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Review Article

HAEMATINICS FOR ANAEMIA IN THE ELDERLY

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KEY FACTS

- Anaemia is the most common haematological problem in the elderly population. Using WHO criteria for anaemia (Hb of <12 g/dL in women and <13 g/dL in men), the prevalence of anaemia in the elderly has been found to range from 8-44% with the highest prevalence in men 85 years and older.[38]
- Anaemia must not be considered simply as part of ageing because in 80% of cases, there is an underlying cause for Hb levels of <12 g/dL in the elderly.[39]
- Anaemia has negative impacts on the quality of life for the elderly and there is evidence of improved morbidity and mortality after correction of anaemia.[40]
- Chronic disease and thalassaemia may also cause microcytic anaemia besides iron deficiency and not all vitamin B_{12} and folate deficiency present with macrocytic megaloblastic anaemia.
- Nutritional deficiency anaemias are common, easily diagnosed, treatments are simple, inexpensive and effective. Tests for nutritional anaemia have to be given priority in the assessment before a patient is subjected to invasive tests to look for less common causes of anaemia. (Refer Figure I)
- Serum ferritin which is the best non-invasive test for the diagnosis of iron deficiency anaemia may be increased in the elderly while serum iron and transferrin decrease with ageing.
- Serum methylmalonic acid (MMA) and homocysteine (HC) levels are sensitive for detecting subclinical vitamin B_{12} and folate deficiency.
- Routine iron therapy in non-anaemic elderly or in those without iron deficiency anaemia is of no use and may be detrimental to their health.
- Folate therapy may improve anaemia but may mask the signs and symptoms of neurological damage due to concomitant vitamin B_{12} deficiency.
- Blood transfusion offers prompt symptom relief of anaemia in patients with terminal malignancy irrespective of the causes for the anaemia.

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INTRODUCTION

It is not uncommon for a Family Physician to come across elderly patients taking inappropriate haematinics on regular basis for many years with the belief that these supplements are essential to maintain good health. In Malaysia, patients are self-referred to general practitioners and private hospital specialists. They often choose who they want to consult; not who they should consult. There is lack of comprehensive and continuity of care by one specific family doctor and haematinics are easily available over the counter without the need of a prescription.

The main theme for discussion on this paper is the use and misuse of haematinics to treat anaemia in the elderly and in patients with terminal illness. Five general practice cases, each with a specific inappropriate haematinic therapy, are presented to provide topics for discussions. They are followed by questions and answers to highlight these common mistakes and to discuss geriatric issues related to management of anaemias, causes of which are broadly categorised as follows:[1]

1. Anaemias due to blood loss and nutritional deficiencies - 34%
2. Anaemias associated with chronic inflammatory diseases - 32%
3. Unexplained and other less common causes of anaemia - 34%

CASE HISTORY 1

Key feature: Routine iron supplements for fatigue and lethargy.

Mr A, a 65-year-old man who is on regular follow up for hypertension and hyperlipidaemia at the Outpatient Department in a general hospital complained of generalised fatigue and lethargy. Clinical examination was normal, with

no significant abnormal findings. Laboratory test results were all within normal range. He was prescribed iron tablets, folic acid and vitamin Bco on regular basis to "boost up" his energy as he was told. Mr A has been taking these haematinics for the past five years.

Questions:

1. Are these routine haematinics necessary or helpful to this patient?

2. What are the harmful side effects of long term iron supplements to Mr A?

Commentary:

There is a general misconception that elderly people lack essential vitamins and nutrients vital for maintaining good health. Elderly people take vitamins and iron because they want to prevent anaemia. As clinical presentation of anaemia is often non-specific, iron is prescribed for non-anaemic elderly patients with vague complaints of lethargy and generalized fatigue. It is believed that these haematinics will "strengthen" and improve their well being. The general concept that "if a little heamatinic is good for their health, more must be better," is certainly not true.[2]

Results from Framingham Heart Study on a cohort of healthy elderly Americans found that about 3% of the study group had too little iron and about 13% had too much.[3] This finding suggests that the use of routine iron supplements in free-living, elderly white Americans is probably unnecessary and could be detrimental.[2]

Although iron is essential for life, too much iron in the body has been implicated in diseases of all systems. There is epidemiological evidence of a relationship between high body iron stores and liver injury especially haemochromatosis,[4] coronary artery disease,[5] non-insulin dependent diabetes mellitus (NIDDM),[6] Parkinson's disease,[7] recurrent infections,[8] cancer[9] and Alzheimer disease.[10] Many of the larger studies supported the association of iron with colorectal cancer risk.[11] One study found that serum ferritin concentrations >200 mcg/L were strongly associated with a 2.2 fold risk of acute myocardial infarction (MI) in men with elevated serum low-density lipoprotein (LDL) cholesterol concentrations.[12] A review of numerous studies has suggested that iron is an important factor in the development process of atherosclerosis.[13]

CASE HISTORY 2

Key feature: Routine iron therapy for hypochromic microcytic anaemia.

Madam B, a 70-year-old lady, living in a residential home for the elderly, was found to have pallor on routine examination for minor ailments 10 years ago. Her yearly blood test results indicated hypochromic microcytic anaemia with normal platelet and white cell count. Haemoglobin (Hb) level was around 9-10 g/dL, mean corpuscular volume (MCV) of about 58 fL, mean corpuscular haemoglobin concentration (MCHC) of 28 g/dL and reticulocyte index of 1.8%. Liver and renal function tests, serology tests for syphilis (VDRL) and Hepatitis B, urine tests, stool for occult blood, chest X-ray and endoscopy done over the years were all normal. She has been prescribed iron tablets for the past seven years but Hb level and full blood count (FBC) indices remained more or less the same. Other than mild hypertension, she does not have any other medical problems. Clinically she is asymptomatic and there is no significant abnormal physical finding.

Questions:

1. Could Madam B's anaemia be due to iron deficiency anaemia (IDA)?

2. What are other causes of microcytic anaemia that need to be considered here?

3. What further tests need to be carried out?

Commentary:

Therapy with iron for so many years without any improvement in the blood indices and with no obvious signs of blood loss, suggested that Madam B's hypochromic microcytic anaemia might not be due to iron deficiency.

IDA typically presents with hypochromic microcytic anaemia. Gastrointestinal (GI) evaluation should be contemplated in all elderly patients with iron deficiency anaemia unless there is an obvious non-GI cause of bleeding.[14] However, microcytosis is also associated with chronic diseases, thalassaemia, sideroblastic anaemia and it may not be seen in combined iron with folate and vitamin B_{12} deficiency.[15]

Madam B does not have other chronic diseases except for mild hypertension, and all other laboratory tests did not suggest any chronic infection, malignancy or organ dysfunction. Peripheral blood film showed hypochromia, microcytosis, and target cells. Iron parameters had to be reviewed, further assessments were necessary to look for other causes of microcytic anaemia.

A low serum iron (<10 μmol/L) with increased total iron binding capacity (TIBC) (>80 μmol/L) and a low percent saturation of transferrin (<15%) may suggest iron deficiency but may be

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Table 1: Full Blood Count (FBC) indices

Differentiation of microcytic anaemia due to iron deficiency, chronic disease and thalassaemia[19]			
	Iron deficiency	**Chronic disease**	**Beta thalassaemia trait**
Haemoglobin	↓	↓	↓
MCV	↓ (usually <76 fL)	N or ↓	↓ (usually 55-75 fL)
Serum iron	↓	N or ↓	N
Ferritin	↓	N or ↑	N
TIBC	↑	N or ↓	N
Transferrin saturation	↓	N or ↑	N
Bone marrow	No Fe stores	Fe stores ↑	Normal Fe stores

unreliable as serum iron and transferrin levels are often decreased in elderly people.[16] (Table 1).

Serum ferritin is the best non-invasive test for the diagnosis of IDA in patients of all age groups.[17] However, in the elderly population it has to be interpreted with care as serum ferritin tends to rise with ageing. When the serum ferritin is <15 μg/L, iron deficiency is virtually certain. Iron deficiency is unlikely if the serum ferritin level is >100 μg/L. Although ferritin levels between 15 and 100 μg/L are moderately predictive of IDA, patients with levels in this range may have IDA, anaemia of chronic disease, or both.[18]

For IDA, oral ferrous iron (ferrous sulphate, ferrous fumarate, ferrous gluconate) is a simple and effective way to restore the body iron store. Hb concentration should rise by 2g/dL after 3-4 weeks. A lack of response implies non-compliance, misdiagnosis, malabsorption or continued blood loss.[14] Iron supplementation should continue for at least 4-6 months after correction of anaemia to replenish the iron stores.[19] Low dose iron therapy (15 mg of elemental iron per day) is an effective therapeutic option with minimal adverse effects and improved compliance for elderly above 80 years of age.[20]

In this particular case, parameters for nutritional deficiency anaemias were all within normal range. Hb electrophoresis showed elevation of HbA_2, indicating beta thalassaemia trait. It was not certain whether Hb electrophoresis was done before in the past years. Madam B denied being told of such diagnosis or perhaps she was told but had forgotten about it. It could be this test was not done before as she had been healthy all these while and very rarely had she consulted any medical doctor for minor ailments that were relieved with self prescribed traditional medicine.

In beta thalassaemia trait, serum iron may be low as in iron deficiency, but TIBC, transferrin and serum ferritin are usually within normal limits. Compared to IDA, thalassaemia patients have lower MCV (55-75 fL), more normal red blood cell (RBC) count and more abnormal peripheral blood smear (hypochromia, microcytosis, and target cells) at modest levels of anaemia. Reticulocyte count may be normal or slightly raised.[21] (Table 1).

Clinically, a patient with beta thalassaemia trait is normal and requires no treatment. More important, patients with microcytosis should be identified so that they are not subjected to repeated evaluations for iron deficiency and inappropriately given supplemental iron for years.[21]

CASE HISTORY 3

Key feature: Routine folate therapy for normochromic normocytic anaemia with leucopenia.

Madam C is a 68-year-old lady who is on regular follow up for hypertension, diabetes and hyperlipidaemia at a specialist clinic in a general hospital. She was found to have pallor eight years ago at one of the routine consultations, but she denied ever having any symptoms related to anaemia. Her yearly blood test results consistently showed normochromic, normocytic anaemia of around 10 g/dL and a leucopenia of around 3.4 x 10^9/L. Platelet count is usually at the low normal range of about 170 x 10^9/L. Full blood picture (FBP) did not show any morphological changes in the red and white blood cells (WBC) and platelets. Renal and liver function tests, serum calcium and phosphates, random blood sugar, $HbA1_c$, cholesterol level and urine tests were all within normal range. X-rays of chest and lumbosacral spine were normal except for minor degenerative changes.

A full workout for multiple myeloma was performed on her five years ago but results of all the relevant tests were negative for this medical condition. She was treated with daily folic acid for past two years without any improvement in the FBC indices. Lately, a new physician took over the practice and suggested that her persistent mild anaemia and leucopenia could be due to myelodysplastic syndrome and she may require a bone marrow biopsy to confirm the diagnosis. Patient is very worried as she was told that myelodysplastic syndrome is a pre-cursor to myeloid leukemia. She consults you for a second opinion.

Questions:

1. Do you agree with this new physician's suggestion?

2. What further simple tests can you recommend her to do before she is subjected to the invasive procedure of bone marrow biopsy?

3. Results of the tests you recommended have come back positive, what is your treatment plan?

4. What would be the clinical implication of long term folic acid therapy without being aware of the correct diagnosis in this case?

Commentary:

A well-known aetiology of anaemia that increases with age is myelodysplasia (MDS). Occult MDS may be an important cause of "unexplained" anaemias in the elderly.[22] This syndrome, thought in the past to represent pre-leukaemia, is characterized by a defect in the development of one of the marrow cell lines, limiting the release of functioning cells. Myelodysplastic syndrome should be a diagnostic consideration when white cell or platelet abnormalities accompany the anaemia. The diagnosis of this syndrome is usually made by bone marrow biopsy.[18]

On routine questioning, it was discovered that Madam C, though not a pure vegetarian, eats mostly vegetables and occasionally fish, but has practically excluded meat from her diet for many years. Laboratory workouts for nutritional deficiency anaemia were not done before. So far, peripheral blood film done 3-4 times in the past did not suggest morphological changes in the blood cells.

Nutritional deficiency anaemias need to be considered and investigated for in this case. Nutritional deficiency anaemias are easily diagnosed, treatments are simple, inexpensive and effective. Laboratory workout for iron, vitamin B_{12} and folate should be given priority to bone marrow biopsy. Red cell folate concentration is more reliable than the serum level and should be considered. Serum homocysteine (HC) level is elevated in 90% of patients with folate deficiency[23] and can be useful for detecting folate deficiency in patients with low-normal serum folate levels. If methylmalonic acid (MMA) level is also elevated, vitamin B_{12} deficiency must be considered even if serum vitamin B_{12} is within low-normal range.[23]

For Madam C, further blood tests indicated low serum vitamin B_{12} of 78 pmol/L while all other parameters for iron and folate were within normal limits.

Vitamin B_{12} deficiency is treated with vitamin B_{12} supplementation, parenterally or orally. The intramuscular dose is 1,000 µg, often given daily for one week to build up stores, then weekly for one month and then monthly thereafter. A response to therapy, characterized by an increase in reticulocytosis, often occurs within a week of the initiation of vitamin B_{12} therapy.[18] In the elderly, the main causes of cobalamin deficiency are pernicious anaemia (20-30%) and food-cobalamin malabsorption (50-70%).[24] Food-cobalamin malabsorption syndrome, which has only recently been identified, is a disorder characterized by the inability to release cobalamin from food or its binding proteins.[25] Absorption of 'unbound' cobalamin (free crystalline) is normal. Oral cobalamin of 1,000 µg daily can be used to treat this condition.

Some facts to note about vitamin B_{12} deficiency:

- Signs of vitamin B_{12} deficiency are not reliably present in the elderly. Only about 60% of patients with vitamin B_{12} deficiency are anaemic.[26]
- Neurologic symptoms of B_{12} deficiency can develop before the patient becomes anaemic.[27]
- Although anaemia due to vitamin B_{12} deficiency is usually macrocytic and megaloblastic, it can be normocytic or even microcytic if there is concomitant iron deficiency or beta thalassaemia trait.
- Serum vitamin B_{12} levels do not reliably reflect vitamin B_{12} deficiency. Up to 30% of patients with low-normal serum vitamin B_{12} levels have anaemia and neurologic disease.[28]
- Serum MMA and HC levels are sensitive for detecting subclinical vitamin B_{12} and folate deficiency, virtually excluding vitamin B_{12} deficiency when they are normal.[23]
- The symptoms of folate deficiency are nearly indistinguishable from those of vitamin B_{12} deficiency. Elderly individuals are frequently vitamin takers and food is often fortified with folic acid. Thus, megaloblastic anaemias due to folate deficiency in the elderly appear to be rare; when they do occur, they are often related to alcohol abuse.[22]
- Identification of vitamin B_{12} deficiency is important: anaemia secondary to vitamin B_{12} deficiency may improve with folate therapy, but folate therapy does not reverse the neurological damage caused by vitamin B_{12} deficiency. Progression of neurological damage may be masked by improvement of anaemia if concomitant vitamin B_{12} deficiency is not corrected accordingly.

CASE HISTORY 4

Key feature: Routine iron therapy for normochromic normocytic anaemia in advanced malignancy.

Mr D, a 75-year-old man, was diagnosed with fourth stage moderately differentiated squamous cell carcinoma of the lungs. He has completed a course of radiotherapy and is currently complaining of giddiness, breathlessness on walking,

palpitation and lethargy. He is alert, mobile, though not as active as before and his general condition is fairly satisfactory except for pallor and recent loss of body weight of about 3 kg, leaving him to be at his current 56 kg status. Result of his Hb level has come back as 7 g/dL; white cell and platelet counts are within low normal range. Serum calcium is within high normal range, liver and renal function tests and blood sugar are normal. Mr D was treated with ferrous fumarate 200 mg *bd*. and folate 5 mg daily for past two months without much improvement.

Questions:

1. Do you think oral haematinics will help to relieve Mr D's complaints of giddiness, breathlessness, palpitation and lethargy?

2. What would be the most appropriate treatment for his anaemia at this stage?

Commentary:

In late stage malignancy, symptoms attributable to the anaemia may also be due to underlying malignancy, chronic inflammation, blood loss, bone marrow suppression or invasion, malnutrition, or haemolysis.[29]

In anaemia of chronic disease, there is an impaired ability to use the iron stored in the reticuloendothelial system. Iron is not available for erythropoiesis, which is the similarity between anaemia of chronic disease and IDA. However, the iron stores are normal or increased, erythrocytes are usually normochromic and normocytic, although one third of patients may have microcytosis. TIBC is usually below normal because iron stores are elevated and as an acute-phase reactant, transferrin is reduced in the presence of acute and chronic stress.[30] Serum ferritin level is the most useful test, differentiating anaemia of chronic disease from IDA in 70% of patients.[31] (Table 1).

Iron supplementation provides no benefit in patients with anaemia of chronic disease and if taken when body iron stores are saturated, iron overload may occur with resultant detrimental consequences.[32] Hence, oral haematinics would not be helpful in alleviating Mr D's complaints.

Early studies showed that erythropoietin reduced the need for transfusions, raised Hb level and improved quality of life in patients receiving cancer treatment.[33] However, a subsequent study was terminated early due to an increased number of thrombotic events in the treatment arm[34] and another showed an increased risk of adverse events, including mortality when Hb was raised to above 11.3 g/dL.[35] Other disadvantages include its cost, its efficacy in only some patients and the 4-8 weeks delay before maximum benefit is achieved. Currently, erythropoietin is not recommended as a treatment for anaemia in palliative care.[36]

S Tanneberger *et al.* concluded that blood transfusion does offer prompt symptom relief and improvement of well-being in anaemic patients with terminal malignancy.[37] RBC transfusions are commonly used as a treatment, whatever the cause of the anaemia, especially when anaemia is symptomatic and the Hb drops below 8 g/dL.[36] Decision to use blood transfusion to palliate symptoms of anaemia requires a pragmatic approach. It means taking into consideration the severity of symptoms, Hb level, possible burden of cost and side effects, actual prognosis, general well being of patients, other organ dysfunction, onset and duration of therapeutic effects, as well as patient's wish and competency to make a valid decision.

CASE HISTORY 5

Key feature: Routine iron therapy for normochromic normocytic anaemia at the end-of-life.

Mr E, who is an 88-year-old man living in a residential home for the aged, has multiple joint deformities and contractions with generalized muscle wasting. He has been confined to bed for past two years and has an extensive deep decubitus ulcer over the lumbosacral area. He has diabetes mellitus (DM) currently controlled with metformin 500 mg *bd.* He has past history of recurrent strokes and mild renal and liver impairment. He is semiconscious, able to respond to calls at times but more often remains unresponsive.

For the past three days, Mr E was having spiking fever temporarily controlled with paracetamol. You noticed that he looked extremely pale and his left knee joint was grossly swollen and inflammed. There was moderate joint effusion with marked tenderness on palpation as deduced from his facial expressions of pain. You checked through his medical record. He has normochromic normocytic anaemia of around 8 g/dL for years and has been treated regularly with oral ferrous fumarate 200 mg daily and folate 5 mg daily for years. You explained that hospitalization was necessary for treatment of his pyogenic arthritis, decubitus ulcer, control of blood sugar, anaemia and possible septicaemia. But his relatives and residential home carers did not agree to any more active medical interventions in the hospital. They requested you to do whatever you can to ease his sufferings at home.

Questions:

1. Do you think that those years of iron and folic acid therapy was useful for Mr E?

2. What better option was there to treat his anaemia in this clinical situation?

3. How would you respond to the relatives' and carers' decisions of not sending him to the hospital for further active medical interventions?

Commentary:

For similar reasons as in Case 4, years of iron therapy provided no benefit but only increased the total body iron stores. Use of RBC transfusion to provide prompt relief of anaemia is also indicated here. However, in view of Mr E's poor general condition, multiple organ dysfunction and bleak prognosis, the risks of blood transfusion outweigh the benefits. Mr E's relatives and carers were requesting for limited treatment plan so as not to prolong his sufferings. When further treatments and investigations are futile in providing cure or comfort, but instead will incur more sufferings, it is justified to withhold them. If Mr E had provided treatment directives, a living will or power of attorney to make decision on his behalf earlier on, it would have been easier to apply this concept of limited treatment plan or DNR (Do Not Resuscitate). Limited treatment plan does not mean no more care for the patient. Palliative care could still be given in the form of good basic nursing care and psychological support for patients and carers.

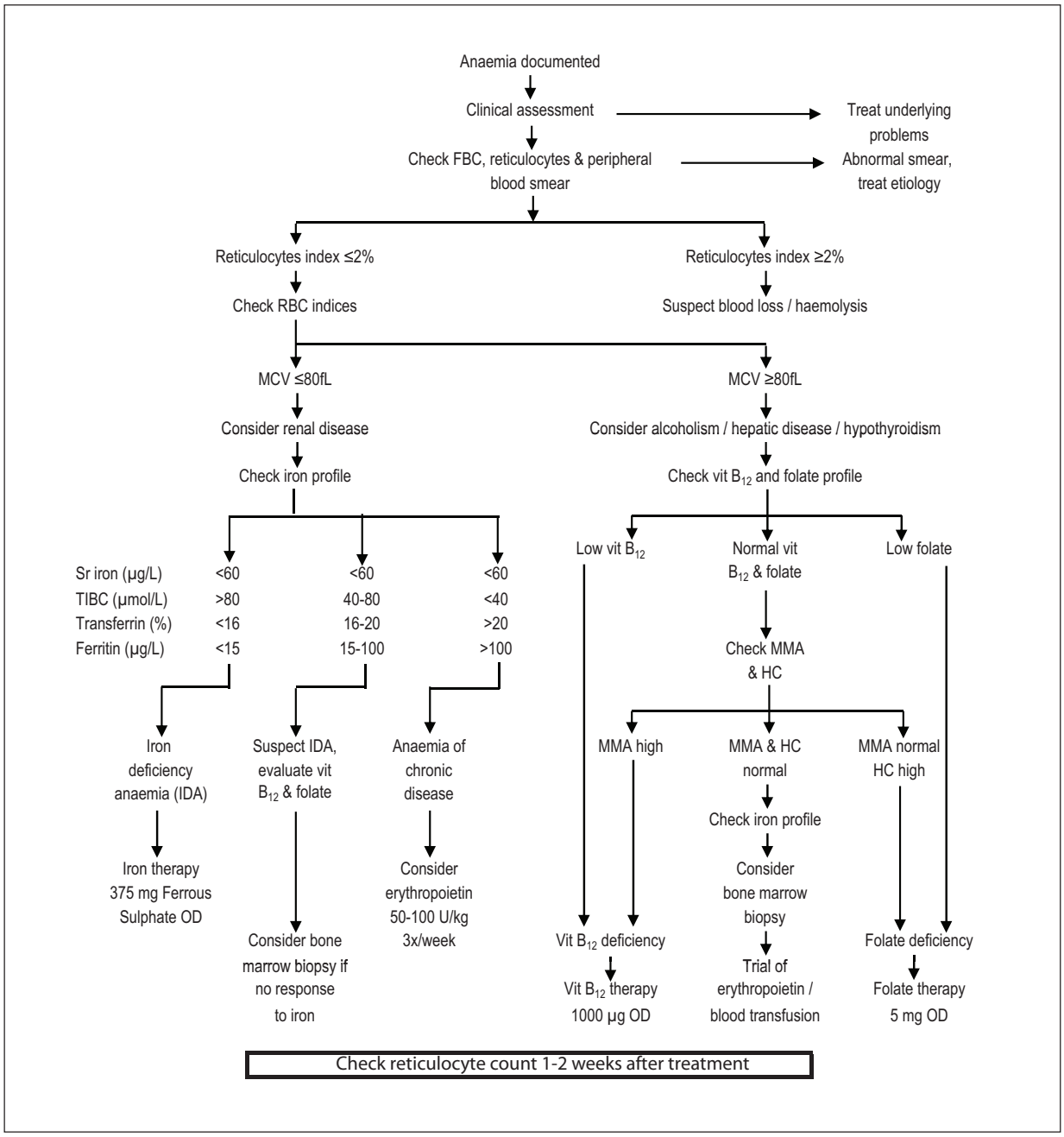

Figure 1: Management of anaemia in the elderly[18]

CONCLUSION

Iron therapy in the absence of iron deficiency may be detrimental to the health of the elderly. Anaemias in the elderly require further investigations and must not simply be considered as part of ageing. Factors that need to be considered in the treatment plan includes the underlying causes of the anaemia, Hb level, symptoms, concomitant illnesses, physical status of patients, prognosis, cost and burden of treatment and whether for curative or palliative intention.

Figure 1 provides a flow chart in the assessments of common causes of anaemia in the elderly.

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Almost half of breast cancer patients presented to doctor six months after first detecting a breast lump

Norsa'adah B, Rampal KG, Rahmah MA, *et al.* Diagnosis delay of breast cancer and its associated factors in Malaysian women. *BMC Cancer*. 2011;11(1):141.
http://www.biomedcentral.com/content/pdf/1471-2407-11-141.pdf
Affiliation of primary author: School of Medical Sciences,Universiti Sains Malaysia, Kelantan, Malaysia.

This study is a cross-sectional survey of 328 breast cancer patients from five medical centers in Malaysia. The frequency of diagnosis delay of more than three months was 72.6% and delay of more than six months occurred in 45.5% of the cases.

Three out of five adults with rectal bleeding consult after two weeks of symptom onset

Syahnaz MH, Khairani O, Tong SF, *et al.* Factors influencing late consultation among patients with rectal bleeding in Universiti Kebangsaan Malaysia Medical Centre. *Asian Pac J Cancer Prev*. 2010;11(5):1335-9.
Affiliation of primary author: Department of Family Medicine, Universiti Kebangsaan Malaysia, Selangor, Malaysia.

This is a cross-sectional study of 80 patients aged 40 and above with rectal bleeding seen in the endoscopy unit, Universiti Kebangsaan Malaysia Medical Centre. The prevalence of delay in the presentation of rectal bleeding (defined as seeking help from medical practitioner after two weeks of symptom onset) was 60%.