Diagnosis of Iron Deficiency Anemia in the Elderly: When to Say “Uncle”

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Of the 40 % of anemic individuals aged 65 and over [1–6], 12–50 % are iron deficient [2]. What does it mean to diagnose iron deficiency in the “elderly?” How much work-up is enough? What happens long term to individuals who have a negative baseline colonoscopy and endoscopy? Does it make a difference in individuals whose iron levels are corrected with supplementation versus those who remain iron depleted? How extensive an evaluation should be made? Does everyone with a negative endoscopy/colonoscopy need small intestinal visualization with CT enterography, capsule endoscopy, or push endoscopy using a single or double balloon enteroscope?

Stay tuned. Soon et al. [7] at the San Diego VAMC and University of California, San Diego, purport to explain all of the forgoing to us and more in the current issue of DDS. What does their study show us? What are the limitations? Can it be generalized to the Medicare population as a whole?

In the present study, 105 men and 9 women with iron-deficiency anemia (IDA) and negative endoscopy and colonoscopy were followed for a mean of 65 months. Of the approximately half who had persistent or corrected anemia, significant pathology was present in only 4.3 %. In contrast, 54 % (6/11) of patients with recurrent anemia were ultimately diagnosed with significant lesions including colorectal cancer (2), gastric ulcer (2), and one case each of duodenal cancer and gastric angiodysplasia. An approximate threefold difference in mortality was noted between patients with resolved (normalization of hemoglobin with iron supplementation) versus persistent

(ongoing anemia despite iron supplementation) or recurrent (recurrent IDA post iron supplementation) anemia (12.5–34.5 %).

Most mortality was independent of IDA, but rather statistically associated with congestive heart failure, anticoagulation or antiplatelet drug use. The authors concluded that elderly veterans with iron-deficiency anemia that resolves with iron supplementation and in whom endoscopy and colonoscopy is negative have a favorable outcome, suggesting that the myriad tests now available to assess the small bowel are unnecessary. In patients with recurrent anemia, in contrast, or those who develop a subsequent significant gastrointestinal hemorrhage during follow-up, simply repeating endoscopy and colonoscopy should be the initial diagnostic steps as the vast majority of bleeding lesions (including three malignancies potentially missed at time of their index procedures) were within range of the initial endoscopy/colonoscopy. This is, of course, self-evident in a study in which small bowel examinations were done infrequently or in which small intestinal imaging studies were suboptimal. As such, 30 of the 114 patients in the Soon et al. study had additional testing with contrast radiology (all normal) and only nine patients (8 %) had capsule endoscopy with two of the nine having findings to potentially explain the etiology of the iron deficiency. That capsule endoscopy has limited use in older patients is a subject of debate that includes not only the incidence of pathology detected but also the resources expended and the outcomes of the endoscopic findings [8]. In a recent study, Tsibouris et al. [9] compared capsule findings in patients with occult or overt bleeding in younger patients and those over age 80 years. There was no difference in either group in the number of ulcerative or neoplastic lesions, although there was a significantly higher incidence of angiodysplasia in the elderly (80 vs. 47 %, $p < 0.0001$).

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Milano et al. [8], in turn, evaluated 189 patients with IDA in older subjects (mean age 68 ± 16.6 years). Those with negative upper and lower endoscopies underwent CT enteroclysis or video capsule endoscopy (VCE). Endoscopy results were positive in 144 of 189 patients (76.2 %) whereas 37/45 (82 %) patients who had no endoscopic findings had positive VCE (78 %) or CT enteroclysis (22 %, $p < 0.001$).

An additional study by Price et al. [5] evaluated 190 anemic patients over age 65. Thirty-five percent had unexplained anemia with increased inflammatory markers compared with controls. Twelve percent of patients had IDA and another 16 % were characterized as having a possible myelodysplastic syndrome. The authors concluded that IDA is difficult to diagnose in the elderly population and may not completely respond to iron supplementation.

Finally, Vannella et al. [6] reviewed 136 consecutive patients with IDA who underwent gastroscopy to include small bowel biopsies for sprue plus colonoscopic evaluation. Bleeding lesions were more common in the elderly (>75 years, 49.5 vs. 29 %, $p = 0.025$), whereas Hp-related pangastritis, atrophic gastritis, and sprue were more common in younger patients.

So what do the forgoing studies teach us relative to the study by Soon et al.? Only that anemia in the elderly, even IDA, is complex, and iron repletion alone may be inadequate to correct the problem [10, 11]. They also teach us that, although uncommon, gluten-sensitive enteropathy is present, even in patients >75 years of age [4, 12]. Limitations of the present study include that sprue was assessed in only 72 patients (63 %) and that small intestinal evaluation was suboptimal or nonexistent in many subjects given multiple previous studies suggesting that small bowel evaluation with VCE is positive in up to 50 % of patients with otherwise undiagnosed IDA and that approximately 10 % of these bleeding sites are small bowel tumors [3, 8, 12].

Nevertheless, the authors of the present study have demonstrated convincingly that in most elderly patients, negative endoscopic and colonoscopic evaluation is associated with long-term survival, particularly if the anemia resolves with iron repletion alone. Who does not do well? Patients with persistent anemia, those with recurrent IDA, patients with a significant GI hemorrhage during follow-up, and those patients who become transfusion dependent all warrant close follow up. That 6/11 patients with recurrent anemia had significant pathology including three malignancies, two gastric ulcers, and one gastric angiodysplasia underscores the point that many bleeding sites were within reach of conventional endoscopic examinations and that a subset with lesions in the right colon and duodenum may have had pathology missed at index endoscopy [12]. The lack of reported small intestinal lesions in the present series

may be a consequence of incomplete small bowel evaluation in most of these patients or use of a technique (barium small bowel series) that misses the majority of lesions. Failure to fully evaluate the small intestine results in a true but self-fulfilling prophecy that repeat endoscopy and colonoscopy are the best diagnostic measures to reassess patients with ongoing or recurrent IDA. It does not change the authors' conclusion that patients with IDA who correct their anemia with iron and have a negative endoscopy and colonoscopy have favorable clinical (survival) outcomes. Should this paper define when and how vigorously to work up iron-deficiency anemia in the elderly? No. Nevertheless, it is reasonable evidence that performing multiple resource-intensive tests for potential small bowel bleeding in elderly patients with IDA may be unnecessary.

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