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Observational Study

Appropriateness of the study of iron deficiency anemia prior to referral for small bowel evaluation at a tertiary center

Jaime Pereira Rodrigues, Rolando Pinho, Joana Silva, Ana Ponte, Mafalda Sousa, João Carlos Silva, João Carvalho

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Abstract**AIM**

To evaluate the adequacy of the study of iron deficiency anemia (IDA) in real life practice prior to referral to a gastroenterology department for small bowel evaluation.

METHODS

All consecutive patients referred to a gastroenterology department for small bowel investigation due to iron deficiency anemia, between January 2013 and December 2015 were included. Both patients referred from general practitioners or directly from different hospital departments were selected. Relevant clinical information regarding prior anemia workup was retrospectively collected from medical records. An appropriate pre-referral study was considered the execution of esophagogastroduodenoscopy (EGD) with *Helicobacter pylori* (*H. pylori*) investigation, colonoscopy with quality standards (recent, total and with adequate preparation) and celiac disease (CD) screening (through serologic testing and/or histopathological investigation).

RESULTS

A total of 77 patients (58.4% female, mean age 67.1 ± 16.7 years) were included. Most (53.2%) patients were referred from general practitioners, 41.6% from other hospital specialties and 5.2% directly from the

emergency department. The mean pre-referral hemoglobin concentration was 8.8 ± 2.0 g/dL and the majority of anemias had microcytic (71.4%) and hypochromic (72.7%) characteristics. 77.9% of patients presented with an incomplete pre-referral study: EGD in 97.4%, with *H. pylori* investigation in 58.3%, colonoscopy with quality criteria in 63.6%, and CD screening in 24.7%. Patients with an appropriate study at the time of referral were younger (48.7 ± 17.7 vs 72.3 ± 12.3 years, $P < 0.001$). Small bowel evaluation was ultimately undertaken in 72.7% of patients, with a more frequent evaluation in patients with a quality colonoscopy at referral (78.6% vs 23.8%); $P < 0.001$ (OR = 11.7, 95%CI: 3.6-38.6). The most common diagnosis regarded as the likely cause of IDA was small bowel angioectasia (18.2%) but additional causes were also found in the upper and lower gastrointestinal tracts of near 20% of patients. Small bowel studies detected previously unknown non-small bowel findings in 7.7% of patients.

CONCLUSION

The study of anemia prior to referral to gastroenterology department is unsatisfactory. Only approximately a quarter of patients presented with an appropriate study.

Key words: Iron deficiency anemia; Colonoscopy; Celiac disease; Esophagogastroduodenoscopy; *Helicobacter pylori*; Small bowel

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Core tip: Iron deficiency anemia is a common cause of referral to gastroenterologists. This study aimed to evaluate the adequacy of iron deficiency anemia workup prior to referral to a gastroenterology department for small bowel evaluation. Most patients (77.9%) presented an incomplete pre-referral study. On 27.3% of patients it was even decided not to proceed with small bowel evaluation. In fact, nearly 20% of patients revealed positive findings in the upper and/or lower GI tracts. Better communication and definition of referral protocols between the different specialties are required to enable patients to be promptly and correctly managed.

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INTRODUCTION

Anemia may present multiple causes, being iron deficiency the most significant contributor, which is responsible for approximately 50% of anemia cases^[1]. Iron deficiency anemia (IDA) represents a major public

health problem and is a common cause of referral to gastroenterologists (4%-13% of referrals)^[2,3]. In the developed world it occurs in 2%-5% of adult men and post-menopausal women and in 5%-12% of otherwise healthy premenopausal women^[2,4].

In developed countries menstrual blood loss is the most common cause of IDA in premenopausal women, while blood loss from the gastrointestinal (GI) tract is the most common cause in adult men and postmenopausal women^[5-7]. Altogether, most IDA are a direct consequence of occult GI blood loss, mostly from the upper and lower GI tract, and malabsorption conditions, namely celiac disease (CD)^[2,3,5,6]. On the other hand, non-GI blood loss can be the source of IDA in up to one third of cases^[2]. There is little consensus as to the level of anemia that requires investigation, however it is recommended that any level of anemia should be investigated in the presence of iron deficiency^[2]. Gastroenterologists should make part of IDA investigation, primarily through exclusion of blood losses from the upper and lower GI tracts and subsequently of small bowel (SB) blood losses.

Published guidelines for evaluation and management of IDA state that it is advisable that in patients referred for SB evaluation, a complete work-up be performed, including: a complete medical history (including gynecological history in premenopausal females); esophagogastroduodenoscopy (EGD) with gastric biopsies to rule out *Helicobacter pylori* (*H. pylori*) infection; exclusion of CD (through serological and/or histopathological investigation); ileocolonoscopy; and, perhaps, hematological evaluation^[8]. In fact, additionally to blood loss investigation, all patients with IDA should be screened for CD^[2,9,10]. In asymptomatic patients with IDA, the prevalence of CD was found to range from 2.3% to 5.0%, whereas it ranged from 10.3% to 15% in symptomatic ones^[11,12]. Patients with unexplained IDA despite an appropriate evaluation should also be tested for *H. pylori* infection. The association of *H. pylori* with unexplained IDA has been conclusively proven in adult and pediatric populations^[13,14].

Even when these examinations are carefully performed, no definitive diagnosis is reached in up to 30% of patients with IDA who are the most likely candidates for SB evaluation^[2,6]. However, taking into account that only a small percentage (5%-10%) of all sources of GI bleeding is attributed to SB sources^[8,15,16] international guidelines recommend that investigation of the SB is generally indicated only for recurrent or refractory and/or transfusion-dependent IDA^[2,17].

Because of its excellent safety profile, patient tolerability, and potential for complete enteroscopy, small bowel capsule endoscopy is recommended as the first-line examination when SB evaluation is indicated^[8,18-20]. Pooling together all studies focusing on IDA^[21-29] the overall diagnostic yield of capsule endoscopy (CE) in IDA patients is 53% (95%CI: 41%-65%)^[8]. However, several authors have reported

Table 1 Clinical characteristics of patients referred to gastroenterology department for iron deficiency anemia study *n* (%)

Characteristics	Total (<i>n</i> = 77)
Age, yr (mean ± SD)	67.1 ± 16.7
Female	45 (58.4)
Provenience	
General Practice	41 (53.2)
Hospital Specialties	32 (41.6)
Hematology	13 (16.9)
Internal Medicine	6 (7.8)
Cardiology	5 (6.5)
Nephrology	5 (6.5)
Pneumology	1 (1.3)
General Surgery	1 (1.3)
Cardiothoracic Surgery	1 (1.3)
Emergency Department	4 (5.2)
Hemoglobin, g/dL (mean ± SD)	8.8 ± 2.0
Microcytosis	55 (71.4)
Hypochromia	56 (72.7)

IDA: Iron deficiency anemia.

a significant incidence of lesions detected by SB studies that were within the reach of conventional endoscopy, inclusively mucosal abnormalities indicative of CD^[22,23,25,26,30-34]. Indeed, after positive CE, up to 30% of patients have been managed by repeating EGD or colonoscopy, an indicator that CE was unnecessarily performed.

These data highlight the importance of a thorough medical history investigation, well performed standard endoscopies, as well as the exclusion of other common causes of IDA. The latter permits identification of specific patient subgroups in which SB studies have the greatest utility, ensuring appropriate use of these resources. This approach will lead to planning of therapeutic endoscopic procedures, with increased patient convenience, reduced costs and perhaps improved patient outcomes through shortened diagnostic evaluation. The aim of this study was to evaluate the adequacy of IDA study in real life practice before referral to a gastroenterology department for SB investigation.

MATERIALS AND METHODS

Patients and study design

All consecutive patients referred to our gastroenterology department for SB investigation due to IDA, between January 2013 and December 2016, were included. Both patients referred from general practitioners or directly from different hospital departments were selected.

Relevant clinical information was retrospectively collected from medical records, including demographic characteristics, analytical data (Hemoglobin [Hg] concentration, red blood cell indices, reticulocyte count, iron metabolism tests and vitamin B12, folic acid and C-reactive protein assays), peripheral blood

smear, endoscopic studies reports including *H. pilory* investigation, CD screening (through serologic testing and/or histopathological investigation), labelled red cell scintigraphy and Gynecology evaluation of female patients younger than 40 years.

An appropriate pre-referral IDA study, the main composite study outcome, was defined by the execution of: EGD with *H. pilory* investigation, colonoscopy with quality standards and CD screening (through serologic testing and/or histopathological investigation). A colonoscopy with quality criteria was defined as complete (with cecal intubation), with reasonable or good intestinal preparation, and performed recently (in the last year before referral).

Patient's subsequent management was based on clinical criteria, at clinician's discretion. Follow-up data regarding further anemia studies post referral and diagnoses regarded as the likely causes of IDA were both recorded. Patients with no follow-up data were excluded from the study.

Statistical analysis

Statistical analysis was performed using the IBM® SPSS® Statistics software (SPSS Inc., Chicago), version 23.0.

Categorical variables are presented as frequencies and percentages while continuous variables are presented as mean ± SD for variables with normal distributions, or medians and interquartile ranges for variables with skewed distributions. Normal distribution of the data was tested with Kolmogorov-Smirnov and Shapiro-Wilk tests or through analysis of skewness and kurtosis (maximum tolerable values of skewness and kurtosis of 1). Categorical variables were compared using the χ^2 test or Fisher's Exact test, as appropriate, while continuous variables were compared using Student's *t*-test for variables with normal distributions or non-parametric tests (Mann-Whitney) for variables with skewed distributions. Odds ratios (OR) with a 95%CI are also presented.

All reported *P* values are two-tailed, with a *P* value of 0.05 indicating statistical significance.

RESULTS

Patient's characterization

A total of 77 patients were referred due to IDA to our department between January 2013 and December 2016. The mean age was 67.1 ± 16.7 years and 58.4% (*n* = 45) were female (Table 1).

Regarding referral, the majority of patients were referred from general practitioners (*n* = 41, 53.2%). The remaining patients were referred from multiple hospital departments (*n* = 32, 41.6%) or directly from the emergency department (*n* = 4, 5.2%). Referrals were most likely to come from Hematology (*n* = 13, 16.9%), Internal Medicine (*n* = 6, 7.8%), Cardiology

Table 2 Pre-referral study

Procedures	n (%)
Appropriate pre-referral study	17 (22.1)
EGD	75 (97.4)
<i>H. pylori</i> investigation	35 (58.3)
Colonoscopy	71 (92.2)
With quality standards	49 (63.6)
Without quality standards	22 (28.6)
Insufficient intestinal preparation	15 (19.2)
Incomplete	5 (6.5)
Non-recent	2 (2.6%)
Celiac Disease screening	19 (24.7)
Serologic testing	10 (13.0)
Duodenal histopathological investigation	7 (9.1)
Both	2 (2.6)
Additional pre-referral study	
Iron metabolism tests	69 (89.6)
C-reactive protein	33 (42.9)
Vitamin B12	27 (35.1)
Folic Acid	27 (35.1)
Reticulocyte count	23 (29.9)
Peripheral blood smear	0 (0.0)
Ileoscopy	14 (20.0)
Gynecology evaluation ¹	3 (50.0)
Capsule endoscopy	3 (3.9)
Labelled red cell scintigraphy	5 (6.5)

¹Including only female patients younger than 40 years. EGD: Esophagogastroduodenoscopy; *H. pylori*: *Helicobacter pylori*.

(*n* = 5, 6.5%) and Nephrology (*n* = 5, 6.5%) departments (Table 1).

The mean Hg concentration before the first gastroenterology appointment was 8.8 ± 2.0 g/dL (Table 1). Most patients had laboratory signs of microcytosis (*n* = 55, 71.4%) and hypochromia (*n* = 56, 72.7%).

Pre-referral study

Concerning our main objective, the evaluation of anemia before referral to our department, 77.9% (*n* = 60) of patients presented with an incomplete study (Table 2). Specifically, almost all patients (*n* = 75, 97.4%) were submitted do EGD, with *H. pylori* investigation in only 58.3% (*n* = 35). Colonoscopy with quality standards had been performed in 63.6% (*n* = 49); on the other hand 7.8% (*n* = 6) had never performed a colonoscopy, 19.2% (*n* = 15) had a colonoscopy with an intestinal preparation deemed as insufficient, 6.5% (*n* = 5) had an incomplete examination and 2.6% (*n* = 2) had a non-recent colonoscopy. Finally, CD investigation was previously undertook in only 24.7% (*n* = 19) patients, in 13.0% (*n* = 10) through serologic testing, in 9.1% (*n* = 7) through histopathologic examination of duodenal biopsies, and on 2.6% (*n* = 2) through both methods.

Additional anemia work-up studies not considered crucial before gastroenterology referral were also evaluated (Table 2). In our sample, 89.6% (*n* = 69) performed iron metabolism tests (including both transferrin saturation and ferritin evaluation), 42.9%

Table 3 Univariate analysis of factors associated with the appropriateness of pre-referral evaluation n (%)

Characteristics	Appropriate (<i>n</i> = 17, 22.1%)	Incomplete (<i>n</i> = 60, 77.9%)	P value ¹
Age, years (mean \pm SD)	48.7 \pm 17.7	72.3 \pm 12.3	< 0.001
Female,	13 (76.5)	32 (53.3)	0.087
General Practice referral	7 (41.2)	34 (56.7)	0.258
Hemoglobin, g/dL (mean \pm SD)	9.0 \pm 2.4	8.7 \pm 1.8	0.645
Microcytosis	13 (76.5)	42 (70.0)	0.750
Hypochromia	13 (76.5)	43 (71.7)	0.640
Female, < 40 yr	6 (100)	0 (0.0)	< 0.001

¹Student's *t*-test, Mann-Whitney *U* test, Fisher's exact test or the χ^2 test, as appropriate; *P* value of 0.05 indicating statistical significance.

(*n* = 33) C-reactive protein measurement, 35.1% (*n* = 27) vitamin B12 and folic acid assays, 29.9% (*n* = 23) reticulocyte count, and none (0.0%) of patients had a peripheral blood smear. Moreover, 20.0% (*n* = 14) had ileoscopy as part of their lower gastrointestinal tract endoscopic examination and 50.0% (*n* = 3) of female patients younger than 40 years were evaluated by Gynecology before referral. Lastly, 3 patients (3.9%) had already performed CE and 5 patients (6.5%) labelled red cell scintigraphy at the time of the first gastroenterology appointment.

Factors associated with an appropriate pre-referral study

On univariate analysis, there was an association between an appropriate study at the time of referral and lower age (48.7 ± 17.7 vs 72.3 ± 12.3 years, *P* < 0.001) (Table 3). Nonetheless, there was no difference between the appropriate and incomplete study groups regarding gender (76.5 vs 53.3% female, *P* = 0.087), referral setting (41.2 vs 56.7 from general practitioners, *P* = 0.258) Hg concentration (9.0 ± 2.4 vs 8.7 ± 1.8 g/dL, *P* = 0.645) and red blood cell indices (76.5 vs 70.0 with microcytosis, *P* = 0.750; 76.5 vs 71.7 with hypochromia, *P* = 0.640) respectively. Additionally, there was a significant statistical association between the group of female patients younger than 40 years and an appropriate study (100% vs 15.5% on the remaining population), *P* < 0.001.

Evaluation after referral

After adequate clinical and analytical evaluation at the gastroenterology department, 11 (14.3%) patients were submitted to EGD (2 of which have never done it before), and 18 (23.4%) to ileocolonoscopy (5 of them also for the first time), as their initially examinations. Patients without previous CD investigation underwent CD screening either through EGD with biopsies or serological testing.

Globally, on 27.3% (*n* = 21) patients a decision not to proceed with small bowel evaluation was undertaken (Table 4); this subgroup includes patients

Table 4 Evaluation after referral *n* (%)

Procedures	<i>n</i> (%)
In patients with further small bowel evaluation	56 (72.7)
EGD	4 (5.2)
Ileocolonoscopy	9 (11.7)
Capsule endoscopy	53 (68.8)
Device-assisted enteroscopy	7 (9.1)
CT-enterography	7 (9.1)
MRI-enterography	4 (5.2)
Meckel's scan	4 (5.2)
In patients without further small bowel evaluation	21 (27.3)
EGD	7 (9.1)
Ileocolonoscopy	9 (11.7)

EGD: Esophagogastroduodenoscopy; CT: Computed tomography; MRI: Magnetic resonance imaging.

Table 5 Univariate analysis of factors associated with the decision to proceed to small bowel evaluation *n* (%)

Characteristics	SB evaluated (<i>n</i> = 56, 72.7%)	SB not evaluated (<i>n</i> = 21, 27.3%)	<i>P</i> value ¹
Age, yr (mean ± SD)	65.0 ± 17.3	72.6 ± 14.2	0.077
Female	35 (62.5)	10 (47.6)	0.238
General Practice referral	27 (48.2)	14 (66.7)	0.148
Hemoglobin, g/dL (mean ± SD)	8.7 ± 2.1	9.2 ± 1.6	0.299
Microcytosis	40 (71.4)	15 (71.4)	0.933
Hypochromia	39 (69.6)	17 (81.0)	0.510
Female, < 40 yr	6 (100)	0 (0.0)	0.118
Appropriate study at referral	15 (26.8)	2 (9.5)	0.104
EGD	56 (100)	19 (90.5)	0.072
Quality colonoscopy	44 (78.6)	5 (23.8)	< 0.001
Celiac Disease screening	17 (30.4)	2 (9.5)	0.059

¹Student's *t*-test, Mann-Whitney *U* test, Fisher's exact test or the χ^2 test, as appropriate; *P* value of 0.05 indicating statistical significance. SB: Small bowel; SD: Standard deviation; EGD: Esophagogastroduodenoscopy.

that underwent EGD and/or colonoscopy (*n* = 9, 11.7%) without requiring subsequent SB studies and 12 (15.6%) patients that were eventually discharged after an eventful follow-up, without additional work-up requirement.

On the other hand, SB evaluation was undertaken in 72.7% (*n* = 56) of patients. SB studies included a different combination of CE (*n* = 53, 68.8%), device-assisted enteroscopy (*n* = 7, 9.1%), CT-enterography (*n* = 7, 9.1%), MRI-enterography (*n* = 4, 5.2%) and Meckel's scan (*n* = 4, 5.2%). Four patients eventually didn't complete the small-bowel study: 2 of them refused CE, 1 suffered an ischemic stroke and a decision not to proceed to CE due to severe functional limitation was made, and another patient refused device-assisted enteroscopy.

Factors associated with a decision to proceed to small bowel evaluation

The proportion of patients with an appropriate study at referral did not differ significantly between patients

with subsequent SB evaluation (26.8%) and without subsequent SB evaluation (9.5%); *P* = 0.104 (Table 5). Specifying each of the components of the composite endpoint, there was also no difference between the group of patients that had their SB evaluated and the group without SB evaluation regarding EGD at referral (100% vs 90.5%); *P* = 0.072. On the other hand, significantly more patients with further SB evaluation had a quality colonoscopy at referral (78.6%) than patients without further SB evaluation (23.8%); *P* < 0.001 (OR = 11.7; 95%CI: 3.6-38.6). Finally, there was a trend towards significance in the association between CD investigation prior to referral and subsequent small bowel studies (30.4% vs 9.5%); *P* = 0.059. Conversely, there was no association between age, gender, referral setting, Hg concentration, red blood cell indices and the subgroup of female patients younger than 40 years and the necessity of small bowel study; *P* > 0.05.

Final diagnosis

After adequate follow-up and study, the diagnoses regarded as the likely cause of IDA, either in the SB or in the remaining GI tract, where: small bowel angioectasia (*n* = 14, 18.2%), inflammatory bowel disease (*n* = 4, 5.2%), colon angioectasia (*n* = 4, 5.2%), gastric angioectasia (*n* = 3, 3.9%), gastric polyp (*n* = 2, 2.6%), nonsteroidal anti-inflammatory drugs (NSAIDs) enteropathy (*n* = 2, 2.6%), small bowel neoplasia (*n* = 2, 2.6%), unspecified enteritis (*n* = 2, 2.6%), colorectal cancer (*n* = 2, 2.6%), gastric antrum vascular ectasia (GAVE) (*n* = 1, 1.3%), erosive gastritis (*n* = 1, 1.3%), small bowel Dieulafoy's lesion (*n* = 1, 1.3%), small bowel inflammatory polyp (*n* = 1, 1.3%) and colonic polyp (*n* = 1, 1.3%). In conclusion, positive findings were found in the upper GI tract in 9.1% (*n* = 7) of patients, mid GI tract in 33.8% (*n* = 26) and lower GI tract in 9.1% (*n* = 7) (Table 6).

In 50.0% (*n* = 26) of patients that ultimately underwent SB investigation (*n* = 52, 67.5%), positive findings were identified. There was no association between positive SB findings and age, gender, referral setting, Hg concentration, red blood cell indices and the appropriateness of study at referral; *P* > 0.05.

Additionally, SB studies detected previously unknown non-SB findings in 7.7% (*n* = 4) of patients, namely erosive gastritis (*n* = 1), gastric polyp (*n* = 1), gastric angioectasia (*n* = 1) and colon angioectasia (*n* = 1), despite thorough clinical, analytical and endoscopic screening before CE at the Gastroenterology department.

DISCUSSION

In developed countries, 5%-11% of women and 1%-4% of men are iron deficient and approximately 5% of women and 2% of men have IDA^[4]. It is a

Table 6 Diagnoses regarded as the likely causes of iron deficiency anemia

Diagnoses	n (%)
Upper GI tract	7 (9.1)
Gastric angioectasia(s) ¹	3 (3.9)
Gastric polyp(s) ¹	2 (2.6)
GAVE	1 (1.3)
Erosive gastritis ¹	1 (1.3)
Small bowel	26 (33.8)
Angioectasia(s)	14 (18.2)
Crohn's disease	4 (5.2)
NSAIDs enteropathy	2 (2.6)
Neoplasia	2 (2.6)
Unspecified enteritis	2 (2.6)
Dieulafoy's lesion	1 (1.3)
Inflammatory polyp	1 (1.3)
Lower GI tract	7 (9.1)
Angioectasia(s) ¹	4 (5.2)
Colorectal cancer	2 (2.6)
Polyp	1 (1.3)

¹Non-small bowel findings detected on SB studies. IDA: Iron deficiency anemia; GI: Gastrointestinal; GAVE: Gastric antrum vascular ectasia; NSAID: Nonsteroidal anti-inflammatory drug.

frequent condition and a common motive for referral to gastroenterologists. Taking this into account, this survey audited investigations and diagnoses in patients with IDA referred to a gastroenterology department for SB evaluation.

Upper and lower gastrointestinal endoscopies are the cornerstone of the investigation of IDA, identifying the cause of IDA in 60%-80% of patients^[2,22]. In the studied population, almost every patient (97.4%) was submitted to EGD, which attests the importance of upper GI endoscopy and its ease of access; also, 92.2% of patients underwent at least one colonoscopy, however only approximately two thirds of them were submitted to a colonoscopy with quality standards, a figure that can seriously hamper adequate patient follow-up.

Beside endoscopic studies, CD screening should make part of the initial IDA investigation^[2,9,10]. Although pretest probability of CD in IDA alone is relatively low (5%), IDA is commonly reported in patients with CD, even if asymptomatic^[2]. The diagnosis is based in serological testing and duodenal biopsies, two easily accessible methods, so European guidelines strongly suggest that CE must be reserved only for cases of equivocal CD diagnosis^[8]. In this study population, only approximately one quarter (24.7%) of patients undertook CD investigation before referral, which may be a sign of lack of awareness for CD as a cause of IDA. Hp infection is another frequent cause of IDA, mainly in adult patients with iron refractoriness or iron dependency in whom other causes of IDA have been previously ruled out^[13,14]. *H. pilory* colonization may impair iron uptake and increase iron loss, potentially leading to iron deficiency^[35] so guidelines on the management of IDA recommend eradication of *H.*

pilory, when present^[2,14]. Recent meta-analyses have shown that *H. pilory* eradication enhances response to iron therapy and increases hemoglobin levels^[36,37]. In spite of solid scientific evidence supporting *H. pilory* eradication and ease of access, only 58.3% of patients underwent *H. pilory* testing in the studied population. Regarding red blood cell characterization, both microcytosis and hypochromia are sensitive indicators of iron deficiency in the absence of chronic disease, hemoglobinopathy or coexistent vitamin B12 or folate deficiency^[2,38] and can also be important aids in anemia study - most studied patients had microcytosis and/or hypochromia, which corroborates iron deficiency as the anemia cause. Finally, despite that the most common IDA cause in premenopausal women is menstrual blood losses, only 50.0% of female patients younger than 40 years were evaluated by Gynecology before referral to gastroenterology appointment. The main factor associated with an appropriate pre-referral study was a lower age of patients, which may be indicative of a more assertive demand by the physician for the cause of anemia in this age group, as well as a greater interest by each patient in understanding its cause.

When initial IDA investigation is negative, patients should be given a trial of iron replacement, and submitted to second-line investigations only if they show an inadequate response to iron therapy, especially if transfusion-dependent^[2,8]. Taking this into account, approximately on a quarter of referred patients a decision not to proceed with small bowel evaluation was made. Although the proportion of patients with an appropriate study at referral did not differ between patients with subsequent and without subsequent SB evaluation, more patients with a colonoscopy with quality criteria at referral had their SB evaluated.

The development and implementation of CE has opened up a new frontier in the field of SB investigation. CE is a non-invasive method that allows the evaluation of the entire small bowel. The diagnostic yield of CE in IDA patients is about 47%-66%^[39], though subsequent retrospective studies have reported relatively low rates of positive CE findings in 26%-44% of patients with IDA^[25,28,30,40]. The diagnostic yield of CE in the setting of IDA without any evidence of overt bleeding has been questioned^[41]. It is known that studies applying strict criteria to CE tend to have a higher diagnostic yield^[21,22] clinically relevant findings on CE are less likely in menorrhagic females^[25]; in order to improve CE diagnostic yield, even though the existing evidence is controversial, it is also important to optimize SB preparation^[42].

In addition, although one study suggested a higher rate of resolution of anemia in patients with positive CE (100% vs 68%, $P = 0.027$)^[27], other studies have shown no improvement in anemia and rebleeding rates, irrespective of CE findings^[23,26,43]. A recent consensus group concluded that CE has a moderate

diagnostic yield in unselected patients with chronic IDA, although it is unlikely to change management or outcomes. It can be considered for some patients, including males or nonmenstruating females with more severe anemia (requiring blood transfusions, Hg level < 100 g/L), or those with persistent or recurrent IDA despite adequate iron replacement therapy^[20].

CE has been shown to be significantly superior to push-enteroscopy and both conventional and cross-sectional radiology, and to be as good as device-assisted enteroscopy in evaluating and finding lesion(s) causing the bleeding^[8,21]. In IDA, the diagnostic yield of push-enteroscopy varies widely (range 30%-70%, mean approximately 40%)^[17,44-49] whereas the diagnostic yield of device-assisted enteroscopy appears comparable to that of CE^[50-53] especially when a complete enteroscopy is achieved^[54]. Accordingly, CE was the SB study most often pursued when a decision to evaluate small bowel was made (94.6%). The diagnostic yield of performed SB studies reached 50.0%, a number in agreement with presented data from other studies. Additionally, in 50.0% of patients that ultimately underwent SB investigation (67.5%), positive findings were identified.

In these population, SB angioectasia (18.2%) was the most common final diagnosis, in accordance with previous evidence^[55], followed by inflammatory bowel disease (5.2%). Despite that the main reason of referral of this patients was SB study, nearly 20% of final diagnoses were located in the upper and/or lower GI tracts, within the reach of conventional endoscopes. In accordance with this data, several authors have reported a significant incidence of lesions detected by SB studies within the reach of conventional endoscopy, including mucosal abnormalities indicative of CD. For example, in series of patients with suspected SB bleeding, suspected sources of bleeding were found within the reach of a standard EGD in 2.8% - 26% of patients^[22,23,25,26,30-34,56-58]. In the series here presented, SB studies also detected previously unknown non-SB findings in 7.7% of patients, data which indicates that CE might had ben unnecessarily performed.

It is evident that many definite lesions are missed during EGD and colonoscopy performed before SB studies. There are various possible explanations of why lesions can be missed. Occasionally, their size, location or intermittent bleeding precludes their proper visualization. A substandard colon preparation may impede visualization of all lesions. Failure to intubate the terminal ileum may hamper the discovery of terminal ileum lesions or blood. Also, some lesions can be missed, at least in part, because of operator's inexperience. Missing these lesions may result in prolonged diagnostic evaluation, patient inconvenience and increased costs.

Considering the drawbacks of SB study, upper and lower GI tract endoscopies often are repeated before SB evaluation. Some authors consider that the endoscopy work-up before CE should always

include two EGDs^[59] but, unfortunately, there is a lack of studies evaluating the cost-effectiveness of this systematic second-look endoscopy before SB exploration in IDA patients. Therefore, at the present time, the decision to perform a second-look endoscopy before SB exploration should be taken on a case-by-case basis^[8]. Data regarding the diagnostic yield associated with repeat upper examinations shows diagnostic yields ranging from 3% to 60%^[30-34,59,60]. Considering the studied population, 9 patients repeated EGD and 13 patients repeated colonoscopy after referral, and eventually most of them did not get further small bowel evaluation, which clearly demonstrates de importance of a quality pre-SB evaluation study.

A fact that cannot be overlooked is that endoscopists performing outsourced EGDs and colonoscopies may have a role in improving pre-referral studies. Endoscopists and facilities performing outsourced endoscopies should be encouraged to perform biopsies for Hp and celiac disease screening in the setting of IDA and ensure that the bowel preparation meets quality standards. In the case of an inadequate bowel preparation, the colonoscopy report should mention the need of a second colonoscopy with an adequate bowel preparation. This improved adherence to IDA management guidelines by gastroenterologists could somewhat optimize the referral of IDA patients to tertiary centers.

The present study has some limitations. It is a retrospective study of a referral population and the number of enrolled patients is relatively small. However, it is noteworthy that this is a real life study, reflecting real life practice, as opposed to previous papers on the topic. In conclusion, the study of anemia prior to referral to gastroenterology department is unsatisfactory. Given that only an adequate study before CE permits identification of specific patient subgroups in which SB studies have the greatest utility and ensures appropriate use of this resources, better communication and definition of referral protocols between the different specialties are required to enable patients to be promptly and correctly managed.

COMMENTS

Background

Iron deficiency anemia (IDA) is a common cause of referral to gastroenterologists (4%-13% of referrals). Most IDA result from occult gastroenterologists (GI) blood loss, mostly from the upper and lower GI tract, and malabsorption conditions, however non-GI causes can be the source of IDA in up to one third of cases. Guidelines for the management of IDA state that in patients referred for small bowel (SB) evaluation, a complete work-up are performed, including a complete medical history, esophagogastroduodenoscopy with gastric biopsies, exclusion of celiac disease and ileocolonoscopy.

Research frontiers

No report has yet addressed the appropriateness of IDA study before tertiary center referral, so the aim of this study was to evaluate, in real life practice, the adequacy of IDA study before referral for SB investigation.

Innovations and breakthroughs

The results of this study show that the majority (77.9%) of patients presented with an incomplete pre-referral study and small bowel evaluation had never been undertaken in more than a quarter of patients. The most common diagnosis regarded as the likely cause of IDA was small bowel angiectasia but additional causes were also found in the upper and lower gastrointestinal tracts of nearly 20% of patients. Specifically, small bowel studies detected previously unknown non-small bowel findings in 7.7% of patients.

Applications

The study of anemia prior to referral to gastroenterology department is unsatisfactory. In order to achieve appropriate use of resources with increased patient convenience, reduced costs and perhaps improved patient outcomes, IDA study must be optimized with careful exclusion of its commonest causes. The definition of referral protocols between the different specialties may be required to enable patients to be promptly managed.

Terminology

IDA, as the name implies, is the type of anemia caused by a decreased in total iron body content, which occurs when iron deficiency is severe enough to diminish erythropoiesis.

Peer-review

It picks up a subject relevant for many specialties, mostly for gastroenterologists.

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