Calprotectin – scientific literature

Content

1. Highlights

What is calprotectin?

Calprotectin is a calcium, zinc and manganese binding protein that is present in the cytosol of neutrophils, but can also found in monocytes and macrophages. It is a heterodimer of 24 kDa consisting of two subunits, S100A8 and S100A9. Following neutrophil disintegration at an inflammatory site, calprotectin is released thereby exerting its antimicrobial activities through the sequestration of zinc and manganese. Depending on the site of inflammation, calprotectin can be found in serum, cerebrospinal fluid, synovial fluid, urine and faeces.[1]

Calprotectin in stool was shown to be highly representative of the amount of neutrophils in the gut lumen and intestinal inflammation.[2] Increased levels have been observed in patients with inflammatory bowel disease (IBD), colorectal cancers and non-steroidal anti-inflammatory drug-induced enteropathy.

What is the normal range of calprotectin?

The normal range for fecal calprotectin in healthy adults is considered to be < 50 µg/g.[1] In children ≤ 4 years, intestinal permeability is higher resulting in higher normal calprotectin concentrations of < 538 µg/g for children < 6 months, < 214 µg/g for children between 6 months and 3 years, and < 75 µg/g for children 3 - 4 years old.[3,4,6]

In children > 4 years old, calprotectin normalizes to adult values.[1] Also in the elderly above 60 (normal values < 112 µg/g) and patients being treated with non-steroidal anti-inflammatory drugs (NSAIDs), increased concentrations can be observed.[1,5]

How is it measured?

Fecal calprotectin is most commonly measured in the stool using a variety of immunoassays, which show, in general, comparable assay performance characteristics.

What is the usefulness of calprotectin for the diagnosis of IBD?

In patients with gastro-intestinal symptoms such as abdominal pain, diarrhea and rectal bleeding with a suspicion of inflammatory bowel disease (IBD), fecal calprotectin testing can help differentiate between IBD and IBS (or non-IBD in children) and reduce the number of unnecessary colonoscopies.

What is the usefulness of calprotectin for the management of IBD?

In patients being treated for IBD, fecal calprotectin can be used as a surrogate marker for disease activity and mucosal healing, as a predictive marker of future (post-operative) relapse and in the decision to stop an IBD drug.

References:

1. *D'Angelo* et al. Calprotectin in Daily Practice: Where do we stand in 2017? Digestion 2017;95:293-301
2. *Roseth* et al. Assessment of disease activity in ulcerative colitis by faecal calprotectin, a novel granulocyte marker protein. Digestion 1997;58:176-180
3. *Oord* et al. Fecal calprotectin in healthy children. Scand J Clin Lab Invest 2014;74:254-258
4. *Zhu* et al. Fecal Calprotectin in Healthy Children Aged 1-4 Years. PLoS ONE 2016;11: e0150725
5. *Joshi* et al. Age-related faecal calprotectin, lactoferrin and tumour M2-PK concentrations in healthy volunteers. Ann Clin Biochem 2010;47:259-263
6. *Rodeck* et al. Pädiatrische Gastroenterologie, Hepatologie und Ernähung. Springer-Verlag 2008;1:684p

2. Benefits of calprotectin measurement

Inflammatory bowel disease (IBD)

IBD is a chronic relapsing-remitting disease of the gastrointestinal tract causing irreversible damage to the bowel if disease is not under control. Typical symptoms are abdominal pain, diarrhea, rectal bleeding, urgency and fatigue. **There are two subtypes of IBD, Crohn's disease and ulcerative colitis.** Whereas the inflammation in ulcerative colitis affects the rectum and/or colon only, inflammation in Crohn's disease can occur from mouth to anus. Approximately 0.5 % of the Western population is burdened with IBD and its incidence is rising.[1] Time of first diagnosis is < 18 years for approximately 25 % of patients.[2]

Calprotectin as a marker for the diagnosis of IBD

The final diagnosis of IBD in patients representing with gastrointestinal symptoms and suspicion of IBD is **endoscopy, an invasive procedure that is highly accurate but not without risks. A lot of patients without IBD**, however, **also undergo endoscopy**, delaying appropriate treatment of these patients and exposing them to an unpleasant and invasive procedure. In this setting, **fecal calprotectin has been introduced as a biomarker for intestinal inflammation that highly specifically differentiates between IBD and non-IBD causes of gastrointestinal symptoms, such as irritable bowel syndrome (IBS)**, reducing the number of unnecessary and costly endoscopies.

Calprotectin as a marker for the management of IBD

Patients with IBD **require lifelong treatment** to control symptoms and prevent irreversible bowel damage and surgery. Today, gastroenterologists can make use of a broad spectrum of drugs, from small molecules to biological drugs, to achieve ever more stringent treatment targets, including endoscopic and histological remission. **Not all patients respond equally well** to these treatments, however, and it is a continuous struggle to find the right treatment for the right patient at the right time. In this setting, **fecal calprotectin has been introduced as a biomarker of disease activity reflecting intestinal inflammation**. It is nowadays used in a comprehensive treat-to-target approach, comprising patient symptoms, disease activity scores (e.g. Crohn's disease activity index), therapeutic drug monitoring and serological biomarkers like CRP and albumin.

References:

1. *Ng* et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet 2017;390:2769-2778
2. *Kugathasan* et al. Epidemiologic and clinical characteristics of children with newly diagnosed inflammatory bowel disease in Wisconsin: a statewide population-based study. J Pediatr 2003;143:525-531

3. Calprotectin as a marker for the diagnosis of IBD

3.1. Adult patients

In adult patients with gastro-intestinal symptoms such as abdominal pain, diarrhea and rectal bleeding with a suspicion of IBD, fecal calprotectin testing can help differentiate between IBD and IBS and thereby reduce the number of unnecessary endoscopies.

Why do we measure?

Adult patients with IBD have significantly higher fecal calprotectin concentrations than healthy patients or patients with irritable bowel syndrome (IBS). Testing for calprotectin may reduce the number of costly and invasive endoscopies.

Interpretation

Following meta-analysis of clinical studies using ELISA, a cut-off of 50 µg/g yielded a sensitivity of 93 % and specificity of 94 % for the differentiation of IBD from IBS (at a prevalence rate of 6.3 %). This cut-off dominated the judgment of the general practitioner in primary care reducing the number of unnecessary colonoscopies in patients without IBD.[1]

3.2. Pediatric patients

In pediatric patients with gastro-intestinal symptoms such as abdominal pain, diarrhea and rectal bleeding with a suspicion of IBD, fecal calprotectin testing can help differentiate between IBD and non-IBD and reduce the number of unnecessary colonoscopies.

Why do we measure?

Pediatric patients with IBD have significantly higher fecal calprotectin concentrations than healthy children or children with non-IBD related gastrointestinal symptoms. Testing for calprotectin may reduce the number of costly and invasive endoscopies.

Interpretation

Following meta-analysis of clinical studies using ELISA, a cut-off of 50 µg/g yielded a sensitivity of 99 % but moderate specificity of 74 %, while a cut-off of 100 µg/g had a sensitivity of 94 % but specificity of 82 % for differentiation of IBD from non-IBD (at a prevalence rate of 47.8 %). Both cut-offs dominated direct referral for colonoscopy in the secondary care setting in a cost-effectiveness analysis.[1]

References:

1. *Waugh* et al. Faecal calprotectin testing for differentiating amongst inflammatory and non-inflammatory bowel diseases: systematic review and economic evaluation. Health Technol Assess 2013;17:xv-xix,1-211

3.3. Cost-effectiveness of calprotectin measurements for suspected inflammatory bowel disease

The level of fecal calprotectin can predict the onset of inflammatory bowel disease with high accuracy and precision. In an economic evaluation commissioned by NICE, Waugh and co-authors demonstrated cost-effectiveness of calprotectin measurements in patients with suspected inflammatory bowel diseases.[1] An independent group confirmed these findings and demonstrated that screening adults and children to measure fecal levels of calprotectin is effective and cost-effective in identifying those with IBD on a per-case basis when the pretest probability is < 75 % for adults and < 65 % for children.[2] The utility of the test is greater for adults than children.[2]

3.4. Diagnostic algorithm for suspected inflammatory bowel disease

The following diagnostic algorithm was proposed using fecal calprotectin as a first screening test prior to endoscopy for the diagnosis of patients with IBD (Figure 1).[3] For patients with borderline positive concentrations (50 - 100 µg/g FC) repeated testing is suggested.

Fecal calprotectin measurements in patients with suspected inflammatory bowel disease has the potential to reduce the need for labor-intensive and invasive endoscopic procedures thereby leading to significant cost-savings.[1]

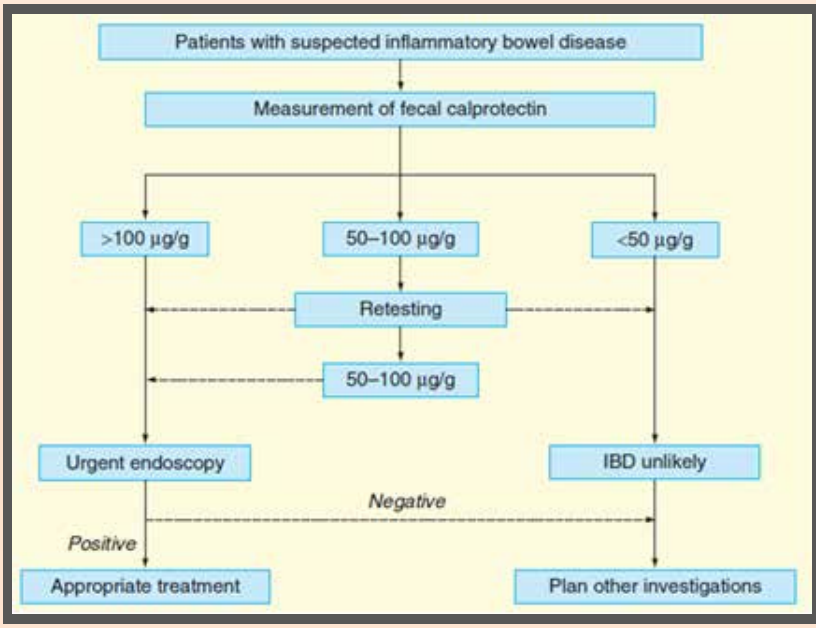

Fig. 1: Diagnostic algorithm for suspected inflammatory bowel disease. Diagnostic algorithm for the evaluation of patients with suspected inflammatory bowel disease that includes fecal calprotectin measurement before endoscopy. If the likelihood of inflammatory bowel disease is high (e.g. gross bleeding with typical symptoms), direct endoscopy might be warranted without prior fecal calprotectin measurement.[3]

References:

1. *Waugh* et al. Faecal calprotectin testing for differentiating amongst inflammatory and non-inflammatory bowel diseases: systematic review and economic evaluation. Health Technol Assess 2013;17:xv-xix,1-211
2. *Yang* et al. Effectiveness and Cost-effectiveness of Measuring Fecal Calprotectin in Diagnosis of Inflammatory Bowel Disease in Adults and Children. Clinical Gastroenterology and Hepatology 2014;12:253-262
3. *Burri* et al. The use of fecal calprotectin as a biomarker in gastrointestinal disease. Expert Rev Gastroenterol Hepatol 2014;8:197-210

4. Calprotectin as a surrogate marker for disease activity in IBD

In symptomatic patients with IBD, fecal calprotectin can be used as a surrogate marker for detecting endoscopically active disease, limiting the need for endoscopy.

Why do we measure?

Fecal calprotectin concentrations are higher in IBD patients with endoscopically active disease compared to IBD patients with quiescent disease, which benefits timely and correct adjustment of treatment while preventing costly and invasive endoscopies. Typical values according to disease severity in Crohn's disease are illustrated in Figure 2.[1]

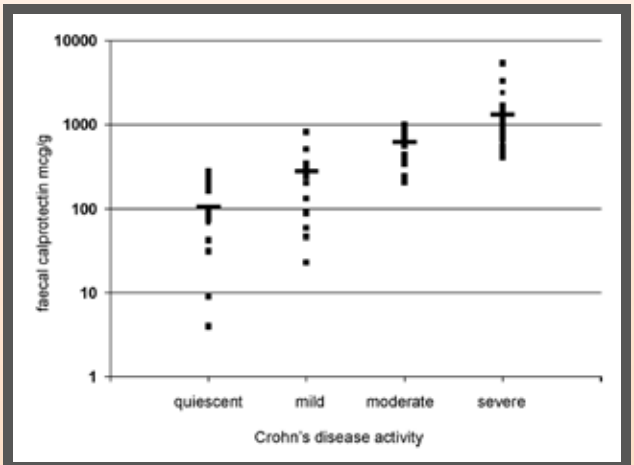

Fig. 2: Fecal calprotectin concentrations logarithmically plotted according to Crohn's disease activity. Disease activity was determined endoscopically in 51 % of cases and radiologically in 53 % of cases.[1]

Interpretation

A large meta-analysis including 19 clinical studies evaluated the diagnostic accuracy of fecal calprotectin for the detection of endoscopically active disease in symptomatic patients. **Irrespective of the used fecal calprotectin cut-off, the mean sensitivity and specificity for detecting endoscopically active disease was 88 % and 73 %, respectively**. Notably, FC showed better specificity in ulcerative colitis compared to Crohn's disease (79 % vs 68 %, resp.).[2]

Based on individual study outcomes, the optimum fecal calprotectin cut-off reported by Mosli and co-authors was 50 µg/g for detecting endoscopically active IBD, but they admit there was significant heterogeneity in the studies warranting further investigation.[2] **Recent studies suggested a cut-off of >250 µg/g to be most representative of endoscopically active disease in patients with IBD.**[3-5]

References:

1. *Turvill.* Frontline Gastroenterology 2014;5:167–175
2. *Mosli* et al. C-Reactive Protein, Fecal Calprotectin, and Stool Lactoferrin for Detection of Endoscopic Activity in Symptomatic Infl ammatory Bowel Disease Patients: A Systematic Review and Meta-Analysis. Am J Gastroenterol 2015;110:802-819
3. *D'Haens* et al. Fecal Calprotectin is a Surrogate Marker for Endoscopic Lesions in Inflammatory Bowel Disease. Inflamm Bowel Dis 2012;18:2218-2224
4. *Buisson* et al. Faecal chitinase 3-like 1 is a reliable marker as accurate as faecal calprotectin in detecting endoscopic activity in adult patients with inflammatory bowel diseases. Aliment Pharmacol Ther 2016;43:1069-1079
5. *Mak* et al. Fecal Calprotectin in Assessing Endoscopic and Histological Remission in Patients with Ulcerative Colitis. Dig Dis Sci 2018;63:1294-1301

5. Calprotectin as a surrogate marker for mucosal healing in IBD

In patients with symptomatic IBD being treated for active disease, fecal calprotectin concentrations can be used as a surrogate marker for mucosal healing and thereby limit the number of endoscopies.

Why do we measure?

Persistent active and endoscopic inflammation is associated with negative outcomes in IBD. Low calprotectin concentrations correlate well with endoscopic and histological remission.

Interpretation

A Belgian study evaluated the predictive value of calprotectin concentrations following infliximab induction therapy in patients with ulcerative colitis and found that **a fast and sharp decrease in FC predicted endoscopic remission**, whilst the absence of a decrease in FC identified patients resistant to treatment. All patients with FC < 50 µg/g after induction therapy were in endoscopic remission.[1]

A more recent study evaluated the correlation between FC and endoscopic and histological remission in ulcerative colitis, identifying **ideal cut-offs for endoscopic and histological remission of < 250 µg/g and < 200 µg/g**, respectively, with a corresponding sensitivity/specificity of 67 %/77 % and 71 %/76 % (Figure 3).[2]

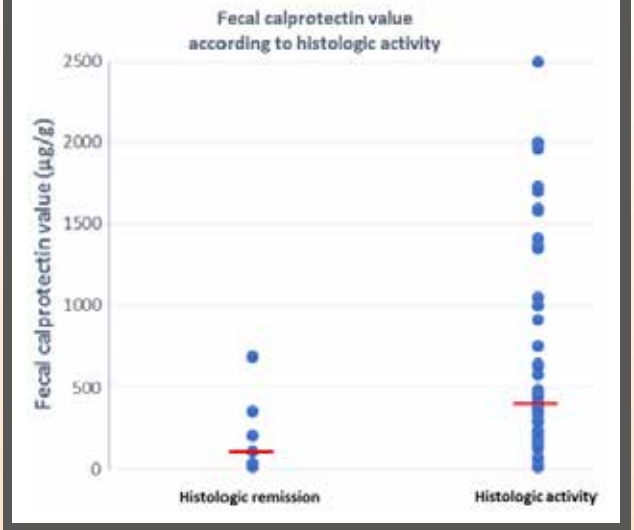

Fig. 3: Comparison of fecal calprotectin level in patients with ulcerative colitis with histological activity or remission.[2]

References:

1. *De Vos et al.* Fast and sharp decrease in calprotectin predicts remission by infliximab in anti-TNF naïve patients with ulcerative colitis. J Crohns Colitis 2012;6:557-562

2. *Mak* et al. Fecal Calprotectin in Assessing Endoscopic and Histological Remission in Patients with Ulcerative Colitis. Dig Dis Sci 2018;63:1294-1301

6. Calprotectin as a predictive marker for relapse in IBD

In asymptomatic patients with IBD, two consecutively high fecal calprotectin measurements can be used to predict an imminent relapse offering a window for timely treatment optimization.

Why do we measure?

Consecutively high fecal calprotectin concentrations may be indicative of subclinical disease activity. Early identification of an imminent relapse allows physicians to timely adjust treatment to prevent future relapse.

Interpretation

De Vos and co-authors demonstrated the clinical utility of **two consecutively high fecal calprotectin concentrations for prediction of relapse** in adult patients with UC receiving infliximab maintenance treatment. A **cut-off of > 300 µg/g** showed the best predictive value with a sensitivity of 61.5 % and specificity of 100 % (pretest probability of 33 % for relapse). **FC levels were elevated as early as 3 months before relapse (Figure 4)**. In contrast, the authors found that a single calprotectin measurement during their study period of one year had only limited predictive value for relapse. Of 30 patients who were in sustained deep remission throughout the study, 23/30 (77 %) had at least one fecal calprotectin concentration > 50 µg/g and 8/30 (27 %) had at least one measurement above 300 µg/g.[1]

A Finnish study monitored calprotectin concentrations in 49 patients who were in clinical and endoscopic remission with FC <100 µg/g and stopped anti-TNF therapy. Patients who relapsed (31 %) had significantly elevated calprotectin concentrations (compared to baseline) up to 6 months before the relapse. **Of patients who maintained remission (69 %), 65 % presented with at least one fecal calprotectin measurement > 100 µg/g**, supporting the use of consecutive fecal calprotectin measurements to estimate the risk of an imminent relapse and guide clinical decision-making.[2]

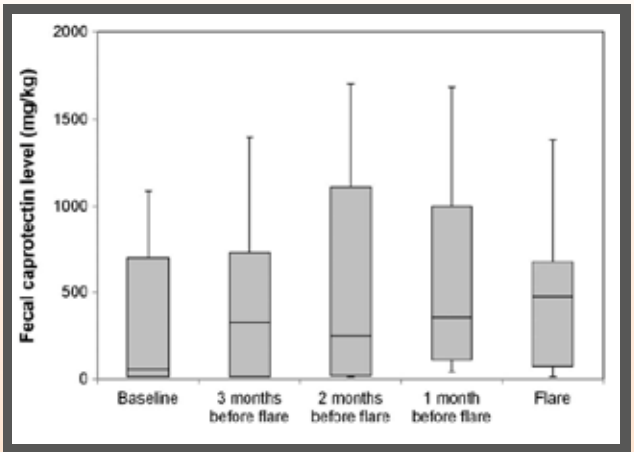

Fig. 4: FC levels in patients with flares. Box plot of FC levels in patients who experienced clinical flare (n=16). Boxes indicate interquartile ranges, with horizontal lines indicating medians and whiskers indicating the upper and lower limits.[1]

These findings were corroborated in a meta-analysis of Heida and co-authors, who reported **that two consecutively elevated FC concentrations, measured in a period of one to three months were most predictive of a clinical relapse in asymptomatic patients**, while consecutive normal FC values were associated with high probability of (maintained) remission in the next 2 - 3 months. Based on their review, the authors also **strongly opposed that a single calprotectin measurement at baseline can accurately predict relapse in the next 12 months**, as fecal calprotectin concentrations typically started to rise 2 - 3 months prior to the relapse.[3]

References:

1. *De Vos* et al. Consecutive Fecal Calprotectin Measurements to Predict Relapse in Patients with Ulcerative Colitis Receiving Infliximab Maintenance Therapy. Inflamm Bowel Dis 2013;19:2111-2117
2. *Molander* et al. Does Fecal Calprotectin Predict Short-Term Relapse After Stopping Tnfα-Blocking Agents In Inflammatory Bowel Disease Patients In Deep Remission? J Crohns Colitis 2015;9:33-40
3. *Heida* et al. Clinical Utility of Fecal Calprotectin Monitoring in Asymptomatic Patients with Inflammatory Bowel Disease: a systematic review and practical guide. Inflamm Bowel Dis 2017;23:894-902

7. Calprotectin as a predictive marker for post-operative relapse in Crohn's disease

In patients with Crohn's disease undergoing a surgical resection of a part of their bowel, measurement of fecal calprotectin can predict the risk of post-operative relapse allowing timely treatment interventions and limiting the number of endoscopies in patients with low fecal calprotectin concentrations.

Why do we measure?

An endoscopic recurrence of inflammation typically occurs before the onset of clinical symptoms.[1] Early detection of subclinical endoscopic lesions may therefore allow a timely treatment in post-operative CD patients. The golden standard endoscopy is a costly and unpleasant procedure. Fecal calprotectin can avoid unnecessary endoscopies and facilitate earlier diagnosis.

Interpretation

In a sub-analysis of the POCER study, *Wright* and co-authors demonstrated that a **fecal calprotectin concentration > 100 µg/g** has good sensitivity (89 %) and NPV (91 %) **to monitor CD recurrence after intestinal resection** (Figure 5)[2,3]; the cut-off was confirmed by *Boschetti* et al. in a French cohort.[4] Moreover, **fecal calprotectin monitoring is superior to C-reactive protein and CDAI** for the prediction of endoscopic recurrence.[3]

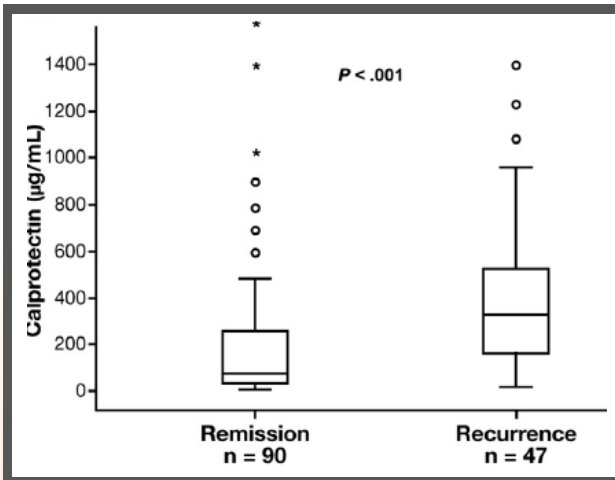

Fig. 5: FC in endoscopic remission vs FC in combined endoscopic recurrences at 6 and 18 months. The median FC concentration in remission vs recurrence was 75 µg/g vs 330 µg/g (P < .001). Open circles indicate outliers; Asterisks (*) indicate extreme outliers.[3]

In patients with endoscopic remission six months post-surgery, low fecal calprotectin concentrations have limited predictive capability of endoscopic recurrence. **Serial measurements of calprotectin at regular intervals are advised to monitor disease activity** in the bowel.[3]

References:

1. *Rutgeerts et al.* Predictability of the postoperative course of Crohn's disease. Gastroenterology 1990;99:956-963
2. *De Cruz* et al. Crohn's disease management after intestinal resection: a randomised trial. Lancet 2015:385:1406-1417
3. *Wright* et al. Measurement of Fecal Calprotectin Improves Monitoring and Detection of Recurrence of Crohn's Disease After Surgery. Gastroenterology 2015;148:938-947
4. *Boschetti* et al. Levels of Fecal Calprotectin Are Associated With the Severity of Postoperative Endoscopic Recurrence in Asymptomatic Patients With Crohn's Disease. Am J Gastroenterol 2015;110:865-872

8. Calprotectin as an aid in the decision to stop an IBD drug

In patients with IBD, fecal calprotectin concentrations can help determine whether or not a patient is eligible for drug discontinuation.

Why do we measure?

It is important to determine whether therapy can be safely interrupted in patients with prolonged and stable remission. Among other parameters, patients with high fecal calprotectin concentrations and other unfavorable clinical and biological parameters at baseline have an increased risk of relapse after discontinuing therapy and should not be stopped.

Interpretation

A Belgian group identified fecal calprotectin concentrations ≥ 300 µg/g, CRP ≥ 5 mg/L, Hemoglobin level ≤ 145 g/L, Leukocyte count > 6 x 10^9/L, male sex and no previous surgical resection as independent risk factors associated with time to relapse in patients discontinuing infliximab therapy after achieving 6 months corticosteroid-free remission (Figure 6). Patients with no more than 2 risk factors of relapse had a low chance of relapse during the study follow-up period.[1]

	Complete multivariable model		Simplified multivariable model without infliximab trough level and CDEIS	
Risk factor	Hazard ratio[a] estimate (95% CI)	*P* value[b]	Hazard ratio estimate (95% CI)	*P* value
Corticosteroid use between 12 and 6 mo before baseline	3.5 (1.1–10.7)	.03		
No previous surgical resection	4.0 (1.4–11.4)	.01	4.2 (1.5–11.6)	.005
Male sex	3.7 (1.9–7.4)	<.001	3.5 (1.7–7.0)	<.001
Hemoglobin level ≤145 g/L	6.0 (2.2–16.5)	<.001	5.5 (2.0–15.5)	.001
Leukocyte count >6 × 10^9/L	2.4 (1.2–4.7)	.01	1.9 (1.0–3.5)	.05
CDEIS >0	2.3 (1.1–4.9)	.04		
hsCRP level ≥5 mg/L	3.2 (1.6–6.4)	<.001	2.7 (1.3–5.3)	.005
Infliximab trough level ≥2 mg/L	2.5 (1.1–5.4)	.02		
Fecal calprotectin level ≥300 µg/g	2.5 (1.1–5.8)	.04	3.1 (1.3–7.2)	.01

CI, confidence interval.
[a]Hazard ratio for each risk factor in Cox model (estimate and 95% CI from the 10 imputations).
[b]Significance level (mean from the 10 imputations).

Fig. 6: Factors Measured at Inclusion Independently Associated With Time to Relapse. Using the simplified model on the right, patients with no more than 2 risk factors had the highest chance to maintain remission over time after drug discontinuation.[1]

References:

1. *Louis* et al. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. Gastroenterology 2012;142:63-70

9. Calprotectin and treat-to-target

Fecal calprotectin can be used as part of a comprehensive treatment approach incorporating objective biomarkers of disease activity along with clinical symptoms to improve patient outcomes.

Why do we measure?

In patients with IBD, fecal calprotectin concentrations can be used as a surrogate marker for endoscopically active disease, reducing the number of costly and unpleasant endoscopies.
A tight treatment monitoring strategy, relying on fecal calprotectin, CDAI, CRP and prednisone use to guide management of patients is better than the use of clinical symptoms and prednisone use alone to achieve clinical and endoscopic targets in patients with Crohn's disease (Figure 7).[1]

Interpretation

In the CALM-study, patients in the tight control group were escalated if any of the following treatment failure criteria were met: **Fecal calprotectin ≥ 250 µg/g, CRP ≥5 mg/L, CDAI ≥ 150 or prednisone use**. The authors conclude 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.[1]

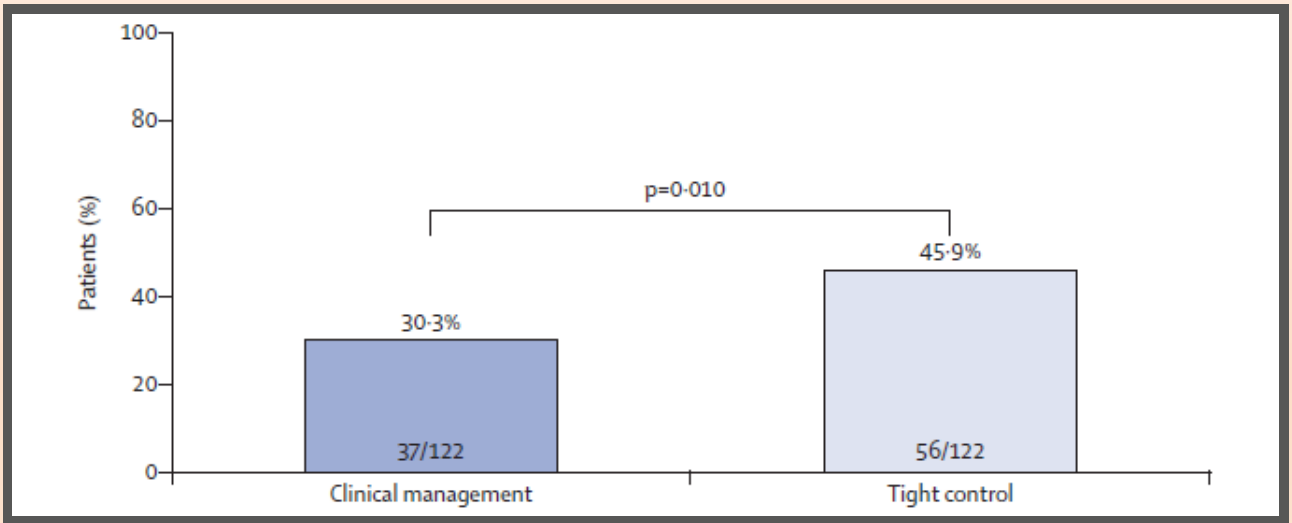

Fig. 7: Proportion of patients with mucosal healing (CDEIS < 4) and no deep ulcers at 48 weeks after randomization (also expressed within the bars as number of patients/total patients in each group).[1]

References:

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

10. Conclusions

Since its first discovery as a potential biomarker in IBD by Roseth and co-authors in 1997, fecal calprotectin cannot be ignored from daily clinical practice as a powerful and objective reflection of bowel inflammation. It offers treatment guidance in a multitude of clinical situations, from first diagnosis of IBD to the management of complicated disease states and has been demonstrated to be cost-effective.

A summary of the indications for calprotectin quantification and proposed cut-offs is presented below in an overview table (Table 1). Importantly, calprotectin concentrations should be interpreted along with the clinical picture of the patient, biological and endoscopic or histological parameters. It is recommended to repeat fecal calprotectin measurements in case of borderline positive results or uncertainty in the test result.

Tab. 1: Fecal calprotectin: Clinical indications and cut-offs

Indication	Cut-off	Reference
Differentiation of IBD from IBS (adults)	50 µg/g **50 µg/g - 100 µg/g**	*Waugh*, Health Technol Assess 2013 ***Burri*, Expert Rev Gastroenterol Hepatol 2014**
Differentiation of IBD from non-IBD (children)	**50 µg/g or 100 µg/g**	***Waugh*, Health Technol Assess 2013**
Marker of (endoscopic) disease activity	50 µg/g **250 µg/g**	*Mosli*, Am J Gastroenterol 2015 ***D'Haens*, Inflamm Bowel Dis 2012** **Buisson, Aliment Pharmacol Ther 2016** **Mak, Dig Dis Sci 2018**
Prediction of mucosal healing	250 µg/g (endoscopic) **200 µg/g (histological)**	*Mak*, Dig Dis Sci 2018 ***Mak*, Dig Dis Sci 2018**
Prediction of clinical relapse	**300 µg/g** **(one single measurement has limited predictive value)** 100 µg/g (one single measurement has limited predictive value)	***De Vos*, Inflamm Bowel Dis 2013** *Molander*, J Crohns Colitis 2015
Prediction of post-operative relapse	**100 µg/g** **(one single measurement has limited predictive value)**	***Wright*, Gastroenterology 2015** ***Boschetti*, Am J Gastroenterol 2015**
Drug stop	**300 µg/g**	***Louis*, Gastroenterology 2012**
Tight monitoring to treat-to-target	**250 µg/g**	***Colombel*, Lancet 2018**

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