OBJECTIVE ARTICLE

Clinicians’ guide to the use of fecal calprotectin to identify and monitor disease activity in inflammatory bowel disease

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BACKGROUND: Objective monitoring of the severity of inflammation in patients with inflammatory bowel disease (IBD) is an essential part of disease management. However, repeat endoscopy to define extent and severity of inflammation is not practical. Fecal calprotectin (FC) is a biomarker that can be used as a surrogate test to distinguish inflammatory from non-inflammatory gastrointestinal disease.

METHODS: A targeted search of the literature regarding FC, focusing primarily on the past three years, was conducted to develop practical clinical guidance on the current utility of FC in the routine management of IBD patients.

RESULTS: It is recommended that samples for FC testing be obtained from the first bowel excretion of the day. FC testing should be used as standard of care to accurately confirm inflammation and ‘real-time’ disease activity when a clinician suspects an IBD flare. Although FC is a standard of care to accurately confirm inflammation and ‘real-time’ disease activity, it is more practical and feasible than endoscopy to define extent and severity of inflammation. Fecal calprotectin is known to peak within the first 24 hours following a bowel movement. FC testing should be used as a tool to monitor disease activity in patients with IBD.

CONCLUSION: FC is a useful biomarker to accurately assess the degree of inflammation and should be incorporated into the management of patients with IBD.

Key Words: Disease activity; Fecal calprotectin; Inflammatory bowel disease; Monitoring

It is stable in feces for up to one week at room temperature. Thus, FC may provide an accurate assessment of the inflammatory burden in the gut.

An ideal biomarker would effectively and accurately distinguish inflammatory from non-inflammatory disease, correlate with endoscopic inflammation, demonstrate response to therapy and predict relapse (1,3-7). In addition, the biomarker test would be readily available, easy to use and affordable. FC meets many of these criteria, is available throughout Canada and has the potential to significantly enhance IBD care. However, although changes in FC demonstrate good sensitivity and specificity in IBD patients, clinicians should be aware that elevated FC levels may be found in several non-IBD conditions (Table 1) (1,3).

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TABLE 1
Factors and conditions associated with elevated fecal calprotectin levels (1,3)

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Inflammatory conditions</th>
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<tbody>
<tr>
<td>Bacterial dysentery</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Giardia lamblia</td>
<td>Autoimmune enteropathy</td>
</tr>
<tr>
<td>Helicobacter pylori gastritis</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Infectious diarrhea</td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Viral gastroenteritis</td>
<td>Diverticulitis</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Neoplasms</th>
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<tbody>
<tr>
<td>Colonic and gastric polyps</td>
</tr>
<tr>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>Gastric carcinoma</td>
</tr>
<tr>
<td>Intestinal lymphoma</td>
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Drugs Other
- NSAIDs Age <5 years
- PPIs Untreated food allergy

NSAIDs Nonsteroidal anti-inflammatory drugs; PPIs Proton pump inhibitors

Blood-based biomarkers, such as C-reactive protein (CRP) are often more acceptable, but they have limited sensitivity, with at least 50% of patients with active ulcerative colitis (UC) having normal CRP levels (8). CRP also has limited specificity, particularly in patients with infections, or rheumatoid or other autoimmune disorders (1). While CRP may be useful in some IBD patients, elevated FC levels demonstrate a significantly superior correlation with active disease compared with CRP measurements (8-13).

The present user’s guide will outline the pragmatic elements a clinician should be aware of relating to the use of FC in practice.

When should samples be collected for FC testing?
FC levels decrease with increasing time between bowel movements; therefore, it is recommended that samples be obtained from the first bowel movement of the day (14). Because of the day-to-day variability in FC levels (14), retrieving samples at similar times over two consecutive days is preferable.

What test should be used?
The standard test to assess FC levels in IBD patients is the ELISA. This method has been used for >20 years, but is time consuming, labour intensive and requires specialized laboratory equipment (7,15). The Bühlmann Quantum Blue Reader (Alpco Immunoassays, USA) device offers an alternative method to the standard ELISA technique. It demonstrates an excellent correlation with standard ELISA assays and provides accurate results within 30 min (7). The ELISA method is cost-efficient for high throughput when running multiple samples simultaneously.

FC testing is available in all provinces in Canada, with the majority of tests being performed using ELISA. However, provincial funding is currently available only in Alberta and Quebec, while in other provinces, the cost must be covered by the patient or a third party.

Should FC levels be measured in asymptomatic IBD patients?
Although FC is a reliable marker of inflammation, the role of routine monitoring of FC levels in clinically asymptomatic patients has not been fully assessed. It is not yet known whether a strategy of routine monitoring coupled with early optimization of therapy on detection of relapse would improve health outcomes (16,17). Nevertheless, this may be a clinically useful approach and warrants further investigation.

When should FC levels be measured, as the standard of care, to monitor IBD patients?
In the context of a suspected flare, assessing FC levels enables accurate and expedient confirmation of inflammation and ‘real-time’ disease activity. Several recent trials and meta-analyses have established that FC is an accurate surrogate marker of active endoscopic disease in IBD patients, with high sensitivity (70% to 100%) and specificity (44% to 100%) (8,13,18-21). In general, FC levels are highest among patients with active disease, less so in patients with quiescent disease and lowest in non-IBD control subjects (21).

What are the potential future applications of FC in IBD care?
Routine use of FC levels to monitor risk for flare in quiescent IBD, response to treatment or postoperative recurrence is not currently recommended, although these indications do warrant further investigation.

Studies suggest that in patients with quiescent disease, serial FC measurements showing increasing levels may be useful to actively monitor the risk for flare (8,17,22-23). In one study involving 53 consecutive IBD patients who were followed for 12 months (9), elevated FC levels (>340 µg/g) indicated an 18-fold higher risk for relapse (Figure 1). Conversely, reductions in FC levels have been associated with better response to treatment in IBD patients (24-27).

As a biomarker of inflammation, FC has been shown to be responsive to treatment intensification. A randomized trial involving patients with quiescent UC found that FC levels were lowered by increasing the dose of mesalamine (28). Moreover, relapse occurred sooner in patients with FC levels >200 µg/g compared with those with lower FC levels (P=0.01). This suggests that FC has a role in the monitoring of UC patients, one that enables the clinician to respond to elevated levels to prevent a clinical flare.

Using FC levels to monitor patients for postoperative recurrence could decrease the need for follow-up colonoscopy at six to 12 months and help optimize IBD outcomes. The predictive value of FC for postoperative recurrence has been established in patients who have undergone ileocolonic resection for Crohn disease (29-32). However, FC levels in the postoperative patient may not be as consistent as they are in other clinical situations (32).

How are test results interpreted?
Suggested potential cut-off values and courses of action are provided in Figure 2; however, individual patient variability exists. Therefore, in a particular patient, rising FC levels over time are the best indicator of...
Use of FC to identify and monitor disease activity in IBD

Figure 2) Interpreting fecal calprotectin (FC) test results

increased disease activity for that individual. Another approach to improve the reliability of FC testing would be to obtain a baseline FC level during a period of known active inflammation. An elevated FC level in this context will help clinicians determine whether this is a reliable biomarker for monitoring inflammation in an individual patient.

Some controversy remains as to optimal cut-off values. Results vary depending on the specific test used (33). The sensitivity and specificity of FC as a marker for active disease was found to differ at various cut-off values. A meta-analysis of 13 studies (n=1471) compared cut-off FC levels of 50 µg/g, 100 µg/g and 250 µg/g, and found that with higher levels the sensitivity decreased, while the specificity increased (19). In patients with a pretest probability of active disease of 66%

REFERENCES


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