Definition:

- Normal Hgb is age and sex dependent
    - Women 120-160
    - Men 140-180
    - Lower in the elderly!
- Anything below the lower limit is considered anemia

Objective One
Assess the risk of decompensation of anemic patients to decide if prompt transfusion or volume replacement is necessary.

Of course the first question should be, is this patient stable or unstable?

a. A patient is unstable if they are hemodynamically compromised. Think of things like tachycardia, hypotension SBP <90, MAP <65) - use your clinical judgement!
b. If you do determine they are unstable, and they can't wait to get transfused you need to get Group O RBCs ASAP.
    i. You can use Group O +ve for males and post-menopausal females
    ii. Group O -ve for all other females

However, If the patient can wait 30 minutes, you can get cross matched blood if the patient happens to have an in-date group and screen test.
Otherwise, you can do an uncrossmatched, ABO/Rh group-specific blood if no in-date group and screen is available.
If no rush, get a group & screen done ASAP.

What is a Group, Screen and Crossmatch?

- Group refers to identifying their ABO blood type and RH status (1-4 hours for group and screen)
- Screen - For other antibodies in the serum
- Crossmatch - Assess how patient's blood reacts with donor blood (45-60 minutes)

- For an actively bleeding patient, we cannot rely on the haemoglobin levels because the fall in numbers will lag behind the actual losses. In this case we transfuse volume based on the estimated losses.
- A loss of 30% of blood volume, which is about 1500mL in an adult, generally produces signs and symptoms and can help guide transfusion volumes.

(Choosing Wisely Canada, May 2019)
For the stable patient you can instead follow some more fixed guidelines.
In general, consider transfusing at a Hgb < 70 in otherwise healthy individuals. Give 1 unit and recheck hgb before transfusing the second unit.
For patients with sepsis, ischemic heart or brain injury consider transfusing once their haemoglobin hits 80g/L or less

Use the minimum amount of PRBCs to accomplish the desired clinical outcome.
A single PRBC unit is expected to raise haemoglobin by 10g/L

One unit is 250mL in volume and is generally transfused over 1-2 hours depending on acuity of situation. Do not exceed 4 hours, to limit risk of contamination.

- With a standard transfusion the first 30 minutes is usually slower in case a transfusion reaction occurs, then the infusion rate gets ramped up

Objective Two
In a patient with anemia, classify the anemia as microcytic, normocytic, or macrocytic by using the MCV or smear test result, to direct further assessment and treatment.

Once you've determined that your patient is anaemic, you need to have a way of breaking down the giant differential for the aetiology into smaller categories. The quickest way to this is by looking at the MCV on your CBC.

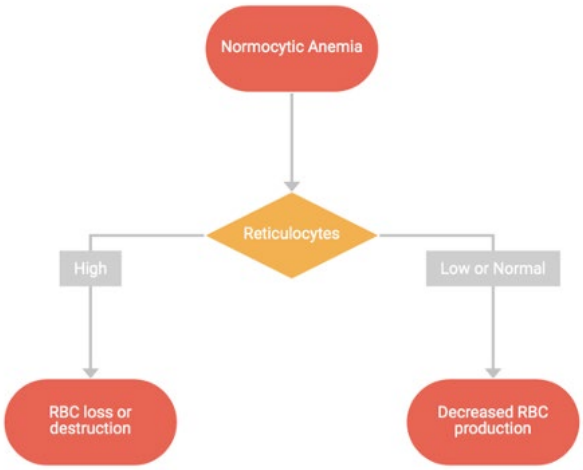
A mean corpuscular volume under 80 is Microcytic

So, the mnemonic we are all accustomed to for microcytic Anaemia is TAILS:

- Thalassemia (2nd most common in Canada)
- Anaemia of Chronic Disease (3rd most common in Canada)
    - Infection, autoimmune disease, CKD, malignancy
- Iron Deficiency,
- Lead Poisoning (most common in Canada)
- Sideroblastic anaemia

With iron deficiency being by far the most common here in Canada.

Now if you get an anaemia with MCV between 80-100, this is normocytic. The simple way to think of this is, either your red cells are exploding for some reason or you are losing too many for your bone marrow to keep up with replacing them (increased losses), or you aren't making enough of them, (reduced production)



When considering some reasons your patient might be losing RBCs faster than usual, a couple major causes to consider are either bleeding from somewhere, or the red cells are haemolysing for some reason.

- If we're thinking it is due to either RBC losses, we need to consider bleeding, or haemolysis.
    - If you want to investigate Bleeding as the cause, some investigations to consider are:
        - Reticulocyte count,
            - assuming normal bone marrow, an elevated reticulocyte count is suggestive of either RBC loss or destruction as the marrow tries to compensate for the losses
        - Low ferritin, because your iron is being lost along with the RBCs
        - Investigations to look for the source: + FIT, urinalysis, DRE, history of melena
        - Your smear in this case might be normal if the bleed is acute, if it is due to chronic losses you may have evidence or iron deficiency on your smear
    - Besides bleeding losses, we can also lose RBCs from Haemolysis
        - Haemolytic anaemia is often taught as a Triad of symptoms:
            - Anemia
            - Jaundice, because your exploding red cells are losing their contents into the serum before the liver can process it
            - Splenomegaly
        - Some investigations to help look for haemolysis as the cause are
            - Increased LDH
            - Increased unconjugated bilirubin
            - Decreased haptoglobin, as this is what binds the free haemoglobin released by exploding red cells. So it's being used up.
            - Positive DAT (if autoimmune)
        - What would you see on peripheral blood smear with haemolysis?
            - Schistocytes, these are scraps of left over RBCs seen on the smear under microscope

what about if you don't see evidence of haemolysis or bleed, then you might wonder if your patient is even producing enough RBCs to begin with.

- This is normocytic anaemia due to decreased RBC Production, think of a few possible aetiologies for this
    1. Early Iron Deficiency Anemia
        - In which case you can find out by getting a ferritin level
    2. Anemia of Chronic Disease
        - Which can be investigated by getting a CRP

3. Aplastic Anemia
    - Which we can investigate by getting
        - A CBC to look for a Pancytopenia, suggesting disease of the marrow affecting other lineages
        - Bone marrow biopsy showing hypocellularity and space occupied by fat
4. Chronic Kidney Disease
    - Investigations:
        - High serum creatinine and by proxy a low eGFR

Last is Macrocytic anaemia if there is an MCV > 100

Objective Three
In all patients with anemia, determine the iron status before initiating treatment.

[BCguidelines.ca]
It is important to not begin iron supplementation with just a microcytic anaemia, but rather to get the Ferritin levels before starting supplementation. As beginning supplementation with a haemoglobinopathy can worsen things.

- Ferritin is the most accurate reflection of iron stores within the body. Of any of the labs, this is diagnostic.
    - But keep in mind the values you get back for ferritin occur on a continuum. These need to be taken in clinical context, based on their risk profile
- A serum iron level, a TIBC and transferrin saturation are not routinely useful for investigating an iron deficiency anaemia
    - However, the fact that ferritin also acts as an acute phase reactant can make interpretation a bit difficult in the case of chronic disease.
    - So, a <u>FASTING</u> serum iron and transferrin saturation <u>may</u> be helpful in this case, looking for:
        - Low serum iron
        - Low or normal transferrin (TIBC) **and** fasting transferrin saturation below 20%

Now, how can we interpret the ferritin results we get back?

In adults:

- Under 15 ug/L is diagnostic of iron deficiency
- 15 to 30 ug/L probably iron deficiency
- Over 30 ug/L iron deficiency is unlikely
- While a ferritin over 100 ug/L is considered normal iron stores
- Over 600 suggests workup for iron overload

In kids:

- A ferritin under 12 ug/L diagnostic of iron deficiency
- 12 to 20 suggests possible iron deficiency
- Over 20 ug/L is considered normal iron stores in kids

Objective Four

In a patient with iron deficiency, investigate further to find the cause.

[BC Guidelines]

You've established with your ferritin labs that your patient is in fact anaemic with a deficit in iron. Now you need to sort out what is causing this iron deficiency so you can reverse it. Some of the more common causes, and ways to investigate include:

a. Bleeding
    i. Menorrhagia is the most common cause among pre-menopausal women, so ask about daily bleed volume and days of flow
        1. Consider referral to gyne and investigations for bleeding diathesis such as Von Willebrand
    ii. FIT or FOBT for occult GI bleed, or a DRE or history suggestive for GI bleeding
    iii. Ask about dyspepsia, melena or haemoptysis for UGIB
    iv. Ask about change in bowel habit, unexplained weight loss, or family or personal history of colorectal cancers
    v. Ask about haematuria and consider getting a urinalysis if suspicion
b. Another common cause is malabsorption, thinking of where iron is absorbed "dude is just feeling ill bro"
c. Finally consider asking about a possible Fe-deficient diet

Unexplained iron deficiency, after using the above history and investigations, especially men and post-menopausal women needs further workup. As causes of blood loss here can be serious, such as underlying malignancy

Objective Five

Consider and look for anemia in appropriate patients. Such as those at risk for blood loss or in patients with hemolysis whether they are symptomatic or not, and in those with new or worsening symptoms of angina or CHF.

Often we may find ourselves in clinic without the privilege of immediate labs for CBC to confirm anaemia.

But is anything even useful for detecting anaemia by physical exam?
Because we almost always have a CBC available, this may be just as interest, but because most of these physical exam items are more specific than sensitive, you just might be surprised on how many patients you will pick up over the years this way.[Evidence Based Physical Diagnosis Steven McGee pp75]

1. The best physical exam test for anaemia is Conjunctival Rim Pallor, +ve LR 16.7, mainly due to 99% specific if present
    a. This looks like pulling down the lower eyelid and looking from the eyeball to the rim of the lower eyelid, a normal conjunctiva looks like more reddish on the rim, and notably more pale nearer the eyeball.
    If the entire lid is pale, this is a positive result
    b. Palmar Crease Pallor is next most useful with a, +ve LR 7.9, again due to 99% specificity
    c. Finally an overall Palmar Pallor, +ve LR 5.6

With less utility for pallor to the tongue, nailbed or anywhere else. The value of the physical exam is if you see these, then suspect anaemia, if you don't it doesn't mean they aren't anaemic.

In particular, patients on anticoagulation are at higher risk of bleeding from any source due to their impaired clotting ability. Patients on NSAIDs are at higher risk of GI bleeding due to increased risk of gastric and duodenal ulcers.

While hemolytic anemia after valve replacement is quite rare, clinically insignificant hemolysis occurs in patients with mechanical valves and bioprosthetic valves.
Symptoms of anemia in these higher risk patients that should cause you to look a little closer include bleeding (GI), SOB, pallor, jaundice, HF exacerbations or worsening angina.

In patients with macrocytic anemia:

a) Consider the possibility of vitamin B12 Deficiency [uptodate]

Macrocytic anemia is divided into megaloblastic and non-megaloblastic anemia.

In Megaloblastic anemia the peripheral blood smear shows oval macrocytes + hypersegmented neutrophils (6-7 lobes)

Causes of megaloblastic anemia include

- Folate or vitamin B12 deficiency and
- Medications interfering with B12 synthesis such as methotrexate
    - We can look for this by simply getting a B12 level
        - While clinically, we can assess for possible B12 deficiency by watching for neurological findings like symmetric parasthesias or numbness and gait problems

- Some causes of NON-megaloblastic anemia include
    - Liver Disease
    - Excessive EtOH intake
    - Hypothyroidism
    - Bone marrow failure, infiltration, or suppression
    - Haemolysis can cause a larger proportion of the physically larger reticulocytes which can skew the measure of average RBC size and give a pseudo macrocytosis

Objective Six

Look for other manifestations of the deficiency in order to make the diagnosis of pernicious anemia when it is present.

[uptodate]

Pernicious anemia occurs when there is an autoimmune attack on the parietal cells of the stomach that produce intrinsic factor. Intrinsic factor is needed to absorb vitamin B12 from dietary sources.

Symptoms of pernicious anemia include

- GI symptoms - glossitis
- Neurologic manifestations - symmetric parasthesias, numbness, gait problems, weakness, ataxia
- Psychiatric manifestations - depression, irritability, cognitive slowing, dementia, psychosis, EPS
- Rare - skin hyperpigmentation, increased risk gastric cancer (pernicious anemia)

Objective Seven

As part of well-baby care, consider anemia in high-risk populations or in high-risk patients

[https://www.cps.ca/en/documents/position/iron-requirements]

Infants are particularly at risk for iron deficiency anemia as their iron requirements are huge with rapid growth and so a deficit in intake can overwhelm their limited stores at birth.

At each well child visit in the first 2 years, assess for risk of iron deficiency, with particular attention to high-risk individuals.

- those living with chronic illness,
- low socio-economic status,
- suboptimal intake of iron-rich foods, or prolonged bottle feeding
- Preterm delivery of birth weight under 2.5kg
- Infants born to mothers with anaemia or obesity
- Early umbilical cord clamping
- High cow's milk intake
- Also note that the prevalence in Canadian Indigenous communities is suspected to be up to 10x higher than the rest of Canada, with some estimates up to 36% prevalence in infants 4-18 months old!

Objective Eight

When a patient is discovered to have a slightly low hemoglobin level, look carefully for a cause as one cannot assume that this is normal for them.

Mild anemias should be worked up thoroughly.
We start by classifying the anemia by MCV and then ordering an initial workup to exclude common causes (ferritin, TSH, B12). Depending on symptoms, past medical history, and family history, other tests can be added.

For example, in a 40 year old male with a hemoglobin of 125 and MCV of 80 whose father was diagnosed with colon cancer at 55, we would order a flexible sigmoidoscopy or colonoscopy to rule out a GI source of occult bleeding.

While a young woman of Mediterranean descent with a hgb of 110 and an MCV of 65 is more likely to have thalassemia trait, so we would order hemoglobin electrophoresis.

Objective Nine

In anemic patients with menorrhagia, determine the need to look for other causes of the anemia.

The crux of this objective is to ensure you don't simply note the menorrhagia and assume this is the only cause for their anaemia. These patients deserve a workup for their anaemia just like anyone else.

Go through the process as you would with anyone else as related above. Get your CBC and look at the MCV, then explore based on the RBC morphology as appropriate. As with any diagnosis, try to prove yourself wrong until the only reasonable explanation is the first one you though. Once you are comfortable this is an iron deficiency anaemia secondary to bleed, then figure out the cause of the bleed.

Be sure to consider other causes of anemia in menorrhaegic patients include hypo and hyperthyroidism, coagulopathies, and gynecologic causes. Workup of hormonal and coagulation related causes should be based on history and physical. A full bleeding history should be taken to ensure coagulopathies are not missed.

Gynecologic causes can be worked up using pelvic u/s to identify lesions and assess the uterus and adnexa. Endometrial biopsy is useful in women at risk for uterine cancer, hyperplasia, or polyps.

Walker, Coffey, & Borgey (2020)