#263 Iron Deficiency Anemia in CKD - Nephmadness 2021

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SUMMARY KEYWORDS

patients, iron, CKD, iron deficiency, hemoglobin, pascal, anemia, oral, dialysis, drugs, nephrology, ferritin, formulations, iv, talking, people, point, ferric, called, thought

SPEAKERS

Matt, Everyone, Matthew Sparks, Joel, Pascal, Stuart, Paul

Joel 01:33
Neph-Madness is a nephrologist take on march madness, and so instead of basketball teams, we have 32 nephrology concepts from eight different academic regions that are all competing at ajkdblog.org. You can read scouting reports on each one of these teams and each one of these concepts to bring you up to speed after you read those scouting reports you can get MLC and cme credit for that but the most important thing is then to go to nephmadness.com and submit your bracket just like you would for march madness you submit your bracket pick your winners and you can and you can win nephmadness

Matt 03:34
and you guys always have some cool swag bragging rights are really what it's all about though

Joel 03:39
yeah it's really about it's really about bragging rights and and and quite honestly this is the this is the ticket to becoming a full professor if you can win neff madness there's no stopping yeah stop with the publish and perish thing this is the way to go

Matthew Sparks 03:53
What about riches? I mean that's really what most people want they don't care about cool professor they want to make the money and you can really go to vegas on this

Matt 04:03
Laughter, I don't know if that's true

Joel 04:10
I mean if the hagfish wins. I have told everyone that I'm getting a hagfish tattoo

Stuart 04:34
Okay so our case we've got Mr tony stark spelled with a 'q' so it's not to be confused with the intellectual properties of a large corporate conglomerate, he presents to your primary care physician or to his primary care physician for routine follow up he's a 49 year old gentleman with hypertension hyperlipidemia and chronic kidney disease stage G3ba2 who takes lisinopril atorvastatin and aspirin dutifully his vitals are 135/85 pulse of 80 and a BMI of 32. Otherwise, his examination is unrevealing. His labs included creatatine of 2.0. That has been stable over the last two years with a calculated EGFR of 38 ml per minute per CKD microalbumin creatinine ratio of 150 milligrams per gram, hemoglobin of 12 and LDL of 95. So Pascal first thing that I'd like to talk about for patient like Mr. Star, not of Stark enterprises, how should we think about his CKD? In the primary care setting? And what are some things that immediately stick out to you about Mr. Stark?

Pascal 05:38
Right, so this patient, as you mentioned, he's a CKD stage three. So in the primary care setting, I think one thing I always want to emphasize is I think once a patient hits that stage, that's when you probably want to start talking to them about seeing a nephrologist. That's step one. Step two, in between when you see them and when they need to go see a nephrologist, things that you should be aware of is out once that GFR hits below 45, we will really start seeing the complications of anemia and mineral bone disorders. And those are a couple of things you really should be paying attention for when you're evaluating these patients. So Mr. Stark has anemia, as you as we will probably be talking much more about in this podcast, but other things to look at are his calcium, phosphorus, vitamin D, and PTH levels, which at this point should probably be checked once every six months to a year. That's part of their mineral bone disorder evaluation. Rarely the patient start having some metabolic acidosis, which is another thing that the primary care physician should be looking out for, because that's one of the few things where correcting metabolic acidosis has been shown to improve or delay CKD progression. So I think those are the three main things I would be thinking of and probably talking to them about seeing an nephrologist

Joel 07:07
I know we're gonna be talking a lot about anemia, but one of the other regions in Neph-madnesses is Primary Care. And one of the things that we talk about there is there are a lot of abnormalities that we see in CKD. And Pascale did a nice job of laying them out. And metabolic bone disease is a perfect one, where we know that there are abnormalities, we know we have medications that can intervene on those abnormalities, but we don't know if those interventions result in any improvement for the patients. And, and I know that in my practice, in my practice, I'm much more cautious about doing those tests and screening for those things, just because I just don't know what to do with those results. And again, that's gonna vary from practitioner to practitioner, I just wanted to put that out there.

Matthew Sparks 07:47
I have to give one more thing. Is that okay?

Matt 07:50
Yeah.

Matthew Sparks 07:51
Okay, so what I've been really doing a lot lately is calculating someone's kidney failure risk. And I think this is something that I'd like to see done more in primary care, you can go to a website called kidneyfailurerisk.com. I do like the KDIGO chart that we were talking about, like putting them on stage. So if you put in this individual's parameters, Tony Stark, you get a two year risk of about 3.4%, and a five year risk of about 10%. And so this is something that when you start doing it, you'll start to recognize, like, you know, puts the patient in more context to see, you know, how much risk they have to progress to needing dialysis in a two year and a five year interval. And so I would, I would classify both of those as this is a moderate to high risk individual, mainly because the 10% five year risk because one in 10 patients that you see with this exact same parameters will be on dialysis in five years, or going to need a kidney transplant.

Stuart 08:54
Okay, so we're gonna go ahead and talk about, so we get his iron labs back. So as iron is 37, transferrin of 400. So his total saturation that was T-sat is 9.3% with a ferritin of 150. So we've established this patient is anemic. So I want to ask you, Pascal, just straight up, is this patient iron deficient? And what are the ferritin goals in CKD?

Pascal 09:24
Yeah, so he is, and I think one nuance is when we're looking at iron deficiency and CKD we really classify it as either absolute iron deficiency or functional iron deficiency. And so by absolute we mean that an individual really has very reduced or absent iron stores and their bone marrow and liver and other organs. So and that can be due to mainly blood loss, occasionally poor iron intake, that basically for those individuals are defined as having absolute iron deficiency if their T-sat is less than 20% or their ferritin is less than or equal to 100 nanograms per ml. So the other iron deficiency type, we talk about a lot and kidney disease as functional iron deficiency, and that's when people have enough iron stores. So when you stay in their bone marrow, they have enough iron there, but they're just not able to use it. And we can talk about a lot of reasons why that may be. But one short answer is inflammation that comes with CKD. And so people are classified as having functional iron deficiency if their t-sat is less than or equal to 20%. And their ferritin is less than or equal to 500. So here, the ferritin goal goes up, because ferritin is an acute-phase reactant, and we expect it to go up. And so Mr. Stark falls. And that definitely is the status low his ferritin is 150. So very close to the absolute iron deficiency goals, but also probably with some functional iron deficiency as well.

Matt 11:01
Pascal, can I point out for the audience? So you you mentioned, so we're talking about like non-dialysis CKD patients cut-offs are t-sat less than 20 and ferritin, less than 100 for absolute iron deficiency less than or equal to 100? Correct. And then for for our patients who don't have CKD, we typically use a ferritin cut off something like less than 30. And so this is higher, because there's some sort of chronic inflammation with patients with CKD. And then I know when we talk about patients on dialysis, it's an even higher cut off as well.

Pascal 11:34
Yes, the cutoff goes up to 200 and those patients on on dialysis.

Paul 11:40
Okay, are you so more broadly, I just wanted to ask just how good are these labs at helping us figure out if someone's truly iron deficient or not, especially in chronic kidney disease? You mentioned, you know, iron, kidney and bone marrow aspirate, which I think so I was, like, 30% error rate in terms of diagnosing someone with it or not. So I'm just wondering, what are these?

Pascal 11:59
Yeah, they're not great. I have to say we, they probably were a bit arbitrarily chosen. So like, I definitely agree with you. But this is what the KDIGO guidelines use. This is what we use to make things a bit more clear cut and easier, but definitely a lot of arbitrary number decisions went into this.

Joel 12:23
Hey, Paul, you said there's a 30% error rate on a bone marrow aspirate? I feel like that's I read that number somewhere. Maybe I'm making it up. What are they comparing it to? I thought that was the gold standard? Like, what?

12:33
What's truth?

Matthew Sparks 12:34
I think it's like, it's more, it's like, yeah, 2% times they actually get the bone marrow? Is that what you're so okay.

Paul 12:41
Let me see if I can find this, that while we're talking or otherwise, then we can just cut all this out and miss my excellent point that this, these sets are not great.

Stuart 12:52
So and the one thing I wanted to ask about is in KDIGO, they mentioned the T-sat less than or equal to 30. And ferritin less than or equal to 500 nanograms per ml. So is that more for the functional iron-deficient patients? Who they suggest treating with iron? Well, we'll get to that in the future. But because you had mentioned us 100

Pascal 13:13
Yeah, less than 100 is for absolute iron deficiency. 500 for functional iron deficiency.

Matt 13:19
Yeah, I was puzzling over that, too. From what from what I read, and Pascal, did you come across this to what I read was that if, if the person has a T sat above 30, and if they have a ferritin, above 500, they're unlikely to respond to iron therapy, you know, with an increase in hemoglobin or an increased response to your erythropoietin - ESA's - you're stimulating agents. And I think that's where they came up with those cut offs. Correct?

Pascal 13:49
Yeah, that's, and we can talk. So this is where like, we think that inflammation is too high, where some people giving more iron will not help.

Stuart 13:58
Yeah, so basically, we're just trying if the ferritin is over, all right, to see if it improves, okay. Yeah. And it just kind of like an aside as one to bring us up somewhere in here that actually uses anisocytosis is the first hematological change that seeing iron deficiency. This is actually from a 1976 article in the British Journal of hematology. This is before we see microcytosis or anemia. So if you see the RDW start shooting up, you need to start thinking about iron deficiency as being the cause or at least one of the causes for anisocytosis.

Matt 14:31

Joel 15:25
And honestly, if I were to see this patient in clinic, and I saw hemoglobin at 12, and I talked to the patient, and they weren't complaining about fatigue or anything, I don't think I'd even order iron studies, I would consider that adequate hemoglobin and the KDIGO says greater than 10. So I'd be fine with this and move along. And I recognize that I can help other things. But really, from the nephrology standpoint, in the CKD standpoint, we really think of it as a treatment of anemia. And in this guy, hemoglobin a 12, move along. We got other we have other things to focus on.

Matt 17:41
Yeah, so So basically, Joe, you're saying you wouldn't have this information that he has a low TSAT and a borderline ferritin point?

Joel 17:48
That's exactly right. That's exactly yeah.

Stuart 17:50
Yeah. That was a question I wanted to ask is, does it even matter if this patient is anemic or not? You're saying if he's asymptomatic that you would just move on at that point?

Pascal 17:58
No, I'm actually Okay. Do you go does say the target hemoglobin for CKD is just greater than 10. So as long as it's, as Joel mentioned above 10, and they're feeling fine. You don't have to feel compelled to do anything.

Matthew Sparks 18:10
So that brings a good point. I think, before we started talking, we mentioned about how once you have anemia, you're already way behind the eight-ball, is this true in CKD? Or should we be considering check something when they're at 10? Or does it have to drop to eight?

Stuart 18:28
I can't answer that question, Unless maybe you guys can?

Matthew Sparks 18:30
Anyone have a thought on that? I mean, you see this very often. And you're like, Okay, at what point should you start to measure iron iron levels?

Pascal 18:40
I personally do a check at 11 or 12. because and I probably won't replete if it's above 100. But if it's less than 100, if ferritin is less than 100 and TSAT is low. I do give them oral iron just because I don't want them to then, like in a couple of months, come back and it's way lower, and I'm late in the game.

Matthew Sparks 19:04
What about colonoscopy as well, and individuals like this?

Pascal 19:08
Yeah, yeah, definitely.

Stuart 19:10
I kind of fall in line with Pascal. But that's probably because I check ferritin on a lot of patients, the cost of ferritin test is pretty cheap. And so an iron test is pretty cheap. And it provides some degree of useful information to say what I need to do right now to prevent complications in the future. And granted, I use that for treatment for the other neurohormonal aspects of iron deficiency, that we're not going to go way into detail here. But Matt, what do you do?

Matthew Sparks 19:37
Yeah, I think I probably err with checking once they get around 10 or 11 and not wait until they're just frankly anemic. That's been my practice that I'll say that, you know, I don't know if I have an algorithm for it or anything but it is curious that you know, we give patients with CKD a cut off a 10 Does that mean you wait until it drops below 10 before you really start to look at the iron parameters which is something that you might be intervening on

Stuart 20:04
yeah it kind of brings up the discussion of how you determine what someone's or how are they fatigued right because there's gonna be a point where oh yeah i spell run two miles now I can only run one mile that you know is that a good surrogate for it but ultimately their lifestyle is going to adjust over time to whatever their energy level is and it's going to be harder and harder to quantify whether or not they feel fatigued subjectively

Matthew Sparks 20:28
should we mentioned what the region is in nephmadness i feel like we've moved very far and we need to talk about the anemia region i mean this is a battle royale against the iron oral versus iv and then epo versus this new kid on the block HIF stabilizers and so we have two battles to discuss and we're right now

going to hit the iron hard and then we're gonna go after EPO and HIF stabilizers later on so that's one thing to keep in mind so we're taught we're getting right we're getting ready to dive into oral and iv iron

Matt 21:05
so pascal can I ask you um since we've been thrown a lot of numbers around can you tell us so for I think we can probably all agree that for our patient without CKD we look for a TSAT below 20% that keeps us in there so an iron problem and if their ferritin is less than 30 we say ferritin less than 30 TSAT less than 20 that's absolute iron deficiency what about for the patient with CKD what what cut-offs do you use just to make it clear for the audience for absolute iron deficiency?

Pascal 21:34
so right for them to be diagnosed with absolute iron deficiency their TSATs would have to be less than or equal to 20% and their ferritin would have to be less than or equal to 100 nanograms per ml

Matt 21:47
and what about for the functional iron deficiency

Pascal 21:51
for the functional iron deficiency that definition is a TSAT of less than or equal to 20% or a ferritin of less than or equal to 500 nanograms per ml

Matt 22:03
got it alright so let's move on and Stuart what are we talking about next year is there another part of the case are we just gonna go talking about iron here

Stuart 22:10
so next part that I have that we're going to talk about or we can skip over this this is the whole neurohormonal aspect of iron deficiency and just a brief aside that iron deficiency isn't it's not just about anemia that there are several different reactions in the body that require iron as a cofactor those are the tetrahydrobiopterin reactions and they lead to things like dopamine norepi, epi serotonin and melatonin in the sympathomimetic pathway but also is important cofactor in endothelial nitric oxide synthase which produces nitric oxide in response to exercise and so severe iron deficiency can lead to neurohormonal deficiencies in those specific axes

Matt 22:53
right and I know that's an area of interest for you right that the non-anemic symptoms of iron deficiency and this pathway is the proposed mechanism why it has such widespread effects fatigue and maybe ties in with mood disorders and some of the cognitive stuff and

Stuart 23:09
Correct

Matt 23:10

pregnancy and yeah there's it's a deep field

Joel 23:14
yeah and I think I think a lot of doctors have found patients that if they're anemic or not and you give patients iron supplements and that to be the most dramatic has been after giving iv iron that the patients come out and they feel tremendously better and like and you check the hemoglobin and it really didn't move that much yet and you're kind of cocked your head and say oh that's that's kind of it let you know that part of your thinking oh placebo effect is pretty powerful but here's a physiologic explanation and I don't think this is an uncommon response i've seen it a number of times

Matt 23:46
yeah and that's dr iron man as he's known when we talked about iv iron and he said if I have a young woman come in hemoglobin seven from menorrhagia i give her 1000 milligrams iv iron she feels better before she leaves the office her hemoglobin is exactly the same

Pascal 24:03
Matt and I were just talking before we started about iv iron and heart failure matt you want to say something since we're talking about all these extra

Matthew Sparks 24:13
yeah I think it's something that maybe I didn't have a really deep appreciation of but in patients that have heart failure with ejection fraction less than 50% and anemia with iron deficiency giving them iv iron decreased rehospitalizations and new hospitalizations for heart failure which i think this is really interesting and something that we need to consider

Stuart 24:42
alright, so at this point, pascal in primary care land should we even be considering an EPO level with this patient before we start on treatment or what should we do in this patient right now.

Pascal 24:53
Okay, never. so my answer is always never so and we'll talk more about it i think later in this in this episode but I think since this patient has some iron deficiency, almost absolute, I think it would be worth starting them on oral iron formulation to help with their just their iron deficiency basically

Stuart 25:19
and which oral form how would you approach oral iron formulation in this patient

Pascal 25:26
yeah good question so before i became an nephrologist i think the only iron i learned, i knew about oral iron as ferrous sulfate and that's the one that's like 325 milligrams for a tablet we give patients one to three tablets a day sometimes alternate every other day but i think that's all i knew but coming to nephrology i think i learned about a few more the newer and much more exciting oral iron formulations so i think they may be worth considering in the primary care setting as well so we can talk about them if you'd like

Matt 26:03
yeah, I think it would be useful maybe as you're mentioning them, I don't know if we have Stewart did you happen to look up any prices on these on like good Rx like do we know if there are?

Stuart 26:11
No I didn't do that actually

Matt 26:12
because i think

Stuart 26:13
I can do that right now yeah

Matt 26:15
so pascal what which ones are available because I think we were talking about this ahead of time a ferrous sulfate is the one that most people get put on so how do you think about this and have you started using anything else in your practice yet

Pascal 26:28
yeah so exactly so ferrous sulfate is considered one of the traditional oral iron formulations. probably one of the oldest, if not the oldest so the newer ones i'm talking about the ones we've been using more of in our practice is there's a couple of FDA approved one so one is ferric citrate which goes by the name Auryxia and the other is ferric malatol mile tall which goes by the name Feraccru and the reason i think why nephrologists know about these and not other specialties for example ferric citrate was initially approved as a phosphate binder so it wasn't even developed to be a oral iron medication but then when patients with hyperphosphatemia were given the medicine they we found that their iron levels are actually improving and so this led to some studies comparing ferric citrate to ferrous sulfate and actually finding that taking ferric citrate- the way it's developed it does contain more elemental iron and so taking that lead to a more significant increase in TSAT and ferritin concentrations and people with moderate to severe CKD and the side effect profile was similar which with oral formulations is mainly just some GI side effects nausea constipation so after that study i think more and more nephrologists are using ferric citrate to treat iron deficiency

Joel 28:03
I just looked I looked up the price it looks like you can get a month's supply for only $1200.

Stuart 28:08
yeah... i just saw that too

Joel 28:11
with the coupon!

Stuart 28:17
price range for 210 tablets anywhere from $6500 to $11,000

Matt 28:22
oh my gosh the

Matthew Sparks 28:24
the ferrous sulfate actually is a gift when you leave the store

Everyone 28:27
Laughter

Matt 28:29
I think the issue is so and working in primary care I'm sure it's the same in nephrology it is oftentimes if someone has taken iron before some patients take it and they don't complain about it and but then there's everyone else that takes it complains about it turns their stool black makes their stomach upset they get constipated it is a real issue and then I've always thought at least in the past few years that inflamed patients patients with CKD patients with heart failure rheumatoid arthritis what have you they are not going to absorb the oral iron pascal does that pan out you know talking even with this and are these new formulations any better do we know that yet

Pascal 29:13
yes, I think we know that these formulations even in end-stage kidney disease patients who are like our most inflamed patients they still do work and occasionally can raise hemoglobin as well as iv iron in some cases so that for ferric citrate i know for ferric maltol which there haven't been there's been some studies in CKD but they haven't been published yet but at least and patients with inflammatory bowel disease so ibd did also increase hemoglobin ferric maltol increase hemoglobin levels pretty considerably and so those are patients who are basically inflamed and so yeah we do see that these newer formulations do better than ferrous sulfate and do work and inflamed conditions as well.

Stuart 30:06
Well, it's actually pretty good.

Matthew Sparks 30:07
I was gonna set the record straight just a bit. Okay? And oh, okay, it No. Oral iron gets a bad rap and Dr. Watto, you know, made those comments, I think everyone sort of says, Well, if you take iron, you're going to black stool and you're going to be constipated, bam, end of story. So let's look at a randomized clinical trial. And just take a look at that. And I think neph-madness made me sort of look at the data again, that's what I really like about Nephmadness is sort of, you can dive deep on these topics. So there's a clinical trial, which I love. I've heard that they're really good at evidence building.(Laughter) And it's called the FIND CKD study. I think it's called, yes FIND CKD published in nephrology, dialysis, transplantation in 2014, randomized patients to oral iron 300 patients. And then 150 of a high and low dose, or IV iron. So it looks at IV versus

oral iron. And those patients actually had a nice increase in hemoglobin, and seem to work. And constipation was only seen in 12% of patients and the ferrous sulfate group.

Matt 31:17
That's shocking. I wonder if it's like a statin myopathy thing where like everybody, everyone thinks they're going to get it

Matthew Sparks 31:26
And the adverse event profile was similar from the IV and in the oral however, constipation was about 10% higher. So 11% oral iron versus about 2-3%.

Joel 31:41
So what you're saying is the NNC, the number needed to constipate was 10.

Stuart 31:49
That's pretty close. Yeah.

31:52
Yeah, there you go. It was good job. (Laughter)

Matt 31:53
We should just had the show with that joke, Joel. Number needed to constipate.

Matthew Sparks 31:57
But it's not as high as what I thought I thought it would be like 80% or something like that. Yeah.

Matt 32:03
Joel, have you been able to get that to get any of these other formulations I've seen like ferric, ferrous gluconate, or ferrous glucan as the as the other one and ferrous sulfate. But I don't know the citrate or the maltol, I have not had the occasion to use yet.

Joel 32:19
The only alternative oral iron I have experienced with is ferric citrate. And this is just like Pascal said that I was prescribing it as a phosphorus binder, it was covered by insurance, the patient got it. It's a particularly good phosphorus binder, which is always a problem in nephrology, you're trying to find medications that control those high phosphorus for dialysis patients and get to admit I, I didn't keep a close enough eye on their iron. You know, the data is clear, the trials have been clear that in dialysis patients, it dramatically reduces iron use. And EPO use pretty impressively. And that, to me is a win. Because I think my sense is that epo, especially at high doses, is pretty toxic to these patients. And so it really seems a it's pretty impressive to me. But as I said, Keep an eye on their eyes.

Matthew Sparks 33:13

I just want to point out that Joel's talking about patients that are on dialysis, and there's currently no FDA approved medication to lower phosphorus in patients not on dialysis. And in fact, if you give a phosphorus binder to someone with CKD, not on dialysis, their phosphorus levels won't change that much. Because the paracellular transport of phosphorus is still intact. And so I would say that ferric citrate might not have much of an effect in patients that are not on dialysis. But I'm still concerned if it's called Ferrick. Talking about phosphorus. Yeah. Let's talk about FOSS. Yeah. And I'd say this is important because ferric citrate is a phosphorus binder. And that's, that's why people want to use it. But I don't I'm still kind of curious as to why they never thought it didn't.

Matt 34:04
When it's called, they should have seen that coming. I agree. So there's there's two other non FDA approved oral forms. And Pascal, do you think those are coming anytime soon? Did you want to briefly mention those? Right? So

Pascal 34:18
the two are lipids omal, iron and sucrose omeo iron. And so, for example, a sucrose oatmeal has a phospholipid bilayer, which allows it to be better absorbed, at least for sucrose, oatmeal did as well as IV iron and correcting anemia and ckg patients. I have to say I am not sure why it's not FDA approved yet. But I do hope we have a new option on the market soon. Yeah, because it sounds like it's good.

Matt 34:48
So this region is oral iron versus IV iron. And is this in either is this non dialysis CKD?

Joel 34:58
Oh, all comers.

Matt 35:03
okay so let's let's talk about then you know when you start pascal when you start reaching for iv iron for your patients with any type of CKD

Pascal 35:14
right so as you mentioned like if I have a patient who really hates oral iron does not want to try it again, that's a great patient for iv iron therapy so patient compliance as a big factor in this patient having side effects or being resistant to oral iron and then basically probably the last thing is patients this severity of the patient's iron deficiency so say they come in with a hemoglobin of eight or nine very iron deficient I want something that will work faster than oral iron that might go to his iv iron other than that I usually have their like hemoglobin like Mr stark doing okay I will try all oral iron for one to three months at least and if things are okay I'll keep it if things are looking worse then that's a reason to also switch to iv iron

36:10
heart failure

Stuart 36:13

i mean to the trials only used iv iron for their heart failure endpoints so is that when you you would recheck their iron stores one or three months later to

Pascal 36:23
Correct, yeah

Matt 36:24
and what outcomes what numbers are you targeting with this

Pascal 36:28
um so basically as I mentioned so hemoglobin greater than 10 and if the hemoglobin is greater than 10 just getting them to their ferritin of greater than 100 and then really there's no need to keep going because you'd also don't want to get into the problem of iron overload

Matt 36:50
yeah and when we were Joel you were mentioning before for patients if they are on dialysis is that in the realm where we just as a primary care maybe we contact the dialysis you know their their nephrologist but we don't we shouldn't really be mucking around as much as with someone that just has straight ckd

Joel 37:09
yeah i think that's exactly right if they're on dialysis they're getting monthly or twice monthly labs done they're on protocols to monitor their iron levels and to provide esa and so that a lot of that's going to be taken care of and i would say that in my patients with advanced CKD once they become anemic if they have any indication of iron deficiency i'm reaching for iv iron it's what i've used for years it works and seeing the cost of these new iron the new the data on the oral irons is really impressive but with these types of prices it's just it just doesn't seem worth it you know again most of these studies showed equivalency not superiority and so i'm gonna i'm gonna reach for the quick therapy

Stuart 37:54
it's kind of surprising how much the like ferric citrate costs

Matt 38:02
yeah i think Stuart Stuart do you need a sec

Stuart 38:05
yeah my daughter's calling me so I'm gonna hand this over to the matt

Matt 38:10
okay

Matthew Sparks 38:11
can I ask a question about the what about some logistical issues of giving the iron and can you tell us about like one shot versus

Matt 38:21
with iv formulation? yeah absolutely

Matthew Sparks 38:23
those are just confusing yeah, the iv formulation so there's kind of confusing, pascal do you want to run through that or

Pascal 38:30
basically as we have newer oral iron formulations we also have these newer iv iron formulations that include ferric carboxymaltose iron isomaltaside and ferumoxytol and so those compared to the traditional iv iron formulations which include iron sucrose iron gluconate and iron dextrans are usually infused within a much shorter period of time so infusions are usually around 15 to 30 minutes so again not taking much of the patient's time as compared to as long as one to four hours of infusion time for the traditional iv island formulations and the other benefit is actually like one dose can provide 500 milligrams of iron versus the traditional iron formulations where one dose provided 100 to 200 milligrams of iron and the patient had to keep coming and four iron infusions so i think what John is saying makes sense where yes it's it's faster but also with the newer iv formulations it's much easier to convince patients to take them it's a shorter infusion time relatively low risk of side effects and one shot every few months is more than enough

Matthew Sparks 39:48
about cost of the IVs?

Pascal 39:50
i have to say I did not look at the costs

Matt 39:53
and i think it's institution dependent to be honest because when i the places where i've worked the they have Something on formulary and you're kind of beholden to that, you're going to be sending them to an infusion center of some sort and, and they iron, sucrose seems to be the most affordable. And unfortunately, that's a multi dose. And usually I'm seeing patients get anywhere from like 100 on the low end to 400 on the high end of that, and so your your target dose is typically around 1000 milligrams for you know, if someone's iron deficient, at least if someone's let's say someone has an absolute iron deficiency usually are getting 1000 milligrams Pascal, is that what you typically shoot for as a treatment? treatment dose?

Pascal 40:35
That's, yeah, that's what we should wear as well. And CKD?

Matt 40:39
Yeah, so with the iron sucrose, it could take them, you know, 10 sessions, it could take them three or three to five sessions. It's

Pascal 40:46

literally giving them 400 per session. That's like four hours sitting there. For that, that infusion.

Matt 40:52
Oh, I see. So that's probably that's probably why sometimes I've seen him get like the 125. And they get they get that less.

Matthew Sparks 40:58
Okay. So like it's for 15 mils of carboxymaltose. That's $1200.

Matt 41:06
Yeah, I guess it might depend, I think people are just gonna have to price it out locally. Certainly the newer dose, the newer ones that are one dose a bigger shot, it's less infusions less time for the patient. So it is relatively patient centered. It's just a matter of, it's just a matter of being able to get it. So, we talked about some of the concerns with the oral formulations, mainly the GI side effects with the IV iron. I know the older formulations, there was this anaphylaxis and there was test doses involved. That's not really a thing with the newer formulations. But what are there any concerns that you have in your review of these agents?

Pascal 41:47
I think historically, IV iron has had a bad reputation, especially with like infectious concerns and cardiovascular concerns. I think these have been overplayed, to be honest, but I think one major concern with the newer iron formulations, specifically ferric carboxymaltose, is, uh, does cause pretty severe hypophosphatemia by inducing kidney phosphate wasting. And some patients can actually develop a hypophosphatemia for several months after administration. And so I don't want to be promoting the drug and then patients ending up with severe debilitating hypophosphatemia. So that's just one thing to keep in mind.

Matt 42:32
Yeah,

Matthew Sparks 42:33
I want to point out, though, that that side effect is also dependent on having two beautiful functioning kidneys, because that's how it works. So if you're on dialysis, it's not going to cause anything like that.

Joel 42:45
And to add to clarify, any functioning kidneys are beautiful.

Matthew Sparks 42:51
I will know even though it can cause this and just want to put put this out there as the the heart failure clinical trials using IV iron use this. And even though it might cause phosphate to below, and as a side effect, we should be aware of the signal of harm wasn't evident in that clinical trial. So the clinical significance is still hard to interpret. But I think if you're using this drug into someone, you should at least be aware of the side effect.

Matt 43:17
Okay, so I think that about wraps up the PO an IV iron and we'll vote in a little bit here. But let's let's take it home with this. So we've treated our patient initially with for their iron deficiency. We tried some oral iron didn't go that well, we gave some IV iron patient did okay. Now back to see us the creatine is increased over the past few years. It's now 2.8 up from two, and his hemoglobin has slowly declined from 12 down to 9.5. Despite his transfer and saturation is 30%. And his ferritin is 600. So that's greater than the 30% and 500 cut offs, you know, in the KDIGO guideline. So by them I guess this patient, Pascal correct me if I'm wrong, this patient's iron-replete. What would you do at this point for this patient's anemia? Right?

Pascal 46:30
So you are correct. So nine is definitely worse anemia than he started off with. And we know that we usually want to target somewhere closer to 10 to improve their anemia associated symptoms. And so this would be a time to start considering erythropoietin or erythropoietin stimulating agents to improve his anaemia.

Joel 46:58
and I think this is a good this is again, you know, my, you know, hemoglobin of nine is below the target. But I definitely want to talk to patients and find out they are having symptoms because we're about to introduce a drug that definitely has real side effects, has it signals for increased cardiovascular disease has signals for malignancy. And if the patient is feeling fatigued or having trouble? I think those that's a good discussion to have. And they may have problems. But I'll tell you what, I talked to a lot of people think hemoglobins a nine, and they're fine. And I'm and and I just you know, this is not a drug that that we have proven benefit from it's well, it's proven to reduce the need for transfusions. And in my book nines pretty far from a transfusion. We're not knocking on that door at that point. Right? nine and a half. Right? Yeah. Lab error within 10. Like you're within kissing distance. Oh, yeah.

Matthew Sparks 47:51
I mean, it's like when it's like a, I mean, not that I do this, but it's like, speed limit. Yeah. One thing I want to say. There is a I just want it just might be for the earlier but I finally came up with a good joke. And as

Joel 48:09
I said, we don't do those on this type of show.

Matthew Sparks 48:12
Yeah, you know, you know, Ted Talks only here. Yeah, Tony Stark's daughter. Her name is Annie cytosis. And I just had to say that

Everyone 48:25
Laughter

Matt 48:27
she's not in the case. You just wanted to let the audience know.

Stuart 48:31

Everyone know,

Matt 48:31
this is a new thing. We're trying to show adding backstory, a rich backstory.

Matthew Sparks 48:40
She's actually the at the appointment. Important.

Matt 48:45
Ah, I like that. Thank you. So Joe, actually, Joe, you kind of anticipated because I was about to throw a question to Paul. Paul, I don't know about you. Do you feel comfortable ordering the ESA yourself? And and do you do you know, like, do you think about that? I mean, it's not something that I do routinely? No, I

Paul 49:08
certainly at this stage. This is I mean, I might check the AICPA level. But this is someone who I at this point would certainly have shunted off to nephrology and asked for their help in terms of sort of managing their their iron stores and turning their hemoglobin more needs to be like, this is not something I'd be trying to do independently.

Pascal 49:20
Yeah. And why would you check their equal levels?

Paul 49:23
It's a Yeah, that's a great question, proof of concept more than anything else. You're right. It's not going to change management all that much at all. So because you've already probably cracked the case with the labs that you already have in the clinical Gestalt. But it just, it's always nice to be smug and feel right about something at least one time in my life, I think, levels a good way to do that.

Pascal 49:39
I was curious,

Matthew Sparks 49:39
I wanted to point out, and this is I think an important thing and Joel just hinted on like this is really important to recognize that there are significant side effects and you know, for our clinic, anyone who is even contemplating putting on retro polytune, we have a list of those individuals with Have one of our extenders are the one that administering it, and they can keep track of it. And so this is a it's really a strict protocol for how we manage it. And we don't just use it indiscriminately. It's our CKD population.

Matt 50:13
And isn't uncontrolled hypertension a relative contraindication? Am I? It is okay. Yeah, yeah,

Pascal 50:19
for sure.

Matt 50:21
Yeah. So, so what we're talking about here, this is a patient with now advanced CKD, probably CKD. For the K Diigo guidelines, which we've quoted a bunch of times here, they pretty much want you to get the hemoglobin above 10, in this person's at 9.5. And Joel's point was, because these agents are not without risk. And what these agents do is reduce the need for transfusion, if this patient doesn't have symptoms, and they're 9.5. And your goal is 10. You know, it's, you're like a lab error away from. And so it might not be worth it.

Pascal 50:56
I actually thought I was nine, which I probably would have started. But we all have different ways of practicing with this. Yeah,

Joel 51:05
yeah. And what a part of this is, I'm still I still have the scars from there was a period in the early 2000s, when we were very aggressively raising hemoglobins, to levels of 13. And those that completely backfired. And this was a real, like, for me, it was a real learning experience. And I you know, it was kind of one of those firsthand. I'm like, I don't trust observational data. Now I want to see interventional data, because I was fooled by all of it. And I, you know, I was a young doctor back then. And it was it really scarred because I am certain that the way I took care of patients harmed patients. And, and it was really intimidating. It's It's, it's, it's really informed a lot of how I think about medicine. And you can we covered this enough madness a few years ago in a section of the whole region called missteps in nephrology, and one of them was normalization of hemoglobin. And we had study after study that was giving us signals that maybe we should do this, maybe we shouldn't do it. And then it was so seductive to try to fix people's hearts and reduce cardiovascular disease by fixing this anemia. That,

52:14
you know,

Joel 52:15
the theory just sounds great. Of course, that would make sense, right? Why would you want to have patients leave patients with anemia? No wonder they get lvh. And no wonder they have all this cardiovascular mortality. And at least with the tools that were available, that and this may change with the tools that we're developing now. It was a big mistake, and we have to people.

Matt 52:35
So speaking of new, exciting tools, and potential risk, because of widespread effects, this new I had not heard of this class of drugs before. So there's these new HIF agents. So Pascal, can you tell people what is this hypoxia-inducible factor? And what what are these? What are these new drugs targeting? How do they work? Yeah, so

Pascal 52:58

these are like a big exciting development and nephrology, so these hypoxia-inducible factor drugs are hefts. So basically, half is present in nearly every tissue. And it's composed of two subunits. So we have the half alpha and the beta. And if alpha is regulated by oxygen tension, and so basically have alpha have beta will combine. And together, they will really result in the activation of probably over 4000 genes. And those are only the ones we know. So you can imagine how widespread their effects are. And so under normal oxygen conditions, however, this enzyme called prolyl, hydroxylase, degrades have alpha and therefore have alpha and if beta cannot combine or cannot dimerize and cannot activate those genes. And so these drugs are basically built on the concept of inhibiting the prolyl hydroxylase and that's why they're called HIV phsi. So hypoxia-inducible factor protocol hydroxylase inhibitors, meaning they keep the alpha have alpha and beta dimerized and keep all these genes activators. And why is this important than ckg? Because a large number of these activated genes are actually having to do with eco eco receptors, the various proteins that have to do with iron handling, including transparent transferrin receptor. So you can imagine if HIV is always activated, then you have higher equal levels, better iron handling and higher hemoglobin levels.

Matt 54:48
Yeah, it kind of reminds me if people know how the DPP four inhibitors work, you know, they they keep your endogenous GLP one around longer so it can keep acting Seems like a similar mechanism where this, you know, blocks this pro-level hydroxylase em enzyme, so the hypoxia-inducible factors can go around, and they're turning on all these genes. But some of it sounded a little bit scary, Paul, right.

Joel 55:16
This feels like malignancy just waiting to happen. Yeah, it's like, terrifying. Okay, so maybe I didn't understand half what you said, I may have misunderstood. I

Matt 55:23
see angiogenesis.

Matthew Sparks 55:25
Yeah, my take on this. Okay. So one of the greatest cyclists to ever roam the planet was a man named Lance Armstrong.

Matt 55:35
I've heard of him

Matthew Sparks 55:37
seven-timetimes in a row Tour de France champion. And one of the things that he did was to take Eco, we know that right. And that's not a secret. We know that, that that happen. But one of the things that cyclists do to train is to go and move to the mountains before a big race. Okay, and why would you want to do that? Well, what happens is you get hypoxic, and then you basically stimulate this pathway to produce Ebo. And so basically, this is a way to endogenously boost your Ico so that when you come out of the mountains, you can really go fast.

Joel 56:22

It's mountain living in a pill.

Matthew Sparks 56:24
Exactly. So this is why I will tell people that this basically hiff pH eyes or hip stabiliser tricks your kidney into being hypoxic making Ebo, and all the other things that it needs. However, I will agree with Paul, this is a little scary 4000 genes, who knows what you're doing with them all. I like to I like the human body to do things normally. But this is trying to do is trick that into thinking that that you've gone to the mountains, and you're training for the Tour de France. So that's, that's how I look at this. And, and that's how I kind of remember what what their effects are.

Joel 57:02
Yeah, there was there was some data A number of years ago that looked at dialysis survival by zip code. And what they found is that zip codes at higher altitudes, had the best dialysis survival. And they also found that they took the least amount of EPO, presumably these patients had endogenous HIV being activated all the time, because they were at high altitudes. But again, this is all suggestive data. That's how can we reassure him? Do we have any long term data on these drugs?

Pascal 57:32
No. Well,

Joel 57:33
we have one year data, right? We have one year data, we have

Pascal 57:35
one. Yeah, I wouldn't call that very long term data, the one year data

Matthew Sparks 57:42
set to say these are not FDA approved. Okay, these are, are right now in the pipeline to be approved, potentially. And there, it's going to be a little while before before we get to them. So Pascal, what is the data show so far that we know

Pascal 57:58
so far, so these drugs, you're gonna hear the names and the weather stat, so roxadustat, that dad is that those are some of these drugs. And so at least a couple of trials, at least a couple have looked at roxadustat as compared in patients with ckg as compared to placebo and found that they actually do increase hemoglobin levels by up to almost two grams per deciliter.

Joel 58:28
And that I want to I just want to interrupt for just a second pestle because it because the fact that they did a placebo-controlled trial is really unique. It's one of the steps that was skipped when Ico was introduced, you know, you got to remember the situation when he was introduced in 1987. You know, dialysis patients were running around with hemoglobins of four and five, there was no, no one was doing a placebo trial, everybody was getting drugs. And because the transfusion requirement was just massive, and it

transformed dialysis overnight. It's one of the more remarkable revolutions in medicine is the introduction of this drug. And there's almost no placebo controlled trials for Ebo. Because of that, and it wasn't until, you know, the 20, the 21st century, when we were looking at treating people to normalize the hemoglobin, like was mentioned a little while ago, that we did get those placebo controlled trials. And that's when we also realized how dangerous this drug these drugs could be. And the fact that right now, even before these drugs are introduced, we have that placebo controlled data, and it looks safe is really important. Sorry, Pascal.

Pascal 59:32
Oh, no, thank you for that. So I think with these, like for example, with roxadustat, as I mentioned, so improved hemoglobin and less transfusion requirements. The nice thing that we've seen with these drugs is that they actually work well even and inflamed conditions. So patients who have high CRP improve as well as those who have lower crps and I'm looking at upside and levels and the trials these drugs seem to improve that so somehow they work on improving that inflammatory component that is present and ckd however I have to say one of the big trials that was presented at our big on nephrology meeting last year looking at a data stat versus darby point and alpha that find that even though varada stat that achieve good hemoglobin levels all that but actually mace was actually worse and divided is that group so that brings us back to what can you tell us what makes is yeah sorry so that's the composite of all-cause mortality non fatal emi and non fatal stroke

Matthew Sparks 1:00:43
with major adverse cardiovascular events and that's called afro to tech like that oh to pro to to attack

Pascal 1:00:51
the data stat versus darby point and alpha so that brings us to like our main concern with these drugs of like what are all these other side effects that we don't know about yet but we'll soon find out once they're FDA approved and we start using them in our patients

Joel 1:01:08
yeah so the just a quick summary two drugs roxa due to stat and validate that the data stat and the rocks that was the first one right one more facts that do stat raksa do the stat it's not rocks i don't know how many ds there's rocks a deuce roxadustat

Paul 1:01:29
there i back yeah

Joel 1:01:30
this one duck yeah i just wanted to put this one does not have a may signal correct and this is the one that was better than placebo and as safe as placebo and ckd so that's one and then the the dad Fidesz that that is that the dad is that that has two ds the data stat that one had the may signal so and so it's interesting because what oversee it and it'll be i don't know if these different drugs result in different genes being turned on but that'll but we're seeing individual drug differences not not a class of races

Matthew Sparks 1:02:08

this has something to do with just call them all do stat and then there's a front part to it so dapra do stat vatta

Joel 1:02:17
okay okay roxa do stat

Matthew Sparks 1:02:20
yeah so just really get to do stat down and then you can just add whatever you want

Joel 1:02:25
it's like a doowop but it's a new stat

Matt 1:02:29
Paul I think we've gotten rid of all the easy to say drugs I think all the all the easy to say drug names or it's just getting... whatever have to ask somewhere and you know like all these yeah the band lamb drug whatever that is for okay let's so pascal for this for this we talked about essays we talked about you know the benefits of them we talked about the risks of them for these hips there they are oral right they're not they're not iv or subcutaneous

Pascal 1:03:02
so that's one of their big advantages is

Matt 1:03:04
there also that will yeah and the big downside is we just don't know the safety stuff yet

Pascal 1:03:11
yes we know short term safety and the short term safety signals seem to be acceptable especially with roxadustat but yes agreed we don't know anything beyond 5-10 years

Matt 1:03:26
okay

Matthew Sparks 1:03:27
well we're ready to vote i'm excited yeah

Matt 1:03:30
so I think let's say that for our patient we didn't quite have it in us yet unless he's gonna get enrolled in a clinical trial I think he's he's stuck with an esa if his hemoglobin drops further, but for right now after his discussion with Joel he decided he did not want to take an esa right now but we're going to monitor his hemoglobin his iron studies every one to three months and see how he does so I think at this point let's go around from my screen actually we'll start with pascal pascal so for the for the two regions who would you refer this region who would you take for your winner and you can do that so there's oral versus iv iron and then there's the ESA s versus the hips

Pascal 1:04:14
yeah definitely an oral iron fan and me enough madness is all about what drugs we think will or what thing will impact nephrology in the coming few years i think HIF eyes are the winners here

Matt 1:04:30
okay and so you'll pick that over oral iron as your to take the region

Pascal 1:04:34
yes it has the potential of making a big change in the field

Matt 1:04:39
okay matt what about you

Matthew Sparks 1:04:41
oh this is i've been waiting for this as everyone knows that i'm a huge hagfish fan and so everything goes back to that and you know definitely oral over iv i think from looking at the studies the iv just you know it's just not as impactful well as it could be so oral over iv iron you know ebo you know even though i love tour de France and in cycling they abused it we had a rough time with ebo i'm going to have to pick if ph eyes however i know this is going to be very controversial i'm going to go for the old school oral iron it hasn't hurt people like the other ones have or potentially could and i'm very nervous to venture into the anemia land of these HIFs at this point so i'm going to go with oral iron is my winner

Matt 1:05:36
alright Joel what about you

Joel 1:05:39
so i i voted exactly like pascal i have oral iron over iV iron in the top of the bracket i have HIF over ESA in the bottom of the bracket and i've hif ph is winning the bracket and i have them winning all of nephmadness

Matthew Sparks 1:05:55
ah wow look at wait a second i thought you used iv iron before oral and you say no no, i absolutely do but i think in the future i think these are i'm really impressed with the data the oral irons and i just think the availability just needs to be there i think my practice patterns are old and busted you know if you've noticed my gray beard it's what i do but i think in the future we're gonna be going to ora. i want to hand that to pascal what a beautifully written scouting report this is a great section really did a nice job with this very nice job

Matt 1:06:34
alright guys so paul what do you want to paul what do you want to do

Paul 1:06:39

yeah so i'll tell you i historically i have done so poorly with nephmadness i'm gonna pull a stanza and go with the opposite of my gut so i feel like i probably would have gone with iv versus HIF but i think i'm gonna reverse that i actually i like orals a lot and i 'm gonna i would have gone with HIF just because i know that nephrologist like the shiny new stuff so i think i'm actually gonna with the essays but with oral to take it so i think i'm gonna end up with oral over ESA with the oral actually take the take the region

Joel 1:07:09
paul i like you (laughter)

Matt 1:07:11
I would pick iv iron i like to i like to cure the patient in the infusion center and i would i would pick hIF over HIF. i've never been a big fan of the essays and i like the shiny new toy and then i think if it's probably gonna go go out and you know take this region just because it's a shiny new thing as you said paul

Paul 1:07:36
Pascal why don't you give us say you're the main takeaway points where listeners should be taken away from this very very exciting region

Pascal 1:07:45
right so especially for the audience listening who's more into primary care and internal medicine I think always remember with CKD stage three and lower look for iron deficiency anemia oral agents are a great tool to deplete iron deficiency, but there are some circumstances when iv iron is necessary and actually iv iron is not as scary as we once thought it was the essays are still our current go-to for people with deficiency and but remember that they are associated with a lot of side effects in fact and especially in patients with a stroke or history of malignancy or high blood pressure and finally I think the thing we're most excited about as the new drugs the HIV ph eyes which hopefully will prove to be a game-changer in the field but again long term data is missing and something we have to keep in mind before we prescribe

Matt 1:08:51
them alright feed that into the outro

Paul 1:08:59
this has been another episode of the curb ciders bringing you a little knowledge food for your brain

Matt 1:10:17
oh yummy

Paul 1:10:18
thank you and goodbye