

AGA Clinical Practice Update on Management of Iron Deficiency Anemia: Expert Review

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DESCRIPTION: In this Clinical Practice Update (CPU), we will Best Practice Advice (BPA) guidance on the appropriate management of iron deficiency anemia.

METHODS: This expert review was commissioned and approved by the AGA Institute Clinical Practice Updates Committee (CPUC) and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership, and underwent internal peer review by the CPUC and external peer review through standard procedures of *Clinical Gastroenterology and Hepatology*. These Best Practice Advice (BPA) statements were drawn from a review of the published literature and from expert opinion. Since systematic reviews were not performed, these BPA statements do not carry formal ratings regarding the quality of evidence or strength of the presented considerations.

BEST PRACTICE ADVICE 1: No single formulation of oral iron has any advantages over any other. Ferrous sulfate is preferred as the least expensive iron formulation.

BEST PRACTICE ADVICE 2: Give oral iron once a day at most. Every-other-day iron dosing may be better tolerated for some patients with similar or equal rates of iron absorption as daily dosing.

BEST PRACTICE ADVICE 3: Add vitamin C to oral iron supplementation to improve absorption.

BEST PRACTICE ADVICE 4: Intravenous iron should be used if the patient does not tolerate oral iron, ferritin levels do not improve with a trial of oral iron, or the patient has a condition in which oral iron is not likely to be absorbed.

BEST PRACTICE ADVICE 5: Intravenous iron formulations that can replace iron deficits with 1 or 2 infusions are preferred over those that require more than 2 infusions.

BEST PRACTICE ADVICE 6: All intravenous iron formulations have similar risks; true anaphylaxis is very rare. The vast majority of reactions to intravenous iron are complement activation-related pseudo-allergy (infusion reactions) and should be treated as such.

BEST PRACTICE ADVICE 7: Intravenous iron therapy should be used in individuals who have undergone bariatric procedures, particularly those that are likely to disrupt normal duodenal iron absorption, and have iron-deficiency anemia with no identifiable source of chronic gastrointestinal blood loss.

**BEST PRACTICE
ADVICE 8:**

In individuals with inflammatory bowel disease and iron-deficiency anemia, clinicians first should determine whether iron-deficiency anemia is owing to inadequate intake or absorption, or loss of iron, typically from gastrointestinal bleeding. Active inflammation should be treated effectively to enhance iron absorption or reduce iron depletion.

**BEST PRACTICE
ADVICE 9:**

Intravenous iron therapy should be given in individuals with inflammatory bowel disease, iron-deficiency anemia, and active inflammation with compromised absorption.

**BEST PRACTICE
ADVICE 10:**

In individuals with portal hypertensive gastropathy and iron-deficiency anemia, oral iron supplements initially should be used to replenish iron stores. Intravenous iron therapy should be used in patients with ongoing bleeding who do not respond to oral iron therapy.

**BEST PRACTICE
ADVICE 11:**

In individuals with portal hypertensive gastropathy and iron-deficiency anemia without another identified source of chronic blood loss, treatment of portal hypertension with nonselective β -blockers can be considered.

**BEST PRACTICE
ADVICE 12:**

In individuals with iron-deficiency anemia secondary to gastric antral vascular ectasia who have an inadequate response to iron replacement, consider endoscopic therapy with endoscopic band ligation or thermal methods such as argon plasma coagulation.

**BEST PRACTICE
ADVICE 13:**

In patients with iron-deficiency anemia and celiac disease, ensure adherence to a gluten-free diet to improve iron absorption. Consider oral iron supplementation based on the severity of iron deficiency and patient tolerance, followed by intravenous iron therapy if iron stores do not improve.

**BEST PRACTICE
ADVICE 14:**

Deep enteroscopy performed in patients with iron-deficiency anemia suspected to have small-bowel bleeding angioectasias should be performed with a distal attachment to improve detection and facilitate treatment. Small-bowel angioectasias may be treated with ablative thermal therapies such as argon plasma coagulation or with mechanical methods such as hemostatic clips.

**BEST PRACTICE
ADVICE 15:**

Endoscopic treatment of angioectasias should be accompanied with iron replacement. Medical therapy for small-bowel angioectasias should be reserved for compassionate treatment in refractory cases when iron replacement and endoscopic therapy are ineffective.

Iron deficiency (ID) is the most common nutritional deficiency worldwide.¹ In the United States, 1% to 4% of men are ID, and an additional 2% have iron-deficiency anemia (IDA).² At least 39% of premenopausal women and 8% of postmenopausal women are ID, and, overall, 4% to 17% of women have IDA.³ Ferritin is the most commonly used marker for diagnosing ID, with varying recommendations for the appropriate threshold. A recent American Gastroenterological Association (AGA) guideline recommended use of a ferritin cut-off value of 45 mg/dL in individuals with anemia because this level was believed to have an optimal balance of sensitivity and specificity.^{4,5} It is important to recognize that patients with inflammatory conditions may have ID or IDA in the setting of a ferritin level greater than 45 mg/dL (usually <100 mg/dL).⁶ Confirmatory testing with transferrin saturation, soluble transferrin receptor, or reticulocyte hemoglobin equivalent may be helpful in these situations. After identification of ID with or without anemia, an appropriate diagnostic work-up should be undertaken including evaluation of dietary iron intake, review of menstrual blood losses in

premenopausal women, and a search for gastrointestinal conditions leading to poor iron absorption or blood loss including *Helicobacter pylori* infection.⁵ Multidisciplinary management including gastroenterologists, hematologists, and nutritionists often is needed in complex cases. Nutritional consultation often is helpful to increase dietary iron intake, and a hematology consultation can help with complex anemia situations or if there is difficulty accessing intravenous (IV) iron.

Iron repletion is needed to improve quality of life and decrease the risk of complications related to anemia. Oral iron supplementation usually is initiated first, but often is tolerated poorly because of side effects such as nausea, abdominal pain, and constipation.⁷ Because of these side effects and the tight regulation of iron absorption,⁸ increasing intestinal iron absorption can be difficult, which has stimulated the development and increasing use of IV iron formulations. In some patients with severe ID or conditions in which oral iron may not be well absorbed, IV iron may be given initially. The goal of this Clinical Practice Update is to review options for oral and IV iron repletion and to review best practices for

management of ID in common gastrointestinal conditions. Recommendations for gastrointestinal evaluation of IDA have been provided in a previous AGA guideline.^{4,5} Although most studies in gastrointestinal conditions have used IDA as an end point, similar considerations can apply to patients with ID without anemia.

Oral Iron Supplementation

Many formulations of oral iron are available (Table 1), without substantial evidence that any one product is better than another—either in effectiveness or tolerance.^{9–13} The ferrous iron salts (ferrous sulfate, ferrous fumarate, and ferrous gluconate) are a reasonable choice to start with because they are often the least expensive. Although some patients may tolerate other products such as ferrous bisglycinate better, there again is no evidence of superiority in clinical trials.¹² Side effects are common with oral iron; a meta-analysis reported constipation in 12% of patients, diarrhea in 8%, and nausea in 11%.¹⁴

When patients take oral iron, levels of serum hepcidin increase in response and will remain increased for up to 48 hours.¹⁵ This increase in hepcidin blocks further iron absorption. Thus, there is no reason to take iron more than once a day because this will not improve absorption but will increase side effects.¹⁶ Early data suggest that taking iron every other day appears to improve tolerance, but this needs to be better studied before being implemented.^{13,17,18}

Certain dietary manipulations may improve iron absorption. A recent iron isotope study showed that taking iron with 80 mg ascorbic acid on an empty stomach improves iron absorption.¹⁹ Vitamin C improves absorption by forming a chelate with iron that prevents the formation of insoluble iron compounds and by reducing ferric to ferrous iron. However, evidence supporting vitamin C administration to improve iron absorption is mixed,^{20,21} and further study is needed to clarify the effectiveness of this practice. Tea and coffee are powerful inhibitors of iron absorption and should not be consumed within an hour after taking iron.²² Although

oral iron is absorbed better when taken on an empty stomach, some patients will better tolerate taking iron with meals. If feasible, taking iron with meat protein will improve absorption, and the use of 500 mg vitamin C will allow iron absorption even if calcium or fiber is present in the meal.^{23,24}

Intravenous Iron Supplementation

IV iron is indicated if a patient cannot tolerate oral iron or if blood counts or iron stores do not improve with oral iron supplementation. In anemic patients, hemoglobin levels should increase by 1 g/dL within 2 weeks in adherent patients on oral iron supplementation.²⁵ A reasonable expectation is ferritin should increase in a month, and if these parameters are not met then IV iron should be used. IV iron also should be used in situations in which oral iron likely will not be effective owing to impaired absorption, such as in patients after bariatric surgery, with active inflammatory bowel disease (IBD), or when iron loss exceeds absorption of oral iron. However, IV iron is substantially more expensive than oral formulations (Table 2).

Several different formulations of IV iron are available that differ in dose and frequency of administration (Table 2). Because there is little difference in overall efficacy of iron repletion and similar risks, formulations that can replace iron deficits with 1 to 2 infusions are preferred. Being truly allergic to IV iron is very rare—almost all reactions are complement activation-related pseudo-allergy, which are idiosyncratic infusion reactions that can mimic allergic reactions.²⁶ For mild reactions, simply stopping the infusions and restarting 15 minutes later at a slower rate will suffice. For more severe reactions, corticosteroids may be of benefit. Diphenhydramine should be avoided because its side effects of mouth dryness, tachycardia, diaphoresis, somnolence, and hypotension can be mistaken for worsening of the reaction.²⁷ Studies have shown that rates of mild reactions are approximately 1:200 and rates of major reactions are approximately 1:200,000.²⁸

Table 1. Common Oral Iron Preparations

Agent	Approximate elemental iron content	Available formulations	Cost of 30 pills ^a
Ferrous sulfate	65 mg per tablet	Capsule, tablet, liquid	\$0.30–\$4.50
Ferrous gluconate	27–38 mg per tablet	Capsule, tablet, liquid	\$1.50–\$3.30
Ferrous fumarate	150–106 per tablet	Capsule, tablet, liquid	\$3.90
Polysaccharide–iron complex	Varies, but milligrams of iron are listed in the name of the product	Capsule, liquid	\$4.20
Ferrous bisglycinate	25 mg per tablet	Tablet, capsule, liquid	\$2.40

^aCost obtained from Lexi-drugs. Waltham (MA): UpToDate, Inc, 2024. Available from <http://online.lexi.com>. The cost of ferrous bisglycinate was obtained from Amazon.com, 2024.

Table 2. Intravenous Iron Preparations

Agent	Typical single dose	Typical dose schedule	Special considerations	Medication cost for typical dose schedule ^a
Ferric carboxymaltose	750–1000 mg	750 mg × 2 one week apart or 1000 mg as a single dose	Risk of hypophosphatemia	\$3470
Ferric gluconate	125 mg	125 mg × 8 given no closer than every other day	–	\$610
Ferric derisomaltose	1000 mg	1000 mg × 1	–	\$3896
Ferumoxitol	510–1020 mg	510 mg × 2 or 1020 mg × 1	Also used as magnetic resonance contrast agent; consult radiology if MRI requested within 3 months of infusion	\$1963
Iron sucrose	100 mg	200 mg × 5 or 300 mg × 3 weekly	–	\$441.50
Low-molecular-weight iron dextran	1000 mg	1000 mg × 1	–	\$405

MRI, magnetic resonance imaging.

^aCost derived from Lexi-drugs. Waltham (MA): UpToDate, Inc, 2024. Available from <http://online.lexi.com>. Does not include cost of infusion visits.

Large studies have shown that all IV iron formulations are associated with adverse effects, so from a safety standpoint no one product is preferred.^{29–31} However, 2 products do have unique considerations. First, ferumoxitol (Feraheme, AMAG Pharmaceuticals) is a superparamagnetic iron oxide coated with carbohydrate that also is approved as a magnetic resonance imaging contrast agent. Thus, the radiologist should be notified if magnetic resonance imaging is obtained within 3 months after infusion. Second, iron carboxymaltose (Injectafer, Daiichi Sankyo Inc) has been associated with hypophosphatemia, particularly with repeated dosing. The hypophosphatemia can be prolonged and lead to complications such as fatigue and osteomalacia.^{32,33} This formulation therefore should be used only with great care in patients with poor absorption or nutrition.

Iron-Deficiency Anemia After Bariatric Surgery

IDA is pervasive after bariatric procedures, especially after procedures such as Roux-en-Y gastric bypass, which disrupts normal duodenal iron absorption.^{34–37} However, bariatric procedures such as adjustable gastric bands or endoscopic or surgical sleeve gastrectomy also can be associated with IDA,^{38–40} as can nonbariatric procedures that interrupt iron absorption. Although the cause of IDA after bariatric surgery often is multifactorial, it most often occurs as a result of inadequate iron absorption. This occurs because iron is absorbed most efficiently in the duodenum and proximal jejunum, which typically is disrupted after most bariatric approaches involving bypass of this part of the gastrointestinal tract, and

because acid, secretion of which often is disrupted, helps to release iron from dietary nutrients and to release heme from ingested hemoglobin/myoglobin (very low pH [<3] also enhances Fe^{2+} and Fe^{3+} solubilization and thus absorption). Anastomotic ulcers also are common after bariatric surgery, which may cause acute or occult gastrointestinal bleeding.⁴¹ Given the propensity for development of anastomotic ulcers after bariatric surgery, causing chronic bleeding and iron loss, patients with postsurgical IDA should undergo an esophagogastroduodenoscopy to exclude ulcer disease.

Treatment of IDA in patients after bariatric surgery involves addressing both the anemia and nutrient absorption after surgery. Iron supplementation strategies used after bariatric surgery often are highly variable, and many do not provide sufficient iron to prevent or treat IDA.⁴² Given the anatomic considerations at play after bariatric surgery, IV iron is preferred in patients after bariatric surgery, particularly in more severe cases or when oral supplementation is ineffective.⁴³ In one study of women developing ID after Roux-en-Y gastric bypass, a single dose of IV iron was more effective and better tolerated than treatment with either oral ferrous fumarate or ferrous gluconate.⁴⁴ If iron stores are slow to recover, evaluation of other micronutrient deficiencies or sources of chronic blood loss may be needed.

Iron-Deficiency Anemia and Inflammatory Bowel Disease

ID and/or IDA have been reported to occur in up to 90% of patients with IBD, including both Crohn's disease and ulcerative colitis.^{45–51} The etiology of IDA in these

diseases often is complicated and typically multifactorial, including elements of (1) gastrointestinal blood loss (both clinically evident, but also occult), (2) poor iron absorption, and (3) inadequate iron intake.^{51–55} Patients with aggressive and active disease, or those who have had intestinal resection, may be particularly challenging to manage.

Given the multiple causes of IDA in patients with IBD, treatment typically first focuses on addressing underlying inflammation, which may cause ulceration and chronic blood loss,⁵² as well as reduced iron absorption.⁵⁵ Treatment (for review see Feuerstein et al^{56,57} and Ko et al⁵⁸) should include optimizing medical management of the underlying inflammation, as well as dietary intervention. Iron supplementation should be given to all patients with IBD and IDA.

There is some controversy about the best route to supplement iron in patients with IBD. Many studies have demonstrated that IV iron appears to be superior to oral iron in patients with IBD.^{59–61} In a systematic review and meta-analysis of 5 randomized controlled trials (RCTs) including 694 adults with IBD and comparing IV with oral iron head-to-head to correct IDA, IV iron had greater efficacy than oral iron in achieving a hemoglobin increase of ≥ 2.0 g/dL (odds ratio, 1.57; 95% CI, 1.13–2.18).⁴⁸ Importantly, IV iron appeared to be better tolerated with lower treatment discontinuation rates (odds ratio, 0.27; 95% CI, 0.13–0.59). Thus, although oral iron commonly is given to patients with IBD and generally is safe, IV iron appears to be more effective and better tolerated than oral iron. In fact, current consensus recommendations by the European Crohn's and Colitis Organization recommend IV over oral iron as first-line therapy for patients with a hemoglobin level <10 g/dL.⁶² Notwithstanding, oral iron may be appropriate in carefully selected patients with IBD who have mild anemia, whose disease is clinically inactive, and who are able to tolerate oral iron. If oral iron is used, close follow-up evaluation is needed to assess patient tolerance and response.

Iron-Deficiency Anemia and Portal Hypertensive Gastropathy

Portal hypertensive gastropathy (PHG) may be associated with IDA,⁶³ and occurs as a result of increased portal pressure, typically found in patients with cirrhosis and portal hypertension. The pathogenesis of PHG is complex and poorly understood, but includes gastric mucosal changes in a typical histologic pattern.⁶⁴ What is known is that portal hypertension is necessary, but does not appear to be sufficient to cause PHG because all patients with PHG have portal hypertension, but not all patients with portal hypertension have PHG. PHG appears to increase in frequency with more severe portal hypertension, advanced liver

disease, longer liver disease duration, and the presence of esophageal varices. The diagnosis of PHG requires endoscopic visualization.

Management of IDA in patients with PHG starts with addressing the underlying cirrhosis and portal hypertension, in particular with interventions to reduce portal pressure. Nonselective β -blockers reduce portal pressure in some patients with portal hypertension, and several clinical studies have suggested that patients with non-bleeding and bleeding PHG treated with propranolol had better outcomes (bleeding severity and mortality) than patients treated with placebo.^{65,66} The most effective approaches to reducing portal pressure in patients with cirrhosis include the use of transjugular intrahepatic portosystemic shunts^{67,68} and liver transplantation.⁶⁹ Endoscopic therapy rarely is helpful in patients with PHG because bleeding typically is from diffuse mucosal lesions.

Beyond management of portal hypertension, all patients with IDA and PHG should receive iron therapy, which may be oral or IV, depending on the severity of iron depletion. Importantly, there is no known malabsorptive defect in patients with PHG, so oral iron therapy should be sufficient. However, there is no contraindication to the use of IV iron in patients with PHG, and this approach is reasonable in those with profound IDA.

Iron-Deficiency Anemia and Gastric Antral Vascular Ectasia

Gastric antral vascular ectasia (GAVE) is associated with several chronic medical conditions including cirrhosis, chronic kidney disease, and systemic sclerosis. It is an uncommon but often difficult-to-manage cause of chronic gastrointestinal blood loss. Although there are no proven pharmacologic therapies for GAVE, treatment with endoscopic band ligation (EBL) or with endoscopic thermal methods such as argon plasma coagulation or radiofrequency ablation leads to decreased blood loss and reduced red blood cell transfusion requirements.^{70,71} Observational studies and RCTs comparing endoscopic thermal therapies with EBL have found high rates of endoscopic success for both modalities, but greater decreases in transfusion requirements (difference in mean transfusions, -2.30; 95% CI, -4.11 to -2.48 favoring EBL) and more pronounced improvement in hemoglobin levels in patients treated with EBL (difference in mean improvement in hemoglobin, 0.59 g/dL; 95% CI, 0.17–1.00 favoring EBL).⁷⁰ EBL also required fewer endoscopic sessions to achieve obliteration of GAVE (mean, 2.63 vs 3.83 sessions) and with favorable safety profiles.^{70,71} All patients with IDA and GAVE should receive iron repletion, which may be oral or IV depending on the severity of iron depletion and tolerance.

Iron-Deficiency Anemia and Celiac Disease

Celiac disease (CD) is present in 2% to 6% of asymptomatic patients with IDA.⁷²⁻⁷⁵ Patients with CD who are anemic at presentation tend to have higher antitissue transglutaminase levels and higher degrees of villous atrophy than nonanemic patients.⁷⁶ ID occurs in CD as a result of epithelial cell injury (and subsequent duodenal villous atrophy), which disrupts normal absorption; however, other causes of ID should be excluded. In most patients without another explanation for ID, anemia will improve after initiation of a strict gluten-free diet even without iron supplementation. In general, improvement in iron status occurs in parallel with normalization of the histologic abnormalities in the small bowel. However, up to 20% of patients will remain iron deficient even with strict gluten avoidance.⁷⁷ The indications for oral or IV iron supplementation in CD are not well defined, and depend primarily on the severity of symptoms, tolerance to oral iron, and presence of alternative sources of blood loss. Many patients with mild ID and less severe histologic abnormalities may respond to a gluten-free diet alone. However, response can be slow because it depends on normalization of small-bowel histology. Oral iron along with a gluten-free diet therefore may be indicated in patients with symptoms potentially related to ID. Oral iron is less likely to be effective in patients with more severe degrees of villous atrophy, and IV iron may be indicated in these patients or in patients with more severe symptoms of ID.⁷⁸ IV iron also may be indicated in patients whose iron stores do not recover sufficiently with oral iron and a strict gluten-free diet. Appropriate evaluation of other micronutrient deficiencies, sources of chronic blood loss, or anemia of chronic inflammation should be undertaken in patients whose iron stores are slow to recover.⁷⁷

Iron-Deficiency Anemia and Small-Bowel Angioectasias

Patients with gastrointestinal angioectasias often have recurrent gastrointestinal bleeding, which may cause IDA. Previous studies have reported a diagnostic yield of 20% to 40% for angioectasias in patients who have undergone a small-bowel evaluation for IDA.^{79,80} The diagnosis and management of angioectasias can be challenging, with a tendency to rebleed despite therapy. For example, a meta-analysis of 14 studies and 623 patients with gastrointestinal angioectasias determined that the overall rebleeding rate was 34% and the rebleeding rate for small-bowel angioectasias was 45%.⁸¹ Endoscopic therapy typically is performed with ablation, with argon plasma coagulation being the most common form of therapy. Hemostatic clips and endoscopic sclerosants also may be used with some evidence of effectiveness.⁸²⁻⁸⁵ Radiofrequency ablation is a newer

modality of therapy, but is technically challenging and potentially risky in the small bowel and is considered experimental. In a case series, Lara et al⁸⁶ observed a 20% rebleeding rate over a 6-month period with the use of radiofrequency ablation. Even though ablation is performed frequently, endoscopic monotherapy for gastrointestinal angioectasias is noted to be insufficient and may be one of the reasons why rebleeding occurs.⁸⁷ This is especially true among gastrointestinal angioectasias diagnosed in the small bowel. Incomplete visualization of the small bowel is one potential reason why the rebleeding rate for small-bowel angioectasias is higher than angioectasias diagnosed in the upper gastrointestinal tract and colon.⁸¹ In small, single-center studies, use of a distal endoscope attachment such as a transparent cap significantly increased the number of gastrointestinal angioectasias identified in the small bowel and therefore facilitated more complete therapy.^{88,89} Further studies are needed to fully define the need for distal endoscope attachments in this clinical scenario and to determine the optimal methods to treat angioectasias as well as their safety.

Current data suggest that adjunct medical therapy including iron therapy and somatostatin analogues may be beneficial in increasing hemoglobin levels, decreasing transfusion requirements, and reducing hospital admissions secondary to rebleeding.⁹⁰⁻⁹² The choice of oral or IV iron in patients with bleeding gastrointestinal angioectasias depends on the severity of iron depletion, symptoms, and patient tolerance. Two meta-analyses have shown that the use of somatostatin analogues may reduce the red blood cell transfusion requirement as well as the rebleeding rate in patients diagnosed with small-bowel angioectasias, although the evidence to date is not robust.^{81,93} Octreotide is noted to be more effective than lanreotide.⁹³ There have been 2 RCTs that have evaluated antiangiogenic therapy, with thalidomide being the most studied. One RCT comparing thalidomide with iron therapy showed that thalidomide led to a significant reduction in the number of transfusions and rehospitalizations secondary to bleeding.⁹⁴ In an RCT comparing thalidomide with placebo in patients diagnosed with small-bowel angioectasias, patients who received thalidomide had a dose-dependent reduction in rebleeding measured 1 year after treatment was completed.⁹⁵ In both studies, there were a significant number of adverse reactions including but not limited to peripheral neuropathy, constipation, and bowel perforation. Therefore, use of antiangiogenic therapy should be reserved for those who have failed all other forms of therapy and should be given by providers with experience with thalidomide.

Conclusions

Management of IDA includes both repletion of iron stores, and, if possible, management of the underlying

etiology. Iron repletion may be through oral or IV routes depending on the etiology and severity of ID, tolerance of oral iron, and likelihood of successful repletion through oral iron administration. Although oral iron often successfully repletes iron stores, IV iron is safe and effective in patients with severe ID or in those whom oral iron is unlikely to be effective. Further studies are needed to determine optimal formulations and routes for iron repletion as well as to identify patients who would benefit from earlier IV iron administration. Additional studies to elucidate optimal gastrointestinal management of difficult-to-treat conditions such as PHG, GAVE, and small-bowel angiodysplasias also are needed.

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Conflicts of interest

The authors disclose no conflicts.

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