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Rare Blood Disorders & Hemoglobinopathies: Updates on Diagnosis & Treatment in the Emergency Department

Announcer:

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Here's your host is Dr. William Mencia.

Dr. Andemariam, Dr. Kaide, welcome to both of you.

Dr. Andemariam:

Thank you. Thank you for having us.

Dr. Kaide:

Thank you, nice to be here.

Dr. Mencia:

Now, later on in our activity we are going to be speaking with Dr. Kaide about hemophilia, but for now, let's start with you, Dr. Andemariam, and focus on sickle cell disease. Can you explain for us what some of the misconceptions surrounding sickle cell and patients who present to the emergency department with vaso-occlusive crises are and how we can get better at identifying patients that require rapid pain control?

Dr. Andemariam:

I think that's a really important question. Individuals living with sickle cell disease in our country really do rely on emergency departments for management of their acute vaso-occlusive pain crises, but it's important for clinicians in the emergency department to know that data gives us clear evidence that, in particular, adults living with sickle cell disease have exhausted all opportunities to treat their pain at home by the time that they presented to the emergency department, and they're there because oral medications or taking a hot shower or trying to rest or using hot compresses really just hasn't worked at home, so they're there out of desperation. Majority of these pain episodes are treated outside of the emergency department. In fact, if you look at the PiSCES data, less than 5% of all acute painful crises in this population ever present themselves in the ED, so they're there for help and support, and they need management that not only includes opioids and nonsteroidal anti-inflammatories but IV fluids, oxygenation, and just some compassion.

Dr. Mencia:

Understanding the nature of these barriers, what suggestions would you make for optimizing recognition of the sickle cell patient in crisis and the importance of starting treatment quickly?

Dr. Andemariam:

Well, I think, first of all, it's really important to recognize that individuals who provide care in the emergency department, whether they are physicians, physician extenders, or nurses, that they are some of the most compassionate people that we have in medicine in our country.

Dr. Mencia:

So, what strategies would you suggest for overcoming some of these negative barriers towards patients in the emergency department?

Dr. Andemariam:

I think the principles, first and foremost, are trust the patient, trust the fact that they're telling you that they have sickle cell disease. As most emergency providers know, there is no rapid test for sickle cell disease like there are rapid tests for other things in the emergency department. For every 99 patients who are coming in and telling you they have sickle cell disease and they are in pain and they need help, there might be 1 patient that is telling you a story, but that wouldn't be the proper reason or rationale to withhold treatment. So, number one is believe the patient. Number two, listen to them when they tell you what works for their pain. And number 3, look for other comorbid conditions, as I mentioned before, that could cause an untimely death, including stroke, infection and the acute chest syndrome.

Dr. Mencia:

So, for managing acute VOC in the emergency department, can you describe your thought process in determining the appropriate treatment based on either current guidelines or best practices? And what changes would you like to see in future ASH guidelines in the updates?

Dr. Andemariam:

When you look at the NHLBI guidelines published in 2014, it was an expert opinion guideline on the management of individuals living with sickle cell disease, and it's very clear that these patients need to be treated with IV fluid hydration, oxygenation, as well as analgesics, most often a combination of nonsteroidal anti-inflammatory drugs as well as IV opioids. And there are many publications in the literature that demonstrate that if you can treat the pain promptly, and ideally within 30 minutes of presentation to the emergency department, you can minimize the chances that that patient will require hospitalization. Depending on where you look in the literature, you can see 50–70% reductions in hospitalization rates when patients are treated in a timely fashion. But it's important to note that it's not just that first dose of pain medication but also the importance of frequent reassessments and re-dosing, ideally, again, on an every 30-minute basis. Many publications out there also demonstrate that if you can dose the patient rapidly with 3 doses of IV opioids within 30 minutes each, that after the third dose you can pretty much be clear whether or not the patient needs to be admitted or can be discharged home. So, if you can institute a protocol of rapid assessment, dosing, reassessment and re-dosing, you can very conceivably get the patient in and out of the emergency department within 1.5 to 2 hours. So, I think this is the most important question you've asked so far of me today.

And I would say to my colleagues in the emergency department to stay mindful that this is an important time in sickle cell disease and to convey to the patients that they're seeing in the emergency department with sickle cell disease that there are lots of new therapies being developed in the pipeline. So, when they try to encourage them to follow up with their hematologist in the outpatient setting after they get better and they leave the emergency department, that there are currently 2 disease-modifying therapies that could be prescribed by their hematologist. One is called hydroxyurea, and one, which is newer, is called L-glutamine, and both of these are oral medications that are taken either once or twice a day and can prevent the frequency of pain crises by up to almost 50%. So, that's the landscape today, and it's very important that patients are knowledgeable that there are disease-modifying therapies on the market now.

And probably more importantly, there are lots of new drugs in the pipeline that are specifically looking at changing the course of sickle cell disease. One very exciting drug is called crizanlizumab. It is a monoclonal antibody against P-selectin. And what we've begun to understand over the last 10 or 20 years is that vaso-occlusion in sickle cell disease is not just merely due to a change in shape of the red cells, which is what we all learned in medical school, but is actually mediated also by adhesion of white blood cells and red blood cells to the endothelium, and P-selectin is a key player in mediating this adhesive process. There's an antibody against P-selectin—it's called crizanlizumab, as I mentioned—and this has been studied in a phase II, randomized, placebo-controlled clinical trial published 2 years ago that showed, compared to placebo, that a once-monthly infusion of crizanlizumab can decrease annual pain crises by about 45%. And, in fact, when looking at the treatment arm, almost a third of patients in the treatment arm had no pain crises during the 12 months that they were on study. So, crizanlizumab is one drug that may very well get approved and will make its way into the new guidelines eventually, and it will change, I think, some of the perceptions of patients presenting to the ED with sickle cell pain because far fewer of them will be there. And there are other pipeline investigative agents including gene therapy and gene therapy strategies that

look like they have significant curative potential.

So, that's what you can convey to patients when they are in the emergency department. You can say, "Let's get over the crisis that you presented with today, but let's be mindful that there are things you can do with your hematologist to improve the quality and quantity of your life."

Dr. Mencia:

The first half of our discussion today with Dr. Biree Andemariam focused on how we can better manage sickle cell disease in the emergency department, but now I'd like to speak with our second guest, Dr. Colin Kaide, about hemophilia.

So, without further adieu, Dr. Kaide, what are your initial concerns when a patient with hemophilia presents to the emergency department?

Dr. Kaide:

Well, like with any other emergency patient, I want to know exactly what emergency I'm dealing with. Did this patient have a spontaneous bleed? Did they have a traumatic event? And if so, what part of their body was injured? And I'm going to treat them pretty much like any other patient with a few notable exceptions. Some of the things that I really want to know is what kind of hemophilia does this patient have, hemophilia A or hemophilia B, because they are essentially different treatments, and do they have inhibitors to factor. As you can understand, when somebody is taking an artificial or a recombinant factor, they can develop antibodies to it, and those antibodies are called inhibitors, such that when they get an injury, if you give them more factor, it's going to be inactivated. I also want to know if the patient is on a different kind of medication as prophylaxis, something like emicizumab, or Hemlibra, which works to activate factor X and factor IX without the need for factor VIII. This information is very important for me when I'm looking at the patient initially. As with any kind of emergency bleeding episode, I want to look for controllable sources and see if I can fix the problem that way. If somebody has, let's say, a head injury, I'm going to want to be doing a CAT scan, or if they have had an abdominal injury, I'm going to want to do a scan in order to evaluate for the degree of injury. The most important thing, however—this is different from regular trauma patients—is that I want to treat them early, and I'm not going to necessarily wait to get results of my testing before ordering factor and finding out the availability. And if I'm in a situation where I don't have factor available, like at a smaller institution, I want to make arrangements to transfer that patient to someplace pretty quickly.

Dr. Mencia:

Now, the most common presentation of hemophilia in the emergency department is hemarthrosis. So, how do you approach these patients?

Dr. Kaide:

Well, this is a very severe complication of hemophilia, and sometimes you don't think of this as being a life-threatening injury, but it is a limb-threatening injury. A lot of these patients will have had a bleed by the time they reach 4 years old, and as they get older, they begin to develop significant joint problems and degenerative changes that occur as a result of these hemarthroses, so I want to find out if this person has had previous episodes of bleeding; I want to find out how much factor they normally take after their injury, and that may guide some of my therapy; and did they take factor immediately after the injury and right before coming in. Most importantly, I want to find out who manages this patient, who their hematologist is, because I don't want to necessarily try to do this by myself. I really want to be able to get the hematologist involved so we can come up with the appropriate dosing for this particular patient.

There are a couple of different scenarios that you run into. If somebody has hemophilia A or hemophilia B without an inhibitor, I'm going to treat them with factor VIII or factor IX. If the person has hemophilia A without an inhibitor but they are on prophylactic immune therapy, such as emicizumab, I'm still going to have to treat them with an additional agent and give them their factor VIII or factor IX, because although this is good prophylaxis, it doesn't completely replace the need for factor. If the person has hemophilia A with an inhibitor, I can't really give them factor VIII or factor IX. I'm going to have to give them something like FEIBA, factor VIII inhibitor bypassing activity—which another way of thinking about that is activated PCC—and that bypasses the need for factor VIII, or I can give them factor VII—we know that as Novo 7—and that will initiate a thrombin burst. If the person has an inhibitor and is on emicizumab, again, as I said before, even though that is a good prophylactic agent, they still need to be treated with either factor VIII or inhibitor bypassing activity or factor VII. And I could come up with a way of calculating my doses, and that's something that... if you need to do that, that's something that's readily available to look up.

Dr. Mencia:

Well, let's change that scenario and say the patient comes in after a major trauma and the patient has a severe, life-threatening bleed. How does that change your approach, Dr. Kaide?

Dr. Kaide:

Okay, so the first and most important thing to remember is this sounds like a very scary scenario, but we take care of patients like this all the time, and what I mean by that is, we take care of anticoagulated trauma patients, and this is essentially a similar scenario. The biggest difference between them is that a person who's taking, say, warfarin or a factor Xa inhibitor, one of the new DOACs, the farther in time away they get from the dose, the last dose that they took, the more normal coagulated they are. In the opposite scenario here with a hemophiliac, they are at baseline anticoagulated, and the farther away they get from taking their factor doses, the more anticoagulated they are. So, if this person was not seen initially as a trauma alert or a trauma activation, I'm going to want to get them back to be seen very quickly because they could have very severe bleeding, just like an anticoagulated patient who falls and hits their head. One of the big things when we take care of trauma patients, normally we're used to doing CAT scans of the head, abdomen, chest and everything else and waiting for those results to know what to do. In patients with hemophilia, you need to be treating them with factor if you have suspicion that there is any significant trauma. And the process of ordering factor may take a little while to get it from your pharmacy, or if you don't actually have factor because you're at a smaller facility and you don't normally treat these patients, you have to make arrangements to get them the treatment very quickly. So, the most important thing to emphasize is don't get freaked out because this person is a hemophiliac. Think of them as an anticoagulated trauma patient who you have to reverse that process, and you should be thinking about doing that quickly and before you get your test results.

Dr. Mencia:

And lastly, Dr. Kaide, before we bring Dr. Andemariam back into your discussion, what recommendations would you make to patients on how they can work with their hematologist in terms of prophylaxis or prevention of future bleeds?

Dr. Kaide:

Well, first of all, any time I can avoid giving somebody the regular factor replacement or decrease the dosing, I'm going to decrease the likelihood of them developing inhibitors, and it's going to reduce their emergency department visits and their need for emergency factor administration. They have a very serious life-altering disease process, and they need to be very compliant and have appropriate contact with their hematologist and take their usual precautions in order to prevent the kind of injuries that they can sometimes sustain. There are some prophylactic medications, one of which is out there right now on the market. The other ones are actually still in testing stages. The first one is emicizumab, or Hemlibra, and this is a bispecific antibody. In other words, it binds to factor IX and factor X and it bypasses the need for factor VIII. Initially, this was approved for patients with hemophilia A who had inhibitors, but now it's approved for use in patients who have hemophilia A without inhibitors. And this is sort of a life-changing kind of medication in terms of it's going to decrease the number of visits to the emergency department and the need for high doses of factor replacement. Although, if these patients come in and they're injured, they still need to get factor replacement. It's going to decrease the amount of factor replacement, and it's going to decrease the number of times that they're going to end up in the emergency department. And this is true of all these agents that are under investigation.

Fitusiran is still in the development process, and this is an interfering RNA therapeutic molecule that decreases antithrombin synthesis and, therefore, helps to control bleeding in the context of receiving factor. BIVV01—that's, of course, the scientific name; it doesn't have a trade name yet—this is an investigational therapy that is a slightly different variant of factor VIII that allows it to last a lot longer in the bloodstream, and that lasts up to 45 hours. And again, this is going to decrease the frequency of use so the patient will have a more steady state of factor VIII level. Fidanacogene elaparovect is a really interesting new type of therapy, and what this is, actually, is an adenovirus vector that implants the factor IX gene into the cells where the factor IX gene is missing, and this allows the patient to actually make more factor on their own. And with this kind of research, it opens the door for possibly doing this kind of similar thing with factor VIII diseases, so these are really important therapies that are coming up.

Dr. Mencia:

Well, this has certainly been a valuable discussion. And before we wrap up, I'd like to hear from both of you on what one take-home message is that you'd like to leave with our audience today. Dr. Andemariam, let's start with you.

Dr. Andemariam:

I think the take-home message, at least with respect to treating acute pain in the emergency department in sickle cell patients, is to believe the patient, treat them quickly, and hopefully be able to discharge them home into the care of an expert hematologist or primary care physician.

Dr. Mencia:

And how about you, Dr. Kaide?

Dr. Kaide:

If you have a patient who has hemophilia, don't get freaked out by it. Think of this patient as somebody who is on anticoagulation, give factor early and quickly, and beware of delayed bleeding in some of these patients because that can certainly happen.

Dr. Mencia:

Well, those are all great things for us to remember when managing complications of rare blood disorders and hemoglobinopathies in the emergency department. And I'd like to thank Drs. Biree Andemariam and Colin Kaide for their insights during this discussion. It was great speaking with both of you today.

Dr. Andemariam:

Thank you.

Dr. Kaide:

Thanks for having us.

Announcer:

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