Angie Onofre:

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Welcome to our live webinar titled PNH 101: Understanding Diagnosis and Treatment. Thank you for joining us. My name is Angie Onofre and I'm the Director of Patient Education at AAMDSIF and I'll be moderating the presentation today. As we get started, I would like to acknowledge Alexion Pharmaceuticals and Achillion Pharmaceuticals for providing educational grants to help support this webinar program.

Today's presenter's Dr. Amy DeZern, Assist Professor of Oncology and Medicine at the John Hopkins University School of Medicine. She attended medical school at John Hopkins and also completed her residency, oncology and hematology fellowships there. She also holds a Masters degree in Clinical Investigation from the Bloomberg School of Public Health. Her primary clinical and research interests are bone marrow failure disorders, including MDS, aplastic anemia, PNH, and other bone marrow failure syndromes.

Dr. DeZern specializes in clinical studies of diagnostics and maintains a database of samples in clinical information for outcomes research and enjoys taking care of patients with these diseases. It is my pleasure to welcome Dr. DeZern.

Dr. Amy DeZern: Thank you, Angie, and welcome to everyone who's joined us this afternoon. I appreciate your time and I hope you'll find it educational. And I'm happy to answer your questions when we finish going through the slides. This is intended as a presentation as a broad overview of PNH in general. And then there will be some nuances as we work through a few cases. So we'll go ahead and get started.

I have no conflicts of interest. And we'll first start by talking about the clinical aspects of PNH. So as many of you probably know, this is a very rare disease, but more specifically, we think of it as a stem cell disorder. And it's also clonal. This means that all the

PNH cells that are causing the disease in any patient come from the same grandmother or grandfather cell. And this is the aspect of clonality that's important to this disorder.

What these PNH cells cause in the patients who have PNH, including hemolytic anemia – and this is the breakdown of the blood cells because of uncontrolled complement activation, which I will explain to you a little bit further on in the presentation; blood clotting, or thrombosis, which can be a dangerous part of the disorder and one that may cause a lot of symptoms; and then the bone marrow failure aspect of PNH, where a patient is unable to make enough blood cells to have normal values on their blood counts when we check them through a phlebotomy blood draw.

What I hope you'll learn at the end of the day is that this is a condition that we kind of quite a lot about now and it's able to treated and controlled so that patients ultimately do very well with it.

So I thought I'd start by classifying PNH. There's something called the International PNH Interest Group, or the IPIG. And a few years ago, Dr. Parker – actually, over ten years ago now – wrote a paper that classified PNH into different ways. And I do find this is a helpful way for me as a clinician to think about the disease with my patients to help them understand where the different treatments fit for their type of PNH disease.

So what many of you are probably most familiar with is what is termed classical PNH. And the textbook definition of this hemolytic and phlebotomic patients – so the breaking down of the red blood cells and the clotting patients who have evidence of PNH clones without having any other bone marrow failure problems. These patients tend to only have anemia and/or the blood clots. They don't usually have problems with other blood counts, like the white cells or the platelets.

The next kind of PNH, which may be something many people have questions about, is called PNH in the context of primary bone marrow disorders, the most common two being aplastic anemia or MDS, myelodysplastic syndrome. And these patients have a little bit of a different picture than the classical PNH patients in that their other cell lines or blood counts, such as the white blood cells or the platelets may be more substantially low and not just anemic like the classical PNH patients.

Finally, there's patients who have what is characterized as sub-clinical PNH. And these people have small PNH clones, so a population of PNH cells that we are able to find when we find these patients' blood in the hospital, but there is not any clinical evidence or laboratory evidence of breakdown of the red blood cells or hemolysis or of any blood clotting. And these different types of PNH do have a little bit of a different approach, which is important from the patient's perspective.

So let's talk about a patient that's near and dear to me, a young male, 43 years old. I've known him for quite some time, but he originally presented with a lot of pain in his belly and he had swelling. At first he thought he was just gaining weight, but ultimately it was realized the swelling was because there were blood clots in very important vessels around the liver and the spleen, and this was making his abdomen fill with fluid.

You may have heard of that. It's called Budd-Chiari. And these blood clots were dangerous to him. But as you can see, with his blood counts, his white blood cell count was normal – 8.2 falls into the normal range. His hemoglobin was 6.4. And hemoglobin for a gentleman of this age normally would be 14 or 15. A 6.4 is very anemic. And the platelets, while a little bit low, are a very safe number at 127. And so these suggested to me that he was going to fall into that classical PNH category that we just spoke about.

The next laboratory value that you may be accustomed to looking at with your PNH is something called the LDH, which is lactate dehydrogenase. And normal is usually less than about 200 in most labs. And you can see her his is over 2,000. And that is a laboratory value that should be followed in patients who have PNH and is indicative of the blood being hemolyzed, or breaking down. And that's what was going on for this gentleman with classical PNH. He was having blood clots and hemolysis, leading to the low hemoglobin and the swelling of his belly.

When we looked at his bone marrow biopsy, it had the classic features of PNH, which means there are a lot of cells there. And erythroid hyperplasia is a term you might see in your bone marrow biopsy reports if you read them, and that just means there's too many red blood cells looking up from the microscope at us.

And then we're gonna talk in great detail about PNH flow cytometry. And his was quite positive. And we'll touch on what this means in greater detail later. But just realize that 99 percent, 98 percent PNH cells are very high and suggestive that he has

classical PNH. We'll come back to this gentleman as we go through the talk.

So let's talk about the natural history of PNH. That was just a patient scenario to give you a flavor for some of the types of patients that suffer with this disease. So a long time ago you might read in some textbooks that aren't as up to date that the median survival was thought to be only 10 or 15 years. This is really changing and there are patients that are living nearly survival times. And please remember that if you read something that feels like it's just more negative than that. But people with classical PNH are doing very well.

The things we have to worry about are the serious blood clots – and we'll talk about how to manage those – or people who have significant or severe pancytopenia, which is just the medical word for all three of the cell lines – the white cells, the red cells, and the platelets – being low. And those pancytopenia patients have more bone marrow failure than the gentleman I just presented. Then those patients we have to manage a bit differently.

And then patients who have frequent symptoms of their PNH, they're often called paroxysms. We'll talk about these symptoms. But some of the darkened urine or that problems related to the hemolysis do have more severe courses.

Blood clots can be dangerous and it's something that we need to focus on and make sure that we're thinking about and treating accordingly. And blood clots are the leading cause of morbidity of less-than-good outcomes in PNH. And they happen in about a third of the patients who have PNH overall.

We do have to remember that because this is a clonal stem cell disorder, as I told you about in the first slide, that a small percentage of these, but very real percentage, of these patients can have trouble later on with other bone marrow problems, such as MDS or AML.

Additionally, about a third of new cases of PNH do come out of patients who previously had aplastic anemia. And this is that second category that I mentioned to you from the IPIG criteria of PNH in the setting of another bone marrow failure disorder. And this is very common. Other people who have classical PNH, we call *de novo*, which means they didn't have bone marrow failure before they go their PNH.

So let's talk about the symptoms. If you or your loved ones have known how PNH manifests itself in patients, these symptoms are very real and they can be very bothersome. In the, it's just a fancy medical term for the darkened urine. It's not actually blood in the urine in the sense that the bladder or part of the GU system are not bleeding. It's breakdown of the red blood cells and it's being urinated out. And some people never see the dark urine, but some people see it in points of high stress or when they're sick and it can be something that is their normal manifestation of the disease.

We've talked about the anemia. Macrocytic is the word for when the red blood cells are large under the microscope and this might show in your labs with a value called the NCV looking big. Patients who constantly break down blood can also become iron deficient. And between iron deficiency and anemia, fatigue is a real symptom of PNH and it's something we have to take very seriously.

I've already explained about the pancytopenia, the all three blood counts being low and bone marrow failure. We've talked about the blood clot. Something that's unique to PNH is the blood clot can be in the vein or in the artery. So the venous or the arterial systems. And not all that many diseases can have blood clots of that nature. Sometimes that's the way patients are diagnosed.

We've talked about abdominal pain. In gentlemen, they can have transient impotence and this has to do with the breakdown of the red blood cells and the way that is causing changes to the smooth muscles in the penis and also in the esophagus. People can feel like they a spasm when they're swallowing or even some chest pains. And this is all related to changes with the smooth muscle because of the hemolysis.

We've talked about the fatigue. And then in terms of the central nervous system, or CNS changes, these can be symptoms that patients experience when they just feel like they're not thinking quite like themselves. And all these symptoms are very real and are things to mention to your doctor if you go through diagnosis and treatment for your PNH.

So let's talk about why all these things happen. So the pathophysiology of this disease is actually very interesting. And some of this may seem in great detail - and it's not intended to be of intent scientific discussion, but can show you that we really understand a lot about this disease and it's how we've been able to come to treat it.

So we've talked about how it's a stem cell disease. And the words that come before stem cell disease here acquired. These diseases that we're talking about are not things that patients are born with. And that's why mostly adults are diagnosed with PNH. It's very rare in children less than about 15. We've talked about the clonal aspect, again, coming from one grandfather or grandmother cell in the bone marrow that caused all the other bad actors.

Now, what's unique about this is we know where the mutation is. It's called the mutation. And that is on the X chromosome. Specifically it's the location noted there on your slides, P22.1. And the mutation that causes PNH is because the gene in our body makes a product that's necessary to make a certain type of protein. And I'm gonna show you pictures that better explain this.

But in the body, to make these proteins, you need this gene product. So that if it's not there, which is in the case in patients with PNH who have the Pig-a mutation, they won't have enough or maybe any of these GPI anchor proteins. And that's where the problem comes in.

So this is just a picture of the gene in our bodies. And there's different ways that these mutations can come to pass. And again, it doesn't matter the details, but just so you know, science really has a great understanding of the way these mutations happen to cause this particular gene to be deranged to cause the disease.

So this is a picture of a cell talking about, again, the GPI anchor proteins and how they're made. That's just the way of saying biosynthesis. It's a complicated ten-step process and there are a lot of different genes involved. But all you really need to know for here is that when they make them, they aren't made correctly and that's why we have the problem in patients who have PNH.

And so what you can see is the GPI anchor protein are supposed to hold CD 59 and CD 55 in the cell membrane in that cell that I just showed you. And unfortunately, when the patient has a mutation in the Pig-a gene, this doesn't happen appropriately. And so people with PNH have loss of CD 59 and loss of CD 55. And what happens is that without these, the cells are not protected from this complement-mediated destruction. And that's why patients end up having hymolytic anemia in PNH.

And that's a picture of the patient's darkly-colored urine. And that's why this happens. And we're gonna talk more about what

complement is and why this happens as we go through. And this is, again, the scientific picture that I think is very helpful for patients to recognize that there's trouble with the alternative pathway of complement in patients who have PNH. And that's because based on what we just learned, when you have a mutation in the Pig-a gene and then you don't have the GPI anchor protein, you're not able to protect against this complement.

And so what happens is when a complement is activated in the body when a person is sick or something else happens to cause stress, we aren't able to protect the cells from something called the membrane attack complex, or the MAC. And this is something that goes and pokes holes in the cell membranes of PNH cells and causes them to _____ or break open. And that's why you see the darkened urine and have a lot of the other symptoms in PNH.

And so let's talk about this complement activation more in words in case the pictures weren't as clear as we'd like. So a complement is successful, as in that picture we just showed, where the membrane attack complex attacks the red cells and they break up. This makes patients become anemic. And with hemoglobin, which is released from the red blood cells, or the RBCs, into the rest of the blood, this causes us problems. This is what I was alluding to in the symptoms.

So this free hemoglobin that's now running around the body of the PNH patient nitric oxide. And patients can have trouble with esophageal spasms, abdominal pains, erectile dysfunction, and just overall feeling really tired. And then we talked about how when this is cleared by the kidney, we urinate it out, and that's why we see the dark urine.

So to give you a little flavor to where you might fit in if you or your loved ones have these symptoms, we can talk about what percentage of these patients based on large studies have the PNH symptoms. And again, every patient is unique in your symptoms or your symptoms, we have to ask these questions and see how you're feeling. But I've mentioned about a third or as many as 40 percent of patients do have that blood clot. Nearly all the patients are anemic.

The bone marrow failure is variable. And that gets back to whether or not there's another primary marrow disorder, problem in the bone marrow, or aplastic anemia was known - these types of questions.

The fatigue - look at that, 96 percent. So this sometimes even impairs people's quality of life. The fatigue is real and you should endorse that to your doctors to make sure that we're treating the whole patient and the symptoms that you're having.

We've talked about the hemoglobin area, or the urinating of the hemoglobin pigments. Abdominal pain is more than 50 percent in patients. Dysphagia is a medical term for esophageal spasm or the difficulty swallowing. And some people will really have trouble getting food down and note the sensation in their sort of upper middle chest that can be quite bothersome.

We've talked about the erectile dysfunction. Sometimes it's something men would rather not discuss, but it's in as many as 50 percent of patients nearly and something we do need to address.

And then the chronic renal insufficiency can be trouble with the kidney. And that's one we've seen in about a third of the patients, but it does happen if the hemoglobin pigments that we've seen in the urine clog up the kidney, so to speak.

So we've talked about the blood clotting. It can be the first symptom that a PNH patient has. And the thing that we have to worry about is that it can contribute to what we doctors all damage, which can mean that it's causing problems, just like in that patient I presented initially, where he was having the swelling of fluid in his abdomen. And that was because the blood clot was around the liver and causing difficulty.

It is something that we're very in tune to and try and be thoughtful about in patients who might have blood clots, because we don't want them to have a bad complication or something worse in that setting.

I mentioned to you that the blood clots can be venous or arterial. And so sometimes you may see commercials about DVTs, which are the blood clots in the legs, and that's about a third. The arterial, or CVA, or MI, which is myocardial infarction, which are arterial clots, are less common, but something that we still keep an eye about.

Again, about a third of patients have them in the abdominal area or the stomach and the trunk. And this again can be one of the reasons that this is how patients end up diagnosed with PNH, because it's unusual to have these blood clots in the hepatic veins, which are the veins for the liver. And that's that Budd-Chiari you might hear

or read about. Or the veins that supply the other areas in the abdomen.

So let's talk about this anemia again, because it can be a little different depending on which PNH that you have. So I've been focusing on classical PNH, but also mentioning the PNH in the setting of another bone marrow failure disorder, such as aclassic anemia. So let's go down the left part of your slide first for classical PNH patients.

And this is a picture from a real PNH patient. And you can see these cells here, which aren't nice and round and even, they look like little broken-up cells. And this is called extravascular hemolysis, which is a hallmark of PNH disease. We've talked about how the laboratory measures include an elevated LDH. The little broken-up cells are called schistocytes. And another lab value, which we're gonna talk about going forward, is reticulocytosis, or a reticulocyte count, which is a measure of how the bone marrow is trying to make new red blood cells for a patient. And this is an important lab value for PNH patients as well.

In terms of the patients who has PNH aplastic anemia anemia, or another bone marrow failure disorder, you can see that things look different. This is a picture of a fairly empty bone marrow. And these patients, while they are breaking down their red blood cells just like this and have a similar picture, their bone marrow is more empty and they are not able to increase their reticulocyte count and make as many new red blood cells as a patient with classical PNH could. And so they end up with a low reticulocyte count, which is reticulocytopenia, as opposed to reticulocytosis, which is a high reticulocyte count in classical PNH patients. And so there's a lot of hints to what sort of disorder you have if you've checked the right labs and follow them for the PNH.

Let's talk about another patient again, trying to bring it back to the clinic and how some of these patients present. This is another dear patient of mine, a young woman. She was originally diagnosed in her late teens with aplastic anemia. She was not able to have a bone marrow transplant because she didn't have any siblings. So she got treated with immunosuppressive therapy and she had a complete remission. And this is a great outcome in somebody with aplastic anemia.

But unfortunately, by the time that she came to meet me, things had changed. And these are her blood counts at that time. Her

absolute neutrophil count, which is a measure of the white cells, was quite low. And normal lower limit of normal for this value would be about 1,500. So already we see that her white cells are low.

And so we might at first think that perhaps just the aplastic anemia had come back, because she also has low platelets and she also has low hemoglobin. And this star here just shows she was already getting transfusions.

Her LDH is high, but not as high as the gentleman with classical PNH that I mentioned to you a moment ago. She had no blood clot, but she had that hypocellular bone marrow, just like I showed you a moment ago in this picture, where there's not a lot of cells here to be making new red blood cells and that's why she's getting the transfusions.

But again, her PNH flow looked very similar to the first person, nearly 100 percent in two of the cell lines monocytes and granulocytes on the PNH flow cytometry. And this is an example of a young patient with PNH in the context of another primary marrow disorder - in this case, aplastic anemia.

So I know I've given you a lot of labs and a lot of background examples, but let’s get into greater detail about how we make the diagnosis and hopefully you may see parallels in your own story. Orthis may generate some questions to make sure everybody is getting the right things followed.

So PNH really is a clinical diagnosis. We ask questions about all those symptoms that we've already talked about. And we confirm it with our blood work. And as I've mentioned, every PNH patient is unique and we have to be thoughtful about the individual patient's own symptoms.

A lot of the extent of how a person feels is related to how much somalosis there is. And this can be different at different times of the disease, all getting back to if that complement is activated not. And I neglected to mention during the complement picture that things that activate complement are things like infection or times of stress or other illnesses. And those can be reasons that patient's hemolysis or PNH symptoms can really ramp up during those times.

The average time from symptom start to diagnosis is usually more than three years. And I have had patients that give a really great

story upon looking back of having had the symptoms for even over a decade and it may have started with feeling more fatigued than they thought they should or some or the esophageal spasm or it just seemed like food wasn't going down. And it may take some time for it to be recognized by the physician.

So who should be screened for PNH? Certainly anybody who has the, anybody who has any sort of hymolytic anemia. If patients are known to have aplastic anemia or something like myelodysplastic syndrome, another bone marrow failure disorder, we do check a PNH clone. And I'll show you how we do that in a moment. And it sometimes can be predictive, similar to that young woman that I just shared with you, of who might end up evolving to have more problems from PNH than at the initial time of their diagnosis with their aplastic anemia or their MDS.

Now, these are a lot of fancy words. But in somebody who has a hymolytic anemia and has had a certain blood test called a Coombs test - and this is something that your doctor might have mentioned to you. If the Coombs is negative, but there's still evidence of having hemolysis, then in the setting of having still a high LDH, we really have to think about PNH.

Somebody who has these unusual clotting symptoms - the first gentleman that I presented to you, that is why a PNH clone was checked in him, because of very astute provider thought why would he have these blood clots around the liver and in his belly? Maybe we should just check a PNH clone.

People who don't have explanations for clots in arteries and then people with the esophageal spasm or the trouble swallowing that I've mentioned, who also have the chronic red blood cells are all people that should have PNH tested.

There is a true overlap and I often show this picture to my patients in the clinic if there's some confusion about what's going on or how everything fits in. And this is part of a bigger Vinn diagram, but for the purposes of this discussion, PNH is relatively rare. All of these disorders are, but PNH is more rare than aplastic anemia, which is more rare than myelodysplastic syndrome.

But as you can see, there's overlap of PNH with aplastic anemia and MDS. And that's because these are patients that can have bone marrow failure with PNH clone. And the HMDS is just hypoplastic MDS. And those are just an overlap of these two syndromes. And they too can have a PNH clone quite possibly.

So there's some fluidity in patients who have marrow failure syndromes of PNH, aplastic anemia, or MDS. And that's why organizations like AAMDSIF are just so helpful in bringing this to the forefront of people's minds and working through it with the patient.

So back to the abnormal lab - and I hope if there are patients in the audience or the caregivers or loved ones of patients, that you are familiar with your lab, because this is something that can help keep you safe and allow you to educate providers that may not be your PNH providers, so that we make sure we keep you safe if you have to get labs checked elsewhere.

So CBC stands for complete blood count. And the things that we usually see are the low hemoglobin in patients who are just predominantly anemic are the pancytopenia, all three cell lines down that we've already talked about.

I quite often find patients are less familiar with following their reticulocyte count, but I put quite a lot of stock in this. This is, again, the measure of production of the red blood cells from the bone marrow. And it is helpful to know what you're reticulocyte count is, because it's possible you are going along, doing well with your PNH, and the reticulocyte count is high and your bone marrow is doing its best. And then if it starts to peter out or the reticulocyte count gets low, we may have to think about if something is changing or if you just have a viral illness or there's something else that we need to be attuned to.

We talked about the lactate dehydrogenase being high as a measure of breakdown of blood cells. And similarly, haptoglobin, which is not something that I think needs to be followed regularly, but it would be low and is, again, a measure of breakdown of blood cells.

I've talked about the Coombs test being negative. That will come back again in a minute in patients who were treated with _____. The elevated bilirubin. Bilirubin is one of the breakdown products when the red cells split apart. And so this would be high. Some people think of bilirubin as associated with the liver, which is true, but this would be an indirect bilirubin that is high. And it's often seen if something gets chemistry or liver function tests on a patient. And it's not of great concern if it's in the appropriate context of the PNH red cell breakdown. And then we talked about the urine. And you can actually check for hemoglobin breakdown

products in the urine, just to demonstrate what's going on for our patient.

So now flow cytometry. This is unfortunately fairly expensive test, but it's the way we diagnose PNH. And something that there's been a lot of active research on and things coming along in recent years to get greater detail from our patients of PNH.

So one thing that is nice and is able to be done in the preferable blood - so this isn't something that has to require a bone marrow biopsy all the time, which I know patients' backsides are grateful for - and we look in the granulocytes, which is a fancy word for one specific type of the white cells, and then red blood cells are erythrocyctes.

And just so you know, checking the flow for PNH on red cells alone is not enough, because when they're being broken down or a patient is getting regular red blood cell transfusions, this value can be inappropriately low, if you will. And the way the test is done is some fancy chemistry using monoclonal antibodies, which is really just the way the target, the GPI anchor protein, such as CD 59 or CD 55 that we already talked about.

And those clone sizes that I mentioned earlier to you, those are the percentage of cells that are missing the GPI anchor protein. So you may recall the two patients I've shown you thus far had percentages in the high 90s. And that suggests nearly all of their cells are missing the PNH clone. A few _____ have a large PNH clone and are missing the GPI anchor proteins.

Another test which some patients hear about or your doctors may mention to you is called FLAIR, which is a acronym for these two big words. But it is a special way, again, to look for GPI anchor proteins and is yet another way to help diagnose PNH. And it's important because the PNH cells are resistant to part of the FLAIR _____, this _____ _____, because they don't have the GPI anchor protein, which again is the path of physiology of the disease.

You may read your own PNH flow cytometry report; you may not. But in case you saw this, I wanted you to have an explanation for the types of PNH cells. So sometimes in a report it would tell a doctor or a patient that there are X percent Type 3 cells and X percent Type 2 cells. And this is a flow cytometry picture. And the percentages are what they're quantifying under these curves for us.

And Type 3 cells have no GPI anchor proteins at all. And Type 2 cells have partial loss of the GPI anchor proteins, whereas in patients who don't have PNH, they would have Type 1 cells or normal GPI anchor proteins in the cells. And so these type of cells are not susceptible to the complemented mediated hemolysis that you showed you the picture of before. These are the most susceptible, because they have none of that protection, because they have none of the GPI anchor proteins holding the right parts in the cell membrane and these are just the partial loss and are susceptible, again, for the hemolysis.

So I talked in here another patient of mine. I don't know if this is anybody in this particular audience, but it's something I see a little more frequently than I wish I did. This is a person who has a low white count, especially low neutrophils. They are anemic. And again, low platelets, but a normal LDH. You may recall that I told you that in most labs, an LDH is normal if it's less than about 200.

This gentleman has dysplasia in the middle D in the act of dysplasia. He actually very clearly had dysplasia. And you can see here that while when we do the PNH flow, he does have what would be considered positive numbers. These are very small, nothing like the 97, 98, 99 percent we saw in our other two patients.

But this is that category of sub-clinical PNH in which patients have a small PNH clone. You see here as one percent or so. But there is no clinical or laboratory evidence of blood clots or breakdown of the red blood cells. This anemia is from the bone marrow failure.

And the reason I bring this up is just because no treatment with eculizumab, which is a drug we're about to talk about for treatment of PNH, is needed here. And some people are started on Soliris or eculizumab for PNH clones this small. And that's really not necessary when the LDH shows that there's no hemolysis and the patient's not having any blood clots. So just something to keep in mind, because it'd be nice for people not to have to get a drug when they really don't need it. So these people are said to have a PNH clone, but they don't truly have PNH disease. And it's that sub-clinical PNH category from the IPIG.

Let’s move into treatment, which may be what most of you are interested in. Historically - and this is a bit outdated, but I want you to hear this, because I think it's helpful to see how far we've come - the management of PNH was supposed to be very conservative and supportive. I'm sure everybody knows about

transfusions. Anticoagulants are blood thinners, such as Coumadin or warfarin, are very important for the blood clots originally. Putting at the scene on folic acid and iron supplements is still done and it's very reasonable.

Before we had a good drug for it, people got steroids or _____ _____. It wasn't terribly helpful. And bone marrow transplant was only used originally in the most ill or highest acuity patients. It was curative, but these patients had a lot of trouble with transplants, and so this was not thought to be the first thing that should be done for these PNH patients. And we'll touch more on transplants a bit in a moment.

We've talked about how this statistic is getting a little out of date. And again, I mentioned it to be positive, not negative. You can see that this is a much older study. And we've come a long way since 1995 and patients are doing better and better with PNH. And this is we're very grateful for.

And the reason for that is eculizumab. And the reason I've presented today's talk in the order I have is I wanted to you to understand the symptoms and the path of physiology and the fact that complement activation is a lot of what causes the disease in patients who don't have the GPI anchor proteins, because they have the mutated Pig-a. And so when we inhibit complements with this drugs, which is eculizumab - the trade name is Soliris – patients do very well, because we're fully working through what we know about the disease.

So this is a picture of what the drug looks like, eculizumab. It is a humanized monoclonal antibody. It binds to C5 and it blocks complement, which you may remember from that picture I showed you with the membrane attack complex. One way the membrane attack complex was formed was with C5, and that is blocked by eculizumab. And it's why it's so successful in treating patients.

So here's a picture. Again, thinking through the alternative pathway of complements. And I've mentioned C5. And you see here the eculizumab blocks right there. And so you don't end up forming the membrane attack complex. And so you can't poke the holes in the red blood cells of these patients who have PNH and cause all the problems.

So eculizumab is a drug that's been studied a lot. Some patients really like to know how a drug that they might be putting into their

body seem to be safe and studied. And there have been several studies that taught us a lot about what we know about eculizumab.

So there was the pilot study, which was a small number of patients. There was a triumph study, which was actually Phase. And then there was the SHEPHERD study, which was a broader patient population than the original study. And then these patients got to go on the Extension trial so that they could continue taking the drug for their disease after these studies had come to a completion.

So let me show you what we learned from these studies. First there's the dosing, which certainly if anybody who's taking it, they're well aware, but just to reiterate, before treatment starts, usually we vaccinate for Neisseria. It's a shot and something that has to be maintained over the lifetime of a PNH patient who's getting eculizumab and this helps protects against this particular infection, which is hard for a patient to protect themselves against when they're on eculizumab blocking complements.

And for four weeks in a row, get a dose of 600, which is called the induction phase. And then begin the maintenance phase, taking 900 every two weeks. And for my patients, I do check those labs every two weeks, give or take, to make sure we know what's going on with the CDC and the LDH and the reticulocyte count so that we can take good care of them. Some patients – and we'll talk about this – do need adjustments to smaller dosing intervals, depending on what's going on with them clinically.

So what is very helpful for some PNH patients is to see how wonderful the drug is from these studies. And you can see that the people who take eculizumab compared to those who don't, the time to transfusions is markedly reduced in eculizumab patients. So this is the patients who avoid transfusions. And these are all patients on the placebo arm, which start getting transfusions as this goes down. And so that's one way that this drug is very helpful. It's blocking complement and blocking the hemolysis.

So ultimately from the original study that I showed you, the Phase , there's a 44 percent reduction in packed red blood cell units transfused, and this great for the patients. It shows that reduction in LDH, the measure of blood breakdown, in both the Phase 3 and then the SHEPHERD study with a broader inclusion criteria. And again, which is helpful to see that once you start the drug, the LDH goes way down. And that's why I like for the patients to see that, so they get immediate gratification when we check their labs once they start the drug.

So again, just showing you some results from that original Phase . The placebo patients still had elevation in their LDH and the patients getting Soliris or eculizumab had a marked reduction.

So we've talked about transfusions. Again, this is just another way of showing you that the patients who are receiving eculizumab, who truly have classical PNH, often end up transfusion independent, which is really wonderful _____ _____ complete responder.

Now let's talk about clotting events, because in many ways I consider this one of the most important, if not the most important, part of eculizumab. All the transfusion reduction stuff that I showed you is super important, but in somebody who's having trouble with blood clots, such as the first gentleman that I mentioned, that is a patient that I want to get on eculizumab ASAP to protect them from any dangerous clots that might be the next one coming along, or propagation of the clot is already in the body. And that can be really something to get started on therapy almost immediately.

So you can see this is how many clotting events were happening in the patients before they got started on treatments and after. It's not zero, but it's much, much less, and this is very important. It's 92 percent fewer events with the treatment, which is wonderful.

So if any of you or your loved ones are taking eculizumab, there are some side effects. So I have to say as an oncologist and hematologist, I consider them a very well tolerated drug. Some people do get headaches when it infuses. It's something that in our clinic we manage very easily. It's something to mention to your doctors, but usually even just an over-the-counter anogy that can help or the headache goes away once the drug is not infusing.

Some people get some upper respiratory or running nose symptoms, back pain – these things were all recorded, but you can see, it's really a very small number, nothing too significant, other than the headaches.

So the things that we learned from those trials that I showed you is that it's a safe drug. The side effects are mild. But I mentioned the need for the vaccination again Neisseria. And that's because it was seen in these studies that there was an increased risk for these type of infections. And it's a small risk, but very real, depending on how you interpret 0.5 percent per year. And that's why maintaining the

vaccination is very important. And again, this is an infection that our bodies normally protect against when eculizumab is not blocking C5.

So it's a very effective drug. I've showed you the way it's decreased the hemolysis and decreased the need for transfusions. It improves the quality of life in patients. So there are patients that the fatigue is very limiting, that the esophageal symptoms, the impotence symptoms, and it's very effective in improving this. And it reduces the risk of blood clots, which certainly is very important.

So there are some drawbacks. And I think it's okay to endorse these as a patient, just so you talk through them with your doctor. It's a lifelong therapy – every 14 days through the veins, which is sort of annoying for patients, 'cause they form their life around it. In terms of cost, it is expensive. So Alexion is great about working with patients to make sure any patients with PNH that needs it can get it.

Something that we'll talk more about is it's not a drug that's as effective in patients who have one of the overlapping bone marrow failure syndromes, like aplastic anemia, because as I've showed you, it treats clotting and it treats transfusion needs for hemolysis, but it does not treat bone marrow failure and it also does not treat extravascular hemolysis, which is something we're gonna talk more about. And I think I'm seeing some questions specifically along these lines, which we'll get to at the end.

So the ideal patient for PNH treatment with eculizumab is a classical PNH patient who has a very large population of PNH cells, a high LDH. They don't really have bone marrow failure, and we see that, because their reticulocyte count is elevated and they're doing their best to make new red blood cells.

Just like that Patient Number 1. And that's because for that gentleman, the way that we are able to reduce the intravascular hemolysis with eculizumab, it improves the anemia, reducing the transfusion. And don't feel it's not successful if your hemoglobin is still 11 or 12. It doesn't have to be perfectly normal for it to be effective and helpful. You just really want to decrease the transfusions and improve the anemia, so a patient feels better, reducing other symptoms as well, and reducing clots.

And just to you know, it really has changed the way PNH patients have to take Coumadin or Warfarin, the blood thinners. Because once complement is blocked by eculizumab and the risk of blood

clotting is gone, many patients are able to get off those drugs for thinning the blood. And this again is great for quality of life and doctors visits and so forth.

So I mentioned Patient 1 was the patient with classical PNH who does very well with eculizumab. He's had no further clotting in his abdomen. He's off all anticoagulation. In his case, his hemoglobin did normalize and he's been getting his drug every two weeks for the past four and a half years, which is great.

We've talked about eculizumab does not do. And I'm just sort of hammering this home as we go through the final portions of the talk. It's not fixing that mutation in the Pig-a gene that I mentioned to you in the beginning. It doesn't treat extravascular hemolysis, which we're gonna talk about, which is why I keep mentioning the Coombs test. And it does not make the bone marrow produce more than it already was. And so that set bone marrow failure component, that it's not able to improve upon. And so if a patient on eculizumab started out with a truly low platelet count and a low white count, those are things that the drug is not going to be able to address.

Things to consider – and I just mention, 'cause sometimes people forget about the vaccinations. Again, usually the case managers for eculizumab are really good about the reminders, and nurses and doctors are good. But it is important to be thoughtful about how there's the increased risk for infections that the body would normally protect against with that complement and the membrane attack complex that I showed you the picture of. And so we have to stay vaccinated.

And if a patient on eculizumab has a fever, seeking medical attention at once is very important. Calling your doctor or nurse practitioner, or whomever, letting them know what's going on. All of my patients know to call me the second they get a fever and they actually have with them a prescription for an antibiotic that I often have them take on the way to the clinic or the hospital, just to make sure that we keep them as safe as we can. And having a little card in their wallet or handbag, just describing the potential complication is important as well. Some people even get medical alert bracelets. That's a personal choice, but very reasonable. I've mentioned the inconvenience, and patients do mention that. And we'll talk about that. And I've mentioned the cost as well.

So we're gonna go through this and talk about people who might not be responding as well and what to do. People with bone

marrow failure don't respond as well. People can have breakthroughs. And this is why I said it's important to know what's going on with your LDH and your reticulocyte count, because sometimes these can herald problems.

So if patients have another inflammatory or autoimmune disease, this can cause trouble in patients who are not responding as well to eculizumab. In the study of illness, almost everybody has increased complement activation and increased hemolysis. And so even if a patient just gets a cold or the flu, they can have some transient increase in their hemolysis. Their hemoglobin can go down. Even an extra transfusion may happen in that window.

Pregnancy also changes what's going on, and so we have to make modifications to the eculizumab dosing, usually in patients who are expecting. And then this concept of extravascular hemolysis can be a bit of an issue as well.

These I just mentioned so you've _____. These are very rare things, so be surprised if our audience is aware of it – or excuse me, are experiencing it, but it's possible. There's specific mutations that don't allow patients, specifically of Japanese population usually, to respond to eculizumab. So it prevents the eculizumab from binding. And so these people aren't gonna have a good response from it.

And then patients who have what called polymorphisms and a specific pain are also associated with less good responses to eculizumab. But if something's going on that doesn't seem right, these are just things that your doctor may discuss with you.

Pregnancy, I've mentioned the temporary breakthrough. There's multiple cases of successful pregnancies in women on eculizumab. That's intended to be reassuring, but they do experience some increased as they go through the trimesters. And so often I'd reduce dosing interval, as required by the time the patient is approaching term.

So let's talk about the extravascular hemolysis and what are some ways that you can see evidence of this? And increases are reticulocyte count, which we've talked about a lot now; the fact that the anemia, despite doing everything right and being on eculizumab, persists; and then one of the reasons I was trying to hammer home on the Coombs test, which is also called the direct antiglobulin test, is that in some patients this test, which is negative at the time of diagnosis of their PNH, once they get on eculizumab,

the Coombs test can turn positive. And that's because a specific something called C3 is being deposited on the cell at this point, which is because of the blockage in the cascade, where I showed you the eculizumab blocks things. And this can be a problem.

For some patients, it can not be a problem. It can be asymptomatic. But in the patients that have this extravascular hemolysis, where the laboratory testing of a Coombs has become positive, they can remain dependent on transfusions and this can be frustrating for our patients. But it's something that needs to be investigating by their providers.

So just as a pictorial representation of why this happens, a patient with PNH – we know they don't have the GPI anchor proteins and so they're missing the CD55 and CD59 that we talked about. They're membrane attack complex causes the intravascular hemolysis, and that's their disease.

But then when they get on eculizumab, as in the lower panel here, they still have the same problem, but at this point instead of the membrane attack complex breaking up the cell, they get these little depositions of C3, which I've just drawn here by these little teepees of sorts.

But the C3 causes a problem and causes the reticular antiphilial system in the liver and the spleen to break down the red blood cells in a different way. And this is why patients on eculizumab can still struggle with extravascular hemolysis and anemia.

So what do we do? There's a lot of different ways to make sure that we are addressing anybody who's a sub-optimal responder. We usually start by decreasing the dosing interval. And again, that's why I mentioned I like to check an LDH right before the next dose is given, because you may see a pattern, where after the dose is given, a 14-day interval on the 13th or 14th day, the LDH is practically back up to wherever it started. But if you go to every 12 days, then there's not that time to allow for the drug to wear off and extra blood breakdown to cause in that time.

Something that is important for patients to ensure there's no ongoing inflammation. Gallbladder issues is common in teenage patients and I've had to remove the gallbladders in a few of my patients, because it was causing a chronic inflammatory picture. Patients remained anemic. We took the gallbladder out, the inflammation went away. And then the eculizumab was able to work to its fullest.

People who have chronic infection or even longer-term infection, something like a mono, may have some trouble with added extra hemolysis from the complement activation from the illness.

Sometimes we transfuse these patients, especially the patients who have a larger aspect of bone marrow failure. And we're always looking for new drugs specific to some of the problems that I've mentioned to you as to why patients don't do as well with the one drug we have.

The only cure though for PNH is a bone marrow transplant. Allogeneic just means one from somebody else, to distinguish it from an autologous transplant, which is a transplant from oneself. And we would not do that in PNH. And the bone marrow transplant from somebody else is the only cure.

We usually only move to it in certain clinical situations and it's very patient-specific. But something that's important to distinguish it from some of those earlier details that I shared with you in the talk is it can done as a procedure with less toxicity now. We know that the higher-dose chemotherapy, which is called myeloablation or myeloablative chemotherapy, is not required. And so that's how we're able to do this a bit more safely for patients. And we do it, again, in specific patients who are not responding as well to eculizumab.

Just to give you a flavor in case you wondered, this is our regimen here for patients. We take transplants. And it's still the real transplant. You get some chemotherapy and you get some radiation, but we are able to make the PNH clone go away in patients with this regimen. And these are patients of ours that we have transplanted for PNH and they were patients that were having trouble with clotting or kidney problems or just ongoing transfusion. And we were able to take the PNH clone from very positive, 99 percent, to zero in these patients. And so that is the way that it is a cure for this disease.

I mentioned those unique situations, and one of them being bone marrow failure, and that Patient Number 2 that I presented to you who had PNH in the setting of another primary bone marrow failure disorder, which is her aplastic anemia, she ended up going to bone marrow transplants and she's actually well over a year out now, more than two years, and has done very well. Her PNH clone has disappeared and her counts has nearly normalized.

So this may be something that's appropriate to consider. It's transplant or even other paths – knowing a patient's transfusion burden is very important and something that we like to know and the patient should be thinking about with their doctors. If their marrow failure, the low white count, the low platelets, and then ongoing anemia are a big problem, we have to think about other paths outside of eculizumab.

And then there's a lot of earlier-phase trials – so Phase 1 or Phase 2 trials. And if these are things that a patient and their family are pursuing, there needs to be a very open discussion of the risks and benefits over eculizumab or over the current paradigm for the individual patient who needs them.

There's a lot of drugsresearch, and hopefully that's helpful and exciting for people with PNH, because it is a rare disease and sometimes rare diseases end up orphan diseases. But this is a disease where there a lot of active research and a neat group of people in the world who are studying it and trying to make it better for patients in lots of different ways. And I don't throw this list up to be exhaustive nor to explain all of it, but just to recognize that these are names of different drugs and different compounds _____ investigation, some even in clinical trials for patients who might not be having a complete response for their PNH.

This is a slide that I go over with my patients in the clinic just to mention, so that the patients are aware of things that are the right way and, in my opinion, for the clinical care of their PNH. We've talked about all of them today, how we make the diagnosis, detecting the PNH clone by those two methods that I showed you, following the blood count, the LDH, the reticulocyte count.

I do do a bone marrow biopsy on my patients if their blood counts, specifically the white count and the platelets, are lower than what I would expect for classical PNH. I do a bone marrow biopsy to make sure I understand if there's any component of bone marrow failure or something tending towards aclassical anemia or MDS.

For their treatment we've had a nice discussion on eculizumab on how you load them, do that induction for four weeks, and then do the maintenance. And there are patients, as you just saw, that we have to have the discussion about whether or not a bone marrow transplant or a tematopoietic stem cell transplant is the right thing for them.

And then always monitoring the effects of our therapy in patients who are on eculizumab. Sometimes every two weeks, but at least monthly, the blood count, the LDH, the reticulocyte count, and the chemistry. I follow people's PNH clone over time. I find it especially helpful in patients who may have more fallen into the second category with another bone marrow failure, because if the PNH clone is enlarging, that may tell us something about what their disease is. And then we've talked about the direct antiglobulin test, or the Coombs test, if we think there's some extravascular hemolysis ongoing.

So it's been a nice hour talk with you guys. I know some of it was in great detail. But I hope you saw the method to my madness and have a better understanding for the clinical symptoms, the path of physiology, our testing and our treatments, and why we do some of the things in the way that we do in PNH. And then now I'm happy to take any questions that the group has. Thank you very much.

Angie Onofre: Thank you, Dr. DeZern. We do have a few questions. Our first question comes from Maria and her brother has aplastic anemia and PNH. And he is currently undergoing Soliris treatment, but lately he's been getting sick in the past month and he has had four blood transfusions. I believe what she's asking is why this may be occurring or what could be possible factors that may be making this happen?

Dr. Amy DeZern: Okay, Maria, well, that's a good question. And it may be related to some of the things I just spoke about. And so it sounds as if your brother has a component of bone marrow failure, and that's the aplastic anemia.

But if he's been getting sick, and I'm not sure from the question if he was sick first before the four red blood cell transfusions or you're viewing that as a manifestation of him getting sick. But if he's having increased hemolysis because he has an ongoing illness, perhaps a virus or a cold or a flu, something this winter, then it's not surprising that patients have that increased need for transfusions, because their complement _____ _____ the setting of the illness.

Unfortunately, in somebody who has aplastic anemia, we also have to think about if the eculizumab or the Soliris is just not able to compensate for the bone marrow not producing enough red blood cells. And that's the other possible reason for needing the transfusions. But I think it's two possible reasons and it may be that the four transfusions are in the past, the illness is being recovered

from and he'll go back to his steady state. But if the aplastic anemia is contributing more to the need for transfusions, then the Soliris is probably not going to be able to keep that in check as well.

Angie Onofre: Okay, thank you. Our next question comes from Amy. She has aplastic anemia and was diagnosed as PNH right after ATG treatment. Her clone size is under 50 percent and she does not need treatment currently. Her LDH is just above normal and she has CVID, which complicates things for her. She's received the meningitis vaccine but did not gain any protection. She is asking if her clone size elevated to a point where I needed treatment – or to a point, I'm sorry – where she needed treatment, would you not suggest Soliris because of the meningitis potential?

Dr. Amy DeZern: That's an excellent question. And often – I'm gonna answer it in a couple ways – often patients who have PNH after response to immunosuppressive therapy for aplastic anemia do not clot. And if you've had a marrow response from the ATG, for the aplastic anemia and the clone is just – it is what it is – 50 percent. Then I think it's a good thing that you and your physician are being thoughtful about not starting treatment with eculizumab.

However, I would not say that the lack of response to the vaccination is an absolute contraindication to eculizumab. I think prophylactic antibiotics with ciprofloxacin, which is an antibacterial for the duration of being on the eculizumab, would be a prudent way to go and just heightened attention on your part and your provider's part for any illness in a setting of being on a complement blocker. But taking a prophylactic antibiotic, which I know is not fun for forever, but I think that would be a way to keep you safe and present any hemolysis.

Angie Onofre: Okay, thank you. Our next question come from Linda. And she has PNH and pancytopenia. Her LDH level is within normal range. And her clone size is small, a .7 percent. She is not yet on Soliris, but she was asking would it help or not at this time?

Dr. Amy DeZern: So let me make sure I know, Angie. Her LDH is pretty normal? Is that what it said?

Angie Onofre: Yeah, she says her LDH level is within normal range and her clone size is at .7 percent. And she's not on Soliris yet.

Dr. Amy DeZern: That is a patient similar to the Patient Number 3 that I mentioned. And it may not be exactly the same, but analogous, Linda. And

usually those are not patients that needed eculizumab. The clone size is small, there's no clotting, and with a normal LDH, it's one of those things that it really wouldn't – the things that it could help, you don't have. And so it's probably good that you don't need it right now.

Angie Onofre: Okay, thank you. Our next question comes from Mischa. And she is asking if eculizumab is increased for a reason of trauma and inflammation and can it be reduced again after with no damage?

Dr. Amy DeZern: Yes. So if I understand the question, in the setting of a particular medical stress and the dosing interval has to be decreased – thus the dosing of the drug is increased. Once the active or the acute insult has passed, can you go back to the every 14-day or whatever the baseline dosing was? And the answer is yes, as long as that stress is gone.

Angie Onofre: Okay, thank you. Our next question comes from Jules. And she is asking what difference is there with I'm assuming it's a dual diagnosis of PNH and MDS.

Dr. Amy DeZern: What difference is there?

Angie Onofre: I think she, treatment-wise and diagnosis-wise, I think she's asking, yeah, what is the difference with a dual diagnosis of PNH and MDS?

Dr. Amy DeZern: So depending on the size of the clone – and I'll go back to that Patient Number 3 example – usually patients who have MDS and may have a sub-clinical small PNH clone, eculizumab does not enter into the therapeutic algorithm as long as there's no clotting and there's no active hemolysis. It's most likely that in the anemia or how the MDS is diagnosed is related to the marrow failure aspect of the MDS. And MDS-specific therapy should be entertained as appropriate for the degree of MDS.

And the PNH clone is usually just something that was found on clinical testing but does not require further intervention and often not further monitoring, if it is truly small, as it was in that example I showed you, where it was .7.

Angie Onofre: Okay, thank you. Our next question comes from Natalie. Her daughter has PNH and they've known since 2013. She is asking how often are they supposed to do a bone marrow biopsy or aspiration? And do they have to do both? Some additional information she included is that her clone size is 98 percent and

they did do a biopsy back in 2013, but she is still in pain in the area it was done and refuses to do another one.

Her HGB varies between 7.5 to 8.5 and she's always fatigued and suffers of abdominal pains, back pains on a daily basis. What would be your recommendation for the bone marrow biopsy or aspiration?

Dr. Amy DeZern: I'm sorry she's still having discomfort here three years later. That's very unfortunate and I know can be a struggle and a stress. I and most people who take care of a number of teenage patients only use the biopsies if they're going to change therapy. And so I would not make a rule, like in somebody who's been on eculizumab for three years, that you had to have on every year. It's nothing like that. It's dictated by the blood counts, the response to the therapy. And if it seems like there's a need for another therapy.

I think the part of the question was do you always need to do an aspiration and a biopsy? And actually, in this case, you probably do, because the aspirate is the first toll of the liquid marrow. And in a case that you're describing for your daughter, Natalie, I would think that given her hemoglobins are still running fairly low on treatment, doing another bone marrow biopsy and looking for specific features of aplastic anemia or something else would be prudent. And that does require the aspirate for the liquid tests, like flow cytometry and stereotyping. And then the core, which is taking the small cylinder of bone out to look at the cellularium, so forth, would be very helpful to make sure everything is optimized for your daughter.

But there are certainly ways that it could be less painful and maybe less stressful if it was done in some certain ways. And so having a good conversation with the person who's gonna consider doing the procedure might alleviate some of the concerns that your daughter has.

Angie Onofre: Okay, thank you. Our next question comes from Rachel. She says that she has been on prednisone for over ten years. She was diagnosed 19 years ago. And her question is will prednisone stop working or cause complications to PNH in the future?

Dr. Amy DeZern: So the question to whether or not it would stop working, I would have to know how it was working now, Rachel. But probably wouldn't just stop.

But the question about longer-term complications, certainly steroids, we know have a lot of complications if steroids are used long term in a lot of diseases. And so if treatment was needed for the PNH, we probably wouldn't continue the steroids indefinitely, depending on the dose that you're on. If it's over 10 milligrams for all that time, we worry about bone thinning, osteoporosis, diabetes, some of these longer-term side effects of steroids.

But they won't – if I'm understanding your question correctly, the steroids themselves won't cause a complication to the PNH itself, because it has no effect on its mechanism.

Angie Onofre: Okay, thank you. Our next question comes from Calzer and they have been receiving Soliris for two years now. And it has helped with their abdominal pain and other symptoms. They still receive blood transfusions every three to four weeks. And platelet and white cell counts are severely low. He is asking would you suggest a bone marrow transplant in this case?

Dr. Amy DeZern: On the situation that you described is not uncommon. And patients do have PNH with some other aspects of bone marrow failure. And I think it's great that the eculizumab improved the abdominal symptoms. And there really is an improvement in quality of life for a lot of people who have these symptoms from their PNH.

The ongoing transfusion dependence, a little bit more frequently than once a month, would suggest that there's something else going on in the marrow, perhaps aplastic anemia or otherwise. And once that was sorted out, if it looked like treatment for aplastic anemia, be it a transplant or immunosuppressive therapy was appropriate, I probably would consider moving towards that, if I understand your clinical situation correctly.

Angie Onofre: Okay, thank you. Now, a few questions that are coming are also asking in regards to possibly seeing you as their specialist. Is there any information that you would like to give our patients in regards an email or a contact information?

Dr. Amy DeZern: Sure. If you go to the Hopkins website or just Google me, it brings up – that's probably the easiest way – it brings up the website. And I see patients at Hopkins all the time and I'm happy to see anybody and everybody. Additionally, my email is my first initial, my last name – so ADeZern1@jhmi – which is Johns Hopkins Medical Institution – dot edu.

Angie Onofre: Okay, thank you. We will go through maybe a couple more questions. There's a question stating are there any risks for PNH patients flying or traveling long distances? And if so, who can they be minimized?

Dr. Amy DeZern: So the short answer is probably no. I would have to know a little bit more about how well the PNH was controlled on eculizumab, if the patient was a clotter or not. But in and of itself, if somebody was gonna travel – and I have patients that traveled to Hawaii with no problem whatsoever. It's just making sure their disease is under control, there's a plan to continue the dosage interval on schedule outside of the travel, so making sure that you don't miss lots of dosages. But otherwise the flight itself is not a risk.

Angie Onofre: Okay, thank you. Our last question comes from Yang Yin. And they're asking for a patient who has no access to Soliris, can steroids be used as a short-term treatment to reduce reticulocyte counts and LDH?

Dr. Amy DeZern: Quite often, yes. And there's certain are counties in the world outside of the United States where eculizumab and Soliris are not nearly as readily available or not available at all. And patients like that can be treated with steroids, folic acid, iron supplementation, and transfusions, as I mentioned. And those are all very reasonable ways to go in that setting.

Angie Onofre: Okay, thank you, Dr. DeZern. Once again, I thank you for your informative presentation and your time. On the behalf of the Aplastic Anemia & MDS International Foundation, I would like to thank each and every one of you for joining us today and making us your resource of choice for information on bone marrow failure diseases.

If we were not able to answer your question today, please send it to us via email at help – H-E-L-P – @aamds.org so that our patient educator can respond. Or visit our online learning center at aamds.org/learn for interviews with experts and other programs that may address your question.

And a reminder, as soon as I am done speaking, a post-event survey will appear, requesting your feedback. We appreciate your time to complete this survey. Again, thank you for joining us and please remember we're here to provide you with answers, support, and help. This concludes today's program.

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