Literatursammlung:

**AG 1 Diagnostik-Frage 1**

**Inhalt: 2 Literaturstellen**

<table>
<thead>
<tr>
<th>Literaturstelle</th>
<th>Evidenzlevel</th>
<th>Studientyp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colombel, J. F. 2018</td>
<td>2</td>
<td>A multicentre, randomised, open-label, active-controlled, two-group, phase 3, efficacy and safety trial.</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Outcome/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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

**Recruitment 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)9 scores 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 finally 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 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 Colisson Foundation outside the submitted work; and institutional support for education from IBD2020, Crohns Colitis Cure, Schering-Plough, Takeda, Synthon, Eli Lilly, Celgene, GlaxoSmithKline, Janssen, Grünenthal, 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, Grünenthal, Johnson & Johnson, Millennium Pharmaceuticals, Merck & Co, Novo Nordisk, Nycomed, Pfizer, Pharmacosmos, Schering-Plough, Salix, Takeda, UCB Pharma, and Vifor outside the submitted work. AA reports personal fees from AbbVie, AstraZeneca, Biogen, Celltrion, Chiesi, Ferring Pharmaceuticals, Hospira, Janssen, Arard, Laboratoires Mayoli-Spindler, Nestlé-Nutrition, and Ferring Pharmaceuticals outside the submitted work. ST 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. RP reports grants and personal fees from AbbVie outside the submitted work. PB reports personal fees from AbbVie.

Articles2788www.thelancet.comVol 390 December 23/30, 2017 from AbbVie, Takeda, Vifor Pharma, Hospira, Janssen, 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 Colisson Foundation outside the submitted work; and institutional support for education from IBD2020, Crohns Colitis Cure, Schering-Plough, Takeda, Synthon, Eli Lilly, Celgene, GlaxoSmithKline, Janssen, Grünenthal, 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, Grünenthal, Johnson & Johnson, Millennium Pharmaceuticals, Merck & Co, Novo Nordisk, Nycomed, Pfizer, Pharmacosmos, Schering-Plough, Salix, Takeda, UCB Pharma, and Vifor outside the submitted work.
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

WJS reports personal fees from AbbVie; AstraZeneca, Centocor, Ferring Pharma GmbH, 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, Nestlé, Novartis, Ocera Therapeutics, Parexel, Philip Morris Institute, Pfizer, Procter & Gamble, Prometheus, Prevention Bio, Robarts Clinical Trials, Sandoz, Second Genome, SetPoint Medical, Sigmoid, TiGenix, UCB Pharma, Zealand Pharma, Zyagenia, 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, Sigmodi Biotechnologies, Tillotts Pharma, AM-Pharma BV, Dr August Wolff, Avaxia Biologics, Zyagenia, 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 2248235), the use of azathioprine to treat Crohn's disease (US 5733915), azathioprine compositions for colonic administration (New Zealand patent 306602; 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, Tramedec, 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, Allergan, 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, Abylnx, 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.
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.


Population Intervention - Comparison Outcomes/Results

Evidence level: 3

Study type: A proof-of-concept randomized double-blind controlled study.

Number of Patients: 122 biologic-naïve adult patients with active CD.

Recruitment Phase: July 2012 through September 2015

Inclusion Criteria: Patients recruited were adults with active luminal CD naïve 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 ileocolonoscopy was reached in 15 (33%) of 45, 10 (27%) of 37, and 16 (40%) of 40 patients in the DIS1, DIS2, and 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 control group by week 12 (P = .070) and in 23 (51%), 19 (51%), and 21 (53%) patients by week 54 (P= .100).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. 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, vs 3.6 ± 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 randomized exploratory trial of patients with active CD, we found 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. Buhllmann 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 Dome, and Pfizer; has served as advisor for Abbvie, Johnson and Johnson, 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 Abbvie, 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 van der 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, Mayoli, UCB, Novartis, Genentech, Pfizer, Novo Nordisk, and Falk. Alexandre Aubourg reports consultancy fees from MSD, Abbvie, and Takeda. Bas Oldenbourg 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, MariekePlerik, Sylvie Chevret, and David Laharie declare no competing interest in the present study. 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 weeks. 

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.
**Literursammlung:**

AG 1 Diagnostik-Frage 2

**Inhalt: 5 Literaturstellen**

<table>
<thead>
<tr>
<th>Literaturstelle</th>
<th>Evidenzlevel</th>
<th>Studientyp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assa, A. 2019</td>
<td>2</td>
<td>Nonblinded, randomized controlled trial.</td>
</tr>
<tr>
<td>Papamichael, K. 2017</td>
<td>3</td>
<td>multicenter, retrospective study</td>
</tr>
<tr>
<td>Papamichael, K. 2019</td>
<td>3</td>
<td>A multicentre retrospective cohort study.</td>
</tr>
<tr>
<td>Vande Casteele, N. 2015</td>
<td>2</td>
<td>Randomized controlled trial</td>
</tr>
</tbody>
</table>

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


<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention - Comparison</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 2</td>
<td>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&lt;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&lt;5mg/mL, meaning that patients with LOR (either clinical and/or biologic) were intensified only if ADL TC was &lt;5mg/mL. Patients in clinical and biologic remission were intensified only if ADL TC was &lt;5mg/mL.</td>
<td>Primary: The primary endpoint of the study was sustained corticosteroid-free clinical remission (PCDAI&lt;10 points) at all visits from weeks 8 to 72. Secondary: Secondary outcomes included corticosteroid-free clinical remission on ADL at weeks 48 and 72; sustained biologic remission (defined by CRP &lt;0.5 mg/dL and fecal calprotectin&lt;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 &lt;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 group 1 and group 2, respectively.</td>
</tr>
</tbody>
</table>
no enhancement on cross-sectional imaging); complicated or draining perianal fistula; 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.

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: Consultation fees 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 ratio stratified 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.


**Population**

| 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. |
| Recruiting Phase: July 2012 through September 2015 |

**Intervention - Comparison**

| 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 |

**Outcomes/Results**

| 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, 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.

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, vs 3.6 ± 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.
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.


<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention - Comparison</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 3</td>
<td>Intervention: Proactive drug monitoring.</td>
<td>Primary: Time to treatment failure.</td>
</tr>
<tr>
<td>Study type: multicenter, retrospective study</td>
<td>Comparison: Reactive drug monitoring.</td>
<td>Secondary: Time to first IBD-related surgery or hospitalization, serious infusion reaction, and detection of antibodies to infliximab.</td>
</tr>
<tr>
<td>Number of Patient: 264 patients</td>
<td></td>
<td>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 &lt; .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&gt;</td>
</tr>
</tbody>
</table>
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 Group for 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:


<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention - Comparison</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 3</td>
<td>Intervention: Proactive TDM.</td>
<td>Primary: Time to treatment failure.</td>
</tr>
</tbody>
</table>
| Number of Patient: 382 patients. | | 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).

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.

Population
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 diagnosis 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 - Comparison
Intervention: All patients were first dose optimized to have an infliximab TC within the interval 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.

Outcomes/Results
Primary: Primary end point was defined as the proportion of patients in 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
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**

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


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 Bewertungen**


**Evidence level/Study Types**

**Evidence level: 1**

**Study type:** systematic 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 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 presented 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 participants for treatment evaluation (less than 100 cases), missing data, not reporting original data and not reporting 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. 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.

**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
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 (rs4843806) [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.
<table>
<thead>
<tr>
<th>Intervention: none</th>
<th>Comparison: Biomarkers</th>
</tr>
</thead>
</table>

**Bou**

**Jou**

**Ket**

**Bio**

**24;2**

**10.1**

**202**

**PMI**

**8**

**Cite**

**Per**

**Hyp**

**Pre**

**Atr**

**Fro**

**2;7;**

**10.**

**eC**

**PMI**

**Rev**

**9**

**Cite**

**Is**

**Tand**

**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**

**Ojir**

**Jim**

**Vay**

**Bos**

**Got**

**Bla**

**Eiz**

**Mer**

**M, Int.**

Knu
Daß
GL,
Bra
Ste
A, I
J, I
Mul
Hol
V.
BM
doi
PMI
24
Cite
Sys
ana
TNf
rhe
Bek
Soc
V.
Phä
Oct
10:
13.
PMI
Rev
25
Cite
A
Tre:
Rec
Infl:
Mul
Pro
Per
Anc
SB,
Byg
Wie
Villi:
J,
Bro
Nie
AB,
Fær
Ste
A, I
J, I
Wei
Nut
doi
PMI
26
Cite
Pot
Tre:
Dru
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:


<table>
<thead>
<tr>
<th>Evidence level/Study Types</th>
<th>P - I - C</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 1</td>
<td></td>
<td>Primary: Biomarker for detection of CD activity</td>
</tr>
<tr>
<td>Study type: systematic review</td>
<td></td>
<td>Secondary: -</td>
</tr>
<tr>
<td>Databases: Pubmed Cochrane</td>
<td></td>
<td>Results: We screened 5303 articles and identified models (from 21 studies) for our analysis. Seven models could be validated externally; in the AILORIX data set, these models identified patients with endoscopic activity with AUROC values ranging from 0.61 (95% CI, 0.51-0.70) to 0.81 (95% CI, 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, 0.77). The AUROC values for the validation in the TAILORIX and/or U data set were similar. In the TAILORIX and/or U data set, 4 of the 7 models, as well as the FC and CRP assays, were able to identify patients with endoscopic activity with positive predictive values of 90% or more. Two of the 7 models (but not the FC CRP values) identified patients with negative predictive values of 90% or more, leading to correct prediction of endoscopic healing in 3.2% to 11.3% of all patients. For example, applying the Herranz-Bachiller model (1 of 7 models) at a NPV of 92.1% and a positive predictive value of 91.9%, correctly identified 35.7% of all patients whom ileocolonoscopy could be avoided as expected endoscopic activity or healing was correctly identified 3.2% of all patients. Moreover, ileocolonoscopies (66.5% in TAILORIX and 72.6% of the UAI of all ileocolonoscopies) could be avoided correctly based on concentrations of FC of 100 µg/g or less and 250 µg/g or higher. However, using the range of FC concentrations to identify patients who 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 incorrectly to have endoscopic activity or healing.</td>
</tr>
<tr>
<td>Search period: feb 14 2018</td>
<td></td>
<td>Author's Conclusion: endoscopy stays the gold standard</td>
</tr>
<tr>
<td>Inclusion Criteria: explained</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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 (i.e., 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 (i.e., 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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusion Criteria: explained</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Methodical Notes**

**Funding Sources:** Medical university

**COI:** declared
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 authors on the Prediction model Risk Of Bias ASsessment Tool (PROBAST). 17 Publications were assessed for risk of bias (inclusion criteria, predictors, outcome, and analyses) and for applicability in

Notes:

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

<table>
<thead>
<tr>
<th>Evidence level/Study Types</th>
<th>P - I - C</th>
<th>Outcomes/Results</th>
<th>Literature References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Databases: Medline and the Cochrane Library</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Search period: April 2017</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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,” “alpha-1-antitrypsin,”</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population: ok</td>
<td></td>
<td>Primary: Fecal calprotectin, comparisons?</td>
<td></td>
</tr>
<tr>
<td>Intervention: none</td>
<td></td>
<td>Secondary: none</td>
<td></td>
</tr>
<tr>
<td>Comparison: ok</td>
<td></td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>Population: ok</td>
<td></td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>Intervention: none</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparison: ok</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
“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-se 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 disorder Loktionov A. World J Gastroenterol. 2019 J
PMID: 31367153 Free PMC article. Review

8
Cite Share

PMID: 30828852 Free PMC article.

9
Cite Share

PMID: 30828114 Free PMC article. Review

10
Cite Share

PMID: 30574192 Free PMC article. Review

11
Cite Share

PMID: 30541017 Free PMC article.
### Evidence level/Study Types

<table>
<thead>
<tr>
<th>Evidence level: 1</th>
<th>Study type: systematic review, metaanalysis</th>
<th>P - I - C</th>
<th>Outcomes/Results</th>
<th>Literature References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Search period: 1/200 to 11/2015</td>
<td>Inclusion Criteria: To</td>
<td>Secondary: -</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Databases: pub/Embase</td>
<td>Notes:</td>
<td>Results: Seven studies (463 patients) were entered into the final analysis. The</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Methodical Notes

- **Funding Sources:** none
- **COI:** none
- **Study Quality:** OK, not specifically addressed
- **Heterogeneity:** low, not specifically addressed
- **Publication Bias:** not addressed

---


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: randomized controlled 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

determined 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 0.71, 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.


3 Cite Share


4 Cite Share


5 Cite Share


6 Cite Share


7 Cite Share


8 Cite Share
Proteomic Evaluation of the Gastrointestinal Irradiation Model. 
Huang W, Yu J, Jones Tudor G, Booth C, Macaluso Caligari R, 
PMID: 30624357 Free PubMed

Usefulness of fecal antibody testing in adult inflammatory bowel diseases: a prospective study. 
Nakamura S, Imaeda K, Matsuura M, Oka H, Watanabe K, Nakase H, Watanabe M, 
PMID: 30301337 Free PubMed

From bench to bedside: the impact of the new treatments for inflammatory bowel disease. 
Mumolo MG, Bertani L, Tedeschi G, Albano E, Tapete G, Galatioto A, 
PMID: 30197475 Free PubMed

Fecal calprotectin for endoscopic recurrence: a systematic review and meta-analysis. 
Tham YS, Yung DE, Fong SP, Eliakim R, Koulaouzidis C, 
PMID: 30034529 Free PubMed

Small bowel imaging in inflammatory bowel disease. 
Gauci J, Sammut L, Sciberras AJ, Cortis K, Ellul P. 
PMID: 29991884 Free PubMed
<table>
<thead>
<tr>
<th>Title</th>
<th>Authors</th>
<th>Journal</th>
<th>DOI</th>
<th>PMID</th>
<th>Cite Share</th>
</tr>
</thead>
<tbody>
<tr>
<td>The role of inflammation in inflammatory bowel disease</td>
<td>Kiely CJ, Pavli P, O'Brien</td>
<td>Gut Microbes.</td>
<td>201</td>
<td>29543557 Free</td>
<td>16</td>
</tr>
<tr>
<td>The Lewis score or the disease activity index in established Crohn's</td>
<td>Yablecovitch D, Lahat B, Ben-Horin S, Eliakim</td>
<td>Therap Adv</td>
<td>14;11:1756283X177477</td>
<td>29399042 Free</td>
<td>17</td>
</tr>
<tr>
<td>Validation of Neutrophil Detect Mucosal Inflammation in Ulcerative</td>
<td>Minar P, Jackson K, T Denson LA.</td>
<td>Inflamm Bowel Dis.</td>
<td>2</td>
<td>29272485 Free</td>
<td>18</td>
</tr>
<tr>
<td>Balloon-Assisted Endoscopy in Suspected Crohn's Disease</td>
<td>Yen HH, Chang CW, Chang HW</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 all 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. Because between the studies included, the DerSimoian–Laird random-effects model was applied. Sensitivity analysis using (defined as trials that were both blinded and published as full manuscripts) was carried out for comparisons with 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:

<table>
<thead>
<tr>
<th>Evidence level/Study Types</th>
<th>P - I - C</th>
<th>Outcomes/Results</th>
<th>Literature References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evidence level:</strong> 1</td>
<td></td>
<td>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.</td>
<td>Cite Share</td>
</tr>
<tr>
<td><strong>Databases:</strong> databases Medline, Web of Science, Cochrane Library, and EMBASE</td>
<td></td>
<td>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).</td>
<td>2 Cite Share</td>
</tr>
<tr>
<td><strong>Search period:</strong> december 2013</td>
<td></td>
<td>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</td>
<td>3 Cite Share</td>
</tr>
<tr>
<td><strong>Inclusion Criteria:</strong> 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.</td>
<td></td>
<td>Factors Associated with Poor Quality of Patients with Inflammatory Bowel Disease: Nazarian A, Bishay K, Gholami R, Scaffid Griller N, Satchwell JB, Baker JP, Grover SC J Can Assoc Gastroenterol. 2020 10.1093/jcag/gwaa014. eCollection 2021 Apr. PMID: 33855267 Free PMC article.</td>
<td>4 Cite Share</td>
</tr>
</tbody>
</table>
COVID-19 Pandemic: Which IBD Patients Scoped Now, Who Can Wait, and how to Res
PMID: 33085973 Free PMC article.

Biomarkers of Crohn's Disease to Support Therapeutic Interventions.
PMID: 32840322

Normal fecal calprotectin levels in healthy children and decrease with age.
Epub 2019 Jun 17.
PMID: 32765164

Analytical and clinical performance of the calprotectin immunoassay from DiaSorin in
Vicente-Steijn R, Jansen JM, Bisheshar R, Haubold J, Koch AK, Bruckmann NM, Saw Langhorst J.
PMID: 32579403 Clinical Trial.

Comparison of 18F-FDG PET-MR and fecal inflammation disease activity in patients with ulcerative colitis.
Li Y, Khamou M, Schaarschmidt BM, Umut Haubold J, Koch AK, Bruckmann NM, Saw Langhorst J.
Gut. 2021 Mar;70(3):499-510. doi: 10.1136/gut
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
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.
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.
PMID: 31751360 Free PMC article. Clinical T

20  Cite Share

Impact of faecal calprotectin measurement patients with Crohn's disease and ulcerative
Bathe AL, Mavropoulou E, Mechie NC, Pet Amanzada A.
PMID: 31647834

Diagnostic accuracy of fecal calprotectin colorectal cancer: A meta-analysis.
Ye X, Huai J, Ding J.
PMID: 30249553 Free PMC article.

32  Cite Share

The Management of Inflammatory Bowe Evidence and Future Perspectives.
Arnott I, Rogler G, Halfvarson J.
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.
PMID: 30197475 Free PMC article. Review.

34  Cite Share

PMID: 30068300 Free PMC article.

35  Cite Share

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


42 Cite Share

PMID: 29491393 Free PMC article.

43 Cite Share


44 Cite Share


45 Cite Share


46 Cite Share


47 Cite Share

Compliance with the faecal calprotectin test in bowel disease.
Maréchal C, Aimone-Gastin I, Baumann Peyrin-Biroulet L.

Selecting children with suspected inflammatory bowel disease: A systematic review.
Heida A, Van de Vijver E, Muller Kobold A, van Rheenen PF.

Clinical Utility of Fecal Calprotectin Monitoring in Inflammatory Bowel Disease: A Systematic Review.
Heida A, Park KT, van Rheenen PF.

Comparison of Fecal Calprotectin Measurement Approaches in Pediatric Inflammatory Bowel Disease.
Kittanakom S, Shajib MS, Garvie K, Turner R, Chetty VT, Macri J, Khan WI.

High-fat diet induced leptin and Wnt expression changes in mouse colonic tissue and human cancer cells:
Penrose HM, Heller S, Cable C, Nakhou M, Crawford SE, Savkovic SD.

Update on clinical and research applications of faecal calprotectin in gastrointestinal diseases.
Siddiqui I, Majid H, Abid S.

Treat to Target in Inflammatory Bowel Disease: A Systematic Review.
Darr U, Khan N.
Utility of Biomarkers in the Management of
Kochhar G, Lashner B.
Curr Treat Options Gastroenterol. 10.1007/s11938-017-0129-z.
PMID: 28138859 Review.

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
PMID: 28018107 Free PMC article.

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

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.

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

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.
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
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.
PMID: 27266773 Free PMC article.

64
Cite Share

Characteristics, Treatment, and Long-Ten
Involvement in Behcet’s Syndrome: A S
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):541-51
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, Shahjib MS, Reinisch W, Khan WJ.

<table>
<thead>
<tr>
<th>Cite Share</th>
<th>Epub 2016 Feb 20. PMID: 26897740 Review.</th>
</tr>
</thead>
<tbody>
<tr>
<td>74</td>
<td>Trimethylamine-N-oxide: A Novel Biomarker of Inflammation.</td>
</tr>
</tbody>
</table>
Inflammatory Bowel Disease.
Wilson A, Teft WA, Morse BL, Choi YH, Woo Tirona RG, Kim RB.
PMID: 26160437

Clinicians' guide to the use of fecal calprotectin for disease activity in inflammatory bowel disease.
Bressler B, Panaccione R, Fedorak RN, Seid Graff LA.
PMID: 26125109 Free PMC article. Review.

The Relationship Among Perceived Stress, Physical Activity, and Alpha-1-Antitrypsin Levels in Persons With Inflammatory Bowel Disease.
Targownik LE, Sexton KA, Bernstein MT, Braude AJ, Graff LA.
PMID: 26470039 Free PMC article. Review.

C-Reactive Protein, Fecal Calprotectin, and Endoscopic Activity in Symptomatic Crohn’s Disease: A Systematic Review and Meta-Analysis.
Am J Gastroenterol. 2015 Jul;110(7):887-911. doi: 10.1038/ajg.2015.120. Epub 2015 May 12.
PMID: 25964225 Review.

Validation of an 8-item-questionnaire predicting real-life implementation in primary care: A diagnostic study.
PMID: 25757949 Free PMC article. Clinical Trial.

Flow cytometry detection of vitamin D receptor expression in Crohn's disease.
PMID: 25707738 Free PMC article.
The clinical value of faecal calprotectin in postoperative Crohn's disease.
Yamamoto T.
PMID: 25653853 Free PMC article. Review.

No association between serum adenosine activity in Crohn's disease.
Sajjadi M, Gholamrezaei A, Daryani NE.
PMID: 25652144

Accuracy of Rapid Fecal Calprotectin Test in Bowel Diseases Under Treatment with TNFα Blockers
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 in using scales yielding a summary score because the interpretation of the summary score was problematic and potentially evaluated the checklist independently. Disagreements were resolved by consensus.

During quality assessment, data extraction, and analysis process, we encountered many obstacles, highlighting the current studies. It is hoped that more widespread multicenter large samples and implementation of the Standards for Accruce 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. Metaincluded pretest probability, blinded design, and sample size. Sensitivity analysis was undertaken to assess the pretest probability (pretest probability more than overall average pretest probability) and small sample studies (sample size.

Publication Bias: Publication bias was assessed using Deeks’ test. P < 0.05 was considered to indicate statistically nonsignificant value (P > 0.425), indicating no publication bias among the included studies.

Notes:


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


29/73
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 follows: 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 sensitivity or specificity); 4) the identification of relapse is based on clinical activity indices or endoscopic findings; and 5) studies 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.
<p>| Cl | Cl | 2C | 1C | PI |
| Cl | 1C | 1C |
| M | In | P | Di | C | A | N | Hl | Bi | Cl | M | 1C | PI |
| 1C | Cl | R | A | C | D | N | 2; | 0' | Pl |
| 1' | Cl |
| CM | FI | Tc | St | Tc | R | C | Cl | Ke | EM | M | R | C | J | D | 1C | St | Pl | R |
| 1' | Cl |
| Fe | Is | Bl | In |</p>
<table>
<thead>
<tr>
<th>K.</th>
<th>U.</th>
<th>2ț</th>
<th>1ț</th>
<th>Pl</th>
<th>Ti</th>
<th>cm</th>
<th>Cl</th>
<th>Yț</th>
<th>Uț</th>
<th>2ț</th>
<th>1ț</th>
<th>Pl</th>
<th>Rț</th>
</tr>
</thead>
<tbody>
<tr>
<td>6ț</td>
<td>Cl</td>
<td>Ti</td>
<td>m</td>
<td>di</td>
<td>Lt</td>
<td>Ti</td>
<td>Jț</td>
<td>1ț</td>
<td>Pl</td>
<td>Rț</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6ț</td>
<td>Cl</td>
<td>Ar</td>
<td>Ci</td>
<td>In</td>
<td>Uț</td>
<td>Ai</td>
<td>Tț</td>
<td>Gț</td>
<td>Di</td>
<td>1ț</td>
<td>x.</td>
<td>Pl</td>
<td></td>
</tr>
<tr>
<td>6ț</td>
<td>Cl</td>
<td>Fr</td>
<td>ac</td>
<td>mp</td>
<td>Bl</td>
<td>Lt</td>
<td>Di</td>
<td>de</td>
<td>Ej</td>
<td>Pl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6ț</td>
<td>Cl</td>
<td>Ti</td>
<td>in</td>
<td>ar</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2¢</td>
<td>1¢</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----</td>
<td>----</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2¢</td>
<td>Pl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pr</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7¢</td>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bi</td>
<td>in</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pr</td>
<td>8¢</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>Pl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cl
Man
Re
78
Cl
M
Re
73
Cl
Fa
Sy
Tim
Pr
Rh
An
B  |
R  |
6;  |
P  |
Pl


46/73
**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 was 0.78, 95% CI: 0.72–0.83, while specificity ranged from 0.62–0.91 (pooled specificity 0.73, 95% CI: 0.68–0.82). 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 sensitivity and specificity were 11.75 (P < 0.0005), 16.68, (P < 0.0005), 12.95 (P < 0.0024), 10.93, (P < 0.00529), and 13.82 (P < 0.0016), respectively. NLR showed no 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:


<table>
<thead>
<tr>
<th>Evidence level/Study Types</th>
<th>P - I - C</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study type: Systematic Review and Meta-Analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Databases: MEDLINE and EMBASE using Ovid SP, the Cochrane Library, and the ISI Web of Knowledge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Search period: to 6 November 2014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusion Criteria: see inclusion</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 for CRP (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 SL: coefficient=−19.34, P=0.117; 95% CI: −63.49 to 21.81)

Notes:

<table>
<thead>
<tr>
<th>Evidence level/Study Types</th>
<th>Evidence level: 1</th>
<th>Study type: Meta-analysis of Prospective Studies</th>
<th>Databases: PubMed, EMBASE, Web of Science, and the Cochrane Central Register of Controlled Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Search period:</td>
<td>1966 to March 2014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion Criteria:</td>
<td>(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 results) 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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusion Criteria:</td>
<td>Studies were excluded if the crude rates of postoperative relapse or remission were not reported</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>P - I - C</th>
<th>Population: CD patients postoperative with endoscopy</th>
<th>Intervention: surgery and endoscopy</th>
<th>Comparison: postoperative recurrence dependent on calprotectin</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Outcomes/Results</th>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Secondary: -</td>
</tr>
<tr>
<td>Results:</td>
<td>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.</td>
</tr>
<tr>
<td>Author's Conclusion: As a simple and noninvasive marker, FC is useful in evaluating recurrence of postoperative patients with CD</td>
<td></td>
</tr>
</tbody>
</table>
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:**


<table>
<thead>
<tr>
<th>Evidence level/Study Types</th>
<th>P - I - C</th>
<th>Outcomes/Results</th>
<th>Literature References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type: systematic</td>
<td>Secondary: -</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICR</td>
<td>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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>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.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Methodical Notes**

**Funding Sources:** none

**COI:** declared

**Study Quality:** Data extraction and quality control were performed independently by two reviewers (YST, SF). A by consensus and involvement of the senior authors. Where additional data were required, the corresponding author was contacted by email in an attempt to obtain the necessary data.

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

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

**Notes:**

**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 predictive roles of FC in activity and relapse of Crohn’s disease.

**Secondary:** -

**Results:** A total of 1,252 CD patients from 18 different studies were included. The pooled sensitivity and specificity of FC at a cutoff value of 150 μg/g to predict activity of CD were 0.91 (95% CI: 0.87–0.95) and 0.85 (95% CI: 0.78–0.91) respectively. The pooled sensitivity of FC at a cutoff value of larger than 150 μg/g to monitor relapse of CD was 0.67 (95% CI: 0.62–0.72) and 0.71 (95% CI: 0.66–0.76) respectively.

**Author’s Conclusion:** As a simple and noninvasive marker, FC can predict the activity and relapse in CD patients, and the capacity of FC to predict CD activity was superior to its application in monitoring relapse.

**Methodical Notes**

**Funding Sources:** none

**COI:** none

**Study Quality:** shown

**Heterogeneity:** Reference-positive patients/ total subjects were used to calculate the pretest probability of CD. FC in a certain study were extracted or calculated using appropriate contingency tables. If there were potential p studies with sensitivities or specificities of 100%, then a value of 0.5 was added to all cells of trials that contain negative likelihood were determined as functions of these summary estimates; the derived estimates of sensitivities were also used to construct a summary receiver operating characteristic (SROC) curve.18 The area under alternative global measure of test performance.18 Diagnostic odds ratio (DOR) and the area under the SROC curve 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-analysis. The present study had relatively high heterogeneity and bias of publication. The sources of heterogeneity and publication populations, disease duration, treatment regimen, time of measuring FC, and cutoff value of FC. Second, the scores were similar in most included studies, but the application of various scoring systems to assess CD activity was a problem. Last, a few studies failed to provide information of interest.

**Notes:**

---


<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention - Comparison</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 2</td>
<td>Intervention: different monitoring</td>
<td>Primary: Adult IBD patients were consecutively randomized to interventions (3M vs OD). Both intervention arms were screening for activity, quality of life and fatigue and were measuring medical care using the constant care web-application according to the screening in 3M. Disease activity was assessed using home measured fecal calprotectin and a disease activity score.</td>
</tr>
<tr>
<td>Study type: RCT</td>
<td>Comparison: monitoring</td>
<td>Secondary: -</td>
</tr>
<tr>
<td>Number of Patient: 102</td>
<td></td>
<td>Results: In total, 102 patients were randomized (n = 52/50 3M/OD). No difference in two screening procedures could be found regarding medical co-morbidity (P = 0.58), fatigue (P = 0.86), quality of life (P = 0.17), mean time spent in remission (P &gt; 0.32), overall FC relapse rates (P = 0.49), FC disease course: time to relapse (P = 0.69) and remission (P = 0.88) during 1 year. Median (interquartile range) numbers of FC home-monitoring test-kits used were significantly different, 3M: 6.0 (5.0-8.0) and OD: 4.0 (2.0-9.0) per patient.</td>
</tr>
<tr>
<td>Recruiting Phase: July 2015 to July 25 2016</td>
<td></td>
<td>Author's Conclusion: The two eHealth screening procedures resulted in increased FC relapse and bringing about remission. However, the OD group used fewer test-kits per patient. Individualized screening procedures can be recommended for adult IBD patients in clinical web-practice.</td>
</tr>
<tr>
<td>Inclusion Criteria: yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusion Criteria: yes</td>
<td>Methodical Notes</td>
<td></td>
</tr>
</tbody>
</table>

**Methodical Notes**

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

**COI:** declared

**Randomization:** yes

**Blinding:** yes

**Dropout Rate/ITT-Analysis:** yes,

**Notes:**

---


<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention - Comparison</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 2</td>
<td>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 treatment was intensified based on plasmatic TC only, meaning that patients with ADL TC&lt;5mg/mL were intensified regardless of disease activity (PCDAI, CRP, and calprotectin).</td>
<td>Primary: study with clinical and continuous ADL treatment for all visits.</td>
</tr>
<tr>
<td>Study type: Nonblinded, randomized controlled trial.</td>
<td>Comparison: In group 2 (reactive group), patients were also assessed during each visit for clinical and biologic disease activity, but ADL treatment was intensified based on plasmatic TC only, meaning that patients with ADL TC&lt;5mg/mL were intensified regardless of disease activity (PCDAI, CRP, and calprotectin).</td>
<td>Secondary: included remission, sustained remission, CRP, and calprotectin.</td>
</tr>
<tr>
<td>Number of Patient: 78 children with CD.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recruiting Phase: July 2015 through December 201</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

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-TNFα 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 on cross-sectional imaging); complicated or draining perianal fistula; 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

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: Consultation fees from Janssen, and lecture fees from AbbVie. Ron Shao: Consultation fees 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 resection postoperative recurrence in Crohn's disease. Dig Liver Dis. . . 2020

Population - Intervention Comparison

Evidence level: 2
Study type: RCT
Number of Patient: 48
Recruiting Phase: November 2014 to September 2017

Outcomes/Results

Primary: The primary endpoint was endoscopic POR at 6 months defined by an endoscopic

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 with

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 predictive value = 77.8%[57.5–91.4] and positive predictive value = 78

Author’s Conclusion: Fcal variation within the first three months after ileocolonic resection 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
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

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) scores 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, 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/L or more, and both.

Comparison
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 mucosal healing, defined as a CDEIS of less than 4 after randomisation.

Secondary: (1) deep remission (CDAI <150, CDEIS of draining fistula, discontinuation of corticosteroid remission (FC <250 μg/g, CRP <5 mg/L, and CDEIS overall CDEIS of less than 4 plus CDEIS of less complete endoscopic remission (CDEIS=0); and (6 decrease of >5 points)

Results: The study’s primary endpoint of mucosal ulcers at 48 weeks after randomisation was met in the tight control group compared with 37 (30%) patients in the clinical management group: deep remission, with a CMH-adjusted risk difference of 16·1% (95% CI 3·9 to 28·3; p=0·014); biological remission, with a CMH-adjusted risk difference of 25·0; p=0·006); and an overall CDEIS of less than 4 at 48 weeks after randomisation, with a CMH-adjusted risk difference of 16·1% (3·9 to 28·3; p=0·010). No significant difference between the groups regarding the proportion of patients in complete remission in the tight control group than the clinical management group, with a CMH-adjusted risk difference of 0·7% [95% CI –1·7 to 2·7]; p=0·728), or endoscopic remission in the tight control group compared with the clinical management group (CDAI <150) at 11, 23, 35, and 48 weeks after randomisation, with a CMH-adjusted risk difference of 5·9% [95% CI 1·7% to 10·3%; p=0·067; ). A significantly higher proportion of patients achieved clinical remission (CDAI <150) at 11, 23, 35, and 48 weeks after randomisation, with a CMH-adjusted risk difference of 5·9% [95% CI 1·7% to 10·3%; p=0·067; ). A significantly higher proportion of patients achieved clinical remission (CDAI <150) at 11, 23, 35, and 48 weeks after randomisation, with a CMH-adjusted risk difference of 5·9% [95% CI 1·7% to 10·3%; p=0·067; ). A significantly higher proportion of patients achieved clinical remission (CDAI <150) at 11, 23, 35, and 48 weeks after randomisation, with a CMH-adjusted risk difference of 5·9% [95% CI 1·7% to 10·3%; p=0·067; ). A significantly higher proportion of patients achieved clinical remission (CDAI <150) at 11, 23, 35, and 48 weeks after randomisation, with a CMH-adjusted risk difference of 5·9% [95% CI 1·7% to 10·3%; p=0·067; ).

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.

Methodical Notes

Funding Sources: Funding AbbVie

COI: J-FC reports personal fees from AbbVie, Amgen, Boehringer Ingelheim, Celgene Corporation, Celltril Pharmaceuticals, Genentech, Janssen, MedImmune, Merck & Co, Pfizer, Protagonist Therapeutics, PPM Se Therapeutics, Shire, Takeda, Theradiag, Intestinal Biotech Development, and Genfit outside the submitted work; and Takeda outside the submitted work. RP reports grants and personal fees from AbbVie outside the submitted work. Articles2788www.thelancet.comVol 390 December 23/30, 2017 from AbbVie, Takeda, Vifor Pharma, Hospira, Janssen and Mundipharma; and reports grants from AbbVie, outside the submitted work. FB reports personal fees from AbbVie, Centocor, Schering-Plough, Bristol-Myers Squibb, Chen Elan Pharma International, Genentech, Giuliani Pharma, Merck & Co, Takeda, Otsuka Pharmaceutical, PDL Bio Pharmace Pharmaceuticals, Warner Chilcott, Proximagen, VHSquared, TopiVert, Ferring Pharmaceuticals, Celgene, Gilead, 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 Press 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 work; education from IBD2020, Crohns Collitis Cure, Schering-Plough, Takeda, Synthon, Eli Lilly, Celgene, GlaxoSmithKline Pharmaceuticals, MSD, Procter & Gamble, Vifor, ICHOM, and Warner Chilcott outside the submitted work. SD reports personal fees from Abbott Laboratories, AbbVie, A Janssen, Celltrion, Danone Austria, Elian, Falk Pharma GmbH, Ferring Pharmaceuticals, Immundiagnostik, Mitsubishi Pharmaceutical, PDL, Pharmacosmos, PLC 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, 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, Elian, Falk Pharma GmbH, Ferring Pharmaceuticals, Immundiagnostik, Mitsubishi Pharmaceutical, PDL, Pharmacosmos, PLC 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 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 Pharma outside the submitted work; and grants from AbbVie, AESCA, Centocor, Falk Pharma GmbH, Immundiagnostik, and MSD outside the submitted work.}

Endoscopic outcomes than symptom-driven decision algorithms: tight control and clinical management. an anti-tumour necrosis factor therapy on the basis with biomarkers in patients with early Crohn's disease.
<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention - Comparison</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 2</td>
<td><strong>Intervention</strong>: 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. <strong>Comparison</strong>: IFX dose increase by 5 to 10 mg/kg if patients had a CDAI &gt;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.</td>
<td><strong>Primary</strong>: The primary corticosteroid-free remission between week 22 and 54 ulcers at week 54 and no abscess and no new fistula. <strong>Secondary</strong>: Prespecified proportion of patients with clinical remission (CDAI remission from week 14 (CDEIS &lt;3) at weeks 12 (decrease of CDEIS score 54, IFX dose increase du μg/mL between weeks 1 use of infliximab, need f abscesses. <strong>Results</strong>: The primary week 22 and 54 off glu fistula and surgery and ileocolonoscopy was rea of 37, and 16 (40%) of 4C the control group, respec. At week 12, 16 (36%), 6 ( no ulcerations on endo control groups (P= .054); increased to 19 (42%), 2</td>
</tr>
<tr>
<td>Study type: A proof-of-concept randomized double-blind controlled study.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Patient: 122 biologic-naive adult patients with active CD.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recruiting Phase: July 2012 through September 2015</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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) &gt;220 with objective signs of active inflammation (high-sensitivity CRP &gt;5 mg/L and/or fecal calprotectin &gt;250 μg/g) and visible ulcers at baseline ileocolonoscopy.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusion Criteria: Patients with an intestinal absorption of nicotine to treat nicotine responsive conditions (Australia patent 718052; US 6238689), the thioguanine to treat colorectal adenomas (US 6166024), and enterically-coated oral dosage forms of pharmaceutical composition for the treatment of inflammatory bowel disease (US 7341741), and intestinal absorption responsive conditions (Canada patent CA2260909), and for obesity treatment and device (US 7803195 B2) that reports personal fees from AbbVie, Bristol-Myers Squibb, Johnson &amp; Johnson, Merck &amp; Co, Takeda, UCB Pfizer, Celgene, Amgen, AstraZeneca, Robarts, outside the submitted work; and reports grants from AbbVie, Jol 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 &amp; Gamble, Roche, Schering-Ploug! UCB Pharma outside the submitted work; and reports grants from MSD, Centocor, Chemocentryx, Genentec; Schering-Ploug, Cytokine PharmaSciences, AM-Pharma, Vivify Health, Takeda, and Gilead outside the submitte 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; and 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 Cotvidien outside the submitted work. ML and AD declare no competing interests.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Randomization: 1:1 ratio. The patient number and group of each stratum were assigned by a central randomisation schedule generated by a designated person in the AbbVie statistics department. The subject randomisation schedule was generated by a designated person in the AbbVie statistics department 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 Concentrations to Achieve Clinical, Endoscopic, and Corticosteroid-Free Remission in Patients With Active Luminal Crohn's Disease. *Inflamm Bowel Dis*. 2018;1351.e1. 2018
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, as an 24 (65%), and 26 (71%), 24 (65%), and 26 (89), and in 28 (62%), 23 (60%), and 26 (62%), respectively (P = .070) and in 23 (51%) by week 54 (P= 1 week 54 (P=.89).

A sustained IFX serum concentration was observed through week 54 in 24 (60%) of the patients in the IFX group, respectively (P= .15): 22 (43%), 7 (16%), and 5 (12%) before week 12 and 54 was observed in 23 (51%) patients continuously achieving remission (CDEIS reduc-

Methodical Notes

Funding Sources: This investigator-initiated trial was financially supported by Merck Sharp Dome and Janssen, with receipt of a grant from Merck Sharp Dome. Buhlmann Laboratories, Switzerland, kindly provided materials for Quantum Blue rapid. measurements of anti-infliximab antibodies. 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 Dome, and Pfizer; has served on Johnson, Merck Sharp Dome, Mundipharma, Pfizer, Prometheus Laboratories/ Nestle, and Sandoz; and received lecture fees from Johnson and Johnson, Merck Sharp Dome, Mundipharma, and Pfizer. Severine Vermeire reports grant support from Pfizer; lecture fees from Abbvie, MSD, Takeda, Ferring, Falk Pharma, Hospira, and Tillotts; and consultancy fees from Genentech/Roche, Shire, Pfizer, Galapagos, Mundipharma, Hospira, Celgene, Second Genome, and Janssen. Fill from Abbvie, Chiesi, Ipsen, MSD, and Roche; and speaker’s and consultancy fees from Abbvie, Falk, Ferring, Janssen, Takeda, and Vifor. Anthony Buisson declares consulting fees for Abbvie, Hospira, and Takeda; and lecture fees from Vifor Pharma, Sanofi-Aventis, and Ferring.ianneke van der Woude received grants from Abbvie, Jansen, Pfizer, Takeda, and consultancy fees from Abbvie, Falk, Ferring, Janssen, Mundipharma, MSD, Pfizer, Takeda, and Vifor. Edouard edouard, MD, Abbvie, Takeda, Ferring, MSD, Chiesi, Mitsubishi Pharma, Hospira, Janssen, and Takeda; and is on the advisory board for MD, Takeda, Hospira, Mitsubishi Pharma, Celltrion, and Prometheus. Matthieu Allez received fees from Abbvie, MSD, Abbvie, Takeda, Ferring, MSD, Chiesi, Mitsubishi Pharma, Hospira, Janssen, and Takeda; and is on the advisory board for MS, 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 from Oldenburg reports grants from MSD, Abbvie, Takeda, Cablon, Ferring, and Falk. Anna Gils has served as a speaker and consultant for Abbvie, Pfizer, Takeda, and Abbvie, and as a consultant for UCB; and has received Investigator-Initiated Research Grants from Bossuyt, Benjamin Pariente, Yoram Bouhnik, Jerome Filippi, Philippe Van Hootegem, Jacques Moreau, Denis Fama, Laurent Peyrin-Biroulet, Hedia Brix, Philip Caenepeel, MariekePierik, Sylvie Chevret, and David Laharie during the present study. KU Leuven licensed the infliximab, adalimumab, and vedolizumab ELISA to apDia and R-Biopharm. The 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-mercaptopurine.

Blinding: Serum samples for IFX concentrations were shipped to and measured at a single laboratory (KU Leuven), 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 44 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 (z.B. IFX-Spiegel) weitere mögliche Faktoren für Dosisanpassung.


<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention - Comparison</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention: endoscopy</td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td>Comparison: relationships between clinical disease activity, CRP normalisation and mucosal healing in Crohn's disease (CD)</td>
<td>Secondary: -</td>
</tr>
<tr>
<td>Evidence level: 3</td>
<td>Number of Patient: 188</td>
<td>Results: 188 patients who had evaluable ileocolonoscopy with at baseline, CDAI scores and CRP values at baseline and week 26 of 136 patients (53%) who had a CDAI&lt;150 at week 26 achieved both CRP normalisation (CRP&lt;0.8 mg/l) and CDAI to detect mucosal healing using 150 as a cut-off respectively. The PPV and NPV of CDAI to detect mucosal healing using 150 as a cut-off for CDAI were 79% and 42%, respectively</td>
</tr>
<tr>
<td>Study type: RCT, but not primary endpoint.</td>
<td>Recruiting Phase: Inclusion Criteria: subjects eligible for inclusion in this trial were adult CD patients with moderate-to-severe disease (CDAI &gt;220 and &lt;450) who have had an inadequate response to one or more conventional therapies (sulfasalazine, mesalamine, antibiotics, budesonide or oral corticosteroids).</td>
<td>Author's Conclusion: Half the patients under azathioprine remission have endoscopic and/or CRP evidence of residual activity, and patients with endoscopic and CRP normalisation have persistent clinical activity as scored by CDAI are not a reliable measure of the underlying disease</td>
</tr>
<tr>
<td>Number of Patient: 188</td>
<td>Exclusion Criteria: only mentioned in the primary publication of the study</td>
<td></td>
</tr>
<tr>
<td>Recruiting Phase:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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)**


<table>
<thead>
<tr>
<th>Evidence level/Study Types</th>
<th>Population</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 3</td>
<td>Number of patients / samples: 327</td>
<td>Results: The mean CDAI score, which decreased 1.08 from baseline to week 26, did not correlate with the mean change in trough infliximab concentration</td>
</tr>
<tr>
<td>Study type: yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Reference standard: yes | $r = 0.099, P = 0.083$), but was associated with the mean ($r = 0.19, P < 0.001$). Trough infliximab concentrations best predicted a $\geq 70$ point increase in the CDAI between 2.7-2.8 lg/mL best predicted CRP $>5$ mg/mL at the either visit decreased the proportion of patients with the levels compared with patients who were ATI negative (13.8% vs. 75.6% at visit 3; $P < 0.001$ for both comparisons). |
| Validation: yes | |
| Blinding: not clear | |
| Inclusion of clinical information: yes | |
| Dealing with ambiguous clinical findings: no | |

**Author conclusions:** This prospective study confirms infliximab concentrations, inflammation and antibodies-to-infliximab. Infliximab trough levels below $3$ lg/mL may increase the likelihood of symptoms and inflammation.

---

**Methodical Notes**

**Funding Sources:** Industry

**COI:** declared

**Notes:**

---


<table>
<thead>
<tr>
<th>Evidence level/Study Types</th>
<th>Population</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 3</td>
<td>Number of patients / samples: 135</td>
<td>Results: Levels of FC were measured in 319 samples from 135 patients. The FC level decreased from $1347$ mg/g before surgery at 6 months after surgery, but was higher in patients in disease recurrence (based on endoscopic analysis score, i2) than in patients in remission ($275$ vs $72$ mg/g respectively; $P &lt; .001$). Combined 6- and 18-month presence ($r = 0.42; P &lt; .001$) and severity ($r = 0.44; P &lt; .001$) of CD recurrence, but the CRP level and CDAI score did not. Levels of FC greater than $324$ mg/g 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 $131$ mg/g at 18 months.</td>
</tr>
<tr>
<td>Study type: Subgroup analysis (POCER)</td>
<td>Reference standard: yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Validation: yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blinding: no</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inclusion of clinical information: Pocer Patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dealing with ambiguous clinical findings: no</td>
<td></td>
</tr>
</tbody>
</table>

**Author conclusions:** In this analysis of data from a prospective clinical trial, FC measurement has superior sensitivity and NPV values to monitor for CD recurrence after intestinal resection. Its predictive value might be useful to identify patients most likely to relapse. After treatment, FC can be used to monitor response to treatment. It predicts which patients will have more accurate than CRP level or CDAI score.

---

**Methodical Notes**

**Funding Sources:** Abbvie

**COI:**

---

Notes: prospektive Beobachtung bei POCER-STudie


<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 5</td>
<td>Intervention:</td>
<td>Primary:</td>
</tr>
<tr>
<td>Study type:</td>
<td>Comparison:</td>
<td>Secondary:</td>
</tr>
<tr>
<td>Number of Patient:</td>
<td></td>
<td>Results:</td>
</tr>
<tr>
<td>Recruiting Phase:</td>
<td></td>
<td>Author's Conclusion:</td>
</tr>
<tr>
<td>Inclusion Criteria:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusion Criteria:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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 of Bowel Disease Treated with Vedolizumab. Dig Dis Sci. 62. 1590-1596. 2017**

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 3</td>
<td>Intervention: clinical data,</td>
<td>Primary: Our aim was to look into week 54 in inflammatory bowel cohort of patients.</td>
</tr>
<tr>
<td>Study type: retrospective observational</td>
<td>Comparison: none</td>
<td>Secondary: none</td>
</tr>
<tr>
<td>Number of Patient: 136</td>
<td></td>
<td>Results: Among 136 to 76 (56%) demonstrated clinical response or remission at week 54. In univariate and multivariate analyses, concomitant initiation of immunomodulator therapy (OR 1.11–6.57), the addition of concomitant biologic therapy (OR 11.49, 3.16–41.75) and C-reactive protein (CRP) levels (OR 1.99–12.15) was associated with clinical response or remission.</td>
</tr>
<tr>
<td>Recruiting Phase: not indicated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion Criteria: All patients 18 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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 response or remission (OR 0.22, 95% CI 0.05–0.88). Addition of an immunomodulator (IMM) 2.15–32.26) remained significant predictor of response or remission.

Author’s Conclusion: patients with IBD demonstrating primary response or remission at week 53 in patients with...
inflammation (see below).

Exclusion Criteria: -

Methodical Notes

Funding Sources: none

COI: declared

Randomization: no

Blinding: no

Dropout Rate/ITT-Analysis: no

Notes:


<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 3</td>
<td>Intervention: none</td>
<td>Primary: To carry out a post-Crohn's Disease Clinical Trial New Long-term Treatment R evaluate the association between trough levels and C-reactive protein levels sustained response to infliximab 14 weeks of induction treatment long-term response (Crohn's disease decrease ≥70 points and red baseline).</td>
</tr>
<tr>
<td>Study type: post hoc analysis of RCT</td>
<td>Comparison: trough levels</td>
<td></td>
</tr>
<tr>
<td>Number of Patient: 573</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recruitng Phase: 2/1999 to 3/2001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion Criteria: Patients included in this analysis were responders at week 14; all received a</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
full induction schedule of infliximab 5 mg/kg infusions given at weeks 0, 2 and 6.

Exclusion Criteria: only those excluded in ACCENT I

Exclusion Criteria: only those excluded in ACCENT I

Results: After induction with (37/147) and 33% (47/144) of 14 response to infliximab 5 mg/kg were 4.0 infliximab 5 mg/kg were 4.0 mg/kg every 8 weeks through week 54. Median we in patients with and without du median we in patients with and without du 14 trough level ≥3.5 mg/mL (ORs (95% CI), 3.5 (1.1 to 11. respectively, in patients with >8.0 mg/L); area under the f both predictors. A ≥3.5 mg/mL serum level did not predict c 10 mg/kg maintenance infli

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


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

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. BactDNA detected in 98 patients (34.0%). A variant-NOD2 genotype (39.6%). Forty patients (14%) relapsed during follow-up. Multivariable bactDNA as an independent risk factor of flare (hazard ratio (HR) and 95% confidence interval (CI)). Hospitalization, surgery, switch of treatment, initiation of tumor necrosis factor (TNF) therapy, steroids initiation, and increased fecal calprotectin levels associated with bactDNA at baseline. A logistic regression analysis identified bactDNA as an independent and significant predictive factor of hospitalization (odds ratio (OR) 8.5 (2.7-27.1); P<0.001), and switch of treatment (OR 3.5 (1.2-9.8)). A relationship was observed between bactDNA and mucosal lesions at admission. Serum pro-inflammatory cytokines were significantly increased in patients with variant-NOD2 genotype. The combination of both factors induced a higher percentage of patients on intensified anti-TNF therapy.

Author’s Conclusion: BactDNA is an independent risk factor of relapse at 6 months in CD patients. BactDNA is also independently associated with increased risk of hospitalization, switch of treatment, and steroids initiation.
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, Fedor Program
COI: declared
Randomization: no
Blinding: no
Dropout Rate/ITT-Analysis: no
Notes:


<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 3</td>
<td>Intervention: termination of infliximab treatment</td>
<td>Primary: We assessed the factors associated with maintenance therapy with infliximab and an antimetabolite 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) had to be at least 1 mg/kg body weight per week. 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) had to be at least 1 mg/kg body weight per week. Exclusion Criteria: a history of severe acute or delayed infusion reaction to infliximab, initial indication for infliximab being predominantly fistulizing perianal disease without significant luminal disease, persistence of active fistulizing disease, predominant jejunal or proximal ileal lesions, an ostomy, severe extraintestinal manifestations, and pregnancy or lactation.</td>
</tr>
</tbody>
</table>
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. 2015

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 3</td>
<td>Intervention: stop of infliximab</td>
<td>Primary: The aim was to evaluate the value of serum calprotectin as a biomarker for Crohn’s disease.</td>
</tr>
<tr>
<td>Study type: prospective cohort trial</td>
<td>Comparison: time to relapse</td>
<td>Secondary: -</td>
</tr>
<tr>
<td>Number of Patient: 115</td>
<td>Results: Medianserumcalprotectin (FC) concentrations after stop of infliximab were significantly higher in Crohn’s disease patients as compared with controls (P &lt; 0.0001). Serum calprotectin was higher in Crohn’s disease (median = 19,584 ng/mL) than for inactive disease (median = 125,000 ng/mL) in controls (P &lt; 0.0001). Serum calprotectin correlated with hsCRP (r = 0.4442, P &lt; 0.0001), but not with CDEIS, on the contrary to CDAI (r = 0.5515, 0.2577 with P &lt; 0.0001, P &lt; 0.0001, P = 0.01 respectively). In a survival analysis, serum calprotectin used as a discrete variable appeared complementary to hsCRP (N 5 mg/l) and fecal calprotectin (median = 19,584 ng/mL) for at least one year and had been corticosteroid-free over the last 6 months.</td>
<td></td>
</tr>
<tr>
<td>Recruiting Phase: 2006 to 2009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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 (azathioprine (N2 mg/kg), 6-mercaptopurine (N1.5 mg/kg) or methotrexate (N 15 mg weekly)) for at least one year and had been corticosteroid-free over the last 6 months.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusion Criteria: -</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Methodical Notes

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

COI: none

Randomization: no

Blinding: no

Dropout Rate/ITT-Analysis: indicated

Notes:


<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 3</td>
<td>Intervention: stop of infliximab</td>
<td>Primary: This prospective multicenter study evaluated calprotectin (FC) concentrations after stopping TNF-α-blocking agents and its ability to predict clinical or endoscopic relapse.</td>
</tr>
<tr>
<td>Study type: Prospective multicenter study</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Number of Patient:  52
Recruitment Phase:  02/2010 to 06/2012
Inclusion Criteria:  Eligible patients were over 18 years of age, had established IBD diagnoses, had received TNFα-blocking maintenance 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.

Comparison:  one cohort, comparison flare or not

Secondary:  we evaluated the impact of histological risk

Results:  Of 52 enrolled patients, 49 (16 colitis/IBD unclassified) provided the stool sample. During the follow-up, 15/49 (3 months before endoscopic relapse. Constipation during the follow-up were highly predictive of remission. Normal FC concentrations in patients relapsing did not significantly exceed their baseline levels for a median of 94 (13–317) days before endoscopic relapse. Consistently, the proportion of patients who achieved the primary end point CDEIS <4 and no deep ulcers 48 weeks after randomization was significantly greater for those with FC <250 μg/g (74%; P < 0.001), with an additional association of FC <250 μg/g with improved endoscopic outcomes was independent of IBD activity, with the greatest association observed for ileocolonic disease. Fecal calprotectin <250 μg/g gave a sensitivity/specificity of 72%/63% and positive/negative predictive values of 72% for FC <250 μg/g. This finding suggests that FC <250 μg/g is a promising marker for predicting and identifying patients at risk of clinical or endoscopic relapse, suggesting that FC may help the decision regarding whether or not to escalate drug treatment.

Author's Conclusion:  FC seems to increase the rate of clinical or endoscopic relapse, suggesting that FC may help the decision regarding whether or not to escalate drug treatment.

Methodical Notes

Funding Sources:  This study was supported by grants from the Helsinki University Central Hospital Research 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

<table>
<thead>
<tr>
<th>Evidence level: 3</th>
<th>Intervention: tight versus conventional monitoring</th>
<th>Primary: Primary endpoint of CALM CDEIS &lt;4 and no deep ulcers 48 weeks after randomization was defined as CDEIS decrease &gt;5 from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type: post-hoc analysis of RCT</td>
<td>Comparison: he association between endoscopic end points and biomarker cutoffs was performed using χ² test.</td>
<td>The purpose of this post hoc analysis of CALM was to identify drivers of treatment response</td>
</tr>
<tr>
<td>Number of Patient: 244</td>
<td></td>
<td>Secondary: -</td>
</tr>
<tr>
<td>Recruiting Phase: indicated in primary publication of CALM</td>
<td></td>
<td>Results: The proportion of patients who achieved the primary end point CDEIS &lt;4 and no deep ulcers 48 weeks after randomization was significantly greater for those with FC &lt;250 μg/g (74%; P &lt; 0.001), with an additional association of FC &lt;250 μg/g with improved endoscopic outcomes was independent of IBD activity, with the greatest association observed for ileocolonic disease. Fecal calprotectin &lt;250 μg/g gave a sensitivity/specificity of 72%/63% and positive/negative predictive values of 72% for FC &lt;250 μg/g. This finding suggests that FC &lt;250 μg/g is a promising marker for predicting and identifying patients at risk of clinical or endoscopic relapse, suggesting that FC may help the decision regarding whether or not to escalate drug treatment.</td>
</tr>
</tbody>
</table>
### Methodical Notes

**Funding Sources:** Abbvie  
**COI:** declared  
**Randomization:** initial CALM study yes  
**Blinding:** yes  
**Dropout Rate/ITT-Analysis:** shown in flow chart  
**Notes:** Posthoc of RCT

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

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Outcomes/Results</th>
</tr>
</thead>
</table>
| Evidence level: 1 | Inclusion Criteria: in detail described in the original publication CALM | Primary: Serum C-reactive protein (CRP) levels at baseline and after infliximab induction therapy were assessed as predictors for maintained response or remission through 54 weeks of treatment in patients with ulcerative colitis who responded to induction therapy.  
Secondary: - |
| Study type: post-hoc analysis of RCT | Inclusion: Infliximab; CRP | Results: A significant association was observed between baseline CRP levels and maintained response or remission. The percentage of patients with baseline CRP ≥ 0.7 mg/dL vs. 22.0% with CRP < 0.7 mg/dL achieved CRP normalization during infliximab treatment (decrease from 0.5 mg/dL at baseline) resulting in higher probability of maintained response (P < 0.001) or remission (P = 0.005). No optimal predictive CRP cut-off point was observed.  
Author's Conclusion: High baseline CRP levels increased the likelihood of maintained remission. Non-normalization of CRP increased the likelihood of maintained response or remission during 1 year of infliximab treatment.  |
| Number of Patient: 573 | Exclusion Criteria: in detail described in the original publication CALM | |
| Recruiting Phase: 26.2.1999 to 15.3.2001 | Comparison: Clinical outcome dependent on CRP |  |
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 medical employee of the Medical Affairs Publication Group, Janssen Biotech, Inc. Critical statistical review was provided by Yinghua Lang, an employee of Janssen Biologics Europe.

COI: declared

Randomization: yes

Blinding: yes

Dropout Rate/ITT-Analysis: shown

### Notes:


<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 1</td>
<td>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.</td>
<td>Primary: To identify patients with 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.</td>
</tr>
<tr>
<td>Study type: cohort study</td>
<td>Comparison: machine learning for prediction of response to ustekinumab</td>
<td>Secondary: -</td>
</tr>
<tr>
<td>Number of Patient: 401</td>
<td></td>
<td>Results: In total, 401 participants, with a mean (SD) age of 36 years, were included. The week-6 albumin level was used as a characteristic curve (AUROC) of 0.78 (95% CI, 0.71-0.82). Baseline baseline measurement of CRP achieved success 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.</td>
</tr>
<tr>
<td>Recruiting Phase: 2011 to 2015</td>
<td></td>
<td>Comparison: machine learning for prediction of response to ustekinumab</td>
</tr>
</tbody>
</table>

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, 482 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

Methodical Notes

Funding Sources: This study was supported by career development grant CDA 11-217 and merit review award IIR.
Wright, E. K. et al. Comparison of Fecal Inflammatory Markers in Crohn's Disease. Inflamm Bowel Dis. 22. 1

### Population

<table>
<thead>
<tr>
<th>Evidence level:</th>
<th>Intervention:</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>surgery, endocopy, fecal markers</td>
<td>Primary: We evaluated fecal calprotectin (S100A12, FC) using endoscopic validation to predict progression of CD after intestinal resection.</td>
</tr>
</tbody>
</table>

### Study type: prospective, randomized controlled trial

<table>
<thead>
<tr>
<th>Number of Patient:</th>
<th>Comparison: recurrence of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>135</td>
<td>S100A12 (FS) using endoscopic validation to predict progression of CD after intestinal resection.</td>
</tr>
</tbody>
</table>

### Recruitung Phase: indicated in the primary publication of the POCER trial

<table>
<thead>
<tr>
<th>Inclusion Criteria:</th>
<th>Exclusion Criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients 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.</td>
<td>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.</td>
</tr>
</tbody>
</table>

### Methodical Notes

<table>
<thead>
<tr>
<th>Funding Sources:</th>
<th>COI: declared</th>
</tr>
</thead>
<tbody>
<tr>
<td>AbbVie, Gutsy Group, Gandel Philanthropy, Angior Foundation, Crohn's Colitis Australia Endowment Fund provided research support. Bühlmann provided fCAL testing kits for Calprotectin. Techlab provided lactoferrin. The National Health and Medical Research Council (NHMRC) supported E. K. Wright, M. A. Kamm, and</td>
<td>COI: declared</td>
</tr>
</tbody>
</table>

### Randomization: POCER trial yes

### Blinding: yes

### Dropout Rate/ITT-Analysis: shown

### Notes:
Literatursammlung:

AG 2 akuter Schub-Frage 3

Inhalt: 5 Literaturstellen

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

OXFORD (2011) Appraisal Sheet: Systematic Reviews: 2 Bewertungen


<table>
<thead>
<tr>
<th>Evidence level/Study Types</th>
<th>P - I - C</th>
<th>Outcomes/Results</th>
<th>Literature References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Databases: A comprehensive literature search was conducted on 22 July 2017 using both PubMed and Embase databases.</td>
<td></td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>Inclusion Criteria: (1) studies evaluating postoperative CD patients using both ileocolonoscopy and FC; (2) adult patients only;</td>
<td>Population: Crohn disease after ICR</td>
<td>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.</td>
<td></td>
</tr>
</tbody>
</table>
(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: -

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. Statistical analyses in this study were carried out using the meta4diag, mada and INLA packages in R version 3.4.2.

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

Notes:


<table>
<thead>
<tr>
<th>Evidence level/Study Types</th>
<th>P - I - C</th>
<th>Outcomes/Results</th>
<th>Literature References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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
**extractions 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.

**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. Ileocolonoscopy was used as the “reference standard” for the “index tests” CE/MRE/US. Statistical analyses were conducted using MetaDiSc 1.4 software (Ramon y Cajal Hospital, Madrid, Spain).

**Heterogeneity:** Study heterogeneity was estimated using the I2 statistic,

**MRI:** The included studies had low heterogeneity.

**US:** selection to achieve reduced heterogeneity

**Publication Bias:** 11 but 1 study were of European origin. Included studies were generally of good quality, with mostly a low risk of bias.

**Notes:**

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


<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study type: randomized controlled trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Patient: 143 randomized,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recruiting Phase: May 2008 to October 2015</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion Criteria: adult patients with crohn’s disease of the terminal ileum who failed &gt;3 months of conventional</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intervention: a) ileoceleal resection b) Infliximab</td>
<td>Comparison: a) ileoceleal resection b) Infliximab</td>
<td>Primary: quality of life and costs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Secondary: costs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Results: laparoscopic ileocaecal resection is a cost-effective treatment option compared with infliximab. No difference in Quality of life</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>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</td>
</tr>
</tbody>
</table>
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 | 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


<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 3</td>
<td>Intervention: postoperative treatment following center standards (defined)</td>
<td>Primary: Endoscopic recurrence 6 month after ICR</td>
</tr>
<tr>
<td>Study type: prospective observational</td>
<td>Comparison: Endoscopic recurrence 6 month after ICR between treatment groups</td>
<td>Secondary: -</td>
</tr>
<tr>
<td>Number of Patient: 21</td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>Recruiting Phase: October 2011 until June 2015</td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusion Criteria: an active</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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-α 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

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

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

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

<table>
<thead>
<tr>
<th>Methodical Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Funding Sources: non</td>
</tr>
<tr>
<td>COI:</td>
</tr>
<tr>
<td>Study Quality:</td>
</tr>
<tr>
<td>Heterogeneity:</td>
</tr>
<tr>
<td>Publication Bias:</td>
</tr>
<tr>
<td>Notes: RCTs und nicht RCTs eingeschlossen</td>
</tr>
</tbody>
</table>

---


<table>
<thead>
<tr>
<th>Evidence level/Study Types</th>
<th>P - I - C</th>
<th>Outcomes/Results</th>
<th>Literature References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study type: Review of literature Databases:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention: none</td>
<td></td>
<td>Secondary: Identification of risk factors</td>
<td></td>
</tr>
</tbody>
</table>
| Results: In randomised controlled trials, clinical recurrence in the first year after surgery occurred in 10–
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 (Rutgeert's 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


<table>
<thead>
<tr>
<th>Evidence level/Study Types</th>
<th>P - I - C</th>
<th>Outcomes/Results</th>
<th>Literature References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study type: Metaanalysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Databases: Cochrane, Embase, Medline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Search period: until July 2018</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td>Population: CD Patients</td>
<td>Primary: Endoscopic recurrence of CD at 12 months after the initial resection.</td>
<td>Journal of Crohn's and Colitis, 2019, 693–701</td>
</tr>
<tr>
<td></td>
<td>Intervention: none</td>
<td>Secondary: Clinical recurrence of CD at 12 months after the initial resection.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comparison:</td>
<td>Results: included 10 RCTs, containing 751 patients, in our primary analysis of endoscopic recurrence of CD at</td>
<td></td>
</tr>
</tbody>
</table>
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

| Evidence level: 2 | Population: CD patients | Primary: Clinical relapse |
| Study type: Metaanalysis | Intervention: no | Secondary: Endoscopic relapse; Radiologic relapse; Surgical relapse; Histologic relapse; Adverse event; Serious adverse events, Life quality |
| Databases: MEDLINE; Embase; PubMed; Cochrane; IBD Group Specialized Register | Comparison: AZA vs placebo or other therapies | 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 efficacy of AZA or 6-MP for maintaining postoperative clinical remission compared to 5-ASA compounds was low. |
| Search period: until 26 July 2018 | | 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. |

**Methodical Notes**

**Funding Sources:** Cochrane

**COI:**

**Study Quality:** Metaanalysis

**Heterogeneity:**

**Publication Bias:**

**Notes:**

---


<table>
<thead>
<tr>
<th>Evidence level/Study Types</th>
<th>P - I - C</th>
<th>Outcomes/Results</th>
<th>Literature References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 2</td>
<td>Population: CD patients</td>
<td>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.</td>
<td>BioMed Research International Volume 2018, Article ID 2615978, 10 pages</td>
</tr>
<tr>
<td>Study type: Metaanalysis</td>
<td>Intervention: none</td>
<td>Secondary:</td>
<td></td>
</tr>
<tr>
<td>Databases: PubMed, Medline, Embase, and Web of Science</td>
<td>Comparison: IFX vs placebo or other therapies</td>
<td>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&lt;0.001), and there was a</td>
<td></td>
</tr>
<tr>
<td>Search period: 2000 until 6/2018</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Exclusion Criteria: significant reduction in rates of clinical recurrence in the Infliximab-treated group (RR =0.519; 95% CI 0.349 to 0.774; p=0.001). Furthermore, Infliximab treatment did not show adverse effects as other systematic therapeutic drugs, indicating that Infliximab treatment is effective and well tolerated.

Author’s Conclusion: Compared with the controls, Infliximab 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


<table>
<thead>
<tr>
<th>Evidence level/Study Types</th>
<th>P - I - C</th>
<th>Outcomes/Results</th>
<th>Literature References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study type: Consensus paper</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Databases: Medline, Embase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Search period: until 3/2017</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion Criteria:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusion Criteria:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population: CD patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention: A systematic review of 88247 publications and a Delphi consensus process involving 81 multidisciplinary clinicians and patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparison:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Results:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author’s Conclusion:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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 6 months 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%).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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%).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statement 70. We suggest that,</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

following ileocolonic resection for Crohn's disease, ileocolonoscopy may be performed at 6 months 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, moderate-quality evidence. Agreement: 100%).

Methodical Notes


<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Study type</th>
<th>Databases</th>
<th>Search period</th>
<th>Inclusion Criteria</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Metaanalysis</td>
<td>Embase, Medline, Cochrane, Web of Science</td>
<td>until 2015</td>
<td>RCTs that met the following inclusion criteria: (1) patients: adults (age &gt; 18 y) with established CD, with a history of small-bowel and/or colonic resection surgery, with removal of macroscopically visible disease; (2) intervention: prophylactic medication after surgery</td>
<td>CD patients</td>
<td>Prophylactic Medication after surgery</td>
<td>Comparison of AZA, placebo, mesalamine and anti-TNF</td>
<td>Preventing clinical relapse and endoscopic relapse.</td>
</tr>
</tbody>
</table>

Results: We identified 21 trials comprising 2006 participants comparing 7 treatment strategies. In a network meta-analysis, compared with placebo, mesalamine (relative risk [RR], 0.60; 95% credible interval [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
established therapies for the management of postoperative prophylaxis for CD including mesalamine, antibiotics, budesonide, immunomodulators, and anti-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 at least 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.

clinical relapse. 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 with antibiotics (RR, 0.16; 95% CrI, 0.04–0.48), and anti-TNF monotherapy (RR, 0.01; 95% CrI, 0.00–0.05), but neither mesalamine (RR, 0.67; 95% CrI, 0.39–1.08) nor budesonide (RR, 0.86; 95% CrI, 0.61–1.22), reduced the risk of endoscopic relapse. Anti-TNF monotherapy was the most effective pharmacologic intervention for postoperative prophylaxis, with large effect sizes relative to all other strategies (clinical relapse: RR, 0.02–0.20; endoscopic relapse: 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 from the National Center for Advancing Translational Sciences, a component of the National Institutes of Health, as well as National Institutes of Health grant EB001981

COI:

Study Quality:

Heterogeneity:

Publication Bias: no

Notes: older review


Evidence level/Study Types: P - I - C

Outcomes/Results

Evidence level: 2
Population: CD patients
Primary:

Inflamm Bowel Dis Volume 19,
### Study Details

**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:**  

### 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 = 0.064), most likely because of study heterogeneity (Cochran Q: 12.36, P = 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.

### Methodical Notes

**Funding Sources:** none  
**COI:** none  
**Study Quality:**  
**Heterogeneity:**  
**Publication Bias:**  
**Notes:**


<table>
<thead>
<tr>
<th>Evidence level/Study Types</th>
<th>P - I - C</th>
<th>Outcomes/Results</th>
<th>Literature References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study type: Review</td>
<td></td>
<td>Primary: QoL after surgery</td>
<td>Inflamm Bowel Dis 2015;21:1187–1194</td>
</tr>
<tr>
<td>Databases: Medline(EBSCOhost) and Cochrane databases</td>
<td></td>
<td>Secondary:</td>
<td></td>
</tr>
<tr>
<td>Search period: January 1970 to August 2013</td>
<td></td>
<td>Results: Remission seems to improve QoL, irrespective of whether it is achieved with drug therapy or surgery</td>
<td></td>
</tr>
<tr>
<td>Inclusion Criteria: Articles on QoLand Crohn's disease</td>
<td></td>
<td>Author's Conclusion: Remission seems to improve QoL, irrespective of whether it is achieved with drug therapy or surgery</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Evidence level/Study Types</th>
<th>P - I - C</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study type: Metaanalysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Databases: PubMed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Search period: until 5 November, 2013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion Criteria:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusion Criteria:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Intervention: Primary:
Secondary:
Results: Fifteen trials involving 1507 patients were included in this analysis. Biological agents were associated with a large and significant reduction of both endoscopic and clinical recurrence compared with placebo, 5-aminosalicylates, or immunomodulators. Immunomodulators showed greater efficacy in terms 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 for postoperative CD prevention. Biologics are found to be the most effective medications to prevent CD recurrence.

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)

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention - Comparison</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 2</td>
<td>Intervention: Drug therapy based on risk of recurrence Escalation of therapy dependend on clinic endoscopic outcome after 6 months</td>
<td>Primary: Presence and severity of endoscopic recurrence 18 months after surgery</td>
</tr>
<tr>
<td>Study type: RCT</td>
<td>Comparison: Colonoscopy after 6 months vs no colonoscopy</td>
<td>Secondary: Clinical recurrence (CDAI&gt;150 or 200), need for further surgery, C-reactive protein (normal ≤5 mg/L), and drug efficacy in prevention of mucosal recurrence.</td>
</tr>
<tr>
<td>Number of Patient: 174</td>
<td></td>
<td>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)</td>
</tr>
<tr>
<td>Recruitng Phase: 2009-2011</td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>Inclusion Criteria: Patients with Crohn’s disease undergoing intestinal resection of all macroscopic disease, with an endoscopically accessible anastomosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 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 received metronidazole after surgery 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

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 2</td>
<td><strong>Intervention:</strong> Therapy with AZA or ADA</td>
<td><strong>Comparison:</strong> AZA vs ADA in patients with AZA-intolerance</td>
<td>Primary: Presence and severity of endoscopic recurrence 6 months after surgery.</td>
</tr>
<tr>
<td>Study type:</td>
<td><strong>Comparison:</strong></td>
<td><strong>Results:</strong> Endoscopic recurrence (Rutgeerts score i2–i4) occurred in 33 of 73 (45%) thiopurine vs. 6 of 28 (21%) adalimumab-treated patients [intentintio-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).</td>
<td></td>
</tr>
<tr>
<td>Subgroup analysis of POCER study</td>
<td><strong>Author’s Conclusion:</strong> In Crohn’s disease patients at high risk of post-operative recurrence adalimumab is superior to thiopurines in preventing early disease recurrence.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Patient: 101</td>
<td><strong>Secondary:</strong> 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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recruitment Phase: 2009-2011</td>
<td><strong>Exclusion Criteria:</strong> Low risk pt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion Criteria:</td>
<td>High risk Pt for recurrence after surgery, &gt; 18y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusion Criteria:</td>
<td>Low risk pt</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention - Comparison</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 3</td>
<td>Intervention: AZA or ADA</td>
<td>Primary: Endoscopic recurrence at 1 year</td>
</tr>
<tr>
<td>Study type: RCT (Superiority)</td>
<td>Comparison: ADA vs AZA</td>
<td>Secondary: Clinical remission at 1y</td>
</tr>
<tr>
<td>Number of Patient: 91</td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>Recruiting Phase: 2012-2015</td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>Inclusion Criteria: &gt;18y, recetion of all inflamed sections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusion Criteria: Postsurgical stoma, resection for short indolent stenosis [&lt; 10 cm], anastomosis that was inaccessible to standard endoscopy, local macroscopic disease after resection, and the usual contraindications to anti-TNFα therapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention - Comparison</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 2</td>
<td>Intervention: 6-MP  Comparison: Placebo vs 6-MP</td>
<td>Primary: Clinical recurrence and need of rescue therapy</td>
</tr>
<tr>
<td>Study type: RCT</td>
<td></td>
<td>Secondary: Endoscopic recurrence, life quality</td>
</tr>
<tr>
<td>Number of Patient: 240</td>
<td></td>
<td>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 effect of mercaptopurine did not significantly differ from placebo for any of the other planned subgroup analyses (previous thiopurines, previous infliximab or methotrexate, previous surgery, duration of disease, or age at diagnosis)</td>
</tr>
<tr>
<td>Recruiting Phase: 2008-2012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion Criteria: Patients aged at least 16 years (Scotland) or 18 years (England and Wales) who had a diagnosis of Crohn’s disease and an ileocolic or small bowel resection within the preceding 3 months were eligible for inclusion.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Methodical Notes</td>
<td></td>
</tr>
</tbody>
</table>

Author’s Conclusion: Mercaptopurine is effective in preventing postoperative clinical recurrence of Crohn’s disease, but only in patients who are smokers. 

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

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level</td>
<td>3</td>
<td>Study type: RCT</td>
</tr>
<tr>
<td>Number of Patient</td>
<td>61</td>
<td>Number of Patient: 61</td>
</tr>
<tr>
<td>Recruiting Phase:</td>
<td>2012 to January 2015</td>
<td>Recruiting Phase: 2012 to January 2015</td>
</tr>
<tr>
<td>Inclusion Criteria:</td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>Exclusion Criteria:</td>
<td></td>
<td>Exclusion Criteria:</td>
</tr>
<tr>
<td>Evidence level</td>
<td>3</td>
<td>Comparison: ADA or AZA</td>
</tr>
<tr>
<td>Study type: RCT</td>
<td></td>
<td>Comparison: ADA vs AZA</td>
</tr>
<tr>
<td>Number of Patient:</td>
<td>61</td>
<td>Interventions: ADA or AZA Comparison: ADA vs AZA</td>
</tr>
<tr>
<td>Recruiting Phase:</td>
<td>2012 to January 2015</td>
<td>Interventions: ADA or AZA Comparison: ADA vs AZA</td>
</tr>
<tr>
<td>Inclusion Criteria:</td>
<td>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.</td>
<td>Interventions: ADA or AZA Comparison: ADA vs AZA</td>
</tr>
<tr>
<td>Exclusion Criteria:</td>
<td></td>
<td>Interventions: ADA or AZA Comparison: ADA vs AZA</td>
</tr>
<tr>
<td>Evidence level</td>
<td>3</td>
<td>Primary: Quality of life during one year of postoperative prophylactic drug therapy after intestinal resection in Crohn's patients</td>
</tr>
<tr>
<td>Study type: RCT</td>
<td></td>
<td>Secondary:</td>
</tr>
<tr>
<td>Number of Patient:</td>
<td>61</td>
<td>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.</td>
</tr>
<tr>
<td>Recruiting Phase:</td>
<td>2012 to January 2015</td>
<td>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.</td>
</tr>
<tr>
<td>Inclusion Criteria:</td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>Exclusion Criteria:</td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>Evidence level</td>
<td>3</td>
<td>Author's Conclusion: HRQoL improved after intestinal resection in CD, irrespective of the postoperative therapy used (ADA or AZA). 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.</td>
</tr>
<tr>
<td>Study type: RCT</td>
<td></td>
<td>Author's Conclusion: HRQoL improved after intestinal resection in CD, irrespective of the postoperative therapy used (ADA or AZA). 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.</td>
</tr>
<tr>
<td>Number of Patient:</td>
<td>61</td>
<td>Author's Conclusion: HRQoL improved after intestinal resection in CD, irrespective of the postoperative therapy used (ADA or AZA). 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.</td>
</tr>
<tr>
<td>Recruiting Phase:</td>
<td>2012 to January 2015</td>
<td>Author's Conclusion: HRQoL improved after intestinal resection in CD, irrespective of the postoperative therapy used (ADA or AZA). 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.</td>
</tr>
<tr>
<td>Inclusion Criteria:</td>
<td>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.</td>
<td>Author's Conclusion: HRQoL improved after intestinal resection in CD, irrespective of the postoperative therapy used (ADA or AZA). 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.</td>
</tr>
<tr>
<td>Exclusion Criteria:</td>
<td></td>
<td>Author's Conclusion: HRQoL improved after intestinal resection in CD, irrespective of the postoperative therapy used (ADA or AZA). 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.</td>
</tr>
<tr>
<td>Evidence level</td>
<td>3</td>
<td>Methodical Notes</td>
</tr>
<tr>
<td>Study type: RCT</td>
<td></td>
<td>Methodical Notes</td>
</tr>
<tr>
<td>Number of Patient:</td>
<td>61</td>
<td>Funding Sources: Abbvie</td>
</tr>
<tr>
<td>Recruiting Phase:</td>
<td>2012 to January 2015</td>
<td>Funding Sources: Abbvie</td>
</tr>
<tr>
<td>Inclusion Criteria:</td>
<td>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.</td>
<td>Funding Sources: Abbvie</td>
</tr>
<tr>
<td>Exclusion Criteria:</td>
<td></td>
<td>Funding Sources: Abbvie</td>
</tr>
<tr>
<td>Evidence level</td>
<td>3</td>
<td>COI:</td>
</tr>
<tr>
<td>Study type: RCT</td>
<td></td>
<td>Randomization: yes</td>
</tr>
<tr>
<td>Number of Patient:</td>
<td>61</td>
<td>Blinding: no</td>
</tr>
<tr>
<td>Recruiting Phase:</td>
<td>2012 to January 2015</td>
<td>Dropout Rate/ITT-Analysis: high dropout</td>
</tr>
<tr>
<td>Inclusion Criteria:</td>
<td>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.</td>
<td>Dropout Rate/ITT-Analysis: high dropout</td>
</tr>
<tr>
<td>Exclusion Criteria:</td>
<td></td>
<td>Dropout Rate/ITT-Analysis: high dropout</td>
</tr>
</tbody>
</table>
### Notes:
- no risk stratification, only small patient group, high dropout

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


<table>
<thead>
<tr>
<th>Evidence level/Study Types</th>
<th>Population</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evidence level: 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study type: Subgroup analysis (POCER)</td>
<td>Number of patients / samples: 135</td>
<td>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 &lt; .001). Combined 6- and 18-month levels of FC correlated with the presence (r ¼ 0.42; P &lt; .001) and severity (r ¼ 0.44; P &lt; .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.</td>
</tr>
<tr>
<td></td>
<td>Reference standard: yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Validation: yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blinding: no</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inclusion of clinical information: Pocer Patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dealing with ambiguous clinical findings: no</td>
<td></td>
</tr>
</tbody>
</table>

### 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.
**Population**

- Evidence level: 3
- Study type: Prospektive, observational
- Number of Patient: 289
- Recruiting 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**

- Intervention: non
- Comparison: non

**Outcomes/Results**

- 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: none
- Randomization: none
- Blinding: none
- Dropout Rate/ITT-Analysis: 64 dropouts, no ITT
- Notes:
**Literatursammlung:**

AG 3 Remissionserhaltung-Frage 2

**Inhalt: 1 Literaturstellen**

<table>
<thead>
<tr>
<th>Literaturquelle</th>
<th>Evidenzlevel</th>
<th>Studientyp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Da, W. 2013</td>
<td>1</td>
<td>Systemic Review</td>
</tr>
</tbody>
</table>

**OXFORD (2011) Appraisal Sheet: Systematic Reviews: 1 Bewert(en)**


<table>
<thead>
<tr>
<th>Evidence level/Study Types</th>
<th>P - I - C</th>
<th>Outcomes/Results</th>
<th>Literature References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study type: Systemic Review</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Databases: The search included PubMed, Google Scholar, and the Cochrane Library using a combination of search terms 'adalimumab AND infliximab 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</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population: Crohn’s Disease patients</td>
<td>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)</td>
<td>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%</td>
<td></td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Literaturquelle</th>
<th>Evidenzlevel</th>
<th>Studientyp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abhyankar, Anita 2015</td>
<td>1</td>
<td>Systematischer Review und Metaanalyse</td>
</tr>
<tr>
<td>Aksan, A 2017</td>
<td>1</td>
<td>Systematischer Review und Metaanalyse von RCTs.</td>
</tr>
<tr>
<td>Avni, T. 2013</td>
<td>1</td>
<td>Systematischer Review und Meta-Analyse von RCTs</td>
</tr>
<tr>
<td>Bonovas, Stefanos 2016</td>
<td>1</td>
<td>Systematic Review und Metaanalyse von RCTs</td>
</tr>
<tr>
<td>Nielsen, Ole Haagen 2015</td>
<td>2</td>
<td>Systematischer Review</td>
</tr>
<tr>
<td>Reinisch, Walter 2013</td>
<td>2</td>
<td>Individueller RCT</td>
</tr>
</tbody>
</table>

OXFORD (2011) Appraisal Sheet: Systematic Reviews: 5 Bewertungen


<table>
<thead>
<tr>
<th>Evidenzlevel/Study Types</th>
<th>P - I - C</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study type:</td>
<td>Systematischer Review und Metaanalyse</td>
<td></td>
</tr>
<tr>
<td>Databases:</td>
<td>MEDLINE, CINAHL, EMBASE</td>
<td></td>
</tr>
<tr>
<td>Search period:</td>
<td>1966-2014</td>
<td></td>
</tr>
<tr>
<td>Inclusion Criteria:</td>
<td>RCTs mit Vgl. i.v. zu p.o.-Eisen</td>
<td></td>
</tr>
<tr>
<td>Primäroutcome Hb-Anstieg &gt; 2g/dl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusion Criteria:</td>
<td>Review Artikel oder keine Information zu Primäroutcome oder keine CED-Patienten</td>
<td></td>
</tr>
</tbody>
</table>

Population: CED-Patienten mit Eisenmangelanämie
Intervention: Eisenpräparat
Comparison: i.v. oder 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 Mittlerer 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


adverse events, when compared with those who received PO iron.

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

| Evidence level: 1 | Population: CED-Patienten mit Eisenmangelanämie | Primary: Hb-Normalisierung oder Hb-Anstieg ≥ 2g/dl | 1Portela inflamms sectional Crossref |
| Databases: PUBMED, SCOPUS, Web of Science and the Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Methodology Register) | Comparison: i.v. vs. po Eisen. Verschiedenen Eisenpräparate. | Results: Eisen iv. gg. überlegen bzgl Primäroutcome Eisen carboxymaltose gg. über Eisensucrose überlegen In Netzwerk-Metaanalyse nur Eisen carboxymaltose oralem Eisen überlegen. Eisensucrose, Eisenisomaltose gegenüber p.o. Eisen mit nicht-signifikantem Vorteil. Bessere Verträglichkeit von i.v.-Eisen gegenüber oralem Eisen. | 3Dignas consens deficien Crohn’s Crossref 4Ebinge care in German 2004; 1985 Wiley O Scholar |
| Search period: Bis Juni 2016 (kein Startdatum). | | | 5Werlin adolesce Gastroe Google Scholar |
| Inclusion Criteria: original studies analysing the efficacy and safety of intravenous iron as monotherapy for iron deficiency anaemia in patients with IBD | | | 6Wells changes cognition patients Wiley O Scholar 7Niessen RW. Eco J Manage PubMed 8Stein manage IBD. Nat Crossref 9Avni T, Treatme systema e75540. Crossref 10Kulnig anaemia 2006; 24 Wiley Science®  |
| Exclusion Criteria: Studien in Kindern und Schwangeren. | | | 11Nielsen Manage |
bowel disease.


25 Mohr, reporting analyses 41. Crossref
26 Furukawa, efficacy, generation, major d BMJ open Crossref
27 Caldwell, comparison indirect 897–900 Crossref
28 Salanti, multiple covariate 62: 857– Crossref
29 Cipriani, Concept analysis Crossref
30 Greco, Zangrillo, outcome 1757–73 Crossref
31 Donegani, C. Assen, a review 323. Wiley O Scholar
32 Kibret, best tre binary o 6: 451–6 PubMed
33 Salanti, network names, generation 2012; 3: Wiley O Scholar
34 Efthimiou, GetReal methodo Wiley O Scholar
35 Dias S consistent analysis Wiley Science
36 Higgins, Measuring research Crossref
37 Mills, treatment complex Crossref
38 Nieuwlaat, Network available
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 für Gemeinsame 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.

Jürgen 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, Thermodiascher and Vifor. Additionally, Dr. Stein has received payment for manuscript preparation from Abbvie, Falk Foundation and MSD. AyseFulu Aksan, Hatice Isık and Heinfried H. Radeke have no conflicts of interest.

Study Quality: Limitationen durch unterschiedliche Behandlungsdauer, Behandlungsintensität und unterschiedliche 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

<table>
<thead>
<tr>
<th>Evidence level/Study Types</th>
<th>P - I - C</th>
<th>Outcomes/Results</th>
<th>Literature Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study type: Systematischer Review und Meta-Analyse von RCTs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. Wells CW, L. 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 changes in hemoglobin function in inflammatory bowel disease in CED patients) [24].

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

17. Gasche C, Inflamm Bowel Dis Scholar]
18. Higgins JPT, reviews of intervention. [Google Scholar]
22. Best WR, Development of a simple clinical article} [PubMed]
anemia in inflammatory bowel disease (FERINJECT) ran 1182–1192. [PubMed] [Google Scholar]
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. Sekundärendpun
Publication Bias: Not reported.

Notes: Systematischer Review und Meta-Analyse von RCTs


<table>
<thead>
<tr>
<th>Evidence level/Study Types</th>
<th>P - I - C</th>
<th>Outcomes/Results</th>
<th>Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 1</td>
<td></td>
<td></td>
<td>1. Fiorino in inflam bowel dis Ther 2014 Cited Her</td>
</tr>
<tr>
<td>Study type: Systematic Review und Metaanalyse von RCTs</td>
<td></td>
<td></td>
<td>2. Fiorino in inflam bowel dis Gastroenterol 2014 Cited Her</td>
</tr>
<tr>
<td>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).</td>
<td></td>
<td></td>
<td>3. Bager in inflam bowel dis year fol 48:1286–1292 Cited Her</td>
</tr>
<tr>
<td>Comparison: i.v. vs. po Eisen mit unterschiedlichen Präparaten</td>
<td>Results: Überlegenheit im Primärausgang von i.v. im Vgl zu po-Eisen (66 vs. 52%) Geringere Rate von Therapiebeendigung bei iv-Eisen vs. po Eisen</td>
<td>6. Gasche in inflam bowel dis year fol 48:1286–1292 Cited Her</td>
<td></td>
</tr>
<tr>
<td>Author's Conclusion: IV iron appears to be more effective and better</td>
<td>7. Tonia in inflam rheumatoid arth [PubMed] [Google Scholar]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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

5. Gisberndiagnosis bowel dis Cited Her
6. Steinmanagen IBD. Nat Cited Her
7. Gasch inflamma Cited Her
8. Digna consensus deficienc Crohns Cited Her
9. Gomol diseases Cited Her
10. Wells in hemo function Bowel Di Cited Her
11. Ershl of patien 2005; 8:6 Cited Her
12. Lee T therapy in deficienc J Crohns Cited Her
13. Stein in patien practice Gastroen Cited Her
14. Abhy with infla meta-ana Cited Her
15. Dane versus inflamma meta-ana 2015: http://ww ID=CRD4 Cited Her
16. Mohe items fo PRISMA 269.W64. Cited Her
17. WH Assessm WHO/UN Organiza Cited Her
18. Edwa definitor 356:1255 Cited Her
19. Higg Cochrane randomis
20. Bono used for included address 250.
22. Man analysis Natl Canc Cited Her
23. DerSi Control C Cited Her
24. Tobia the meta- Cited Her
25. Begg rank corr 50:1088– Cited Her
26. Egge meta-ana 1997; 31f Cited Her
27. Cocl different Cited Her
28. Higgi inconsist Cited Her
29. Higgi in a meta Cited Her
30. Higg Systemat Collabor: www.coc Cited Her
31. Guy: emerging strength Cited Her
32. Balsh guideline Epidemio Cited Her
33. R D Environn Foundati Cited Her
34. Schw News 20f Cited Her
35. Erich fumarate inflamma 40:1058– Cited Her
36. Kuln intravenous inflamma (FERINJE
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 Unterschiedliche Behandlungszeiträume

Heterogeneity: Wenig Heterogenität.

Publication Bias: Keine Evidenz für Publication Bias.

Notes: Systematic Review und Metaanalyse von RCTs


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...
April 29, 2015.


60. Werner T, Wagner SJ, Martinez I, et al. Deple
ting intravenous iron isomaltoside 1,000 (monofer) prevents Crohn’s disease-like ileitis. Gut 2011; 60:165C:1174–1194. Cited Here | View Full Text | PubMed | CrossRef
61. FDA: Highlights of Prescription In
to its medical and public health settings. JAMA 2015; 314:1547–1554. Cited Here | PubMed | CrossRef
62. EMA: New recommendations to manage re
commendations for allergic reactions to doc
carboxymaltose treatment in patients with inflam
carboxymaltose for iron deficiency anemia in Cited Here | PubMed | CrossRef
77. Evstatiev R, Marteau P, Iqbal T, et al. FF-carboxymaltose for iron deficiency anemia in Cited Here | PubMed | CrossRef
Cited Here

Cited Here

Cited Here

Cited Here

Cited Here

Cited Here

Cited Here

Cited Here

Cited Here

Cited Here

Cited Here

Cited Here

Cited Here | View Full Text | PubMed | CrossRef

Cited Here | View Full Text | PubMed | CrossRef

Cited Here | View Full Text | PubMed | CrossRef
Cited Here | View Full Text | PubMed | CrossRef
Cited Here | View Full Text | PubMed | CrossRef
Cited Here | View Full Text | PubMed | CrossRef
25:1456–1463.
Cited Here | View Full Text | PubMed | CrossRef
Cited Here | PubMed
Cited Here | View Full Text | PubMed | CrossRef
Cited Here | PubMed
Cited Here
Cited Here | View Full Text | PubMed | CrossRef
Cited Here | View Full Text | PubMed | CrossRef
Cited Here | PubMed | CrossRef
49:785–798.
Cited Here | PubMed | CrossRef
Cited Here | PubMed | CrossRef
113. Ganz T. Systemic iron homeostasis. Physiol Rev 2018;
Cited Here | View Full Text | PubMed | CrossRef

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, and MChave 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 administered), different enrollment populations as well as different lengths of therapy, and outcomes. Further, in some period was employed, although it is questionable whether such a short interval is always effective for the complete 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)**


<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention - Comparison</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type: Individueller RCT</td>
<td>- Gruppe A1: 1000mg Eisenisomaltosid i.v. pro Woche bis zum errechneten Bedarf</td>
<td>Secondary: Hb Konzentrationsänderungen in der gesamten Studienzeit.</td>
</tr>
<tr>
<td>Number of Patient: 225</td>
<td>- Gruppe A2: 500mg Eisenisomaltosid i. v. pro Woche bis zum errechneten Bedarf</td>
<td>Keine signifikanten Unterschiede zwischen den Gruppen bezüglich der primären Endpunkte.</td>
</tr>
<tr>
<td>Eisenisomaltosid, 113 Eisensulfat</td>
<td>Comparison: 200mg Eisensulfat täglich für 8 Wochen</td>
<td>Keine signifikanten Unterschiede bezüglich der sekundären Endpunkte.</td>
</tr>
<tr>
<td>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 &lt; 12 g/dl (7.45 mmol/l), and a transferrin saturation (TSAT) &lt; 20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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 inflammation, untreated vitamin B12 / folate deficiency, pregnant or nursing women, and patients with extensive active bleeding necessitating blood transfusion or with planned elective surgery during the study.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Methodical Notes**

Funding Sources: The 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. Thomsen 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). The block size was 6.

The randomization list was prepared centrally by a Contract Research Organization, Max Neeman International Data Management Centre, using a validated computer program (Statistical Analysis Software (SAS) 9.1.3, SAS Institute Inc, Cary, NC) PROC PLAN procedure). The randomization was stratified 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
Literatsammlung:

AG 7 Ernährung, Psycho, Komplementär-Frage 1

Inhalt: 10 Literaturstellen

<table>
<thead>
<tr>
<th>Literaturstelle</th>
<th>Evidenzlevel</th>
<th>Studientyp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bennebroek Evertsz', Floor 2017</td>
<td>2</td>
<td>RCT</td>
</tr>
<tr>
<td>Berrill, James W 2014</td>
<td>2</td>
<td>RCT</td>
</tr>
<tr>
<td>Keerthy, Divya 2016</td>
<td>3</td>
<td>RCT</td>
</tr>
<tr>
<td>Levy, Rona L 2016</td>
<td>2</td>
<td>RCT</td>
</tr>
<tr>
<td>Mikocka-Walus, Antonina 2017</td>
<td>2</td>
<td>RCT</td>
</tr>
<tr>
<td>Mikocka-Walus, Antonina 2015</td>
<td>2</td>
<td>RCT</td>
</tr>
<tr>
<td>Stapersma, Luuk 2018</td>
<td>2</td>
<td>RCT</td>
</tr>
<tr>
<td>Szigethy, Eva 2015</td>
<td>3</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>Wynne, Brona 2019</td>
<td>2</td>
<td>RCT</td>
</tr>
</tbody>
</table>

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


Population

Study type: RCT
Number of Patients: 118
Recruiting 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

Outcomes/Results

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.
### 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:


### Evidence level: 2
- **Study type:** RCT
- **Number of Patient:** 66
- **Recruiting 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 - Comparison

- **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:


Population

Evidence level: 3
Study type: RCT
Number of Patient: 70
Recruiting 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

Intervention: One year of psychotherapy

Comparison: healthcare utilization 12-months prior to psychotherapy compared to the 12 month following the conclusion of psychotherapy

Outcomes/Results

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:


<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 2</td>
<td>Study type: RCT</td>
<td>Number of Patient: 185</td>
<td>Recruiting Phase: Pediatric GI clinics at Seattle Children's Hospital and Mary Bridge Children's Hospital in Tacoma, WA.</td>
</tr>
<tr>
<td>Inclusion Criteria: (1) child aged 8 to 17 years</td>
<td>Intervention: (1) cognitive behavioral therapy condition</td>
<td>Comparison: (2) an education support condition designed to control for time and attention.</td>
<td>Primary: - quality of life - number of missed school days due to CD or UC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Secondary: - Parent report only - Child report only - Parent and Child Report - Physician Report</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>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).</td>
</tr>
</tbody>
</table>
| | | | 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 participating 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 evaluations
(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

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-Analys: 16

Notes:


<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention Comparison</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 2</td>
<td>Intervention: cognitive-behavioural therapy (CBT) over</td>
<td>Primary: remission at 24 months (established using the CDAI)</td>
</tr>
<tr>
<td>Study type: RCT</td>
<td></td>
<td>Secondary: - subjective view of IBD activity</td>
</tr>
</tbody>
</table>
Number of Patient: 176
Recruiting 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 controlled 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 influence 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 manuscript 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
Recruiting 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 psychologists 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) Relationship 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: Future 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: Given 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

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention - Comparison</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 2</td>
<td>Intervention: The PASCET-PI is a disease-specific CBT protocol, developed for adolescents with IBD and depression.</td>
<td>Primary: Primary analysis concerned the reliable change in anxiety and depressive symptoms after 3 months (immediate posttreatment assessment).</td>
</tr>
<tr>
<td>Study type: RCT</td>
<td>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).</td>
<td>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.</td>
</tr>
<tr>
<td>Number of Patient: Number of patients: 70. CAU group: 33; CAU + CBT group: 37.</td>
<td>The original PASCET-PI was developed for depression, therapists were instructed how to make the exercises more</td>
<td>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</td>
</tr>
</tbody>
</table>
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-by-step 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 age-appropriate.

Comparison: The control group received standard medical care (care-as-usual, CAU) only, as this resembles the current care best.

CAU consisted of regular medical appointments with the (pediatric) gastroenterologist every 3 months, 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 age groups (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 AbrVie (advisory board). E.M.S. received financial support from NIH (grant), Crohn and Colitis Fund America (grant), AbbrVie (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:


<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention - Comparison</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 3</td>
<td>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 audiorecorded to allow for quality assurance and to ensure treatment fidelity. Each treatment was tailored to the developmental level of each youth.</td>
<td>Primary:</td>
</tr>
<tr>
<td>Study type: Randomised controlled trial</td>
<td></td>
<td>Secondary:</td>
</tr>
<tr>
<td>Number of Patient: From the</td>
<td></td>
<td>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 disease.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recruiting 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.</th>
<th>Up to 75% of sessions could be completed by telephone. More detailed descriptions of each intervention have been described previously.33</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion Criteria: inclusion criteria see literatur #20</td>
<td>Comparison: supportive nondirective therapy (supportive listening). Randomized subjects underwent up to 12 weekly sessions of either CBT 22,23 or SNDT.</td>
</tr>
<tr>
<td>Exclusion Criteria: Up to 75% of sessions could be completed by telephone. More detailed descriptions of each intervention have been described previously.33</td>
<td>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.</td>
</tr>
</tbody>
</table>

**Methodological 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, GlaxoSmithKline, 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.


Population
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.

Recruiting 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 SFT was modified to focus on fatigue management.

Comparison: Care as usual (CAU).

Outcomes/Results
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

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

Comparison: treatment as usual, standard IBD medical care 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.

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 intention-to-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.

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:
Inhalt: 4 Literaturstellen

<table>
<thead>
<tr>
<th>Literaturstelle</th>
<th>Evidenzlevel</th>
<th>Studientyp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levine, Arie 2019</td>
<td>2</td>
<td>investigator-initiated prospective randomized controlled trial with 2 interventional arms comparing CDED with 50% PEN (group 1) with EEN (group 2) administered orally over 12 weeks in a pediatric population with mild to moderate active luminal disease</td>
</tr>
<tr>
<td>Limketkai, Berkeley N 2019</td>
<td>1</td>
<td>Cochrane Review</td>
</tr>
<tr>
<td>Narula, Neeraj 2018</td>
<td>1</td>
<td>Cochrane Review</td>
</tr>
<tr>
<td>Pigneur, Bénédicte 2019</td>
<td>2</td>
<td>prospective randomised induction trial</td>
</tr>
</tbody>
</table>

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


<table>
<thead>
<tr>
<th>Evidence level/Study Types</th>
<th>P - I - C</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study type: Cochrane Review</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Databases: The Cochrane IBD Group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population: Patients with active crohn's disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention: The intervention is a controlled manipulation of the subject's oral diet by a deliberate change in the consumption of food (i.e. no formulas or supplements used) for a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary: Induction of remission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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]), fecal biomarkers (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 Inflammatory Bowel Disease Questionnaire (IBDQ), Short Inflammatory Bowel Disease Questionnaire (SIBDQ), or related surveys; 7. Hospitalizations; 8. Need for surgery; 9. Progression of disease from a state of inflammation-only disease to stricturing or obstructing to penetrating/fistulizing disease; 10. Escalation of therapy including the need to add or modify pharmacologic therapy due to lack of efficacy at inducing or maintaining remission after enrollment in the trial; 11. Adverse events; 12. Withdrawal due to adverse events; and 13. Serious adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Results: The effect of high fiber, low refined carbohydrates, low microparticle, low calcium, see pdf</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 nutrition were excluded.

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 nutrition were excluded.

Comparison: symptoms-guided diet and highly restricted organic diet clinical remission in active CD is uncertain. In one study, remission was achieved at 4 weeks in 100% (4/4) of low refined carbohydrates participants compared to 0% (0/3) of usual diet participants. In a pooled analysis of two studies, 44% (23/52) of low microparticle participants achieved remission at 16 weeks compared to 25% (13/51) of usual diet participants. One study found that 50% (16/32) of symptoms-guided participants achieved remission compared to 0% (0/19) of usual diet participants. One study found that 50% (4/8) of high-restricted organic diet participants achieved remission at 24 weeks compared to 50% (5/10) of usual diet participants. One study found 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 provided through a larger NIHR Cochrane Programme Grant in the UK.

COI: Berkeley N Limketkai: None known Zipporah Iheozor-Ejiofor: None known Teuta Gjuladin-Hellon: None known Alyssa Parian: None known Laura E Matarese: None known Kelly Bracewell: None known John K MacDonald: None known Morris Gordon has received travel fees to attend international scientific and training meeting such as DDW, Advances in IBD, ESPGHAN, BSGPHAN 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 on the 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:


Evidence level/Study Types | P - I - C | Outcomes/Results | Literature References
--- | --- | --- | ---
Evidence level: 1 | | Primary: The primary outcome was clinical remission. | see reference list
Study type: Cochrane Review | | Secondary: Secondary outcomes included adverse events, serious adverse events and withdrawal due to adverse events | |
Databases: MEDLINE, Embase and | | Results: Meta-analysis of eight trials (223 participants) demonstrated no difference in remission rates between EN and steroids. Fifty per cent (111/223) of patients in the EN | |
Intervention: exclusive EN as | | | |
<table>
<thead>
<tr>
<th>CENTRAL</th>
<th>primary therapy to induce remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Search period: from inception to 5 July 2017.</td>
<td></td>
</tr>
<tr>
<td>Inclusion Criteria: Randomized controlled trials involving patients with active CD were considered for inclusion. Studies comparing one type of EN to another type of EN or conventional corticosteroids were selected for review.</td>
<td></td>
</tr>
<tr>
<td>Exclusion Criteria:</td>
<td></td>
</tr>
</tbody>
</table>

| CENTRAL | group achieved remission compared to 72% (133/186) of patients in the steroid group (RR 0.77, 95% CI 0.58 to 1.03; GRADE very low quality). Subgroup analysis by age showed a difference in 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 achieved remission compared to 61% (17/28) of steroid patients (RR 1.35, 95% CI 0.92 to 1.97; GRADE very low quality). A per-protocol analysis produced similar results (RR 0.93, 95% CI 0.75 to 1.14). The per-protocol subgroup analysis showed a difference in remission rates 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 in adverse event rates (RR 1.39, 95% CI 0.62 to 3.11; GRADE very low quality). However, patients on EN were more likely to withdraw due 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 in adults with active CD. Very low quality evidence also suggests that EN may be more effective than steroids for induction of remission in 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 Janssen and received travel expenses from Abbvie to attend an IBD 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, Ocea, Otsuka, PDL, Pharmacosmos, Pfizer, Procter & Gamble, Prometheus, Robarts Clinical Trial, Schering-Plough, Setpoint Medical, 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 significant 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


<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention - Comparison</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 2</td>
<td>Intervention: Group 1 received the CDED stage 1</td>
<td>Primary: The primary endpoint of this study was the patient's tolerance to the diet</td>
</tr>
</tbody>
</table>
Study type: Investigator-initiated prospective randomized controlled trial with 2 interventional arms comparing CDED with 50% PEN (group 1) with EEN (group 2) administered orally over 12 weeks in a pediatric population with mild to moderate active luminal disease.

Number of Patients: Seventy-eight patients were randomized (40 to CDED + PEN and 38 to EEN) and included in the analysis from 10 pediatric IBD clinics in Israel (from September 2013) and 2 in Canada (from December 2016) until May 2018.

Recruitment Phase: from September 2013 until May 2018.

Inclusion Criteria: Children (aged 4–18 years) with mild to moderate luminal CD, defined by a pediatric CD activity index (PCDAI) of 10 and 40 and evidence for active inflammation at enrollment, such as elevated C-reactive protein (CRP) >5 g/L, erythrocyte sedimentation rate >20 mm/h, or calprotectin >200 mg/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 adjustment of immunomodulators, past or current biologics use, primary colonic disease with significant rectal involvement, or active perianal disease.

Comparison: with 50% PEN for calculated energy requirement (Modulen; Nestlé Health Science, Vevey, Switzerland) for the first 6 weeks, and then the stage 2 diet with 25% PEN for the next 6 weeks. Group 2 received standard of care EEN (Modulen) for 6 weeks followed by 25% PEN during weeks 6 to 12, with gradual reintroduction of table foods between week 6 and 9 as per local preference, such that all patients were exposed to PEN-free diet by week 12. All formulas could be given only orally.

Comparison: by week 6 defined by withdrawal from the study because of patient’s refusal to continue 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 (defined as PCDAI <10 as well as by the more stringent <10, or less than 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 withdrew from the study because of intolerance by 48 hours, 74 patients (mean age 14.2 ± 2.7 years) were included for remission analysis. The combination of CDED and PEN was tolerated in 39 children (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 in corticosteroid-free remission vs 20 (59%) of 34 children given EEN (P<.38). At week 12, 28 (75.6%) of 37 children given CDED plus PEN were in corticosteroid-free remission compared with 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 in inducing remission by week 6. The combination CDED plus PEN induced sustained remission in a significantly higher proportion of patients than EEN.

Methodical Notes

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

COI: AL reports grants, from Nestlé Health Science, and grants from Janssen unrelated to this field; advisory boards, travel, speaker fees or DSMBs from Celgene, Takeda and AbbVie, and allicensing and consulting agreement with IP with Nestlé health to develop new products based on diet. EW reports personal fees from Janssen, personal fees from AbbVie, outside the submitted work. RSB reports personal...

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention - Comparison</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 2</td>
<td>Intervention: Exclusive enteral nutrition [EEN] (Modulen IBD) over 8 weeks</td>
<td>Primary: achievement of mucosal healing with a Crohn’s Disease Endoscopic Index of Severity [CDEIS] less than 3 points or a drop of &gt;70% at follow-up endoscopy [8 weeks] compared with initial diagnostic endoscopy.</td>
</tr>
<tr>
<td>Study type: prospective randomised induction trial</td>
<td>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.</td>
<td>Secondary: clinical remission defined as a Harvey-Bradshaw Index [HBI] less than 5 and biological remission [mucosal and systemic inflammatory parameters].</td>
</tr>
<tr>
<td>Number of Patient: Nineteen patients with new-onset active CD (Harvey-Bradshaw index [HBI] &gt;5), aged from 6 to 17 years, were included in this prospective randomised induction trial with CS [n = 6] or EEN [n = 13]</td>
<td>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%.</td>
<td></td>
</tr>
<tr>
<td>Inclusion Criteria: Children/adolescents with newly diagnosed CD [age range: 6–17 years] with active disease (Harvey-Bradshaw Index [HBI] &gt;5)</td>
<td>Inclusion Criteria: Children/adolescents with newly diagnosed CD [age range: 6–17 years] with active disease (Harvey-Bradshaw Index [HBI] &gt;5)</td>
<td></td>
</tr>
<tr>
<td>Exclusion Criteria: treatment by antibiotics during the 4 weeks preceding inclusion, corticosteroids, biologic therapies, immunosuppressive treatment, iso-lated oral or perianal disease location, risk of non-adherence to study protocol, and potential need for surgical therapy</td>
<td>Exclusion Criteria: treatment by antibiotics during the 4 weeks preceding inclusion, corticosteroids, biologic therapies, immunosuppressive treatment, iso-lated oral or perianal disease location, risk of non-adherence to study protocol, and potential need for surgical therapy</td>
<td></td>
</tr>
</tbody>
</table>

**Methodical Notes**

**Funding Sources:** The present work was supported by a non-restricted grant of Nestlé 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%.
**AG 7 Ernährung, Psycho, Komplementär-Frage 3**

**Inhalt: 3 Literaturstellen**

<table>
<thead>
<tr>
<th>Literaturstelle</th>
<th>Evidenzlevel</th>
<th>Studientyp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bao, Chun-Hui 2014</td>
<td>2</td>
<td>RCT</td>
</tr>
<tr>
<td>Sun, Jing 2015</td>
<td>2</td>
<td>RCT</td>
</tr>
<tr>
<td>Zhu, Weiming 2015</td>
<td>2</td>
<td>RCT</td>
</tr>
</tbody>
</table>

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


**Population**

<table>
<thead>
<tr>
<th>Evidence level: 2</th>
<th>Study type: RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type: RCT</td>
<td>Number of Patient: Baseline 92 (n=46 treatment and control group)</td>
</tr>
<tr>
<td>85 patients completed the trial (treatment n=43, control n=42)</td>
<td>follow up: 77 patients (treatment n=40, control n=37)</td>
</tr>
</tbody>
</table>

**Recruiting 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 Acupuncture Moxibustion 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.

**Outcomes/Results**

- 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 decreased CRP 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 months 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.


<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention - Comparison</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level:</td>
<td>Intervention: highdose-group 2.0 mg/kg daily (maximum, 120 mg/d) lowdose-group 1.5 mg/kg daily</td>
<td>Primary: The primary endpoint was clinical recurrence, defined as CD Activity Index score (CDAI) &gt; 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.</td>
</tr>
<tr>
<td>Study type: RCT</td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>Number of Patient: 198 (mesalazine n=59, high-dose n=71, low-dose n=68)</td>
<td>Comparison: mesalazine 3 g daily</td>
<td>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 5 0.05). In addition, compared with lowdose TwHF and mesalazine, the authors also detected significant superiority of highdose TwHF arm in the decrease of CDAI and SESCD (P 5 0.05).</td>
</tr>
<tr>
<td>Recruiting Phase: e</td>
<td>Author's Conclusion: 2.0 mg/kg daily TwHF was</td>
<td></td>
</tr>
<tr>
<td>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).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion Criteria: Inclusion criteria were as follows: Patients were 16 to 75 years old with a</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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.\textsuperscript{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 below 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 \textsuperscript{3} 10\textsuperscript{9}/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-α 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%
dropout 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 ± standard deviation (M ± 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)


<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention - Comparison</th>
<th>Outcomes/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence level: 2</td>
<td>Intervention: TwHF 1.5 mg/kg/day The patients assigned to the TwHF group</td>
<td>Primary: presenting symptoms of CD having to undergo another medical or surgical treatment, with the recurrence being confirmed by</td>
</tr>
</tbody>
</table>

Number of Patient: 90

Recruiting 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 at inclusion (<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/or AZA intolerance 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.

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% of the 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.

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-observation-carry-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
Überarbeitung von: 08/2021
Nächste Überprüfung geplant: 07/2026

Die AWMF erfasst und publiziert die Leitlinien der Fachgesellschaften mit größtmöglicher Sorgfalt - dennoch kann die AWMF für die Richtigkeit des Inhalts keine Verantwortung übernehmen. Insbesondere bei Dosierungsangaben sind stets die Angaben der Hersteller zu beachten!

Autorisiert für elektronische Publikation: AWMF online