Laboratory Findings

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Abstract

Diagnosing and treating inflammatory bowel disease (IBD) is a challenging process. Several criteria are required for a definite diagnosis. These include clinical presentation, endoscopic appearance, histological findings, as well as biochemical and laboratory investigations (ECCO, J Crohns Colitis 11(1):3–25, 2017; Vermiere et al., Gut 55:426–431, 2006). Laboratory investigations are noninvasive and usually accessible and inexpensive and an integral part of diagnosis and overall IBD management. They are essential in detecting infection and inflammation, in assessing malabsorption and nutritional deficiencies, and in monitoring the response to therapy. Considering the relapsing and remitting course of IBD, certain investigations or laboratory markers are available that can help guide detection for early intervention, which can lead to improved outcomes. Both serum and fecal markers are used routinely in IBD clinical practice. The most widely studied and used markers in IBD are C-reactive protein (CRP) and fecal calprotectin (FC). Several laboratory markers have been described in the literature but are not routinely used in clinical practice either because they are not readily available or have not gained favor. These include serum amyloid, alpha-1 antitrypsin, orosomucoid, and interleukin 6. Other essential laboratory markers in the management of IBD are also reviewed.

6.1 Introduction

Laboratory investigations are noninvasive and an integral part of diagnosis and overall management of inflammatory bowel disease (IBD). They are essential in detecting infection and inflammation, in assessing malabsorption and nutritional deficiencies, and in monitoring the response to therapy. Laboratory markers that are essential throughout the trajectory of disease, from diagnosis to relapse and to ongoing monitoring, will be reviewed (Table 6.1).

6.2 Initial Laboratory Investigations: Suspected IBD

When evaluating a patient who presents with symptoms of suspected IBD, initial laboratory investigations should include complete blood count (CBC), liver profile, electrolytes, albumin,

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Table 6.1 Laboratory investigations in IBD

Routine investigations		Markers of IBD activity
• Complete blood count	• Folate	• C-reactive protein
• Albumin	• Iron studies	• Fecal calprotectin • Fecal lactoferrin
• Liver profile	• Vitamin B12	• Platelets
• Electrolytes	• Clostridium difficile	• Ferritin
• Renal profile	• Stool culture and sensitivity • Stool ova and parasite	• Fecal leukocytes

iron studies, ferritin, renal function, vitamin B12, and C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) (Papay et al. 2013; Batres and Baldassano 2003). Stool microbiological testing for clostridium difficile or other pathogens is important in order to rule out intestinal infection (Fig. 6.1).

CRP is a marker that may have a role in the initial workup but is not specific for IBD. It is an acute phase protein produced by hepatocytes in response to cellular injury. CRP testing is inexpensive and both widely and readily available. It has a short half-life (19 h) (Vermiere et al. 2006) and can help differentiate functional from inflammatory disease. It is important to note that there is a cohort of IBD patients who are nonproducers of CRP and will not have elevations despite active disease. In UC inflammation is limited to the mucosa, and despite mucosal damage, serum CRP levels often remain low, whereas in CD, a transmural disease, values are often higher. Because of this, CRP appears to be more useful in CD than in UC, with up to 50% of UC patients having normal levels during active disease (Kopylov et al. 2014). Infection and other autoimmune disorders may alter CRP values, so this must also be considered when using it in clinical practice (Kopylov et al. 2014).

Fecal calprotectin (FC) is a calcium- and zinc-binding protein derived from neutrophils and monocytes (Vermiere et al. 2006; Kopylov et al. 2014; Däbritz et al. 2014; Bressler et al. 2015). It is released from inflamed gastrointestinal tissue and picked up in the stool. FC can be used to differentiate inflammatory from functional (noninflammatory) conditions such as irritable bowel syndrome (IBS) (Däbritz et al. 2014). However, its specificity for differentiating IBD from infection of the gut is low (Kopylov et al. 2014).

Ferritin and platelet counts may be elevated in acute inflammatory conditions such as IBD, whereas iron, folate, B12, and albumin deficiencies may signal poor nutritional status due to lack of absorption or gut losses due to inflammation.

Laboratory markers in suspected IBD are used to help with the differential diagnosis of IBD. Physicians aim to rule out infectious and functional etiologies with the help of laboratory markers, but a definitive diagnosis will require endoscopic and histologic confirmation.

6.3 Laboratory Markers: Assessment of IBD Relapse

Patients in remission may experience a recurrence of symptoms of their IBD suddenly or over a period of time before presenting to clinic. A thorough history is always the starting point, followed by appropriate laboratory markers to help determine the cause. Intestinal infection should always be considered either as the cause of worsening symptoms or as a trigger of IBD relapse (Fig. 6.2).

Fecal calprotectin (FC) is an important biomarker for assessing relapse. It can differentiate between active and quiescent disease and correlates with the degree of mucosal inflammation (Papay et al. 2013). Levels of FC are sensitive and specific to intestinal inflammation. A recent meta-analysis reported a pooled sensitivity and specificity of 49 and 92% for detecting endoscopic activity in IBD (Mosli et al. 2015). In some units, FC kits are available for point-of-care testing. Take-home kits are also available in some locations for patients to measure their FC levels at home (Kopylov et al. 2014). There is an ongoing discussion among IBD specialists as to the ideal "cutoff" values for fecal calprotectin in Crohn's disease and ulcerative colitis, with acknowledgment that variation also exists between assays (Chang et al. 2015). It is generally accepted however that an ELISA value of >200 (mcg/g) signifies active inflammation (Kopylov et al. 2014).

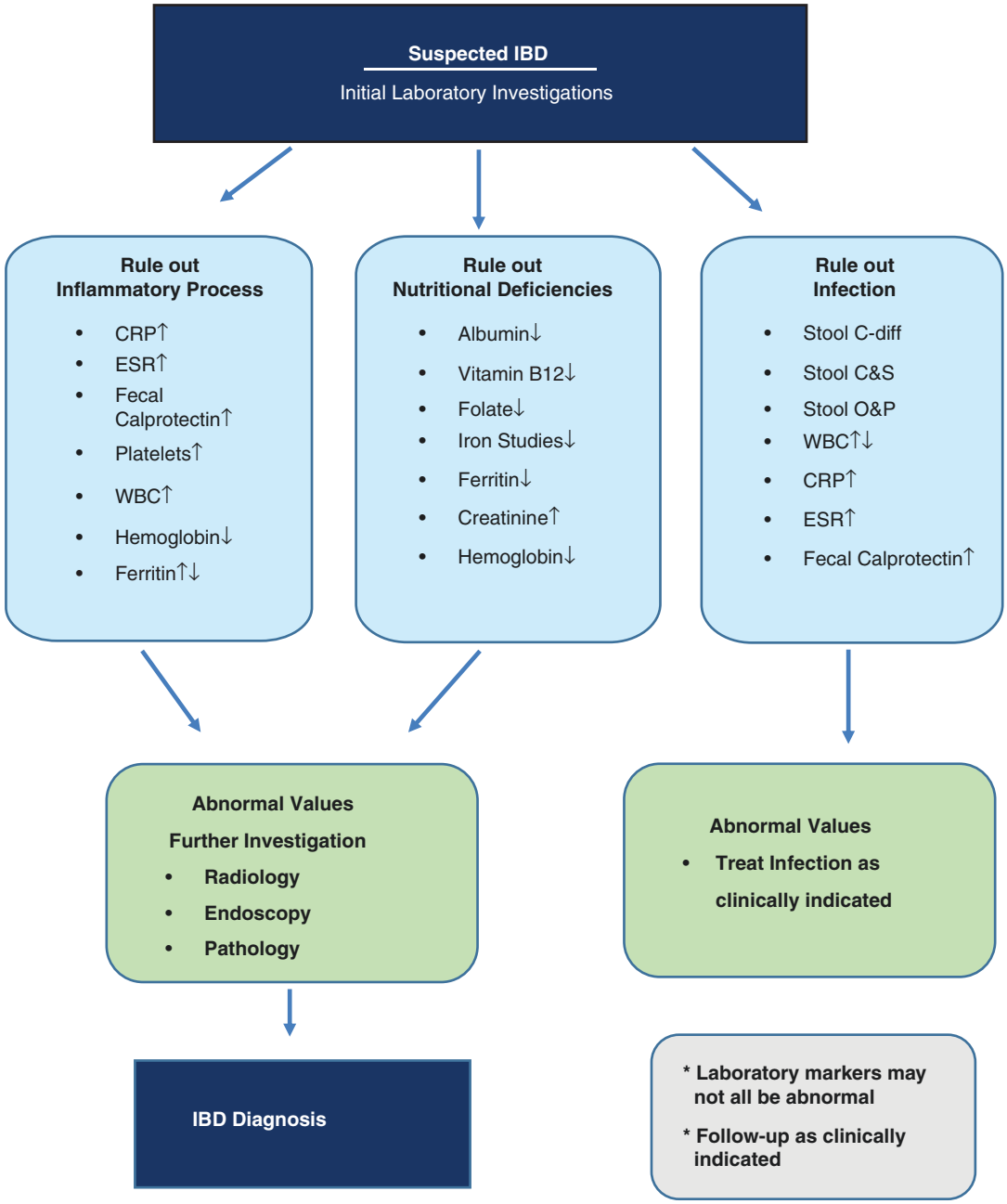

Fig. 6.1 Suspected IBD

6.4 Laboratory Markers: Monitoring IBD (Fig. 6.3)

There exists best practice in IBD consensus statements. For example, the European Crohn's and Colitis Organization (ECCO), among others, has consensus guidelines which recommend regular serum and fecal marker follow-up to monitor and possibly predict IBD flares (ECCO 2017).

Considering its short half-life, C-reactive protein (CRP) is an ideal marker to use to assess response to treatment. A decrease or normalization of CRP levels indicates response to treatment. CRP can also be useful as a predictor of

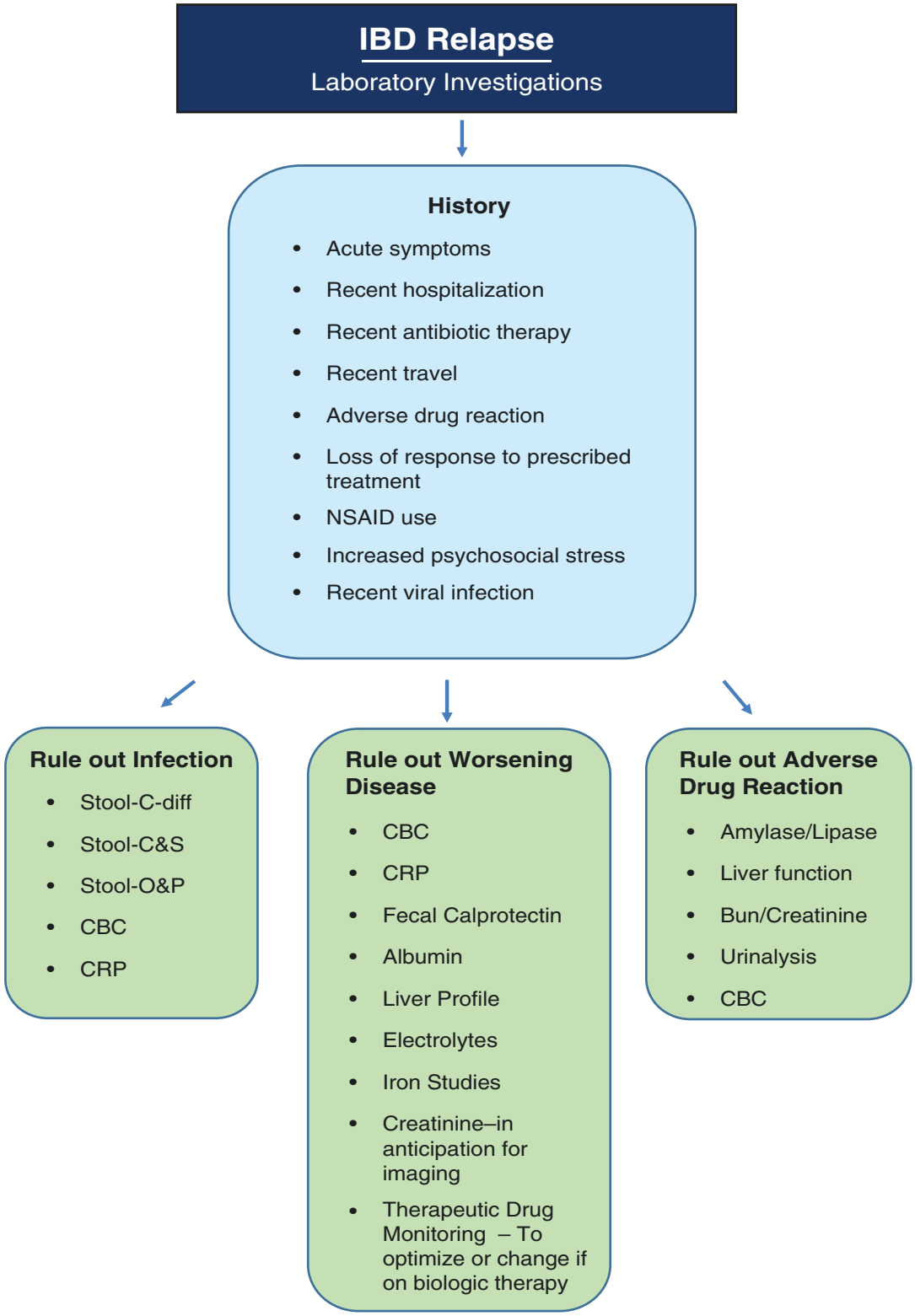

Fig. 6.2 The bubble worsening of disease

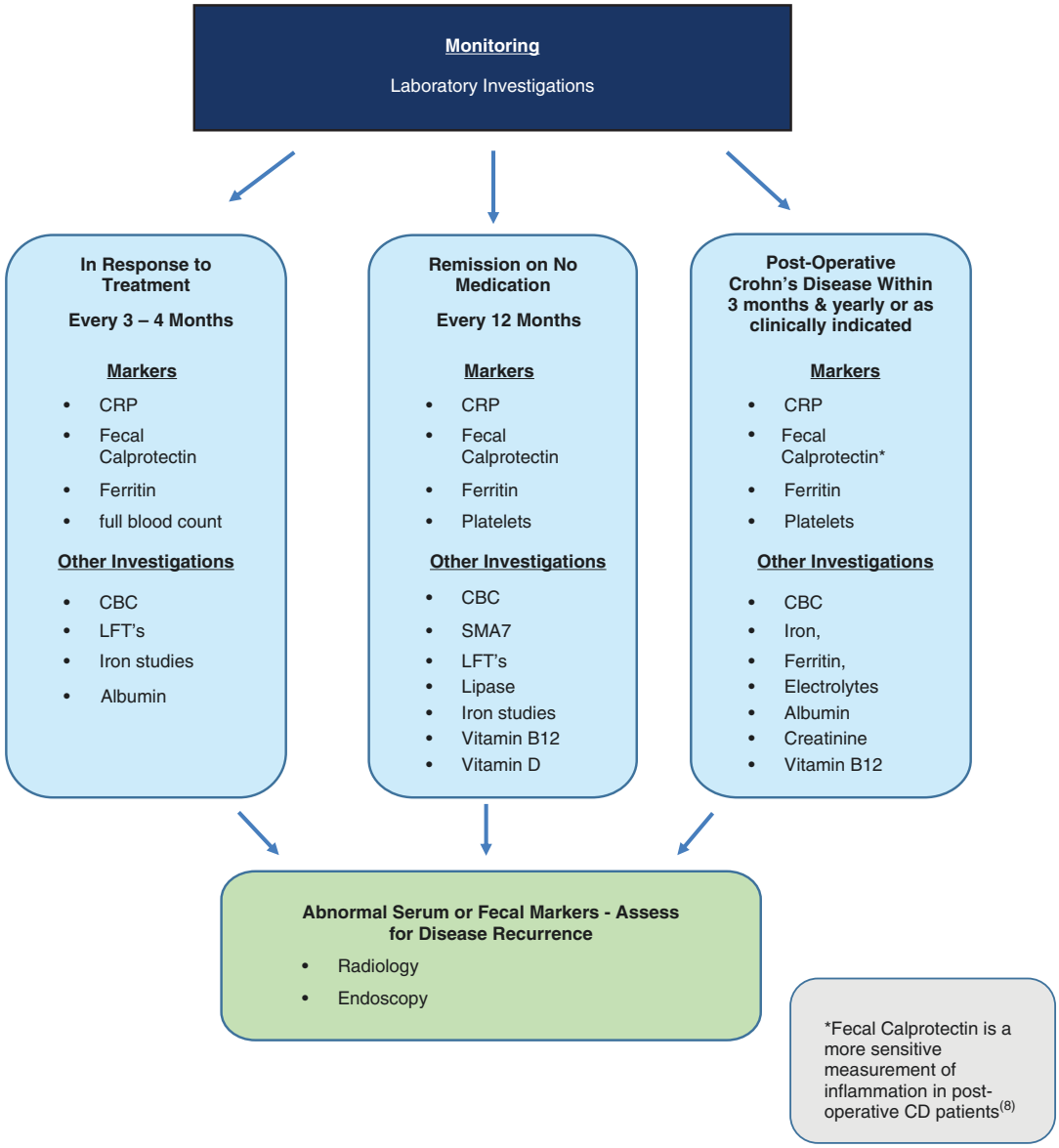

Fig. 6.3 Monitoring Laboratory Investigations

disease relapse. In a recent study, levels of CRP in Crohn's disease were shown to rise 4–6 months prior to a relapse, suggesting that routine measurement of CRP may be useful in the prediction of relapse in patients in clinical remission (Chang et al. 2015). Considering CRP is more reliable in cases of transmural inflammation, CRP may not be the most reliable biomarker for predicting CD recurrence postoperatively (Chang et al. 2015). For UC patients with normal CRP levels, it is important to consider that endoscopic disease may still be present (Chang et al. 2015). Elevation in CRP correlates with clinical relapse and is also seen in patients who lose response to treatment (Chang et al. 2015).

Fecal calprotectin (FC) can also be used as a monitoring tool to assess response to treatment. Normalization of FC level is a good indicator of improved or resolved intestinal inflammation (Papay et al. 2013). Elevated FC levels in an

asymptomatic patient can predict relapse within a 3-month period. It can be particularly useful in patients who lose response to biologics in order to objectively confirm the loss of response before adjusting therapy. The frequency of FC measurement in patients in stable clinical remission should be every 3–4 months. FC is also a more reliable indicator than CRP for monitoring postoperative recurrence (Chang et al. 2015). There is evidence that levels should return to normal at 8 weeks postoperatively (Vermiere et al. 2006; Kopylov et al. 2014; Däbritz et al. 2014; Bressler et al. 2015).

6.5 Serum Laboratory Markers: Importance in IBD

6.5.1 C-Reactive Protein (CRP)

- Increased in suspected IBD and relapse.
- Useful in monitoring disease in remission or impending relapse.
- Useful in monitoring response to therapy.
- Only 60% of individuals mount a CRP response.

6.5.2 Erythrocyte Sedimentation Rate (ESR)

- An acute phase reactant elevated in response to systemic inflammation.
- Nonspecific for intestinal inflammation (Däbritz et al. 2014).
- ESR is slow to both rise and decrease once an event is over, making it less useful and less relied upon than CRP in clinical practice (Vermiere et al. 2006).

6.5.3 Ferritin

- Acute phase reactant
- Reflects iron stores
- May be decreased or increase in active IBD

6.5.4 Platelets

- Thrombocytosis is associated with disease activity (Voudoukis et al. 2014).
- Platelet activation—increased risk of thrombotic events in the IBD population (Batres and Baldassano 2003; Voudoukis et al. 2014).

6.6 Fecal Laboratory Markers: Importance in IBD

6.6.1 Fecal Calprotectin (FC)

- Surrogate marker of gut inflammation.
- Can help differentiate functional versus inflammatory conditions.
- Increased in suspected IBD and relapse.
- Useful in monitoring disease in remission or impending relapse.
- Sensitivity and specificity depend on cutoffs.
- Despite stability there is day-to-day variability in FC.
- Serial measurements of FC can be more useful than a single measurement (Kopylov et al. 2014).
- NSAID's and PPI's can elevate FC levels (Bressler et al. 2015).

6.6.2 Fecal Lactoferrin (FL)

- Surrogate marker of gut inflammation
- Not readily or widely used
- An iron-binding protein released from neutrophils of the gut mucosa
- Correlates well with inflammation endoscopically and clinically (Papay et al. 2013)
- FL less widely accepted and less studied than FC as a marker in IBD (Papay et al. 2013; Vermiere et al. 2006; Kopylov et al. 2014; Bressler et al. 2015)

6.6.3 Fecal Leukocytes

- Present in bacterial infection, parasitic (amebiasis) invasion, or inflammation (Walk-in-Lab n.d.)
- Can assist in the differential diagnosis in those with diarrhea (Walk-in-Lab n.d.)
- Detected with methylene blue staining

6.7 Other Laboratory Investigations: Importance in IBD

6.7.1 Complete Blood Count (CBC)

- An indicator of general health status.
- Insight to possible infection, anemia, and inflammation.
- Anemia can signal active disease in otherwise asymptomatic patients.
- Leukocytosis—a response to inflammation, infection, and/or steroid use.
- Leukopenia—viral illness and medications, i.e., thiopurines and methotrexate.

6.7.2 Albumin

- Serum colloid protein lowered in inflammation and infection.
- Hypoalbuminemia is associated with chronic disease, infection, inflammation, and nutritional status (Qin et al. 2016).

6.7.3 Renal Profile

- Creatinine (Cr)—high levels indicate altered filtration and/or dehydration.
- Medications such as methotrexate and 5-aminosalicylates may result in interstitial nephritis.
- Blood urea nitrogen (BUN)—elevations reflect decreased GFR and dehydration (Mayo Clinic n.d.).

6.7.4 Liver Profile

- Hepatobiliary extraintestinal manifestations are associated with or common in IBD, e.g., fatty liver and primary sclerosing cholangitis.
- Drug-induced liver toxicity, i.e., sulfasalazine, methotrexate, thiopurines, and anti-TNF.
- Assess liver profile every 4 months or as clinically indicated (UpToDate n.d.-a).

6.7.5 Vitamin B12

- Increased risk of developing B12 deficiency in Crohn's disease (CD).
- Risk factors—ileal disease, resection of the TI, bacterial overgrowth, and gastritis (UpToDate n.d.-b).
- With deficiency, increased risk of developing megaloblastic anemia and dysfunction of the nervous system with symptoms such as numbness, paresthesia, gait disturbances, or memory impairment.
- B12 levels should be monitored in all patients with ileal CD and in those who have undergone an ileal resection (UpToDate n.d.-b).
- IF If vitamin B12 is low, methylmalonic acid [MMA] and homocysteine [Hcy] should be performed in order to confirm true B12 deficiency.

6.8 Conclusion

Inflammatory bowel disease is a systemic, immune-mediated lifelong disease that requires a comprehensive approach to management. Laboratory markers are essential throughout the trajectory of the disease, from diagnosis to relapse and to ongoing monitoring. Fecal calprotectin and C-reactive protein are the most widely used markers in the management of IBD. Considering elevations in these markers can present months prior to the onset of symptoms, routine testing could potentially alter the course of the disease. The cost versus benefits of this type of management have yet to be determined, but the possibility of improving the

natural course of IBD is exciting for those involved in the care of this increasing and challenging population.

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