Vitamin and mineral deficiencies in inflammatory bowel disease

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Literature review current through: Jan 2022. | **This topic last updated:** Jan 21, 2021.

INTRODUCTION

Individuals with inflammatory bowel disease (IBD), and particularly those with Crohn disease, are at risk for a variety of nutritional deficiencies because of decreased nutrient intake, malabsorption, increased energy expenditure, and/or increased losses. The most common deficiencies are iron, vitamin D, vitamin B12, and zinc (table 1). Some of these micronutrient deficiencies are more prominent at disease diagnosis, while other deficiencies persist or even worsen during treatment.

Several factors contribute to deficits in energy and protein in IBD. Patients with active disease often have reduced nutrient intake due to anorexia, which is associated with disease activity and may be mediated by proinflammatory cytokines, such as tumor necrosis factor-alpha. Malabsorption, maldigestion, increased energy expenditure, and gastrointestinal protein loss also contribute to deficiencies of energy and protein and are usually correlated with disease activity. Similar mechanisms contribute to vitamin and mineral deficiencies in IBD. In addition, the activity and location of a patient's intestinal disease determines their risk for specific micronutrient deficiencies because some nutrients are digested and absorbed in specific segments of the gastrointestinal tract.

Vitamin and mineral deficiencies in adults and children with IBD will be reviewed here. Other aspects of nutrition in patients with IBD are discussed in separate topic reviews:

- (See "Growth failure and poor weight gain in children with inflammatory bowel disease".) – Focuses on pathogenesis, assessment, and management of undernutrition and pubertal delay in children with IBD.
- (See "Overview of the management of Crohn disease in children and adolescents".) – Includes discussion of exclusive enteral nutrition and supplemental enteral nutrition.
- (See "Nutrition and dietary management for adults with inflammatory bowel disease".) – Includes discussion of specific diets (eg, specific carbohydrate diet [SCD]).

RISK FACTORS FOR NUTRIENT DEFICIENCIES

- **Disease activity** – Individuals with newly diagnosed or active IBD are at greater risk for nutrient deficiencies through several different mechanisms. First, intestinal inflammation is associated with malabsorption and maldigestion, which contribute to deficiencies of energy, protein, and micronutrients. Second, patients may have anorexia and increased energy expenditure, which are mediated by the inflammatory cytokines that are associated with active disease. Third, they may voluntarily limit their intake of foods that exacerbate their symptoms. Finally, these inflammatory mediators also specifically interfere with absorption or utilization of certain nutrients, especially iron and vitamin D. (See 'Iron' below and 'Vitamin D' below.)
- **Disease location** – The risk for specific nutrient deficiencies is also related to the location and extent of the mucosal inflammation within the intestinal tract. As examples:
  - **Terminal ileum** – Active disease may lead to deficiencies of vitamin B12 or fat-soluble vitamins
  - **Proximal small intestine** – Active disease interferes with iron and calcium absorption

- **Diffuse small bowel disease** – Extensive disease with profuse diarrhea may lead to zinc deficiency
- **Severe colonic disease** – Colon mucosal ulceration may lead to ongoing blood loss and iron deficiency

These mechanisms are discussed in the sections on each of these deficiencies below.

- **Growing children** – Due to increased requirements for growth and development, growing children are at greater risk for nutrient deficiencies. Children have greater needs for micronutrients and minerals such as calcium. For example, the recommended dietary allowance (RDA) of calcium for children ages 9 to 18 is 1300 mg per day, while the RDA for adults ages 19 to 70 is 1000 mg calcium per day [1]. Nutrients directly impacting bone health and subsequently linear growth include calcium, magnesium, copper, phosphorus, iron, and vitamin D. Whereas the maintenance of bone health is a goal in adults with IBD, growth in children requires accrual of bone and muscle mass. Importantly, adequate control of inflammation is critical as inflammatory cytokines have a direct impact on bone formation and muscle formation.

- **Fat malabsorption** – Deficiencies of fat-soluble vitamins (vitamins A, D, E, and K) are most likely to occur in patients with fat malabsorption. Fat malabsorption may be caused by bile acid deficiency due to terminal ileal disease or resection (because bile acids undergo active resorption in the terminal ileum) or by the use of medicines, such as cholestyramine, that bind bile acids. As a result, these deficiencies occur primarily in patients with Crohn disease and active terminal ileal disease or resection. Vitamin D or A deficiencies are most common, while vitamin E and K deficiencies are rare. (See 'Vitamin D' below and 'Vitamin A' below.)

- **Surgical resection** – A large proportion of patients with IBD, particularly those with Crohn disease, eventually require surgical resection of some portion of the bowel. Surgery for patients with Crohn disease often involves the ileum and portions of the colon. The terminal ileum is the site of vitamin B12 absorption, and larger ileal resections (ie, greater than 100 cm) can disrupt the enterohepatic circulation and result in intestinal losses of bile salts. The consequences may

include choleretic diarrhea, steatorrhea, and fat-soluble vitamin deficiencies. In general, jejunal resections are less likely to result in nutrient deficiencies than ileal resections.

ANSWERS TO COMMON CLINICAL QUESTIONS

The following questions often arise during the care of an IBD patient:

- **Do all patients with IBD need a multivitamin supplement?** – No. The most important strategy to address micronutrient deficiencies is to treat the patient's underlying disease to minimize inflammation and any associated malabsorption and anorexia. Once remission is achieved, most patients can get adequate quantities of micronutrients from food sources if they have a well-balanced diet, including recommended proportions of protein, fruits, vegetables, and fortified dairy products, except that vitamin D supplementation is commonly needed (see 'Vitamin D' below). Patients with specific, pronounced deficiencies may require other vitamin or mineral supplements, tailored to their individual needs. (See "Healthy diet in adults" and "Dietary history and recommended dietary intake in children".)

- **Are patients who follow the specific carbohydrate diet (SCD) at risk for micronutrient deficiencies?** – The risk depends on the individual patient; patients who choose to follow the SCD should have dietary counseling and follow up to ensure adequate nutrition. The SCD is a restrictive diet that is postulated to have beneficial effects on inflammation from IBD and has generated broad interest from patients and families. The diet involves the elimination of all grains, refined sugars, "processed" foods, and the majority of dairy products (although yogurt fermented for 24 hours and certain hard cheeses are allowed). Limited data from case series have suggested a beneficial effect on inflammation in IBD [2,3]. A study evaluating partial enteral nutrition plus a whole-food elimination diet (termed the Crohn Disease Exclusion Diet) has shown greater compliance and equivalent steroid-free remission rates in comparison to exclusive enteral nutrition [4] (see "Overview of the management of Crohn disease in children and adolescents", section on 'Partial enteral nutrition with specific exclusion diet'). However, concerns have arisen about the possibility of weight loss, negative

psychosocial impact, and risks for nutrient deficiencies for patients following the SCD. In case series in children following the SCD with appropriate guidance from a dietitian, nutrient intake was similar to that in a healthy reference population [5]. However, there was considerable variation in nutrient adequacy within this patient population, similar to healthy populations. For any patient who chooses to follow an exclusion diet, it is important to provide counseling by a dietitian and ongoing monitoring of nutritional status.

Other dietary strategies for patients with IBD, including lactose avoidance and elimination diets, are discussed separately. Patients who follow any restriction diet for IBD should have close follow-up with a dietitian and gastroenterologist. (See "Nutrition and dietary management for adults with inflammatory bowel disease".)

- **What is the optimal route of iron therapy for patients with IBD?** – Both enteral and parenteral routes are acceptable, and the choice depends on the characteristics of the individual patient, including the severity of the iron deficiency and tolerance of oral iron therapy. Experimental evidence from animal models suggests that enteral iron supplementation increases oxidative stress and exacerbates intestinal inflammation. In humans with IBD, low-dose enteral iron supplementation (60 mg elemental iron/day) has not been shown to significantly increase disease activity in IBD [6,7]. Moreover, both enteral and intravenous (IV) iron supplementation are effective at increasing serum hemoglobin concentrations. A clinical approach is outlined below. (See 'Iron therapy' below.)

- **Is there a role for antioxidant vitamins for therapy of IBD?** – Probably not. Patients with Crohn disease have biomarkers that suggest greater oxidative stress than healthy individuals, even at times when their disease is relatively quiescent. As an example, one study reported that adult patients with Crohn disease had elevated oxidative stress (as measured by breath pentane and ethane output) compared with healthy controls [8]. Depletion of dietary antioxidants has been suggested as a possible mechanism. A few randomized trials using supplementation of antioxidants (vitamins A and E, selenium, fish oil, omega-3 fatty acids) in various combinations generally reduced measures of oxidative stress but did not affect disease activity [9-11].

Thus, there is no direct evidence that supplementation with antioxidant vitamins can reduce inflammation in patients with IBD. Moreover, high-dose supplementation of vitamins A or E may have adverse effects on bone or cardiovascular health, respectively, and is not recommended [12]. (See 'Vitamin A' below and 'Vitamin E' below.)

LABORATORY MONITORING FOR NUTRIENT DEFICIENCIES

Laboratory monitoring of nutritional status for patients with IBD depends on the patient's disease activity and location, general nutritional status, and specific risk factors such as exclusive parenteral or enteral nutrition. In our practice, we use the following approach:

Routine monitoring — In patients with quiescent IBD, we perform routine monitoring for nutritional deficiencies every 6 to 12 months (table 2). We perform this monitoring more frequently for patients with active disease, those receiving targeted nutrient supplementation, and for growing children. Routine tests are:

- Complete blood count (CBC) with red blood cell parameters to screen for iron deficiency
- C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR), as markers of inflammatory status
- Serum albumin, as a marker of inflammatory status and disease activity rather than protein intake
- Serum 25-hydroxyvitamin D

Conditional tests — The following tests are not routinely needed but should be performed in selected patients:

- Ferritin, serum iron, total iron-binding capacity, transferrin saturation – To be checked at baseline, then as needed for patients with anemia of unclear etiology.
- Vitamin B12 – For patients with Crohn disease involving the ileum or with an ileal resection, at least every one to two years.

- Calcium, phosphorus, magnesium, and potassium – For patients with chronic diarrhea or active small bowel disease, or during refeeding in severely undernourished patients.

- Vitamins A and E, and prothrombin time (PT) or international normalized ratio (INR) – For patients at risk for fat malabsorption, eg, those with active terminal ileal disease or resection, or those using medicines such as cholestyramine that bind bile acids (see 'Risk factors for nutrient deficiencies' above). If hyperlipidemia is present, the results for vitamin E should be adjusted for serum lipids. (See "Overview of vitamin E".)

- Zinc – For patients with excessive enteral losses due to ostomies, fistulas, or profuse diarrhea (eg, >8 watery stools daily).

- Folate – For patients who are taking a medication that may affect folate status (eg, sulfasalazine or methotrexate) and also have other symptoms or screening laboratory abnormalities (eg, anemia).

- Fecal calprotectin – For patients without elevation in serologic markers of inflammation but who have symptoms suggesting active intestinal inflammation.

We do not usually test for deficiencies of selenium or copper unless a patient has profuse diarrhea (eg, >8 watery stools daily, or ostomy output >1500 mL/day or >20 mL/kg/day in children) and exhibits other signs of nutritional deficiency or other risk factors for these deficiencies, such as insufficient intake through parenteral or enteral nutrition. (See 'Other' below.)

CONSIDERATIONS FOR PATIENTS WITH ANEMIA

Anemia is reported in approximately 16 percent of outpatients and up to 70 percent of inpatients with IBD, with particularly high rates in children [13-15]. Potential contributors are:

- **Iron deficiency** – Iron deficiency is probably the most important contributor to anemia for many patients with IBD. (See 'Iron' below.)

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Anemia of chronic inflammation – Another important mechanism is anemia of chronic inflammation (previously known as anemia of chronic disease), which is characterized by suppressed erythropoietin production and altered iron metabolism caused by proinflammatory cytokines [16]. Hepcidin, a key hormonal regulator of iron homeostasis, is increased and negatively regulates iron absorption from the gastrointestinal tract [17,18]. For patients with this disorder, oral iron is often ineffective, whereas intravenous (IV) iron is sometimes effective and is generally safe [19,20]. (See "Anemia of chronic disease/anemia of inflammation" and "Treatment of iron deficiency anemia in adults", section on 'Oral versus IV iron'.)

- **Vitamin B12 or folate deficiency** – Some patients with IBD are at risk for vitamin B12 or folic acid deficiencies, both of which cause a macrocytic anemia. Factors contributing to vitamin B12 deficiency include disease or resection of the terminal ileum, gastritis, and bacterial overgrowth. Patients on sulfasalazine therapy are at increased risk for folic acid deficiency. (See 'Vitamin B12' below and 'Folic acid' below.)

- **Drug-induced anemia** – A variety of drugs may cause anemia, including sulfasalazine (due to multiple mechanisms) or methotrexate and thiopurines (due to bone marrow suppression), which are often used for treatment of IBD. (See "Sulfasalazine and 5-aminosalicylates in the treatment of inflammatory bowel disease", section on 'Sulfasalazine' and "Overview of azathioprine and mercaptopurine use in inflammatory bowel disease", section on 'Adverse effects'.)

COMMON DEFICIENCIES

Iron — Iron deficiency is a common nutritional deficiency in IBD and is probably the most important contributor to anemia in this population [13]. However, patients may have other contributors to anemia, which complicate the evaluation and management of iron deficiency. (See 'Considerations for patients with anemia' above.)

Prevalence and risk factors — Literature reviews report iron deficiency in 35 to 90 percent of adults and 30 to 88 percent of children with IBD [14,21,22]. Iron deficiency has a significant negative impact on quality of life and can lead to developmental and

cognitive abnormalities in children and adolescents [23], and iron repletion can improve quality of life [22].

Several mechanisms contribute to iron deficiency in IBD. First, acute or chronic intestinal bleeding is a common source of iron loss. Second, patients with duodenal disease are at increased risk because iron is predominantly absorbed in the duodenum. Third, inflammation directly inhibits erythropoiesis and acts via upregulation of hepcidin to decrease enteric absorption of iron and also decrease mobilization of iron stores from the liver and spleen.

Assessment — Patients with IBD should be screened for iron deficiency periodically by measuring a complete blood count (CBC) with both C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) to provide context on inflammatory status. In the initial evaluation for anemia, it may be helpful to include serum iron, ferritin, and total iron-binding capacity to help distinguish between iron deficiency and other causes of anemia. (See 'Considerations for patients with anemia' above.)

A low serum ferritin is always consistent with iron deficiency, but normal or elevated ferritin does not exclude iron deficiency. This is because ferritin is an acute phase reactant and may be falsely normal in the setting of inflammation, including in patients with active IBD or acute infection. In patients without biochemical or clinical evidence of inflammation, iron deficiency is indicated by a serum ferritin <30 mcg/L. In the presence of inflammation (as suggested by an elevated CRP or ESR), serum ferritin levels below 100 mcg/L should be considered abnormal [14,24]. In addition, serum ferritin may be falsely normal in a patient with hypoalbuminemia. Fecal calprotectin may have value as a surrogate marker of intestinal inflammation. (See "Clinical presentation and diagnosis of inflammatory bowel disease in children", section on 'Stool tests'.)

In patients with a microcytic anemia and low serum ferritin, iron deficiency is the most likely cause. The diagnosis is confirmed if the laboratory abnormalities resolve with iron therapy.

In patients with anemia that does not fit these characteristics and/or that does not respond to iron therapy, other causes of anemia should be considered. These include anemia of chronic inflammation (anemia of chronic disease), vitamin B12 or folate deficiency, and underlying hemoglobinopathy (eg, thalassemia). Other tests of iron

status may help to distinguish between these disorders (table 3) but may not be definitive, especially in anemia caused by mixed mechanisms. (See 'Considerations for patients with anemia' above.)

Interpretation of laboratory tests in patients with anemia is discussed in detail separately. (See "Iron deficiency in infants and children <12 years: Screening, prevention, clinical manifestations, and diagnosis", section on 'Evaluation for suspected iron deficiency anemia' and "Iron requirements and iron deficiency in adolescents", section on 'Evaluation and presumptive diagnosis' and "Causes and diagnosis of iron deficiency and iron deficiency anemia in adults", section on 'Diagnostic evaluation'.)

Iron therapy — A presumptive diagnosis of iron deficiency or iron deficiency anemia can be made after the laboratory testing outlined above and is an indication for iron therapy. A definitive diagnosis can be made if the hemoglobin and ferritin normalize after iron therapy.

Patients with IBD present unique challenges regarding iron therapy. Either oral or intravenous (IV) iron therapy may be appropriate, and the choice depends on the characteristics of the individual patient, including the severity of the iron deficiency and tolerance of oral therapy:

- **Our approach** – We suggest the following approach to iron supplementation in patients with IBD and evidence of iron deficiency:

  - For patients with mild IBD activity and mild or moderate anemia (hemoglobin 10 to 12 g/dL in children and women or 10 to 13 g/dL in men), we suggest iron supplementation by the oral route as an initial trial. Specific suggestions for initial treatment are presented elsewhere. (See "Iron deficiency in infants and children <12 years: Treatment", section on 'Oral iron therapy' and "Treatment of iron deficiency anemia in adults", section on 'Choice of oral preparation'.)

  - For adult patients with moderate to severe IBD activity or severe anemia (hemoglobin <10 g/dL), or for those who do not tolerate or respond appropriately to oral iron, we suggest IV supplementation. Specific suggestions for the choice of agent, use of a test dose and/or premedication, and calculation of the dose of iron are presented in depth elsewhere. Blood

transfusion is generally reserved for patients with severe anemia with symptoms or hemodynamic instability. (See "Treatment of iron deficiency anemia in adults", section on 'Intravenous iron' and "Treatment of iron deficiency anemia in adults", section on 'Severe/life-threatening anemia'.)

- For children and adolescents with IBD, we suggest the same approaches as adults [15]. The safety of IV iron in pediatric patients has been demonstrated [25-27]. (See "Iron deficiency in infants and children <12 years: Treatment", section on 'Oral iron therapy' and "Iron requirements and iron deficiency in adolescents", section on 'Management'.)

- If the anemia fails to respond, or only partially responds, to treatment with IV iron, this may indicate either an erroneous diagnosis of iron deficiency or the presence of a component of the anemia of chronic inflammation (anemia of chronic disease). In such cases, further treatment of active inflammation and/or addition of erythropoietin to the regimen may result in improvement of the anemia [28,29]. (See "Anemia of chronic disease/anemia of inflammation".)

The above approach is based on the following considerations:

- **Oral iron** – Oral iron therapy is convenient and inexpensive. However, its use is limited by the following considerations:
  - Many individuals with IBD are intolerant of oral iron preparations, especially those with moderate or severe disease activity [30-32]
  - High doses of oral iron may worsen IBD disease activity [30]
  - Individuals with IBD may have ongoing inflammation that may interfere with iron absorption
  - Oral iron is not effective if the anemia is caused by chronic inflammation

- **IV iron** – Because of these potential limitations of oral iron therapy, IV iron therapy is appropriate for many patients with IBD, as suggested by several expert panels [15,24,33-36]. Numerous studies have demonstrated the safety and efficacy of various IV iron preparations in these patients [19,28,37]. In Europe, IV iron is standard first-line therapy for IBD-associated iron deficiency

[38]. (See "Treatment of iron deficiency anemia in adults", section on 'Inflammatory bowel disease'.)

Vitamin D — Vitamin D insufficiency is common in patients with IBD. In one study, 25 percent of adults with Crohn disease had deficient serum 25-hydroxyvitamin D (calcidiol) concentrations (<10 ng/mL) [39]. Studies in children report that 6 to 36 percent of children with IBD have deficient 25-hydroxyvitamin D concentrations (<15 ng/mL) [40-42]. Vitamin D deficiency is one of several mechanisms for bone disease in IBD. (See "Metabolic bone disease in inflammatory bowel disease".)

Because patients with IBD have an increased risk for vitamin D insufficiency and metabolic bone disease, we suggest focused dietary counseling to ensure adequate intake of vitamin D, with supplementation as needed. The recommended intake of vitamin D for individuals with IBD is the same as for healthy individuals (table 4) [1,43,44]. We also suggest close monitoring of 25-hydroxyvitamin D levels (eg, every 6 to 12 months) and titration of supplements as appropriate to achieve target serum levels. (See "Overview of vitamin D", section on 'Requirements' and "Vitamin D deficiency in adults: Definition, clinical manifestations, and treatment".)

Several factors contribute to the variability in reported serum 25-hydroxyvitamin D concentrations, including genetic and environmental factors (diet and sun exposure), vitamin D supplements, and factors related to the IBD itself (malabsorption and anorexia). In addition to low serum levels of 25-hydroxyvitamin D, patients with IBD may have abnormal vitamin D metabolism due to inflammatory processes, reflected by lower concentrations of parathyroid hormone (PTH) and 1,25-hydroxyvitamin D [45,46]. These abnormalities improve with appropriate control of inflammation, suggesting that the inflammation has negative effects on PTH, which in turn affects renal 1-alpha-hydroxylase activity. Malabsorption of vitamin D also may play a role, but one study suggests that this occurs in only approximately 10 percent of patients with IBD [47].

Because vitamin D is involved in regulating the immune system, it has been investigated as a possible adjunctive therapy in IBD [48,49]. There is insufficient evidence to determine if vitamin D supplementation is effective in this role. (See "Vitamin D and extraskeletal health", section on 'Immune system'.)

Vitamin B12 — Laboratory evidence of vitamin B12 deficiency has been reported in approximately 20 percent of adult and pediatric patients with Crohn disease [50,51], although it appears to be rare in children with newly diagnosed IBD [52]. Factors contributing to vitamin B12 deficiency include disease or resection of the terminal ileum, gastritis, and bacterial overgrowth. Vitamin B12 deficiency may present with macrocytic anemia or peripheral neuropathy symptoms.

Serum vitamin B12 levels should be monitored periodically (eg, every 12 to 24 months) in all patients with ileal or ileocolonic resections. Occasional monitoring also may be warranted for patients with ulcerative colitis who have undergone ileal pouch anal anastomosis, due to changes in morphology from small bowel mucosa to large bowel mucosa [53]. If the serum vitamin B12 results are inconclusive or discordant with other clinical features, the diagnosis can be confirmed by measuring serum homocysteine levels and methylmalonic acid. The diagnosis and treatment of this issue is discussed in separate topic reviews. (See "Clinical manifestations and diagnosis of vitamin B12 and folate deficiency" and "Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults", section on 'Malabsorption'.)

Zinc — As many as 65 percent of patients with Crohn disease have decreased serum zinc concentrations [52,54,55]. However, serum zinc levels vary with albumin and correlate poorly with total body zinc stores; clinically significant zinc deficiency is probably much less common. A deficient state is often reflected by a decreased serum alkaline phosphatase concentration because alkaline phosphatase is a zinc metalloenzyme. In a large prospective registry study, zinc deficiency was associated with increased risk of hospitalization, rate of surgery, and disease-related complications [56]. (See "Overview of dietary trace elements", section on 'Zinc'.)

Certain patients with IBD may be at risk for clinically significant zinc deficiency if they have excessive losses due to ostomies, fistulas or profuse diarrhea (eg, >8 watery stools daily), or are on prolonged parenteral nutrition without trace mineral supplementation. Active inflammatory disease of the small bowel contributes to zinc malabsorption and also may increase losses of endogenous zinc stores via intestinal epithelial sloughing and interruption of reabsorption.

Several clinical manifestations of zinc deficiency have been described. The dermatologic manifestations are most distinctive, usually consisting of dry, scaly

eczematous plaques, often on the face and anogenital area, which may resemble psoriasis. Many other manifestations, such as growth failure, are nonspecific and are more likely to be caused by mechanisms other than zinc deficiency in pediatric patients with IBD. (See "Zinc deficiency and supplementation in children" and "Growth failure and poor weight gain in children with inflammatory bowel disease".)

For patients with IBD and suspected zinc deficiency (as indicated by low serum levels of zinc and alkaline phosphatase, and risk factors or symptoms of zinc deficiency), we suggest the following approach to zinc supplementation:

- For asymptomatic patients with low serum zinc concentrations, we suggest working with a dietitian to ensure adequate dietary intake or supplementation using maintenance doses of elemental zinc near the recommended dietary allowance (RDA) (table 5). The symptoms of zinc deficiency may be subtle, and zinc supplementation at these doses is generally safe.

- For patients with symptoms caused by zinc deficiency (primarily the dermatitis), treat with oral or parenteral zinc at replacement doses of 25 to 50 mg of elemental zinc two to three times daily for two weeks, followed by reassessment of clinical status and serum zinc level. This should be followed by either additional zinc replacement if needed or maintenance dosing near the RDA.

  Patients with chronic diarrhea should have periodic monitoring of zinc levels and dose adjustment as needed.

Because zinc supplementation has been useful in the treatment of chronic diarrhea, it has been suggested that supraphysiologic zinc replacement might be a helpful adjunct to treatment of patients with IBD. A small uncontrolled study of patients with Crohn disease in remission suggested that zinc supplementation reduced intestinal permeability, but the clinical relevance of this finding has not been shown [57]. Zinc is also a common component of antioxidant combinations that are occasionally given to patients with Crohn disease, although there is little evidence to support this practice. (See 'Answers to common clinical questions' above.)

Calcium — IBD patients often have negative calcium balance, which is reflected in decreased bone mineral density, and also often have inadequate intake of calcium in their diets [58-60] (see "Regulation of calcium and phosphate balance"). In a series of

women with IBD, 70 percent had inadequate calcium intake [61]. Malabsorption from Crohn disease also can contribute to a calcium deficit. Calcium malabsorption may be caused by vitamin D deficiency, the binding of calcium to undigested fats in the intestinal lumen and rapid transit due to intestinal inflammation and damage, and/or direct effects of glucocorticoids on calcium balance [62]. Many patients restrict their intake of dairy because of concerns about lactose intolerance, resulting in low calcium intake [63]. Other factors also contribute to bone disease in patients with IBD. Calcium malabsorption also predisposes to formation of calcium oxalate kidney stones. (See "Metabolic bone disease in inflammatory bowel disease" and "Kidney stones in adults: Epidemiology and risk factors".)

The recommended intake of elemental calcium for children and adults with IBD is the same as for the general population [1]:

- 1 to 3 years – 700 mg daily
- 4 to 8 years – 1000 mg daily
- 9 to 18 years – 1300 mg daily
- Men and premenopausal women – 1000 mg daily
- Postmenopausal women and men older than 70 years – 1200 mg daily

To minimize risks for metabolic bone disease, patients with IBD should be given focused nutritional counseling and calcium supplementation to meet the recommended target for calcium intake. This is particularly important in patients with additional risk factors for bone disease, which include glucocorticoid therapy and pubertal delay (either current or in the past). In patients with extensive Crohn disease of the small bowel, somewhat higher doses of calcium may be needed. (See "Metabolic bone disease in inflammatory bowel disease" and "Calcium requirements in adolescents".)

Negative calcium balance does not usually cause hypocalcemia, because the bones serve as a reservoir for calcium. Hypoalbuminemia reduces the total plasma calcium concentration but does not affect the physiologically important ionized (free) calcium concentration. If the serum ionized calcium is low, this may be caused by concurrent vitamin D deficiency or hypoparathyroidism. (See "Relation between total and ionized serum calcium concentrations" and "Etiology of hypocalcemia in adults".)

The evaluation and management of IBD-associated bone disease in children differs in several respects from that in adults, as discussed separately. (See "Important health maintenance issues for children and adolescents with inflammatory bowel disease", section on 'Bone mineral density'.)

LESS COMMON DEFICIENCIES

Folic acid — Folate deficiency may contribute to the development of anemia in patients with IBD, but this is uncommon, except in patients with specific risk factors, which include treatment with sulfasalazine or methotrexate.

Folate deficiency was observed in 20 to 60 percent of adults with IBD in older series but is uncommon in studies from the last decade [13,58]. This historical difference may reflect changes in medical therapy (eg, less use of sulfasalazine) and/or higher levels of folate intake through supplements or foods. In modern series of children with newly diagnosed IBD, folate concentrations were normal or higher than those of controls [52,64]. The clinical implications of this finding have yet to be determined.

Causes of folate deficiency in patients with IBD include insufficient dietary intake [58,64]. In addition, treatment with sulfasalazine may exacerbate folate deficiency since the drug's sulfa moiety can bind folate in the gut lumen, leaving it unavailable for absorption. This is not true for other aminosalicylates, such as mesalamine. Treatment with methotrexate (a folic acid antagonist) can also contribute to folate deficiency. Supplementation with folic acid reduces the incidence of liver enzyme abnormalities and methotrexate-associated nausea [65].

Supplementation of folic acid is recommended for IBD patients who are treated with sulfasalazine or methotrexate and for those with low serum folate levels on laboratory screening. However, there is insufficient evidence to support the use of supplemental folic acid for other patients with IBD. (See "Sulfasalazine and 5-aminosalicylates in the treatment of inflammatory bowel disease", section on 'Side effects' and "Overview of the management of Crohn disease in children and adolescents" and "Major side effects of low-dose methotrexate", section on 'Prevention of side effects with folate'.)

It is unclear if folate supplementation might decrease or increase colorectal cancer risk, based on mixed results of studies in populations without IBD. (See "Colorectal

cancer: Epidemiology, risk factors, and protective factors", section on 'Folic acid and folate'.)

Vitamin A — Laboratory evidence of vitamin A (retinol) deficiency occurs in a substantial proportion of patients with IBD and occasionally is severe enough to cause clinical symptoms. Patients with extensive small bowel involvement and/or fat malabsorption are at increased risk because vitamin A is a fat-soluble vitamin. In one study of adult patients with Crohn disease (40 percent of whom were hospitalized), 5 percent had clinically significant vitamin A deficiency characterized by impaired dark adaptation [66].

Low serum levels of vitamin A do not always indicate clinical deficiency, because this finding can be caused by hypoproteinemia and also because serum levels are not well correlated with total body stores. In a small study that used a dose-response test to determine functional vitamin A sufficiency, 37 percent of patients with Crohn disease had abnormal results compared with 12 percent of controls [67]. (See "Overview of vitamin A", section on 'Measurement'.)

Patients with laboratory evidence of vitamin A deficiency who are asymptomatic should be managed by optimizing treatment for the IBD and ensuring recommended intake of the vitamin (table 4), with further monitoring to ensure that levels normalize. Patients with ocular symptoms or severe malnutrition should be further evaluated for xerophthalmia and treated with replacement doses of vitamin A. (See "Overview of vitamin A", section on 'Clinical manifestations' and "Overview of vitamin A", section on 'Targeted supplementation for disease'.)

Excessive vitamin A supplementation should be avoided because high intakes of vitamin A are associated with an increased risk of bone fractures, as well as other effects including pseudotumor cerebri. (See "Overview of vitamin A", section on 'Adverse effects on bone'.)

Vitamin A is considered an antioxidant, but there is no clear evidence that deficiency of this or other antioxidants are involved in the pathogenesis of inflammation in IBD. (See 'Answers to common clinical questions' above.)

Vitamin E — Laboratory evidence of vitamin E (alpha-tocopherol) deficiency is unusual in IBD, and clinically significant deficiency is rare. In one study, mean levels of vitamin

E were lower in adult patients with IBD compared with healthy controls [68]. In another study, 6 percent of children with IBD had low serum levels of vitamin E (defined as <5 mg/L), and this was correlated with disease activity [69]. Mechanisms for vitamin E deficiency in IBD include fat malabsorption and low dietary intake. The majority of individuals with IBD consume less than the recommended intake of vitamin E [58,70].

The recommended intake of vitamin E for most patients with IBD is the same as for a healthy population, which is expressed as the dietary reference intake (DRI) in the United States (table 4) [71]. High-dose vitamin E supplementation is not necessary or recommended, because it may be associated with increased mortality in individuals without IBD [12]. Patients with significant fat malabsorption may need a water-soluble form of vitamin E supplements and/or higher doses, titrated to achieve normal serum levels. (See "Overview of vitamin E", section on 'Requirements' and "Overview of vitamin E", section on 'Risks and benefits of supplementation'.)

The DRI refers to alpha-tocopherol, which is the primary bioactive form of vitamin E, but gamma-tocopherol and several related compounds have been described. Both alpha- and gamma-tocopherol exhibit antiinflammatory properties. Vitamin E acts as a free radical scavenger, protecting cell membranes from peroxidation. It has been suggested that depletion of vitamin E and other antioxidant vitamins may contribute to the pathogenesis of IBD, but such pathways have not been established. (See 'Answers to common clinical questions' above.)

Vitamin K — Biochemical evidence of vitamin K deficiency (based on measurements of protein induced by vitamin K absence-II [PIVKA-II]) have been reported in more than 40 percent of children with IBD [72]. In a series of adult patients with IBD, evidence of vitamin K deficiency was seen in 25 percent of those with Crohn disease but in only 4 percent of those with ulcerative colitis [73]. Contributing mechanisms may include decreased intake due to anorexia or dietary restrictions, fat malabsorption (particularly with terminal ileal disease or resection), and/or antibiotics (which interfere with vitamin K production by intestinal bacteria). (See "Overview of vitamin K".)

Vitamin K is a cofactor in the carboxylation of osteocalcin, a protein essential for calcium binding to bone. Vitamin K deficiency may be a cause of decreased bone mineral density in patients with Crohn disease [73-76]. However, this association is

confounded by disease activity and corticosteroid exposures. Whether supplementation with vitamin K in patients with IBD can help prevent or treat bone disease has not been established. (See "Drugs that affect bone metabolism", section on 'Warfarin' and "Metabolic bone disease in inflammatory bowel disease".)

Other — Deficiencies of the following nutrients occasionally occur in patients with IBD and reflect generalized malnutrition rather than specific risks from IBD. Recommended intake and upper limits for selenium, copper, and other trace minerals are shown in the table (table 5).

- **Selenium** – Selenium concentration in whole blood and glutathione peroxidase activity are often somewhat lower in adults or children with IBD compared with healthy individuals, but biochemical or clinical evidence of deficiency is rare [77-79]. Deficient levels of selenium are more common among patients with Crohn disease who have undergone small bowel resection of >200 cm, those receiving exclusive enteral nutrition [80-82], and patients receiving long-term parenteral nutrition without trace minerals [83-85].

  Selenium occurs naturally in meats, cereals, and fish. It has multiple biologic roles. It is a component of the antioxidant glutathione peroxidase and is also required for formation of thyroid hormone. Clinical manifestations of prolonged selenium deficiency include erythrocyte macrocytosis and muscle dysfunction, cardiomyopathy, and encephalitis. (See "Overview of dietary trace elements", section on 'Selenium'.)

  Like zinc, selenium may be included in the antioxidant combinations that are occasionally given to patients with Crohn disease, although there is little firm evidence to support this practice. (See 'Answers to common clinical questions' above.)

- **Phosphate** – Malnourished patients with Crohn disease and chronic diarrhea are at risk for hypophosphatemia and require close monitoring and phosphate replacement. Phosphate stores can be depleted in patients with chronic diarrhea because of malabsorption of phosphate and vitamin D. In malnourished patients, sudden increases in nutrition can cause acute hypophosphatemia (refeeding syndrome), which is uncommon in patients with IBD but can potentially result in life-threatening complications due to acute fluid and electrolyte shifts. Poor

intake alone is rarely responsible for phosphate depletion because of rapid renal adaptation. (See "Hypophosphatemia: Causes of hypophosphatemia" and "Anorexia nervosa in adults and adolescents: The refeeding syndrome".)

- **Copper** – Most adults and children with IBD do not demonstrate copper deficiency; indeed, some series report relatively high copper levels [54,78,79,82,86]. However, increased losses are observed in those with profuse diarrhea, or high-output fistulas or ostomies (eg, >8 watery stools daily, or ostomy output >1500 mL/day or >20 mL/kg/day in children), or those maintained on parenteral nutrition without mineral supplements [87,88]. Because copper and zinc are competitively absorbed from the jejunum, high doses of zinc (eg, from prolonged ingestion of zinc supplements) can result in copper deficiency. (See "Overview of dietary trace elements".)

  Copper is an essential trace element used in many enzyme complexes and is required for normal iron absorption. Clinical manifestations of copper deficiency include abnormally formed hair, depigmentation of the skin, and microcytic anemia. The neurologic manifestations include ataxia, neuropathy, and cognitive deficits that can mimic vitamin B12 deficiency. (See "Overview of dietary trace elements", section on 'Copper'.)

- **Magnesium** – Magnesium deficiency in patients with IBD may result from decreased oral intake, malabsorption, or increased intestinal losses [89,90]. Chronic magnesium deficiency may contribute to osteopenia, fatigue, and muscle cramps. (See "Hypomagnesemia: Clinical manifestations of magnesium depletion".)

  Mild or chronic deficiencies can be supplemented orally with magnesium chloride. However, large doses given orally can lead to diarrhea, so parenteral administration of magnesium may be necessary in patients with very low serum magnesium levels.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links:

Pediatric iron deficiency" and "Society guideline links: Inflammatory bowel disease in children" and "Society guideline links: Vitamin deficiencies".)

SUMMARY AND RECOMMENDATIONS

- Historically, nutritional deficiencies or the inability to maintain ideal body weight were common in adults with inflammatory bowel disease (IBD) and especially those with Crohn disease. Mechanisms include reduced nutrient intake, malabsorption, increased energy expenditure, and enteral loss. Advances in diagnosis and medical therapy have decreased the incidence of this problem. These issues continue to be a concern in children with IBD, due to increased nutrient needs during growth and development. (See "Growth failure and poor weight gain in children with inflammatory bowel disease".)

- Vitamin and mineral deficiencies are common in patients with IBD; the frequency depends on the type of disease (most are more common in Crohn disease than in ulcerative colitis), disease activity, disease location, age (growing children are at increased risk), and surgical bowel resection (table 1). Iron deficiency is clinically important and common, especially in patients with chronic or acute gastrointestinal blood loss and/or high levels of disease activity, or those who have had intestinal resection. Active disease of the terminal ileum may lead to deficiencies of vitamin B12 or fat-soluble vitamins, while extensive disease of the small intestine with profuse diarrhea may lead to zinc deficiency. (See 'Risk factors for nutrient deficiencies' above.)

- The most important strategy to address micronutrient deficiencies is to treat the patient's underlying disease to minimize inflammation and any associated malabsorption and anorexia. Patients with specific, pronounced deficiencies may require vitamin or mineral supplements, tailored to their individual needs. (See 'Answers to common clinical questions' above.)

- Routine laboratory studies indicated for nutritional assessment in patients with IBD include a complete blood count (CBC), albumin, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and vitamin D (table 2). Ferritin, serum iron, and total iron-binding capacity should be evaluated when anemia is present. We also monitor vitamin B12 in patients with Crohn disease and active

disease or resection of the terminal ileum. Measurement of serum concentrations of vitamins A and E, prothrombin time (PT), magnesium, calcium, phosphorus, zinc, and folate may also be indicated based upon disease severity and location. (See 'Laboratory monitoring for nutrient deficiencies' above.)

- Anemia in patients with IBD is usually related to iron deficiency but may also be caused by anemia of chronic inflammation (anemia of chronic disease). Occasionally, it is caused by other mechanisms, including vitamin B12 or folate deficiency, drug-induced (eg, due to sulfasalazine or thiopurine therapy), or by multiple mechanisms. Laboratory tests sometimes help to distinguish among these causes, but a trial of iron therapy is necessary to confirm a diagnosis of iron deficiency anemia. (See 'Considerations for patients with anemia' above.)

- For patients with mild IBD activity and mild or moderate anemia (hemoglobin 10 to 12 g/dL in children and women or 10 to 13 g/dL in men), we suggest low-dose iron supplementation by the oral route as an initial trial (**Grade 2C**). For those with moderate to severe IBD activity or severe anemia (hemoglobin <10 g/dL), or for those who do not tolerate or respond appropriately to oral iron, we suggest intravenous (IV) iron supplementation (**Grade 2B**). The decision to use the oral versus IV route may also depend on patient preference or cost considerations. We commonly use IV iron because it is effective and safe. Several formulations of IV iron are available that have established efficacy and safety in this population. (See 'Iron therapy' above.)

- Bone disease (osteopenia or osteoporosis) is an insidious but common complication of IBD. Important contributors to bone disease include malnutrition (particularly vitamin D deficiency), glucocorticoid treatment, and active inflammation. Pubertal delay, which is common in adolescents with undiagnosed or active IBD, is also associated with lower bone density because of lower levels of sex steroids. All patients with IBD should be counseled to ensure recommended intake of calcium (1300 mg daily in adolescents and 1000 to 1200 mg daily in adults) and vitamin D (600 international units [15 mcg] daily) and monitored for vitamin D deficiency. (See 'Vitamin D' above and 'Calcium' above and "Metabolic bone disease in inflammatory bowel disease".)

ACKNOWLEDGMENT

The UpToDate editorial staff acknowledges Jonathan Teitelbaum, MD, who contributed to an earlier version of this topic review. The editorial staff is also saddened by the death of Paul Rutgeerts, MD, who passed away in September 2020. UpToDate gratefully acknowledges Dr. Rutgeerts' work as our Section Editor for Gastroenterology.

Topic 5887 Version 39.0

GRAPHICS

Laboratory evidence of nutritional deficiencies reported in adults with inflammatory bowel disease

Deficiencies	Percent
Common	
Anemia	60 to 80
Iron deficiency	39 to 81
Vitamin D deficiency	75
Vitamin B12 deficiency*	20 to 60
Zinc deficiency	40 to 50
Calcium deficiency¶[1]	18 to 42
Hypoalbuminemia (primarily reflects inflammation)	25 to 80
Less commonΔ	
Folic acid deficiency◇	
Magnesium deficiency	
Vitamin A deficiency	
Vitamin E deficiency	
Vitamin K deficiency	
Copper deficiency	
Vitamin C deficiency	
Vitamin B1 (thiamine) deficiency[2]	
Niacin deficiency	

The frequency of vitamin and mineral deficiencies in patients with inflammatory bowel disease varies widely, depending on the patient population and criteria used to define deficiency. In this table, deficiencies are listed as "less common" if they are typically reported in 10% or less of the population studied.

DXA: dual-energy x-ray absorptiometry.
* The frequency of vitamin B12 deficiency depends on extent of ileal involvement or ileal

resection.

¶ Negative calcium balance as defined by bone mineral density T-score <–2.5 as measured by DXA.

Δ Cases reported but prevalence not described.

◇ The prevalence of folic acid deficiency in this population varies widely in different reports. It appears to be uncommon in reports from the last decade, perhaps due to reduced use of sulfasalazine and/or higher levels of folate intake[3].

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Graphic 72725 Version 6.0