EVALUATION OF THE GASTROINTESTINAL TRACT IN PATIENTS WITH IRON-DEFICIENCY ANEMIA

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Abstract *Background.* Idiopathic iron-deficiency anemia in adults is assumed to be the result of occult chronic blood loss from the gastrointestinal tract. The aim of this study was to determine an effective clinical strategy for managing this common clinical problem.

Methods. We prospectively studied 100 consecutive patients with iron-deficiency anemia, using colonoscopy and esophagogastroduodenoscopy and, in patients with negative endoscopic studies, enteroclysis (radiographic examination of the small intestine).

Results. Gastrointestinal endoscopy revealed at least one lesion potentially responsible for blood loss in 62 of the 100 patients. Endoscopic examination of the upper gastrointestinal tract showed a bleeding source in 36 patients, and colonoscopy showed a lesion in 25; 1 patient had lesions in both the upper and lower gastrointestinal tracts. The most common abnormality in the upper gastrointestinal tract was peptic ulceration (duodenal ulcer in 11 patients, gastric ulcer in 5, and anastomotic ulcer in 3). Cancers, detected in 11 patients, were the most common colonic lesions. Enteroclysis was performed in 26 of the 38 patients with negative endoscopic studies, and the results were normal in all instances. Symptoms at a specific site in the gastrointestinal tract were predictive of disease in the corresponding portion of the bowel. In addition, the combination of positive tests for fecal occult blood and symptoms in the lower gastrointestinal tract had a positive predictive value of 86 percent for detecting a lesion in the lower gastrointestinal tract.

Conclusions. Gastrointestinal lesions (in both the upper gastrointestinal tract and the colon) are frequently found in patients with iron-deficiency anemia. Since site-specific symptoms are predictive of abnormalities in the corresponding portion of the bowel, the initial evaluation should be directed by the location of the symptoms. Concomitant lesions of the upper and lower gastrointestinal tract are rare; thus, detection of a likely source of blood loss during the initial examination may obviate the need for further procedures. (N Engl J Med 1993;329: 1691-5.)

OCCULT bleeding from the gastrointestinal tract is widely believed to be the most common cause of iron-deficiency anemia in patients without an obvious source of blood loss. A thorough examination of the gastrointestinal tract, particularly the colon, has therefore become standard practice.[1,2] Indeed, many clinicians advocate colonoscopy or barium-enema radiography regardless of signs or symptoms of disease in the upper gastrointestinal tract. Previous studies of patients with iron-deficiency anemia were performed in nonhomogeneous populations with an assortment of radiographic and endoscopic techniques, resulting in a variety of recommendations for evaluating such patients.[3-10] In addition, the usefulness of examining the small bowel is unclear. Our study was designed to determine the diagnostic value of a thorough gastrointestinal evaluation in patients with idiopathic iron-deficiency anemia and to identify clinical features that may predict the likelihood of detecting a gastrointestinal lesion.

METHODS

All patients with suspected iron-deficiency anemia who were referred to the gastroenterology service from June 1990 through November 1992 were prospectively screened for enrollment in the study. Iron-deficiency anemia was defined as a hemoglobin concentration ≤12.5 g per deciliter (7.8 mmol per liter) for men (normal range, 13.5 to 17.5 [8.4 to 10.9]) and ≤10.6 g per deciliter (6.6 mmol per liter) for women (normal range, 11.6 to 15.8 [7.2 to 9.8]), accompanied by at least one of the following laboratory values consistent with iron deficiency: a serum iron concentration ≤45 μg per deciliter (8.1 μmol per liter; normal range, 50 to 150 [9.0 to 27.0]) with a transferrin saturation no higher than 10 percent (normal range, 16 to 60 percent), a serum ferritin concentration ≤20 μg per liter for men (normal range, 20 to 450) and ≤10 μg per liter for women (normal range, 10 to 250), or the absence of iron stores in bone marrow–biopsy specimens. The criteria for excluding patients from the study were an obvious cause of blood loss (e.g., epistaxis or heavy menstrual flow), active gastrointestinal hemorrhage, severe cardiopulmonary disease, a serum transferrin concentration ≤2.16 g per liter (normal range, 2.16 to 3.99), reported or suspected pica, age under 18 years, and an inability to give informed consent for endoscopy.

During the study period, 163 patients were referred to the gastroenterology service for evaluation of purported iron-deficiency anemia. Thirty patients were ineligible for the study because they did not meet the criteria for iron-deficiency anemia. Another 33 patients were ineligible for the following reasons. Iron studies were not completed in 11 patients who had been referred for suspected iron-deficiency anemia on the basis of red-cell indexes: 4 patients began iron therapy before the blood tests were performed, 3 had tests only for serum iron, 2 were lost to follow-up, and 2 declined further blood studies. Sixteen patients were excluded because their serum transferrin values were less than or equal to 2.16 g per liter, suggesting that they had anemia associated with chronic disease. Six patients with documented iron-deficiency anemia were excluded because they were unable to give informed consent (two patients), had an obvious nongastrointestinal source of blood loss (two patients), or had unstable cardiovascular status (two patients).

Detailed clinical data were obtained for all patients enrolled in the study, with an emphasis on gastrointestinal symptoms. The specific symptoms of the upper gastrointestinal tract that patients were asked about included dysphagia, odynophagia, heartburn, dyspepsia, nausea, vomiting, anorexia, and upper abdominal pain related to eating or relieved by antacids. The specific lower gastrointestinal symptoms inquired about included hematochezia, a change in bowel habits, diarrhea, constipation, and lower abdominal pain that was colicky or changed with the passage of stool. Patients were also asked about the use of aspirin, other nonsteroidal antiinflammatory drugs, and alcohol. Before the endoscopic evaluation was performed, stool samples obtained by the patient or by digital rectal examination were tested for occult blood with the use of Hemoccult II slides (SmithKline, Sunnyvale, Calif.).

Patients were sedated for sequential endoscopic procedures with intravenous midazolam, meperidine, or both, while vital signs and oxygen saturation were monitored and electrocardiography was performed. The colonoscopy was performed first, followed immedi-

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ately by esophagogastroduodenoscopy with the same anesthetic. The cecum was reached in all patients. There were no complications of the endoscopic procedures. If both upper and lower endoscopic examinations were negative, patients were referred to the radiology department for enteroclysis, which was performed by fluoroscopic intubation of the duodenum and instillation of barium and methylcellulose into the small intestine.[11]

For the colonoscopic examination, the following lesions were judged to be sources of substantial occult blood loss: a carcinoma, one or more adenomatous polyps over 1.5 cm in diameter, vascular ectasias that numbered five or more or were at least 8 mm in diameter, active colitis, or a colonic ulcer more than 1 cm in diameter. Diverticula were judged not to be a source of chronic blood loss. For the endoscopic examination of the upper gastrointestinal tract, the lesions considered to be sources of blood loss included esophagitis with erosions involving at least 5 percent of the mucosal surface of the esophagus,[12] erosive gastritis (defined as at least 50 erosions of 1 mm or more with white bases encircled by erythema),[13] a duodenal or gastric ulcer more than 1 cm in diameter, a carcinoma, adenomatous polyps, and vascular ectasias (the last two as described above). Hiatal hernias and esophageal varices were not considered to be causes of chronic blood loss. In the patients undergoing enteroclysis, mass lesions more than 1 cm in diameter, ulcerations, and extensive mucosal inflammatory changes were judged to be probable sources of blood loss. Endoscopic evidence of bleeding was noted, including hemorrhagic mucosa and a visible vessel in an ulcer.

Statistical analyses were performed with SAS software.[14,15] The upper confidence limit for a binomial parameter was computed exactly.[16]

Results

Clinical Features

The study group consisted of 73 outpatients and 27 inpatients, 51 of whom were women. The mean (±SD) age was 60±14 years, with a range of 20 to 85 years. Nine women were menstruating; none had a history of unusual or heavy flow. All the patients were anemic, with serum ferritin levels or transferrin-saturation values that were consistent with iron deficiency (Table 1). Bone marrow–biopsy specimens from two patients had no stainable iron.

In 22 patients the presenting symptoms (e.g., fatigue and shortness of breath) were related to end-organ compromise. Thirty-three patients had the following concomitant medical illnesses: organic heart disease (13 patients), chronic liver disease (8 patients), chronic renal disease (4 patients), nongastrointestinal cancer (4 patients), rheumatologic disorders (3 patients), and miscellaneous disorders (4 patients). Three patients had two illnesses each.

Endoscopic Findings

A substantial gastrointestinal lesion was detected in 62 of the 100 patients (Table 2). Colonoscopy revealed a likely bleeding site in 25 patients, whereas esophagogastroduodenoscopy demonstrated a lesion in 36 patients; 1 patient had both a gastric and a colonic lesion. Cancer was the most common lesion in the colon, accounting for 11 (8 in the right colon and 3 in the left) of the 26 colonic lesions (42 percent). Three patients had Dukes class B cancers, three had Dukes class D, and five had Dukes class C.[17] All the colon cancers were ulcerated. Five patients with cancer had symptoms. Among the 10 patients with colon cancer who had valid stool guaiac tests (see below), 8 had positive tests. Only one patient with colon cancer both was asymptomatic and had a negative test for occult blood. Of the five patients with vascular ectasias (three cecal and two left colonic), four had multiple lesions; all five patients were treated endoscopically. Of the two patients with colitis, one had radiation colitis, and the other idiopathic ulcerative colitis. One of the cecal ulcers was idiopathic, and one was tuberculous. Fifteen patients with colonic lesions had stigmata of recent bleeding (11 of the 15 had cancer, and 1 each had vascular ectasia, tuberculous cecal ulceration, radiation colitis, and a polyp).

Table 1. Results of Laboratory Tests in 100 Patients with Iron-Deficiency Anemia.*

Test	Value	Normal Range
	mean ±SD	
Hemoglobin (g/dl)	7.8±2.1	11.6–17.5
Men	7.9±2.2	13.5–17.5
Women	7.7±1.9	11.6–15.8
Mean corpuscular volume (μm^3)	71.5±10.0	80–100
Serum iron (μg/dl)	22.9±12.4	50–150
Serum transferrin (g/liter)	3.83±0.77	2.16–3.99
Transferrin saturation (%)	5.6±3.3	16–60
Serum ferritin (μg/liter)	9.2±9.4	10–450
Men	9.9±9.6	20–450
Women	8.4±7.1	10–250

*Values for serum iron, serum transferrin, and transferrin saturation are based on data from 94 patients; serum ferritin values are based on data from 74 patients (36 men and 38 women). To convert values for hemoglobin to millimoles per liter, multiply by 0.62; to convert values for serum iron to micromoles per liter, multiply by 0.18.

Peptic ulceration (of the duodenum, stomach, or gastroduodenal anastomosis) was the most common lesion identified in the upper gastrointestinal tract, accounting for 19 of 37 lesions (51 percent) (Table 2). Six patients had giant ulcers (>2 cm in diameter): five had duodenal ulcers, and one had a gastric ulcer. Five patients had previously undergone a partial gastrectomy with Billroth II anastomoses, and four of the five had associated abnormalities (anastomotic ulcers in three patients and severe gastritis in one). None of the patients had an actively bleeding ulcer; one visible vessel in a giant duodenal ulcer was treated endoscopically. Two patients with gastritis were taking nonsteroidal antiinflammatory drugs: one had a Billroth II anastomosis, and one had chronic liver disease. Four of the six patients with esophagitis had severe inflammation with extensive erosions and ulceration. Three patients had multiple vascular ectasias (gastric in two patients and proximal duodenal in one); all were treated endoscopically. The patient with gastric cancer had a stage T3N2M0 tumor.[18] Nine patients had stigmata of recent bleeding (four had severe esophagitis and one each had a duodenal ulcer with a visible vessel, vascular ectasia, gastritis, portal hypertensive gastropathy, and a gastric polyp).

Thirteen patients had unexplained weight loss: seven with upper gastrointestinal abnormalities, four with cancer of the right colon, and two with no lesions.

Table 2. Endoscopic Findings in 100 Patients with Iron-Deficiency Anemia.*

Procedure and Lesion	No. of Patients
Colonoscopy	
Colon cancer	11
Polyp†	5
Vascular ectasia	5
Colitis	2
Cecal ulcer	2
Parasitic infestation	1
Total	26
Esophagogastroduodenoscopy	
Duodenal ulcer	11
Esophagitis	6
Gastritis	6
Gastric ulcer	5
Vascular ectasia	3
Anastomotic ulcer	3
Gastric cancer	1
Other‡	2
Total	37

*One patient had two lesions (gastritis and a colonic polyp). Thirty-eight patients had no detectable lesions.

†Two patients had two polyps each.

‡One patient had portal hypertensive gastropathy, and one had a gastric adenomatous polyp.

The mean weight loss was 13 kg (range, 2 to 36), 12 kg (range, 2 to 18), and 7 kg (range, 2 to 12) in those with upper gastrointestinal lesions, colon cancer, and no lesions, respectively.

Twenty-one patients reported long-term use of substances that irritate the gastrointestinal mucosa, including nonsteroidal antiinflammatory drugs other than aspirin (11 patients), aspirin (4 patients, none of whom took more than 325 mg per day), and alcohol (6 patients). Seven of the patients taking nonsteroidal antiinflammatory drugs had no identifiable lesions, two had lesions in the upper gastrointestinal tract (gastritis in both cases), and two had lesions in the lower gastrointestinal tract. One patient taking aspirin had colon cancer, and three had no detectable lesions. Of the six patients who drank alcohol regularly, three had lesions in the upper gastrointestinal tract (esophagitis, vascular ectasia, and duodenal ulcer in one each), and three had no lesions.

Radiographic Findings

Thirty-eight patients with negative endoscopic examinations of the upper and lower gastrointestinal tract were referred to the radiology service for enteroclysis. Twenty-six underwent this examination, and three additional patients underwent a small-bowel follow-through study after swallowing barium (because of difficulty with insertion of the enteroclysis perfusion tube). No lesions were identified in any of these patients.

Statistical Analysis

Values for hemoglobin, mean corpuscular volume, serum ferritin, and transferrin saturation did not differ significantly between patients with positive endoscopic studies and those with negative endoscopic studies.

Site-specific symptoms were significantly associated with lesions in the portion of the gastrointestinal tract where the symptoms originated, and these symptoms were predictive of abnormal findings (Tables 3 and 4). Although site-specific symptoms were strongly associated with site-specific lesions, the absence of symptoms did not exclude the possibility of detecting a lesion. For the statistical analysis, a valid test for fecal occult blood was defined as at least one positive test or at least three negative tests; 90 patients had valid tests for stool blood. Stool testing alone had a relatively low sensitivity for detecting disease and a positive predictive value of 75 percent overall. Among patients with site-specific symptoms and positive tests for fecal occult blood, the positive predictive value for detecting lesions in the lower and upper gastrointestinal tracts increased to 86 percent and 82 percent, respectively.

No clinical feature distinguished patients with colon cancer from those with other colonic lesions. The 95 percent confidence limit for detecting colon cancer in a patient who had an upper gastrointestinal lesion was 0.08. This computation assumes that all patients with iron-deficiency anemia have an equal (i.e., high) risk of colon cancer. However, since some patients (such as those who are young and those with symptoms and lesions in the upper gastrointestinal tract) may be at lower risk for colon cancer, our confidence limit may be falsely high. No patient with a lesion in the upper gastrointestinal tract had colon cancer.

Patients with Negative Endoscopic and Radiographic Studies

Lesions considered unlikely to be responsible for chronic blood loss in the 38 patients with negative endoscopic and radiographic studies included small polyps (1 cm in 1 patient, 0.5 cm in 1 patient, and less than 4 mm in 4 patients), hemorrhoids alone in 4 patients, antral hyperemia in 3 patients, small esophageal varices in 2 patients, and minimal esophagitis in 1 patient. No stigmata of bleeding were identified in connection with any of these lesions.

Table 3. Relation of Lesion Site to Location of Symptoms and Results of Fecal Occult-Blood Tests.*

Symptom Location and Fecal Occult Blood	Lesion Site			
	Upper GI Tract	Colon	Both	Neither
	no. of lesions			
Upper GI tract				
Positive (n = 10)	9	0	0	1
Negative (n = 12)	8	0	0	4
Lower GI tract				
Positive (n = 7)	0	6	0	1
Negative (n = 4)	0	3	0	1
Asymptomatic				
Positive (n = 33)	10	11	1	11
Negative (n = 34)	9	5	0	20

*GI denotes gastrointestinal. The upper gastrointestinal tract was examined by esophagogastroduodenoscopy, and the colon by colonoscopy. Fecal occult blood was tested with Hemoccult II slides.

Table 4. Association of Site-Specific Symptoms and Fecal Occult Blood with Gastrointestinal Lesions.*

Lesion	True Positive/ All Positive	P Value	Odds Ratio
Site-specific symptoms			
Upper GI lesion	17/22	<0.001	9.9
Lower GI lesion	9/11	<0.001	16.9
Both	0	—	—
Either	26/33	0.02	3.2
Fecal occult blood			
Upper GI lesion	13/23	>0.05	—
Lower GI lesion	16/26	0.02	3.5
Both	1/11	>0.05	—
Either	30/40	0.03	3.0

*GI denotes gastrointestinal. Statistical calculations involving positive stool tests were based only on valid tests for occult blood (≥1 positive test or ≥3 negative tests). Ten patients with negative endoscopic studies had a positive test for occult blood. Since the source of bleeding could have been either the upper or lower gastrointestinal tracts or both, we considered these patients to have false positive tests for all three possibilities. P values and odds ratios are for a lesion in the indicated location as compared with no lesion in that location.

All 38 patients were empirically treated with oral iron; 36 of them were seen for follow-up tests 6 to 38 months later (mean, 20 months). Iron-deficiency anemia had resolved (defined as an increase in hemoglobin above the lower limit of normal) in 30 of the 36 patients (83 percent). All six patients in whom iron therapy was not effective had underlying medical illnesses. Three of the six patients had severe chronic renal insufficiency: two underwent long-term dialysis, and the third had an episode of melena but declined evaluation. Of the three other patients who did not have a response to iron therapy, one subsequently presented with calcinosis, Raynaud's phenomenon, esophageal hypomotility, sclerodactyly, and telangiectasia (CREST syndrome) and reported recurrent epistaxis; one had multiple medical problems, including chronic liver disease; and one with degenerative joint disease later reported having taken nonsteroidal antiinflammatory drugs, and a repeat esophagogastroduodenoscopy showed severe gastritis. Two patients died: one from chronic renal failure and the other (who had responded to iron therapy) from chronic liver disease.

Discussion

Idiopathic iron-deficiency anemia in adults is widely believed to result from chronic colonic blood loss due to mass lesions.[1,2] However, there are no study-based guidelines for efficiently managing this disorder. In an attempt to establish such guidelines, we prospectively studied 100 patients with iron-deficiency anemia, using upper gastrointestinal endoscopy and colonoscopy followed by small-bowel enteroclysis. We identified lesions consistent with chronic blood loss in 62 of the 100 patients. Although colorectal cancers were found in 11 patients, more lesions were detected in the upper gastrointestinal tract.

Symptoms that could be traced to either the upper or lower gastrointestinal tract were strongly associated with identification of a lesion by esophagogastroduodenoscopy or colonoscopy, respectively. Furthermore, the combination of a positive test for fecal occult blood and site-specific gastrointestinal symptoms increased the likelihood of detecting a bleeding source in the corresponding site. These results strongly suggest that for iron-deficient patients with specific symptoms, the initial examination should be directed by those symptoms. However, asymptomatic patients, particularly those who are elderly, since they have an increased risk of colorectal neoplasia,[19] should undergo colonoscopy, followed immediately by an endoscopic examination of the upper gastrointestinal tract if the colonoscopic examination is negative.

For patients in whom a substantial upper gastrointestinal lesion (according to our criteria) has been detected by esophagogastroduodenoscopy, the decision to examine the lower gastrointestinal tract may be controversial. Our data suggest that a synchronous lesion is unlikely. Clinicians may therefore reasonably elect not to undertake a colonic evaluation if a lesion has been detected in the upper gastrointestinal tract. This approach should limit the costs and potential risks of additional studies. Clinical judgment and follow-up, however, are essential. For example, since most of the substantial lesions of the upper gastrointestinal tract are related to acid-peptic disease, an intensive course of anti-acid therapy and iron replacement can be expected to correct the anemia. If the anemia does not resolve or if it returns after therapy has been discontinued, then a reevaluation, including a colonic examination, is recommended.

Nonsteroidal antiinflammatory drugs and alcohol have been associated with acute and chronic injury of the upper gastrointestinal mucosa.[20-24] We were unable, however, to find any correlation between the use of these irritants and lesions in the upper gastrointestinal tract. The patients who were taking nonsteroidal antiinflammatory drugs may have had ulcers that had healed by the time of our investigation, or the drugs may have induced small gastric or small-bowel lesions that were not detected by endoscopy.

Chronic blood loss from the distal small bowel may be responsible for iron-deficiency anemia.[1,2,25] Enteroclysis theoretically should reveal substantial mass lesions or severe ulcerative processes but not subtle mucosal abnormalities. In this regard, we may have failed to identify vascular ectasias or subtle abnormalities of the small-bowel mucosa. Although it is possible that some of our patients had occult small-bowel disorders, such as adult celiac disease or Whipple's disease, that were not detected, this possibility seems unlikely. No patients had symptoms of malabsorption, and the majority of patients with negative studies had a response to oral iron therapy. The role of enteroscopy in identifying abnormalities in the small bowel is controversial.[26] Vascular ectasias and other subtle mucosal lesions have occasionally been detected by this procedure in patients with occult gastrointestinal bleeding or iron-deficiency anemia.[27,28] Although theoretically appealing, small-bowel enteroscopy is expensive and

time consuming, requires special equipment, and has not been rigorously studied.

Over one third of the patients in our study had no lesions compatible with gastrointestinal bleeding. Follow-up data in these patients suggested a favorable prognosis, and the subsequent discovery of gastrointestinal tract lesions was rare. Most of these patients were asymptomatic. Conditions such as unreported menstrual losses (potentially in three patients in our study) or insufficient dietary intake of iron may have been responsible for occult iron deficiency. Alternatively, ulcerations or benign lesions may have caused blood loss in the past but then healed and thus were not detected. Although less likely, small ulcers or polyps may have led to chronic bleeding. Finally, abnormalities such as polyps or vascular ectasias may have been missed during the endoscopic examination. All the patients with persistent anemia had serious underlying medical illnesses, which is consistent with the possibility that their anemia was associated with chronic disease.

We conclude that substantial gastrointestinal lesions, particularly those of the upper gastrointestinal tract, are common in patients with iron-deficiency anemia. Therefore, a thorough evaluation of all such patients is mandatory. Many patients believed at first to be iron-deficient may not have decreased iron stores, and careful screening is therefore important before potentially expensive and unproductive studies are undertaken. We believe that the initial investigation should be directed toward site-specific symptoms. In asymptomatic older patients, the colon should be examined first. Patients with negative colonic studies should then undergo an upper gastrointestinal evaluation. Since synchronous lesions of the upper and lower gastrointestinal tract are rare, once an obvious source of potential blood loss has been identified, further examination of the gastrointestinal tract (but not further follow-up) appears to be unwarranted.

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References

1. Peterson WL. Gastrointestinal bleeding. In: Sleisenger MH, Fordtran JS, eds. Gastrointestinal disease. 4th ed. Vol. 1. Philadelphia: W.B. Saunders, 1989:415-6.
2. Ahlquist DA. Approach to the patient with occult gastrointestinal bleeding. In: Yamada T, ed. Textbook of gastroenterology. Vol. 1. Philadelphia: J.B. Lippincott, 1991:616-33.
3. Kerlin P, Reiner R, Davies M, Sage RE, Grant AK. Iron deficiency anemia — a prospective study. Aust N Z J Med 1979;9:402-7.
4. Croker JR, Beynon G. Gastro-intestinal bleeding — a major cause of iron deficiency in the elderly. Age Ageing 1981;10:40-3.
5. Hershko C, Vitells A, Braverman DZ. Causes of iron deficiency anemia in an adult inpatient population: effect of diagnostic workup on etiologic distribution. Blut 1984;49:347-52.
6. Cook IJ, Pavli P, Riley JW, Goulston KJ, Dent OF. Gastrointestinal investigation of iron deficiency anaemia. BMJ 1986;292:1380-2.
7. Calvey HD, Castleden CM. Gastrointestinal investigations for anaemia in the elderly: a prospective study. Age Ageing 1987;16:399-404.
8. Wroblewski M, Ostberg H. Ulcer disease among geriatric inpatients with positive faecal occult blood test and/or iron deficiency anaemia. Scand J Gastroenterol 1990;25:489-95.
9. Tan CC, Guan R, Tay HH, Yap I, Math MV. The diagnostic yield of upper gastrointestinal endoscopy in the investigation of anaemia. Singapore Med J 1991;32:157-9.
10. Zuckerman G, Benitez J. A prospective study of bidirectional endoscopy (colonoscopy and upper endoscopy) in the evaluation of patients with occult gastrointestinal bleeding. Am J Gastroenterol 1992;87:62-6.
11. Maglinte DDT, Lappas JC, Kelvin FM, Rex D, Chernish SM. Small bowel radiography: how, when, and why? Radiology 1987;163:297-305.
12. Hetzel DJ, Dent J, Reed WD, et al. Healing and relapse of severe peptic esophagitis after treatment with omeprazole. Gastroenterology 1988;95: 903-12.
13. Sauerbruch T, Schreiber MA, Schussler P, Permanetter W. Endoscopy in the diagnosis of gastritis: diagnostic value of endoscopic criteria in relation to histological diagnosis. Endoscopy 1984;16:101-4.
14. SAS/STAT users's guide: version 6. 4th ed. Cary, N.C.: SAS Institute, 1990.
15. SAS language and procedures: introduction, version 6. Cary, N.C.: SAS Institute, 1990.
16. Cox DR. The analysis of binary data. London: Methuen, 1970:43-8.
17. Newland RC, Chapuis PH, Pheils MT, MacPherson JG. The relationship of survival to staging and grading of colorectal carcinoma: a prospective study of 503 cases. Cancer 1981;47:1424-9.
18. American Joint Committee on Cancer. Manual for staging of cancer. 3rd ed. Philadelphia: J.B. Lippincott, 1988:69.
19. Schottenfeld D. The epidemiology of cancer: an overview. Cancer 1981;47: Suppl:1095-108.
20. Graham DY, Smith JL. Gastroduodenal complications of chronic NSAID therapy. Am J Gastroenterol 1988;83:1081-4.
21. Laine L, Weinstein WM. Histology of alcoholic hemorrhagic "gastritis": a prospective evaluation. Gastroenterology 1988;94:1254-62.
22. McCarthy DM. Nonsteroidal antiinflammatory drug-induced ulcers: management by traditional therapies. Gastroenterology 1989;96:662-74.
23. Fries JF, Miller SR, Spitz PW, Williams CA, Hubert HB, Bloch DA. Toward an epidemiology of gastropathy associated with nonsteroidal antiinflammatory drug use. Gastroenterology 1989;96:Suppl 2:647-55.
24. Carson JL, Strom BL, Soper KA, West SL, Morse ML. The association of nonsteroidal antiinflammatory drugs with upper gastrointestinal tract bleeding. Arch Intern Med 1987;147:85-8.
25. Ress AM, Benacci JC, Sarr MG. Efficacy of intraoperative enteroscopy in diagnosis and prevention of recurrent, occult gastrointestinal bleeding. Am J Surg 1992;163:94-9.
26. Krevsky B. Enteroscopy: exploring the final frontier. Gastroenterology 1991;100:838-9.
27. Morris AJ, Wasson LA, Mackenzie JF. Small bowel enteroscopy in undiagnosed gastrointestinal blood loss. Gut 1992;33:887-9.
28. Foutch PG, Sawyer R, Sanowski RA. Push-enteroscopy for diagnosis of patients with gastrointestinal bleeding of obscure origin. Gastrointest Endosc 1990;36:337-41.