Coping strategies; 7) Assertiveness training; 8) Relationships and communication; 9) Attention and distraction; and 10) Relapse prevention for mental health problems. Attendance at each weekly session was noted by the psychologist and registered by the CBT website in the case of online groups.Compliance with the program was monitored by the psychologist on a regular basis and strategies to minimise attrition included regular reminders (telephone, email). Non-compliant patients were contacted by the psychologist individually and inquired about their views on how this may be improved. Withdrawing patients were asked for permission to retain data to date. Treatment fidelity was maintained by using the same protocol for both groups within the CBT arm. Online CBT was provided using the university IT infrastructure support. Comparison: standard care	participants classified as ‘in need’ (young, high baseline IBD activity, recently diagnosed; poor mental health) were examined in the post-hoc analysis (n = 74, 34 CBT and 40 controls), CBT significantly improved mental QoL (p = .034, d = .56) at 6 months. Online CBT group had a higher score on Precontemplation than the F2F group, which is consistent with less developed coping with IBD in the cCBT group (p = .045). Author's Conclusion: uture studies should direct psychological interventions to patients ‘in need’and attempt to recruit larger samples to compensate for significant attrition when using online CBT.

Methodical Notes

Funding Sources: the study received additionally unsolicited funding from Abbott Australia, MSD Australia and Janssen. Support was also provided by untied research funding held in the Department of Gastroenterology and Hepatology at the RAH and from JMA’s personal research fund earned from consulting work for pharma and educational lectures. No editorial support was received in the

preparation of this paper. Study sponsors had no involvement in the study design, in the collection, analysis and interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication.

COI:

Randomization: A simple randomisation method was used using a table of computer generated random numbers (in blocks of four) in the proportion of 2:1 (experimental vs. control). This proportion was used as we predicted problems in recruiting to the experimental arm (due to a larger participant burden) and assumed that we needed to approach twice as many experimental participants to eventually obtain the same number of participants in both groups. A randomisation schedule was created by the researcher with no direct patient contact using computer software (AE). Participants were enrolled by Research Nurses (not this study's investigators) who also assigned participants to interventions.

Blinding: iven impossibility of blinding the intervention, we decided to withdraw the information regarding the intervention from the controls.

Dropout Rate/ITT-Analysis: High number in losses to follow-up: Intervention group: n=92, follow up 6 month: n=51, follow up 12 month: n=42. Control group: n=84, follow up 6 month: n=65, follow up 12 month: n=64.

Notes:
groups do not seem similar at the start of the trial. No p-values mentioned. High numbers in losses to follow-up.

Stapersma, Luuk et al. Effectiveness of Disease-Specific Cognitive Behavioral Therapy on Anxiety, Depression, and Quality of Life in Youth With Inflammatory Bowel Disease: A Randomized Controlled Trial. J Pediatr Psychol. 43. 967-980. 2018

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type: RCT** **Number of Patient: Number of patients: 70. CAU group: 33; CAU + CBT group: 37.** **Recruitung Phase: Initially, only patients 10–20 years old were included. A few months after the start of the recruitment,patients of age 21–25 years were also included, to include more patients in young adulthood as well, to cover the transition phase.** **Included for baseline screening for symptoms of anxiety and depression were adolescents and young adults of age 10–25 years with a confirmed diagnosis of IBD (CD, UC, or inflammatory bowel disease-unclassified [IBD-U]; Figure 1). Between October 2014 and October 2016, patients were consecutively recruited**	**Intervention: The PASCET-PI is a disease-specific CBT protocol, developed for adolescents with IBD and depression.** **The PASCET-PI contained 10 weekly individual sessions, delivered in 3 months. Conform the protocol, six of these sessions were face-to-face, the remaining four sessions were by phone at a prearranged moment (to advance adherence and lower the treatment burden). In addition, three family sessions (for patients and their parents) were held (only for patients equal or younger than 20 years), and following the weekly sessions, three monthly individual booster sessions were held by telephone (this was after the immediate post[-treatment] assessment).** **The original PASCET-PI was developed for depression, therapists were instructed how to make the exercises more**	**Primary: Primary analysis concerned the reliable change in anxiety and depressive symptoms after 3 months (immediate posttreatment assessment).** **Fisher's exact test:** **In the primary analysis, RCI values did not differ between the two groups for both anxiety and depression. Overall, patients in both groups either remained stable or improved in their symptoms of anxiety and depression.** **Exploratory analyses:** **The same pattern was seen. No significant time–group interaction effect was found for anxiety and IBDQ the effect of time was significant, whereas for the CDI, this was not the case. These findings show that, after 3 months, all patients improved in their symptoms of anxiety and depression, as well as in their HRQOL. Even when**

from the pediatric or (pediatric) gastroenterology departments of two academic hospitals and four community hospitals. Inclusion Criteria: Inclusion baseline screening: Included for baseline screening for symptoms of anxiety and depression were adolescents and young adults of age 10–25 years with a confirmed diagnosis of IBD (CD, UC, or inflammatory bowel disease-unclassified [IBD-U]. Inclusion RCT: Only youth with subclinical anxiety and/or depressive symptoms were included in the RCT. Exclusion Criteria: Exclusion baseline screening: Exclusion criteria were (1) intellectual disability; (2) current treatment for mental health problems (pharmacological and/or psychological); (3) insufficient mastery of the Dutch language; (4) a diagnosis of selective mutism, bipolar disorder, schizophrenia/psychotic disorder, autism spectrum disorders, obsessive-compulsive disorder, posttraumatic or acute stress-disorder, substance use disorder (parent- or self-reported or from medical file); (5) CBT in the past year (at least eight sessions); and (6) participation in another interventional study, all assessed by the treating physician using medical files (unless otherwise specified). Exclusion RCT: Patients with clinical anxiety and/or depression were excluded, as we deemed it unethical to randomize them.	anxiety-tailored, an anxiety hierarchy and step-bystep exercise was added, and an extra anxiety handout was provided to the patients. For patients of age 21–25 years, the practice book was made more ageappropriate. Comparison: The control group received standard medical care (care-asusual, CAU) only, as this resembles the current care best. CAU consisted of regular medical appointments with the (pediatric) gastroenterologist every 3months, consisting of a 15-min consultation discussing overall well-being, disease activity, results of diagnostics tests, medication use, and future diagnostic/treatment plans.	these analyses were carried out only in patients who showed relatively “high” subclinical problems (“high” n=40 vs. “low” n=30), no group differences were found on the anxiety and depression outcomes (data not shown). Over all: No group differences were found on the anxiety and depression outcomes. Secondary: Additional research questions were as follows: (1) What is the course of anxiety and depressive symptoms and HRQOL in subgroups based on age, regarding the effect of CBT? (2) What is the influence of age, gender, and disease type on the course of anxiety and depressive symptoms and HRQOL, regarding the effect of CBT? By these questions, we aim to examine which patients may benefit most from the diseasespecific CBT. (1) In exploratory analyses for the four separate agegroups (classified by the four age-attuned questionnaires: SCARED [10–20 years], HADS [21–25 years], CDI [10–17 years], BDI-II [18–25 years]), no differences were found between the groups as to the change in anxiety, depression, or HRQOL. Over all: No age effect. (2) We explored the possible influence of gender and disease type on the effect of the PASCETPI by conducting linear mixed model analyses separately in subgroups (male vs. female and CD vs. UC and IBD-U). Overall, none of the subgroup analyses showed a difference between two groups on anxiety, depression, or HRQOL, except for a significant lower score on the BDI-II in the CAU group (n=6) than in the CBT group (n=3) for the subgroup analysis in men (data not shown). Over all: Gender and disease type do not seem to influence the effect of CBT.

		Results: Overall, all participants improved significantly in their anxiety and depressive symptoms and HRQOL, regardless of group, age, gender, and disease type. Primary chi-square tests and exploratory linear mixed models showed no difference in outcomes between the PASCET-PI and the CAU group. **Author's Conclusion: In youth with IBD and subclinical anxiety and/or depressive symptoms, preliminary results of immediate post-treatment assessment indicated that a diseasespecific CBT added to standard medical care did not perform better than standard medical care in improving psychological symptoms or HRQOL.**

Methodical Notes

Funding Sources: This work was supported by Stichting Vrienden van het Sophia (grant number 985 to J.C.E.), Stichting Crohn en Colitis Ulcerosa Fonds Nederland/Maag Lever Darm Stichting (grant number 14.307.04 to E.M.W.J.U.), Fonds NutsOhra (grant number 1303-012 to E.M.W.J.U.), and Stichting Theia (grant number 2013201 to E.M.W.J.U.). J.C.E. received financial support from MSD (research support), Janssen (advisory board), and AbbVie (advisory board). E.M.S. received financial support from NIH (grant), Crohn and Colitis Fund America (grant), AbbVie (consultancy), Merck (consultancy), and IHOPE Network (consultancy) and royalties for book editing from APPI. For the remaining authors, none was declared.

COI: None declared.

Randomization: Patients with subclinical anxiety and/or depressive symptoms were randomized to PASCET-PI and CAU versus CAU alone, with a ratio of 1: 1.
An independent biostatistician provided a computer-generated blocked randomization
list with randomly chosen block sizes and stratification by center using the blockrand package in the R software package, thereby providing numbered envelopes per center. Patients were enrolled by one of the investigators (GB).

Blinding: The interviewer (LS) and treating physicians were
blinded for the result of randomization (they were not informed and had no access to files containing this information). Patients could not be blinded.

Dropout Rate/ITT-Analysis: 2 patients in the CAU + CBT group were lost for follow up.

Notes:

Szigethy, Eva et al. Effect of 2 psychotherapies on depression and disease activity in pediatric Crohn's disease. Inflamm. Bowel Dis. 21. 1321-8. 2015

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 3 **Study type: Randomised controled ? trial** **Number of Patient:** **From the**	**Intervention: Randomized subjects underwent up to 12 weekly sessions of either CBT 22,23 or SNDT. Therapists (n = 10) experienced in treating physically ill youth were trained in both manual-based interventions and received weekly supervision. All sessions were audiotaped to allow for quality assurance and to assure treatment fidelity. Each treatment was tailored to the developmental level of each youth.**	**Primary:** **Secondary:** **Results: Total CDRS-R scores in the overall sample significantly decreased over time after both treatments (P , 0.0001). Treatment with CBT was associated with a significantly greater improvement in the Pediatric Crohn's disease Activity Index (P = 0.05) and somatic depressive subtype (P = 0.03) in those with active**

161 with CD, 82 were randomized to CBT and 79 to SNDT. At 3 months, 69 youth completed CBT, and 66 completed SNDT treatments. Recruitung Phase: Youth ages 9 to 17 years with either CD or UC and their parents were recruited from Children's Hospital of Pittsburgh and Boston Children's Hospital between 2008 and 2012 using a protocol approved by the Institutional Review Boards at both sites. Inclusion Criteria: inclusion criteria see literatur #20 Exclusion Criteria:	Up to 75% of sessions could be completed by telephone. More detailed descriptions of each intervention have been described previously.33 Comparison: supportive nondirective therapy (supportive listening). Randomized subjects underwent up to 12 weekly sessions of either CBT 22,23 or SNDT.	inflammatory bowel disease (n = 95) compared with supportive nondirective therapy. After excluding those on steroids (n = 34), there was a significant improvement in total CDRS-R (P = 0.03) and in Pediatric Crohn's disease Activity Index (P = 0.03) after CBT. Author's Conclusion: Psychotherapy may be a useful adjunct to treat depression in the context of CD-related inflammation in youth who are not concurrently on higher dose steroids.

Methodical Notes

Funding Sources: E. Szigethy currently has a senior investigator research grant from the Crohn's and Colitis Foundation of America (CCFA) and has received funding from NIH Directors
Innovator Award (DP2 OD001210), has served as a consultant for Merck and AbbVie Advisor Boards, has received honoraria from Imedex, the CME organizers for the
CCFA for educational presentations and is co-editor of the book, Cognitive Behavioral Therapy for Children and Adolescents for which she receives royalties from APPI
Press. She is also a consultant for iHOPE Network. J. Weisz is a co-editor for the book, Cognitive Behavioral Therapy for Children and Adolescents. J. Gonzalez-Heydrich
has received grant support from the Tommy Fuss Fund, the Al Rashed Family, GlaxoSimthKline, Johnson & Johnson, Abbott Laboratories, Pfizer Inc., AkzoNobel/Organon,
and the NIMH. He has been a consultant for Abbott Laboratories, Pfizer, Johnson & Johnson (Janssen, McNeil Consumer Health), Novartis, Parke-Davis, GlaxoSmithKline,
AstraZeneca, and Seaside Therapeutics. D. Kupfer holds joint ownership of copyright for the Pittsburgh Sleep Quality Index (PSQI); he and his spouse, Dr. Ellen Frank are
stockholders in Psychiatric Assessments, Inc. and Health Rhythms, Inc. He is stockholder in AliphCom. Dr. Frank also received royalties from the American Psychological
Association and Guilford Press; is a member of the Advisory Board of Servier International, and Editorial Consultant for American Psychiatric Press.

COI: The remaining authors have no conflicts of interest to disclose.

Randomization:

Blinding: The Pediatric Crohn's Disease Activity Index Score was rated by a blinded gastroenterologist.

Dropout Rate/ITT-Analysis: In the parent study, a total of 765 unique subjects with IBD were screened (550 with CD) with a total of 217 meeting criteria for randomization. From the 161 with CD, 82 were randomized to CBT and 79 to SNDT. At 3 months, 69 youth completed CBT, and 66 completed SNDT treatments.

Notes:
Primary and Secondary measures were not defined.

An possible limitation is the lack of adjustment for the overall level of statistical significance of the study for multiple comparisons as the study was hypothesis-generating in nature.

Vogelaar, Lauran et al. Fatigue management in patients with IBD: a randomised controlled trial. Gut. 63. 911-8. 2014

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type: RCT** **Number of Patient: Overall, 98 patients were enrolled in the study, 49 in the SFT group and 49 in the CAU group. One patient declined further participation after randomisation.** **Recruitung Phase:** **Inclusion Criteria: Men and women aged ≥18 years and diagnosed with IBD with a CIS-fatigue score of ≥35 were eligible for inclusion. Patients had to be in remission defined as a Crohn's Disease Index (CDAI) <150 or Clinical Activity Index (CAI) (ulcerative colitis index) <10 and a C-reactive protein (CRP) <10. The diagnosis of IBD (at least 6 months in duration) was radiologically or endoscopically/histologically confirmed.** **Exclusion Criteria: Pregnant or breastfeeding women were not included. Patients were also excluded if they had a history of lymphoproliferative disease or cancer, other than skin basocellular carcinoma; other gastrointestinal disease than**	**Intervention:** **Solution-focused therapy (SFT): 7-session solution-focused course, focussing on coping styles for fatigue. The course consisted of six group sessions during 3 months,and was completed by a booster session at month 6. Duration of each session was 1.5 h. Each group consisted of seven patients. In the fifth session, a partner, family member, or close relative participated. The course consisted of psychoeducation about IBD and fatigue and SFT. SFT is a brief form of psychotherapy. The focus is on the existing adequate coping abilities of patients, rather than on their problems. For the purpose of this study, the SFTwas modified to focus on fatigue management.** **Comparison: Care as usual (CAU).** **Not further defined.**	**Primary: The primary objective of the study was to assess the effect of SFT on fatigue and QoL at month 6. This was measured with the CIS,28 Fatigue Severity Scale-9 (FSS-9),29–31 Inflammatory Bowel Disease Questionnaire (IBDQ),32 33 Short Form-36 (SF-36)34 35 and EuroQol (EQ-5D)36 at baseline, month 3, month 6 and month 9.** **Secondary: The secondary objective was to investigate the effect of SFT on anxiety and depression, sleep quality, disease activity, medication use, side effects to medication and laboratory parameters (CRP, leucocytes and haemoglobin). Measurements of these items were performed at baseline, month 3, month 6 and month 9 with the Hospital Anxiety and Depression Scale (HADS),37 Pittsburgh Sleep Quality Index (PSQI),38 CDAI39 40 or CAI,41 a questionnaire focusing on current medication use and side effects, and laboratory parameters on full blood.** **Results: Ninety-eight patients were included, of whom 63% were women, mean age was 40.1 years.** **After the SFT course, 17 (39%) patients in the SFT group had a CIS-fatigue score below 35 compared with eight (18%) of patients in the CAU group (p=0.03).** **The SFT group also showed a greater reduction in fatigue across the first 6 months compared with the CAU group (CISfatigue: p=<0.001 and CIS-total: p=0.001).** **SFT was associated with a significant higher mean IBD questionnaire change at 3 months (p=0.020).** **At 9 months, no significant differences between the two groups were observed.** **Author's Conclusion: SFT has a significant beneficial effect on the severity of fatigue and QoL in patients with quiescent IBD. However, this effect diminished during follow-up.**

IBD; listeriosis; HIV infection; immunodeficiency syndrome; central nervous system (CNS) demyelinating disease; chronic hepatitis B or C virus infection or untreated tuberculosis. Patients were excluded if they had poorly controlled medical conditions, including anaemia, low iron levels, diabetes mellitus, kidney disease, liver disease and unstable ischaemic heart disease; a known pre-existing condition that could interfere with the patient's participation such as psychiatric conditions or CNS trauma or active seizure disorders. Additionally, patients were excluded if they had undergone surgery in the past 12 weeks prior to the screening visit. Patients with a history of clinically significant drug or alcohol abuse in the last 2 years were not allowed to participate in this study.		

Methodical Notes

Funding Sources:

COI: All authors state that there are no potential conflicts of interest during the work under consideration for publication. CW has participated in the advisory board of Centocor, MSD, FALK Benelux, Abbott laboratories and Ferring during the last 3 years and received financial compensation for these activities.

Randomization: Patients were randomised to the treatment or control arm in blocks of 14 subjects using randomisation lists drawn from a computer-generated series of random numbers. Randomisation was conducted by the second author. The randomisation lists were anonymised for the randomisation process.

Blinding: Due to study design, blinding was not possible.

Dropout Rate/ITT-Analysis: One patient in the intervention group declined further participation and did not receive allocated intervention.

Notes:
Methological quality seems good. Care as usual was not further defined.

Wynne, Brona et al. Acceptance and Commitment Therapy Reduces Psychological Stress in Patients With Inflammatory Bowel Diseases. Gastroenterology. 156. 935-945.e1. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type: RCT** **Number of Patient: 122**	**Intervention: The ACT (Acceptance and commitment therapy) program consisted of 8 90-minute weekly sessions in groups of 14–16**	**Primary: The primary endpoint was change in stress symptoms, assessed with the Depression Anxiety Stress Scale.** **Secondary: Secondary endpoints included**

Recruitung Phase: between March 2015 and October 2016 Inclusion Criteria: IBD patients with psychosocial dysfunction at screening, based on a perceived stress score of 5 or more on a scale ranging from 1 to 1024 or a quality-of-life score of greater than 80 on a scale ranging from 0 to 400 (with higher scores indicating a poorer quality of life),25 were eligible for the study. Patients with radiologic and histologic diagnosis of Crohn's disease or ulcerative colitis. Participants aged between 18 and 65 years with inactive or stable mildly active disease, as defined by a physician based on symptoms, physical examination, and laboratory blood tests and by incorporating the short Crohn's Disease Activity Index (CDAI) or short Mayo score during the assessment as appropriate,26,27 were eligible. Exclusion Criteria: Pregnant women, participants previously exposed to a stress management program, those attending psychiatric or psychological services, and those receiving antidepressant medication were excluded from the study. Steroids were not permitted in the 3 months before screening because of their potential psychological and endocrinologic effects, and participants were required to have been taking stable doses of all IBD medications at screening for a minimum of 3 months.	participants. The course manual was based on contemporary ACT models and tailored toward IBD patients with an emphasis on reducing stress, and all program materials are available in the supplementary materials. A single experienced psychologist who was a peer-reviewed ACT trainer provided all interventions. Each treatment session was observed and rated by an independent psychologist to assess the therapists' adherence to the treatment protocol. Comparison: treatment as usual, standard IBD medical care	changes in perceived stress, anxiety, depression, quality-of-life domains, disease activity, and cortisol concentration in hair. Results: Overall, 79 participants were included in the complete case intention-to-treat analysis. There were 39% and 45% reductions in stress in the treatment group from baseline to 8 and 20 weeks, respectively, compared with 8% and 11% in the control group (group time interaction, P ¼ .001). ACT was associated with reduced perceived stress (P ¼ .036) and depression (P ¼ .010), but not anxiety (P ¼ .388), compared with control individuals. In the intentionto-treat analysis, changes in all 4 quality-of-life domains over time were similar in the ACT and control groups. In the per-protocol analysis, the overall well-being quality-of-life domain improved in the ACT group compared with the control group (P ¼ .009). Subjective and objective disease activity measurements were similar between groups over the study period (all P values >.05). Hair cortisol concentrations correlated with stress (rs ¼ 0.205, P ¼ .050) and anxiety (rs ¼ 0.208, P ¼ .046) at baseline but did not change significantly in the ACT group over the study period compared with the control group (P ¼ .831). Author's Conclusion: In a randomized controlled trial of patients with IBD, an 8-week ACT therapy course improved stress and other indices of psychological health.ClinicalTrials

Methodical Notes

Funding Sources: This work was partly supported by an educational grant from Tillotts Pharma AG, which had no role in study design, data acquisition, data analysis, or manuscript writing. KH is a University College Dublin Newman Fellow sponsored by Boston Scientific.

COI: CR has served as a speaker for Janssen, MSD, and AbbVie. GD has served as a speaker, a consultant, and an advisory board member for AbbVie, Merck,

Sharp & Dohm, Pfizer, Amgen, Janssen, Shire, Takeda, and Tillotts and has received research funding from AbbVie, MSD, and Pfizer. HM has served as a speaker for Dr Falk Pharma and MSD, serves as a consultant for Boston Scientific, and has received funding from Pfizer. The remaining authors disclose no conflicts.

Randomization: Eligible participants were randomly assigned 1:1 to a group. A stratified randomization procedure was used with participants allocated to treatment and control groups according to sex and disease type with a Web-based randomization protocol by a researcher not involved in recruitment.

Blinding: Blinding not possible. Randomization with a Web-based randomization protocol by a researcher not involved in recruitment.

Dropout Rate/ITT-Analysis: 122 patients
21 withdrew
22 failed to attend 1 of their follow-up visits
--> 79 included in the itt-analysis, drop-out 35%

Notes:

Literatursammlung:

AG 7 Ernährung, Psycho, Komplementär-Frage 2

Inhalt: 4 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Levine, Arie 2019	2	nvestigator-initiated prospective randomizedcontrolled trial with 2 interventional arms comparing CDEDwith 50% PEN (group 1) with EEN (group 2) administeredorally over 12 weeks in a pediatric population with mild tomoderate active luminal disease
Limketkai, Berkeley N 2019	1	Cochrane Review
Narula, Neeraj 2018	1	Cochrane Review
Pigneur, Bénédicte 2019	2	prospective randomised induction trial

OXFORD (2011) Appraisal Sheet: Systematic Reviews: 2 Bewertung(en)

Limketkai, Berkeley N et al. Dietary interventions for induction and maintenance of remission in inflammatory bowel disease. Cochrane Database Syst Rev. 2. CD012839. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Cochrane Review Databases: The Cochrane IBD Group Specialized Register, CENTRAL, MEDLINE, Embase, Web of Science, Clinicaltrials.gov and the WHOICTRP from inception to 31 January 2019 were scanned. Also scanned reference lists of included studies, relevant reviews and guidelines.	Population: Patients with active crohn's disease Intervention: The intervention is a controlled manipulation of the subject's oraldiet by a deliberate change in the consumption of food (i.e. noformulas or supplements used) for a	Primary: Induction of remission Secondary: 1. Clinical improvement as defined by the included studies;2. Corticosteroid-free remission;3. Surrogate biomarkers of inflammation (i.e., erythrocytesedimentation rate [ESR] and C-reactive protein [CRP]), fecalbiomarkers (i.e., calprotectin);4. Endoscopic endpoints of improvement and remission;5. Histologic endpoints of improvement and remission;6. Health-related quality of life as measured by the InflammatoryBowel Disease Questionnaire (IBDQ), Short Inflammatory BowelDisease Questionnaire (SIBDQ), or related surveys;7. Hospitalizations;8. Need for surgery;9. Progression of disease from a state of inflammation-only diseaseto stricturing/obstructing to penetrating/fistulizing disease;10.Escalation of therapy including the need to add or modifypharmacologic therapy due to lack of efficacy at inducing ormaintaining remission aRer enrollment in the trial;11.Adverse events;12.Withdrawal due to adverse events; and13.Serious adverse events Results: The effect of high fiber, low refined carbohydrates, low microparticle, low calcium,	see pdf

Search period: to 31 January 2019 Inclusion Criteria: randomized controlled trials (RCTs) that compared the effects of dietary manipulations to other diets in participants with IBD were included Exclusion Criteria: Studies that exclusively focused on enteral nutrition, oral nutrient supplementation, medical foods, probiotics, and parenteral nutritionwere excluded.	specified period of time. Comparison: normal diet	symptoms-guided diet and highly restricted organic dieton clinical remission in active CD is uncertain. In one study, remission was achieved at 4 weeks in 100% (4/4) of low refined carbohydratesparticipants compared to 0% (0/3) of usual diet participants. In a pooled analysis of two studies, 44% (23/52) of low microparticleparticipants achieved remission at 16 weeks compared to 25% (13/51) of usual diet participants. One study found that 50% (16/32) ofsymptoms-guided participants achieved remission compared to 0% (0/19) of usual diet participants. One study found that 50% (4/8) ofhighly-restricted organic diet participants achieved remission at 24 weeks compared to 50% (5/10) of usual diet participants. One studyfound that 37% (16/43) of low-calcium participants achieved remission at 16 weeks compared to 30% (12/40) of usual diet participants. Author's Conclusion: The effects of dietary interventions on CD are uncertain.	

Methodical Notes

Funding Sources: Funding for the Cochrane IBD Group (May 1, 2017 - April 30, 2022)has been provided by Crohn's and Colitis Canada (CCC).Funding for ZIE, TH, and partial funding for MG was providedthrough a larger NIHR Cochrane Programme Grant in the UK.

COI: Berkeley N Limketkai: None knownZipporah Iheozor-Ejiofor: None knownTeuta Gjuladin-Hellon: None knownAlyssa Parian: None knownLaura E Matarese: None knownKelly Bracewell: None knownJohn K MacDonald: None knownMorris Gordon has received travel fees to attend international scientific and training meeting such as DDW, Advances in IBD, ESPGHAN,BSPGHAN and Cochrane focused international events from companies including: Abbott, Nutricia, Biogaia, Ferring, Allergan, and Tillots.Gerard E Mullin has received grants or grants pending (paid to institution) from Abbott Laboratories; and royalties from Rodale Press,Oxford University Press, and CRC Press for books written and or edited on nutrition, generically, and only a few chapters as an expert onthe role of diet in IBD

Study Quality: The majority of studies have small numbers.

Heterogeneity: Due to different interventions and small study population there is a relevant heterogeneity

Publication Bias:

Notes:

Narula, Neeraj et al. Enteral nutritional therapy for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 4. CD000542. 2018

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 1 Study type: Cochrane Review Databases: MEDLINE, Embase and	Population: Patients with active crohn's disease Intervention: exclusive EN as	Primary: The primary outcome was clinical remission. Secondary: Secondary outcomes includedadverse events, serious adverse events and withdrawal due to adverse events Results: Meta-analysis of eight trials (223 participants) demonstrated no difference in remission ratesbetween EN and steroids. Fifty per cent (111/223) of patients in the EN	see reference list

CENTRAL **Search period: from inception to 5 July 2017.** **Inclusion Criteria:** **Randomized controlled trials involving patients with activeCD were considered for inclusion. Studies comparing one type ofEN toanother type of EN or conventional corticosteroids were selected for review.** **Exclusion Criteria:**	**primary therapy to induce remission** **Comparison: steroid therapy**	**group achieved remission compared to 72% (133/186) ofpatients in the steroid group (RR 0.77, 95% CI 0.58 to 1.03; GRADE very low quality). Subgroup analysis by age showed a differencein remission rates for adults but not for children. In adults 45% (87/194) of EN patients achieved remission compared to 73% (116/158) of steroid patients (RR 0.65, 95% CI 0.52 to 0.82; GRADE very low quality).In children, 83% (24/29) of EN patients achievedremission compared to 61% (17/28) of steroid patients (RR 1.35,95% CI 0.92 to 1.97; GRADE very low quality). A per-protocolanalysis produced similar results (RR 0.93, 95% CI 0.75 to 1.14). The per-protocol subgroup analysis showed a difference in remissionrates for both adults (RR 0.82, 95% CI 0.70 to 0.95) and children(RR 1.43, 95% CI 1.03 to 1.97). There was no difference inadverse event rates (RR 1.39, 95% CI 0.62 to 3.11; GRADE very low quality). However, patients on EN were more likely to withdrawdue to adverse events than those on steroid therapy (RR 2.95, 95% CI 1.02 to 8.48; GRADE very low quality).** **Author's Conclusion: Very low quality evidence suggests that corticosteroid therapy may be more effective than EN for induction of clinical remission inadults with active CD. Very low quality evidence also suggeststhat EN may be more effective than steroids for induction of remissionin children with active CD.**	

Methodical Notes

Funding Sources: no information

COI: Neeraj Narula has no known declarations of interest to declare.Amit Dhillon has no known declarations of interest to declare.Dongni Zhang has no known declarations of interest to declare.Mary Sherlock has served as an advisory board member for Abbvie and Jannsen and received travel expenses from Abbvie to attend anIBD meeting in 2015.Melody Tondeur has no known declarations of interest to declare.Walter Reinisch has served as a speaker, a consultant or an advisory board member for Abbott Laboratories, Abbvie, Aesca, Amgen, AMPharma, Aptalis, Astellas, 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 Therapeutics, Millenium, Mitsubishi Tanabe Pharma Corporation, MSD, Novartis, Ocera, Otsuka,PDL, Pharmacosmos, Pfizer, Procter & Gamble, Prometheus, Robarts Clinical Trial, Schering-Plough, Setpointmedical, Shire,Takeda,Therakos, Tigenix, UCB, Vifor, Yakult, Zyngenia, and 4SC.Mary Zachos has served as an advisory board member for Abbvie,Janssen and Ferrin

Study Quality:

Heterogeneity: adult and pediatric population: statistically signifi-cant heterogeneity was identified (I2= 67%).
adult population alone: o significant heterogeneity was demonstrated for this analysis (i2= 36%)

Publication Bias:

Notes:
The review was done as a Cochrane Review

OXFORD (2011) Appraisal Sheet: RCT: 2 Bewertung(en)

Levine, Arie et al. Crohn's Disease Exclusion Diet Plus Partial Enteral Nutrition Induces Sustained Remission in a Randomized Controlled Trial. Gastroenterology. 157. 440-450.e8. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2	**Intervention: Group 1 received the CDED stage 1**	**Primary: The primary endpoint of this studywas the patient's tolerance to the diet**

Study type: nvestigator-initiated prospective randomizedcontrolled trial with 2 interventional arms comparing CDEDwith 50% PEN (group 1) with EEN (group 2) administeredorally over 12 weeks in a pediatric population with mild tomoderate active luminal disease **Number of Patient: Seventy-eight patients were randomized (40 toCDEDþPEN and 38 to EEN) and included in the analysisfrom 10 pediatric IBD clinics in Israel (from September2013) and 2 in Canada (from December 2016) until May2018,** **Recruitung Phase: from September 2013 until May 2018** **Inclusion Criteria: Children (aged 4–18 years) with mild to moderate luminalCD, defined by a pediatric CD activity index (PCDAI)10 and40 and evidence for active inflammation at enrollment, suchas elevated C-reactive protein (CRP)>5 g/L, erythrocytesedimentation rate>20 mm/h, or calprotectin>200mg/g,within 36 months from diagnosis, were eligible for enrollment.** **Exclusion Criteria: Exclusion criteria consisted of recent use of steroids or recent initiation or dose adjustmentfor immunomodulators, past or current biologics use, primarycolonic disease with significant rectal involvement, or activeperianal disease.**	**with 50% PEN forcalculated energy requirement (Modulen; Nestlé Health Science, Vevey, Switzerland) for thefirst 6 weeks, and then thestage 2 diet with 25% PEN for the next 6 weeks. Group 2received standard of care EEN (Modulen) for 6 weeks followedby 25% PEN during weeks 6 to 12, with gradual reintroductionof table foods between week 6 and 9 as per local preference,such that all patients were exposed to PENþfree diet by week12. All formulas could be given only orally** **Comparison:**	**by week 6 defined bywithdrawal from the study because of patient's refusal tocontinue the diet.** **Secondary: response, defined as a drop in PCDAI of 12.5 points or remission, on an ITT analysis at week 6; remission at week 6 (definedas PCDAI<10 as well as by the more stringent<10, or lessthan 7.5 without height component). Other secondary endpoints included decrease or normalization of inflammatory markers at week 6 (CRP, ESR, calprotectin), remission and normalization of CRP at week 12, and poor adherence.** **Results: our patients withdrewfrom the study because of intolerance by 48 hours, 74 patients(mean age 14.2±2.7 years) were included for remissionanalysis. The combination of CDED and PEN was tolerated in 39children (97.5%), whereas EEN was tolerated by 28 children(73.6%) (P=0.002; odds ratio for tolerance of CDED and PEN,13.92; 95% confidence interval [CI] 1.68–115.14). At week 6,30 (75%) of 40 children given CDED plus PEN were incorticosteroid-free remission vs 20 (59%) of 34 children givenEEN (P¼.38). At week 12, 28 (75.6%) of 37 children givenCDED plus PEN were in corticosteroid-free remission comparedwith 14 (45.1%) of 31 children given EEN and then PEN (P=0.01; odds ratio for remission in children given CDED and PEN,3.77; CI 1.34–10.59)** **Author's Conclusion: CDED plus PEN was better tolerated than EEN in children with mild to moderate CD. Both diets were effective ininducing remission by week 6. The combination CDED plus PENinduced sustained remission in a significantly higher proportion of patients than EEN,**

Methodical Notes

Funding Sources: nitial funding for the study in Israel was provided by unrestricted grants fromthe Azrieli Foundation and Nestlé Health Science to AL. Nestlé HealthScience also kindly provided Modulen to all participating sites to ensureuniformity of the formula used among participants and provide the formulato enrolled patients for the duration of the study. The conduct of the studyin Canada (Halifax, Edmonton) was supported by local divisional funds, aWomen and Children's Health Research Institute (WCHRI) ResearchCapacity Building Award (EW) and a Canadian Institutes of Health Research(CIHR) New Investigator award (JVL)

COI: AL reports grants, from Nestlé HealthScience, and grants from Janssen unrelated to thisfield; advisory boards,travel, speaker fees or DSMBs from Celgene, Takeda and AbbVie, and alicensing and consulting agreement with IP with Nestlé health to developnew products based on diet. EW reports personal fees from Janssen,personal fees from AbbVie, outside the submitted work. RSB reportspersonal

fees from Consulting to Nestlé Health Science, during the conductof the study; personal fees from Invited speaker by Nestlé Health Science,personal fees from Invited speaker by Takeda, outside the submitted work.RS reports personal fees from Janssen, AbbVie, Mead Johnson, Lapidot andAbbott, outside the submitted work. JVL reports consulting, travel and/orspeaker fees and research support from AbbVie, Janssen, Nestlé HealthScience, Merck, P&G, GSK, Illumina, Otsuka.

Randomization: Patients were randomized 1:1 in previously generatedrandom blocks of 6.

Blinding: Blinding was not possible

Dropout Rate/ITT-Analysis: 4 patients, an ITT analysis was performed

Notes:

Pigneur, Bénédicte et al. Mucosal Healing and Bacterial Composition in Response to Enteral Nutrition Vs Steroid-based Induction Therapy-A Randomised Prospective Clinical Trial in Children With Crohn's Disease. J Crohns Colitis. 13. 846-855. 2019

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type: prospective randomised induction trial** **Number of Patient: Nineteen patients with new-onset active CD (Harvey-Bradshaw index [HBI] >5), aged from 6 to 17 years, were included in this prospective randomised induction trial with CS [n = 6] or EEN [n = 13]** **Recruitung Phase: A total of 19 patients [13 EEN/6 steroids] were included over 36 months, with an overall acceptance rate of participation in this trial of 23%.** **Inclusion Criteria: Children/adolescents with newly diagnosed CD [age range: 6–17 years] with active disease (Harvey-Bradshaw Index [HBI] >5)** **Exclusion Criteria: treatment by antibiotics during the 4 weeks preceding inclusion, cor-ticosteroids, biologic therapies, immunosuppressive treatment, iso-lated oral or perianal disease location, risk of non-adherence to study protocol, and potential need for surgical therapy**	**Intervention: Exclusive enteral nutrition [EEN] (Modulen IBD) over 8 weeks** **Comparison: Corticosteroids initially 1 mg/Kg per day [up to a maximum of 60 mg] during the induction period [4 weeks] and then tapered over 3 months.**	**Primary: achievement of mucosal healing with a Crohn's Disease Endoscopic Index of Severity [CDEIS] less than 3 points or a drop of >70% at follow-up endoscopy [8 weeks] compared with initial diagnostic endoscopy.** **Secondary: clinical remission defined as a Harvey-Bradshaw Index [HBI] less than 5 and biological remission [mucosal and systemic inflamma-tory parameters].** **Results: At 8 weeks, clinical remission [HBI <5] was achieved in 13/13 patients on EEN and 5/6 patients on steroids; the mucosal healing rate was significantly higher in the EEN [89%] compared with steroid group [17%].** **Author's Conclusion: Both steroid and EEN induced clinical remission. However, patients with EEN-induced remission showed a higher rate of mucosal healing**

Methodical Notes

Funding Sources: The present work was supported by a non-restricted grant of Nestle France (producer of the enteral nutrition product)

COI: OG received financial support for research from Danone, Fresenius Kabi, Biocodex, Shire. JD received financial support for research from Danone, fees for lecture and editorial work from Janssen and Biocodex, consultancy and shares as co-founder from Enterome and MaaT Pharma. FR has received research supports from Nestlé Nutrition Institute, AbbVie, MSD, Jansen and Jansen, and lecture fees from AbbVie, Danone, Nutricia, Nestlé, and served as member of advisory board: DEVELOP [Centocor], CAPE [AbbVie], LEA [AbbVie], SAC for MSD France, Nestlé Nutrition Institute, Nestlé Health Science, Danone, MeadJohnson; Nutricia, Takeda, Celgene, Biogen, Shire, Pfizer, Therakos.

Randomization: randomisation was amended to a 1 to 2 ratio [one in the CS group for 2 patients in the EEN group

Blinding: not possible

Dropout Rate/ITT-Analysis: overall acceptance rate of participation in this trial of 23%.

Notes:

Literatursammlung:

AG 7 Ernährung, Psycho, Komplementär-Frage 3

Inhalt: 3 Literaturstellen

Literaturstelle	Evidenzlevel	Studientyp
Bao, Chun-Hui 2014	2	RCT
Sun, Jing 2015	2	RCT
Zhu, Weiming 2015	2	RCT

OXFORD (2011) Appraisal Sheet: RCT: 3 Bewertung(en)

Bao, Chun-Hui et al. Randomized controlled trial: moxibustion and acupuncture for the treatment of Crohn's disease. World J. Gastroenterol. 20. 11000-11. 2014

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: RCT Number of Patient: Baseline 92 (n=46 treatment and control group) 85 patients completed the trial (treatment n=43, control n=42) follow up: 77 patients (treatment n=40, control n=37) Recruitung Phase: From January 2010 to April 2013, CD patients treated at the acupuncture outpatient center for inflammatory bowel disease of the Shanghai Institute of Acupuncture and Meridian, the Endoscopy Center of Zhongshan Hospital at Fudan University, the Department of AcupunctureMoxibustion of Shuguang Hospital affiliated with the Shanghai University of Traditional Chinese Medicine, and	Intervention: The treatment group received herb-partitioned moxibustion combined with acupuncture. The acupoints are listed in Table 1 and Figure 1; these acupoints were selected based on TCM principles according to the clinical manifestations of the patients. All of these acupoints were shown to be effective for the treatment of CD. 3 times a week for 12 weeks. Comparison: The control group received wheat ban-partitioned moxibustion and superficial acupuncture 1-2 cm beside the acupoint. 3 times a week for 12 weeks.	Primary: CDAI (CD activity index) Secondary: laboratory indicators such as hemoglobin (HGB), C-reactive protein (CRP), erythrocyte sedimentation rate, quality-of-life, endoscopic ratings, and intestinal histology scores. Results: The CDAI scores of both the treatment and control groups were significantly reduced after treatment compared with those measured before treatment. However, the degree of improvement in the treatment group was significantly greater than that of the control group. The improvement in symptoms in patients of the treatment group was sustained at follow-up, whereas that of the control group was not. The overall efficacy of the treatment was significantly greater than that of the control. Both groups demonstrated significant improvements in quality-of-life ratings after treatment, but the improvement was significantly greater in the treatment group than in the control group. In addition, the patients in the treatment group showed significantly increased HGB and significantly decreasedCRP levels and histopathological scores at the end of treatment, whereas the control group did not exhibit significant changes. Author's Conclusion: Moxibustion with acupuncture provided significant therapeutic benefits in patients with active CD beyond the placebo effect and is therefore an effective and safe treatment for active CD.

the Yueyang Hospital of Integrated Traditional Chinese and Western Medicine affiliated with the Shanghai University of Traditional Chinese Medicine were recruited as subjects for this study **Inclusion Criteria: Patients who** **- had a confirmed diagnosis of mild or moderate CD (CD Activity Index (CDAI) values ranging from 151 to 350)** **- had not taken medications such as salicylic acid drugs and/or prednisone (at a dose ≤ 15 mg) for at least 1 month** **- had not taken immunosuppressants or used anti-TNF-α biological agents for 3 month prior to enrollment in the study** **Exclusion Criteria: - Pregnant or lactating patients** **- patients with serious diseases of the heart, brain, liver, kidney, or hematopoietic system** **- patients with mental illness** **- patients with other severe diseases**		

Methodical Notes

Funding Sources: Supported by Shanghai Municipal Health Bureau, No. 20124028; The Ministry of Education Program for New Century Excellent Talents, No. NCET-13-0907; Shanghai Municipal Science and Technology Commission, No. 13ZR1439400; and Shanghai Top Clinical Medical Center of Acupuncture, Moxibustion and Tuina

COI: nothing mentioned

Randomization: Yes.
Simple random sampling method by generating a random number table using the SPSS 16.0 software.

Blinding: Yes.
All patients were blinded during the trial and were therefore unaware of the specific treatment they received. All subjects in each treatment session were treated in a private room to avoid potential communication and comparison among subjects. In addition, a blinded evaluation was conducted in which a third researcher who was unaware of the group assignments assessed the treatment outcomes. Blinded statistical data analysis was also conducted in which the researchers, operators, and statisticians were separated from one another.

Dropout Rate/ITT-Analysis: The effective rate of acupuncture and moxibustion in the treatment of CD is 56%.
In this study they previously used a non-randomized concurrent

control method to conduct a pilot study that demonstrated an effective rate of herb-partitioned moxibustion and acupuncture in the treatment of CD of 86.67%.
Therefore, the current study established an expected effective rate value of 85%.
The required sample size for each group was equal to 42 (n = 42 patients). With the addition of a 10% dropout rate (four patients), the two
groups needed to include no less than 92 patients. The PP analysis indicated that the total treatment efficacies of the treatment and control groups were 83.72% and 40.48%, respectively, with a statistically significant difference (P = 0.000). The ITT analysis indicated that
the total treatment efficacies of the treatment and control
groups were 78.26% and 36.96%, respectively, with a statistically significant difference (P = 0.000) (Table 4).

Notes:
After enrollment, the patients who were using CD medications maintained their drug dosage unchanged. If their conditions deteriorated during the treatment period
or if the patients needed to increase their dose or take other medications, these subjects were withdrawn from the study. During the follow-up period, patients were allowed to adjust their dose of Western medicine after recording each adjustment. If patients increased their dose, became sicker, or took other drugs, these subjects were also withdrawn.

Sun, Jing et al. Tripterygium wilfordii Hook F as Maintenance Treatment for Crohn's Disease. Am. J. Med. Sci. 350. 345-51. 2015

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 Study type: RCT Number of Patient: 198 (mesalazine n=59, high-dose n=71, low-dose n=68) Recruitung Phase: e Inflammatory Bowel Disease Center of Jinling Hospital during the period of December 2010 to January 2014. The protocol of the study was approved by Ethics Committee of Jinling Hospital, Medical School of Nanjing University (date: June 20, 2010; Project number 175). Inclusion Criteria: Inclusion criteria were as follows: Patients were 16 to 75 years old with a	Intervention: highdose-group 2.0 mg/kg daily (maximum, 120 mg/d) lowdose-group 1.5 mg/kg daily The high-dosage regimen was determined referring to previous clinical trial testing the effects of similar Tripterygium wilfordii Hook F extracts for the CD and nephritis. All recruited patients were evaluated at baseline, every 2 weeks for 8 weeks and every 4 weeks since then. Vital signs and laboratory values (blood cell count, liver enzymes, serum bilirubin, creatinine, blood urea nitrogen and C-reactive protein) were measured at each study visit. Patients received ileocolonoscopy in a 26-week interval or when patients have clinical symptom indicating recurrence. An endoscopist who was blind to the treatment assignment performed the ileocolonoscopy. Comparison: mesalazine 3 g daily	Primary: The primary endpoint was clinical recurrence, defined as CD Activity Index score (CDAI) > 150 points together with an increase of 60 points.25 In addition, a recurrence also included any patient who required medical or surgical treatment with or without a measurement of the CDAI score. Secondary: The secondary endpoint was drug adverse events at 26 and 52 weeks since drug adverse events at 26 and 52 weeks since initiation. The following were also analyzed: the changes in scores of CDAI, Inflammatory Bowel Disease Questionnaire (IBDQ) and Simple Endoscopic Score for Crohn’s Disease (SESCD) throughout the study. Drug adherence was assessed using a daily diary and by pill counts. Results: A total of 137 patients completed the study. At week 52, a significant lower proportion of patients in the high-dose TwHF group (7/71) had clinical recurrence compared with patients in the low-dose TwHF (15/68, P 5 0.047) or mesalazine group (17/59, P 5 0.006), whereas the difference between the lowdose TwHF group and the mesalazine group was not significant (P 5 0.503). Patients receiving mesalazine experienced less adverse events than those receiving high-dose TwHF (P 5 0.029) and those receiving low-dose TwHF (P 5 0.048), but no significant difference was found about drug adverse events resulted withdrawal in the 3 groups (P . 0.05). In addition, compared with low-dose TwHF and mesalazine, the authors also detected significant superiority of highdose TwHF arm in the decrease of CDAI and SESCD (P , 0.05). Author's Conclusion: 2.0 mg/kg daily TwHF was

confirmed diagnosis of CD. The diagnosis of CD was based on radiologic, endoscopic or histologic evidence at least 6 months before receipt of study treatment.21 The activity of CD was mild to moderate (a CD Activity Index score from 150 to 450) before induced remission with medications and was remission (a CD Activity Index score bellow 150) when patients were enrolled. **Exclusion Criteria: The exclusion criteria were as follows: Patients who had active infection, short bowel syndrome, leucopenia (white blood cell count, 4 3 109/L), cancer, or clinically important renal or hepatic disease, and any condition associated with poor compliance with medical treatment. For women, pregnancy tests were performed during the study, and they were required to have negative results. Patients who were pregnant, breastfeeding or had pregnancy plan were not eligible. Patients were**		**well tolerated and prolonged remission in patients with CD.**

also not eligible if they had a history of TwHF and/or mesalazine intolerance or had received treatment with anti-TNF-a agents, corticosteroids, oral antibiotics or nonsteroidal antiinflammatory drugs (NSAIDs) within the preceding 4 weeks.		

Methodical Notes

Funding Sources: ? not known

COI: The authors have no financial or other conflicts of interest to disclose.

Randomization: Yes.
The patients were randomized according to a computer-generated randomization schedule.

Blinding: ? not known

Dropout Rate/ITT-Analysis: 137/198 patients reached week 56 --> total dropout 61 (=30,8%)
mesalazine: 36/59 finished, dropout: 39%
high-dose 55/71 finished, dropout: 22,5%
low-dose 46/68 finished, dropout: 32%
dropuout till week 26:
mesalazine n=11
high-dose n=8
low-dose n=12
dropout from week 26 till week 52:
mesalazine n=12
high-dose n=8
low-dose n=10

Notes:
The authors estimated that 177 patients would have to be studied to detect a 20% absolute difference in the proportion of patients maintaining remission while taking the most effective dose of TwHF, assuming a recurrence at
week 52 of 30% in the mesalazine group (a 5 0.05; b 5
0.20), according to a predetermined proportion of 1:1:1. Clinical recurrence was evaluated in the intention-to-treat population. The analyses used last observation carried forward in our assessments. To analyze cumulative remission maintain rates, the authors used the Kaplan-Meier method, and differences in clinical recurrence were assessed with the log-rank test. Fisher's exact test and chi-square test were also used. Quantitative variables were described using the mean 6 standard deviation (M 6 SD) and were compared using a 2-sided Mann-Whitney
U-test. P , 0.05 was considered to be statistically significant.
Each statistical analysis was performed using the Dr. SPSS II
program, version 19.0 for Windows (SPSS, Inc, Chicago, IL)

Zhu, Weiming et al. Tripterygium wilfordii Hook. f. versus azathioprine for prevention of postoperative recurrence in patients with Crohn's disease: a randomized clinical trial. Dig Liver Dis. 47. 14-9. 2015

Population	Intervention - Comparison	Outcomes/Results
Evidence level: 2 **Study type: RCT**	**Intervention: TwHF 1.5 mg/kg/day** **The patients assigned to the TwHF group**	**Primary: presenting symptoms of CD having to undergo another medical or surgical treatment, with the recurrence being confirmed by**

Number of Patient: 90 **Recruitung Phase: Between November 2009 and October 2012, eligible patients with ileal or ileocolic CD undergoing macroscopic disease resection with anastomoses, which were side-to-side and stapled, were recruited for this study.** **Inclusion Criteria: eligible patients with ileal or ileocolic CD undergoing macroscopic disease resection with anastomoses, which were side-to-side and stapled,** **Exclusion Criteria: Women of childbearing age were required to have a negative pregnancy test and to use adequate birth control measures during the entire study. Patients who received proximal intestinal resections or had an ileocolonic stoma or strictureplasty at the time of ileocolic anastomosis were excluded. Patients with short bowel syndrome, who wished to become pregnant during the study, who had a low white blood cell(WBC) count atinclusion (<4000), or who had malignancies and/or ongoing infectious disease (such as active hepatitis) were also excluded. Patients were not eligible if they had a history of TwHF and/orAZAintolerance or had received treatment with anti-tumour necrosis factor (TNF-) agents, corticosteroids, oral antibiotics, or non-steroidal anti-inflammatory drugs (NSAIDs) within the preceding 4 weeks.**	**received oral administration of TwHF (Taizhou Pharmaceutical Co., Jiangsu Province, China) 3 times per day. The following medications were prohibited during the study: other immunosuppressants, corticosteroids, thiopurinol, allopurinol or oxipurinol, 5-ASA, antiTNF therapy, oral antibiotics for more than 2 weeks, NSAIDs for more than 1 week, and AZA-containing or TwHF-containing drugs other than the study drug.** **Comparison: azathioprine 2.0 mg/kg/day The following medications were prohibited during the study: other immunosuppressants, corticosteroids, thiopurinol, allopurinol or oxipurinol, 5-ASA, antiTNF therapy, oral antibiotics for more than 2 weeks, NSAIDs for more than 1 week, and AZA-containing or TwHF-containing drugs other than the study drug.**	**endoscopic evidence** **Secondary: The secondary end point of this study was the proportion of patients with significant endoscopic recurrence in the neoterminal ileum at 26 and 52 weeks after surgery, defined as an endoscopic index ≥2 according to Rutgeerts' endoscopic score.** **Results: 47 patients completed the trial. Clinical recurrence was observed in 6/45 patients in the TwHF group and 4/45 patients in the azathioprine group at week 26 (P = 0.74). At week 52, 8/45 azathioprine patients and 12/45 TwHF patients had clinical recurrence (P = 0.45). During the first 26 weeks, 56.8% ofthe patients in the TwHF group versus 47.7% in the azathioprine group experienced endoscopic recurrence (P = 0.52). However, at week 52, 74.4% of patients in the TwHF group and 50% in the azathioprine group had endoscopic recurrence (P = 0.03).** **Author's Conclusion: TwHF was less effective in maintaining endoscopic remission at week 52, even though TwHF was comparable to azathioprine for preventing postoperative clinical recurrence**

Methodical Notes

Funding Sources: This work was partly supported by National Ministry of Health for the Digestive Disease (Grant 201002020) and National Natural Science Foundation of China (Grants 81200263 and 81170365).

COI: non declared

Randomization: Yes.
The patients were randomized in a 1:1 ratio of AZA 2.0 mg/kg/day or TwHF 1.5 mg/kg/day using a randomization programme.

Blinding: Not mentioned.

At weeks 26 and 52, an ileocolonoscopy was performed by an endoscopist who was blind to the treatment assignment

Dropout Rate/ITT-Analysis: Dropout till week 26/52:
TwHF n=8/6, azathioprin n=7/12
ITT:
Clinical recurrence was evaluated in the intention-to-treat (ITT) population. Endoscopic examinations were analyzed in all ITT patients in whom endoscopy was performed at week 26 and at week 52 or at the time of study withdrawal. The analyses employed non-responder imputation (NRI) and last-observationcarried-forward (LOCF)in many assessments. To evaluate the effect of drug therapy on endoscopic recurrence and clinical recurrence between the treatment groups at 26 and 52 weeks, Fisher's exact test or the chi-square test was used. Quantitative variables were described using the mean ± standard deviation (SD) and were compared using a two sided Mann–Whitney U-test. P < 0.05 was considered to be statistically significant.

Notes:

Versionsnummer:	**5.0**
Erstellungsdatum:	**11/1996**
Überbarbeitung von:	**08/2021**
Nächste Überprüfung geplant:	**07/2026**