CLINICAL UPDATE

Fecal Lactoferrin Testing

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G&H What is fecal lactoferrin, and how can it be tested?

BA Fecal lactoferrin is an iron-binding protein found inside neutrophils. The amount of lactoferrin released by neutrophils has been shown to correlate with the severity of inflammation in the gastrointestinal (GI) tract. Lactoferrin is stable in feces for several days at room temperature, and even longer if the stool is refrigerated. Fecal lactoferrin can be tested using commercial enzyme-linked immunosorbent assays, although only fecal lactoferrin diagnostic tests by TechLab are cleared by the US Food and Drug Administration to provide quantitative or qualitative results. Fecal lactoferrin testing can help physicians for the differentiation of inflammatory bowel disease (IBD) from irritable bowel syndrome (IBS), the initial evaluation of IBD severity and correlation to endoscopic findings, the monitoring of IBD activity, and potentially the prediction of IBD relapse.

G&H How can fecal lactoferrin be an additional aid to help differentiate active IBD from IBS?

BA Fecal lactoferrin testing is very useful when a patient presents with nonspecific GI symptoms, such as abdominal pain and diarrhea, especially without evidence of alarm symptoms of weight loss or GI bleeding. These nonspecific symptoms could be due to a functional etiology, such as IBS, or from IBD or GI infections. If the patient's fecal lactoferrin level is undetectable, low, or normal, the symptoms are not likely to be related to inflammation or infection, and are more likely to be functional. On the other hand, a high fecal lactoferrin level should prompt an evaluation for either IBD (Crohn's disease or ulcerative colitis) or infectious etiologies through stool panel testing, colonoscopy, or both. With low fecal lactoferrin levels, the need for further workup can be reduced or avoided, and health care costs in the long run can potentially be lowered.

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Fecal lactoferrin testing can be quite useful for the primary care physician, as the testing can help determine how urgently a patient with GI symptoms should be referred to a gastroenterologist. For example, in the setting of elevated fecal lactoferrin with acute symptoms, GI infections should always be ruled out, but for chronic symptoms, referral to a gastroenterologist should be warranted.

G&H What fecal lactoferrin concentrations are typically associated with active IBD and IBS?

BA A fecal lactoferrin baseline cutoff level less than 7.25 µg/g indicates lack of intestinal inflammation and, for a patient with GI symptoms, suggests a functional cause (eg, IBS). When the level is far above this cutoff, the need for further evaluation is clear. However, when a patient has borderline results just above this level, the physician's discretion should be used to determine whether further testing is warranted, or if this level should be rechecked at a later time for improvement. In patients with fibrostenotic disease, where there may not be active inflammation, fecal lactoferrin levels may be low despite clinical symptoms. As with any laboratory testing, this tool should be used as an adjunct to the patient's full clinical picture to make management decisions.

G&H How can fecal lactoferrin testing help predict IBD relapse or flare?

BA If a patient in remission of his or her IBD starts experiencing GI symptoms, it may be unclear whether the symptoms are due to an IBD flare or to another cause. In such a scenario, elevated fecal lactoferrin can help identify inflammation. Following fecal lactoferrin levels in patients who are asymptomatic can also be useful to predict clinical recurrence. A study by Yamamoto and colleagues showed that increasing levels of fecal lactoferrin predicted clinical recurrence prior to the patient developing symptoms.

G&H How can fecal lactoferrin testing help in the initial assessment of IBD severity?

BA In a new diagnosis of IBD, ileocolonoscopy is the gold standard to determine the location and severity of the disease. However, with fecal lactoferrin levels, it is possible to follow the resolution of inflammation over time without having the patient undergo repeated colonoscopies. Once the initial endoscopic assessment is made, fecal lactoferrin levels can be monitored for improvement in inflammation after the start of medical therapy. This initial assessment is important, as extremely high fecal lactoferrin levels may predict either higher disease severity or larger areas of disease. For example, a patient with isolated severe disease in the ileum of approximately 1 to 2 cm in area may not have as high of a fecal lactoferrin level compared to a patient who has moderate inflammation throughout the entire colon. The fecal lactoferrin level will not help the physician find the location of the inflammation, but it can help determine the overall severity, and the reduction in levels can be followed over time to confirm that the medical therapy is efficacious.

After medication adjustments are made, fecal lactoferrin can be used to assess response to those changes and monitor for improvement prior to a patient achieving clinical remission or endoscopic healing.

G&H Why is it useful to supplement or replace colonoscopy with fecal lactoferrin testing when managing IBD patients?

BA As previously mentioned, if a newly diagnosed patient undergoes a colonoscopy and starts a medical therapy, it is ideal to check whether the fecal lactoferrin level is elevated and correlates with the patient's endoscopic score. The goal of IBD treatment is no longer just clinical remission; we should also be working on achieving mucosal healing. It is recommended to repeat a colonoscopy in approximately 6 to 12 months to assess for mucosal healing after starting medical therapy. However, patients often do not want to undergo repeat colonoscopy due to the cost and need to take time off from school or work. Therefore, it would be helpful if an alternative tool could be used to determine the same outcome. Fecal lactoferrin testing is cheaper and less invasive than colonoscopy, does not require taking time off from school or work, and can be performed any time after starting therapy. Often, with the convenience of this testing, fecal lactoferrin levels can be checked earlier (within weeks to months after the start of treatment) to confirm that the patient is on the correct path of improvement so that changes to medication dosing or other adjustments can be made early. Levels can be rechecked after adjustments far more frequently than having the patient undergo a colonoscopy every 2 to 3 months.

However, monitoring fecal lactoferrin levels should not and does not replace colonoscopy for colon cancer surveillance in IBD patients (ie, 8 years or more after diagnosis, or annually from diagnosis for patients who also have primary sclerosing cholangitis).

G&H How else can fecal lactoferrin concentrations be used for therapeutic drug monitoring and IBD management?

BA Fecal lactoferrin can be used in conjunction with therapeutic drug monitoring for medical management of IBD patients. In those with active disease, in whom fecal lactoferrin is elevated and therapeutic drug monitoring is performed, the clinician typically makes appropriate medication adjustments based on drug levels and the presence or absence of antidrug antibodies. After medication adjustments are made, fecal lactoferrin can be used to assess response to those changes and monitor for improvement prior to a patient achieving clinical remission or endoscopic healing. We have evidence that patients' clinical symptoms may not always correlate to endoscopic disease activity; thus, fecal lactoferrin can be useful to determine whether there is objective evidence of improvement in these patients.

G&H What are the main benefits of using fecal lactoferrin compared with blood biomarkers, such as C-reactive protein?

BA Physicians have traditionally used blood testing such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) as biomarkers. Most patients undergo laboratory work for their medications or to monitor conditions such as anemia, so using these blood biomarkers is easy and convenient. The main drawback is that ESR and CRP are not specific for the GI tract. Thus, these blood biomarkers may increase from inflammatory causes unrelated to the GI tract, such as upper respiratory illnesses, a urinary tract infection, or other inflammatory conditions, such as arthritis, making it difficult to distinguish the etiology. In contrast, lactoferrin is a stool marker; therefore, it is specific for the GI tract and will not be elevated in non–GI-related inflammatory conditions.

G&H Does fecal lactoferrin have a role as a noninvasive tool in children and pregnant women with IBD?

BA Fecal lactoferrin is very useful in both of these special populations. In the pediatric setting, if a young child has nonspecific GI symptoms, a colonoscopy would be invasive and is often unnecessary. However, it is important not to miss a diagnosis of IBD, as the efficacy of medical therapy early in the disease is significantly higher than treatment many years after diagnosis. Thus, fecal lactoferrin can be a great noninvasive tool to evaluate the need for further testing, such as a colonoscopy, in a young child.

Likewise, fecal lactoferrin can be quite useful in pregnant IBD patients. It is well known that ESR can be elevated during pregnancy, making it a futile test to evaluate for inflammation. In addition, in pregnant patients, colonoscopy is often avoided to prevent any dehydration from bowel preparation, and also to minimize anesthesia. Thus, using fecal lactoferrin, which does not increase in pregnancy, can help differentiate GI symptoms related to inflammation and avoid unnecessary testing while more reliably predicting disease activity in IBD patients who are pregnant.

G&H Can fecal lactoferrin be used together with fecal calprotectin for assessing patients for IBD and/or IBS?

BA They can be used together; however, this is not recommended since both overlap in the evaluation of GI inflammation.

G&H Does fecal lactoferrin offer any advantages over fecal calprotectin?

BA The main advantage is that fecal lactoferrin has been covered easily by private insurance and Medicare, making it accessible for physicians to utilize the testing frequently for patient care. In contrast, fecal calprotectin has had coverage issues, especially when ordered for patients under a diagnosis of ulcerative colitis or Crohn's disease.

In addition, since there is only 1 cutoff value, this makes it significantly easier to interpret a patient's results over time compared with a patient who may undergo calprotectin testing from different laboratories with different cutoff values.

G&H Are there any limitations associated with fecal lactoferrin testing?

BA The limitations of this testing are few. Lactoferrin testing may not be appropriate in breastfeeding infants because human breast milk can contain 8 to 10 mg of lactoferrin. However, the likelihood of an infant having IBD is quite low and, thus, may not be clinically relevant.

A more practical limitation is that fecal lactoferrin requires patients to collect stool. This requires more than drawing another tube for blood testing, such as with ESR or CRP. However, the higher specificity of this testing is worth the collection. Sometimes, a patient may not be able to provide stool at the time of the clinic visit, but the patient can collect stool at a later time and return it to the laboratory on a different day, as lactoferrin can remain stable for several days at room temperature and longer if the stool is refrigerated.

G&H What are the next steps of research for fecal lactoferrin testing?

BA Further studies assessing the levels of fecal lactoferrin in patients who have small bowel disease vs those with colonic disease should be addressed. It is known that neutrophils are found in the small intestine. However, due to the disproportionately larger area of inflammation in left-sided or universal ulcerative colitis compared to ileal Crohn's disease, levels of fecal lactoferrin may not be as high due to a smaller location of disease despite active inflammation. Thus, some physicians may find that fecal lactoferrin is not as useful with small bowel disease, but I believe that we should take the disease location and severity into context when we order this test. We need to understand the baseline area of inflammation along with the baseline lactoferrin levels, follow those over time, and compare changes within that patient to utilize this testing as a tool to guide therapeutic management.

In addition, future studies correlating fecal lactoferrin with histologic severity can be useful for physicians following patients into deep remission.

Dr Abraham has no relevant conflicts of interest to disclose.

Suggested Reading

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