# The dedicated iron deficiency anaemia clinic – a fifteen-year experience

Helen Stone [1], Orouba Almilaji [1 2], Christopher John [1], Carla Smith [1], Susan Surgenor [1], Lachlan Ayres [1], Elizabeth Williams [1], Jonathon Snook [1]

[1] Gastroenterology Unit, Poole Hospital NHS Foundation Trust, Poole, UK

[2] Clinical Research Unit, Bournemouth University, Bournemouth, UK

**Correspondence address :**

Dr Jonathon Snook

Consultant Gastroenterologist

Poole Hospital NHS Foundation Trust

Longfleet Road

Poole

Dorset BH15 2JB

Tel : 01202 442357

E-mail : Jonathon.Snook@gmail.com

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| | | |
|---|---|---|
| IDA | - | iron deficiency anaemia |
| GI | - | gastro-intestinal |
| Hb | - | blood haemoglobin concentration |
| MCV | - | mean cell volume |
| IQR | - | inter-quartile range |
| CRC | - | colorectal cancer |
| BCSP | - | Bowel Cancer Screening Programme |
| BDE | - | Bidirectional endoscopy |

**Abstract**

**Objective :** To report our cumulative experience from a dedicated IDA clinic over the last 15 years – with particular emphasis on referral rate, uptake of investigation, impact on endoscopy services, diagnostic yield of GI investigation, and the issue of recurrent IDA.

**Method :** A series of analyses of a register of 2808 referrals to the Poole IDA clinic between 2004 and 2018.

**Results :** The study population of 2808 had a sex ratio of 1.9 (F/M) and a median age of 72 years (IQR : 60 - 79). A rising referral rate over the study period appears to be plateauing at around 2 cases per 1000 population per annum. On the basis of a snapshot audit, investigation of IDA may now account for over 20% of all diagnostic endoscopies.
Overall, 86% of cases underwent examination of the upper and lower GI tract. Significant GI pathology was identified in 27% of the investigated cohort. Adenocarcinoma of the upper or lower GI tract was found in 8.3%, the majority in the right colon. The prevalence of recurrent IDA was estimated at 12.4%, and the results of investigation of this sub-group are reported.

**Conclusion :** Unexplained IDA is common, particularly in those over 60 years, and may be the first indication of underlying GI malignancy in over 8% of cases. Unresolved challenges include accommodating the resulting endoscopy workload, establishing a risk / benefit ratio for investigating those with major co-morbidities, and the management of recurrent IDA.

**Summary box**

1. ***What is already known about this subject?***

IDA is common, and may be the first indication of underlying GI malignancy

2. ***What are the new findings?***

The referral rate of IDA felt to warrant investigation is about 2 cases per 1000 pa, and this may account for over 20% of the total diagnostic workload in Endoscopy. IDA is recurrent in about 12% of cases following negative examination of the upper and lower GI tract

3. ***How might it impact on clinical practice in the foreseeable future?***

A dedicated service should be considered by general hospitals to standardise and streamline all aspects of the investigation and management of IDA

## Introduction

Iron deficiency anaemia (IDA) is a common clinical problem. The major causes are dietary insufficiency, malabsorption and low-grade blood loss [1] [2]. Approximately 30% of men and older women investigated for IDA have significant underlying gastro-intestinal (GI) pathology, often in the absence of any other clinical clues, and around a third of these prove to have GI malignancy [3] [4]. For this reason, national guidelines advocate examination of the upper and lower GI tract in adult males and post-menopausal females with unexplained IDA [5].

Historically IDA has been something of an orphan condition. Whilst commonly seen in both primary care and across the range of disciplines in secondary care, it generally didn't fall within the remit of any particular medical specialty. As a result, IDA was sometimes poorly or incorrectly diagnosed and managed, and investigations were often slow and incomplete [6] [7].

In an attempt to address these issues, a dedicated IDA service based on a nurse-led clinic was established under the supervision of the Gastroenterology Department at Poole General Hospital in 2004. Our IDA team of two part-time specialist nurses (providing 1.0 whole time equivalents) with secretarial support ensure that all new referrals, whether referred via the 2 week wait pathway or not, are assessed face-to-face and counselled promptly, given iron replacement by the appropriate route, investigated and followed up according to the investigation findings. We have previously detailed the set-up of this service, and the impact of it on the management of IDA [7]. The current paper details aspects of our experience with a dedicated IDA clinic over the last 15 years, and reflects on some challenges that remain in the management of IDA.

## Method

A patient register has been maintained since the inception of our nurse-led IDA clinic in 2004, which has been invaluable for the purposes of clinical follow-up, service audit and observational research. By 2018 the service had seen over 2800 referrals with confirmed iron deficiency. The diagnosis of iron deficiency was confirmed primarily on the basis of a serum ferritin and/or transferrin saturation below the lower limit of normal, or in the absence of that information, blood film appearances (pencil cells etc) and haematological response to iron replacement therapy [5].

This report is derived from analyses of the register as described below, and all patient-specific data was anonymised prior to analysis. It summarises our cumulative experience over the 15 years of the IDA service, with a particular emphasis on:

1. Annual referral numbers
2. The decision to proceed to invasive GI investigation
3. The knock-on effect in terms of endoscopy workload
4. The diagnostic yield of GI investigation
5. The prevalence and investigation yield in recurrent IDA

For the purposes of this analysis, initial investigation was considered "complete" if the upper GI tract had been examined by gastroscopy, coeliac disease had been excluded, and the colon had been fully imaged either by colonoscopy or CT colonography. The availability of CT colonography has helped to improve the

uptake of colonic investigation in those with major co-morbidities, although the test has some limitations. CT of the abdomen and pelvis may be a pragmatic "rule out" test of lower GI tract malignancy in those unable to tolerate any form of preparation, but for the purposes of this analysis was not considered adequate.

## Results

### Study group

A total of 2808 referrals with confirmed iron deficiency were assessed by the service during the study period, comprising 1823 females and 965 males (F/M sex ratio - 1.9), with a median age of 72 years (IQR : 60 - 79). As shown in Figure 1, the number of new referrals has risen progressively to over 400 per annum in recent years, giving a population incidence estimate for IDA of almost 2 cases per 1000 per annum. The age-adjusted incidence in the over 60 age group is considerably higher, at around 6 cases per 1000 per annum.

These figures are likely to be a considerable underestimate of the true incidence of IDA in the general population however, for three reasons. The first is that IDA may not be diagnosed unless the individual concerned happens to have a blood test – and currently this is not a systematic process at population level. The second is that diagnosed IDA may not be referred to the IDA clinic if hospital intervention is not thought to be required – for example, in the case of a young female with menorrhagia. The third is that some subjects with IDA may have been referred to other hospital specialities such as haematology or elderly care.

*Figure 1 Referral numbers over the study period, and number of cancers revealed by GI investigation*

### Incomplete initial investigation

Of the 2808 referrals with confirmed iron deficiency, initial investigation as defined above was incomplete in 385 (13.7%). There were a number of reasons for this. In 14 cases it was because the initial investigation (usually gastroscopy) revealed a cancer, and so the planned second investigation (usually of the colon) was cancelled. For the purposes of analysis, investigation of these cases was considered "complete", to avoid under-estimating the prevalence of malignancy.

Far more commonly however, incomplete investigation was the result of informed patient preference, concurrent illness, or major co-morbidity including frailty. The relationship between incomplete investigation rate and age is shown in Figure 2. As anticipated, the percentage of incomplete investigations was highest in those under the age of 40 and over the age of 80.

*Figure 2 Percentage in each age-band undergoing complete initial GI investigation*

**Endoscopy workload**

To estimate the impact of investigation for IDA on the workload of the Endoscopy Unit, a snapshot audit undertaken for one week in September 2018. This revealed that IDA was the major indication for 22% of diagnostic gastroscopies and 26% of diagnostic colonoscopies (excluding those in the BCSP). It also demonstrated that 86% of referrals for the investigation of IDA were from the IDA clinic rather than other sources, implying that most patients with IDA are now being referred through the IDA service - and therefore that the referral rate to the IDA clinic is likely to plateau over the next few years (Figure 1).

**Diagnostic yield**

As previously described [4], the findings on GI investigation in IDA fall into five broad pathological categories – coeliac disease, vascular (malformations), inflammatory, neoplastic (benign) and neoplastic (malignant). Low grade peptic inflammation, uncomplicated diverticular disease and benign polyps less than 1cm in diameter were not considered convincing explanations for IDA. By these criteria, significant GI pathology was identified in about 27% of those fully investigated, with two or more unrelated pathologies in 40 cases (1.7%). The distribution of the five major diagnostic categories by age at presentation is shown in Figure 3.

A carcinoma in the upper or lower GI tract was identified in 200 (8.3%) of the study group - of those, 172 (86%) were in the lower GI tract; and of those, 140 (81%) were in the right colon. A further 21 cases had a malignancy felt likely to have contributed to the development of IDA – these comprised an array of different pathological types including cancers of the renal tract (5), neuroendocrine tumours (3), gastrointestinal stromal tumours (6), small bowel adenocarcinoma (1), and metastatic disease or lymphoma with evidence of GI involvement (6). The overall prevalence of a relevant malignancy was therefore 9.1% in the investigated cohort.

There was a downward trend in the yield of GI cancer over the duration of the study, falling from 10.8% of investigated subjects in the first triennium to 7.1% in the last (Figure 4). This corresponds to subtle changes in the major predictors of GI cancer in IDA [8], with small but statistically significant rises in mean Hb (by 0.5 g/l/year ; $P < 0.002$) and MCV (by 0.4 fl/year ; $P<0.001$) at presentation over the study period, and a marginal increase in the F/M sex ratio (by 0.02/year ; $P< 0.04$).

*Figure 3 The distribution of pathological findings in the major diagnostic categories by age-band*

*Figure 4 The percentage of investigated subjects with GI cancer in the upper or lower GI tract by triennium*

**Recurrent IDA**

An audit of 693 cases investigated through the IDA service between January 2016 and September 2017 revealed that 86 (12.4%) had recurrent unexplained IDA. For the purposes of this study, recurrent unexplained IDA was defined as one or more previous episodes of confirmed IDA at least 12 months earlier,

with a complete haematological response to iron replacement therapy and no significant abnormalities reported on index investigation of the upper and lower GI tract.

Significant pathology was revealed on repeat assessment of the upper and lower GI tract in 12 cases (14%), including 4 cancers. All 4 of these cancers were found in those re-presenting more than two years after the index episode of IDA. Those with no significant abnormalities were offered small bowel investigation by MR enterography and / or capsule endoscopy if there was a reasonable prospect that the findings would influence management.

A more extensive analysis of our capsule endoscopy records revealed 83 procedures for recurrent unexplained IDA over the last four years of the study period. Potentially significant pathology was revealed in 52 cases (63%), with vascular malformation(s) in 31 (37%), Crohn's disease in 17 (20%), NSAID-enteropathy in 3, and adenocarcinoma in 1 case.

## Discussion

IDA is a common clinical problem with fairly clear diagnostic criteria, a degree of case homogeneity, and relatively straightforward algorithms for treatment and investigation [5]. These features make the condition eminently suitable for management in a dedicated nurse-led IDA clinic [7]. The snapshot endoscopy audit reported here has helped service planning by demonstrating that most cases of investigated IDA are now being channelled through the IDA clinic. We deduce from this that referral numbers to the IDA clinic are likely to plateau over the next few years, at a figure of around 2 per 1000 population per annum.

Our experience with the development of an IDA clinic is that it has markedly streamlined service provision [7]. It has also fulfilled a previously unmet need, and the relentless rise in referral numbers over the last 15 years is testament to this. This change in referral practice from primary and secondary care has occurred with little in the way of advertising other than periodic education sessions. Benefits of the service include improved understanding amongst referrers of the diagnostic criteria for IDA resulting in fewer inappropriate referrals, and a marked reduction in the time from referral to diagnosis [7] - which is particularly important for those who prove to have an underlying malignancy.

The format of the IDA clinic ensures that patients and carers have the opportunity to ask questions and gain all of the information required to make a considered decision as to whether to proceed with invasive investigation. Patient feedback indicates that this aspect is highly valued. The face-to-face setting in the IDA clinic provides an excellent forum for what can sometimes be quite complex conversations taking into account patient wishes, ensuring that consent is truly informed, and following the good practice principle of avoiding invasive investigation if the perceived risk outweighs the benefit, and / or the outcome is unlikely to alter management. This cannot be matched by virtual clinics, particularly for the relatively elderly patient population in question.

Although investigation is declined or felt clinically inappropriate in 14% of cases, the endoscopic workload generated by the IDA service is considerable. The snapshot audit indicates that IDA referrals may account for over 20% of all diagnostic gastroscopies and colonoscopies (excluding BCSP cases). The importance of investigating IDA is demonstrated by the yield of underlying GI pathology, and in particular of GI malignancy. The majority of these are colorectal cancers (CRC), and our records show that the annual CRC yield from the IDA service and BCSP are numerically similar (unpublished data).

The problem is that many endoscopic investigations in IDA will reveal no significant pathology at all, and less than 1 in 20 procedures will reveal a cancer. This issue is accentuated by the falling prevalence of GI cancer in IDA over recent years, as shown in figure 4. The evidence suggests that this fall reflects referral of an increasing proportion of cases with less severe IDA, and so in one sense the IDA service is perhaps a victim of its own success. Nevertheless, a case could be made that the widespread investigation of IDA is not good use of precious investigational resources.

A solution to this problem may be risk stratification [9] [10]. It is evident that the pre-test probability of cancer varies considerably between subjects presenting with IDA. As shown in figure 3, age is an important variable - but it is not reliable in isolation, with some cancers found in the under 50s and a few in the under 40s. However, there is now good evidence that the combination of four simple, independent and objective predictors of cancer risk (age, sex, Hb and MCV) identifies a substantial sub-population with IDA who are at extremely low cancer risk and may therefore (with appropriate precautions) not require invasive investigation [8].

The majority with IDA will show a complete and sustained haematological response following a course of iron replacement therapy, following treatment of abnormalities found on investigation of the upper and lower GI tract if appropriate. There are no agreed definitions for “persistent” and “recurrent” IDA, but broadly the former corresponds to an incomplete haematological response to adequate iron replacement, whilst the latter describes a situation where the initial haematological response is complete, but IDA reappears after an undefined time period.

If recurrent IDA is due to GI disease, this could be the result of pathology missed on previous investigation, out of the range of previous investigation (ie in the small bowel), or newly evolved and therefore not the cause of the previous episode. Our findings would suggest that all three explanations may be relevant.

The literature on recurrent IDA is sparse, as are guidelines for management. Our finding of a prevalence of 12.4% is consistent with other reports [11] [12], but this figure is likely to be an underestimate, as some cases of recurrent IDA may not be referred back to the service. A difficult issue is whether recurrent IDA warrants re-examination of the upper and lower GI tract, and our experience would suggest that it does – particularly if there was any question of inadequacy of the previous examination(s), or if more than two years have elapsed since previous investigation. The finding of a high prevalence of small bowel pathology in recurrent IDA with negative BDE is in accord with others [13] [14].

In summary, there are ongoing challenges in the management of IDA. Many of these revolve around investigational decisions in those with a low predicted risk of underlying cancer, with major co-morbidities and with recurrent IDA. Nevertheless, our experience with a dedicated IDA clinic over the last 15 years is that it has been invaluable in streamlining the management of this common and important clinical condition.

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