OPINION

Investigating for GI malignancy in iron-deficiency anaemia—the case for risk stratification

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Iron deficiency anaemia (IDA) is a common clinical problem, with an incidence in excess of one case per 1000 of population per annum.¹ Large case series^{2–4} have consistently shown that about 10% of men and postmenopausal women with IDA have underlying gastrointestinal (GI) malignancy, often in the absence of any other clinical pointer to the diagnosis. It is for this reason that IDA is recognised as an urgent indication for GI investigation.⁵ Tumours responsible for IDA may lie anywhere along the GI tract, though the commonest site is in the proximal colon.

Bidirectional endoscopy (BDE), combines gastroscopy and colonoscopy in the same session, and is an efficient means of assessing the GI tract in IDA.^{4,5} As well as identifying cancer, it may pick up a myriad of less serious GI pathology (eg, coeliac disease, vascular malformations) in a further 20% of cases.^{2–4} BDE is labour-intensive, however, taking up to an hour to complete for each patient, and carries a small but significant risk of complications, particularly in the elderly and those with major comorbidities. Furthermore, the number of patients that need to be investigated (NNI) to find one cancer is about 10, and the majority of examinations will be negative—this is an important drain on resources in a typical UK Endoscopy Unit, where investigation of IDA may account for up to 10% of all procedures.

It follows that a simple and reliable pretest predictor of the risk of underlying GI malignancy that is highly discriminating could considerably improve the efficiency of investigation in IDA. The ideal would be a clinical tool that identifies relatively large subgroups of patients who are at particularly high risk of malignancy, so warranting fast-track BDE; and even more importantly those at extremely low risk, who could

reasonably be managed without full endoscopic investigation.

Analyses of large case series by James *et al* from Nottingham³ and our group⁴ have demonstrated that three simple and objective clinical variables—age, sex and haemoglobin concentration (Hb)—are independent predictors of the risk of underlying GI malignancy in IDA. Combining these variables in the IDIOM study,⁴ the prevalence of GI malignancy ranged from more than 30% in high-risk subgroups (NNI=3) to less than 2% in low-risk subgroups (NNI>50).

Faecal occult blood (FOB) testing is a simple investigation for detecting the presence of microscopic quantities of haemoglobin in stool. FOB testing has fallen into some disrepute over the years, probably because it is a non-diagnostic test that was being used in an unfocussed way, but has of course recently resurfaced as the primary screening test in the highly successful National Bowel Cancer Screening Programme.^{6,7}

Chowdhury *et al*⁸ from Portsmouth report the value of FOB testing in IDA using two guaiac methods. There is logic to exploring this avenue, since occult bleeding is the major mechanism underlying the development of IDA in GI malignancy. In their study of 292 patients with IDA, 37 (13%) proved on subsequent investigation to have GI malignancy—including 34 with colorectal cancer (CRC). Depending on the test method used and the threshold for positivity, FOB testing yielded figures for sensitivity and negative predictive value of up to 0.97 and 0.99 for CRC—though to achieve these impressive figures multiple stool samples were required, and there was no *a priori* hypothesis as to the optimal cut-off threshold.

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The findings are consistent with a previous study by Nakama *et al.*,⁹ who reported a Japanese cohort of 1132 subjects with IDA. Their subjects were rather younger, and therefore had a lower overall CRC prevalence of 2.7%. FOB testing yielded a sensitivity of 0.87 for CRC, with a negative predictive value of 0.996.

There is more work to be done, as Chowdhury *et al* stress. First, it is important to confirm the practical application of FOB testing in a clinical as opposed to research setting. In this regard, faecal immunochemical testing for haemoglobin has major advantages over traditional guaiac-based methods, offering simpler and more patient-friendly sample collection requirements as well as enhanced sensitivity for pathology.^{10–12}

Second, a large prospective study is required to establish whether FOB testing is a predictor of cancer risk independent of the clinical factors identified in the IDIOM study, and whether the combination of low clinical risk and negative FOB testing can identify a subgroup of patients with IDA who have a sufficiently low cancer risk to make management without BDE a realistic strategy. This approach is analogous to what has become standard practice for venous thromboembolic disease, where clinical assessment and the result of D-dimer testing are combined to identify a large low-risk subgroup in whom further investigation can be safely avoided.¹³

Clearly, an approach to the management of IDA based on pretest stratification, with non-investigation of patients at ultralow risk of malignancy, would require rigorous validation before acceptance into clinical practice. There are some simple ways of introducing further safety checks into such a system—for example, automatic endoscopic investigation of the minority who fail to exhibit a sustained haematological response to a short course of iron supplementation.¹⁴ On the other hand, this type of strategy could substantially reduce the number of negative investigations undertaken by already overburdened endoscopy units, so allowing prioritisation of the investigation of individuals predicted to be at high risk for cancer.

Competing interests None.

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