Abstract
Iron deficiency anaemia (IDA) is common in older adults and associated with a range of adverse outcomes. Differentiating iron deficiency from other causes of anaemia is important to ensure appropriate investigations and treatment. It is possible to make the diagnosis reliably using simple blood tests. Clinical evaluation and assessment are required to help determine the underlying cause and initiate appropriate investigations. IDA in men and post-menopausal females is most commonly due to occult gastrointestinal blood loss until proven otherwise, although there is a spectrum of underlying causative pathologies. Investigation decisions should take account of the wishes of the patient and their competing comorbidities, individualising the approach. Management involves supplementation using oral or intravenous (IV) iron then consideration of treatment of the underlying cause of deficiency.
Future research areas are outlined including the role of Hepcidin and serum soluble transferrin receptor measurement; Quantitative faecal immunochemical testing (qFIT); alternative dosing regimens and the potential role of IV iron preparations.

Keywords
Iron deficiency anaemia, Serum ferritin, qFIT, endoscopy, CT colonography

Key-points

- Anaemia is common in older adults and it is important to differentiate iron deficiency from other causes
- Serum ferritin is the most reliable marker of iron status in the absence of systemic inflammation with levels of <45 μg/L almost invariably iron deficient, and above 100 μg/L excluding deficiency
- Investigations for occult blood loss causing IDA should take account of patient preferences and comorbidity
- Further research is needed to determine the role of novel diagnostic tests such as serum hepcidin and faecal immunochemical testing.
- IV iron has a role in the treatment of confirmed IDA in older people, if oral iron preparations cannot be tolerated

Background
Iron deficiency anaemia (IDA) is common in older people, particularly those in hospital.[1] Anaemia is associated with a range of adverse outcomes including frailty, cognitive decline, hospitalisation and mortality.[2-4] However, this likely reflects an association with the underlying aetiology of the anaemia. Nevertheless, this supports the view that a robust diagnostic approach should be followed when anaemia is identified to diagnose the form, target investigation of the underlying cause and offer treatment where this is appropriate and desirable for the individual.

This review focuses on IDA in older people. Recent developments have increased the numbers of diagnostic tests, and new treatment strategies are available. These changes come with potential costs to healthcare services and it is important that those involved in the delivery of frontline healthcare services understand the role of these innovations and how they should be incorporated in practice.

Our aim is to provide a contemporaneous and practical review of the diagnosis, investigation and management of IDA in older adults, focusing on recent developments, relevant research and future potential developments.

Iron homeostasis
Iron is essential for synthesis of haemoglobin (Hb), myoglobin, DNA and for generating energy from mitochondria.[1] Adults typically have 3-5g of iron in total body stores of which 20mg are needed daily for red cell production and metabolism.[5] Iron as haemoglobin is usually efficiently recycled from red blood cells by macrophages in the liver and spleen, with only 1-2mg per day required from dietary intake to replace losses. Iron absorption occurs principally in the duodenum.

In cells, iron is stored in ferritin,[6] circulating iron is largely bound to the plasma protein transferrin, which is approximately 30% saturated in healthy conditions.[7] Iron absorption and release from hepatocyte stores and macrophages are suppressed by the key regulator protein hepcidin; this is of particular significance as hepcidin levels rise with inflammation.

Diagnosing IDA
Anaemia is usually defined using the 1968 World Health Organization criteria of a Hb concentration of <130g/L in men and <120g/L in women, derived from population surveys of <65yr-olds.[8] However, Hb declines with age in healthy populations, with some advocating a cut-point of <115g/L after 80 years for both sexes.[9]

The classic laboratory picture of IDA is of hypochromic (low Mean Corpuscular Haemoglobin), microcytic (low Mean Corpuscular Volume) red cells, but some patients can be normochromic. There is no gold standard test for IDA. Even bone marrow biopsy in 10% of samples fails to provide marrow granules or core biopsy suitable for iron staining. It is also invasive and seldom required to establish a diagnosis of IDA.[10] As Hb values fall so serum ferritin levels rise with increasing age.[11] However, serum ferritin has consistently been noted to be the most reliable investigation in anaemia in older people, with levels correlating well with iron stores on bone marrow biopsy.[12] A serum ferritin of <15µg/L is absolute evidence of iron deficiency.[6] Older adults with a serum ferritin <45 µg/L are almost invariably iron deficient, while levels >100 µg/L effectively exclude deficiency.[12, 13]

Iron indices are affected by systemic inflammation.[14] Measuring serum iron is not recommended in diagnosing IDA as it can be affected by diet, inflammation and infection.[6] Transferrin saturation does not provide a reliable quantitative reflection of body iron stores.[6] Serum ferritin is positively correlated with CRP and inversely correlated with albumin.[14] Assessment for IDA should preferably occur when CRP <10 mg/L,[6] however this is not always feasible in clinical practice.

In the future, laboratory testing for hepcidin or serum soluble transferrin receptor levels may have a role in distinguishing IDA from anaemia of chronic disease. [15, 16] However, large-scale studies are awaited, and these tests are not yet routinely available in clinical practice.

Functional iron deficiency occurs when individuals have a normal serum ferritin and stainable iron in the bone marrow, but there is insufficient iron incorporated into erythroid precursors.[17] This is a particular issue for patients with Chronic Kidney Disease on erythropoiesis-stimulating agents. Measuring the percentage of hypochromic red cells or reticulocyte haemoglobin content may help in identifying functional iron deficiency, but these laboratory tests are not currently available in all centres.[17]

What is the aetiology of IDA in older adults?

An underlying cause for IDA should be considered for all patients and may be multifactorial. **Figure 1** summarises a classification of the possible causes evaluating these three categories: inadequate dietary intake; impaired absorption and excess iron loss.[1, 18, 19] Thorough history and clinical evaluation will help delineate between these aetiologies.

Antiplatelet medications and anticoagulants may "unmask" malignancy or other causes of chronic blood loss, causing IDA to be recognised sooner.[20] However, rates of malignancy in those investigated for IDA are similar for those on such drugs as those who are not, meaning IDA should not be attributed solely to these medications without further investigation.[21]

Recent UK observational evidence from primary care has demonstrated an increased risk of IDA with long term proton-pump inhibitor use.[22] However, the nature of this association requires further exploration. There is a recognised association between reduced gastric acid production interfering with non-haem iron absorption[23] so this may be the plausible explanatory mechanism. Eradication of Helicobacter Pylori infection is efficacious in improving iron deficiency anaemia treatment.[24]

When to consider investigations?

With growing recognition of the impact of multimorbidity and treatment burden as core concepts in chronic disease management,[25] it is essential for those caring for older adults to act with these in mind. Decisions should be individualised and take account of the person, their other comorbidities and their care context – sharing decisions around investigation and management strategies, weighing risks and benefits.

IDA in males and postmenopausal females is due to occult gastrointestinal blood loss until proven otherwise, although it is important to recognise there is a spectrum of underlying pathologies.[18] Identifying malignancy is understandably a priority for clinicians and patients. Pre-test risk can be stratified by patient characteristics, but older age itself increases malignancy risk.[26] Lower Hb levels are associated with higher risk of malignancy in the presence of IDA especially if Hb<100g/L for women and <110g/L for men.[27] Determining a threshold to initiate investigations is based on an assessment of the individual. Reviewing trends in results can be helpful, as a drop in Hb from 140 to 110g/L over a few months would cause greater concern than a persistent Hb of 100g/L over several years.

Where chronic inflammation co-exists, distinguishing IDA from anaemia of chronic disease can be challenging. It may be appropriate to trial oral iron supplementation with the intention to discontinue if no improvement is seen after three weeks.[17]

Symptoms of rectal bleeding, weight loss, abdominal pain and tenderness are positively predictive for colorectal cancers (1.1-2.4%).[28] Right-sided bowel tumours, such as those arising from the caecum, more commonly present silently, with no symptoms other than IDA.[29] Alarm symptoms for upper GI cancer have a lower predictive value 0.1%.[30] Studies in older adults with IDA suggest an overall yield rate for malignancy of approximately 10-15%.[21, 31, 32]

In the presence of iron-deficiency without anaemia and with negative coeliac serology, further investigation is not recommended unless iron deficiency reoccurs within 12 months of appropriate treatment.[18]

What investigations to consider?

This section presents an evaluation of the investigations to consider for the older adult with IDA, with our proposed approach summarised in **Figure 2**.

Simple tests

The British Society of Gastroenterology recommend that coeliac serology, using tissue transglutaminase antibody, should be tested in all patients with IDA and this is considered sufficient to exclude coeliac disease unless there are additional clinical features suggesting malabsorption.[18] Urine dipstick for microscopic haematuria is recommended by current guidelines as part of routine workup for IDA.[18] However, typically bladder and renal cancers present with macroscopic haematuria in 85-90% of cases.[33] Investigations for microscopic haematuria alone carry high false-positives: one large cohort study found malignancy in just 3.4% of those aged ≥60 years with microscopic haematuria.[34]

Faecal analysis

Traditionally faecal analysis was limited to guaiac faecal occult blood tests (gFOBT). gFOBT has a sensitivity of 54% and specificity of 80%.[35] A negative gFOBT makes colorectal malignancy very unlikely, but does not exclude pre-cancerous adenomas so should be reserved only for when other investigations are precluded.[36]

Quantitative faecal immunochemical testing (qFIT) is replacing gFOBT as the bowel cancer screening test across the UK.[37] Key features are described in **Table 1**. It is increasingly recommended as a tool in primary care for symptomatic individuals to identify who requires onwards referral to secondary care for investigation.[38] It has a sensitivity of 92.1% and specificity of 85.8% for colorectal cancer; however between 22.5-93% of those with a positive qFIT and no colorectal cancer will still have other significant bowel pathologies.[38] The evidence around qFIT testing is evolving, but this may be a beneficial development for decision-making in frail older adults. The role of qFIT testing for those with IDA without other symptoms needs to be established through applied health research studies.

Endoscopic techniques

The standard investigation for GI sources of blood loss is oesophagogastroduodenoscopy (OGD) and optical colonoscopy, but these may not always be appropriate in the older person. OGD allows inspection and biopsy of the oesophagus, stomach and duodenum. OGD is considered as safe and effective in the elderly as in younger patients,[39] but consideration of co-morbidities and discussion of risks is still important. Many of the risks are associated with use of sedation, which is not essential for the procedure but reduces discomfort and may increase procedure tolerance.[39, 40]

Optical colonoscopy, where successfully completed, allows inspection from rectum to caecum and can allow for diagnostic biopsy and treatment with immediate removal of any polyps in a pre-cancerous stage. Older patients have a higher risk of perforation and other complications after colonoscopy.[41] Inability to complete the colonoscopy is more likely in older patients and in women.[42] Sensitivity for lesions and completion rate to the caecum is reduced where bowel preparation is inadequate, and inadequate bowel preparation is more likely in the elderly.[43] In the frail elderly, bowel preparation itself carries a risk of dehydration and electrolyte disturbance.[44] Flexible sigmoidoscopy may have a role where there are confirmed radiological abnormalities, a history of polyps or rectal bleeding, but again some bowel preparation is required for the test to be useful.[45]

Capsule endoscopy has been successfully used in older adults, but at present remains a specialist investigation reserved for use by Gastroenterologists where IDA is refractory to treatment and bidirectional endoscopy has not identified a diagnosis.[18]

Radiological investigations
Computed Tomography Colonography (CTC), sometimes known as virtual colonoscopy, is a radiological technique described in **Table 1**. CTC offers an alternative approach to investigating those who are unable to tolerate optical colonoscopy. Meta-analysis reports a 96.1% sensitivity of CTC for colorectal cancer.[46] Pragmatic randomised trial data found CTC had a comparable sensitivity to colonoscopy for malignancy and large polyps with both methods detecting lesions in 11% of those symptomatic individuals assessed.[47] However, 30% of those undergoing CTC required additional colonoscopic investigation for diagnosis compared to 8.2% of those receiving colonoscopy at randomisation.[47] CTC missed 1 of 29 colorectal cancers, colonoscopy detected all 55 in that group.[47]

There may be a role for unprepared contrast CT, in order to diagnose a likely malignancy where other investigations or treatment is not appropriate. Data are inevitably limited as this is not a recommended diagnostic approach. One cohort study of individuals diagnosed with colorectal cancers highlighted that 11 patients had CT scans in the two years before diagnosis, eight of whom having multiple scans, which did not identify their malignancy.[48] Another abstract quoted a lower sensitivity than CTC (missing approximately 6% of endoscopically detectable lower GI malignancies and 3.7% of upper GI cancers).[49] Most colorectal cancers develop from polyps (which can cause occult blood loss prior to progression) which progress to adenomas then carcinomas, usually over several years.[50] Accordingly, for very frail patients and those with limited life expectancy, a smaller lesion not detectable on unprepared CT may not be life-limiting. For example in one cohort of ten patients >65 with negative CT scans in the preceding few years who were subsequently diagnosed with colorectal cancer: five died by the end of the study period (time from CT to death ranging from 382 to 1033 days) with the remainder alive after 1068-1709 days of follow-up.[51]

How to treat and follow-up the older adult with IDA
Alongside investigation for the underlying cause, patients with IDA should be offered supplementation. Meta-analysis of trial data demonstrates both oral and parenteral iron reduce the proportions of individuals requiring blood transfusion and increase Hb but have no statistically significant impact on mortality.[52] In the trials comparing IV and oral iron, Hb was higher in the IV arm by a mean difference of 53g/L (95%CI 31-75) – the clinical impact in terms of symptom burden is not reported.[52]
Blood transfusion is not recommended in the standard treatment of IDA. UK guidance advocates this be reserved for those with symptomatic anaemia despite iron therapy or those at risk of cardiovascular instability due to their anaemia.[18] Transfusion should restore Hb to safe levels, rather than seeking to normalise Hb, and be followed by iron supplementation to replenish stores.[18]

Oral iron therapy
Supplementation using oral iron compounds are recommended for treating IDA.[18] Elemental iron doses vary between compounds: there is 68mg in a 210mg tablet of ferrous fumarate, 65mg in a 200mg tablet of ferrous sulfate and 35mg in a 300mg tablet of ferrous gluconate.[53] Low doses (15mg elemental iron/day) may be efficacious and better tolerated than higher doses, particularly among older adults.[54] With emerging evidence of single daily dosing or alternate day administration as beneficial in correcting low serum ferritin values, these findings need to be replicated in older adults and in those with IDA.[55]

Common side effects include constipation, diarrhoea and dyspepsia[56] which are recognised to be exacerbated at higher doses of elemental iron and vary depending on the iron preparation used.[18] No specific data on tolerability in older adult populations were identified to understand the role of adverse effects in effectiveness of treatment.

Despite the prevalence of IDA among older adults, research evidence in this population is limited. A 2015 systematic review identified only three randomised trials of oral iron supplementation in older adults with IDA.[57] This found haemoglobin levels rise by 35g/L after 4-6 weeks of treatment, but there was limited data on patient-focused outcomes.[57] Cochrane systematic review of supplementation found three trials

using oral iron, resulting in low quality evidence that oral iron does not reduce mortality or complications after hip fracture in older people.[58] Routinely collected linked data suggest there is room for improvement with respect to iron prescription and administration among older adults following inpatient rehabilitation.[59] One of the reasons for lack of benefit may have been inclusion of a significant proportion of subjects who were not iron deficient. Only 84% of those prescribed iron had appropriate blood tests performed and 23% showed no deficiency and 23% showed only possible deficiency, yet treatment was given to both groups.[59]

Follow-up

Oral iron should be prescribed for three months to replenish iron stores. The British Society of Gastroenterology advise monthly surveillance of full blood count (FBC) for those on oral iron. Once the FBC is normal they advocated continued oral iron for three months and ongoing surveillance of FBC every three months for a year and then a final routine check a year after this.[18] Further investigations are recommended for those who are unable to achieve or maintain a normal FBC level despite compliance with therapy.[18]

Intravenous (IV) iron

The National Institute for Health and Care Excellence (NICE) advise that: "iron salts should be given by mouth unless there are good reasons for using another route", these include: "where oral therapy is unsuccessful as the patient cannot tolerate oral iron, or does not take it reliably, or if there is continuing blood loss or in malabsorption".[60] Criteria to define lack of response to treatment have not been defined in older adults. It is important to assess if therapy is tolerated, with potential adaptations such as changing the strength of preparation or dosing frequency, advising to take with or after meals, considering need for laxative prescription for constipation.[61] After these have been addressed, an improvement of less than 20g/L after four weeks should prompt specialist review.[61]

Randomised trial data in all age groups using IV iron found increased Hb and reduced need for red cell transfusion.[62] However, there was also an increased risk of infection compared to oral or no iron supplementation (RR 1.33, 95% 1.10-1.64).[62] Coupled with the recognised risk of anaphylaxis (noted to be highest for iron dextran and lowest for iron sucrose preparations),[63] these data serve as important reminders that the treatment is not without associated hazard. The risk of anaphylaxis among older adults has not been reported, however it is now recognised reactions can occur in those who have previously received IV iron without incident, as well as in new cases, thus test doses are no longer advised.[64] IV iron preparations are also significantly more expensive than oral,[18] incorporating both the medication costs and the requirements for administration under appropriate supervision, in light of the risk of anaphylaxis. While treatment with IV iron results in a more rapid improvement in Hb concentration, results after 12 weeks are comparable to oral therapy.[18]

RAINDroP (Randomised Iron Deficiency Anaemia Management Pilot) is a multicentre UK-based randomised pilot trial comparing continued oral iron, switching from oral to IV iron or discontinuation of oral iron therapy for older adults with unresponsive IDA.[65] Recruitment is ongoing and primary outcomes are around feasibility of recruitment to a larger trial.[65]

A recent randomised trial of IV iron following acute hip fracture demonstrated efficacy in altering haematological parameters, but no statistically significant reduction in need for transfusion.[66] These pragmatic studies involving older adults reflect the need for a robust evidence base to inform clinical practice.

How to approach special populations with iron deficiency

Heart Failure

Older adults with heart failure represent a special population within this review as iron deficiency with/without anaemia has emerged as a novel treatment target in international guidelines.[67] Iron deficiency is common among both those with preserved ejection fraction (HFpEF)[68] and those with

reduced ejection fraction (HFrEF),[69] although the majority of the clinical trial evidence to-date is in HFrEF populations and focuses on IV iron.

The IRONOUT HF trial randomised 225 participants (median age 63) with HFrEF and iron deficiency to oral iron versus placebo for 16 weeks.[70] Oral iron supplementation was not associated with changes in exercise capacity, leading the authors to conclude: "these results do not support use of oral iron supplementation in patients with HFrEF".[70] Treatment resulted in changes in transferrin saturation (+3.3%), serum ferritin (11.3 ng/mL) and hepcidin levels (+1.7ng/mL).[70] Data directly comparing oral and IV iron in heart failure populations are limited, including just 18 participants in a randomised trial.[71]

The European Society of Cardiology advocate treatment for those with HFrEF with/without anaemia who fulfil these criteria: serum ferritin <100µg/L or between 100-299 µg/L and transferrin saturation <20%.[67] In reality most had a serum ferritin of <100µg/L. Meta-analysis of five randomised trials found reduced heart failure hospitalisation, improved exercise capacity, reduced New York Heart Association class and improved health related quality of life.[72] However, this evidence is based on a total of 851 participants (509 received IV iron) with a mean age of 67-76 and treatment had no statistically significant effect on all-cause or cardiovascular mortality.[72] Cost effectiveness analysis drawing on the largest trial which had a 24-week follow-up, estimates the incremental cost-effectiveness ratio of IV iron compared to placebo at €4414 per quality-adjusted life year gained.[73] More evidence is needed to determine if these benefits are sustained.

Looking ahead, IRONMAN is a multicentre UK trial aiming to recruit 1300 participants with HFrEF to address these questions over longer follow-up.[74] FAIR-HFpEF is an ongoing German trial seeking 200 participants aiming to evaluate IV iron in those with HFpEF.[75] Both these and other ongoing studies should help improve understanding of the role of IV iron in heart failure populations.[76]

Chronic kidney disease (CKD)
The use of iron in the treatment of anaemia for older adults with CKD falls beyond the scope of this review. Those with Stage 4 or 5 CKD will be under the care of a Nephrologist and anaemia management is a core part of care. A summary of the recommendations regarding anaemia made in the NICE CKD guidance is available.[77]

Conclusions and future research
Addressing IDA in older adults is underpinned by a robust diagnosis – first to confirm the nature of the anaemia and then to determine the likely cause. Novel tests are likely to play an increasing role in the future, but the value of fundamental tests must not be overlooked.

Clinical trials evaluating the optimal treatment of IDA must ensure they use outcomes important to older adults, which are sensitive to change and feasible to collect to inform service design. Single daily dosing and alternate day dosing regimens require evaluation in older adults with IDA. Cost-effectiveness data is needed in older adult populations around the administration of parenteral iron. Specific consideration is required around the feasibility of administration and the settings of care in which this can be delivered.

IDA investigation and management requires a multidisciplinary approach in which gastroenterologists and radiologists can help ensure those caring for older adults are supported to deliver evidence-based approaches, tailored to the heterogenous population in our care.

Tables & Figures

Table 1: Additional features of investigations to investigate the underlying aetiology of IDA

Test	Current role	Strengths	Limitations
GFOBT[35-37]	Formerly used in bowel cancer screening Available in some secondary care settings		Requires two samples from three bowel motions Affected by diet and medications so higher false positive rate Binary outcome does not quantify risk/result Poor sensitivity 54%
qFIT[38]	Bowel cancer screening (asymptomatic individuals) Possible role in primary care for suspected colorectal cancer	Single stool sample required, so more acceptable to patients Specific to human Hb Quantitative result which correlates to level of risk May help indicate those who do not require colonoscopy	Evidence currently focused on performance in asymptomatic populations or those with symptoms of colorectal cancer (rather than IDA) Role in diagnostic pathway not fully delineated Use at present restricted to primary care settings
CT colonography[47, 78]	Recommended for use where patient anticipated not to tolerate optical colonoscopy – due to frailty, patient preference or risks of sedation	Shorter procedure than optical colonoscopy Avoids need for sedation Better tolerated May identify pathology outside of the bowel	Requires bowel preparation, insufflation of carbon dioxide at rectum and position changes, so not suitable for very frail Can identify small polyps and other findings of uncertain significance necessitating colonoscopy or other investigations, with some of these representing false positive results

Abbreviations
CT – computerised tomography
GFOBT – guaiac faecal occult blood test
qFIT – quantitative faecal immunochemical testing

Figure 1: Common causes of iron deficiency[1, 18, 19]

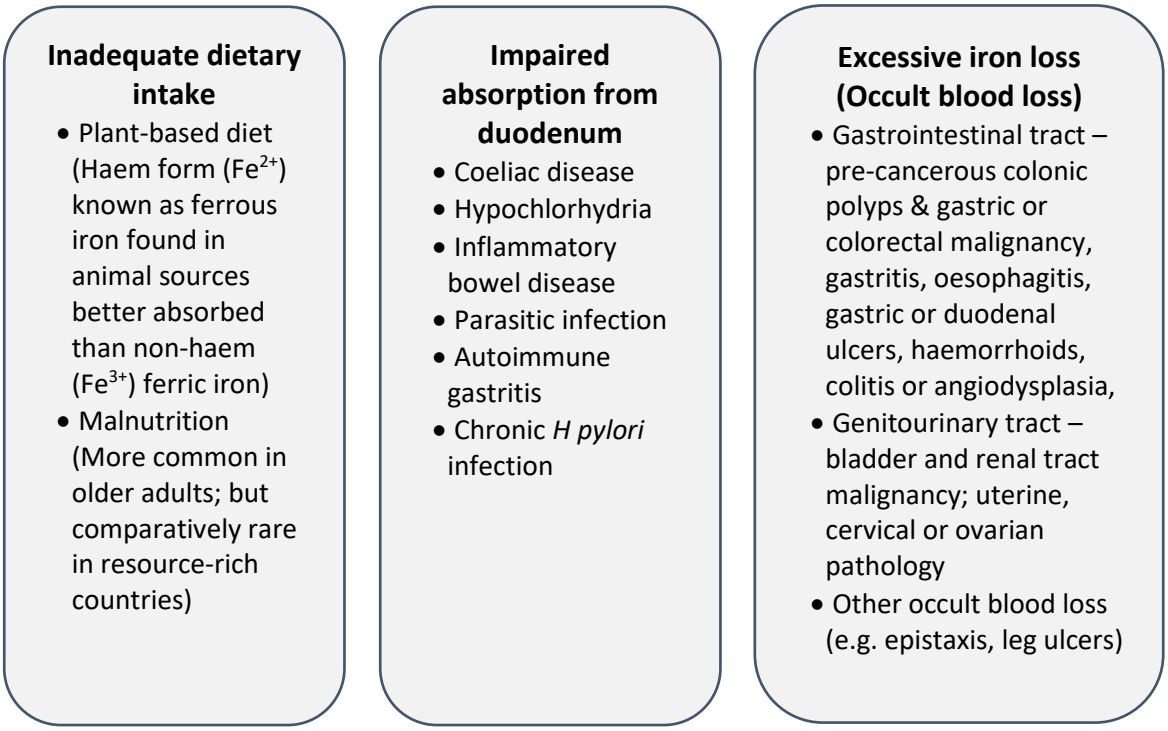
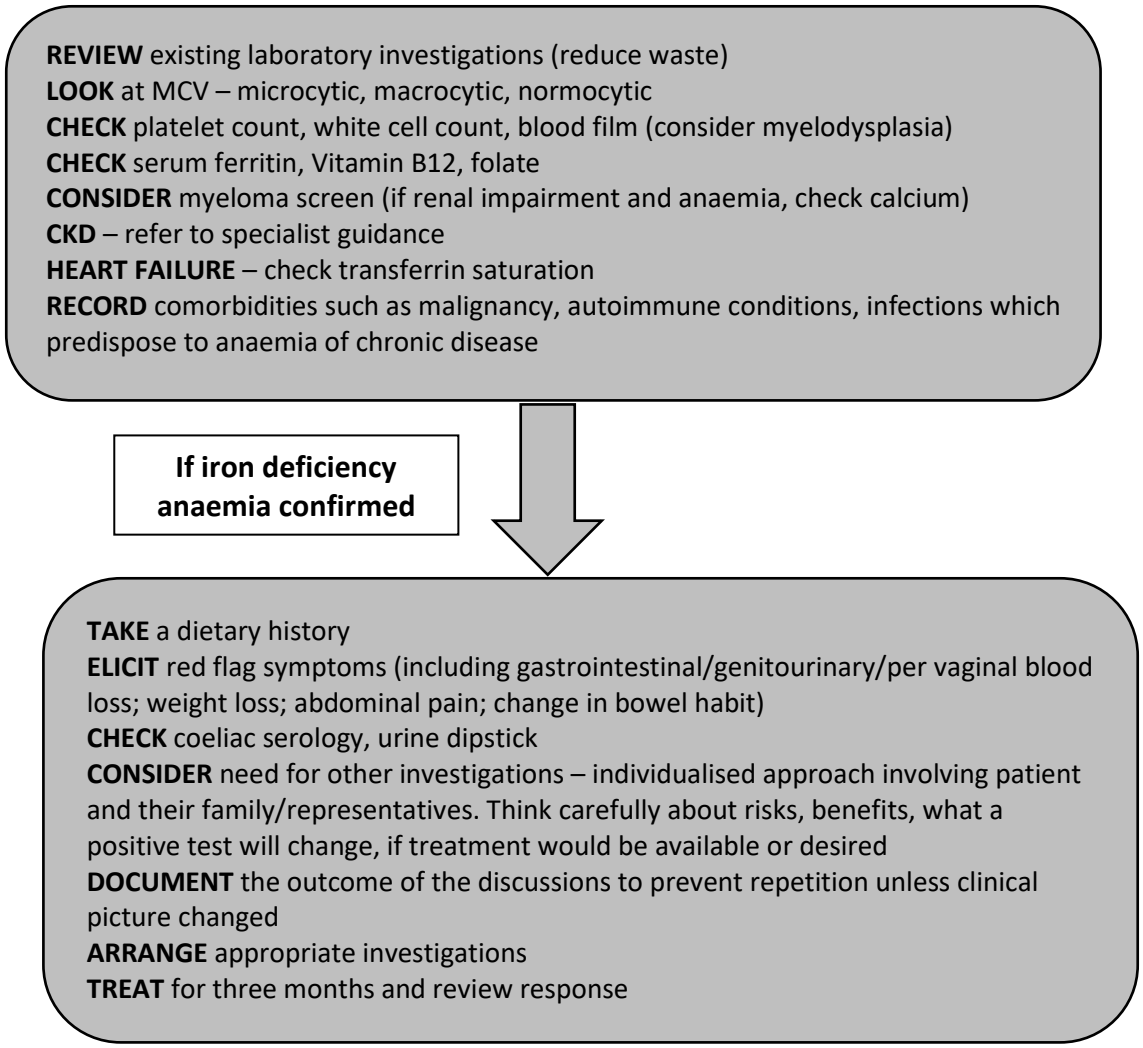


Figure 2: Flowchart presenting proposed approach to older adult with anaemia attending day hospital/outpatient clinic/acute care



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