# English Transcript

Interview with Dr. Christopher Denton

**Dr. Eyal Ben-Isaac:**

Hello and welcome to the Perspectives on Pediatrics podcast. I am your host, Dr. Eyal Ben-Isaac, recording from Children's Hospital Los Angeles. I had the pleasure of talking to Dr. Christopher Denton. Dr. Denton is a Pediatric Hematologist at Children's Hospital Los Angeles and an Assistant Professor of Pediatrics at the USC Keck School of Medicine. I got to chat with Dr. Denton on the topic of anemia, a relatively common diagnosis we see in the office setting and a concern often brought up by parents.

**Dr. Eyal Ben-Isaac:**

Dr. Denton did a great job of reviewing the diagnosis and evaluation of anemia and how to use clues within the complete blood count, or CBC, to help us figure out the etiology of the anemia. This was a very informative and clinically applicable session for all of us who care for infants, children and teenagers. Here's my conversation with Dr. Denton.

**Dr. Eyal Ben-Isaac:**

Hello, everyone. Today we are here with Dr. Christopher Denton from Children's Hospital Los Angeles. Welcome, Chris.

**Dr. Christopher Denton:**

Thank you. Good to be here.

**Dr. Eyal Ben-Isaac:**

Thank you for joining us and teaching us about anemia. I thought maybe we could start with a case to help our discussion. A two year old comes in for a well-child exam. There are no complaints and the child has a normal exam. A routine point of care hemoglobin comes back at 9.7 grams per deciliter. Maybe we could start by going over the average or normal hemoglobin at the various ages and when you suspect we need to do further evaluation.

**Dr. Christopher Denton:**

Sure. Hemoglobin does vary by age. So it is important to consider that first when evaluating for anemia. Newborns are relatively polycythemic, with average hemoglobin around 18 and the lower limit of normal around 13. And then as erythropoiesis switches from primarily fetal hemoglobin, or hemoglobin F, to adult hemoglobin, or hemoglobin A, the decrease in oxygen affinity causes a shift in the hemoglobin oxygen dissociation curve, leading to higher oxygenation in the tissues, which is necessary after the newborn takes its first breath and starts using its pulmonary circulation rather than the placental circulation to oxygenate the red blood cell. The higher tissue oxygenation leads to a drop in erythropoietin release due to negative feedback, causing a trough in hemoglobin production from 5 to 9 weeks of life. This is called the physiologic nadir.

**Dr. Christopher Denton:**

So hemoglobin reaches a minimum of 9 to 10 around two months of life, and then slowly trends up to be at least 10 by six months of life. And then 11 by one year. Hemoglobin sits in the 11 to 12 range until school age, or about six years old. And then the minimum is 12 by 11 years of life or pre-puberty, and then a range of 13 to 16 in the post-pubertal adolescent. Based on these reference ranges, I would say that the child in our clinical case has mild anemia.

**Dr. Eyal Ben-Isaac:**

Thank you for reviewing the physiologic nadir and the progression of the hemoglobin as children get older. I know there are many ways to discuss anemia. For example, based on the MCV or based on production or destructive processes or based on age. Which do you like best and how do you break down the etiologies for us?

**Dr. Christopher Denton:**

Well, mean corpuscular volume, or MCV, is an important means of describing anemia and helps initially differentiate various etiologies. MCV also changes with age, with normal being 80 to a hundred at birth, then drifting down to 70 to 90 by one year of age, then 75 to 90 by two years old. And then the normal range drifts up to 80 to 95 by pre-adolescence and stays pretty consistent after that. Microcytic anemia, or low MCV, is most likely iron deficiency or a thalassemia trait. Iron deficiency doesn't present until after six months old, unless the child was born prematurely, because the fetus gets plenty of iron in the third trimester of

gestation. So microcytic anemia in an infant less than six months old is more concerning for a thalassemia trait.

**Dr. Christopher Denton:**

Iron deficiency is otherwise very common in a child who is transitioning from breast milk to solid foods, and especially in a child who drinks a lot of cow's milk, which not only takes away calories from more iron rich foods, but also can cause some intestinal irritation that decreases iron absorption. Iron deficiency is less common in a school-aged child, though. And unless iron deficiency is diagnosed in a post-menarcheal girl, occult GI blood loss or intestinal malabsorption is of greater concern.

**Dr. Eyal Ben-Isaac:**

What are some of the important macrocytic causes of anemia that you think about?

**Dr. Christopher Denton:**

Macrocytic anemia with high MCV can be due to poor red cell production or increased destruction. Nutritional deficiencies, such as folate, B12 or copper, would decrease red cell production and is of high concern in a child of any age with poor growth or failure to thrive. Inflammation may also cause macrocytosis. Bone marrow failure with aplastic anemia, or myelodysplasia, may also present with macrocytosis. And in that case, the clinical history and physical exam can provide some clues to the possibility of such etiologies. Macrocytic anemia may also reflect destruction, or hemolysis, because younger red cells that are produced in

compensation are generally larger in size. Hemolysis may also present as a normocytic anemia though if the reticulocyte count is not high enough to produce a change in the MCV.

**Dr. Eyal Ben-Isaac:**

And how about normocytic causes of anemia?

**Dr. Christopher Denton:**

Normocytic anemia, where the MCV is normal, can occur due to acute blood loss, which is unlikely except in a trauma setting, or a drop in red cell production. Lead poisoning, which is screened in the primary care setting in toddlers and young children, can lead to anemia by both decreased hemoglobin synthesis and hemolysis. It is important to differentiate iron deficiency and lead poisoning, because the risk factors are similar for either of these problems. Higher lead level is associated with lower dietary iron intake in prior studies. Whereas iron deficiency anemia typically presents as microcytic and reticulocytopenic and can be severe, anemia due to lead poisoning is usually mild and normocytic with an elevated reticulocyte count.

**Dr. Christopher Denton:**

As I said, though, because there is some overlap between iron deficiency and lead poisoning, it could often seem that lead poisoning presents with microcytic anemia, but really I think it's the iron deficiency that's causing microcytic anemia in that case.

**Dr. Eyal Ben-Isaac:**

What about pure red blood cell aplasias, can you review those?

**Dr. Christopher Denton:**

I do want to talk about pure red cell aplasia, which is an isolated anemia with reticulocytopenia. And that can be congenital or acquired. Diamond-Blackfan anemia, or DBA, is a congenital pure red cell aplasia due to genetic mutations in ribosome synthesis. Most patients with DBA are diagnosed in the first year of life due to progressive anemia with reticulocytopenia. Many patients also have associated congenital abnormalities, including characteristic facial features with hypertelorism, flattened nasal bridge, ear anomalies and high arched or cleft palate. Erythrocyte deaminase activity is elevated in most DBA patients. So that's an important serum marker to screen for that. Some patients respond to steroid therapy, but others require chronic transfusions to maintain an adequate hemoglobin for growth and development. The ultimate cure would be a stem cell transplant.

**Dr. Christopher Denton:**

Transient erythroblastopenia of childhood, or TEC, on the other hand, is an acquired pure red cell aplasia. The usual presentation is a previously healthy toddler with normal growth and development and no congenital abnormalities, who now has anemia, which is often asymptomatic. The etiology is unknown, but children do have a preceding viral illness in about a half of cases. Of note, parvovirus B19 was previously associated with TEC, but, that subtype is primarily

associated with aplastic crisis in patients with chronic hemolysis. So although parvovirus of others serotypes have been associated with TEC, parvovirus B19 really isn't associated with that.

**Dr. Christopher Denton:**

TEC is, as its name suggests, transient, being a temporary cessation of the erythrocyte production with spontaneous recovery over weeks to months. That differentiates it from DBA, which generally does not recover without stem cell transplant, although some patients with DBA experience resolution of their pure red cell aplasia by young adulthood. Additionally, DBA is typically macrocytic, while TEC is normocytic. Certain drugs and auto-immune processes can also lead to acquired pure red cell aplasia and should be considered in evaluating the patient.

**Dr. Christopher Denton:**

Moving on to decreased erythrocyte production or erythropoietin production, whether at the physiologic nadir or due to kidney disease, leads to normocytic anemia as well. Hyperthyroidism can also cause normocytic anemia. And finally, hematologic malignancy, in which the bone marrow is replaced by an infiltration of an abnormal immature cell clone, can present this way.

**Dr. Christopher Denton:**

So going back to our clinical case, a point of care hemoglobin was drawn. So we don't know whether the child's mild anemia is microcytic, macrocytic or normocytic. My guess is that the child has iron deficiency, because it is relatively common in this

age group. So it would be reasonable to empirically prescribe iron supplementation with ferrous sulfate at 3 mgs per kg per day. If it is iron deficiency, then the hemoglobin should show improvement at about a month of therapy. And the typical course to fully correct iron deficiency is three months. So it would be wise to obtain a full CBC at one month of therapy in order to see the MCV and send iron studies to assess the child iron stores.

**Dr. Eyal Ben-Isaac:**

Wonderful review. It really points out how the MCV is really helpful in distinguishing many different etiologies for anemia. Along those lines, can we review all the different components of a CBC, such as the red blood cell count, the MCHC, the RDW, or red cell distribution width? And what do they mean? Do you find them helpful? Or how can we find them helpful in trying to figure out the etiology of the anemia?

**Dr. Christopher Denton:**

Sure. There are a lot of different components to the CBC. I think some are helpful and others not so much. Starting with the RBC, which is the red blood cell count, and that reflects just how many red cells are in the sample. I don't really pay too much attention to this value, because it's not as valuable as the hemoglobin. But a normal RBC is about 4 to 6 million cells per microliter. If the RBC is low, then I think about nutritional deficiency leading to poor production, like an iron deficiency or blood loss. If the RBC is high, then the marrow is somehow trying to compensate for poor hemoglobin production, like in thalassemia. MCHC stands for mean

corpuscular hemoglobin concentration, which yields a value of grams of hemoglobin per 100 milliliters of RBC and that's expressed as a percentage. Again, I don't really pay much attention to this value except in certain situations.

**Dr. Christopher Denton:**

MCHC can vary based on the technology used. So the reference range for the specific laboratory should be checked. A normal MCHC is typically around 33 to 34%. So a low MCHC is considered hypochromic and hypochromic anemia is seen in both iron deficiency and thalassemia. Hyperchromic, or high MCHC anemia, is classic for hereditary spherocytosis. MCHC can also be elevated in sickle cell disease or megaloblastic anemia. And importantly, MCHC is falsely elevated when there is agglutination of red cells in the sample, which would falsely lower the measured RBC. Plasma opacification can also falsely increase the MCHC by falsely increasing the measured hemoglobin. That can occur with hyperbilirubinemia, hypertriglyceridemia and elevated free plasma hemoglobin. MCHC can therefore provide further diagnostic clues in certain situations and might actually tell about the sample as well as the potential diagnosis.

**Dr. Eyal Ben-Isaac:**

How about the red cell distribution or the RDW?

**Dr. Christopher Denton:**

Red cell distribution width, or RDW, describes the variability of red cell sizes in the sample and the pathologic term would be, anisocytosis. RDW is typically around 12

to 14%. RDW is very helpful in differentiating iron deficiency, which leads to a high RDW from thalassemia, in which RDW is typically normal. High RDW generally indicates defective erythropoieses and other settings such as anemia of inflammation. There actually have been some studies showing an elevated RDW in PICU patients. So there is some concern that perhaps RDW could be used as a marker of impending organ failure or mortality.

**Dr. Eyal Ben-Isaac:**

Thank you. We often just look at the WBC count, the hemoglobin hematocrit and platelet count, and sometimes forget about all the other important information in that CBC that is so helpful. So thanks for that review. When do you recommend we order reticulocyte count? Or maybe a Coombs test or any other tests besides the CBC?

**Dr. Christopher Denton:**

Honestly, I wish the reticulocyte count were included in the CBC, because I use the reticulocyte count as the initial decision point in my diagnostic algorithm rather than the MCV. Reticulocytes are the younger, larger red blood cells. And the reticulocyte count is typically reflected as a percentage of the total red blood cells in the sample. That percentage is typically around 1 to 2%. But that percentage can vary based on the RBC level. In a patient who has a low RBC and sickle cell disease or iron deficiency, for example, looking at the percentage won't really be that helpful. So it can be even more helpful to think about the absolute reticulocyte count, which is found by multiplying the reticulocyte percent by the red cell count.

In the setting of anemia, the appropriate hematologic response is to increase the absolute reticulocyte count to greater than a hundred. A value less than that would suggest a problem with red cell production.

**Dr. Christopher Denton:**

An elevated absolute reticulocyte count, on the other hand, would suggest compensation for blood loss or destructive disorder, such as hemolysis. Other clinical clues may point to hemolysis, such as jaundice or dark urine, which would reflect the release of bilirubin from lysing red cells. In that case, a positive DAT, or direct antiglobulin test, which is the Coombs test, would identify immune mediated hemolysis. A negative DAT does not rule out hemolysis, though. And sometimes it doesn't actually rule out an immune mediated hemolysis, but there are other red cell disorders leading to hemolysis that can come up with a negative DAT, because they're not immune mediated. Those are membranopathies, like hereditary spherocytosis or elliptocytosis or enzymopathies, like G6PD deficiency or pyruvate kinase deficiency, which would lead to hemolysis with a negative DAT.

**Dr. Christopher Denton:**

Mechanical heart valves and hemoglobinopathies can also lead to hemolysis, so it's important to keep those in mind. And again, the reticulocyte count would be elevated in the setting of anemia.

**Dr. Eyal Ben-Isaac:**

How do you use the peripheral blood smear to help you determine the etiologies of the anemia?

**Dr. Christopher Denton:**

The peripheral blood smear is another means of differentiating anemia, because certain morphologic features, aside from the size of the red blood cell or the severity of anemia, point to various etiologies. Schistocytes, spherocytes or blister cells suggest hemolysis, for example, and each finding is associated with certain types of hemolysis. Schistocytes are seen in microangiopathic hemolytic anemia, or MAHA, such as hemolytic uremic syndrome, thrombotic thrombocytopenic purpura and diffuse intravascular coagulation. Spherocytes, as you might expect, are seen in hereditary spherocytosis.

**Dr. Christopher Denton:**

Elliptocytes, would suggest hereditary elliptocytosis. And those are really just oval-shaped red cells with sort of parallel sides and curved ends. That's also due to a red cell membrane defect that is similar to hereditary spherocytosis. Blister cells, which are due to disruption of the red cell membrane with removal of oxidized hemoglobin, are pretty classic for G6PD deficiency. And sickle cells, of course, are seen in sickle cell disease, which is also a chronic hemolysis.

**Dr. Christopher Denton:**

Although we've already discussed a few characteristics of the CBC that help differentiate iron deficiency and thalassemia, there are also a number of important

findings on the peripheral smear that help differentiate those two. So various abnormal cell types are seen in iron deficiency, like cigar or pencil-shaped cells. Those contribute to the elevated RDW. Basophilic stippling, which consists of aggregated ribosomes with degraded RNA and just look like little blue dots surrounding the outer edge of the red cell, as well as target cells, are seen in thalassemia.

**Dr. Christopher Denton:**

Moving on to more macrocytic anemias, megaloblastic changes, which describe hyperlobulated neutrophils, in addition to anemia, or macrocytic anemia, would indicate B12 or folate deficiency. And then any sign of dysplasia in the white cells would raise concern for MDS or other malignancy. So it is helpful to look at other cells, other than the red cells, in really determining the etiology of the anemia on the peripheral smear.

**Dr. Eyal Ben-Isaac:**

What are teardrop cells and what do they indicate?

**Dr. Christopher Denton:**

Teardrop cells, which have a blunt side and a thinning tip that looks like the cell is kind of leaking, are seen in a variety of situations. They are rarely seen in healthy subjects, but more often in anemia of chronic disease or thalassemia. And most often in marrow infiltration or fibrosis, leading to extramedullary hematopoiesis. That said, many red blood cells can look like artificial teardrops cells due to slide

preparation as the cover slip sort of compresses the blood sample and smooshes the cell. But in that case, all of the teardrops are facing in the same direction. So that's an important clue.

**Dr. Christopher Denton:**

For all of these types of findings in the peripheral blood smear, the relative amount of a given type of cell correlates with how likely the associated pathology is present. So significant anisocytosis with a variety of red cell forms, including pencil cells and a few teardrop cells, would describe iron deficiency anemia, for example. While a lot of teardrop cells that are not all facing in the same direction would raise concern for something like myelofibrosis.

**Dr. Eyal Ben-Isaac:**

Thank you, again. It just points out again how much information we can get from the lab and the pathologist reading the smear.

**Dr. Christopher Denton:**

Absolutely.

**Dr. Eyal Ben-Isaac:**

How do you generally approach the treatment of anemia?

**Dr. Christopher Denton:**

I think initially it's important to consider that the severity of the patient's anemia and whether the patient would require a blood transfusion. The TRIPICU study, which was published in the New England Journal of Medicine in 2007, randomized over 600 pediatric ICU patients to a restrictive PRBC transfusion threshold at hemoglobin 7, versus a more liberal threshold of hemoglobin 9.5. The study showed a greater than 50% reduction in transfusions in the conservative group with no difference in multiorgan dysfunction or survival. That was really important, because the study established hemoglobin 7 as a typical transfusion threshold. But we really need to keep in mind that this study was done in pediatric ICU patients who have different risks and exposures than the general pediatric population. The etiology of the anemia is also really important.

**Dr. Christopher Denton:**

For example, in this child, who has iron deficiency, but really in a child with more severe iron deficiency anemia, which typically develops over months as iron stores are depleted, may tolerate a hemoglobin less than 7, but I would worry about impending cardiac failure if the hemoglobin decreases to less than 5. Supplementing with iron would lead to rapid improvement in hemoglobin through substrate and tissue hypoxia-driven erythropoiesis, but the child may require a blood transfusion if the anemia is that severe.

**Dr. Christopher Denton:**

If the child does not having a nutritional deficiency that can be corrected, then the decision to transfuse should be based on the hemoglobin level, the child's

symptoms and whether the anemia is expected to recover. Whereas a child with TEC can be monitored until the hemoglobin eventually recovers, a child with ongoing hemolytic anemia may need a transfusion if the child's own erythropoiesis cannot sufficiently compensate for the hemolysis. Aplastic anemia, or hematologic malignancy, are also cases in which the child's hemoglobin is unlikely to recover without transfusional intervention.

**Dr. Christopher Denton:**

In our clinical case, the child most likely has iron deficiency anemia, which should respond to oral ferrous sulfate, provided that there is no concern for malabsorption. Treating with oral iron is safe given that the child is only mildly anemic. Parents should be informed that ferrous sulfate does not taste very good, but the ascorbic acid does help with absorption. So this might actually be the only time that a pediatrician would recommend orange juice along with an iron supplement to make it more palatable and improve absorption. It is very common to experience abdominal discomfort and constipation with iron therapy as well. And that may contribute to poor adherence.

**Dr. Eyal Ben-Isaac:**

What if oral iron therapy doesn't work?

**Dr. Christopher Denton:**

In a child who fails oral iron therapy, as if the child in our clinical case returned with worsened anemia, despite oral iron supplementation, and we're confident that the

diagnosis is iron deficiency anemia, then IV iron is a very efficient and effective way to replete iron stores. In a patient with severe iron deficiency anemia presenting with hemoglobin less than 7, giving IV iron ensures that the patient will actually receive the prescribed medication. And hemoglobin typically improves within just a few days.

**Dr. Christopher Denton:**

It is also appropriate to use IV iron when the patient's etiology of iron deficiency anemia is unclear, such as occult GI loss or malabsorption in which IV iron is necessary to bypass the enteral route. I would also say that in a patient for whom oral iron has failed, IV iron seems like a very good choice. We use ferric carboxymaltose at CHLA, which leads to iron repletion in two doses that are separated just one week apart. The doses have to be given in this way, because hypophosphatemia can develop with rapid iron absorption in a large load like that.

**Dr. Christopher Denton:**

Patients are also monitored for infusion reaction when they get the dose. But that is of much less concern with ferric carboxymaltose than with the older form of IV iron, which is called ferric sucrose. Although it may seem invasive to give a child iron intravenously rather than orally, parents are often relieved that they can correct their child's iron deficiency with just two visits to our infusion center, rather than dealing with three months of a course and their child taking a nasty iron supplement.

**Dr. Eyal Ben-Isaac:**

Thanks for the tip on the orange juice, because definitely parents come in and say, "Oh, my kid did not want to take the iron," and therefore they did not give it. So thanks for that little trick. When should we involve the help of a specialist?

**Dr. Christopher Denton:**

First of all, I think I speak for all hematologists when I say that you should involve us if you have any concern or uncertainty regarding the diagnosis or management of anemia. Iron deficiency anemia is very common in older infants and toddlers. A general pediatrician should be familiar with starting enteral iron therapy. If anemia persists after a few months of iron therapy, though, then a referral to hematology would be warranted.

**Dr. Christopher Denton:**

If iron studies are normal or the child is not at the usual age for iron deficiency, then a hematologist should be involved in that case as well. Hemolysis is an etiology of anemia in which it is very important to consult a hematologist, because rapid treatment is necessary to prevent poor outcomes. Involving a hematologist early in other cases of anemia is also helpful to establish continuity and ensure that the child follows up with us, if necessary, until the anemia recovers or is adequately treated.

**Dr. Eyal Ben-Isaac:**

Chris, are there any specific resources either you use or you would recommend for clinicians to look at, to keep up to date with anemia, etiologies, maybe management treatment options?

**Dr. Christopher Denton:**

Absolutely. In my training, we would talk about horizontal learning to get the basics of things and then vertical learning when you really want to get more in depth. For my horizontal learning and basic understanding, I'd start with a textbook. The textbook that I think is most valued in our field would be, Williams Hematology. I believe the sixth edition is the latest one. But it's also a very thick book, so the older editions would work really well as a doorstop, if the information isn't as accurate anymore.

**Dr. Christopher Denton:**

And then the journal that is, I'd say, the most heralded and maybe considered the Bible in our field would be the Journal of Blood. And that's published by the American Society of Hematology. They have really excellent articles called, How I Treat, and those articles are published by experts in the field and talk about anemia or Diamond-Blackfan anemia, or aplastic anemia and give good information about how they would specifically treat something. So those are super helpful.

**Dr. Christopher Denton:**

To focus on pediatric hematology, the American Society of Pediatric Hematology/Oncology publishes Pediatric Blood and Cancer. They similarly publish

an article called, How I Approach. So those kinds of articles are really nice just to learn from an expert on what they would do in a certain clinical situation. Both Blood and Pediatric Blood Cancer also will occasionally publish guidelines on different types of management, so those are helpful, too. But I think those two journals are probably the most helpful that I would recommend.

**Dr. Eyal Ben-Isaac:**

Thank you, again. This was incredibly informative and very educational. Are there any specific takeaway points that you would love our audience to keep in mind?

**Dr. Christopher Denton:**

Sure. As in any clinical didactic, as we've been told many times throughout our medical training, the most important step is taking the history and physical exam, especially considering the patient's age, symptoms and any prior medical history. Until the reticulocyte count is included in a routine CBC, I do want to emphasize the value of the reticulocyte count in differentiating anemia. If the reticulocyte count is elevated, then the problem is either hemolysis or blood loss. And if it's inappropriately normal or low, then you can use the MCV to differentiate a cause of poor production.

**Dr. Christopher Denton:**

The reticulocyte count is readily orderable and can be added onto a routine CBC if it's requested within a few hours. So if we're consulted on the inpatient service, that's probably what we're going to suggest, is to add on a reticulocyte count. The

peripheral blood smear can also provide helpful clues, so don't be afraid to contact your hematology lab or the hematopathologist. And finally, always feel free to consult your friendly neighborhood hematologist if you have any questions or concerns.

**Dr. Eyal Ben-Isaac:**

Thank you so much, Chris. Thank you for always educating me. Thank you for educating our audience today.

**Dr. Christopher Denton:**

Thanks again for having me.

**Dr. Eyal Ben-Isaac:**

I hope you enjoyed my conversation with Dr. Denton as much as I certainly did. If you'd like to hear more from pediatric experts, subscribe wherever you listen to podcasts. And keep in touch with us by subscribing to learnwithopen.org. And check out the links and resources in our show notes. If you liked what you heard, please rate us and leave a review. This podcast is produced by the Online Pediatric Educational Network and Mindy Lee. This episode was mixed and edited by Daniel Lev. Our music was created by Daniel Lev and Juan Espinosa.