

## OPINION

# Faecal calprotectin—ready for prime time?

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## INTRODUCTION

Calprotectin is a heterodimer of calcium-binding proteins which belongs to the S-100 protein family. It is released from neutrophils and monocytes during cellular activation (or death) at sites of active inflammation, and accounts for upto 60% of the cytosolic protein in the granules of these cells. It is a highly stable protein, resists enzymatic degradation and can be detected in stool samples kept at room temperature for up to 7 days. It was first studied by Roseth *et al*<sup>1</sup> in the early 1990s, both for the diagnosis of colorectal cancer and inflammatory bowel diseases (IBD). Tibble *et al*<sup>2</sup> reported its efficacy in assessing intestinal inflammation in Crohn's disease (CD) in 2000 and discriminating from irritable bowel disease, with 100% sensitivity and 97% specificity at a cut-off value of 30 mg/L. There has been a steady increase in the use of faecal calprotectin (FC) in the UK in the last few years, and the National Institute for Health and Care Excellence (NICE) released a Diagnostic Guidance on Faecal Calprotectin in October 2013 (DG11) for its use in the evaluation of patients suspected to be suffering with IBD in adults.<sup>3</sup> The test is now approved for use in primary care, and a number of clinical pathways have incorporated the FC test in the evaluation of patients with suspected IBD and also to aid diagnosis of irritable bowel syndrome (IBS).

It is important to recognise that FC is a neutrophil protein and therefore expected to be elevated in the stool of patients with any inflammatory bowel condition, such as acute resolving infective colitis, diverticulitis, and non-steroidal-induced colitis, and even in colonic adenomas and cancer. It is not a specific diagnostic test for IBD, and it should not be regarded as such.

## THE TWIN UTILITY OF FC TESTING

FC can be used in clinical practice in two ways: (1) as a diagnostic aid in primary

and secondary care to differentiate diarrhoea-predominant IBS from IBD in patients presenting to healthcare practitioners and (2) as a monitoring tool for assessing inflammatory activity in the mucosa for treatment response in IBD, and to predict recurrence of disease.

NICE Guidance DG11 refers only to the use of FC as a diagnostic investigation. Most studies in the literature have looked at cut-off values ranging from 30 µg/g of stool to 100 µg/g. A diagnostic meta-analysis published in the *BMJ* in 2010 by van Rheenen *et al*<sup>4</sup> included 13 studies in adults and children comparing the diagnostic accuracy of FC compared to a reference standard of histology. A total of 670 adults and 371 children who had FC testing before endoscopy were analysed in the meta-analysis, with a sensitivity of 0.93 (range 0.85–0.97) and specificity of 0.96 (range 0.79–0.990 in adults). The corresponding values in children and teenagers were slightly lower. In adults with suspected IBD, the use of FC testing at a pretest probability of 32% increased the post-test probability of a positive diagnosis of IBD to 91% (95% CI 77% to 97%), while a normal FC test reduces the probability of IBD to 3% (95% CI 3% to 11%).

The NICE Diagnostics Committee looked at 12 commercially available fully quantitative ELISA, fully quantitative rapid tests and semiquantitative point-of-care tests (POCT) for FC testing using a reference standard of histology after endoscopy. Sensitivity of diagnostic testing was consistently high at a cut-off of 50 µg/g, around the 93% mark (range 83–100%), with a specificity of around 91%, with a more varied range (51–100%). Increasing the cut-off to 100 µg/g decreases sensitivity slightly but increases specificity.

With regard to the use of FC for monitoring response to treatment of Ulcerative colitis (UC) and CD, there is increasing



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evidence from published papers and abstracts presented at international meetings that it performs very well as a surrogate marker for mucosal inflammatory activity and correlates well to endoscopic scoring systems for UC and CD, such as Ulcerative colitis endoscopic index of severity (UCEIS) and Crohn's disease endoscopic index of severity (CDEIS). It also performs better than conventional markers of inflammation such as C-reactive protein, white cell count and the Crohn's Disease Activity Index (CDAI). Most studies suggest that a post-treatment FC of  $<200 \mu\text{g/g}$  indicates good mucosal healing response. In UC, a FC  $>250 \mu\text{g/g}$  correlates with large ulcerations in the mucosa, and in CD a similar value of FC predicts disease relapse with a lead time of about 6 months before clinical symptoms. It may also be a useful test to aid decision making for escalation of treatment. In one study, patients with CD treated with anti-tumour necrosis factor (TNF), a biologic agent, had a median FC of  $105 \mu\text{g/g}$  in quiescent disease,  $282 \mu\text{g/g}$  in mild disease and  $611\text{--}1314 \mu\text{g/g}$  in moderate to severe disease.<sup>5</sup>

#### THE TWO ARTICLES IN THIS JOURNAL

The first paper on FC in this journal by Banerjee *et al* aims to address the issue of cut-off values for differentiating IBS from IBD in a secondary care setting. In their study of 219 patients, FC had a 100% sensitivity to detect any mucosal inflammation in the gut at a level of  $8 \mu\text{g/g}$ . A high negative predictive value (NPV) of the test would be useful to exclude inflammation although a low specificity will result in significant false positives among those clinically categorised as IBS-D. A FC cut-off of  $50 \mu\text{g/g}$  retained a 100% sensitivity, with an acceptable specificity of 60% for the diagnosis of IBD. There seems to be consistency in this cut-off value of  $50 \mu\text{g/g}$ , evidenced by several other publications and the recent Health Technology Assessment report.<sup>6</sup> By balancing sensitivity and specificity of the test, by using FC as a stratifying tool, gastroenterologists will be able to decide the need for colonoscopy in a young patient presenting with chronic diarrhoea, and reduce unnecessary colonoscopies, saving the NHS money and avoid delays in starting treatment for IBS-D.

The second paper by Dhaliwal *et al* is a prospective analysis of 311 FC samples in patients with IBS-D, UC and CD by ELISA with a subset comparison of three different commercially available monoclonal ELISA kits. Similar to the previous paper, FC testing with a cut-off of  $50 \mu\text{g/g}$  has a sensitivity of 88%, specificity of 78%, PPV of 79% and NPV of 87% to distinguish IBS from IBD. Increasing the cut-off to  $100 \mu\text{g/g}$  again decreased the sensitivity but retained a high specificity and NPV. For monitoring the course of IBD, a FC with a value of less than  $250 \mu\text{g/g}$

correlated with remission of disease activity, both by colonoscopy and histology.

#### SO WHAT'S THE CONSENSUS?

From the two studies in the journal, and from the published evidence, it is now reasonably clear that FC is now ready for prime time, to be incorporated in our clinical pathways for both diagnostic and monitoring purposes. The cut-off values for the diagnostic pathway to decide for colonic evaluation is probably best retained at  $50 \mu\text{g/g}$ , although more work needs to be done to find out whether raising the cut-off to  $100 \mu\text{g/g}$  might be better, without any significant risk of missed diagnoses. For the purpose of monitoring response to treatment of IBD, values between 200 and  $250 \mu\text{g/g}$  are likely to indicate mucosal remission of disease activity. In CD, FC has a good correlation with MR enterography findings in all grades of disease severity and is better than other laboratory tests. There is some evidence emerging that treatment decisions for IBD, particularly escalation of therapy with anti-TNF agents can be better made by combining FC levels  $>250 \mu\text{g/g}$  with trough serum anti-TNF levels and antibodies to anti TNF status. Normalisation of FC levels in UC has also been reported to be a predictor of long-term clinical remission. FC levels also predict the post-operative recurrence of CD and correlate well with Rutgeert's scores.

There is a word of caution though—my experience of the use of FC in the last 5 years has identified a small but distinct cohort of patients who have an elevated FC, often on serial testing as well, but have negative colonoscopies, ileal biopsies and MR enterography and video capsule endoscopy. The cause of the FC elevation, therefore, remains unclear in these patients, and may be due to non-steroidal anti-inflammatory drug (NSAID) use.

#### AND THE FUTURE?

There are several areas where FC work might progress in the future, particularly related to IBD management. These might include using FC responses to assess primary response to anti-TNF therapy, in conjunction with clinical scoring systems; using FC testing at 3-month intervals to detect secondary loss of response to anti-TNF treatment; using FC in a postoperative setting to stratify need for ileocolonoscopy to detect recurrence of CD and so on.

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