How do I distinguish between Irritable Bowel Syndrome (IBS), Inflammatory Bowel Disease (IBD), and GI cancer?

This conundrum faces family physicians, pediatricians, and gastroenterologists frequently. Irritable Bowel Syndrome (IBS) accounts for up to 12% of primary care consultations and 28% of referrals to gastroenterologists.¹Because symptoms often overlap, early Inflammatory Bowel Disease (IBD) is often misdiagnosed as IBS. In fact, over one quarter of patients with IBD (particularly Crohn's disease [CD]) are given the diagnosis of IBS in the prodromal stages of their disease.² This misdiagnosis leads to extensive and invasive radiographic and endoscopic testing to make a “diagnosis of exclusion” in patients with IBS. This is usually an uncomfortable, inconvenient, and expensive endeavor.

The most profound difference between IBD and IBS is that IBS is a non-inflammatory condition. However, this in itself does not always allow clear differentiation between the two conditions. Laboratory assessments of disease activity in IBD, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell count, interleukin-6, interleukin-1, and tumor necrosis factor, have achieved only limited success.⁴⁻⁸ This is because these markers can all be affected by malabsorption, mechanical obstruction, poor nutrition, and drug therapy, as well as other infective or inflammatory conditions.

Even alpha-1 antitrypsin, a relatively good indirect measure of gut inflammation, shows a variable relation to disease activity in IBD and correlates poorly with 111-indium-labeled granulocytes—the “gold standard” for direct measurement of mucosal inflammation.⁹

However, measuring 111-indium-labeled leukocytes (or technetium-99) is very costly and impractical in the primary care setting. The inconvenience of a 4-day stool collection and the potentially harmful exposure to radioactive isotopes for the patient are additional drawbacks to this test.

Calprotectin, a neutrophil-derived protein that can be measured in stool, provides a much more convenient and sensitive noninvasive alternative for assessing inflammatory activity in IBD. Fecal calprotectin levels have been shown to correlate significantly with histologic and endoscopic assessment of disease activity in ulcerative colitis (UC)¹⁰ and with 111-indium-labeled white blood cell counts in patients with Crohn's disease (CD).¹¹ Indeed, increased levels of fecal calprotectin have been found in over 95% of patients with IBD, and appear to correlate well with IBD disease activity.¹²

The Rome 1 criteria are a set of consensus definitions proposed to help in the diagnosis of IBS. They consist of a number of IBS-related symptoms (pain, bloating, stool frequency, passage of mucus, etc.) which are scored and tallied.¹³

The combination of Rome 1 criteria plus fecal calprotectin has been shown to provide a significantly better screening tool (odds ratio [OR] 13.3 and 27.8, respectively) for discriminating between patients with organic vs. non-organic intestinal disease than other commonly used laboratory parameters such as CRP and ESR (OR 4.2 and 3.2, respectively). Additionally, investigators have found that intestinal permeability (IP) is a good predictor of small bowel disease (OR 8.9).¹⁴

Moreover, based on the combination of positive Rome 1 criteria, normal calprotectin, and normal IP, OR for IBS was 46.1, which is exceptionally high. Specificity was 98% and positive predictive value was 0.97 (with 1 being a perfect correlation). When this combination of diagnostic criteria was used, sensitivity dropped to 50%; however, it should be remembered that these are not diagnostic tests for IBS, but rather, tests in which “normality” infers an absence of organic disease.
Indeed, Tibble et al. showed that at a cutoff level of 50 µg/L (150 mg/L), fecal calprotectin exhibited 100% sensitivity and 97% specificity in discriminating between active CD and IBS.

In summary, this means that a patient presenting with positive Rome 1 criteria and a normal fecal calprotectin level < 50 µg/L has virtually no chance of having active IBD. The addition of another new analyte on the CDSA 2.0, eosinophil protein X (EPX), will also make it easier to discern whether a patient has organic or functional disease.

There is increasing evidence that eosinophils are functionally involved in the pathophysiology of various inflammatory disorders of the gut. Eosinophils contain a number of highly cationic proteins such as EPX. These cationic proteins have potent cytotoxic properties and are released from the eosinophils after being activated.

Peterson et al. showed that increased fecal EPX levels were present in patients with UC, and that the capacity of EPX to discriminate between individuals with UC and those without it was superior to other eosinophil markers. They also showed a clear relationship between disease activity in CD and fecal EPX levels, and concluded that EPX was the best eosinophil marker for studying GI inflammation in IBD.

The presence and participation of eosinophils in the pathophysiology of the active phase of IBD is clear from the literature. Saitho et al. observed that patients with CD who relapsed clinically within three months had higher eosinophil cationic protein and EPX concentrations in the feces, even in the inactive phase of the disease. They recommended that “fecal levels of eosinophil markers should be examined serially and chronologically in patients with IBD.” However, activation of EPX is not a common feature in all patients with IBD, and may reflect mucosal involvement rather than a true quantitative measure of disease activity.

Calprotectin, on the other hand, does reflect disease activity in IBD.

How do I order this test?

For CDSA 2.0 test kits, Interpretive Guidelines or information, please call a GSDL Accounts Receivable representative at 888-201-8333 or use our secure web contact center at www.gsdl.com/billing.

References


This information is for the sole use of a licensed health care practitioner and is for educational purposes only. It is not meant for use as diagnostic information. All claims submitted to Medicare/Medicaid for GSDL laboratory services must be for tests that are medically necessary. “Medically necessary” is defined as a test or procedure that is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. Consequently, tests performed for screening purposes will not be reimbursed by the Medicare program.