

Pediatrician's Corner

A Conversation with a Pediatric Hematologist

Editor's Note: This is a transcript of an online course released in May 2025. It has been edited for clarity.

Nisha Rathore, MD: Hi, and welcome to the Pediatrician's Corner podcast brought to you by PNCE.org and the Annenberg Center for Health Sciences. I'm Dr. Nisha Rathore, a board-certified general pediatrician. Thank you so much for joining us today.

Our guest today is Dr. Clay Cohen. Dr. Cohen is an associate professor of pediatrics at Baylor College of Medicine. He works at Texas Children's Cancer and Hematology Center in Houston, Texas. Thank you so much for joining us today.

Dr. Cohen, you and I go way back to our residency days. You're now a practicing hematologist, I'm a general pediatrician and I think, for both of us, in our scopes of practice, there are definitely some areas of overlap. So, I think that your insight today is going to be really helpful to shed a little bit of light on the big hematology topics that come up in the general population. And I think the first topic that comes up, that both of us see and work with, is iron deficiency anemia. Now, iron deficiency anemia really can happen at any point in someone's life, but it seems like, in development, there are specific times where certain populations are more at risk. Can you kind of fill us in on when we should be screening our patient and why certain populations are more at risk than others?

Clay Cohen, MD: This is really central to every pediatric hematologist's practice. We see a lot of iron deficiency and there are 2 time periods in childhood that are the highest risk and the most likely to developing iron deficiency with or without anemia. Those time periods are early in life and then in adolescence. So, I can touch on iron deficiency in young children first. So, iron deficiency in young children is almost always because of nutrition and inadequate iron in the diet which, for most young kids, and when I say young kids, I'm speaking of the first couple of years of life, for most young kids, it's driven by drinking too much cow's milk. I think, there seems to be a perception just in society in general and most parents seem to think that cow's milk is very good for their children's health and, in many aspects, that's probably true, but many families kind of emphasize that, maybe more than they should. But because of that, a lot of kids' diet ends up being a lot of cow's milk and cow's milk ends up causing iron deficiency in young children for 3 main reasons. The first is cow's milk doesn't have a lot of

bioavailable iron and if a lot of calories that kids are getting in their diet are from cow's milk, they're not going to get any iron from that. It's also going to suppress their appetite and make them less likely to eat iron-rich foods. And then in kids that are really drinking an excess amount of cow's milk, north of 20, 30 plus ounces a day, it's thought to cause a small amount of bleeding from the GI tract that you may not be able to see in their stool, but that inflammation is there and causing that. So, the combination of those 3 things very commonly leads to iron deficiency with or without anemia in young children.

Specifically to our youngest children, within the first year and just beyond the first year, the ones that are at the highest risk of iron deficiency are those children that were born premature as newborns get most of their iron in the third trimester. So, children born premature are at a very high risk of developing iron deficiency and they should be monitored very closely. And it's also important to remember that those children under 1 year of life that are predominantly breast fed, so if they get more than 50% of their nutrition from breast milk, they need to be started on iron supplementation around 6 months of life. If not, they're at a very high risk of developing iron deficiency.

In older children, adolescents, the main demographic of patients that we see are adolescents who are undergoing their menstrual cycles. So, it's very common for those that just start having their menstrual cycles to have heavier bleeding the first couple of years after menarche starts and they're at very high risk of developing iron deficiency from blood loss. The other thing about adolescents is that, as I come to learn more and more, is that their diets aren't great either. It seems that a lot of adolescents that I ask who I'm treating with iron deficiency, a lot of them eat 1 or 2 meals a day and most of the food that they tend to eat are not iron-rich foods either. So, it's important to address both the dietary and the blood loss in the adolescent time period. But young children and then the adolescent, especially adolescent females, are at the highest risk of developing iron deficiency.



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Nisha Rathore, MD: Now, when we think about anemia, there are so many different labs we can order, when we think about anemia in general. Specifically for iron deficiency, say that we order something like an iron panel. There's a number of things coming back on that panel that are very nuanced and mean very specific things about how much iron a person has. Can you fill us in on what you feel like is pertinent to order and how that can be applied to our pediatric population?

Clay Cohen, MD: Honestly, I feel like diagnosing iron deficiency can be way more complicated than it needs to be. Often, people will order iron panels that has a set of 4 or 5 different lab values, but the main thing that we use, really the only thing that we use is a ferritin. So, in the vast majority of children, a ferritin is enough to check for and rule out iron deficiency. Different people or different centers will use different cut-off, but in general a cut-off of 20 is a good place to start. If you have a ferritin above 20 without symptoms, then you're likely iron sufficient. If you have a ferritin under 20, then you have iron deficiency, regardless of any of the other values. And a ferritin under 20 should be treated with iron. A lot of different labs will put different normal values on ferritin and a lot of labs will say a ferritin of 10 is normal, a ferritin of 15 is normal, but just know if you see a ferritin value less than 20, with or without the presence of anemia, that's iron deficiency and should be treated.

The other things that come in the iron panel which can come into play and can be helpful for some, especially if it's a child with chronic inflammation or some chronic illness, that the ferritin can be elevated in the setting of inflammation or physiologic stress and some of those other values can help interpret that ferritin, but for the most part, for most healthy kids, or most without underlying chronic inflammation, the ferritin is all you need in terms of screening for iron deficiency. So, I would suggest, and in my practice, I very rarely order the full iron panel. I get a ferritin and go from there and I think that make things a lot more simple and less confusing in terms of diagnosing iron deficiency. We commonly get calls from pediatricians with a confusing iron panel picture, you know, the iron value says this, the transferrin saturation says this, they seem to contradict, but then we always focus on what the ferritin is. So, I would focus on that value and kind of put the others aside for the majority of children.

Nisha Rathore, MD: It sounds like the ferritin is really quite an important marker. If, for example, we have a patient and we're looking at some labs and, for whatever reason, we

don't have access to a ferritin, if we're only looking at a CBC, are there certain markers on the CBC, does it look a certain way if we're either starting to become iron deficient or we're already there?

Clay Cohen, MD: If you have a patient that you feel is particularly high risk for having iron deficiency, whether they're in 2 of those demographics, being a young child or a female adolescent who's having heavy menstrual bleeding, you have a high suspicion for them having iron deficiency, a CBC that has a low MCV or demonstrates microcytosis is very likely to be representative of iron deficiency in that patient, even if they do not have anemia, if their hemoglobin is normal. You can have—I would say the majority probably have—iron deficiency without anemia, so having a normal hemoglobin doesn't rule out iron deficiency. A low MCV can be very suggestive of that. Things like a high RDW, which is the red cell distribution width, goes along with iron deficiency as well. And then, it's also associated with an elevated platelet count. So, if you have a patient that you feel is at high risk, they have a low MCV, that's probably enough to empirically start treating iron and then, if you notice elevated RDW, high platelet count, those can go along with it as well.

Nisha Rathore, MD: So, say that we have a patient whose CBC is showing that they're anemic. They're in a certain age group. They're in a certain population. We're going to assume, okay, this is probably iron deficiency anemia. We go ahead and send that ferritin or we send labs and they really come back mostly normal. At that point, what else do you feel like, as a pediatrician, we should be thinking about and what other work-up would you recommend doing?

Clay Cohen, MD: If you're concerned for iron deficiency because the patient has anemia and then the labs come back and it doesn't look like iron deficiency at all, the ferritin's like 60, they might not be microcytic, maybe their MCV is normal, I think you have to broaden your differential diagnosis beyond the anemia being caused by iron deficiency. I think the next best thing to do and, as a hematologist we obtain these with all of our CBCs, is to get a reticulocyte count. The reticulocyte, as you know, measures the production of newly made red blood cells which is what a reticulocyte is. So, if you have an anemia, and you get a reticulocyte count, that can kind of push your likely differential diagnosis one way or another. For example, if you have an elevated reticulocyte count in the setting of anemia, that's going to tell you that their body is actively trying to replace the red blood cells that are being lost and their bone marrow is doing its best to pump them



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out. So, that would suggest ongoing hemolysis which there can be a number of different causes of hemolysis, or it can be indicative of maybe chronic blood loss and those should be investigated. If the reticulocyte count is very low in the setting of anemia or if it's normal, a normal reticulocyte count by the range that you're given in light of anemia, then that could suggest that there's something going on with the bone marrow itself. It could be nutritional, obviously not from iron deficiency in this case. There's some other things, like folate deficiency, B12 deficiency, or it could be a bone marrow problem itself in producing red blood cells. So, the reticulocyte is always going to be very important in terms of how to interpret anemia, especially if you rule out iron deficiency. And that's something, as hematologists, we do a lot, and of course we'd be happy to do that, but if you were able to obtain one, then that can really help move towards getting to the correct diagnosis.

Nisha Rathore, MD: Now let's take a patient that's a little bit different. They come in anemic, we do iron studies, it's confirmed. They do have iron deficiency anemia. Tell us, in those cases, talk to us about what our treatment options are. Are there particular details about dosing or frequency that you feel would be helpful for us to know?

Clay Cohen, MD: So, to start with, iron should not be dosed more than once a day. The maximal frequency that iron should be given is once a day and the reason for that is that dosing iron more than once a day actually ends up being counterproductive and the intestinal absorption of the iron decreases when you give it more than once a day. The reason for that is your liver makes a molecule called hepcidin whose job it is is to limit the amount of iron absorption and it's directly influenced by how much iron you take in. So, just remember, don't ever dose iron more than once a day. Once a day is the way to go. You can also even consider, if someone has more of a mild iron deficiency, if they're having difficulty taking the iron, you could dose them every other day and the absorption is probably even better than dosing it daily. Obviously, we do daily dosing for the majority of our patients, but maybe if someone has a very mild iron deficiency, maybe they're towards the end of their treatment course and you just want to get that ferritin over that 20 threshold, doing something like every other day might be a good choice for them as well.

Then, in terms of the dose that we do once a day, so the general dose is 3 mg/kg of elemental iron, dosed once a day. That's the most true for young kids and then for adolescents, we tend to use the standard . . . the standard

iron pill has 65 mg of elemental iron and for the vast majority, one 65 mg pill once a day is the correct dose to treat their iron deficiency by oral medication. Of course, iron, especially liquid iron, tastes awful to kids and it can be very hard for kids to take the medication, especially in liquid formulation. So, a lot of parents have difficulty with that.

It's important to know that iron should be given on an empty stomach, as well, as its absorption is blocked by food, and that its absorption can be enhanced with vitamin C, like in orange juice. So, often we'll recommend for the parents to administer iron on an empty stomach, with orange juice, which may help the palatability of the iron liquid itself. And then it can cause constipation and other GI upset issues, so we will always advise them to maybe get a bottle of Miralax or some other stool softener at home that they can have available if that starts to become an issue. And if a kid has problems with chronic constipation, then it's probably best to just kind of start the stool softener along with the oral iron medication off the bat to prevent that from being an issue.

In our adolescents that have more significant iron deficiency anemia, sometimes we'll start them with 2 of the 65 mg iron tablets, once a day, and, as their symptoms improve, then maybe back it down to 1 tablet once a day. But if we're doing 2 tablets, we still do it once a day. In general, iron is needed to be taken for at least 3 months to replete the iron stores and there's an expected response, if you have a kid that either you're concerned about them taking it or you're concerned about compliance or you're concerned about their response, there is an expected response that you can monitor. So, after you start the oral iron, in 1 week you expect to see an increase in their reticulocyte count. So, if you start someone on oral iron and you see them back a week or 2 later because you're particularly concerned about them and the reticulocyte count has not budged, that's probably a sign of either they're not taking it or they're not absorbing it. In 1 month, you would expect to see a near normalization of their hemoglobin if they were anemic. If they're really severely anemic, they might not get totally back to normal, but pretty close. At least their hemoglobin should have increased by 2 to 3 grams and then the ferritin should normalize by about 3 months. In reality, it seems to take a little bit longer than 3 months in many, but in general that's the timeline of treatment. So, if you're going to be treating a kid with iron deficiency, counsel them that you're going to need to take it every day on an empty stomach once a day for at least 3 months.



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Nisha Rathore, MD: Wow, okay. And if we have a kid that you kind of mentioned that we know they're iron deficient, we're doing a trial of iron, we're rechecking those labs and we're really not seeing much improvement. Maybe, like you said, there's an issue with absorption, maybe it's noncompliance or we have a young kid who, even if we're doing the every-other-day dosing, they're spitting it out, they're vomiting, for whatever reason we're just not tolerating oral iron, what should we be thinking about in those cases? What could we, what would be next steps there?

Clay Cohen, MD: One potential option would be to change the iron formulation. There are some actually over-the-counter supplements, there are iron polysaccharide complexes that are more palatable than the traditional ferrous sulfate. So, often I will try to transition to one of those products at the same dose, 3 mg/kg. Those will take a little bit longer to reach the normal ferritin threshold. They've been demonstrated to take longer than the 3 months, but they still are effective if they're taken appropriately. But, for many in our practice, they're just not able to get that ferritin to a normal value or they're not able to tolerate it or, especially with a lot of adolescents, they just don't take it. They forget to take it, it's hard for them to remember to take it. So, we commonly administer iron via intravenous route to those patients. So, in general, I think of giving IV iron to either a young kid or an adolescent if they've been on oral iron medication for 3, 3-plus, 6 months, and they haven't repleted their iron stores. At that point, I tend to move towards giving iron through an IV. Also, if it's just clear up-front they're not going to take the iron medicine, nothing can be done to get the kid to take it, then that would be worth a referral to hematology for IV iron. So, I think this is one really important and good indication for referral to a hematologist to administer IV iron for those that are refractory to oral iron medication which is usually because they have difficulty taking it, but even still if they just can't get their ferritin up to normal, then yeah, that would be worth referring so you don't have to keep them on oral iron for months to a year plus because, at that point, it's just not going to work.

Nisha Rathore, MD: That's really helpful to know, in the setting of iron deficiency, when to refer. That's really helpful. And you kind of mention, you know, we talked about CBCs in the context specifically of iron deficiency anemia, but let's talk a little bit more about CBCs because, really, CBCs, when you're trying to interpret them for the pediatric population, it can be a little bit nuanced, it can be a little bit complicated. When we get CBCs back, oftentimes

there are numerous things flagged as abnormal. Are there things on a CBC that you look at as a hematologist and you kind of say, you know, I don't think we need to work this up right away, I don't necessarily think that they need hematology right away, you actually feel a little bit more reassured. Are there any things like that?

Clay Cohen, MD: One common finding on a CBC which kind of plays into what we were talking about is an elevated platelet count or thrombocytosis. So, a normal platelet count is between 150,000 to 450,000, and having a platelet count above that in children is, quite frankly, very common. Elevated platelet counts are almost always secondary. There are primary causes of thrombocytosis, but in children those are extremely rare. So, causes of an elevated platelet count in children, it's usually 1 of 2 things. The most likely thing is inflammation from a recent or current infection that can . . . platelets kind of tend to act as a marker of inflammation. So, if you get a CBC on a sick child, you're likely to see an elevated platelet count. And there's really no specific platelet number that, for us as a hematologist, gives us like certain pause or is like a threshold that we need to do something, but a platelet count in the 500, 600, 700, 800 range in the setting of an illness or a recent illness, there's not going to be anything to do in that circumstance. Other than repeating it, maybe, when they're well in a couple of weeks to months.

The other common cause of an elevated platelet count is iron deficiency. So, if it's a well child and their platelet count is elevated to the 600s, you don't really have another explanation, I would definitely check a ferritin. And if that's low, then it's probably likely to resolve with resolution of the iron deficiency. But we commonly do get referrals for elevated platelet counts and outside of platelet counts over 2, 3 million which we very rarely see, often it's due to most likely inflammation or iron deficiency. So, repeating that while they're well is probably the way to go.

Another common thing that is seen on the blood count is a decreased white blood cell count and that can be from a number of different reasons. It is particularly worrisome to many when it's in the setting of a decreased neutrophil count as well. Obviously, as a hematologist, we take neutropenia, especially marked neutropenia, very seriously, so I'm not trying to brush that aside, but mild reductions in the white blood cell count, mild reductions in the absolute neutrophil counts are most commonly from recent infections, recent viral infection, recent antibiotics. These can cause reductions in the white blood cell count and neutrophil count. So, it's always important to know the



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child's count, and this is assuming that these are isolated values. You know, if a kid comes in with decreased white blood cells, hemoglobin and platelet, that's a different story in and of itself. But a mildly decreased white blood cell, maybe with a mildly decreased neutrophil count, in and of itself isn't necessarily concerning, especially if the child does not have a marked infectious history. If they've only had very common childhood infections and no serious bacterial infections, then simply repeating the blood count when they're doing well and off antibiotics is probably the way to go. However, if they've had a low white blood cell count, they've had a low neutrophil count their entire lives, then maybe that warrants a little bit more of a discussion. But there is also another factor that could be causing a reduced white blood cell and/or neutrophil count that's important to know as well and this is called the Duffy-null phenotype. So, in those with certain ethnic backgrounds—and it's very predominant in those with African backgrounds—they will lack the specific Duffy proteins on their white blood cell and their red blood cell surface which we do tests for in our hematology clinic. And if they lack . . . there are 2 Duffy-null proteins we check for and if they lack both of them, then their white blood cell and their neutrophil counts are going to be lower than the common-used ranges that are in most CBCs. So, in individuals of those specific ethnic backgrounds, that's an important consideration and it may be worth referral, especially if there's a lot of anxiety over their reduced counts, just to check and make sure that that's the reason why. But often, in those certain ethnicities, a Duffy-null phenotype is the cause for their slightly reduced white blood cell and neutrophil count and it's not associated with any increase in infection or malignancy or really anything else other than having slightly lower numbers than others.

Nisha Rathore, MD: When we get these CBCs, they come with these kind of range values with every marker on there. As pediatricians, can we take those ranges of normal values at face value? Do they apply to our pediatric patients?

Clay Cohen, MD: This is an important question because we'll often get referrals for a child with anemia with a hemoglobin of, you know, a 2-year-old with a hemoglobin of 10.8. So, a lot of labs that clinics use apply adult normal ranges to the CBC values which, maybe for an older adolescent, is fine and is accurate, but for children, adult values are not the norm. So, in a 2-year-old, a hemoglobin of 10.5, that is normal but if you apply that to an adult normal, then it's going to be anemic every time. Similarly, if you have a normal value for an adolescent male which they are expected to have higher hemoglobins, 13, 14, 15, that's

going to be vastly different from a newborn. So, especially with hemoglobin values, it's always important to know that the specific normal range you're using is age specific. And there are a number of different resources that are easily obtainable online, but I think that can cause a lot of angst for families to hear that their young child has anemia when, in fact, it's not anemia. So, whenever you're reviewing your blood count, always make sure that the reference range and the normal range you're using, especially for hemoglobins, are age appropriate.

I also tell my patients that they should expect to have some red flag abnormalities on their blood count. It's exceedingly rare and it almost seems weird, when I get a blood count and there's no red flags outside of the normal ranges. These normal ranges are statistical norms and all of these values, for all of us, fluctuate as the day, week, year goes on and so you have to take some of these normal values, these normal and abnormal values, in light of what's going on with the kid and in light of what the kind of important indexes that we see are. So, I think that's another important thing to remind your patient families when you're getting a blood count is there's likely to be some abnormalities that the lab tells you about, that doesn't necessarily mean that there's a problem. But a lot of times, just the presence of a red flag on a CBC definitely causes a lot of anxiety for families.

Nisha Rathore, MD: Now you touched on something called the reticulocyte count when you were talking about iron deficiency and it seems like that's a really important marker of a CBC when you're really trying to understand where is this anemia coming from. Can you kind of fill us in, maybe it's a situation that isn't iron deficiency, as a hematologist, when you're looking at that retic count, how are you using that to kind of help you figure out what may be going on with the anemia?

Clay Cohen, MD: I think 2 different scenarios where the reticulocyte count is very important is a situation of someone that has chronic hemolysis, whether it's from G6PD deficiency, hereditary spherocytosis, both of those things will be heavily prominent in the family history. So, checking a family history, of course, is going to be very important in those cases where the reticulocyte count is chronically going to be high. So, reticulocyte count in that situation can be super helpful, whereas there's kind of a transient and acquired disorder called TEC or transient erythrocytopenia of childhood, I have to say that slowly, where essentially it's a brief and acquired pure red blood cell aplasia, probably from a viral infection. I don't think it's



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truly known as to why it's happened, but for a couple of weeks, in young children, their body can just kind of stop producing red blood cells. And the reticulocyte count will be essentially zero and their hemoglobin will drift down with it, but they usually look and are acting fine. But they can have some very low hemoglobin values. So, seeing a very low hemoglobin value in the setting of a reticulocyte count of zero, that's very different than seeing their reticulocyte count that is way higher than the norm. So, getting reticulocyte count along with a CBC is very important to differentiate between those 2 situations. And those with hemolysis, you would expect to have some descriptions of jaundice, a family history of jaundice, maybe individuals have had their spleens taken out or gallbladders taken out, so that's going to be important to know as well. But getting that reticulocyte count can definitely help you differentiate between other causes of anemia.

Nisha Rathore, MD: We talked earlier about things on the CBC that, for you as a hematologist, are a little bit reassuring. You don't get super-worried when you see certain abnormalities. Let's flip that coin and tell us, as a hematologist, when you look at a CBC, what makes you say uh-oh, I think we do need to work this up? What patterns on a CBC or what markers kind of make you feel a little bit concerned?

Clay Cohen, MD: I'll start with white blood cell count and neutropenia. I think that a truly reduced neutrophil count, an absolute neutrophil count below 1,000, below 500, below 200 definitely gets your attention because the risk of infection goes up as the neutrophil count declines. An important thing to know is if you just have 1 blood count in front of you is have they had previous blood counts done. It's, one situation, if you have a 5-year-old with a reduced neutrophil count but they've had an annual blood count and all of their white blood cell counts and neutrophil counts have been normal to date, that's reassuring. It's, another situation where all of their blood counts have demonstrated a low white blood cell count and a low neutrophil count, then it makes you wonder could this be some sort of genetic or congenital neutropenia that needs to be evaluated and worked up. So, the presence of the abnormality being consistent and demonstrated over time, that's definitely a red flag that needs to be investigated rather than just 1 isolated value.

Also, just the trends. If an individual has a neutrophil count that is low and has maybe had it sporadically in the past, but has had plenty of normal ones as well, that's important to take into account as well. Also, some maybe mild

abnormalities that are persistent on a blood count, like a mildly reduced platelet count for example. If a child has had a slightly reduced platelet count consistently over time, I mean that may be an indication of an inherited platelet disorder as well. So, I think demonstrating the abnormality consistently over time is something that likely needs to be worked up. Also, if it is declining over time, then that needs to be worked up as well. And then, of course, if it goes along with symptoms. So, in a child with an isolated reduced platelet count, in the absence of bleeding symptoms, is likely not as worrisome but if you could isolated reduced platelet count with bleeding symptoms, they're having nosebleeds, they're having purpura in their mouths that are concerning, then that is something concerning that needs to be treated. So, always remember to couple the numbers with the patient as well.

Nisha Rathore, MD: That's really helpful to know. I think it's helpful to hear when a hematologist is worried about something. Now, something you just kind of touched on is abnormal bleeding and I think that that topic really does come up in the general population a decent amount. Sometimes, a parent will come in and say, I feel like my child is bleeding for too long when an injury happens or I feel like the volume of blood seems too much, given the context of the injury. Tell us what do you feel like is abnormal bleeding and when do you think it's appropriate to refer to hematology?

Clay Cohen, MD: That's an important question and I can start with one of the most common reasons that we have patients referred to hematology which is heavy menstrual bleeding. So, I mentioned that it's very common for adolescents who are menstruating to have heavy bleeding, especially after the first couple of years of menarche. And there are a bunch of different definitions for what exactly heavy menstrual bleeding means, a lot of them are unhelpful. The most important definition is if it's a degree of bleeding that's interfering with their quality of life. If they're having menstrual cycles that are lasting longer than 7 days, if they're having to change their menstrual products frequently, if they're bleeding onto their clothes or bedding, these are red flags that should be evaluated. In these situations, it can be helpful to refer menstruating individuals that are having reduced quality of life because of their menstruation to hematology for a number of reasons. One is to treat and deal with their iron deficiency. It seems that this population really benefits from IV iron because they are adolescents, they often have issues with compliance with oral iron and they often get a lot of benefit



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from a dose of IV iron. So, there's 1 potential reason to refer them.

Another is a significant amount of these individuals that are having heavy menstrual bleeding will end up being diagnosed with a bleeding disorder, with the most common being von Willebrand disease. So, for those 2 reasons, I think if someone is having heavy menstrual bleeding, interfering with their quality of life, referring them to hematology is a good idea.

Another common scenario is nosebleeds. That's a common referral that hematologists get and that can maybe be a little tricky because it seems that a lot of kids will end up having nosebleeds in the middle of the night and I think, you know, when you bleed and the blood hits a surface, the blood spreads and I always hear that it looked like a murder scene when I went into their room. That's what parents always say, it looked like a murder scene when I woke them up in the morning. So, that can be a little bit tricky, but the red flags, to me, is if the bleeding is happening frequently, more than once a week, the bleeding is lasting, meaning there's actual bleeding that's lasting longer than 10 to 15 minutes. Another red flag is if these nosebleeds are being accompanied by iron deficiency. If they're bleeding so much that they're bleeding more than they're able to supplement with dietary iron, that's a red flag that should be referred. If it's sporadic and it stops with local pressure and they're not anemic and they're not iron deficient, if there's no family history of abnormal bleeding symptoms, that's another important thing, you know if a kid has a history of frequent nosebleeds and everyone in their family has nosebleeds, someone bled with delivering a child, if there's red flags in the family history, then that would warrant referral as well.

Another thing is bleeding after surgeries. That can be a little bit, a little tricky as well. I will say that it's always reassuring to know if a child has gone through a surgery before and has not had a bleeding complication. A big one is a tonsillectomy, an adenoidectomy. If a child has gone through a tonsillectomy and has not had bleeding complications, that is very reassuring to me because that is a procedure that a lot of children have bleeding complications, it can have delayed bleeding complications with, even if they don't have a bleeding disorder. So, that's reassuring. Same thing with circumcision. If I see a child that has had a circumcision, did not have bleeding complication, that gives me a lot of reassurance that maybe the likelihood of a bleeding disorder may be less. It doesn't rule it out, but it maybe makes it less. So, if they've had a previous surgery,

how they dealt with that surgery, how their hemostatic system dealt with that surgery is also very important.

We will sometimes get referrals for easy bruising and that's a little bit, that's a little bit tougher. As a hematologist, it feels like every child I expect to be covered with bruises over the front of their legs. So, bruises covering bony prominences, over your leg, over your elbow, that is normal and that does not warrant, in my opinion, an evaluation for a bleeding disorder. The bruises that get hematologists' attention a little bit more is bruising over fleshy areas, their cheek, over their buttocks, over areas that are not related to compression against the bone. That maybe is a little bit more worrisome and maybe warrants a work-up, but the common kid bruising, I know it's very concerning to a lot of parents, but bruising over bony prominences don't need to be referred to a hematologist.

Nisha Rathore, MD: As pediatricians, when we're trying to understand abnormal bleeding, is there something that we can obtain from the history that you feel like is helpful to kind of start the process of differentiating is this normal vs abnormal?

Clay Cohen, MD: I mentioned it, but I think the family history is the most important. We treat a lot of individuals with bleeding disorders and one, for example, von Willebrand disease, it is very common to talk about, especially the women in the family, if they have had heavy menstrual bleeding and it's important to define what heavy menstrual bleeding is because, in some families, that's just normal. If the families have von Willebrand disease in their family, heavy menstrual period is a normal period to them. So, defining that. Is it lasting more than 7 days? Have you needed iron infusions before? Have you had iron deficiency your whole life? These sort of things. Then that can be, that can be very helpful in differentiating the likelihood of the presence of a possible bleeding disorder.

Nisha Rathore, MD: Say that I have a patient that comes in, I'm worried about abnormal bleeding due to maybe something that came up in the history or maybe something on exam or maybe I just have a parent that's really concerned. Is there some really high yield testing that I can do from the get-go that would help start the process of figuring this out?



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Clay Cohen, MD: That's a good question, and the often initial frontline tests that are done to screen for a possible bleeding disorder are coagulation tests, like the prothrombin time or the PT or the PTT, and a lot of people will get von Willebrand testing as well. These are definitely first-line tests that we do as well, as hematologists, if we're suspicious of a bleeding disorder, but I will say that it is known that a lot of send-out labs, due to necessary processing delays, often those labs will come back falsely abnormal. So, we often will get referrals for a child that is having nosebleeds, for example, that had a PTT that might be slightly high or a von Willebrand testing that was slightly low at a send-out lab and they're referred to us and the parents are worried, of course, and we repeat the tests, we're fortunate enough to have a coagulation lab tied to our clinic. We send the test, it's run immediately and is normal, and then we brush aside the initial abnormal values. So, I guess what I would say is that if you have a high enough suspicion that someone may have a bleeding disorder, if there's a family history, if there's definitely abnormal bleeding, then maybe it would be worth simply referring them to hematology rather than doing some of these outside coagulation labs that are prone to coming back abnormal and maybe saving the potential angst that goes along with that. That being said, if you do the PT, the PTT, even if you do von Willebrand testing, if they're normal, that is reassuring. The von Willebrand testing itself is reassuring, but those other tests, if you have a high enough suspicion for a bleeding disorder, it's probably not enough to rule it out. So, it may be worth just referring to hematology to kind of do the testing of their hemostatic system to kind of putting that to bed. So, I guess, bottom line, doing some of these send-out coagulation tests can be helpful, but they can also be very problematic because of the high rates of falsely abnormal tests.

Nisha Rathore, MD: Okay, well Dr. Cohen, thank you so much for your insights today. It's been so helpful to hear you talk about these big hematology topics that come up and I think discussions like this, between a hematologist and a general pediatrician, are so important to help kind of keep everyone on the same page. I know both of us in our practice are practicing evidence-based medicine, we're trying to use evidence-based resources to take the best care of our patients. In your opinion, are there resources that you like to use, that you think would also be helpful for a general pediatrician that we both could use to tackle some of these topics that come up?

Clay Cohen, MD: I think a lot of different pediatric societies have kind of evidence-based or expert-consensus guidelines on really everything, but like iron deficiency, for example, the diagnosis, management and treatment of it. The American Academy of Pediatrics has a guidance and I believe they'll be coming up with an updated one soon. And then the same thing for us hematologists dealing with bleeding disorders, the American Society of Hematology has a number of different guidelines that are very helpful for us. I think one of the things that I did mention that will be important for any pediatrician to have quick and easy access to is the AH normal values that are seen in a CBC. So, maybe have that easily available. I know that there was a *Pediatrics in Review* article that covered a CBC that has a table on age-appropriate values for hemoglobin, so having a table like that easily available will be really helpful in interpreting some of these labs that you're obtaining.

Nisha Rathore, MD: I feel like, as a pediatrician, there's a frontline role of getting the history, doing the initial work-up and then really getting to that decision point, do we need to refer to a subspecialist or not. In the situations where we feel like we do need some more expertise, open communication with a subspecialist is so critical, not just to kind of handle the details of the case, but also to think about what is the plan for this patient going forward. In your experience as a hematologist, how do you prefer to communicate with the physicians that you share mutual patients with?

Clay Cohen, MD: Honestly, I think whatever works best for the pediatrician. It's their patients and they're the ones that have the initial concerns and are sending them in. So, I commonly talk to pediatricians on the phone. Within our medical records system, I'll commonly be sent messages and we'll communicate that way. I think whatever works best for each provider. As long as there's open communication, professional communication, I think the more communication, the better. So, yeah, I'm always happy to talk with any general pediatrician about any issue. I commonly will get calls about some of the things that we talked about and are able to reassure about whatever the initial worry was actually is a normal thing. So, yeah, it's very important to have open communication between subspecialists and those that are seeing the children up-front.



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Questions and Answers

Are there any clinical red flags that should prompt immediate referral to a hematologist for iron deficiency anemia in infants under 12 months of age?

Clay Cohen, MD: I think, if you have a severe iron deficiency, so much so with a significant anemia, especially if it's causing symptoms, if it's causing poor feeding, lethargy, if it's causing them to be too sleepy, and if that's affecting their growth, then yeah I think they should be referred and maybe a more up-front IV iron rather than trying a course of oral iron would be important. So, I think it depends on the severity. If it's a very severe case of iron deficiency in a very young child, I think quick referral to hematology, if you have access to one quick, is important.

How can pediatricians ensure an infant is getting enough iron during feeding transitions in that first year?

Nisha Rathore, MD: So, it sounds like maybe when they're starting solids, if they're doing baby-led weaning or maybe if they're exclusively breastfeeding.

Clay Cohen, MD: That's a hard one for sure. I think it starts with limiting the amount of cow's milk that they're taking in. Honestly, a max of 2 or 3 cups a day of cow's milk. I think that's an important starting point. And then otherwise, as I'm sure many recommend doing, just offering a variety of iron-rich foods. Iron-rich foods . . . well, iron comes in 2 different formulations, there's hem iron which is in meats mainly, well exclusively, really any meat, red meat, chicken, fish, and then there's non-hem iron which is in green vegetables, which is in beans, lentils. So, trying to have foods with either source consistently and offering a variety is important. But I think just offering the iron-rich foods, limiting cow's milk is a good way to start.

Can you walk us through your approach distinguishing between iron deficiency anemia and other causes of microcytic anemia in adolescent patients, particularly when dealing with athletes or patients with heavy menstrual bleeding?

Clay Cohen, MD: The differential diagnosis for microcytic anemia, iron deficiency is going to be at the top, but thalassemia is a hemoglobin disorder that is also in the differential. Another thing that could be possible, probably much less likely in adolescents, is lead toxicity which does correlate with iron deficiency. But, yeah, honestly iron deficiency and thalassemia, those are the top. So, if you

have an adolescent who is microcytic and you've ruled out iron deficiency, the next thing to consider would be to do a hemoglobin electrophoresis. The family history is going to be important there, but that can help you understand the underlying potential thalassemia. But then it's important to know that a normal hemoglobin electrophoresis could be seen in someone with alpha thalassemia trait, for example. So, if you have an adolescent with microcytosis, you've ruled out iron deficiency with a ferritin and you do hemoglobin electrophoresis, that can either identify like a beta thalassemia or, if it's normal, likely indicates an alpha thalassemia trait. If their hemoglobin is normal, it's probably less likely to be clinically significant to the point that they need active treatment for it.

We see a lot of alpha thalassemia in our practice. Is that something that we should refer to hematology for or not?

Clay Cohen, MD: I think it depends on the level of concerns or the amount of questions that the family has. Oftentimes, we will see a child that has microcytosis and we rule out iron deficiency. We do the hemoglobin electrophoresis. If that's normal, it's most likely due to alpha thalassemia trait. Many families feel like that's a disease, they get very anxious about that and that anxiety alone I think warrants a hematology referral. It's probably just going to be a 1-time discussion and it's probably nothing that needs to be routinely followed up afterwards, but if there is enough family anxiety, I do think it's worth it because other individuals in the family are likely to be affected as well. So it can probably help the whole family out by having a discussion with hematology. I think that's an okay reason to refer.

Our next listener is wondering about the dose and the frequency of IV iron when you're using that to treat maybe refractory iron deficiency anemia.

Clay Cohen, MD: We use a couple of different formulations. Our preferred has recently been ferric carboxymaltose because you can give it over a short amount of time and it's tolerated very well without really any allergic reactions. And then the other one that we give, if we don't have the ability from insurance approval of giving ferric carboxymaltose, is iron dextran, and that does have some allergic reactions, so you have to premedicate with steroids and it goes in over a couple of hours. General approach for how often to give IV iron, often we'll tell a family that this shouldn't be a recurrent thing that kids are needing or adolescents are needing. The goal is to get them up to a normal value. In individuals with iron deficiency without anemia, typically 1



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dose of IV iron will be enough to replete their iron stores. If they have a significant iron deficiency causing anemia, especially if they're an adolescent, it might take 2 doses, separated by at least a month, to get them replete. And then I'll typically follow them a couple of months afterwards to ensure that their ferritin has normalized and then I often will follow them about 6 months after to make sure that the ferritin hasn't drifted down again. So, in terms of the actual dose, the max dose we tend to give is about 750 mg of each of those formulations.

Is there an online tool where we can enter a CBC and gain insights into how to interpret it or is there another similar tool?

Clay Cohen, MD: Maybe I should figure out how to do that. I don't know of one, honestly, because I guess I'm the one, or we, as hematologists, are the ones to interpret that, but maybe we can get together and develop one. So, to answer your question, I honestly don't know of one because I think, if people saw me using a CBC tool, they would, yeah, they would fire me as a hematologist. So, there may be one; I'm just unaware.

What is the indication to investigate a hemolytic anemia in a neonate that has severe hyperbili?

Clay Cohen, MD: Hyperbilirubin anemia can be because of a number of different causes. If it's in the presence of a positive DAT, then obviously you have to be worried about ABO or RH incompatibility and that may need specific therapy, IVIG or steroids and other therapies. If there is a family, if there's a strong family history of hemolysis, hereditary spherocytosis, membrane disorders like hereditary spherocytosis can be worse in the neonatal time period. So that's important to know. I would say if you have significant hyperbilirubin anemia that's accompanied by a significant anemia, then that does warrant evaluation by a hematologist for an underlying cause of hemolysis as the cause of hyperbilirubin anemia.

Nisha Rathore, MD: On behalf of the Annenberg Center for Health Sciences, myself and Dr. Cohen, thank you for taking time to learn with us today. We're grateful for your attention.

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