**Sheet 2 Iron deficiency Pathway**

- **All patients:** commence iron therapy
- **Hb < 120g/L women**
  - **Hb < 130g/L men**
  - WITH MCV <80fl and ferritin <15µg/L
  - OR MCV Normal (80-100fl) AND Ferritin 15-50µg/L
  - + Transferrin saturation ≤20%
- **If Hb <50g/L or very symptomatic consider admission**
- **Referral to gynaecology, haematology, urology etc as appropriate**
- **Coeliac Screen (TTG)**
  - **Positive**
    - **OGD with duodenal biopsy**
  - **Negative**
    - **Colonoscopy**
- **HSC205**
- **No**
- **Exclude obvious causes:**
  - i.e. Menorrhagia / haematuria
  - By history and urine dipstick
  - Dietary and drug history
  - **Dyspepsia/Colorectal Guidelines**
    - **Consider urgent referral if:**
      - Weight loss
      - Progressive dyspepsia
      - Mass in abdomen
      - PR bleed
      - Change in bowel habit >6/52
      - Age >60
    - **Urgent referral HSC205**
- **GI symptoms**
  - **Yes**
    - **Careful history/examination including assessment of family history**
    - **Coeliac Screen (TTG)**
  - **No**
    - **Check haemoglobinopathy screen**
      - **If abnormal; see sheet 6)**
  - **Inadequate response**
    - **Iron replacement for 3/12 & correct potential causes of losses then reassess**
- **Dyspepsia/Colorectal Guidelines**
  - **Consider urgent referral if:**
    - Weight loss
    - Progressive dyspepsia
    - Mass in abdomen
    - PR bleed
    - Change in bowel habit >6/52
    - Age >60
  - **Urgent referral HSC205**
- **Strong family history of colorectal ca**
- **Non-menstruating or minimal periods**
- **Menstruating**
  - **Female**
  - **Male**
  - **Strong family history of colorectal ca**
  - **Consider colonoscopy if:**
    - Aged >50 yrs or family history of colorectal cancer
  - **HSC205**
  - **OGD + Duodenal Bx Colonoscopy**
Sheet 2 Iron deficiency Pathway

2-5% of population have iron deficiency anaemia (IDA), but this makes up 4-13% of referrals to gastroenterology. The commonest gastrointestinal causes are colorectal and gastric carcinoma and coeliac disease.

Investigation
Do a urine dipstick, 1% of IDA with have renal malignancy. Consider aspirin / NSAIDs as cause but investigate all IDA. A significant family history for colon ca is two 1st degree relatives or one if <40yrs. Consider OGD as first investigation as will exclude colonoscopy in gastric ca and coeliac and avoids bowel prep. Consider colonoscopy if: aged >50 yrs or family history of colorectal ca even in patients with confirmed coeliac disease.

Treatment
• Patients with established iron deficiency anaemia should be given 100-200mg elemental iron daily. This can be achieved with oral ferrous sulphate 200mg bd
• Patients should be advised on correct administration to optimise absorption, including the use of ascorbic acid 500mg daily, taking on empty stomach, avoiding other medications or antacids at same time.
• All patients should be counselled regarding diet including details of iron rich food sources and factors that may inhibit or promote iron absorption. This should be consolidated by the provision of an information leaflet in the appropriate language.
• Link to iron in your diet leaflet: http://hospital.blood.co.uk/library/pdf/2011_Iron_English.pdf
• For nausea and epigastric discomfort, preparations with lower iron content should be tried. Slow release and enteric coated forms should be avoided.
• If not responsive to oral iron, consider non-compliance as a cause.
• Once Hb is in the normal range, supplementation should continue for three months.
• Parenteral iron should be considered for patients with confirmed iron deficiency who fail to respond to or are intolerant of oral iron. Parenteral iron is currently administered intravenously in a hospital setting.
• Consider first line if:
  – History of oral iron intolerance or poor compliance
  – Impaired gastrointestinal absorption
  – Haemodialysis
  – Major surgery must take place in < 3 weeks
• Blood transfusion should be reserved for those with risk of further bleeding, imminent cardiac compromise or symptoms requiring immediate attention. Iron treatment should follow transfusion to replenish stores.

<table>
<thead>
<tr>
<th>Iron salt</th>
<th>Amount</th>
<th>Contents of ferrous iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous fumerate</td>
<td>200mg</td>
<td>65mg</td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>300mg</td>
<td>35mg</td>
</tr>
<tr>
<td>Ferrous sulphate</td>
<td>300mg</td>
<td>60mg</td>
</tr>
<tr>
<td>Ferrous sulphate, dried</td>
<td>200mg</td>
<td>65mg</td>
</tr>
</tbody>
</table>

Iron盐

Amount	Contents of ferrous iron
Ferrous fumarate 200mg 65mg
Ferrous gluconate 300mg 35mg
Ferrous sulphate 300mg 60mg
Ferrous sulphate, dried 200mg 65mg

Page 2 of 2
Anaemia or clinical suspicion – check B12

B12 ≥200ng/L

B12 <200ng/L

BUT strong clinical suspicion (e.g.: macrocytic anaemia/neuropsychiatric symptoms/glossitis)

Check Intrinsic factor Antibodies (specificity 95% sensitivity 50%)

If <150ng/L or symptomatic (e.g: neuropsychiatric symptoms/glossitis)

Referral to dietician if poor diet

Referral to gastro if: malabsorption not pernicious anaemia Or Pernicious anaemia with IDA/ folate def Or GI symptoms (URGENT if ?Gastric Ca)

Check FBC/ retics after 10/7 of Treatment
If no improvement check folate / ferritin
Check FBC/ retics again at 8/52

Initial Treatment
If neurological symptoms:
IM hydroxocobalamin 1000mcg every 2nd day until no improvement
If no neurological symptoms:
IM hydroxocobalamin 1000mcg x3/week for 2 weeks

See below for maintenance

Causes of vitamin B12 deficiency
• Pernicious anaemia
• Gastric causes
– Gastrectomy
– Gastric resection
• Inadequate dietary intake of B12 eg: vegan diet
• Intestinal causes
– Malabsorption
– Ileal resection
– Crohn’s disease
• Medications
– eg: colchicine, metformin, anticonvulsants
– long term use of PPIs and H2blockers
Food based malabsorption associated with gastric atrophy either age related or associated with long term PPI use –likely cause for 30-50% of cases with sub clinical B12 deficiency.
Investigation

Pregnant women with low B12
Serum B12 levels of 150 to 200 ng/l in pregnancy may be physiological and other biochemical tests to determine tissue deficiency are unproven. Check anti-intrinsic factor antibodies and treat as pernicious anaemia if positive. If negative, in order to limit extensive investigation with resultant anxiety, three injections of hydroxocobalamin are suggested to cover the pregnancy, and serum B12 levels checked two months post-partum to ensure resolution to normal levels.

Patients on oral contraceptive or hormone replacement therapy
These therapies can result in a low B12 level that does not require further investigation and treatment unless a strong clinical suspicion of B12 deficiency.

Patients with type 2 diabetes on long term Metformin (longer than 12 months)
These patients should have serum B12 monitored at 6 monthly intervals. If serum B12 levels fall, patients should have tests for anti-intrinsic factor antibody. If positive, they should have lifelong treatment with replacement hydroxocobalamin. If negative, the reduced level may be purely as a result of metformin. Treatment with three injections of hydroxocobalamin with subsequent monitoring of serum B12 at 6 monthly intervals is suggested.

Treatment

For patients with neurological symptoms
Initial treatment:
- Intramuscular (IM) injections of hydroxocobalamin 1000mcg every second day until no further improvement
Maintenance:
- IM injections of hydroxocobalamin 1000mcg every 2 months for life
Oral cobalamin is not currently recommended for those with neurological symptoms.

For patients without neurological symptoms
Initial treatment:
- Intramuscular (IM) injections of hydroxocobalamin 1000mcg on x 3/week for 2 weeks
Maintenance:
Long-term treatment where the underlying cause is not dietary:
- IM injections of hydroxocobalamin every 3 months for life
Long-term treatment where the underlying cause is dietary:
  Advise either: oral cyanocobalamin tablets 50–150 micrograms daily between meals (in adults); or
  Twice-yearly hydroxocobalamin 1000mcg injection - may be preferable in the elderly who are more likely to have malabsorption
In vegans, this treatment may need to be life-long
In non-vegans treatment can be stopped once vitamin B12 levels have been corrected and diet has improved – but monitor B12 levels 6 monthly
Advise consumption of foods rich in vitamin B12, eg: foods fortified with vitamin B12 - some soy products, and some breakfast cereals and breads, meat, eggs, and dairy products
Further monitoring is generally considered unnecessary - exceptions to this are:
  Suspected lack of compliance with treatment
  Recurrence of anaemia
Sheet 4 Folate deficiency

Low serum folate <3 µg/L or 3-4.5µg/L with symptoms

Ensure Vitamin B12 is normal prior to commencing treatment with folate

Consider Coeliac disease (check TTG)

Treatment
Dietary advice
Folic acid 5mg daily for 4 months
Longer if underlying cause is persistent

Causes of folate deficiency
- Dietary deficiency eg: alcoholism, dietary fads
- Malabsorption eg: coeliac disease
- Excessive requirements
  - Physiological
  - Malignancy
  - Haemolytic anaemia
- Medication
  - Cholestyramine, sulfasalazine, methotrexate

Follow up FBC/retics in 10 days to ensure normalising

Consider referral

Haematology
If suspect haematological malignancy or other blood disorder
Cause Unclear

Gastro
Malabsorption
Coeliac

Dietician
If cause is poor diet
**Folate deficiency**

**Treatment**
Give information on improving diet with natural sources of folate, eg:
- broccoli
- brussel sprouts
- asparagus
- peas
- chickpeas
- brown rice

Offer daily oral folic acid:
Treatment for 4 months is usually sufficient to replenish body stores if inadequate dietary intake is the cause treatment may be required for longer if the underlying cause is persistent.

**Follow up**

FBC and reticulocyte count should be performed:
- After 10 days to check response to treatment: there should be a rise in the haemoglobin level and an increase in the reticulocyte count to above normal range.
- After 8 weeks to confirm normal blood count
- On completion of treatment to confirm response

NB: If haemoglobin (Hb) initially responds and then stops, check ferritin to see if a secondary iron deficiency has occurred.
Further monitoring is generally considered unnecessary - exceptions to this are:
- Suspected lack of compliance with treatment
- Recurrence of anaemia
Consider investigating and treating anaemia if:

- Hb ≤ 110 g/L
- Symptoms attributable to anaemia develop

Serum ferritin > 100µg/L

Yes

- ?functional iron deficiency
  - Ferritin > 100µg/L
  - and <800µg/L
  - Transferrin saturation <20%

No

Yes

Optimise iron stores
- Oral iron if intolerant of oral iron
- or poor response, consider IV iron
  (via Nephrology clinic referral)

Iron replete (serum ferritin > 100 µg/L and functional iron deficiency excluded, Hb <110 g/L refer to local Nephrologist, patient may require erythropoiesis stimulating agents (ESA))

Consider other causes for anaemia (see Sheet 1)

If anaemia continues

Iron deficient
- Iron deficiency pathway
  Sheet 2
Inherited disorders of haemoglobin (haemoglobinopathy) should be considered in all individuals with microcytic anaemia, particularly if there is no evidence of iron deficiency or red cell changes persist after adequate iron replacement. Although these conditions are more frequently associated with individuals of non northern European origin, they may be found in all ethnic groups.

Conditions most frequently associated with microcytic hypochromic indices include:
1. Alpha thalassaemia
2. Beta thalassaemia
3. Delta beta thalassaemia
4. Haemoglobin E
5. Other haemoglobin variants

Carriers for these haemoglobinopathies are asymptomatic. Milder carriers may have a normal haemoglobin with minimal reduction in MCV and MCH while other carriers will have mild anaemia with more marked reduction in MCV and MCH. Carriers for haemoglobinopathy do not need haematology follow up however, individuals with more severe anaemia (> 20g/l below lower limit of normal) or those with symptoms or splenomegaly should be referred for a haematological review.

It is important to recognize carrier states for these haemoglobinopathies as they do not require iron treatment and the information may be important for genetic counseling for themselves or other members of their family. Women who have had pregnancies in recent years or partners of women with significant carrier states may have been screened as part of the national antenatal screening programme and may be aware of their haemoglobinopathy results. It is also useful to refer back to historical results, for Hb, MCV and MCH, if available, as these remain relatively constant throughout adult life for a given individual; any significant deviation indicates an additional cause for anaemia.

Further information for health professionals and information for carriers may be found on the following websites and these contain useful genetic counselling information for those contemplating pregnancy.

- [http://www.chime.ucl.ac.uk/APoGI/data/html/hb/menu.htm](http://www.chime.ucl.ac.uk/APoGI/data/html/hb/menu.htm)
- [www.screening.nhs.uk/sickleandthal](http://www.screening.nhs.uk/sickleandthal)

Leaflets and further advice are also available from the Manchester Sickle Cell/ Thalassaemia Centre Tel: 0161 2743322

**Beta thalassaemia**
Carrier states for beta thalassaemia are asymptomatic and have a mild anaemia often with marked microcytosis. Carriers should be informed for genetic counselling purposes as homozygous beta thalassaemia produces a clinically significant condition causing severe anaemia and a need for regular blood transfusion. Beta thalassaemia is typically diagnosed on the finding of a raised Hb A2 level with other phenotypic evidence suggesting beta thalassaemia. In these cases a haemoglobinopathy card may be issued.

**Other significant haemoglobinopathies causing anaemia**
This includes other types of thalassaemia and some haemoglobin variants. In such cases further information should be sought from the Manchester Sickle cell and thalassaemia centre.
Further information on Alpha Thalassaemia

Alpha thalassaemia is caused by deletions or mutations affecting the alpha thalassaemia gene and results in deficient production of alpha globin chains. Alpha thalassaemia is usually suspected in a patient with a hypochromic, microcytic blood picture (with or without anaemia) where other causes for these findings such as beta thalassaemia or iron deficiency have been excluded. Definitive diagnosis of alpha thalassaemia can only be made by DNA studies. This is not usually necessary except in certain circumstances (see below).

There are 4 genes controlling alpha thalassaemia (2 on each chromosome) and the number of defective genes will dictate the clinical features:

Persons with 1 or 2 defective genes are usually asymptomatic and do not need any further investigation or treatment. Iron treatment is not effective and should not be given unless concomitant iron deficiency is proven.

The only indication for further testing is in the antenatal context where it is important to distinguish those who have alpha zero (2 defective genes on the same chromosome) from those who have homozygous alpha + (2 defective genes on opposite chromosomes). The former will require partner testing to establish the risk of haemoglobin H or Barts hydrops whilst the latter requires no further action. Alpha zero cannot be distinguished from homozygous alpha plus on blood indices alone.

Alpha plus thalassaemia is extremely common being found in up to 30% or persons of African origin. It is also common in all parts of Asia, particularly in South East Asia. Alpha zero is found in some Mediterranean populations but its highest frequency is in individuals from south East Asia. This forms the basis of the antenatal screening algorithm.

Issue of alpha thalassaemia reports

Possible alpha thalassaemia may be picked up on routine testing or in the course of screening for haemoglobin disorders. In the antenatal or pre-conceptual counselling context, the national screening algorithm will dictate those women for whom partner screening is indicated. This will be on the basis of blood results and that woman's ethnic origin. Partner screening is indicated if the woman's MCH is < 25pg and she comes from a high risk ethnic group. Partner testing will be arranged by the screening midwife in the ANC.

Outside the antenatal setting, reports may be issued as follows:

Suggestive of alpha thalassaemia – This is reported when hypochromic microcytic indices coexist but with normal ferritin levels and haemoglobin electrophoresis.

Possible alpha thalassaemia/alpha thalassaemia can not be excluded – This will be reported when microcytic hypochromic indices are present, Hb electrophoresis is normal but iron levels are not available or are borderline low/unreliable. In this situation iron levels should be checked if no result available. If iron levels are low or borderline, a short course of iron should be given with repeat blood count after 4 weeks. If hypochromic microcytic indices persist despite adequate iron levels then alpha thalassaemia is likely. Iron deficiency should be investigated and managed in the usual way.
Anaemia with low/normal MCV
Ferritin >50µg/L
And Transferrin Saturation >20%

If Hb <50g/L or very symptomatic
consider admission

Look for causes (see box)
Take careful history/examination
Check TFT’s/Blood glucose/Calcium
And other tests as suggested by history

Refer to relevant specialist if required

Treat underlying cause

IV iron if transferrin saturation <20%

Symptomatic affecting quality of life

Consider referral for erythropoietin
(ensure iron stores replenished)

Causes of Anaemia of Chronic disease

• Collagen vascular and autoimmune disorders
  (e.g., rheumatoid arthritis, SLE, dermatomyositis, giant cell arteritis, polymyalgia rheumatica, scleroderma, inflammatory bowel disease)
• Chronic infection (e.g., tuberculosis, chronic fungal infections, hepatitis, osteomyelitis, HIV)
• Acute infection (e.g., pneumonia, pyelonephritis, endocarditis, cellulitis, and soft tissue infections)
• Chronic diseases (e.g., chronic kidney disease, diabetes mellitus, congestive heart failure, major recent thrombosis, chronic pulmonary disease)
• Malignancy (e.g., lymphoma, renal cell carcinoma, multiple myeloma)
• Critical illness and major trauma.
Anaemia of chronic disease (ACD) is a common, if misleading, name for a syndrome in which the anaemia is due to an inflammation-mediated reduction in RBC production and sometimes in RBC survival.

Symptoms and signs
- There may be a history of an underlying autoimmune, malignant, or infectious disorder or of recent major surgery, major trauma, or a critical illness.
- Common presenting features of such underlying disorders include fever, anorexia, night sweats, arthralgia, myalgia, weight loss, the presence of a mass, adenopathy, hepatomegaly, splenomegaly, decreased breath sounds with rales, stiff neck, rash, abdominal tenderness, and tenderness of joints, shoulder girdle, or bones.
- History of bleeding is unusual and, if present, an alternative or additional workup is required.

Initial investigations
FBC, blood film, reticulocyte count, ferritin, seru iron studies, CRP/ESR/PV, creatinine, LDH, and liver function tests are the tests to order first. The ACD syndrome is defined by the following constellation laboratory test results:
- Mild to moderate anaemia that is either normocytic normochromic or microcytic hypochromic
- Otherwise normal RBC morphology
- Elevated serum ferritin
- Transferrin saturation <15%
- Elevated CRP
- Significantly elevated ESR

Treatment approach
- The treatment of choice in ACD is first and foremost treatment of the underlying disorder.
- Patients with non-severe ACD whose cause cannot be treated, or in whom such treatment does not improve the Hb level, do not usually require treatment for the anaemia. Simple observation suffices.
- In patients with anaemia that significantly impairs their quality of life or with comorbidities in which a non-severe anaemia imposes additional risk (e.g., heart failure, significant pulmonary disease), and in whom the underlying disorder is not responsive to treatment (or requires time to respond), intravenous iron, or erythropoiesis-stimulating agents (ESAs) to stimulate endogenous RBC production, are two possible treatment choices.
- Iron deficiency should be ruled out prior to initiating therapy. Because ESAs often produce functional iron deficiency in iron-replete subjects, supplementary iron therapy may be required to achieve an adequate therapeutic response. This decision is also best made in consultation with specialists, as the distinction between whether an initially poor response to ESAs is due to inadequate iron supply versus ESA under-dosing is difficult. Iron therapy should be considered if the transferrin saturation is <20%. Intravenous iron is preferred because optimal ESA effect requires that transferrin saturation be raised, ideally to the 30% to 40% range, and this cannot usually be accomplished with oral iron in ACD. However, intravenous iron should not generally be given in patients with active infection, as iron promotes growth of many micro-organisms.
**Sheet 8 Haematology Referrals**

**Red flags**
Film suggestive of leukaemia. Features of spinal cord compression, hypercalcaemia, acute renal failure. If Hb <50g/L or very symptomatic consider admission

**Admit to hospital straight away**

**Urgent referral:**
Suspected haematological malignancy:
- lymphadenopathy persisting for six weeks or more
- lymph nodes increasing in size
- lymphadenopathy associated splenomegaly
- hepatosplenomegaly
- bone pain associated with anaemia and a raised erythrocyte sedimentation rate (ESR) or plasma viscosity
- constellation of three or more of the following:
  - fatigue
  - night sweats
  - weight loss
  - Itching
  - breathlessness
  - bruising
  - recurrent infections
  - bone pain

**Referral to haematology on HSC205 pathway**

**Referral to haematology**

- Persistent unexplained anaemia
- Anaemia with abnormal blood film and / or abnormal white cell count / platelet count
- Anaemia with increased reticulocytes (>2%), jaundice (raised bilirubin) suggestive of haemolysis
- Anaemia with persistent unexplained macrocytosis (exclude liver disease, alcohol excess, B12/folate deficiency, hypothyroidism)

If unsure how quickly a patient needs to be seen please contact local haematologist on call

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