

Music intro clips:

AC/DC – If You Want Blood

Taylor Swift – Bad Blood

Foreigner – Hot Blooded

Bon Jovi – Blood on Blood

Introduction

CB: Hello and welcome back! This is Cathy

MC: and Mike

CB: and this is the second episode of The Med Thread, a medication information station from the School of Pharmacy at Memorial! Each month we will bring you an exciting topic related to medications, disease conditions, pharmacy practice and more!

MC: In case you didn't catch our last episode, let's reintroduce ourselves.

CB: I am a clinical pharmacist at the Medication Therapy Services Clinic here at Memorial. I work with clients and their healthcare providers to make sure they're on the best medications for them! I'm keen on deprescribing and smoking cessation too.

MC: And I am the Drug Information Pharmacist at the School of Pharmacy. I answer any questions about medications, treatments and curiosities from health care professionals all over the province.

CB: Alright let's get down to business. We talked last episode about insomnia and that triggered me to think of other reasons why people could be tired. I have a lot of clients that say they must be anemic because they're so sleepy in the daytime. But is this why? What does anemia mean? How did we discover it? What do we do to treat it? Is it a life-long thing? Is iron the cure for all?

Well we'll answer these questions today!

Clip: The Addams Family Theme

History of anemia

CB: Anemia is defined by lower than normal red blood cells or hemoglobin, this causes a decrease in the amount of oxygen carried in the blood. Sounds simple right? If we look at its impact on global public health it is definitely not a simple problem. It affects people all over the world and its effects can be debilitating.

MC: And it's not a new problem; there are stories of anemia dating back thousands of years. The word "anemia" has Greek roots and literally means 'lack of blood'.

CB: That's funny to me because I am always cold, and my Newfoundlander father always says – "maid you must not have any blood in ya".

MC: Well yeah, people equated blood to life and also realized that it warmed the body. The word 'hema' is derived from the word aetho which means to "make red-hot, roast, warm or heat" so there's definitely some history linking your father's expression to blood.

CB: Ah cool! I also read that anemia or "bloodlessness" was often mistaken for a symptom of a vampire attack. Those suffering from anemia would gradually become paler and more and more tired and it was recognized that this was due to having low blood. Superstitious doctors centuries ago could have easily suspected these poor people to have been sucked of their blood by a vampire.

MC: It's funny and fascinating because the reverse was prescribed too. Blood-letting was a treatment for a whole slew of medical conditions up until the 19th century. But the ancient Greeks had it right, recognizing that blood was a necessary nutrient of the living body, just like plants would die without water and nutrients, humans die when they lose blood.

CB: Yes and if you look at treatments over the years, one of the first cures for these symptoms was to drink the blood of animals.

MC: Wow! I don't know if I'd do that, but I do enjoy blood sausages or blood pudding once in a while.

CB: Yeah me neither! It's important to realize that anemia is often a symptom or sign, not a condition itself. There are a lot of different causes, including blood loss as a result of injury or destruction of blood cells in conditions like sickle cell disease. And we've got diseases affecting the bone marrow like leukemia and some other cancers, kidney disease, hypothyroidism, and more.

MC: Sometimes you're not getting enough of the building blocks of blood cells. A whole host of conditions can impact the absorption of nutrients like celiac, inflammatory bowel disease, or chronic alcoholism.

CB: Don't forget, some drugs can do it too, like common reflux therapies, which is often a good reason for me to help deprescribe them. We'll talk about these essential vitamins and minerals in the episode.

And we've got to consider blood loss, females who are menstruating are at a higher risk for anemia. A loss of 100 mL of blood contains about as much iron as the average western world diet would contain in 40 days!

MC: When I first saw that, I thought there was no way it was true. But then I came across a study as far back as 1933, they estimated, 100 mL of blood has 50 mg of iron! And from the Canadian Dietician Association, we may get less than 1 mg of iron per day from average food intake.

So...lots of causes...and also a lot of symptoms, right?

(Helmer, 1934, Nutrition Working Group, 2016)

CB: Definitely. Symptoms can be mild at first but can progress to major fatigue and impaired memory and concentration. Skin temperature decreases and the skin and mucus membranes

can become pale, there can be chest pain, and trouble breathing when exercising. Anemia can also impair your immune system as well – No body system is left unscathed.

MC: We obviously shouldn't just ask about fatigue when assessing anemia then!

CB: Definitely not. I had one client explain their anemia as a 'teddy bear without enough stuffing', it can also be seen as being suffocated from the inside – as each organ doesn't get enough oxygen.

MC: That seems pretty morbid! But it really drives the message home. Okay, let's talk a little about diagnosis.

Diagnosis

Therapeutic information adapted from: Therapeutic Choices (CPhA, 2018), Pharmacotherapy (DiPiro, 2017), Goodman and Gilman's (Brunton, 2017), and Canadian Dietician Association (www.dieticians.ca)

CB: I see clients in the community who often say, "I'm so tired all the time, I think I'm iron-deficient" or I need B12 and then just take over-the-counter supplements. But it's important not to jump to that conclusion, as we said, it's often not that simple.

MC: Oh for sure, we talked about insomnia in the last episode and how many things can cause you to be fatigued, jumping to conclusions without talking to a healthcare provider is not a good idea sometimes, as supplements can have side effects.

CB: So let's start with how anemia is diagnosed.

MC: The medical diagnosis is defined as a reduction in hemoglobin concentration but you can also look at something called hematocrit, a way to count red blood cells.

CB: And there are differences between males and females.

MC: Not to give too many numbers, but for men, if you have hemoglobin less than 130 g/L you have anemia, and non-pregnant females are anemic with hemoglobin levels less than 120 g/L.

CB: And interestingly, these cut off levels may be different for some people. Like patients living at high altitudes who have higher values than those living at sea level, and those who smoke who have higher hematocrit than nonsmokers.

MC: Yes, ethnicity is also a factor and there are some genetic causes too. African Americans tend to have slightly lower hemoglobin levels than Caucasians. And there are many forms of thalassemia, a genetic condition leading to abnormal hemoglobin synthesis. In those people, their normal blood cell size and amount of hemoglobin may be smaller.

(Beutler, 2005)

CB: And although diagnosing anemia may be simple by looking at a patient's symptoms and hemoglobin level, in order to be effectively treated we have to figure out the type of anemia, or what is causing the anemia. This is where I start to feel like Sherlock Holmes...

Clip: Basil Rathbone as Sherlock Holmes

MC: Me too, but we do have clues to look at, like the size of your blood cells.

CB: If cells are smaller than normal, or microcytic, then iron deficiency is likely. And if cells are larger than normal, or macrocytic, then anemia is likely due to folate or Vitamin B12 deficiency. This helps guide us to where we look next.

MC: Sometimes it's easier to think about as an analogy. Imagine you're on a long circular road operating a taxi fleet. The passengers are families of 4 oxygens and the cars are your red blood cells. Normally, you've got a comfortable 4 seats and you can pick up and drop off with no problem.

But you run out of steel, you can't make cars anymore so you make motorcycles. Now you can only carry 1 person at a time. This would be like your iron deficiency, microcytic anemia.

Alternatively, let's say you've run out of wheels, you've got enough steel, so you decide to make stretch limos. Now you've got fewer cars on the road. You may think that you could just fit more families in the limo, but hey, they don't want to sit together and so you can't carry more people per trip. This is your vitamin B12 or folate deficiency, macrocytic anemia.

CB: Ok, now I'll never forget that! So for small cells, or the motorcycles— we think iron deficiency. Next we look at ferritin, this is the iron that is kept in storage within the body. It is important to know that ferritin can be affected by inflammation, infection, pregnancy or obesity.

MC: Other iron-related levels include transferrin, which is the iron that is moving around in the blood; if this is high then stores are low, all of our steel is on the assembly line and there's nothing left in stock.

CB: OK and if cells are large, picturing the limos, then folate or B12 deficiency is likely. We can look at serum folate, which fluctuates short-term, or red blood cell folate which reflects the average folate available and is more reliable. And we check out serum B12 levels too.

MC: Well it's clear that there isn't just one cause of anemia and blood work, and sometimes genetic testing, is absolutely necessary for a medical diagnosis. And it follows that we shouldn't just use one therapy to treat all anemias. Before we forget, we are pharmacists, so are there drugs that can cause anemia?

CB: Of course! There's chemotherapy agents, methotrexate, methyldopa, some anti-inflammatories and some anticonvulsants. Some of these affect the bone marrow and others we don't really know how they cause anemia. And there's also all those drugs that can affect the gastrointestinal tract and nutrient absorption.

MC: Right, those anti-acids, proton-pump inhibitors, laxatives and more! It's on the mind of pharmacists, so definitely a good question to ask about your medications.

CB: We do need to mention the hemolytic anemias, these are conditions where the RBCs are being destroyed faster than they are produced. All those cars we're making are breaking down on the road and the assembly line can't keep up!

MC: There are a wide range of these conditions accounting for about 5% of all anemias. These include sickle cell anemia, G6PD deficiency, autoimmune hemolytic anemias, drug-induced causes and others.

CB: We don't necessarily use drugs to treat these patients, but there are some drugs that can worsen the conditions and patients should be made aware of these.

Okay, let's dive into the first type – iron deficiency anemia.

Iron deficiency

CB: Iron deficiency continues to be the most common cause of anemia worldwide, affecting about 20% of the world's population. It accounts for about half of all anemia cases in the world and is most prevalent among women.

MC: In underdeveloped countries, iron deficiency is often as a result of, insufficient dietary intake, parasitic infections like hookworms, and multiple pregnancies.

And in high-income countries, it is a result of certain eating habits like vegetarian diet or no intake of red meat, or a pathologic condition like chronic blood loss or malabsorption.

CB: I've spent some time working in Haiti and it was interesting to see how common anemia was there, but for much different reasons than here at home in Canada.

Iron is critical, to respiration, energy production and even DNA synthesis. There are some features that give us clues to look for iron deficiency anemia. Things like painless swelling of the tongue, spoon-shaped nails and pica, which is unusual craving for things that aren't food like when you hear stories of children eating soil.

These can all be signs that there could be an underlying iron deficiency present.

MC: Important too that you can have iron deficiency for a while before it develops into anemia. Everyone with a diagnosed iron deficiency with or without anemia should be encouraged to increase dietary iron from red meats or seafood such as oysters, tuna, salmon and shrimp. I've included a link to the Dietitians of Canada list of these food sources on our webpage. Typically though, people will also need supplementation, especially if following a plant-based diet.

CB: Iron is absorbed in the duodenum and jejunum, parts of the small intestine, and it isn't readily absorbed on its own. Only about 10% of the iron we eat will be absorbed! Iron bound to heme – found in red meat – is much more readily absorbed than iron found in green vegetables. Phosphates and phytates in some vegetables lead to formation of unabsorbable iron complexes, so you can see why vegetarian diets can be a problem here.

MC: That's important, and it's neat that vitamin C enhances the absorption of nonheme iron. And tea and coffee can actually block its absorption.

CB: And when we have patients with iron deficiency it is important to look for potential bleeding either by endoscopy (putting the light down), or colonoscopy (putting the light up)

MC: Yes, always think about the cause before we look to treat. So what are the treatments?

CB: Treatment should be aimed at correcting the anemia and replenishing iron stores. It sounds simple but there are various options for oral supplements, with different amounts of iron in each version so reading labels is key. The target dose is 105-200 mg/day of elemental iron in divided doses, and the WHO recommends 120 mg/day.

MC: Iron tablets are famous for side effects like nausea, heartburn, and constipation. They are best absorbed on an empty stomach, but people may have to take them with food in order to tolerate them. And don't forget the vitamin C – taking the supplements with orange juice can help absorption.

CB: Because nausea and stomach upset are such a problem we should recommend increasing the dose over time, like starting with a single tablet with one meal for a week, and adding another tablet with a different meal a week later if tolerance allows. If all goes well, gradually shift the timing of the dose to before the meal.

MC: Instead of iron salts, there are also heme iron pills, vegan sources, and iron complexed to different molecules to try and help with absorption. Each of these have their own benefits and drawbacks. And oral tablets aren't the only option. Patients who have issues with absorbing iron, have had intolerable side effects from the pills, or have ongoing blood loss can use injectable iron.

Intramuscular and intravenous iron requires administration in a hospital or outpatient clinic as it carries a risk of allergic reactions. Intramuscular iron can also be quite painful and it's given in the bum, so not the most pleasant. Intravenous iron is usually reserved for severe deficiencies.

CB: Speaking of iron clinics, I've noticed a new one has opened up here in St. John's which offers iron infusions along with other infusions including one for hangovers.

MC: Oh wow, maybe we can talk about that in another episode! Honestly, there's so much, we could probably do a whole episode on iron!

CB: Absolutely, but it is neat to know that there are options out there for people that can't tolerate the pills.

MC: Yes, it's important too that treatment is continued for 3 months after reaching a target hemoglobin to make sure we get enough iron in storage so the patient doesn't go deficient again. You can look at the blood cells to gauge response and you should see hemoglobin increases every week.

CB: Let's not forget iron deficiency in pregnancy; iron requirements go up when pregnant and all pregnant women should be screened.

MC: And is treatment the same in pregnant women?

CB: Yes it is, and it's also the same in women who are breastfeeding. Simple oral iron salts are recommended in pregnancy, but we talked about the nausea and stomach upset. You can imagine some pregnant women have this already and just can't tolerate the iron tablets. If this is the case, we can try to lower the dose or recommend taking it with meals.

You can see why iron supplements are kept behind the counter at the pharmacy by law, there are a lot of things to consider before just taking them off the shelf!

MC: Absolutely, and there have been cases of overdose because high doses of iron are toxic, especially to children. So it is definitely better to talk to a health professional before taking them.

CB: Now ... let's get to the other types of anemia!

Clip: Ingrid Michaelson – Blood Brothers

B12 deficiency

CB: Now we've got the macrocytic anemias, the limos as we think of them.

MC: And what causes these?

CB: Usually impaired DNA synthesis while making red blood cells due to a deficiency of vitamin B12 or folate. Let's dive into B12 deficiency anemia first.

MC: This anemia was so important that there were two Nobel prizes awarded for studies on treatment and figuring out the chemical structure of B12.

(www.nobelprize.org)

CB: In the early 1900s George Whipple showed that blood cell formation was stimulated by a diet rich in liver in dogs. William Murphy and George Minot used this finding to look at people with a condition called pernicious anemia. If patients ate large amounts of liver, their condition improved. And this shed light on the cause of pernicious anemia, a shortage of B12 which is found in the liver. Later, Dorothy Hodgkin and her co-workers went on to use X ray crystallography to discover the structure of Vitamin B12.

MC: Some features of the anemia include a sore tongue – opposite of iron deficiency, and people can show signs of dementia, weakness, sensory neuropathy and paresthesias, or tingling in the hands and feet.

CB: So nothing to take lightly!

MC: Absolutely not. B12 deficiency is common in strict vegan diets because B12 is only found in food of animal origin like meat, fish, eggs, cheese and milk.

Clip: The Simpsons – Lisa the Vegetarian

CB: It is also known that in order to absorb B12 we have to have intrinsic factor, a special compound produced in the stomach. Some people don't have enough intrinsic factor, most common in people of northern European descent.

MC: Right, so if someone gets a total gastrectomy, removing the stomach, there's no more intrinsic factor!

CB: The rest of the intestinal tract is important too. I saw a client who was eating copious amounts of B12-containing foods and couldn't get his levels up at all. When investigated it turned out he had Crohn's disease and couldn't absorb it, therefore we used the injectable forms and voila!

MC: There are a lot of things that can cause B12 deficiency, but this anemia usually takes 2-3 years to develop because luckily, our bodies store enough of it! It's kept in the liver until it's needed, and that's why liver worked for the puppies!

But when it does happen it can be serious, Vitamin B12 works together with folate to make DNA, without it there isn't proper DNA synthesis. We think this is related to the neuropathy symptoms.

CB: Restoring normal dietary intake of vitamin B12 can be enough to reverse the problem; but if neurologic deficits are present patients should be treated with supplementation.

So what supplements do we have?

MC: Just like iron, we've got oral supplements and injectables. The doses we usually see on the shelf range from 100 to 1000 mcg per tablet.

CB: This seems high when the dietary reference for B12 is 2.4 mcg/day, and doses over 100 mcg/day are more than the body can handle. But the excess is not toxic and is readily excreted by the kidneys, therefore there is a tendency to give more rather than less especially in patients with neurologic deficits.

MC: And patients with pernicious anemia don't have intrinsic factor to help with absorption so they actually require high doses in order to tap into passive absorption through the intestine wall. Essentially, taking a lot to get a little. This is where the injections come in as well.

CB: The injections can be used to correct severe symptoms and then the patient can be switched to oral if absorbed properly and things have improved.

MC: Yes, many patients with B12 deficiency will require life-long replacement therapy. Unless there is something specific causing the problem. Like this episode of House.

Clip: House MD – Insensitive

CB: Yeah and hopefully we don't actually get that problem! The recommended doses vary but standard treatment for pernicious anemia is vitamin B12 injection 100 mcg injected daily for 1 week, and then 200 mcg weekly until hemoglobin goes back to normal. Lifelong maintenance is 100 mcg injected monthly or oral supplements in doses of 500 – 2000 mcg daily. But in community we see this used more frequently don't we.

MC: We sure do. I see a lot of prescriptions for injecting 1000 mcg per week but even though it might be overkill, as we mentioned, the excess is simply excreted.

What's good about B12 supplements is that patients feel better within a day or 2 of taking them. The hemoglobin takes much longer to return to normal but some patients say they can feel the need for another dose close to their next appointment.

CB: And unfortunately, the neurological damage may be irreversible. If it's a recent onset of tingling hands and feet, these symptoms often improve somewhat but any major nerve damage is irreversible even with best therapy.

MC: OK that's a lot about B12. And we've also got folate so let's jump to that.

Clip: Pulp Fiction

Folate Deficiency

MC: For folate, we don't have Samuel L. Jackson's problem because it's found in all sorts of fruits and veggies!

CB: But...folate deficiency anemia is a problem as our bodies don't store as much folate as we do B12, and as soon as there is an increase in folate demand or we stop getting folate in the diet, deficiency occurs quickly. We can treat this with folic acid oral supplementation of 1-5 mg daily.

MC: Again, that seems like a lot when the dietary requirement is only 400 mcg a day, but these large doses allow us to get sufficient folate. In pregnancy, folate requirements increase so folic acid is recommended before and during pregnancy to prevent neural tube defects.

CB: And unlike B12, thankfully, folic acid is readily absorbed throughout the gut. The oral route is sufficient even in patients with malabsorption syndromes!

MC: Treatment with folic acid usually only requires 4-6 months of supplementation, not life-long. Patients can start to feel better after a few days, but it does take months to replenish their blood count.

CB: One thing that is important is the relationship between B12 and folate. Lack of B12 can trap folate and interfere with DNA and RNA synthesis. If we just assume a patient has folate deficiency without looking at B12 and we start treating with high doses of folic acid there can be

a partial response. The blood picture starts to look normal but the neurological damage continues and the root of the problem isn't resolved. It is important to check for vitamin B12 deficiency and exclude it before treating folic acid deficiency.

(Visentin, 2014, Hoffbrand, 1993)

MC: Ok, noted! And just to recap, how do we monitor for a response?

CB: Red blood cells will increase after 3-4 days of vitamin B12 or folic acid therapy, with an increase in hemoglobin by 1-2 weeks. Full resolution happens in about 2 months, but therapy will continue for longer.

MC: We've also got to consider when anemia is really severe, and iron, B12 or folic acid isn't going to cut it. Since hemoglobin delivers oxygen, if this drops low enough it may leave our vital organs without oxygen.

CB: And this is where blood transfusions come in. There are a lot of different guidelines out there on when to give blood transfusions, but in general, we always want to make sure any active bleeding is corrected and then consider giving blood products.

MC: And of course, like any drug, there are risks to transfusions. We've come a long way and numerous checks are done to minimize risks like infection from pathogens in the donor blood and immune reactions to blood types.

CB: So that covers anemia caused by iron, b12 and folate deficiency.

But there's one more kind of anemia...

Clip: Shawn Mendes – In My Blood

Chronic Disease

MC: Yes, the elusive anemia of chronic disease!

CB: This is the second most prevalent cause of anemia. During periods of inflammation or infection, our bodies sequester iron and remove it from circulation. This seems sinister but it is the body's way of protecting our iron, just like valuables were hidden and protected during war.

MC: You can see why this is common in disorders associated with inflammation like arthritis, cancers, and inflammatory bowel disease. Thinking back, this can be an anemia where blood cells are normal sized, not bigger nor smaller. The assembly lines making cars for our taxi fleet are just not working efficiently!

CB: Right! There seems to be some sort of impaired response to erythropoietin or EPO. EPO is one of those drugs you'll recognize from athlete doping scandals. It's a hormone produced by the

kidney that promotes the formation of red blood cells by the bone marrow. And hepcidin also plays a role.

MC: Hepcidin is a tricky but helpful little character produced in the liver. It removes iron from circulation when bacteria or cancer cells are present so that they can't use this necessary nutrient for fuel, blocking them from growing. Unfortunately, this means there is a decrease in iron for our blood cells too!

CB: And anemia of chronic disease patients have the same symptoms of anemia PLUS their symptoms of the chronic inflammatory disease causing the problem. So it can be a big quality of life issue for patients.

MC: Absolutely, and it may not be possible to completely fix the anemia but we can address the underlying inflammatory disorder and try to limit its impact on the blood.

CB: We use iron supplements only if there is a functional iron deficiency and we may give EPO or transfusions in some cases.

MC: Yes, we may see it used in patients with chronic renal failure, HIV or Hepatitis C, or patients getting chemotherapy.

Conclusion

CB: Wow, we've gone over a lot!

MC: Yes. It's obvious that anemia is not a minor issue, and there are a variety of causes and treatments so it is important to get the proper investigations done before jumping to taking B12 or iron supplements.

CB: Absolutely, and public health initiatives have had a tremendous impact. The Canadian Food Inspection Agency has a list of foods to which vitamins, minerals, nutrients and amino acids may or must be added. This has increased the level of folic acid and iron we get from breakfast cereals and flour, as well as simulated egg and meat products for vegetarian and vegan diets.

(<http://inspection.gc.ca/>)

MC: Way to go Health Canada!

CB: So that's a wrap on anemia! Check out our website for resources and if you have topics you want to hear about or just want to send us a comment, find us on Facebook via the School of Pharmacy or mtsclinic.ca, or email medthread@mun.ca.

And if you're suspecting that you may have anemia, contact our clinic for an appointment or speak with your doctor before jumping to treatment over the counter.

MC: Thanks for joining us for another episode of the Med Thread!

Anemia: Why Am I So Tired?

CB: And tune in next time, when we will be exploring the timely topic of cannabis.

MC: Until next time, I'm Mike

CB: And I'm Cathy – don't let your blood boil!

Clip: My Chemical Romance – Blood

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