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**Disease monitoring in inflammatory bowel disease**

Chang S *et al*. Biomarkers in monitoring IBD

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**Abstract**

The optimal method for monitoring quiescent disease in patients with Crohn’s disease (CD) and ulcerative colitis is yet to be determined. Endoscopic evaluation with ileocolonoscopy is the gold standard but is invasive, costly, and time-consuming. There are many commercially available biomarkers that may be used in clinical practice to evaluate disease status in patients with inflammatory bowel disease (IBD), but the most widely adopted biomarkers are C-reactive protein (CRP) and fecal calprotectin (FC). This review summarizes the evidence for utilizing CRP and FC for monitoring IBD during clinical remission and after surgical resection. Endoscopic correlation with CRP and FC is evaluated in each disease state. Advantages and drawbacks of each biomarker are discussed with special consideration of isolated ileal CD. Fecal immunochemical testing (FIT), traditionally used for colorectal cancer screening, is mentioned as a potential new alternative assay in the evaluation of IBD. Based on a mixture of information gleaned from biomarkers, clinical status, and endoscopic evaluation, the best treatment decisions can be made for the patient with IBD.

**Key words**: Inflammatory bowel disease; Crohn’s disease; Ulcerative colitis; Fecal calprotectin; C-reactive protein; Fecal immunochemical test; Biomarkers; Remission; Postoperative recurrence

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**Core tip**: C-reactive protein (CRP) is not specific for intestinal inflammation but does have modest correlation with clinical and endoscopic findings in inflammatory bowel disease patients. CRP can be falsely low despite active mucosal inflammation and is more reliable in cases of transmural inflammation. Fecal calprotectin (FC) is more specific than CRP for intestinal inflammation, except in isolated ileal disease. FC better correlates with endoscopic findings than CRP and is useful in monitoring Crohn’s patients for postoperative recurrence. Optimal FC cutoffs are still being determined.

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**Introduction**

The clinical course of inflammatory bowel disease (IBD) varies widely from patient to patient. Whereas some patients are able to stay in remission for years with minimal treatment, other patients have a chronic, relapsing course with frequent flares despite aggressive therapy[1]. Twenty percent of Crohn’s patients will relapse yearly, and 67% of Crohn’s patients cycle between relapse and remission in the first 8 years after diagnosis. In ulcerative colitis (UC), there is a 9% to 21% 10-year cumulative risk of colectomy[2]. Given the known risk of disease progression in IBD, it is important to monitor for active disease and optimize treatment plans accordingly.

In the past, physicians have focused on clinical symptoms and clinical remission to guide treatment. However, it has been established that a patient’s clinical symptoms, particularly with Crohn’s disease (CD), are frequently inconsistent with endoscopic findings[3]. More recently, the goal of mucosal healing has emerged as the new treatment target[4]. In multiple trials, mucosal healing has been shown to improve long-term outcomes such as avoidance of surgery and fewer hospitalizations[5-7]. While endoscopic evaluation is the gold standard for assessment of mucosal inflammation, less invasive and less time-consuming modalities for assessing inflammation are valuable in day-to-day management.

Relapses are often difficult to predict. The goal of disease monitoring is to identify patients at risk for relapse in order to treat earlier, with the hope of maintaining remission and avoiding irreversible bowel damage such as fistulas and strictures that may lead to surgery.

The optimal method for monitoring disease activity in CD and UC is still being defined. Current modalities for assessing disease activity include colonoscopy, clinical assessment tools, serum biomarkers, fecal biomarkers, and imaging examinations such as CT enterography, small bowel follow-through, and MR enterography.

Many quantifiable laboratory assessments have been studied for evaluation of disease activity in IBD. Examples of commonly available serum lab assays include C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), leukocytes, platelets, ferritin, haptoglobin, ceruloplasmin, α-1-antitrypsin, plasminogen, complement factors, and fibrinogen[8]. More experimental serum assays that are not widely commercially available include orosomucoid (α-1-acid glycoprotein), interleukin 6 (IL-6), sialic acid, and serum amyloid A. Stool assays for detecting inflammation include fecal calprotectin (FC), lactoferrin, polymorphonuclear elastase, myeloperoxidase, metalloproteinase-9, and neopterin. MicroRNA species[9] and proteomic profiles[10], available only in research settings, have also been shown to differentiate active *vs* inactive IBD.

Of these diverse assays, CRP and FC are the most widely adopted in clinical practice for disease monitoring in IBD. This is a review of the current medical literature regarding the use of these two commonly utilized biomarkers for monitoring of disease to predict relapse in patients in clinical remission and in the postoperative setting.

**CRP**

C-reactive protein was first described in 1930 by Tillet and Francis[11]. Patients with pneumonia were noted to have serum that precipitated when brought in contact with bacterial “Fraction C” substance in the supernatant. This precipitant was no longer present in serum after the pneumonia resolved but was persistently present in lethal cases.

CRP is a pentameric, acute-phase protein made by hepatocytes[12]. The half-life of CRP is 19 hours, which allows for rapid rising and falling of levels with onset of and resolution of inflammatory states, respectively. Healthy individuals have low levels of CRP in circulation, usually less than 1 mg/L, but levels can rise 100-fold in periods of acute inflammation[13].

CRP is not a specific marker for intestinal inflammation. Measurements of CRP may be elevated for other reasons such as infection or extraintestinal inflammation. CRP has been studied outside of gastroenterology to predict disease outcomes after myocardial infarction and diagnosis of multiple myeloma[14,15]. In IBD, CRP has been significantly associated with other biomarkers of inflammation including ESR, thrombocytosis, anemia, and hypoalbuminemia[16]. As a biomarker, CRP is appealing because it is inexpensive, minimally invasive, and quick to result.

**CRP Correlation with Endoscopy**

CRP is often used to monitor for occult internal inflammation when patients are clinically asymptomatic. In general, CRP is more frequently elevated in active transmural CD than in mild to moderate mucosal inflammation associated with UC[17-20]. Though not always accurate or specific, clinical disease activity in adults and children with CD has been shown to correlate with CRP level[16,21,22]. However, 20%-25% of CD patients having flares do not exhibit increased CRP due to genetic single nucleotide polymorphisms in the CRP gene, which affects CRP production[23].

Several studies have reported good correlation between CRP levels and findings seen during endoscopy[16,24,25] (Table 1). Solem *et al*[16] reported a retrospective cohort of 104 CD patients. CRP was found to be normal in 75% of the CD patients with normal ileocolonoscopy. On the other hand, CRP elevations were significantly associated with active mucosal inflammation on colonoscopy (OR = 3.5, 95%CI: 1.4-8.9) defined as erosions, ulcerations, spontaneous bleeding, exudate, friability, granularity, cobblestoning, extensive erythema, inflammatory-appearing nodularity, and masses. CRP elevations (> 0.8 mg/dL) were significantly associated with moderate to severe clinical activity (OR = 4.5, 95%CI: 1.1-18.3) as defined by ACG clinical practice guidelines[26] (Table 2). Notably, in this study, there was no significant correlation between abnormal small bowel imaging and CRP elevation, suggesting that CRP could be normal in patients with isolated small bowel CD, but there was no subgroup analysis of isolated endoscopic ileitis in relation to CRP.

Henriksen *et al*[27] studied CRP levels according to disease subtype in 176 Crohn’s patients and 371 UC patients. For CD, there were no significant differences in CRP levels based on disease localization (ileitis, colitis, or ileocolitis), showing that isolated ileal disease also caused a rise in CRP. For both UC and CD, CRP responses increased based on extent of disease. However, the mean and median levels of CRP in UC were within the normal range for CRP (< 10 mg/L) for all disease subgroups, making CRP less informative in UC disease monitoring.

In a prospective study of 64 CD patients on anti-TNF therapy, endoscopic SES-CD activity score correlated better with CRP (*r =* 0.56, *p <* 0.001) than with clinical indices including the CD Activity Index (CDAI) (*r =* 0.40, *p <* 0.001) and the Harvey Bradshaw Index (HBI) (*r =* 0.32, *p <* 0.001)[25]. However, CRP was not reliable in predicting endoscopic remission; the CRP was falsely negative (< 3 mg/L) nearly twice as often as the SES-CD indicated endoscopic remission.

Mosli *et al*[29] completed a meta-analysis comprised of 19 studies (*n =* 2499 IBD patients) to characterize CRP correlation with endoscopic disease activity. For IBD, CRP levels had a pooled sensitivity and specificity of 49% and 92%, respectively. There were an insufficient number of studies to calculate separate CRP performance metrics for UC and CD. The authors suggested a CRP cutoff of greater than 5mg/dL to indicate active endoscopic disease.

**Prediction of relapse using CRP**

High CRP levels correlate with clinical relapse in both short-term and long-term follow up[30-33]. Various studies have reported an increased risk of relapse with the relative risk ranging from 3 to 58[31-33]. In severe UC flares, high CRP, combined with high stool frequency and low serum albumin, has been associated with higher likelihood of failure to respond to medical therapy[34,35].There is also a 6-times higher risk of hospitalization (OR = 6.82, 95%CI: 2.5-18.58; *p <* 0.0001) with elevated CRP in CD patients[36].

In analysis of the GETAID trial, 71 CD patients in medically-induced clinical remission had CRP, complete blood count, erythrocyte sedimentation rate (ESR), alpha-1 antritrypsin, and orosomucoid, checked every 6 wk[33]. Thirty-eight patients clinically relapsed, defined as a CDAI greater than 150 or increase of at least 100 points from baseline, after a median of 31 weeks. Only ESR greater than 15 mm and CRP greater than 20 mg/L predicted clinical relapse. Levels of CRP were noted to rise 4 to 6 mo prior to clinical relapse, suggesting that routine measurement of biomarkers every 3-4 mo could alert the clinician that an alteration in therapy may be necessary.

Achieving not only clinical remission but also mucosal healing may lead to higher rates of long-term response or remission. In post-hoc analysis for the ACCENT-1 trial, 137 CD patients in clinical remission had CRP levels measured after induction with infliximab. At week 14, 56.6% of patients with a CRP less than 0.5 mg/dL *vs* 37.2% of patients with a CRP greater than 0.5 mg/dL maintained response to infliximab through 54 wk (*p =* 0.005)[28].

Rapid normalization of CRP levels correlates with sustained long-term response to infliximab[37] and adalimumab[24]. Jurgens *et al*[37] evaluated 268 CD patients who had responded to infliximab induction. Of these patients, 197 patients (73.5%) had increased CRP levels at baseline. Ninety-two patients (46.7%) had CRP normalization (< 3 mg/L) at week 4, and another 29 (14.7%) had CRP normalization after 10 weeks. Kaplan-Meier curves indicated that CRP normalization after 4 weeks of therapy had long-term benefit (*p <* 0.001) out to 5 years with a PPV of 63%. Karmiris *et al*[38] reported similar findings for CD patients with baseline elevated CRP and normalization of CRP (< 3 mg/L) at both weeks 4 and 12 predicting less frequent discontinuation of adalimumab and longer sustained clinical benefit up to 2 years of follow up. Kiss *et al*[24] reported low CRP at week 12 (< 10 mg/L) as being a predictor of clinical remission at 52 wk (OR = 4.61, *p <* 0.001) during the first year of adalimumab therapy.

Conversely, CRP levels are frequently elevated in patients who lose response to biologics[37]. Elevated CRP may be a sign of low drug level and a harbinger of ensuing loss of response and clinical relapse. In Jurgens *et al*[37], 57 CD patients who were responders to induction with infliximab had CRP and infliximab levels evaluated at week 14. In 75% of the patients who had clinical response after induction, a decrease in infliximab levels preceded loss of response by week 54. In 60% to 80% of patients with elevated CRP greater than 5 mg/L, the infliximab level was less than 1 μg/mL. CRP has also been shown to correlate better with low infliximab levels (< 1 μg/mL) than with clinical assessment using CDAI[39].

Higher CRP levels are also associated with an increased risk of surgery. In a Norwegian study, UC patients with a CRP above 23 mg/L at diagnosis were 4.8 times more likely to have surgery in the future (95%CI: 1.5-15.1, *p =* 0.02). At 1 year, UC patients with a CRP level greater than 10 mg/L were 3 times more likely to require surgery in the next 4 years (95%CI: 1.1-7.8, *p =* 0.02)[27]. CD patients with terminal ileitis were 6 times more likely to need future surgery if CRP levels at diagnosis were above 53 mg/L (95%CI: 1.1-31.9, *p =* 0.03).

**Predicting Postoperative Recurrence With CRP**

Postoperative recurrence of CD is common. Up to 80% of CD patients will require surgery during their lifetime, and 70% of these patients will need a second surgery[40]. Predicting recurrence of CD after intestinal resection for strictures and fistulizing disease is difficult. Half of patients in clinical remission have ileocolonic ulcerations on endoscopic examination[41]. Treatment is tailored to the individual patient based on his or her risk of recurrence. The best biomarker for determining which postoperative CD patients are at highest risk of recurrence is not known. There are few studies dedicated solely to the evaluation of CRP and postoperative CD recurrence.

Previous studies report mixed results regarding the use of CRP for monitoring for postoperative recurrence in CD. Regueiro *et al*[42] reported a prospective cohort of 25 postoperative CD patients with CRP levels measured prior to surgery and then at 54 weeks postoperatively. At 54 weeks, there was no significant increase in CRP in patients who relapsed as compared to patients remaining in remission. CRP also did not correlate significantly with endoscopic scores in this study.

A smaller study has shown correlation between CRP and postoperative recurrence[43]. In 12 postoperative CD patients on infliximab without endoscopic or clinical recurrence after 3 years, infliximab was stopped; ten of 12 patients had endoscopic recurrence after 16 weeks (Rutgeerts score > i2). After cessation of infliximab, CRP increased significantly in all patients compared to baseline (12.5 ± 4 *vs* 3.0 ± 1.4 mg/L; *p <* 0.001)[43]. Once infliximab was resumed in a dose-dependent fashion (1 to 3mg/kg), the CRP significantly decreased (*p <* 0.0001). In this study, CRP significantly correlated with postoperative endoscopic recurrence, but again, the main limitation of this study is the small sample size. A recent study of 86 CD patients who underwent ileocolonic resection found a weak but significant difference in high sensitivity CRP (hsCRP) concentrations between patients in endoscopic remissions and patients with recurrence (3.0 ± 0.7 *vs* 8.5 ± 1.4 mg/L; *p =* 0.0014)[44].

In summary, an elevated CRP has been shown to positively correlate with endoscopic disease activity and may predict ensuing relapse while a patient is in clinical remission. Therefore, a persistently elevated CRP in both CD and UC should prompt further investigation with further blood work, stool studies for infection, and endoscopic evaluation to evaluate for active disease. On the other hand, normal CRP levels in UC patients should be interpreted with caution as endoscopic disease may still be present. For predicting postoperative recurrence of CD, there is not strong data supporting the use of CRP or hsCRP.

***FC***

First described in 1980, calprotectin is a 36 kilodalton inflammatory protein found in the cytosol of human neutrophils, macrophages, and monocytes[45,46]. Calprotectin comprises up to 60% of neutrophil cystolic proteins. The presence of calprotectin in the feces is directly proportional to neutrophil migration into the gastrointestinal tract during times of inflammation[12].

FC is a stable marker, resistant to degradation, that can be detected in stool for more than one week at room temperature[47]. Two FC assays are currently available: ELISA and a quantitative point-of-care-test (FC-QPOCT)[48]. Fecal lactoferrin, another stool neutrophil protein, is frequently paired with FC in clinical studies and generally has similar to slightly lower sensitivity and specificity when compared to FC[49-52].

Many gastrointestinal conditions can lead to elevations in FC concentrations including IBD, pouchitis, diverticulitis, malignancy, infections, nonsteroidal anti-inflammatory drug (NSAID) enteropathy, celiac disease, and microscopic colitis[53-55]. Though calprotectin is nonspecific and may be elevated in other gastrointestinal conditions, there is a substantial body of evidence supporting the use of FC in management of IBD.

Calprotectin levels have been reported to have low day-to-day variability in CD. Naismith *et al*[56] measured three consecutive days of FC levels in 98 patients with CD in clinical remission. An intraclass correlation (ICC) of 0.84 (95%CI: 0.79-0.89), low variability across patient samples, was reported. On the other hand, FC levels in UC patients have been shown to have high within-day variability[57]. Sampling the first bowel movement of the morning has been suggested to avoid falsely low measurements[58].

To further complicate matters, variations exist in FC levels depending on age. FC levels have been shown positively correlate with age in 320 normal adult subjects, ages 50 to 70[59]. Likewise, normal volunteers 60 years or older had higher FC levels than patients aged 10 to 59[60]. However, infants[61] and children less than 10 years old[60] have higher FC levels than adults.

**FC Correlation with Endoscopy**

FC has been used to monitor patients during periods of quiescent disease. There is poor correlation between clinical assessment tools such as the CDAI with endoscopic inflammation in CD patients[3,49,62].

UC patients in clinical remission tend to have FC levels that positively correlate with endoscopic inflammation[63-66]. A study by Schoepfer *et al*[65] reported better correlation of endoscopic activity with FC than with other markers of inflammation including CRP, platelets, and serum leukocytes. In a recent study by Takashima *et al*[67], there was significant correlation of Mayo endoscopic scores with FC (*r =* 0.58; *p <* 0.0001) in 92 patients with UC.

In the meta-analysis by Mosli *et al*[29], FC predicted endoscopic activity with overall higher sensitivity than CRP, as expected. The pooled sensitivity and specificity of FC for endoscopically active IBD was 88% and 73%, respectively. When UC and CD were considered separately, UC exhibited equivalent sensitivity (88% *vs* 87%, respectively) but superior specificity (73% *vs* 67%) when compared to CD. An optimal FC cutoff of greater than 50 μg/g was calculated to signify endoscopically active disease. Stool lactoferrin had similar sensitivity and specificity (82% and 79%, respectively). A lactoferrin cutoff of greater than 7.25 μg/mL was calculated for endoscopically active disease.

In CD, clinical remission does not consistently correlate with FC levels[68,69]. Detecting subclinical inflammation is a high priority in CD to prevent long-term complications such as fibrostenotic strictures and perianal fistulae. However, endoscopic scores have been shown to correlate with FC levels in adults[25,49,62,64,70,71] and children[72,73] (Tables 3 and 4). In a group of 87 CD patients, D’haens *et al*[64] showed a significant correlation in adults between FC and CDEIS scores (*r =* 0.419, *p <* 0.001) and SES-CD (*r =* 0.49, *p <* 0.001) scores. Using receiver operating characteristic (ROC) curves, a cutoff of less than 250 μg/g correlated with endoscopic remission (CDEIS < 3) with high sensitivity (94.1%), moderate specificity (62.2%), and high negative predictive value (96.6%). Roseth *et al*[70] found that 44 out of 45 patients with a FC level < 50 mg/L had completely normal ileocolonoscopies. Moreover, by evaluating 18 of the stool samples from these same patients during previously active disease, the median FC level had been elevated to 3000 mg/L (*p <* 0.0001).

Isolated ileal CD impacts FC correlation with endoscopic scores. In a series of 87 consecutive ileocolonoscopies, there was a significant correlation with FC and ileocolonic or colonic disease (*p <* 0.001)[49]. However, in isolated ileal CD, FC did not correlate with endoscopic SES-CD scores (*p =* 0.161) but did correlate with histology (*p <* 0.001). In a slightly larger study of 115 ileocolonoscopies, endoscopic findings exhibited excellent correlation with FC in ileocolonic disease (*r =* 0.879; *p <* 0.001) but only moderate correlation in ileal disease (*r =* 0.437; *p =* .016)[74]. Sipponen *et al*[75] found low sensitivity (59%) and moderate specificity (71%) when using FC to predict inflammatory small bowel lesions on subsequent capsule endoscopy.

In a more recent study of 44 patients with CD, 9 patients with isolated ileal disease had significantly lower FC levels when compared to patients with ileocolonic disease (297 ± 81 μg/g *vs* 1523 ± 97 μg/g, *p <* 0.0001)[76]. However, even though the levels of FC were significantly lower in isolated ileal disease, the FC levels were still elevated. Despite lower FC levels in patients with isolated ileal disease, there was still good overall correlation with SES-CD endoscopic scores (*r =* 0.76, *p <* 0.0001). Separate analysis of SES-CD correlation with FC levels in isolated ileal disease was not reported.

Schoepfer *et al*[77] described good correlation between FC levels and SES-CD for isolated ileal disease (*r =* 0.649, *p <* 0.001), but again, correlation between FC levels and SES-CD for ileocolonic disease was better (*r =* 0.795, *p <* 0.001).

In a study of children with CD, levels of FC were similar between isolated ileal disease and ileocolonic disease. In 60 newly diagnosed children with untreated CD, the median level of FC did not differ between children with isolated small bowel disease (47 patients) (2198 μg/g) and children with colonic involvement (2400 μg/g)[78].

**Prediction of Relapse Using FC**

Despite continuous treatment, the majority of IBD patients will relapse. Evaluating which asymptomatic patients have smoldering subclinical inflammation is key to preventing further intestinal damage. Anticipating and altering treatment proactively helps prevent long-term complications. Approximately 35% of CD patients develop at least one fistula during the course of disease, and fistulas recur in one-third of patients[79]. Twenty-five percent of CD patients will have at least one small bowel stricture[80].

FC has been shown to correlate with histologic inflammation and to successfully predict relapses[81]. In a single-center, prospective study, 92 Crohn’s patients in clinical remission (CDAI < 150) were observed for 12 mo. Ten patients (11%) relapsed by the end of one year. Median levels of FC were higher for relapsers than nonrelapsers (414 μg/g *vs* 96 μg/g, respectively; *p <* 0.005)[82]. In this study, Naismith *et al*[82] calculated that a FC greater than 240 μg/g was associated with a 12 times increased risk of relapse (Table 5). A meta-analysis of 6 studies with a total of 672 IBD patients (318 UC and 354 CD) reported a composite sensitivity of 78% (95%CI: 72-83%) and specificity of 73% (95%CI: 68%-77%) for predicting relapse using FC[83]. However, this meta-analysis did not report an optimal cutoff value for predicting relapse nor did the authors include CD patients with isolated ileal disease. Several studies have calculated optimal FC cutoffs to predict presence of endoscopic disease (Table 6).

Elevated FC levels have been reported to be present up to three months prior to clinical presentation of a UC flare[84,85]. De Vos *et al*[84] used FC levels to prospectively follow 87 patients with UC on maintenance infliximab therapy. FC levels were collected every 4 wk. Of these patients, 30 (34.4%) sustained deep remission (partial Mayo score < 3 and endoscopic Mayo score of 0 at one year) while 13 (14.9%) relapsed (Mayo score ≥ 2 or need for change in treatment) during one year follow-up. Those patients in deep remission maintained very low FC levels (< 40 mg/kg) with each sample analysis. Patients who flared exhibited elevated FC levels (> 300 mg/kg) beginning 3 mo prior to relapse. Interestingly, two consecutive FC levels greater than 300mg/kg could predict relapse with a sensitivity of 61.5% and specificity of 100%.

Molander *et al*[85] monitored patients in endoscopic remission after infliximab cessation. Over one year of follow up after infliximab cessation, 15 UC patients (31%) and 34 CD patients (69%) relapsed. The patients who relapsed were found to have consistently elevated FC levels for a median of 94 d prior to relapse. There was a significant increase in FC levels at 2, 4, and 6 mo before endoscopic relapse (*p =* .0014, .0056, .0029, respectively). This suggests that the trend, rather than an isolated measurement, may be more valuable in predicting relapses.

Lasson *et al*[86] conducted a prospective, randomized, controlled study focused on altering therapy based on FC levels. They collected monthly FC levels in 91 UC patients with mild to moderate UC. If the FC value was higher than 300 μg/g on two consecutive measurements within one week, the dose of 5-aminosalicylates (5-ASAs) was escalated to try to prevent relapse. Of the patients with FC greater than 300 μg/g, the patients who had dose escalation of 5-ASAs had significantly reduced relapse rates as compared to patients in the control group (*p <* 0.05). In 18 of 28 patients (64.3%) in the dose escalation arm, their FC values dropped to less than 200 μg/g.

Calprotectin has been used to predict response to anti-TNF treatment during short-term follow-up periods. Several studies reported a significant correlation between decreases in FC and short-term endoscopic remission[50,87,88]. In one Dutch study of 53 patients with UC, patients in endoscopic remission at week 10 after infliximab induction had a steep decrease in week 2 FC levels as compared to pretreatment levels. At week 10, there was an excellent AUC for endoscopic remission and FC (AUC 0.91; 95%CI: 0.81-1.0)[87].

FC has also been used to predict long-term response to anti-TNFs. Molander *et al* defined a cutoff of FC greater than 139 μg/g after completion of induction therapy to predict a risk of clinically active disease after 1 year for patients with IBD treated with either infliximab (*n =* 42) or adalimumab (*n =* 18). In pediatric IBD patients, long-term response (1.1 years median follow-up) after infliximab induction therapy was retrospectively linked to FC response between weeks 2 and 6[89]. Children who stopped therapy within the first year due to inadequate effect had higher median FC levels during induction than patients who responded (633 μg/g *vs* 219 μg/g; *p <* 0.025).

In children, the utility of FC varies greatly based on report. Sipponen *et al*[90] followed 72 children with IBD. The median age was 13. Twenty-five (35%) children clinically relapsed within the subsequent year with poor predictive value of FC for relapse (39.6% for FC > 100 μg/g; 42.9% for FC > 1000 μg/g). However, a systematic review of 34 pediatric studies determined that FC can be a marker of active inflammation with high sensitivity (range 94.4%-100%) and moderate specificity (71.9%-100%)[91]. As with adult studies, the cutoff range for detecting active IBD was large (50-275 μg/g).

**Predicting Postoperative Recurrence Using** FC

Multiple studies have looked at FC for monitoring for postoperative recurrence of disease in CD with mixed results[44,52,74,92-96]. FC levels correlate with clinical indices such as the HBI[52] but not with the CDAI[51]. Several studies have reported that FC correlates with disease relapse both clinically[52] and endoscopically[44,51,74,95,96]. Papamichael *et al*[96] followed a group of 59 CD patients after ileocecal resection. Persistently elevated FC levels (> 60 μg/g) were found in 100% (15/59) of patients who had postoperative endoscopic recurrence (Rutgeerts score ≥ i2) after ileocecal resection whereas CRP elevations (> 0.5mg/dl) were present in only half of the patients (*p =* .017).

Various cutoffs have been suggested to predict postoperative recurrence of disease (Table 7). Boschetti *et al*[44] reported a cutoff of 100 μg/g (sensitivity 95%, specificity 54%) to correlate with endoscopic recurrence (Rutgeerts score ≥ i2) in 86 asymptomatic CD patients after ileocolonic resection. When evaluating correlation with Rutgeerts scores, FC performed better (*r =* 0.65, *p <* 0.001) than hsCRP (*r =* 0.34, *p =* 0.0016). This study excluded patients with perianal disease. Stool samples were collected one week prior to endoscopic evaluation.

Yamamoto *et al*[92] collected stool samples from 20 asymptomatic postoperative CD patients at the beginning of the study then followed them for 1 year. The mean duration from surgery to endoscopic evaluation was 7.2 mo. A calculated FC cutoff of 140 μg/g predicted endoscopic recurrence whereas a cutoff of 170 μg/g predicted future clinical recurrence.

On the other hand, several studies reported that calprotectin was not consistent in predicting recurrence after surgery. Scarpa *et al*[94] retrospectively studied 63 CD patient FC levels for a median of 40.5 mo after surgery. There was no significant difference in FC levels between patients who remained in clinical or endoscopic remission and patients who had a recurrence of disease. The authors cited the limited correlation of the CDAI with inflammation and the lag in time between stool sample collection and endoscopy as possible explanations for lack of significance. However, there was a significant difference in FC levels between patients who required further ileocolonic resection and patients who did not need more surgery (*p =* 0.04), but this result is limited by small sample size (5 patients required further surgery). Lasson *et al*[97] reported a nonsignificant trend towards lower FC levels in patients in remission and higher FC levels in patients with endoscopic recurrence at one year postoperatively (*p =* 0.25). The small sample size of 30 patients and follow-up time were limitations to the study; one patient from the remission group ended up having a flare 6 mo after the study ended.

In a more recent prospective, randomized control trial in Australia and New Zealand, CD patients who underwent intestinal resection were followed up to 18 mo postoperatively. The median FC level decreased from 1347 μg/g prior to surgery to 166 μg/g at 6 mo postoperatively. Patients with endoscopic disease recurrence had higher median FC levels than patients who maintained remission (275 μg/g *vs* 72 μg/g, respectively; *p <* 0.001)[95]. Of note, CRP levels and clinical CDAI scores did not correlate with CD recurrence or severity of disease. A cutoff FC level of greater than 100 μg/g indicated endoscopic recurrence with a sensitivity of 89%, specificity of 58%, and negative predictive value of 91%. The high NPV of 91% suggests that endoscopy may be able to be avoided or deferred in patients with FC measurements less than 100 μg/g.

Overall, FC is a useful biomarker that is more specific for intestinal inflammation than CRP. FC correlates better with ileocolonic disease than with isolated ileal disease. FC is useful in predicting clinical and endoscopic relapse while in clinical remission, as well as monitoring response to medical therapy. Evidence suggests that monitoring for postoperative recurrence is more reliable with FC than CRP.

**New Applications: Fecal Immunochemical Test**

Fecal immunochemical test (FIT) is an alternative modality being considered for use in IBD, much less utilized than FC or CRP. Quantitative FIT testing measures stool hemoglobin concentrations using an antibody specific for human hemoglobin[98]. FIT has mainly been publicized as a method for screening for colonic neoplasia[99]. As shown in a capsule endoscopy study, positive FIT tests can be explained by isolated small bowel lesions without colonic pathology[100].

Specifically relating to IBD, FIT has been used to predict mucosal healing in patients with UC with a 92% sensitivity and 71% specificity[98]. In a recent prospective trial from Japan, FIT was compared with FC to evaluate for mucosal healing in 92 patients with UC[67]. Of the 105 colonoscopies done, 77 (73%) were in patients in clinical remission. However, only 42% of colonoscopies demonstrated complete mucosal healing (Mayo score 0). Both the FIT and FC levels significantly correlated with the Mayo score. There was also significant correlation between the FIT values and FC levels (Spearman's correlation coefficient 0.64, *p <* 0.0001). The sensitivity and specificity of FIT for predicting mucosal healing was 95% and 62%, respectively, for a fecal hemoglobin concentration less than 100 ng/ml. Comparatively, for a FC cutoff less than 250 μg/g, there was lower sensitivity at 82% and equivalent specificity at 62% for predicting mucosal healing.

FIT is currently less expensive than FC. There may be a future role for FIT in disease monitoring in IBD, but more trials are needed.

**CONCLUSION**

Our goals of treating IBD patients have evolved over the past few years to include mucosal healing in addition to clinical remission. Ideally, by monitoring disease activity via noninvasive blood or stool markers, we may be able to identify patients with subclinical disease activity and thereby optimize treatment prior to a clinical flare.

Furthermore, the practice of medicine is changing in the face of healthcare spending reforms. Cost cannot be overlooked. In the future, procedures such as colonoscopy may not always be cost-effective or time-efficient. Consistently reliable, noninvasive assays to evaluate subclinical disease activity will be valuable for determining which endoscopic evaluations may be deferred.

CRP and FC have emerged as two of the most commonly used biomarkers to evaluate for subclinical disease activity in IBD. There are pros and cons to keep in mind when ordering each biomarker.

CRP is low-cost, easy to obtain with simple bloodwork, and quick to deliver data. CRP has been reported to have modest correlation with endoscopic and clinical findings, generally better with CD than UC. The major downsides to CRP are its lack of specificity for intestinal inflammation and moderate false negative rate. Genetic variations in CRP likely contribute to its overall lower sensitivity[23].

CRP does not reliably predict postoperative recurrence in CD. Just as postulated in active UC with normal CRP, early inflammation in postoperative recurrence may not be detectable using CRP due to lack of transmural inflammation. Existing data suggests that FC is a more sensitive measure of recurrent intestinal inflammation in postoperative CD patients.

FC is more expensive but is a more specific marker of intestinal inflammation. FC tends to correlate better with endoscopic findings in IBD than CRP, except in cases of isolated small bowel CD where FC levels are lower. CRP still plays a role in evaluation of isolated small bowel disease.

When considering the utility of FC in predicting endoscopic relapse in IBD and postoperative recurrence in CD, a noteworthy limiting factor for real-world use is the wide variation in defined cutoffs for inactive *vs* active disease (Tables 4-6). Generally, very high levels of FC indicate active disease, and FC levels less than 50 μg/g indicate inactive disease. However, many clinicians may find themselves questioning the significance of moderately elevated or upper limit of normal FC values.

The type of assay used (ELISA *vs* FC-QPOCT) may contribute to the wide range of cutoffs reported. Moreover, variations in calprotectin extraction methods can result in different FC quantitations from the same stool sample. During a quality assurance study, Whitehead *et al*[101] reported an average of 7.8% to 28.1% under-recovery of FC with different ELISA assays.

Heterogeneity in study design also may be a factor affecting FC cutoff levels. The definition of endoscopically inactive disease varies among studies. Also, time points for stool collection vary widely among studies. For example, one study may collect a stool sample on the day prior to colonoscopy[74] whereas another study may collect stool at an unspecified time point prior to clinical flare[102]. In the postoperative studies, there is variation in clinical status (remission *vs* symptomatic), disease phenotypes included, timing of postoperative endoscopic evaluation, as well as length of study follow up.

Perhaps a “one size fits all” approach does not pertain to calprotectin cutoffs in IBD. Optimal cutoffs may differ by disease (UC, CD), distribution of inflammation, age of patient, brand of assay used. For example, given that FC levels have been shown to be lower in isolated ileal disease, lower cutoff values may be needed for ileal CD without colitis. Also, in adults, the increase in FC with age may also need to be taken into account. Future investigations are needed to further define these cutoffs.

In our practice, we use both CRP and FC to monitor patients in clinical remission. FC is preferred but not always sent due to cost and lack of coverage by certain insurance carriers. If FC is less than 50 ug/g, we do not routinely further evaluate the patient, whereas if the FC is greater than 250 ug/g, we rule out infection with stool studies and then consider an endoscopic evaluation. If the FC level is between 50 and 250 ug/g, we like to complete a colonoscopy at that time to correlate levels with endoscopic appearance. Still, in most cases, since levels vary from person to person, we find it most helpful to make treatment decisions based on a combination of FC, CRP, and endoscopic findings.

In the postoperative setting, we do not use CRP because of the lack of efficacy. We send FC levels at month 3. If elevated, we evaluate with colonoscopy. If normal, a colonoscopy is performed between 6 and 12 mo after resection.

Due to the nature of clinical research, most clinical studies focus on short-term patient responses to treatments. Less is known about long-term results of chronic biologic and immunomodulators therapies. The ultimate goal of therapy in IBD patients is to minimize the long-term sequelae of chronic inflammation while avoiding exposing the patient to unnecessary risks such as infection and neoplasia[103]. In 2009, the STORI trial evaluated stopping infliximab in patients on combination therapy who had been in steroid-free clinical remission for at least 6 mo[104]. Other studies have evaluated stopping immunomodulators while patients are maintained solely on infliximab[105]. The optimal duration of these drug holidays is unknown. With future trials underway evaluating the safety and logistics of withdrawing therapy, the role of monitoring clinically silent disease will be key in differentiating those patients who will remain quiescent and those who should re-escalate therapy.

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**Table 1 Endoscopic score correlation with C-reactive protein**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ref.** | **Disease** | **Endoscopic tool** | **Correlation** | ***p*-value** |
| Sipponen *et al*[88] | CD | CDEIS | *r =* 0.608 | < 0.001 |
| Schoepfer *et al*[77] | CD | CDEIS | *r =* 0.75 | < 0.01 |
| Af Bjorkesten *et al*[25] | CD | SES-CD | *r =* 0.56 | < 0.001 |
| Lobaton *et al*[48] | UC | Mayo | *r =* 0.307 | < 0.001 |

CDEIS: Crohn’s disease endoscopic index of severity; SES-CD: simple endoscopic score for Crohn’s disease; r: Spearman’s rank correlation coefficient.

**Table 2 C-reactive protein values and correlating endoscopic scores**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ref.** | **Disease** | **Endoscopic tool** | **Endoscopic score (descriptor)** | **Calculation** | **CRP scores** |
| Falvey *et al*[71] | CD | SES-CD | 0-2 (inactive)  3-6 (mild)  7-15 (moderate)  > 16 (severe) | Mean (95%CI) | 2.9 mg/L (1.8-4.6)  4.0 mg/L (2.6-6.1)  5.1 mg/L (3.0-9.0)  22 mg/L (12.5-38.9) |
| Sipponen *et al*[88] | CD | CDEIS | < 3 (inactive)  3-9 (mild)  9-12 (moderate)  ≥ 12 (severe) | Median (95%CI) | 0.0 mg/L (0-21)  0.0 mg/L (0-26)  8.5 mg/L (0-85)  16.5 mg/L (0-211) |
| Schoepfer *et al*[77] | CD | SES-CD | 0-3 (inactive)  4-10 (mild)  11-19 (moderate)  ≥ 20 (high) | Mean (Range) | 12 mg/L (3-94)  8 mg/L (3-53)  23 mg/L (3-172)  40 mg/L (5-121) |

CDEIS: Crohn’s disease endoscopic index of severity; SES-CD: simple endoscopic score for Crohn’s disease.

**Table 3 Endoscopic score correlation with fecal calprotectin**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ref.** | **Disease** | **Endoscopic tool** | **Correlation** | ***p*-value** |
| Af Bjorkesten *et al*[25] | CD | SES-CD | *r =* 0.56 | < 0.001 |
| Sipponen *et al*[88] | CD | CDEIS | *r =* 0.831 | < 0.001 |
| Sipponen *et al*[49] | CD | SES-CD | *r =* 0.642 | < 0.001 |
| Sipponen *et al*[62] | CD | CDEIS | *r =* 0.729 | < 0.001 |
| Schoepfer *et al*[77] | CD | SES-CD | *r =* 0.53 | < 0.01 |
| Lobaton *et al*[74] | CD | CDEIS | *r =* 0.7221  *r =* 0.7692 | < 0.001  < 0.001 |
| Lobaton *et al*[48] | UC | Mayo | *r =* 0.7411  *r =* 0.7272 | < 0.001  < 0.001 |
| Takashima *et al*[67] | UC | Mayo | *r =* 0.58 | < 0.0001 |
| Roseth *et al*[66] | UC | Mayo | *r =* 0.57 | < 0.0001 |
| D’haens *et al*[64] | UC  CD  CD | Mayo  CDEIS  SES-CD | *r =* 0.623  *r =* 0.419  *r =* .490 | < 0.001  < 0.001  < 0.001 |

1FC-ELISA; 2FC Q-POCT (quantitative-point-of-care test). CDEIS: Crohn’s disease endoscopic index of severity; SES-CD: simple endoscopic score for Crohn’s disease; r: Spearman’s rank correlation coefficient.

**Table 4 Fecal calprotectin values and correlating endoscopic scores**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ref.** | **Disease** | **Endoscopic Tool** | **Endoscopic Score (descriptor)** | **Calculation** | **Calprotectin scores** |
| Falvey *et al*[71] | CD | SES-CD | 0-2 (inactive)  3-6 (mild)  7-15 (moderate)  16+ (severe) | Mean (95%CI:) | 55 μg/g (25-123)  167 μg/g (97-288)  366 μg/g (192-698)  732 μg/g (338-1587) |
| Sipponen *et al*[49] | CD | SES-CD | ≤ 3 (inactive-mild)  > 3 ( | Median (range) | 37 μg/g (13-166)  686 μg/g (18-15326) |
| Sipponen *et al*[62] | CD | CDEIS | < 3 (inactive)  3-9 (mild)  9-12 (moderate)  > 12 (severe) | Median (range) | 63 μg/g (11-869)  170 μg/g (17-2440)  1014 μg/g (123-2284)  2066 μg/g (323-18575) |
| Schoepfer *et al*[77] | CD | SES-CD | 0-3 (inactive)  4-10 (mild)  11-19 (moderate)  ≥ 20 (high) | Mean (range) | 104 μg/g (10-725)  231 μg/g (12-1009)  395 μg/g (68-912)  718 μg/g (93-1327) |
| Lobaton *et al*[48] | CD | CDEIS | < 3 (endoscopic remission)  ≥ 3 (endoscopic activity) | Median (range) | 101.8 μg/g (30-1620.9)  1211.9 μg/g (122-1800) |

CDEIS: Crohn’s disease endoscopic index of severity; SES-CD: simple endoscopic score for Crohn’s disease.

**Table 5 Calprotectin cutoffs for predicting clinical relapse**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ref.** | **Disease** | **FC value** | **Relative Risk** | **Sensitivity (%)** | **Specificity (%)** |
| Garcia-Sanchez *et al*[106] | UC  CD | > 120 μg/g  > 200 μg/g | 6  4 | 80 | 60 |
| Tibble *et al*[107] | UC/CD | > 50 μg/g | 13 | 90 | 83 |
| Kallel *et al*[108] | CD | > 340 μg/g | 18 | 80 | 90.7 |
| Naismith *et al*[82] | CD | ≥ 240 μg/g | 12.18 | 80 | 74.4 |
| Costa *et al*[109] | UC  CD | > 150 μg/g  > 150 μg/g | 14  2 | 89  87 | 92  43 |
| D’inca *et al*[102] | UC/CD | > 130 mg/kg | - | 68 | 67 |

FC: fecal calprotectin.

**Table 6 Calculated fecal calprotectin cutoffs based on endoscopic score**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Disease** | **Endoscopic Tool** | **Score** | **FC cutoff** | **Sensitivity**  **(%)** | **Specificity**  **(%)** | **PPV**  **(%)** | **NPV**  **(%)** |
| Guidi *et al*[110] | UC/  CD | CDEIS | < 3 (mucosal healing) | 121 μg/gq | 79 | 57 | - | - |
| D’haens *et al*[64] | CD  UC | CDEIS  Mayo | < 3 (inactive)  1-3 (any inflammation) | 250 μg/g  250 μg/g | 94.1  71 | 62.2  100 | 48.5  100 | 96.6  47.1 |
| Sipponen *et al*[88] | CD | CDEIS | ≥ 3 (active) | 200 μg/g | 87 | 100 | 100 | 70 |
| Af Bjorkesten *et al*[25] | CD | SES-CD | 0 (inactive) | 94 μg/g | 82 | 78 | - | - |
| Lobaton *et al*[48] | UC | Mayo | 0-1 (inactive-mild)1  0-1 (inactive-mild)2 | 250 μg/g1,b  280 μg/g2,b | 73.5  75.4 | 89.7  89.1 | 86.2  86 | 79.5  80.3 |
| Takashima *et al*[67] | UC | Mayo | 0 (inactive) | 250 μg/g | 82 | 62 | 61 | 83 |

1FC-ELISA; 2FC-POCT; a*p* = 0.038; b*p <* 0.001 *vs* control. CDEIS: Crohn’s disease endoscopic index of severity; SES-CD: simple endoscopic score for Crohn’s disease; FC: fecal calprotectin.

**Table 7 Predicting postoperative recurrence with fecal calprotectin**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Type of recurrence** | **Follow-up time** | **FC value** | **Sensitivity (%)** | **Specificity (%)** | **PPV (%)** | **NPV (%)** |
| Lasson *et al*[97] | Endoscopic | 1 yr | 100 μg/g  200 μg/g  250 μg/g | 85  54  46 | 35  53  53 | 50  47  43 | 75  60  56 |
| Wright *et al*[95] | Endoscopic | 6 mo  18 mo | 135 μg/g  127 μg/g | 91  88 | 62  67 | 55  58 | 93  91 |
| Orlando *et al*[93] | Endoscopic | 1 yr | 200 mg/L | 63 | 75 |  |  |
| Yamamoto *et al*[51] | Endoscopic  Clinical | 1 yr | 140 μg/g  170 μg/g | 70  83 | 70  93 | 70  83 | 70  93 |
| Lobaton *et al*[74] | Endoscopic | Not specified | 203 μg/g1  283 μg/g2 | 75  67 | 72  72 | - | - |
| Boschetti *et al*[44] | Endoscopic | Within 18 mo | 100 μg/g | 95 | 54 | 93 | 77 |

1FC-ELISA test; 2FC Q-POCT (quantitative-point-of-care test). FC: fecal calprotectin.