

AUDIT

Audit of the investigation of iron deficiency anaemia in a district general hospital, with sample guidelines for future practice

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Abstract

Iron deficiency anaemia commonly presents in patients who are asymptomatic. In the absence of published guidelines the search for a cause in such cases is frequently uncoordinated, and risks delay in the diagnosis of pathologies requiring urgent attention. This audit was undertaken to determine how thoroughly patients referred to the gastrointestinal unit in a district general hospital between 1990 and 1995 had been investigated, and to draw up guidelines for future practice on the basis of its results. From the case notes of 334 patients examined endoscopically for anaemia 126 were identified as having both proved iron deficiency and a lack of clinical pointers to its cause. The percentage and details of diagnoses made during initial study and a median follow up period of 28 months were ascertained, together with the certified diagnoses of patients who had died. A cause of iron deficiency was identified in 48 (38%) of patients, 22 with cancer. Ten others received a diagnosis during follow up, of whom three died from the condition to which their anaemia had been attributed. Death certificates supplied diagnoses of potential relevance in three further cases. The main gaps in endoscopic coverage consisted of omitting duodenal biopsy or colonoscopy after negative upper gastrointestinal endoscopy. Moreover, diagnosis of certain extraintestinal pathologies, including cancers, was sometimes delayed for lack of liaison between gastroenterologists and other specialists. These and other points have been addressed in the guidelines now proposed.

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Prospective studies in the investigation of iron deficiency anaemia have shown that this is associated with a high frequency of gastrointestinal lesions.¹⁻⁶ Some protocols have included formal dietary assessment to estimate the contribution of poor iron intake,^{1,2,4} but none has been designed to explore also the role of excess menstrual loss in a population routinely referred for endoscopy. Other extraintestinal causes of occult iron deficiency are

probably rare, but carcinoma of the bladder has been reported as a late finding after negative gastrointestinal studies,² and in a district-wide survey, which excluded women under 50 years of age, bleeding lesions of the urinary tract predominated.⁷

It is doubtful whether many hospitals have yet considered establishing a policy for the investigation of iron deficiency anaemia. Our hospital offers no guidance on this subject, and the present audit was undertaken to determine whether the absence of a policy and the effective assumption by the gastrointestinal unit of responsibility for finding its cause in most cases was conducing to poor practice. Since the anaemia in such cases had usually been an unexpected finding we chose to confine the study to those in which no hint as to its origin had emerged from prior work-up.

Patients and methods

PATIENTS

The case notes of 334 patients recorded as having undergone endoscopy for anaemia between 1 March 1990 and 28 February 1995 were searched for evidence of iron deficiency, but also for any aspect of the history, physical signs, or tests already completed which could have suggested to the endoscopist the site or nature of the causative lesion, and would therefore disqualify the case for this study. Excluded thus was any case in which the patient had admitted taking non-steroidal anti-inflammatory drugs within the past three months.

Anaemia was defined by a haemoglobin concentration of <120 g/l in males, <115 g/l in females, and was accepted as being due to iron deficiency if accompanied by a mean corpuscular volume of <80 fl and either a serum ferritin of <10 µg/l or a response to iron repletion.

INVESTIGATIONS

The dates and results of all endoscopies, contrast radiographs, and radioisotope scans carried out as part of a single programme of investigation, begun or completed during the five year study period, were recorded. Any clinician responsible for a patient's care might have initiated a programme without seeking gastroenterological advice, but once endoscopy had been performed almost all subsequent tests were chosen by the specialist concerned.

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FOLLOW UP OF UNDIAGNOSED PATIENTS

Data were taken from case notes or sought from general practitioners on a standard questionnaire. Copies of the death certificates were obtained for patients who had died outside hospital.

Results

CASES STUDIED

The inclusion criteria were met in 126 (38%) cases. Of the patients qualifying 84, that is two thirds, were female. The age range was 15–94 (median 70).

DIAGNOSES

“Diagnosis” was defined as the discovery of any lesion that could be considered definitely or probably the cause of a patient’s anaemia. Such diagnoses were made in 48 (38%) patients. They included four of extraintestinal conditions (menorrhagia in two cases, dietary iron deficiency and carcinoma of endometrium in one each), which were confirmed by the results of appropriate management. That of endometrial carcinoma was made by a gynaecologist asked to advise on the aetiology of a non-haemorrhagic vaginal discharge.

Table 1 lists the diagnoses by age group. The rare finding of an oesophagogastric haemangioma was the only instance in which a potential bleeding lesion of the upper gastrointestinal tract occurred in a patient less than 65 years of age. The 22 malignancies constituted 45% of all diagnoses. Of these 15 were colonic, with the distribution: caecum (7), ascending colon (2), transverse colon (2), and sigmoid colon (4).

Diagnoses considered as only possible causes of the iron deficiency, and therefore excluded from analysis, were: gastritis (8), oesophagitis (6), colonic polyps of less than 1 cm diameter (3), marginal dietary iron intake (2), bulbar duodenitis, non-specific duodenal villous abnormalities, third degree haemorrhoids, and malignant cachexia (one case each).

Pathology of at least possible relevance in both upper gastrointestinal tract and colon was found in five instances. In all upper gastrointestinal endoscopy had been the first proce-

dure, showing a healing chronic gastric ulcer in one patient as the only lesion considered likely to have contributed to the anaemia. The other upper gastrointestinal findings comprised oesophagitis in one case, gastritis in another, and duodenitis in two. Four of the colonic lesions were carcinomas (in patients aged 64, 71, 77, and 80), one polyposis in a 68 year old. The combination of oesophagitis with gastric antral erosions was rejected as the cause of one patient’s anaemia two weeks before she was found to have endometrial carcinoma.

SITE OF PATHOLOGY RELATED TO AGE AND CHOICE OF PROCEDURE

Since in the group of patients up to age 44 all except one of the five gastrointestinal tract diagnoses were of coeliac disease and the other a jejunal leiomyosarcoma, neither colonoscopy nor barium enema proved positive in the 13 examinations of large bowel to which 12 of the 21 patients were subjected.

In the group aged 45–64, however, five out of nine gastrointestinal lesions were colonic. One of the four caecal carcinomas was identified by small bowel meal in a patient for whom this had been requested before any formal large bowel study. The age of the patient with polyposis coli was 60, and those of the patients with carcinoma 45, 57, 62, and 64 respectively.

Seven of the 16 diagnoses among patients aged 65–74 were made by colonoscopy, and two by barium enema. In one further case a carcinoma of the distal transverse colon was missed at colonoscopy but discovered on colonic follow through of the subsequent small bowel meal. The six remaining diagnoses in this group were made at upper gastrointestinal endoscopy.

Among patients over 75 the discovery of a colonic lesion was due more often to barium enema (five cases) than to colonoscopy (three cases), probably because the radiography was preferred for 22 of the 33 large bowel studies in this group. A relevant lesion of the upper gastrointestinal tract was found at one in seven endoscopies.

Table 1 Diagnoses by age group

Diagnoses	Age group			
	<44 (n=21)	45–64 (n=28)	65–74 (n=33)	>75 (n=44)
	Coeliac disease	Oesophagogastric haemangioma	Ca stomach	Oesophageal ulcer
	Coeliac disease	Coeliac disease	Ca stomach	Oesophageal candidiasis
	Coeliac disease	Coeliac disease	Ca stomach	Ca stomach
	Coeliac disease	Leiomyosarcoma jejunum	Gastric adenomas	Gastric ulcer
	Leiomyosarcoma jejunum	Colonic polyps	Gastric ulcer	Gastric ulcer
	Dietary deficiency	Ca colon	Duodenal ulcer	Duodenal ulcer
	Menorrhagia	Ca colon	Colonic polyps	Colonic polyps
		Ca colon	Colonic polyps	Ca colon
		Ca colon	Colonic polyps	Ca colon
		Menorrhagia	Colonic polyps	Ca colon
			Colonic polyps	Ca colon
			Ca colon	Ca colon
			Ca colon	Ca colon
			Ca colon	Ca colon
			Ca colon	Ca colon
			BLH	
			stomach/colon	
			Ca endometrium	
No (%) of patients diagnosed	7 (33)	10 (36)	17 (52)	14 (32)

BLH = benign lymphoid hyperplasia; Ca = carcinoma.

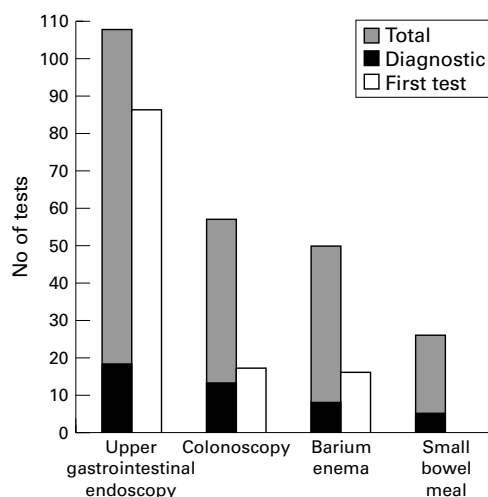


Figure 1 Number and diagnostic yield of the four principal procedures, with number of each performed as first procedure.

DIAGNOSTIC UTILITY OF INDIVIDUAL PROCEDURES
Figure 1 shows how frequently each of the four main procedures was used, relating this both to diagnostic yield and to the number of patients for whom each had been chosen as the first examination. Percentage of diagnoses achieved was: colonoscopy 24, upper gastrointestinal endoscopy 17, small bowel meal 15, and barium enema 14. The disproportion between choice as first examination and diagnostic yield was most marked for upper gastrointestinal endoscopy. Other procedures comprised: radioisotope scan for Meckel's diverticulum (5), flexible sigmoidoscopy (3), and barium meal (1), none of which gave a diagnosis.

PROCEDURES OMITTED

There were 17 instances in which non-diagnostic upper gastrointestinal endoscopy was not followed by a colonic examination. Of these nine involved patients over 75, some of whom were stated to be too frail to undergo purgation and then a longer procedure. In four

cases a recommendation of colonoscopy was not taken up. In one colonoscopy was cancelled when the anaemia resolved, and in another the patient defaulted, leaving two patients under 45 whose investigation was presumably considered complete at this stage.

Upper gastrointestinal endoscopy was omitted after a normal colonic study in 12 patients. Of these four underwent no further investigation because their anaemia had resolved, menorrhagia had been diagnosed in another, and two patients declined the examination. No reason was given in the five remaining cases.

Duodenal biopsy was performed at only 42% of upper gastrointestinal endoscopies reported as showing no gross pathology.

FOLLOW UP OF UNDIAGNOSED PATIENTS

At the time of review 74 (95%) of the 78 patients undiagnosed were either still attending the hospital, still on the list of the referring doctor, or known to have died with ascertainable diagnoses.

Median length of follow up was 28 months (range 1-75).

Table 2 shows that during follow up 10 patients were given a diagnosis which their doctors had accepted as the cause of their anaemia, leaving at least 64 (51%) of the total 126 patients still undiagnosed. No less than half these late diagnoses were of menorrhagia, two of dietary iron deficiency, and three of carcinoma.

From table 2 it can also be seen that during follow up the anaemia had resolved in 33 of the 74 patients. In two this followed hysterectomy after a late diagnosis of menorrhagia, and in a third, with hypernephroma, resolution was unexplained. Anaemia therefore failed to recur in at least 30 (47%) of patients for whom a potential cause was never identified.

Fifteen (20%) of the patients had died. Table 3 relates possibly relevant diagnoses at death in six to the gastrointestinal procedures they had initially undergone. It seems unlikely that fuller investigation would have revealed the source of the anaemia in more than three of these. Two died after admission to hospital as emergencies, one with caecal carcinoma, the other with small bowel obstruction. The hypernephroma of a third would have been evident in an ultrasound scan. The only three definitive diagnoses included a second urinary tract carcinoma.

Discussion

Published figures for diagnostic yield in retrospective studies of the investigation of iron deficiency anaemia vary from 49% to 75%,⁸⁻¹⁰ so that all seem to compare favourably with the 38% reported here. There would appear to be two main reasons for this. Firstly, the audit excluded patients who came to investigation with one or more clinical features suggesting a site for the causative pathology; secondly, we were unable to accept as potential causes of iron deficiency certain lesions of the upper gastrointestinal tract cited as such by other workers. Oesophagitis, gastritis, and duodenitis were excluded because never clearly haemorrhagic, and in no case were enough gastric ero-

Table 2 Follow up of anaemia, cause undetermined by initial investigations

State of anaemia	Resolved (n=33)	Controlled (n=21)	Persisting (n=20)
Median age at first test (range)	69 (31-93)	71 (15-89)	70 (19-94)
Median months follow up (range)	30 (7-75)	27 (5-69)	25 (1-73)
Still undiagnosed	30	16	18
Diagnoses given to remainder	Menorrhagia Menorrhagia Hypernephroma	Menorrhagia Menorrhagia Menorrhagia Dietary deficiency Ca bladder	Ca caecum Dietary deficiency

Ca = carcinoma.

Table 3 Procedures performed and possibly relevant diagnosis at death in patients with initially undiagnosed cause of iron deficiency anaemia

Patients		Procedures	Certified diagnosis
Sex	Age		
M	75	UGIE, colonoscopy, MDS	Ca bladder
F	80	UGIE, barium enema	Hypernephroma
M	84	UGIE, barium enema	Small bowel obstruction
M	88	UGIE	Carcinomatosis ? primary
F	89	UGIE	Gastroenteritis
F	95	UGIE, flexible sigmoidoscopy	Ca caecum

Ca = carcinoma; MDS = radioisotope scan for Meckel's diverticulum; UGIE = upper gastrointestinal endoscopy.

sions found to incriminate these as an important source of bleeding. The fact that even hiatus hernia, a non-haemorrhagic disorder, has been accepted by some authors^{1 2 8 11} serves only to emphasise the extent to which figures for diagnostic yield in the investigation of iron deficiency depend on the significance attached to "borderline" pathology of the upper gastrointestinal tract. A recent quantitative study of gastrointestinal blood loss in patients with iron deficiency anaemia attributed to endoscopically diagnosed lesions found that only eight of 42 were losing more than 2 ml daily. Only two of these had upper gastrointestinal pathology, and the patient losing least had ulcerative oesophagitis.¹²

A few undiagnosed patients in the present series were inappropriately denied a complete endoscopic survey; and one, perhaps in this category but aged 95 at the time, died of caecal carcinoma two years after negative upper gastrointestinal endoscopy. In no case where major pathology was discovered at the first examination was it felt necessary to exclude a separate lesion elsewhere, and in none of these did such a lesion emerge at follow up. In this context it may be noted that important dual pathology has rarely been found in studies requiring that every patient should undergo examination of both upper gastrointestinal tract and colon.^{4 5 13} It thus seems that a careful choice of first procedure and a conservative attitude to potentially causative pathology should together provide the basis for a safe minimum of gastrointestinal investigations.

Malabsorption of iron is one of the principal effects of damage to the mucosa in coeliac disease. In the present series all but one of the patients under 45 whose anaemia could be attributed to gastrointestinal pathology had coeliac disease, and there were two further cases in the next group, making a total of six (5%). This frequency accords well with the 2%–6% found in other studies,^{4 6 9 11 14} although if recognised good practice had been followed routinely here, with biopsy of the duodenum whenever no gross lesion was found in the upper gastrointestinal tract, more cases might have been discovered. In formulating guidelines we have used the finding that in our study group coeliac disease was the only gastrointestinal condition associated with chronic anaemia to select patients giving this

history—whatever their age—for upper gastrointestinal endoscopy as first examination.

Enteroscopy, extending access to the small bowel for inspection and biopsy, has an undoubted place in the investigation of iron deficiency anaemia, with a success rate of 20% in a recently reported study of 131 patients undiagnosed after routine endoscopy.¹⁵ Mesenteric angiography has also shown promise in a small series.¹⁶ Although the small bowel meal has disappointed elsewhere,^{5 6 9} it was in this instance the means by which two jejunal and two colonic cancers were diagnosed.

Of extraintestinal causes emerging in the present study dietary iron deficiency and menorrhagia were commonest, but referral of suspect cases for formal assessment was casual and slow. The Oxford survey of 371 patients, published in 1965, suggests that in the days before fibroendoscopy these possibilities were routinely pursued, and concludes that a diet deficient in iron was contributory in 19% of the entire group, menorrhagia in 37% of the women.¹¹ The authors of a later study from Australia claimed that poor iron intake was a factor in over half their cases.¹

Even before the coming of fibroendoscopy the prognosis for both resolution of the anaemia and survival without malignancy in patients whose condition had eluded diagnosis was excellent.¹¹ More recently 30 of 36 such patients followed up for a mean 20 months were found to have recovered completely. The remainder had serious co-morbidity.⁵ A review of 83 patients with unexplained iron deficiency anaemia investigated during the period 1980–88 found that after a mean six years 10 had died of unrelated conditions and that in none had cancer been diagnosed.¹⁷ Few of the survivors were still taking iron supplements. Those in the majority whose anaemia had resolved in the absence of any detectable cause were held to have suffered from "transient cryptogenic iron deficiency anaemia", a diagnosis by exclusion which seems likely to hold true for more patients than any other. It applied to 47% of those who never received a positive diagnosis in the present series.

This audit supports the results of all previous studies in finding that lesions of the gastrointestinal tract account for most cases in which a cause is found for an iron deficiency anaemia presenting to hospital, and suggests that a sub-

Table 4 Sample guidelines for investigation of iron deficiency anaemia

Programme A: for all patients	
Patients 45–74 with recently diagnosed anaemia	<ul style="list-style-type: none"> ● Colonoscopy. If no major lesion perform ● Upper GI endoscopy/duodenal biopsy at same session
Patients <45, >75 with recently diagnosed anaemia and	<ul style="list-style-type: none"> ● Upper GI endoscopy. If no major lesion include ● Duodenal biopsy. Also perform
All patients with chronic anaemia	<ul style="list-style-type: none"> ● Colonoscopy at same session in patients >45
Colonoscopy incomplete	<ul style="list-style-type: none"> ● Barium enema
Programme B: for patients still undiagnosed	
All patients	<ul style="list-style-type: none"> ● Stop iron supplements
To complete investigation select from	<ul style="list-style-type: none"> ● Full dietary history by dietitian ● Gynaecological review for women menstruating ● Renal ultrasound scan for patients >50 ● Small bowel contrast radiology or enteroscopy
Anaemia recurs in absence of diagnosis	<ul style="list-style-type: none"> ● Regular follow up. Consider repeat or further investigation

GI=gastrointestinal.

Learning points

- The investigation of iron deficiency anaemia is seldom pursued systematically; this can cause readily diagnosable cancers to be missed.
- Iron deficiency may be the sole presenting feature of coeliac disease, with its potential for causing ill health, which is reversible once the diagnosis has been made.
- All hospitals should adopt guidelines, arrived at by agreement between the relevant specialties, to ensure thorough investigation of iron deficiency anaemia.

stantial further group of cases may be attributed to dietary insufficiency of iron. The investigation of iron deficiency is, therefore, a task appropriately entrusted to the gastroenterologist. However, the frequency with which excess menstrual loss appeared as a diagnosis at follow up, and the more serious late diagnosis of two cancers of the urinary tract, indicate that this responsibility involves recognising when the expertise of another specialty is required. We suggest that the best way of ensuring satisfactory investigation of iron deficiency is for the appropriate specialties to agree guidelines which prescribe a sequence for gastrointestinal procedures and include any other measures that might be needed.

The sample scheme proposed here (table 4) assumes a lack of clinical pointers and allows for minimal work-up before endoscopy, though if the history given by a patient under 45 should hint at inadequate iron intake or excess menstrual loss it would be preferable to explore this possibility first. In the plan for endoscopy it distinguishes between patients on the grounds of our findings in relation to age and the known duration of the anaemia. This eliminates colonoscopy for patients under 45 and gives the elderly a chance to avoid it if, as is not uncommon, they have important pathology of the upper gastrointestinal tract that is clinically silent. The excessive use of upper gastro-

intestinal endoscopy as first procedure implied by our results would therefore seem to apply chiefly to those patients aged between 45 and 74, in whom neoplasia occurred more than three times as frequently in the colon as in the upper gastrointestinal tract. Colonoscopy is preferred to the combination of flexible sigmoidoscopy with barium enema because the former offers better diagnostic power at a single session and allows resection of polyps.

Any such scheme should be tested by prospective audit.

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