

Original Article

Benefit of Capsule Endoscopy in the Setting of Iron Deficiency Anemia in Patients Above Age 65

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Abstract

Background: Iron deficiency anemia (IDA) is a common indication for a capsule endoscopy (CE), which is often offered after a negative bidirectional endoscopy. Since malignancy is a concern in the older population with IDA, upper and lower endoscopic exams are typically performed. If these tests are negative, CE may be offered to evaluate the small intestine. However, choosing the ideal candidates who are most likely to benefit from a CE study is challenging.

Aims: The goal of this study was to assess the outcomes for CE in patients with IDA over age 65 and assess which factors are more likely to contribute to a positive CE yield.

Methods: A retrospective review of all CE studies at St. Paul's Hospital from January 2010 to June 2016 was conducted after ethics approval. Inclusion criteria included the following: age >65, hemoglobin <120 g/L, serum ferritin <70 µg/L, and at least one high-quality complete EGD/colonoscopy performed before CE. Variables to assess factors that are more likely to contribute to a positive capsule yield included use of anticoagulation medications, NSAIDs, PPIs, transfusion burden and cardiac disease. A Chi-Square test was then used to determine clinical predictive factors of a positive and negative study.

Results: There were 1149 CE studies that were reviewed, of which 130 CE studies met inclusion criteria. Fifty-one studies (40.6%) had positive findings, and from this group, 30 (58.8%) recommended active intervention (i.e., EGD, n = 8; colonoscopy, n = 12; push enteroscopy, n = 3; double-balloon [DB] enteroscopy, n = 2; small bowel resection, n = 3; escalation of Crohn's therapy, n = 2), while 21 (41.2%) were managed supportively, typically with iron supplementation. Most negative studies (73 of 79) recommended supportive therapy (other recommendations included hematological workup, n = 3; hiatal hernia repair, n = 1; proton-pump inhibitors [PPI] initiation, n = 1; stop donating blood, n = 1).

A history of cardiac disease had a significant association with positive findings (0.54 versus 0.33, $P = 0.001$). Conversely, a known history of low ferritin levels (0.84 versus 0.68, $P = 0.046$) and a known history of hiatal hernia (0.25 versus 0.08, $P = 0.012$) were associated with a negative study.

Conclusions: These findings suggest that the clinical yield of CE in IDA in patients above age 65 is relatively low. The majority of all CE studies recommended supportive therapy or repeat endoscopic exams (EGD/colonoscopy) of areas previously assessed and lesions missed. Provided that initial endoscopic exams were thorough and Crohn's disease management was optimized, the overall rate of changing management significantly was low at five of 130 studies (two DB enteroscopies and three resections) or 3.8%. Clinical factors focusing on cardiac history, ferritin levels and the presence of a hiatal hernia may be of utility to predict benefit of CE. Emphasis on these data may help select more appropriate patients for capsule endoscopy.

Keywords: *Iron deficiency anemia; Capsule endoscopy; Capsule; Anemia; Elderly*

Capsule endoscopy (CE) is a diagnostic tool used to visualize and detect pathologies in the small intestine. Its widespread use has been facilitated by the noninvasive nature of the test compared with a standard endoscopy (1). Due to its ease of administration and ability to assess the small bowel in detail, iron deficiency anemia (IDA) presents as a common indication for a capsule endoscopy study (1), which is often offered after a negative bidirectional endoscopy (2).

The underlying etiology of iron deficiency anemia varies greatly depending on the patient demographic, including sex and age (3). In young women, menorrhagia presents as a common reason for IDA, which can be treated supportively (4) and, therefore, does not necessitate the use of CE. However, because menorrhagia is no longer a factor in the older population, IDA in this group should bring up suspicions regarding underlying luminal malignancies and is routinely explored with upper and lower gastrointestinal (GI) endoscopies (5) because aging has been known to increase GI pathologies including both functional and organic disease (6, 7). If these tests are inconclusive, a CE study may be offered as the next step to evaluate the small intestine (2). However, due to the variability of its diagnostic yield (8), challenges arise when attempting to determine ideal candidates who will benefit from a CE study. Because CE is not widely available or easily accessible in many areas, ideal selection of patients is important.

To better evaluate the indications for CE in IDA in patients over age 65, we conducted a retrospective study assessing the management plans following CE and the predictive factors of a positive CE finding. We hypothesize that the diagnostic yield may be greater in the older population than the younger population due to increased risk of GI pathologies such as angiodysplasia (9) and malignancies (10) with advanced age. The clinical variables we chose aligned with variables that were found to have an association with more positive CE findings from a previous study (11). This is a quality improvement project with the intention of optimizing our use of CE by ensuring that appropriate patients are selected for CE.

METHODS

Capsule Endoscopy Studies

A retrospective review of all CE studies at St. Paul's Hospital, Vancouver, British Columbia, from January 2010 to June 2016 was conducted after ethics approval. There were 1149 CE studies that were reviewed using electronic medical records, and missing data were gathered by contacting the subject's general practitioner's office via fax. All CE

procedures included in the study were performed using the PillCam[®] (Given Imaging, Israel), Mirocam[®] (IntroMedic, Korea), EndoCapsule System[®] (Olympus, Japan), CapsoCam[®] (CapsoVision, Medical Innovations, US) and interpreted by a single gastroenterologist with expertise in CE. Patients were asked to undergo bowel preparation the day before, which included a clear liquid-only diet the evening prior and 2 L polyethylene glycol-electrolyte (PEG) solution taken orally during that time frame.

To be included in the study, the patients had to meet the following eligibility requirements: age over 65 years and proven IDA as defined by a hemoglobin level below 120 g/L and a serum ferritin level below 70 µg/L. Also, before CE, all patients must have undergone at least one high-quality EGD and colonoscopy.

Incomplete CE studies due to equipment failure, retention in the stomach or failure to reach the cecum with small bowel imaging in less than 1 hour were excluded from our study. In addition, those with a known active chronic pathology potentially inducing severe anemia were excluded: end-stage kidney disease (glomerular filtration rate inferior to 15 mL/min), hemoglobinopathies such as thalassemia, myelodysplastic syndromes, hematological malignancies, aplastic anemia, metastatic cancer or autoimmune conditions resulting in anemia (autoimmune hemolytic anemia and systemic lupus erythematosus).

We then separated these studies into two groups: (A) positive CE findings and (B) negative CE findings.

Group A patients were classified into six subgroups according to findings: (1) ulceration (2) vascular lesion, (3) nonbleeding polyp, tumour or mass, (4) erosion or inflammation, (5) blood or (6) other.

Group B patients were classified into one subgroup—negative study.

In both groups, we assessed whether or not the gastroenterologist advised for any specific management strategies. Clinical variables to assess factors that are more likely to contribute to a positive capsule yield included extreme old age, use of acetylsalicylic acid (ASA), anticoagulation medications, nonsteroidal anti-inflammatory drugs (NSAIDs), proton-pump inhibitors, transfusion burden and cardiac disease.

Statistical Analysis

Patient characteristics were used to determine clinical predictive factors of a positive and negative study. Differences in clinical factors were analyzed using the Chi square tests for categorical variables. P-values of <0.05 were considered statistically significant.

RESULTS

A total of 130 CE studies from 121 patients were reviewed after meeting inclusion criteria (Figure 1). Five patients underwent repeat CE studies for re-evaluation of the small bowel due to a suspected new or missed lesion.

Baseline characteristics

The baseline characteristics show the gender, age and laboratory values for all patients who underwent CE (Table 1). More females were represented in our study than males (60.8% versus 39.2%, $P = 0.01$). The mean values for hemoglobin (79.2 g/L) and ferritin (7.0 µg/L) were well below the cutoff (120 g/L and 70 µg/L, respectively) for our study.

Group A: Etiology, Location and Management Recommendations for Positive Findings

Fifty-one studies (39.2%) had positive findings, which were reported as clinically significant and the likely cause or a major contributor to the underlying anemia (Table 2 and Table 3). Most of the findings were within the small bowel (SB): proximal SB ($n = 12$), mid-distal SB ($n = 20$) and ileocecal valve/terminal ileum ($n = 6$) (Table 2). The most common findings in the SB were vascular lesions ($n = 13$), ulcerations ($n = 11$) or presence of blood ($n = 10$) (Table 2). Outside of the small bowel, nine gastric and four colonic pathologies contributed to positive findings (Table 3).

Thirty of the fifty-one studies (58.8%) recommended active intervention (e.g., endoscopic management, small bowel

resection, treatment of Crohn's disease [CD]) (Table 4). On the other hand, 21 of 51 (41.2%) positive findings were managed conservatively, typically with iron supplementation, monitoring lab values (hemoglobin and ferritin), blood transfusions or discontinuing NSAIDs (Table 4).

Specific Small Bowel Interventions for Positive Findings

Overall, seven CE studies recommended specific small bowel interventions beyond standard endoscopy (Table 5). These included two double-balloon (DB) enteroscopies for active bleeding lesions, three surgical resections for blood, polyps or ulcerations, and two Crohn's disease treatment for SB ulcerations, which were managed with medications. A follow-up of these patients revealed that six of seven patients underwent the recommended therapy, while one of seven refused to undergo SB resection. The results from these interventions led to

Table 1. Baseline characteristics

N total	130
Males	51 (37.7%)
Females	79 (62.3%)
Mean Age	73.8
Mean Hemoglobin	79.2 g/L
Mean MCV	82.0 fL
Mean Ferritin	7.0 µg/L
Mean GFR	86.0 ml/min

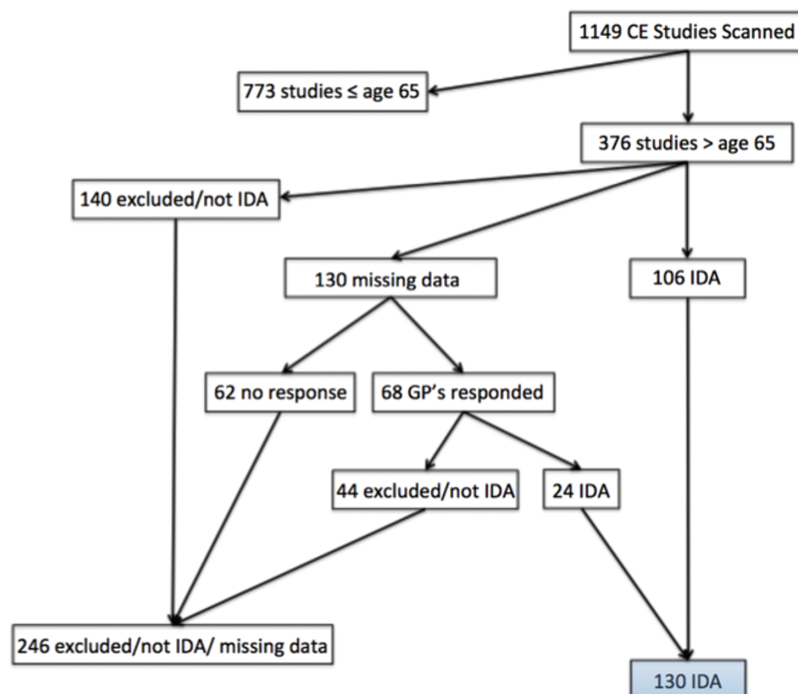


Figure 1. Flow chart of CE studies scanned and analyzed.

Table 2. Etiology, prevalence and location of positive CE findings in the small bowel (n = 38)

Findings	N
Ulceration (n = 11)	
Proximal small bowel	1
Mid-distal small bowel	7
Ileocecal valve/terminal ileum	3
Vascular Lesion (n = 13)	
Proximal small bowel	8
Mid-distal small bowel	5
Polyp/Tumour/Mass (n = 1)	
Mid-distal small bowel	1
Erosion/Inflammation (n = 1)	
Ileocecal valve/terminal ileum	1
Blood (n = 10)	
Proximal small bowel	3
Mid-distal small bowel	6
Ileocecal valve/terminal ileum	1
Other (n = 2)	
Abnormal Mucosa (Mid-distal small bowel)	1
Loss of Villi (Ileocecal valve/terminal ileum)	1

Abbreviations: SB = Small bowel, ICV = Ileocecal Valve, TI = terminal ileum

Table 3. Etiology, prevalence and location of positive CE findings outside of the small bowel (n = 13)

Findings	N
Vascular Lesion (n = 5)	
Gastric	3
Colon	2
Polyp/Tumour/Mass (n = 2)	
Gastric	2
Erosion/Inflammation (n = 3)	
Gastric	3
Blood (n = 3)	
Gastric	1
Colon	2

argon plasma coagulation to vascular lesion in the SB (n = 1), supportive therapy for no SB lesion being found (n = 1), resection of SB adenocarcinoma (n = 1), resection of SB leiomyoma (n = 1), CD diagnosis and initiation of therapy (n = 1), and escalation in CD therapy (n = 1).

Group B: Management Recommendations for Negative Findings

Seventy-nine studies (60.8%) had negative findings with normal or nonclinically significant findings of the small bowel (Table 6). Seventy-three out of the 79 studies (92.4%)

Table 4. Recommended management of positive CE findings (n = 51)

Recommended Management	N
Supportive Therapy	
Oral or Intravenous Iron Supplementation and Monitor Hemoglobin/Ferritin	16
Discontinue NSAIDs	5
Endoscopy	
Esophagoduodenoscopy	8
Enteroscopy (Push/Double balloon)	5
Colonoscopy	12
Laparotomy/Surgery	
Small Bowel Resection	3
Treatment of positive finding	
Crohn's Disease	2

recommended supportive therapy, which typically consisted of iron supplementation, monitoring laboratory values (hemoglobin and ferritin) and blood transfusions, as needed. Other recommendations included hematological workup (n = 3), hiatal hernia repair (n = 1), PPI initiation (n = 1), and a cessation of donating blood (n = 1).

Clinical Factors for Positive CE Findings

Several clinical factors including laboratory values, medications and past medical history were gathered and analyzed to observe associations with positive findings (Table 7). A history of cardiac disease (e.g., arrhythmias, valvular heart disease, myocardial infarction and coronary artery disease) had a significant association with positive findings (0.55 versus 0.27, $P = 0.001$). Conversely, a low ferritin level $<20 \mu\text{g/L}$ (0.84 versus 0.68, $P = 0.046$) and a known history of hiatal hernia (0.25 versus 0.08, $P = 0.012$) were associated with a negative study (Table 7).

Discussion

A review study in 2014 showed that the diagnostic yield (DY) of CE in setting of IDA is heterogeneous, quoting 26% to 78% among all-comers (8). This could be attributable to a lack of uniform and validated scoring criteria in evaluating the small bowel and the significance of findings being subject to the interpreter. To minimize variations in interpretation, a single gastroenterology board-certified expert in capsule endoscopy reported all CE findings in our study. Despite eliminating menorrhagia as the culprit for IDA by selecting the elderly population, the DY in our study (~40%) remained similar to a previous study conducted at the same institution looking at all age groups (11) and did not increase as we had expected.

Previous reports suggest that, in general, the DY of CE for IDA increases with age—especially in those aged ≥ 85 (8). Our

Table 5. Positive studies requiring specific small bowel interventions (n = 7)

CE Recommendation (N)	CE Indication	CE Findings	Follow-up Results
DB Enteroscopy (2)	1.IDA 2.IDA	1- Active bleeding in ileum. 2- Active bleeding in proximal jejunum.	1- Retrograde DB enteroscopy with APC to non-bleeding ileal vascular lesion. 2- DB enteroscopy with no significant lesions seen. Suggest supportive therapy.
SB Resection (3)	1.IDA and SBO 2.IDA 3.IDA	1- Blood in the mid-SB. 2- Polypoid lesion found in mid SB. 3- Ulcerations in the distal SB. Thought to be from CD or NSAIDS.	1- SB resection with pathology showing adenocarcinoma of the SB. 2- SB resection with pathology showing leiomyoma. 3- Patient refused surgery.
Treat Crohn's Disease (2)	1.Query CD with IDA 2.Known CD with worsening biomarkers	1- Diffuse SB ulcerations consistent with CD. 2- Ulcerations in duodenal bulb.	1- CD diagnosed, started on infliximab. 2- Crohn's therapy escalated with good response.

Abbreviations: APC = argon plasma coagulation, SBO = small bowel obstruction.

Table 6. Recommended management of negative CE findings (n = 79)

Management	N
Supportive Therapy	
Oral or Intravenous Iron Supplementation and Monitor Hemoglobin/Ferritin	73
Treatment for known underlying disease	
Fix Hiatal Hernia	1
Proton pump inhibitor therapy	1
Rule out other causes of Anemia	
Hematological workup	3
Other	
Stop donating blood	1

study did not find this association with increased age. However, this may be because we had very little representation of patients over age 85 (n = 6). We found vascular lesions to be the most common positive finding of CE as reported previously in elderly patients with IDA (8). In comparison, a recent study on younger patients who underwent capsule endoscopy for IDA showed a DY of 32.3% (12). In addition, higher rates of Crohn's disease findings (6.8%) were reported (12) compared with our study (1.5%), likely because the likelihood of Crohn's disease being diagnosed at a younger age remains higher than the small subset of patients who are diagnosed later in life (13). Vascular lesions remained the most common positive finding in the young population, albeit at lower rates compared with the elderly (9.1% versus 13.8%) (12).

The clinical yield (i.e., a change in the management of the IDA) was drastically different from the diagnostic yield. Regardless of the study being positive or negative, the majority of CE studies

recommended supportive therapy. These findings suggest that the clinical yield of CE in IDA patients above age 65 is very low, and management strategies to optimize a patient's therapy are ideal often without a capsule study.

Of those studies recommending active therapy, most suggested repeat endoscopic exams (EGD/colonoscopy) of areas previously assessed where pathologies were either missed or not recognized initially. Therefore, provided that initial endoscopic exams were thorough and Crohn's disease management was optimized by monitoring biomarkers such as fecal calprotectin (or ileoscopy via colonoscopy), the overall rate of changing management with specific small bowel therapies was low at five of 130 studies (two DB enteroscopies and three resections) or 3.8%. This rate is strikingly similar to the rate of specific small bowel therapies required in a previous CE study for IDA (4%) (11), in which younger patients were included.

Because capsule endoscopy is designed to evaluate the small bowel but has no therapeutic potential, all interventions after the initial diagnosis of a pathologic finding requires time-sensitive planning and follow-up with an interventionalist or a surgeon. Our study showed seven out of 26 cases where specific interventions of the small bowel were recommended with good compliance (six of seven or 85.7%). However, 23 of 30 (76.6%) positive findings were within reach of standard endoscopes (EGD, n = 8; push enteroscopy, n = 3; colonoscopy, n = 12). In those with intermittent bleeding events, we recognize the challenge of identifying lesions in the initial upper and lower endoscopies, but this highlights the importance of the initial endoscopy assessment and the need of a re-look should the patient continue to exhibit signs of anemia from a GI bleed despite negative endoscopic evaluations. Therefore, as suggested by Clere-Jehl et al. (5), our findings also support and favour a

Table 7. Clinical factors associated with positive findings

Clinical Factor	Positive	Negative	P-value
	N = 51	N = 79	
	N (%)	N (%)	
Lab values			
Lowest documented hemoglobin <70 g/L	18 (35.3)	24 (30.4)	.559
Lowest documented hemoglobin <80 g/L	26 (51.0)	42 (53.2)	.808
Ferritin <20 ng/ml	35 (68.2)	66 (83.5)	.046
Meds			
ASA	15 (29.4)	23 (29.1)	.971
AC (warfarin and DOACs)	15 (29.4)	12 (15.2)	.051
PPI	29 (56.9)	43 (54.4)	.785
NSAIDS	4 (7.8)	6 (7.6)	1.000
Steroids	3 (5.9)	5 (6.3)	1.000
Previous iron supplementation	35 (68.6)	55 (69.6)	.905
Clinical History			
Age ≥80	10 (19.6)	13 (16.4)	.646
Age ≥85	2 (3.9)	4 (5.1)	1.000
Abdominal pain	5 (9.8)	6 (7.6)	.751
Changes in BM (constipation or melena)	7 (13.7)	9 (11.4)	.693
Weight loss	4 (7.8)	10 (12.7)	.387
Diverticulosis	14 (27.4)	29 (36.7)	.273
GAVE	2 (3.9)	0 (0)	.152
Crohn's disease	3 (5.9)	0 (0)	.058
Celiac	0 (0)	1 (1.3)	1.000
Hemorrhoids	7 (13.7)	15 (19.0)	.435
Transfusion (any # of units)	32 (62.7)	56 (70.9)	.332
Transfusion > 5 units	17 (33.3)	20 (25.3)	.323
Hiatal hernia	4 (7.8)	20 (25.3)	.012
Cardiac disease*	28 (54.9)	21 (26.6)	.001
PVD/CVA	10 (19.6)	9 (11.4)	.195
CKD	5 (9.8)	7 (8.9)	1.000
Rheumatologic disease	4 (7.8)	8 (10.1)	.764
Lung disease	10 (19.6)	11 (13.9)	.390
Liver disease	7 (13.7)	7 (8.9)	.382
GI surgeries (Gastrectomy or small bowel resection)	0 (0)	1 (1.3)	1.000
Dietary (vegetarian or vegan)	0 (0)	3 (3.8)	.279

Abbreviations: ASA = aspirin, AC = anticoagulants, DOAC = direct oral anticoagulants, BM = bowel movement, GAVE = gastric antral vascular ectasia, PVD = peripheral vascular disease, CVA = cerebrovascular accident, CKD = chronic kidney disease.

*Coronary artery disease, myocardial infarction, valvular disease, arrhythmias.

second look upper or lower endoscopy over capsule studies in patients over age 65 with an initial negative bidirectional endoscopy for IDA.

Current literature quotes different cutoff values for serum ferritin in the diagnosis of IDA in elderly populations, ranging from 12 to 100 µg/L (14). Thus, a firm cutoff value has not been established, and the great variability likely is accounted by the chronic inflammatory comorbidities accompanying many elderly patients, which may raise ferritin independent of true iron

stores (14). We used the ferritin cutoff of 70 ng/mL used in a similar study (5); however, the mean value of ferritin in our cohort was well below this cutoff at 7 ng/mL, suggesting that this patient group had significant iron deficiency.

Previous studies have demonstrated bowel preparation as a modifiable variable which affects the quality and yield of CE (15–17). Generally, bowel preparation on top of a clear-fluid diet is thus recommended before CE with 2 L of PEG as the first-line agent to use (15). A 2009 meta-analysis of 12

studies showed that purgative bowel cleansing before capsule endoscopy improves the small bowel visualization quality and increases the diagnostic yield but does not alter the completion rate (18). Our cohort of patients adhered to this protocol of using 2 L of PEG in order to maximize our diagnostic yield.

The clinical variables that were analyzed were preselected before data collection by predicting variables that could lead to higher rates of positive findings on CE. These included laboratory values, medications and clinical history. Due to the general association of GI bleeds with anticoagulants, ASA, and NSAIDs (19–21), we anticipated their use to be associated with positive findings, but this was not the case in our study. In addition, weight loss and abdominal pain, which are noted to be 'red flag' symptoms in IDA that are concerning for luminal malignancies or inflammatory bowel diseases (22), failed to find associations with positive studies.

Clinical history of cardiac disease was associated with more positive findings on CE, perhaps because of associated GI angiodysplasias. Most notably, Heydes syndrome is a recognized phenomenon in aortic stenosis, where the mechanical shear stress of the stenotic valve leads to an acquired Type 2A von Willebrand disease, manifesting as angiodysplasias in the GI tract (23). However, independent to valvular dysfunctions, there is emerging evidence that cardiac diseases such as arrhythmias and congestive heart failure also have associations with GI angiodysplasias (24). We did not observe a statistically significant association with chronic kidney disease, peripheral vascular disease, or the use of ASA or anticoagulants with positive findings.

Ferritin is a marker for iron stores in the body (14). Interestingly, a very low ferritin level had an inverse relationship to the yield of CE studies. We postulate that low ferritin levels indicating chronic blood loss are more likely to be associated with a negative study because chronic, intermittent blood and iron loss is less likely to be found positive on capsule study, as opposed to brisk bleeds (which are more likely to lead to positive studies), where iron loss is only temporary.

Hiatal hernias (HH) refer to conditions where a part of the stomach slides superiorly through the esophageal hiatus at the diaphragm into the mediastinum (25), and IDA has been observed in up to 50% of patients with paraesophageal HH (26). In our study, those with a documented HH had a higher likelihood of having negative findings, likely because of associated Cameron erosions being the underlying cause of IDA, rather than pathologies in the small bowel. While up to 20% of patients with large HH have concurrent Cameron erosions (27), HH have been documented to be a real cause of IDA, with or without visible Cameron erosions (28). Interestingly, despite HH being accounted as the underlying cause of the anemia in many negative studies, only one patient was advised to fix it surgically in our study. This is congruent with the Society of American Gastrointestinal and Endoscopic Surgeons' (SAGES)

guidelines reporting that patients who have a HH without overt symptoms such as dysphagia, chest pain or severe reflux can be managed nonsurgically (26).

Limitations

We did not subtype cardiac disease into its respective categories, and it would be interesting to know whether future studies can find a link between specific cardiac conditions (e.g., aortic stenosis and Heydes syndrome (23)) contributing to positive CE findings. After initial scanning through electronic medical records, 130 CE studies had missing data. Attempts to gather this missing information by contacting the patients' family physicians via fax yielded a response rate of about one-half (68 of 130; 52.3%), and of those, only 24 of 68 fulfilled the inclusion criteria. Some of these patients had been referred for a capsule study with iron studies consisting of iron level, total iron binding capacity and transferrin saturation levels, but with no ferritin values. However, a large portion of these patients were not being referred for iron deficiency per se but rather for brisk and obscure GI bleeds and would likely have had normal ferritin levels and, thus, would not have met inclusion criteria.

CONCLUSION

These findings suggest that the clinical yield of CE in IDA in patients over age 65 is relatively low, and the benefit of CE studies for investigating IDA in this population should be raised into question. The majority of all CE studies recommended supportive therapy or repeat endoscopic exams (EGD/colonoscopy) of areas previously assessed. Although capsule endoscopy remains the gold standard to evaluating the small bowel in IDA, care providers must remain cognizant of the fact that the majority of CE studies will not lead to a change in management, regardless of findings. Clinical factors focusing on cardiac history, ferritin levels and the presence of a hiatal hernia may be of utility to predict CE results. Emphasis on these data may help select more appropriate patients for capsule endoscopy.

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