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REVIEW

From bench to bedside: Fecal calprotectin in inflammatory bowel diseases clinical setting

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Abstract

Fecal calprotectin (FC) has emerged as one of the most useful tools for clinical management of inflammatory bowel diseases (IBD). Many different methods of assessment have been developed and different cut-offs have been suggested for different clinical settings. We carried out a comprehensive literature review of the most relevant FC-related topics: the role of FC in discriminating between IBD and irritable bowel syndrome (IBS) and its use in managing IBD patients In patients with intestinal symptoms, due to the high negative predictive value a normal FC level reliably rules out active IBD. In IBD patients a correlation with both mucosal healing and histology was found, and there is increasing evidence that FC assessment can be helpful in monitoring disease activity and response to therapy as well as in predicting relapse, post-operative recurrence or pouchitis. Recently, its use in the context of a treat-to-target approach led to a better outcome than clinically-based therapy adjustment in patients with early Crohn's disease. In conclusion, FC measurement represents a cheap, safe and reliable test, easy to perform and with a good reproducibility. The main concerns are still related to the choice of the optimal cut-off, both for differentiating IBD from IBS, and for the management of IBD patients.

Key words: Fecal calprotectin; Inflammatory bowel diseases; Crohn's disease; Ulcerative colitis; Irritable

bowel syndrome

Core tip: This manuscript is a review of current literature on clinical use of fecal calprotectin in distinguishing irritable bowel syndrome from inflammatory bowel diseases and in the long-term management of inflammatory bowel disease patients, which includes monitoring of disease activity, response to therapy, disease relapse and post-operative recurrence. Concerns about the optimal cut-off in different settings have also been discussed.

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INTRODUCTION

Calprotectin is a 36 kDa calcium and zinc binding protein, which represent about 60% of soluble proteins of the cytoplasm of granulocytes[1]. It is heat and proteolysis resistant heterocomplex of S100A8 and S100A9 consisting of 2 heavy (14 kDa) e 1 light (8 kDa) chains, each binding 2 Ca^{2+}.

Functions of calprotectin include: competitive inhibition of zinc-dependent enzymes, potential biostatic activity against microbes through chelation of zinc ions, apoptosis induction in malignant cells, and regulation of the inflammatory process[2,3].

Fecal calprotectin (FC) is one of the most sensitive non-invasive marker in distinguishing inflammatory bowel diseases (IBD) from functional disorders. Several factors, however, may influence FC levels, such as colonic cleansing[4], age, diet, exercise[5], and the faecal amount of mucus or blood in stools[6].

A further limitation is a low specificity in discriminating ulcerative colitis (UC) from Crohn's disease (CD), active IBD from non-IBD intestinal inflammation (infections, non-steroidal anti-inflammatory drugs-related damage, cancer, diverticulitis). FC is a more sensitive marker than C-reactive protein (CRP) for detection of mild mucosal inflammation, although in severely active cases CRP better reflects systemic inflammation[7,8].

PITFALLS IN FC ASSESSMENT

Stability

Roseth, in 1992, demonstrated the stability of calprotectin in stools for up to 7 d at room temperature[9,10], which offers advantages for its use in clinical practice[11].

In a more recent study, however, calprotectin concentrations in stool samples were unchanged only for 3 d at room temperature, while after 7 d a significant decrease ($P < 0.01$) was found[12].

Variability

Day-to-day variation of FC was demonstrated by Husebay *et al*[13] in patients without colonic inflammation or neoplasm and confirmed by Moum *et al*[14], in patients with mild-to-moderate active CD, where significant differences in 63 pairs of stool samples collected in 2 consecutive days were found. A lower variability was observed in fecal samples collected for 3 d from 93 CD patients in clinical remission[15]. Dobrzanski *et al*[16] confirmed that variability seems to be relevant only in active IBD, particularly in UC where large amounts of mucus and blood are present in stools.

The most reliable results were provided by analyzing 3 in-wk samples from the first bowel movement in the morning[12]. Higher variability was found in patients with the highest levels of FC; further, the test results were influenced by the sample consistency and by the interval between the bowel movements, supposedly related to the accumulation of leukocyte-derived proteins in the gut lumen.

A good correlation was found between the FC concentrations assessed in two randomly different samples collected from the same bowel movement[12]. Calafat *et al*[6] did not find any influence of the timing of stools sampling, or the presence of blood on FC concentrations, in particular in patients with moderate-to-severe active UC, where the decision-making strategies based on single quantitative FC determinations are not advisable.

Methods of assessment

Different methods can be used for the quantitative assessment of FC, most of them based on the enzyme-linked immunosorbent assay (ELISA); chemiluminescence immunoassays (CLIA), fluoro enzyme immunoassays (FEIA) and particle enhanced turbidimetric immunoassays (PETIA) were also introduced.

Oyaert *et al*[17] compared six automated immunoassays: Thermo Fisher EliA Calprotectin assay on the Phadia 250 (Thermo Fisher Scientific, Uppsala, Sweden), Diasorin Calprotectin assay on the Liaison (Diasorin S.P.A., Saluggia, Italy), Inova QUANTA Flash Calprotectin (research use only) on the Inova BIO-FLASH instrument (Inova Diagnostics, San Diego, CA, United States), Bühlmann fCAL Turbo (Bühlmann Laboratories AG, Schönenbuch, Switzerland) on the Roche Cobas c501 (Roche Diagnostics, Mannheim, Germany), Euroimmun Calprotectin assay (Euroimmun; Lübeck, Germany), on an automated ELISA instrument (QUANTA-Lyser 2, Inova) and Orgentec Calprotectin assay on the Alegria (Orgentec Diagnostika, Mainz, Germany). The authors found that all assays had a sensitivity of 100% when the cut-off of the manufacturer was used (*i.e.*, 50 μg/g),

Table 1 Fecal calprotectin cut off values and performance in different populations

Ref.	Patients and disease (*n*)	Cut-off	Sensitivity (%)	Specificity (%)
Lin *et al*[23]	1471 IBD (active *vs* inactive)	50 μg/g	92	60
		100 μg/g	84	66
		150 μg/g	80	82
Limburg *et al*[24]	110 patients with chronic diarrhea (prediction of inflammation)	100 μg/g	83	83
Von Roon *et al*[25]	IBD *vs* no IBD			
	1267	50 μg/g	89	81
	328	100 μg/g	98	91
D'Haens *et al*[27]	126 IBD (large ulcers)	250 μg/g	60.4	79.5
	87 CD (Endoscopic remission) 39 UC (Active mucosal disease)	250 μg/g	94	62.2
		250 μg/g	71	100
Sipponen *et al*[29]	77 CD (active *vs* inactive)	50 μg/g	91	44
		100 μg/g	81	69
		200 μg/g	70	92
Kittanakom *et al*[21]	40 inactive pediatric CD (prediction of relapse)	400 μg/g (PhiCal Calprotectin - EIA) 500 μg/g (Buhlmann POCT)	100	75.9
		800 μg/g (EliA-Calprotectin)	100	75.9
			100	75.9
Vazquez Moron *et al*[31]	71 CD (active *vs* inactive)	170 μg/g	77.6	95.5

IBD: Inflammatory bowel diseases; UC: Ulcerative colitis; CD: Crohn's disease.

while the specificity at the same cut-off value ranged from 58.4% to 78.5%.

Furthermore, while qualitative correlation among the methods from the different manufacturers was found to be good, quantitative agreement was poor, which means that the result of one method cannot be replaced by the result of another. This data are in line with a study from the United Kingdom National External Quality Assessment Service, where up to 3.8-fold differences among methods from different manufacturers were observed[18]. This suggests that the antibodies used in the different assays were directed against different protein complexes. Alternatively, the difference could be explained by the use of different antibodies (monoclonal *vs* polyclonal) of different origins (recombinant *vs* native) with different immunoassay techniques (ELISA *vs* PETIA *vs* CLIA *vs* FEIA).

Further quantitative tests for calprotectin are available including the Quantum Blue® Calprotectin Rapid Test (Bühlmann Laboratories AG, Schönenbuch, Switzerland), which has been shown to be a suitable alternative to ELISA in a clinical setting[19], although an overestimation of FC levels in comparison with Calprest® ELISA test was found[20].

In pediatric IBD patients, an automated ELISA test (Bühlmann PhiCal Calprotectin-EIA) , an EliA (Phadia 250 EliA-Calprotectin), and Bühlmann immunochromatographic Point-of-Care Test (POCT) displayed similar performance in predicting relapse[21].

Cut-off

Although many studies have suggested different cut-off values, which take into account the type of assay used and the population that the tests were applied to (Table 1), a cut/off value of 50 μg/g of FC has been the most commonly adopted both in literature and by commercially available ELISA kits, for adults and children over 4 years to differentiate IBD from other forms of inflammation[22]. Moreover, Lin *et al*[23] suggested 50 μg/g as a screening cut-off value for further endoscopy examination in clinical practice, with specificity of 60% and pooled sensitivity of 92%.

A single cut-off level of 100 μg/g was agreed by an expert panel as appropriate for this purpose based on results from previous studies, which reported increased diagnostic precision for discrimination of colorectal inflammation in patients with CD and UC at this cut-off[24,25]; a higher cut-off level would be desirable to maximize the negative predictive value (NPV) and reduce incorrect diagnoses of IBD.

A negative test result at the lowest cut-off level (30 to 50 μg/g) suggests a diagnosis of a non-inflammatory condition, such as irritable bowel syndrome (IBS). A positive result at the cut-off of 100 μg/g may indicate IBS, with the recommendation to repeat the test in 6 wk to confirm the initial result[26].

As the cut-off value increases, sensitivity becomes lower and specificity higher. A FC value of 250 μg/g was deemed appropriate for monitoring disease activity in IBD. D'Haens *et al*[27] examinated 126 IBD patients (87 CD and 39 UC) and proposed a FC cut-off of 250 μg/g for indicating IBD remission.

The same cut-off was recommended by a recent meta-analysis[28] to contemplate escalating therapy with pooled sensitivity of 80% and specificity of 82%; in UC the test performed better than in CD.

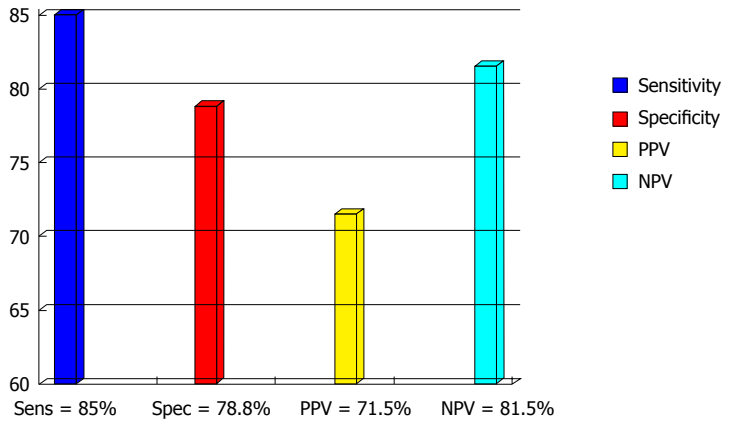

Figure 1 Pooled fecal calprotectin sensitivities, specificities, positive predictive value and negative predictive value of fecal calprotectin in discriminating between intestinal inflammation and functional disorders. PPV: Positive predictive value; NPV: Negative predictive value.

An earlier study by Sipponen *et al*[29] proposed a cut-off value of 200 μg/g for identification of endoscopically inactive CD. In another study of 115 CD patients, FC less than 300 μg/g was associated with a reduced risk of disease relapse[30].

Even a 400 μg/g cut-off was agreed by an expert panel with 1000 μg/g proposed for monitoring response to therapy in patients with severe active IBD[26].

In pediatric patients the optimal FC cut-offs to differentiate active from inactive IBD were 400, 500, and 800 μg/g measured by different methods (PhiCal Calprotectin-EIA, Bühlmann POCT, and EliA-Calprotectin)[21].

In CD, FC concentration of ≥ 170 μg/g predicted endoscopic activity with 77.6% sensitivity, 95.5% specificity and likelihood ratio +17.06, while values ≤ 71 μg/g were predictive of mucosal healing with sensitivity of 95.9%, specificity of 52.3% and likelihood ratio -0.08[31].

Larger prospective studies were suggested to be carried out to validate the cut-off values in clinical practice for UC, using endoscopy as a reference. Once established for UC, cut-off values for CD could then be developed and validated, although harder to establish due to the lack of consistent evidence. In addition, small bowel disease activity is reflected by FC correlates less reliably than in case of colonic involvement[32,33].

Age-related concerns

FC levels have a significant negative correlation with age[28]. Children in the first months of life have high FC concentrations, which could reflect an increased trans-epithelial migration of either granulocytes or newly recruited macrophages as well as inability to regulate the microbial gut flora related to immaturity of the mucosal barrier function[28]. The increase of intestinal permeability during the first weeks of life was suggested in healthy newborns with high FC levels[34]. The type of feeding also influences FC concentrations: breastfed infants have higher FC levels than non-breastfed ones in the first months of life, reflecting the influence of immunomodulatory factors in human milk on the gut mucosa[28].

A statistical difference was found between FC in healthy children aged 1-3 mo and those aged 3-6 mo (375.2 μg/g *vs* 217.9 μg/g, $P < 0.001$), as well as between 1-6 mo and 6-18 mo (median: 282.7 μg/g *vs* 114.9 μg/g; $P < 0.001$)[28]. The results clearly indicate that different cut-offs are necessary for children less than 4 years old. Oord *et al*[35] proposed 538 μg/g for 1-6 mo, 214 μg/g for 6 mo-3 years, and 75 μg/g for 3-4 years.

Finally, in newborns FC concentrations may increase up to 30% when the sample is collected from a diaper, which may be explained by the water absorption into the diaper[35].

FC IN DISCRIMINATING BETWEEN IBD AND IBS

The role of FC as a screening test to differentiate patients with IBD from IBS was firstly proposed by Tibble and co-workers[36,37] who demonstrated the high sensitivity and high NPV of the test. In a population of 602 unselected patients with intestinal symptoms, FC levels < 30 μg/g and Rome I criteria positivity were highly predictive for not having IBD[38]. Since then, a considerable body of literature has been published corroborating these results (Figure 1), yet with wide variation in reported sensitivity and specificity, which may be related to the use of different ELISA kits, different patients populations and different cut off values. Summerton and colleagues[39] reported sensitivity and specificity in line with Tibble, while Carroccio *et al*[40] in a prospective study carried out in adults and children with chronic diarrhea of unknown origin found similar specificity (84%), but lower sensitivity (66%), attributed by the authors to the high number among their referrals of possible celiac patients, where FC levels are usually low. A major problem is represented by the assessment of the optimal threshold, as many authors used only the manifacturer's recommended

cut offs, mostly 50 μg/g. In the first study carried out on southern European patients by our group[41], the ROC curve showed that a value of 60 μg/g offered a diagnostic accuracy of 83% with sensitivity, specificity, positive predictive value (PPV) and NPV of 81%, 88%, 93% and 71% respectively. Li *et al*[42] found median FC concentrations of 466 μg/g in patients with chronic inflammation, 159 μg/g in colorectal cancer and 12.21 μg/g, not statistically different from healthy subjects and IBS patients. In a prospective study[8] where the accuracy of fecal markers, CRP, blood leucocytes, pASCA and pANCA for differentiating IBD from IBS was assessed, fecal tests performed best with overall accuracy of 90% and 89% for fecal lactoferrin (FL) and FC respectively. These results were confirmed by Otten *et al*[43], who found sensitivity and NPV of 100% for FC and 78% and 95% for FL, and by Langhorst *et al*[44] who reported in active UC significantly higher FL and FC levels (152 and 103.5 μg/g respectively) in comparison with IBS (8.3 and 18.6 μg/g)

In the first study which assessed the role of FC in routine general practice in 962 patients with persistent gastrointestinal symptoms[45], at the manufacturer's cut-off of 50 μg/g the NPV was 98% while PPV dropped to a disappointing 28%, showing the impact of evaluating a population with a low prevalence of organic disease on the test performance. Increasing the cut off to 150 μg/g the PPV raised to 71%, saving an acceptable 69% sensitivity. In the systematic review by Waugh *et al*[46] evaluating FC testing for distinguishing between inflammatory and non-inflammatory bowel diseases, 28 studies in both adult and pediatric populations where included; at a cut off level of 50 μg/g, FC showed in adults a pooled sensitivity of 93% (83%-100%), while the specificity ranged between 60% and 100% with a pooled value of 94%. In pediatric patients, at the same cut off sensitivity and specificity ranged from 95% to 100% and from 44% to 93% respectively ; for overlap values between 50 μg/g and 150 μg/g repeated assessments were suggested; point-of-care and ELISA testing proved equally reliable and in a primary care setting FC turned out to reduce the number of referrals and endoscopies.

The potential of FC to discriminate between intestinal inflammation and functional disorders has been highlighted by a large number of further studies. Chang *et al*[47]confirmed significantly higher FC values in IBD than in IBS and healthy controls ($P < 0.0001$). Using the manufacturer cut off value Caviglia *et al*[48] found 100% sensitivity and NPV (with corresponding specificity and PPV 52.4% and 70.6%) for discriminating between patients with and without intestinal inflammation; similar results were reported by Banerjee *et al*[49]. In a systematic online database search, at ≤ 40 μg/g, less than 1% probability of having IBD was reported[50]. Lower values (76% sensitivity and 53% NPP) where reported by Fu *et al*[51] in a comparative study among fecal B cell-activating factor, FC and fecal occult blood test.

Adopting a cut off value > 164 μg/g Kalantari *et al*[52] found sensitivity and specificity of 57% and 75% respectively for discrimination between UC and IBS.

In conclusion, FC is currently the most widely used fecal marker for differentiating between IBD and IBS; due to the high NPV it is highly accurate in ruling out intestinal inflammation both in primary and secondary care. Among IBD patients apparently in remission with IBS-like symptoms, FC tends to be significantly higher than in IBS, suggesting the presence of an undercurrent low-grade inflammation[53,54].

FC IN IBD

Monitoring the disease activity

As IBD are chronic relapsing diseases, regular monitoring is needed for prediction of imminent flares and for tailoring treatment[55]; it includes clinical, biochemical, endoscopic and histologic evaluations.

Many physicians treating IBD still adopt a clinically-based management[56], even if recent data suggest that many IBD patients in clinical remission still have subclinical mucosal inflammation[57]. FC is correlated with clinical activity evaluated either by Sutherland criteria[58] or Partial Mayo Score[59]. In a study by Xiang *et al*[58], FC concentrations were useful to discriminate patients with active UC, inactive UC and control, with a cut-off point of 50 μg/g showing 91.9% sensitivity and 79.4% specificity; in patients with UC, FC had a better correlation with clinical activity than CRP. Moreover, in a prospective study, FC assessment after 3 mo of the initial treatment could predict the clinical course of UC patients after 3 years of follow up[60].

Although colonoscopy is considered the gold standard to assess disease activity, current ECCO guidelines emphasize that routine endoscopy for IBD patients in clinical remission is unnecessary, unless it is likely to change patient management[61]. Therefore, a marker reflecting intestinal inflammation in patients in clinical remission is needed. Many studies showed that FC is the most promising noninvasive marker for assessing mucosal inflammation. In a study by D'Haens *et al*[27] FC had a significant correlation with endoscopic disease scores in both CD and in UC: a cut-off value of 250 μg/g suggested the presence of large ulcers with sensitivity of 60.4%, specificity of 79.5%, PPV 78.4% and NPV 62.0%) in CD, while in UC, a FC > 250 μg/g gave a sensitivity of 71.0% and a specificity of 100.0% (PPV 100.0%, NPV 47.1%) for mucosal disease activity (Mayo > 0). In UC, FC levels reflect the degree of inflammation rather than the disease extent[10].

Interestingly, FC were significantly related to symptom scores in UC ($r = 0.561$, $P < 0.001$), but not in CD. A study by Theede *et al*[62] found a strong correlation both with Mayo Endoscopic Score and Ulcerative Colitis Endoscopic Score. A correlation with Rachmilewitz and modified Baron Score was also

demonstrated. Schoepfer and colleagues[63,64] found that FC was the only marker able to discriminate among mild, moderate and severe disease. A recent Korean study[59] highlighted how not only the ELISA, but also the Quantitative POCT predicted endoscopic inflammation (Mayo endoscopic score ≥ 1) in UC at a cut-off value of 201.3 μg/g and 150.5 μg/g respectively. In CD, a significant correlation with endoscopic activity was found both in colonic[33] and in small bowel CD[36], as well as with capsule endoscopy[65].

In a prospective study on 58 pediatric patients[66] FC showed a high correlation both with endoscopy (r = 0.655) and histology grading (r = 0.699); it proved the most accurate tool (sensitivity 94%, specificity 64%, PPV 81%, NPV 87%) to detect active mucosal inflammation when compared to clinical scores and serum markers. The highest accuracy was found in patients with apparent clinical and laboratory remission (sensitivity 100%, specificity 80%, PPV 67%, NPV 100%).

Guardiola *et al*[67] prospectively evaluated UC patients in clinical and endoscopic remission; those with histologic features of inflammation were reliably identified based on their FC levels at a cut off of 155 μg/g with a sensitivity of 78% and a specificity of 71%. More recently, Zittan *et al*[68] confirmed that FC could predict histological remission, with a cut-off of 100 μg/g. A recent study comparing the predictive value of FC measurement and histological scoring in IBD patients, found that FC performed better, especially in UC[69]. This finding was confirmed in a subsequent study by Theede *et al*[70], who showed that in UC baseline FC more than 321 μg/g predicted relapse both at 6-mo and 12-mo in contrast to histological activity, CRP, or length of remission. A study by Puolanne *et al*[71] confirmed the correlation between FC, clinical activity, and histopatologic findings in 72 patients with colonic IBD.

In an English study[72], calprotectin concentration in the colonic mucosa of UC patients correlated with histological remission; moreover, a median value > 5/HPF were independently associated with worse outcome (corticosteroid use, hospitalisation, or colectomy during a 6-year follow-up). Moreover, in a short report by Roseth *et al*[73], low FC levels were closely associated with mucosal healing.

Predicting disease relapse

A major challenge in managing IBD is a timely detection of patients at risk for impending clinical relapse. Tibble et al. firstly suggested that a high FC concentration could identify those IBD patients in remission who were at risk of early relapse without any difference between UC and CD[74]. Conversely, we showed a 14-fold increase in the relapse risk in patients with UC and a two-fold increase in CD patients in clinical remission with FC concentration higher than 150 μg/g concluding that FC was a stronger predictor of clinical relapse in UC than in CD[32]. In CD, D'Incà *et al*[33] found a significant correlation between a positive FC test and probability of relapse (P < 0.001) only for colonic localization at 130 μg/g cut-off level. On the other hand, a meta-analysis by Mao *et al*[3] was not able to demonstrate that the overall accuracy of FC for predicting relapse was different in UC and CD because of the heterogeneity across studies, due to different criteria to define remission and relapse; however, due to the limited data, the ileal involvement was not assessed.

In asymptomatic patients with IBD, Heida *et al*[75] found that increase of FC levels were correlated with increased (from 53% to 83%) probability of relapse within the next 2 mo to 3 mo, while consecutive normal FC values were associated with 67% to 94% probability of remission in the next 2 mo to 3 mo.

In patients under maintenance therapy with Infliximab (IFX), levels > 160 μg/g were related to probability of relapse higher than 60% over the following 8 wk[76].

In a subanalysis of the STORI trial, serial measurements of FC in CD patients in clinical remission after stopping IFX, showed that in those who relapsed, the FC levels had started to increase 4-6 mo earlier[77]. Despite the test reliability, the ideal FC threshold for monitoring disease relapse is still awaiting to be defined.

Monitoring the therapy effectiveness

In clinical practice, "Treat-To-Target" is currently considered the most important strategy for therapy adjustment.

A study by Wagner *et al*[78] in patients with UC or CD treated with 5-aminosalicilic acid, prednisone or Azathioprine, showed that FC were correlated with clinical scores after 4 wk and 8 wk of treatment in UC and in CD, respectively, and in patients with complete response to therapy there was a significant decline in FC levels (P < 0.01) after 4 wk, which was not observed in partial or non-responders. In children with active disease treated with steroids, FC levels declined in line with clinical improvement but seldom fell within the normal range[79].

In the biologic era, many studies confirmed the role of FC in monitoring the effectiveness of therapy. Molander *et al*[80] demonstrated that a normal FC (< 100 μg/g) after induction therapy with anti-TNFα predicts sustained clinical remission in the majority of patients, both in CD and UC; a cut-off of 139 μg/g for FC had 72% sensitivity and 80% specificity to predict the risk of clinically active disease after 1 year. According to De Vos *et al*[81] two consecutive FC measurements over 300 μg/g are more specific than a single assessment for predicting relapse in UC patients under maintenance treatment with IFX.

Interestingly, even after discontinuation of anti-TNFα therapy, an increase of FC could predict clinical and endoscopic relapse[82]. This data is in accordance with the STORI study[30,77], where FC was comparable to endoscopic assessment in predicting the relapse

risk after stopping TNFα-blocking therapy, starting to increase 4-6 mo before the clinical relapse. A prospective study[83] in IBD patients (20 UC and 52 CD) under treatment with anti-TNFα, showed that the diagnostic accuracy of rapid FC seems to be higher in predicting persistence of endoscopic lesions than clinical remission.

Both in monitoring of therapy and in prediction of relapses FC seems to be more effective in UC than in CD[32]. Nevertheless, in a prospective study of Laharie *et al*[84] in patients responding to IFX induction regimen, FC measurement at w14 could not predict CD clinical relapse at one year. In severe acute colitis, FC evaluation could be helpful in timely prediction of clinical course: Ho et colleagues[85] demonstrated that FC was higher in patients requiring colectomy with a trend toward significance when compared to responders, suggesting that FC in patients with severe acute colitis could be included among the prognostic criteria.

Shifting the therapeutic target from clinical remission to mucosal healing has been supported by population-based cohort studies, post hoc analysis of clinical trials, and meta-analysis, both for CD and UC[86-90]. The STRIDE recommendations[91] defined FC as an adjunctive target in IBD patients, while a Mayo Endoscopic Score ≤ 1 for UC and the resolution of ulcerations in CD are the best target to reach, besides patient reported outcome. The recently published CALM study[92], for the first time used FC as a target despite clinical activity in CD patients, in whom therapy was escalated if FC was ≥ 250 μg/g in a group of patients, while the control group was treated on the basis of clinical activity. The tight control algorithm led to rapid optimization of therapy and, therefore, to a higher proportion of patients achieving mucosal healing [CD Endoscopic Activity Index of Severity (CDEIS) < 4] and no deep ulcers on endoscopy, deep remission [CD Activity Index (CDAI) < 150 and CDEIS < 4 and no deep ulcers, no draining fistula, and no prednisone use for 8 wk or more], biological remission (FC < 250 μg/g, CRP < 5 mg/L, and CDEIS < 4), and steroid-free remission (CDAI < 150 with no prednisone for 8 wk). A limitation is represented by the discretional taper schedule of prednisone at study entry, that, affecting the treatment option at randomization (the use of prednisone defined treatment failure in the tight control group) could have led to an earlier introduction of adalimumab and positively affected the outcomes.

Monitoring the post-operative recurrence

Despite the increasing use of immunosuppressants and biologics, IBD patients frequently need surgery. Approximately 80% of CD patients require intestinal surgery within 20 years after diagnosis and 10%-30% UC patients need colectomy, at 25 years following diagnosis[93]. Surgery is not curative, and is followed by post-operative recurrence (POR, in CD patients) and pouchitis (in UC patients) in a high percentage of cases. The post-operative monitoring, mainly based on endoscopy, is crucial to identify those patients who require early treatment. Non-invasive markers of intestinal inflammation, especially FC, represent an easy, quick and cheap tool for the early diagnosis of post-operative recurrence or pouchitis.

Post-operative recurrence: POR after ileo-colonic resection is a feature of CD. Early studies by the Leuven group reported an endoscopic and histological recurrence rate of 73% within one year from surgery although only 20% of the patients had symptoms[94]. A more recent review, focusing on historical population-based studies, showed that the cumulative risk of POR after 10 years is around 44%-55%[95]. As endoscopic recurrence occurs before the onset of symptoms[94], the early detection of asymptomatic endoscopic lesions may allow a timely treatment in post-operative CD patients. Conventional ileocolonscopy within 6-12 mo is currently recommended to evaluate CD recurrence, graded according to the Rutgeerts' score. The Post-Operative Crohn's Endoscopic Recurrence (POCER) study showed that postoperative endoscopic monitoring, together with treatment escalation for early recurrence, is superior to standard drug therapy alone in preventing disease recurrence, at least in the short term[96]. However, it is not established the timing of endoscopic re-evaluation. Ileocolonoscopy is expensive, time-consuming, often not well accepted by the patient and not devoid of risks. Moreover, endoscopic examination of the neo-terminal ileum is not always technically feasible[97].

Although the role of FC in early detection of POR is still to be established, several studies suggest that FC could avoid unnecessary endoscopies and facilitate earlier diagnosis. FC and FL assay have been suggested as non-invasive, inexpensive and reproducible biomarkers in post-operative CD patients[98].

Orlando *et al*[99] prospectively evaluated 50 CD patients who had undergone surgery; a FC value > 200 μg/g within 3 mo showed 63% sensitivity and 75% specificity in predicting endoscopic recurrence at one year, superior to ultrasound, whose sensitivity and specificity was 26% and 90% respectively.

In asymptomatic CD patients who had undergone ileo-colonic resection with a median follow-up of 40.5 mo, long term high levels of FL and FC were observed, interpreted as sign of ongoing intestinal inflammation, although partially influenced by the systemic post- operative inflammatory status[100].

In a small cohort of 13 post-operative CD patients followed for 1 year, FC and FL were more accurate in predicting clinical disease activity than CRP, platelet count or endoscopic appearance[101]. Accordingly, FC and FL levels positively correlated with both clinical recurrence and severity of endoscopic findings in the neo-terminal ileum who remained in remission during 6-12 mo after

ileocolonic resection[102]. At 170 μg/g cut-off, sensitivity and specificity of FC were higher than FL (83% and 93% *vs* 67% and 71% respectively) in predicting risk of clinical relapse. More recently, the same authors showed that in asymptomatic patients after ileo-colonic resection for CD, sustained low FC levels predict low risk of endoscopic recurrence, avoiding unnecessary endoscopic examinations[103].

These data are in line with Boschetti *et al*[104], who found were significantly higher (473 ± 78 μg/g) FC levels in asymptomatic CD patients with endoscopic recurrence after ileo-colonic resection in the last 18 mo when compared with those in remission (115 ± 18 μg/g, $P < 0.0001$). Sensitivity analysis excluding patients with both ileal and colonic recurrence did not change the results (456 ± 68 μg/g *vs* 115 ± 18 μg/g; $P < 0.0002$). The best cutoff point for FC to distinguish between endoscopic remission and recurrence was 100 μg/g as determined by the ROC curve, and its sensitivity, specificity, PPV and NPV, as well as overall accuracy were 95%, 54%, 69%, 93%, and 77%, respectively. Taking into account the high NPV of FC, a threshold below 100 μg/g could avoid systematic ileocolonoscopies in 30% of patients.

In the retrospective study by Herranz Bachiller *et al*[105] 97 patients with CD and ileocolic resection who had undergone FC measurement and subsequent ileo-colonoscopy were included. FC was related to endoscopic recurrence more than any clinical or serological parameters. Unlike other studies, the optimal cut-off was 60 μg/g.

Lobatón *et al*[106], compared the accuracy of ELISA test with the new quantitative POCT for the prediction of endoscopic activity and POR in CD patients. FC levels correlated more closely with CDEIS than leucocytes, platelets or CRP. The prediction of endoscopic remission (CDEIS < 3), using the quantitative POCT (cut-off 272 μg/g) and the ELISA (cut-off 274 μg/g) presented an area under the curve of 0.933 and 0.935, respectively. Median POCT levels discriminated endoscopic (Rutgeerts) score i0-i1 from i2-i4 (98 μg/g *vs* 234.5 μg/g). These results suggest that FC determined by rapid quantitative test predicts endoscopic remission as well as endoscopic postoperative recurrence in CD patients.

Disappointing results came from a Swedish study[107], that found no significant difference in FC concentrations between patients in endoscopic remission and relapsing patients one year after ileoceacal resection. However, the significant variation over time of FC concentrations highly influenced these results, especially in patients with diarrhea, which implies that a single measurement of FC has limited clinical utility in predicting POR.

The sub-analysis of the POCER study by Wright *et al*[108], demonstrated that FC has good sensitivity and NPV to monitor CD recurrence after intestinal resection. Levels of FC were measured in 319 samples from 135 patients. FC concentration was markedly increased before surgery and decreased substantially after resection of all macroscopically involved segments at 6 mo. Combined 6- and 18-mo FC levels correlated significantly with endoscopic recurrence, whereas CRP and CDAI did not. A cutoff of FC > 100 μg/g detected patients with endoscopic recurrence with 89% sensitivity, 58% specificity and 91% NPV. In this cohort, colonoscopy could be avoided in 47% of cases with endoscopic remission, at the cost of missing 11% of patients with endoscopic recurrence. Also, FC decreased in patients who underwent therapy intensification supporting its role in treatment monitoring. A FC level < 51 μg/g in patients in remission at 6 mo after surgery predicted remission at 18 mo, with 79% NPV; sensitivity, specificity and PPV were less satisfying (50%, 68% and 36%, respectively), suggesting a limited value of FC measurement in long-term prediction of endoscopic recurrence.

Large scale studies should be carried out to clarify controversial points. The optimal cut-off value of FC as a surrogate marker of POR needs to be established and the measurement procedures to be standardized. Nevertheless, our overview suggests the use of FC as promising alternative to ileo-colonoscopy in POR , especially in asymptomatic CD patients after initial negative post-operative endoscopy, and in monitoring response to treatment.

Pouchitis: Ileal pouch anal anastomosis (IPAA) after restorative proctocolectomy is currently the preferred surgical treatment for refractory or complicated UC. *De novo* inflammation of the ileal reservoir, the so-called pouchitis, is reported in about half of the patients. Even though the etiology of pouchitis remains unknown, several influencing factors have been suggested, such as fecal stasis, bacterial overgrowth, dysbiosis, genetic susceptibility and immune alteration. More recently, a CD-like complication of the pouch, has been described which can involve up to 13% of the patients following proctocolectomy with IPAA for UC. This entity is characterized by inflammation in the afferent limb (prepouch ileitis), presence of proximal small bowel strictures, or perianal or internal fistulae unrelated to surgery[109].

In 1994, the pouchitis disease activity index (PDAI), a composite score evaluating symptoms, endoscopic and histologic alteration has been developed to standardize the definition of pouchitis and to assess its severity. Patients with a total PDAI score of ≥ 7 points are classified as having pouchitis. The diagnosis of pouchitis therefore requires endoscopic confirmation with mucosal biopsies. Few studies have evaluated the value of FC measurement in these patients. However, available data show possible benefit with accurate diagnosis and management of pouch disorders as well as cost reduction.

In the small study by Thomas *et al*[110], significantly

increased FC levels were found in all 9 patients with endoscopic and histologic evidence of pouch inflammation compared with those without it. The first-morning FC levels correlated well (r = 0.91, $P \leq 0.0001$) with 24-h stool collection, with endoscopic and histologic scores, and with the percentage of CD15+ mature neutrophils and CD14+ macrophages within the lamina propria.

These findings were confirmed in a larger study carried out in 46 patients with UC and in 8 with familial adenomatous polyposis, who had undergone restorative proctocolectomy[111]. Using a threshold of 92.5 μg/g, FC levels correlated closely with the PDAI with a sensitivity of 90% and a specificity of 76.5%.

In pediatric UC, FC levels after restorative proctocolectomy positively correlated with subsequent pouchitis (r = 0.468, $P < 0.01$), with mean FC values of 71.50 μg/g among patients with no history of pouchitis, 290 ± 131 μg/g among those with a single episode of pouchitis, and highest level 832 ± 422 μg/g among patients with recurrent pouchitis (P = 0.019 between recurrent pouchitis and no pouchitis). A history of recurrent pouchitis was a significant predictor of FC higher than 300 μg/g (OR = 51; 95%CI: 1.2-2200; P = 0.040). Sensitivity, specificity, PPV, and NPV for FC concentration over 300 μg/g in detecting recurrent pouchitis were 57%, 92%, 67%, and 89%, respectively[112].

Yamamoto *et al*[113] prospectively evaluated the serial monitoring of FC and FL for the early detection of pouchitis after restorative proctocolectomy. Stool samples were collected every 2 mo up to 12 mo from 60 patients who had undergone ileostomy closure following total proctocolectomy and IPAA for UC. Endoscopy was performed in all asymptomatic patients at 12 mo and as soon as symptoms suggestive of pouchitis occurred. In the 10 patients (17%) who developed pouchitis FC and FL levels were already increased 2 mo before the diagnosis of pouchitis, while in the others both markers remained constantly at low levels. At cut-off values of 56 μg/g for FC and 50 μg/g for FL, sensitivity and specificity were 100% and 84%, and 90% and 86% respectively. At the time of endoscopy, the median FC and FL levels were significantly higher in patients with pouchitis than those without. Nevertheless, several questions can be raised on how to implement these findings into clinical practice. Current guidelines do not recommend routine pouchoscopy in patients in clinical remission as symptoms seem to reflect underlying inflammation in the pouch[114]. The results by Yamamoto *et al*[113] are in line with these recommendation. None of the 47 asymptomatic patients developed pouchitis during the 12-mo follow-up period, whereas in 10/13 symptomatic patients the inflammation of the pouch was confirmed. Thus, the NPV of 100% of the PDAI score < 7 could be considered as referral criteria for pouchoscopy in symptomatic patients[115].

In conclusion, even in patients with IPAA FC could allow the early detection of subclinical inflammation. Prospective studies need to establish whether this strategy could reduce the rate of chronic pouchitis and subsequent pouch failure.

CONCLUSION AND PERSPECTIVES

We reviewed the role of FC in various settings of IBD clinical management. About 20 years after the study by Roseth[10], FC has been confirmed as one of the most reliable, non-invasive diagnostic tools for management of IBD in clinical practice both in adults and children.

A considerable body of evidence confirms the high sensitivity and NPV of FC in distinguishing IBD from IBS in patients with clinical suspicion of intestinal inflammation. In those with established diagnosis of IBD, a growing number of studies suggest an increasingly recognized role of the test in monitoring disease activity and response to therapy, as well as in predicting disease relapse and POR, including pouchitis. The main concerns are still related to the choice of the optimal cut-off, both for ruling out intestinal inflammation and for the management of IBD patients.

Recently the CALM study[92] included FC measurement among the treatment failure criteria for escalating therapy in patients with early CD, and showed that adjustment of therapy based on the combination of clinical symptoms and biomarkers leads to better outcomes than symptoms-driven decision. These results support the use of FC in the context of the "Treat-To-Target" strategy and may open the way for a higher standard of care in IBD patients, if confirmed by further studies with a longer follow up. Finally, similarly designed studies are awaited in UC, where FC appears to perform best.

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