

Pemphigus and Pemphigoid Disease Overview Transcript- August 16, 2022 Patient Education Webinar

Becky: Hi, everyone. I'm Becky Strong, the Outreach Director at the IPPF, and I'll be your host for today's webinar. Thank you for joining us. Today, we're joined by Dr. Cory Simpson from the University of Washington for today's Patient Education Webinar. This webinar is now being recorded. I'd like to thank you for being on the call with us and to our sponsors, Sanofi Regeneron, Genentech, and argenx for making today's call possible. "Information is a key factor in living and treating your condition. However, everybody's situation is unique. The IPPF reminds you that the information found on the internet or during presentations like today should be discussed with your own doctor or health care team to determine if it applies to your specific situation." Before we begin, I'd like to take a quick poll, just to see who we have with us today. So, take a moment and answer the question of which condition have you been diagnosed with, pemphigus, pemphigoid, or are you undiagnosed. While we're launching the poll, let me introduce you to our speaker for today.

Becky: Dr. Simpson is a board-certified dermatologist and Assistant Professor in the Division of Dermatology at the University of Washington. In 2012, he graduated from the Medical Scientist Training Program at Northwestern University in Chicago, earning both his Ph.D. and M.D. His thesis research focused on the cellular functions of desmoglein 1, which is targeted in pemphigus, and led him to pursue clinical training in dermatology. After an internship in internal medicine through the University of Chicago, Dr. Simpson moved to the University of Pennsylvania for dermatology residency and served as Chief Resident in his final year at Penn. Upon finishing his clinical training in 2016, he obtained grants from the National Institutes of Health and the Dermatology Foundation, allowing him to return to research, applying genetic tools and imaging techniques to a model of human skin grown in the lab. In 2021, he was recruited to the University of Washington, where he is building a lab focused on understanding how the skin is compromised in dermatologic disorders and identifying potential new treatments to promote tissue regeneration for those with rare skin diseases. Dr. Simpson's weekly clinic in Seattle focuses on both autoimmune and genetic skin diseases, including pemphigus, pemphigoid, Darier, and Hailey-Hailey disease. So now before we begin, I'd like to go over a few housekeeping items... (REVIEWS HOUSEKEEPING SLIDES).

Becky: Now, it's my pleasure to turn things over to Dr. Simpson.

Dr. Simpson: Great well, thank you very much. It's really my pleasure to give one of these webinars to patients and caretakers, or family members, or loved ones, who might be joining us today. And I hope to provide you with a basic overview of these diagnoses that you may have recently come into or that you may have had for years. There's a lot of information here, and I hope this will be helpful to you. As Becky mentioned, I'm currently at the University of

Washington and see patients one day a week in a specialty clinic focused on blistering disorders. Then I also run a laboratory where we're trying to do some research, to better understand certain blistering diseases. I do have a couple of disclosures. I recently served on an advisory board for argenx, which is testing a new therapy for pemphigus, trying to help them with their trial design. And I'll be discussing therapies that are off label, which means they're not officially approved by the FDA. That's very common in rare diseases because there aren't very many FDA approved therapies.

Dr. Simpson: So I'd like to talk a little bit about my training and how I came into pemphigus. As Becky mentioned, I did a PhD as part of my medical school training with this wonderful person here named Kathy Green, who's been a scientist interested in this structure here, which is called a desmosome that we'll talk about later. So Kathy's lab helped to understand how these structures in the cell get compromised in diseases like pemphigus. So her lab made some of the early discoveries to understand how it is that pemphigus happens. So normally you have these cells in the skin that we'll talk a little bit more about later that are basically stapled to one another at the sites of adhesion, where they stick together through things called desmosomes. And when those get compromised, in pemphigus, that leads to blistering like that's shown here where you have blisters and open sores. But, these can also be compromised and lead to skin blistering and diseases called Darier and Hailey-Hailey disease which are some of the diseases my lab is working on, which can have some similarities to pemphigus. So one of the questions that was submitted was about that. As opposed to pemphigus which is an immune system issue, a Hailey, Hailey, and Darier disease are genetic disorders that get passed down from parents to children. So, all that scientific training that I did in the lab really helped me to understand the need for research to better understand these diseases and how they can impact patients who suffer from these rare disorders. And so I went on to do clinical training at Penn in Philadelphia and learn from two wonderful mentors, Amy Payne and John Stanley, who are both physicians and scientists that have helped to really make some critical discoveries in the science that helps us to understand pemphigus and pemphigoid. Now I've moved to the University of Washington in Seattle to do my own independent research lab here.

Dr. Simpson: Pemphigus and pemphigoid are two very similar sounding diseases but two different diseases. They both share a root in the word pemphix, which is from the Greek word bubble or blister. So we're going to talk a little bit about what are the similarities and differences between these two diseases? How does the blistering in these diseases actually occur? What are the steps that you need to know about to get a diagnosis? And then what types of treatments or therapies are generally used for these diseases?

Dr. Simpson: So pemphigus and pemphigoid are both caused by autoantibodies. So what does that mean? Well the word auto means self and autoimmune means making an immune system reaction against yourselves. Antibodies are normally very helpful proteins that protect

humans. They bind to and they destroy things like bacteria, viruses, or parasites, and they're a big part of our immune system. But when you develop autoantibodies, that means you make an antibody that recognizes yourself and that's a problem. So these are harmful proteins that will then damage a specific part of yourself. So you may know people with other autoimmune diseases. Some examples are rheumatoid arthritis, where there is damage to joints or nerve damage that occurs in a disease like multiple sclerosis. In pemphigus and pemphigoid the auto antibodies, so the antibodies that recognize your own self, these are harmful proteins that bind to and damage the adhesive structures that help the skin and the mucosal membranes to stick together. So that's why in these diseases, you get blisters and you get sores that affect the skin and also the mucosa also referred to as mucous membranes. That's the wet lining of the eyes, nose, mouth, the genital tracks, et cetera. So both of those types of tissues can be compromised in diseases like pemphigus or pemphigoid. When we talk about these being autoimmune diseases it means it's your own immune system that has somehow got confused and started turning on your own body and making antibodies that attack your own skin and mucous membranes.

Dr. Simpson: So, the skin and the mucosa are very similar in structure, they're multi-layered protective tissues that serve as sort of a barrier to protect our bodies from the outside world. As I mentioned, the mucosal linings are the gums, the inside of the mouth, the tongue, eyes inside of the nose, the larynx or voice box, the esophagus, which is the deeper part of the throat, the genitals, the urinary tract, and the perianal area. So all of those areas can actually be attacked in pemphigus or pemphigoid and lead to blisters or open sores. So it's not just a skin disease, it can really affect any one of these other tissues. That's why sometimes it becomes challenging to assemble the right team of providers that have different areas of expertise. So you might initially go to an oral surgeon to help get a biopsy, but you might end up being managed by a dermatologist. Or you might initially see a rheumatologist because you have an autoimmune disease but they may then eventually need to send you to a specialist who knows a little bit more about the skin like a dermatologist. So it often requires what we call an interdisciplinary team or different doctors that have different specialties to cooperate together to find the best diagnosis and treatment plan. When we think about the skin, I'll be showing a lot of slides that depict the skin in what's called a cross-section. If you actually think about your skin, if you took a little cookie cutter and sort of removed the little cylinder of skin, this is what it looks like if we're looking at it from the side. So these brown layers of the outside of your skin that you can touch. The first next deeper layer is called the epidermis, deeper to that is called the dermis, and then below that is where the fat. So all these different layers are contained in the thin tissue of the skin. When we think about doing a biopsy, what happens is they take a little piece of skin out and they cut it with a blade along the long axis to get what's called a cross-section so that we can see the skin and all of its different layers from the side. That is what a pathologist does when they take that piece of your skin and try to make the diagnosis for your doctor.

Dr. Simpson: This is what that ends up looking like in what we call pathology or histology, where it shows what the tissue looks like and all of the different cells that make up the tissues.

This is what the skin and mucous membrane looks like. These dark purple structures are nuclei if you remember some biology from maybe high school. Cells have a nucleus in the middle and they have cytoplasm and they're round structures. But in the skin, they form multiple different layers that stack on top of one another and form a protective barrier on the outside of your body. So these cells in the skin are hooked together by things called desmosomes.

Desmosomes are sort of like rivets or spot welds that basically take the skin cells and staple them together so that they don't fall apart. So if you push on your skin or move it, the skin has the ability to resist that mechanical stress from falling or from pinching or from rubbing. But if you have a compromise of those sticky structures, the skin cells then rip apart and that's what causes a blister. The blistering in pemphigus we will talk about first. Pemphigus targets the sticky spot welds that sort of normally stick the skin cells together. The name desmosome comes from desmos, which means a bond or a link and somas which means body. So a desmosome means a bonding body or linking body that links two cells together so that they don't fall apart and that's what allows your skin to be a barrier for your body and to not break apart.

Dr. Simpson: This is what skin cells look like. You can see a lot of these little pin point attachments between the cells. Here's one cell and here's its neighbor. You can see all these little stringy connections between the cells, and that's where the desmosomes are and that's what basically are stapling your cells together in the skin so they don't fall apart. So we can zoom in and see that there are these really nice structures that basically glue the cell together at various points along their intersection. That's really important in tissues like the skin and the heart also.

Dr. Simpson: What happens in pemphigus? Normally we have these spot welds or sticky points that keep the cells attached to one another. In pemphigus these are called Desmoglein 1 and Desmoglein 3 and as you get to be familiar with these diseases, you'll realize you almost have to learn a new language. These odd words have a lot of syllables, and they're kind of hard to understand. But these are basically the glue that sticks your skin cells together. When you get a test for antibodies, we test whether they recognize these particular sticky proteins called Desmoglein 1 and 3. You may have had a test called an ELISA and that shows that you had antibodies to one of these different proteins. We draw an antibody as one of these Y-shaped proteins and these come in there and stick to the desmosomes, which is that adhesive structure. The problem is when you have an antibody, which gets in the way of these adhesive structures, they fall apart. What happens in pemphigus is those antibodies go in there and they get in the way of the glue that is supposed to hold your cells together and then they fall apart one another. What that leads to is the skin tissue falling apart. So all of those cells that are supposed to be really tightly linked to one another, now began to fall apart. That's when fluid from the inside of your body can reach into those spaces that are created, and that's what causes the blisters to form. If we take a biopsy of something like pemphigus, what we'll see is that normally the skin should be a solid tissue, there shouldn't be all this white space in here. That's what a blister looks like in a cross-section on a biopsy. This is an example of what pemphigus looks like when your doctor takes a biopsy. You can see there's all this white space

in the middle of the skin cell and that's where the fluid has come in because the skin cells have fallen apart.

Dr. Simpson: So this is what pemphigus vulgaris can look like on the skin. They're often deflated or what we call flaccid blisters. They're not tight or taught. So they sort of leak fluid because they're not very strong blisters. The other word for blisters is bullae, that's the other word for it. But oftentimes, the blisters will pop and they'll leave behind things like this, which are called erosions or open sores as people might call them. The end result of pemphigus is that you end up getting these open sores. Then you can also get the sores that get dried out and crusty, or scabs on top like shown here. We call those crusts. So this is how pemphigus can look. You can have blisters that have fluid in them, like here. You can have open erosions where the skin is sort of exposed and wounded, or you can have crusts or scabs that look like this over here. But pemphigus can also have this form where it's called vegetative. And there was a question submitted about pemphigus vegetans and this is what this can look like. It's really just a different form, or a different name for pemphigus vulgaris, it's a more specific type of it where you tend to get these really thick heaped up scabs or crusts. And that's why they call them vegetative because they almost look like they've sort of grown on top of one another into multiple thick layers. This is a patient from a paper that we published a while back that had these really thick, almost like armor plates, on the body that have just been scabs, that sort of heaped up and kept growing. So this is what vegetative pemphigus vulgaris can look like. Really it's the same disease as pemphigus vulgaris, it's just a different subtypes of it. So the same pathogenic process when you make those same antibodies.

Dr. Simpson: But pemphigus can also attack the mucous membranes. Inside the mouth is the most common area to get pemphigus but you'll rarely see blisters because you're always swallowing and chewing and moving food around so they often don't stay inflated, the blisters will pop and they leave behind these open sores or erosions. They can affect the inside of the lips or the outside of the lips, the gums. As you can see here, the normal gum tissue is a slight pink, and here you have this raw area around the teeth. It can be on the sides of the cheeks like here, we have a big, open erosion, or it can be on the palette, which is sort of the back of your throat. If you ever have a sore throat or a cold and you look back at that and say ah, sometimes you can see different erosions on the palette, which is the top part of the throat.

Dr. Simpson: As opposed to pemphigus vulgaris this is pemphigus foliaceus, they are very similar diseases, but a little bit different in that these tend to cause more superficial or shallow blistering. So they have very thin roofed blisters like this here, where it's kind of like a thin tissue paper almost. They cause more shallow erosion, so the open sores are not as deep as in pemphigus vulgaris and there's often a lot of crusting and flaking like in this right picture here. The other thing is I tried to include in the photos multiple different skin tones. So here is a more heavily pigmented skin tone, whereas here's a more fair pigmented skin tone. So you can see that pemphigus can look quite different based on your background pigmentation level.

Dr. Simpson: So this is another example of pemphigus foliaceus, which can be on the face as shown here with crusting across the nose and the cheeks. Here it is around the mouth. Or it can even take over almost the entire body surface and this is what we call the erythroderma meaning the entire body surface looks red and scaly. So that's what this looks like. So when it looks like this, sometimes doctors have a hard time making a diagnosis because it can look like something almost like psoriasis or eczema, which are much more common than pemphigus. And that's why it really becomes important that you get a biopsy at some point to really find a specific diagnosis because pemphigus is treated differently than something like eczema or psoriasis. Again, here, you can see how in a fair-skin type you might see more redness or pinkness, whereas in a patient with more heavily pigmented skin, you might not see as much red or pink it may look a little more purple or brown. But still we have superficial crusting and scaling that's very typical of pemphigus.

Dr. Simpson: So moving to pemphigoid which is a related disease, they're very similar in that they're both caused by autoantibodies who make antibodies that attack your own body but in this case it's a deeper blister. So in this case the antibodies are actually targeted against the other types of adhesions in the skin which are called hemidesmosomes. These are like staples that basically take the whole epidermis, this outer layer, and kind of staple it down to its foundation, which is the dermis or basement membrane. So desmosomes link two different skin cells together so now you have two skin cells, where hemidesmosomes which is a half desmosomes it links just one cell down to its foundation. So you have desmosomes that link the cells together and then hemidesmosomes which basically stick the whole skin cell one down to the basement membrane, so that it won't peel off and form a blister.

Dr. Simpson: If we have that in a little cartoon as shown here, we have all of these different, sort of hooks that go into these loops that are here, and I often compare it to Velcro. So you have all of these different hooks that are coming from the skin cells and they have to hook into all these different loops that they're sitting on top of. And that is what a hemidesmosome does. They basically form Velcro to stick the outer layer of the skin, called the epidermis and stick it down to its foundation so that it doesn't peel off. In pemphigoid, a hemidesmosome is made up of a bunch of different proteins that basically staple the skin cell down to its foundation, and so you can think of this like a chain link. So that if any one of these proteins gets targeted by an antibody, it breaks that chain of interactions. And if you break any one link in the chain, it falls apart, right? So if you have antibodies against something like BP 180 or BP 230 or laminin or collagen 7 like in other diseases, that basically breaks this really important chain link and causes the skin to fall apart. But, the blistering here is a little bit different. If you have antibodies that come in, they bind to the bottom part of the cell and sort of lift it off from its foundation. So now, the Velcro can't stick anymore and the whole epidermis basically peels away from its foundation. So instead of the skin cells falling apart from one another, now, the entire outer layer of skin basically peels off from its foundation which is shown here, where you get the entire roof of the epidermis that lifts off of its foundation, which is called the basement membrane. Then that allows fluid to come into that new space that's open up and that's what causes you to get fluid accumulating in the blisters of the skin. If you look at a biopsy from

pemphigoid you can see here the entire epidermis, which is this sort of darker pink layer that's totally lifted off of its basement. This is where the blister fluid is where all this sort of white space is and that shouldn't be there. It should be nicely stapled down to its foundation. That is what happens in pemphigoid, it's a little deeper blister.

Dr. Simpson: So you'll often see because the roof of the blister is a little thicker in pemphigoid you will more often see what we call fluid-filled or tense blisters that are taught and filled with fluid like this here. They're often larger in size. I've seen patients who get very, very large blisters that are almost a foot in size. In some cases, those often need to be punctured to release the fluid. These blisters are called bullae which is where the name bullous pemphigoid comes from. These again are different skin tones showing you that pemphigoid can look a bit different depending on how much pigmentation in your skin. In the middle fair-skinned patient, you can see there's a lot of pink area surrounding the blisters. Whereas, in patients with more pigmentation in their skin, you might not be able to see as much pink here. But the biopsy will look exactly the same under the microscope. So it's really important that you get a biopsy to help make these diagnoses.

Dr. Simpson: Blisters in pemphigoid can also pop so you won't always see blisters. Let's say you had a blister on the side of your leg or on your belly and then that rubs against your clothing, that's not going to stay filled with fluid very long, it's going to pop. And when it pops, it leaves behind an open sore or what we call an erosion. Then you can get weeping of fluid that comes out of these raw areas on the skin so they can be very wet and leak a lot of fluid. Sometimes that fluid can then dry up and cause crusting like it's shown here. You can see these scabs that are stuck down to the skin, that's the result of the fluid leaks out then dries and forms a crust. So this is what pemphigoid can look like in different skin tones. Someone asked about pigmentation results from wounds from pemphigoid. This is a patient of mine who even though this area is healed you can see that the scar looks quite different. You can see the pigmentary pattern looks very different. You can see a lot of areas of pink and brown mixed together and that can take many, many months or even years to fully regain the normal pigmentation. That can be something that's very frustrating to patients, especially if it's in highly visible areas.

Dr. Simpson: Pemphigoid can look a little bit differently sometimes, it can actually look almost like hives. This is urticarial or or hive-like pemphigoid where it can almost look just like hives, where you don't really see any big blisters. It can look like this sometimes so that's why it can be a little tricky to get the right diagnosis because it doesn't always look exactly like the textbooks that teach doctors what pemphigoid should look like. So it can be a little tricky sometimes.

Dr. Simpson: Pemphigoid can also affect the mouth. So somebody asked the question: does pemphigoid cause erosions inside of the mucosa or the mouth? And it can. So again, because

you're constantly chewing and moving food around and stuff, you won't usually see actual blisters and the mouth, you'll usually just see the open sores or erosion where the gum tissue has sort of fallen away from the gums. You can see in these pictures that there are these raw areas that get more red. This middle picture is a pretty extreme example where the normal light pink gum tissue has just totally peeled away from the gums revealing these sort of open areas of bright red tissue, which are erosions. And then it can also affect the sides of the tongue, or the sides of the mouth as shown here.

Dr. Simpson: Mucous membrane pemphigoid is another version of pemphigoid also called cicatricial pemphigoid, so those are actually the same thing. So MMP and cicatricial pemphigoid are actually the same in my book. But this can also affect the eyes in a disease called ocular pemphigoid and this can lead to scarring of the eyes. So it's very important to get the right diagnosis and to get onto treatment as soon as possible. You can see redness in the eyes or erosions or open sore in the eyes and this can lead to sticking of the eyelids to the eyeball. Then as shown on the right here, it can actually lead to scarring. Early scarring can look like this, with sticky portions where the eyelid actually sticks to the eyeball. At the end it can look like a whole sheet of scar over the surface of the eye. And unfortunately, that results in blindness. So, it's really important to get the correct diagnosis and treatment plan to avoid some of these long term complications.

Dr. Simpson: So, that's why the IPPF has this campaign called Biopsies Save Lives. It's really important if you're struggling with a diagnosis or know someone who is, to try to get them diagnosed with a biopsy. That may need to be a skin biopsy, which is a little simpler than a mucosal biopsy which might be done inside the mouth or on the gums or on the roof of the mouth, that can be a little trickier. Biopsies done inside of the eye are especially tricky. If you only have eye symptoms sometimes it needs to be done from the eye so you might need to see an ophthalmologist, for example. If you're having a biopsy done on the roof of your mouth or your tongue you might see an oral surgeon or a periodontist. So oftentimes we need to get multiple specialists involved to really help to get patients the right biopsy, so that we get a proper diagnosis. The other testing that's done with those biopsies is something called immunofluorescence tests, which I'll explain in just a minute and then ELISA tests, which is sort of a more specific way to find those auto antibodies that are causing these diseases.

Dr. Simpson: But it's really important that when the diagnosis is in question, to get a biopsy so that we have some proof of what the disease actually is. It's really important to get a biopsy and what this does is it takes a small piece of the blistered tissue. Remember we talked about taking a little tiny cookie cutter which is often called punch biopsy and you can take the edge of the blister. Normally the skin would look like this with the three different layers: the epidermis, the dermis, and the fat. But at the edge of a blister it's going to have a missing piece where the top layer has sort of peeled away from the bottom layers. That's really helpful for a pathologist

to be able to see where that break in the skin occurs because that can help them to diagnose you with pemphigus foliaceus or pemphigus vulgaris or a form of pemphigoid.

Dr. Simpson: So again, if we take a cross-section through the skin biopsy, this is what it ends up looking like when the pathologist looks at it. So if you have normal skin it's going to all look intact. All the skin cells are held together normally and the entire skin is stapled down to its foundation, there's none of that white space. But if you lose those staples, for example in pemphigoid, again the entire epidermis lifts off and fluid comes in. Then the biopsy will look quite different. So this is a normal biopsy on the right, where someone with pemphigoid has a biopsy that looks like this on the left. There's all this fluid here and then there are also all of these immune cells and that can help a pathologist to give you a diagnosis, of something like bullous pemphigoid versus mucous membrane pemphigoid or other types of blistering diseases. That's how a biopsy becomes very, very helpful. The pattern of where the break in the skin happens and the types of immune cells that come into the skin to cause the redness and itching and all of that can be very helpful for the pathologist to be able to make the diagnosis.

Dr. Simpson: These are three different examples of biopsies. A pathologist goes through training to look at these different patterns of biopsies to help know that the one on the left is bullous pemphigoid where the whole epidermis has lifted off. The one in the middle is pemphigus vulgaris where you have a few layers left behind. Then the one on the right is pemphigus foliaceus, where you have a more superficial blister that doesn't go as deep into the skin. This is why a biopsy becomes very important to help give you a more specific diagnosis.

Dr. Simpson: The other way that we helped to get a more specific diagnosis is by trying to find those antibodies in the skin and this is through immunofluorescence. This uses a special chemical process that allows the antibodies to glow in the dark. A pathologist can use a dark room microscope and actually see your antibodies on a slide that they look at with the microscope. There's something called a D.I.F, which is a direct immunofluorescence and that looks for antibodies that are deposited in your skin. That requires a biopsy, you need to send a piece of tissue to find those antibodies, where are they in the skin and that can help get a diagnosis for you. Then there's something called indirect immunofluorescence, which is a little less direct. So it looks for antibodies that are actually in your bloodstream that are circulating through your body. And so this requires you to get blood drawn to test for those antibodies that are circulating.

Dr. Simpson: So the direct test looks for the antibodies that are deposited at the skin versus the indirect test requires them to take blood out and to look for the antibodies that might be circulating through your body. But both of them can be very useful in finding the specific antibodies that cause pemphigus or pemphigoid.

Dr. Simpson: This is how it works. If you have antibodies that your body has made and they're not helpful antibodies, they end up going into your skin and attacking your skin, let's say they bind to the basement membrane zone, as shown here in pemphigoid. What the lab can do is to add a new antibody to find that other antibody and it glows in the dark. If they take it on a dark field microscope, they can see this sort of fluorescent green line that lines the border between the top layer of the skin on the bottom layer. That can allow them to say, this is pemphigoid based on the pattern of the antibodies that have deposited in the skin. Whereas in pemphigus, which if you remember attacks the desmosomes which are between the cells, you can use fluorescent antibodies to help identify those, it looks different, it looks like this, where you have all of these circles. These are like chicken wire, we call it. So it's a very different pattern in pemphigus which sort of surrounds each of the circular cells because antibodies are between the cells versus pemphigoid where it's lining along the foundation of the skin. This is what allows the pathologist to tell the difference between pemphigus and pemphigoid. This again, is another tool that your doctors can use to give a diagnosis that's more specific.

Dr. Simpson: The other test that will sometimes be done is something called a salt-split skin test and this basically takes the skin and splits it to help to identify are the antibodies on the roof of the blister or are they on the floor of the blister? If we split the skin and lift the top layer off, and the antibodies stay on the basement here or the floor, that can be a very different pattern. If it splits and the antibodies are on the roof, that might mean you have bullous pemphigoid but if they're on the floor, it may mean you have something called mucous membrane pemphigoid. You don't have to understand the details of all this testing but this is why your doctor may order a bunch of different tests and multiple biopsies and all of this because they are trying to get more specific information so that we can get to a more specific diagnosis so that we can better know what's the best treatment for your particular type of disease. This sort of takes the velcro and peels it apart and then says do the antibodies localize to the top of the velcro or to the bottom. So that helps your doctor to make a more specific diagnosis.

Dr. Simpson: So, why does it matter? Why does it matter what specific antibodies you have? I think that was one of the questions submitted as well. Well the different antibodies can mean you have a different disease altogether. In pemphigus vulgaris or PV, that is mostly anti desmoglein3 and typically affects the mucous and the skin. Whereas pemphigus foliaceus usually only has antibodies against desmoglein1 and typically does not have mucous membrane erosions, it's usually just the skin. That was another question that was asked, does pemphigus foliaceus affect the mucous membranes? In classic pemphigus foliaceus it should not, it should only be a skin disease. You can tell the difference because of the specific antibodies that they have in this disease versus pemphigus vulgaris. The other disease is paraneoplastic pemphigus which is quite a different disease that's often associated with cancers like lymphoma. This has a different family of antibodies called anti-plakins. So those can all look different in the different tests that your doctor may order, to help decide whether you have pemphigus vulgaris, do you have pemphigus foliaceus or might you have actually paraneoplastic pemphigus which is very rare.

Dr. Simpson: Then on the other hand in pemphigoid, there are a different family of antibodies. So you might have heard of BP 230 or BP 180 or heard your doctor talking about these tests. Those can predict patients to have either mucosal or skin disease. Whereas if you have something called laminin 332 which is a different antibody, that can mean you might have the disease called mucous membrane pemphigoid and it's important to know that one because it can sometimes be associated with certain cancer types. Then in ocular pemphigoid, there's often a different antibody called Beta-4 integrin. This is important to know because that tends to need to be treated pretty aggressively because it can cause inflammation and scarring of the eye and can lead to blindness. So even though your skin and the inside of your mouth can heal quite well without scarring, if the eye gets involved that can lead to scarring which can be quite difficult and sometimes irreversible. This is why it matters, this is why you have to get all these tests done and why sometimes insurance companies get really stingy about paying for tests and all of that. Usually, it's because your doctor is really trying to get a more specific diagnosis for you. So there is a lot of testing involved and that's important to do.

Dr. Simpson: The other test is called an ELISA. What that does is takes your blood and measures how much of those antibodies you have. So it allows us to quantify is your disease more toward remission, or is it sort of flaring up and getting worse so we can track the level of the bad antibodies with an ELISA test. If you have a lot of antibodies, which again are those Y shaped proteins shown in the blood here, that can lead to a really bright stain on the immunofluorescence, meaning a very high disease activity. But maybe after you've been on treatment for a while or if your disease goes into remission, you might only have a few antibodies and that might look like a much fainter stain on that fluorescent test that they do. So these are some of the ways that we can track the disease and see how it is behaving or responding to treatment. This is why your doctor might want you to get something like an ELISA test or an immunofluorescence test periodically during your treatment, every few months or so, to check how the disease is doing and how your blood level is doing with the antibodies.

Dr. Simpson: So what are the goals of treatment in pemphigus and pemphigoid? Well, short-term is really to try to reduce the amount of inflammation that's in your skin or the mucous membranes and that's often done at the first step using oral or topical steroids because these work generally fast, but they tend to have a lot of side effects. So these treatments tend to reduce the immune cells that are attacking the skin or mucous membranes and get them to stop so that your body can then be allowed to heal. The first goal is to stop all new blistering from happening. The sores and the erosion that you have can take a long time to heal but the very first step is to stop getting new blisters so that ones you have can have a chance to heal up. And that's often done with oral steroids like prednisone. Then long term, the goal is to really stop your body from making those harmful auto antibodies so that it stops attacking your own skin or mucous membranes. We really want to get the disease into remission, but that can take quite a long time, in some cases. It can take several months to really get into a remission so you have to be patient with this disease, which can be very frustrating and sometimes but it does take time to get the body to stop doing that to itself, and to sort of reduce those antibody

levels. Once the disease is in remission for several months, your doctor might start reducing some of the medicines and trying to reduce the number of medications that you need to take to allow your immune system and your normal antibodies to recover.

Dr. Simpson: It's really important that you might need to get some screening blood work before you start getting certain therapies to know which therapies might be right for you and how high risk those therapies might be because some people may not know that they carry around a silent infection. Something like Hepatitis B, or Hepatitis C, or HIV, or tuberculosis, TB, you might have those infections that are sort of hidden in your body and your normal immune system is keeping those infections from becoming a real problem for you. But the problem is, if you have pemphigus or pemphigoid and need to go on what we call immunosuppressive therapy, where we push down the immune system so it starts attacking your own body, that can then allow these other infections to take hold in your body. So there's often really a need to get these tests done before you start treatment so that we know how high-risk are certain treatments for you. Do you happen to have hepatitis C from an old blood transfusion that you got as a child, or something like that, or from a surgery? That can happen to patients and they may not even know it. It's important to get that type of testing done, to make sure that the risk of the therapy is not too high. Then oftentimes we'll check blood counts and liver and kidney function to make sure that you're going to be able to tolerate certain therapies to make sure you're not getting anemic or low blood counts. Or to make sure there's not being damage to your liver or your kidneys. So it's really important that you get these tests done to make sure that your doctor knows that the medications your on are safe and not causing problems or other side effects.

Dr. Simpson: There are a bunch of different treatment categories. As I mentioned, we often start with steroids or also called corticosteroids. There are some anti-inflammatory antibiotics, non steroid immunosuppressants, B cell biologic therapies, what's called immuno-modulatory therapies and then blood filtration or plasmapheresis. I'll go through each one of these briefly and we will try to finish at least in time for questions.

Dr. Simpson: So there's a bunch of different steroids that people can use. There's topical meaning they're applied directly to the skin or to the mucosa. There's creams, ointments, gels, solutions, pastes, nasal spray, a bunch of different examples and you may have tried a number of different ones. Steroids can be taken as oral pills like prednisone or dexamethasone. They can be solutions that you switch around in the mouth and sometimes you might swallow or spit them out. That's something called dexamethasone. Steroids can be injected into the skin. So if you have a particularly painful blister that just won't heal up, sometimes a doctor might inject some steroid called triamcinolone or Kenalog, directly into the blister. It can be injected into the muscle, sort of a depo formation that lasts usually several weeks or months, and that can be done to sort of help gradually bring it into a remission. Then it can also be done through an IV. That's usually done in a hospital setting, maybe you need a very high dose of steroids, and that

can be done in a hospital setting through an IV. Steroids can often get pemphigus and pemphigoid under control, but they tend to have a lot of side effects, so we try to use them for a shorter period as necessary, but it's often months and we gradually reduce the dose through what's called a taper, where you sort of gradually reduced the dose every week or so.

Dr. Simpson: There are also certain antibiotics that are used, which may seem kind of confusing. Antibiotics are normally for infections, but they also have anti-inflammatory effects in the skin so they may reduce the destruction of the adhesive protein that happens in pemphigus or pemphigoid. These antibiotics can actually be helpful for pemphigus or pemphigoid. Tetracycline, doxycycline or minocycline are three different ones that are sometimes use and sometimes they are combined with something called niacinamide or nicotinamide, which have antioxidant properties and may help them to work a bit better. So they're not really used as an antibiotic even though their primary use in other diseases is as an antibiotic. That can be confusing to patients, why am I taking an antibiotic long term? Well it happens to also be effective for anti inflammation to sort of reduce the inflammation that causes pemphigus or pemphigoid.

Dr. Simpson: An anti-inflammatory medicine called Dapsone which was originally medication for leprosy, that's been found to be helpful in some forms of pemphigus or pemphigoid because it inhibits the immune system in certain ways. It inhibits these two different cell types called neutrophils and eosinophils which can be part of the reason that you have pemphigus. Those are those immune cells that come into the skin and cause the blisters and it usually works best when you have what's called an IgA type of autoantibodies, so that's something you have to talk with your doctor about.

Dr. Simpson: Then there are non-steroid immunosuppressants. These are designed to inhibit T cells and B cells. These are two parts of your immune system that make antibodies and recognize infections but in the case of pemphigoid and pemphigus, you have T and B cells that are basically turning on your body, and they've got confused and they're attacking your own skin and mucous membranes. So we can use different medicines to basically inhibit those different cell types, and to get them to stop attacking your own body. These will reduce the production of the bad antibodies that can cause pemphigus and pemphigoid but the problem is they can also reduce your normal production of antibodies. So there are risks associated with these types of therapies so it's important to be cautious when you're on an immunosuppressant medication to make sure that you're not taking too many risks toward getting an infection and that's been a problem during the recent pandemic. Some examples of these are drugs like methotrexate which can be pills, or can be injected, mycophenolate or Cellcept which also can be pills or liquid. And then Azathioprine or Imuran which are just pills. So any of these work similarly to one another, but they're helping your body to reduce the production of those bad antibodies to allow your skin to heal.

Dr. Simpson: Blood filtration is something called plasmapheresis, where your blood is removed through a vein, it's filtered and then it is returned back to your body after the antibodies are removed. The bad B cells continue to make the auto antibodies but you're filtering out those antibodies and trying to reduce them so you basically use, almost like a vacuum cleaner to sort of suck out the bad antibodies, but you also lose some good antibodies in that process so it's not without risk either. This treatment isn't really used all that common.

Dr. Simpson: The other therapy is called immunoglobulin therapy or intravenous immunoglobulin, often abbreviated IVIg. In this treatment, you're basically flooding your own immune system with a bunch of healthy antibodies from donors. These antibodies are pooled from donors who donate their serum to patients like you. And I can actually dilute out the bad antibodies. It doesn't suppress your immune system, which is one nice aspect of this therapy but it does require IV infusions that have to be pretty slow and it's usually pretty frequently done, like five days per month, often. So it can be kind of a large commitment of time, and effort to do this. Some people have worked it out to get it done at home and that can be a little bit more convenient, but it's often hard to get this approved by insurance as well. You're basically putting in a whole bunch of good antibodies to dilute out these bad antibodies and that can be helpful in pemphigus or pemphigoid.

Dr. Simpson: Then there's a new class of medicine called B cell biologic therapies, which basically take B cells here which are in charge of making the antibodies and this is an antibody that doctors have engineered to get rid of the B cells. It basically goes in and destroys your B cells so that they stop making those harmful antibodies. But the problem is it also destroys the good B cells so you stop making as many helpful antibodies as well, the ones that protect you from infections like viruses and bacteria. But it can be a very, very effective therapy for pemphigus or pemphigoid. Rituximab is the main one that's been FDA approved for pemphigus but not for pemphigoid, so that's an example where the treatment might be different. There are now some, what are called biosimilars or generics that are made. So it may be that you used to use Rituximab but now your insurance company has made you switch to something called Truxima. It's the same basic treatment, it's just a generic version of it. So that can be frustrating for patients on the same medicine for a long time. Sometimes this happens and that can be a frustrating part of insurance these days. There are two other versions of B cell destruction antibody, one's called Ofatumumab and this is a human antibody. So if you've had an allergic reaction to Rituximab and can't take it, it could be possible for you to try this antibody. That's something to discuss with your doctor. There's another one called Veltuzumab and the nice thing about that one is it's not an IV infusion, it's actually an injection, which is a lot more convenient for patients. So neither one of those has been approved for pemphigus but we're hoping maybe in the future they might.

Dr. Simpson: Oftentimes, people will ask, well, what's the best treatment in your opinion? I think this is a really hard question to answer, because we don't really have really strong, unbiased clinical data that can really drive the answer to that question. Also, likely the answer

is different for pemphigus versus pemphigoid so it may depend on a certain type of the disease that you have. The good news though is that there is increasing interest from companies that make new drugs. They're interested in rare diseases like pemphigus and pemphigoid which is really great. And there are ongoing research studies that are trying to find out whether existing medications could be used to treat these diseases. So, there's a lot of hope that I think patients should have. Patients are really dependent on these studies so if you get the chance to be a part of a clinical study, I encourage you to try to do that. One, because it could work for you and could help to get your disease under control, but two you're sort of contributing to our knowledge about these diseases and maybe helping other patients to understand whether a new drug might work or not. Really, it comes down to a more specific question, which is, what is the best treatment for you? This is not a simple answer since every patient is unique, and the treatment choice really depends on a lot of different factors, like how severe is your disease, how old are you, what's your medical history? Do you have things like diabetes or hypertension to worry about? What other medications to take? How did you tolerate a certain medication? Certain people are more sensitive to side effects. What are your personal preferences? Do you really hate needles, or would you rather take pills? Then what's your social situation? Are you able to get to infusion appointments? Do you have transportation? A lot of these different factors can come into the decision to understand what's the best therapy for you. Then there's more of a general approach based on all the data that we have from clinical studies. We call this a therapeutic ladder which means there are different steps in the ladder that we generally use based on how severe the disease is that a patient has. These are just examples, again, like Becky mentioned at the start, these don't necessarily apply to every single patient and every single disease state. I want to put that word of caution, but I wanna give you sort of an idea of what might be a typical therapeutic ladder as your disease might start out mild, and get worse with time. So if the disease is real mild, if you have really mild pemphigus with just a few blisters here and there, you might just use something like a topical steroid like Clobetasol or Triamcinolone which is even a little less strong and that might be enough to control those small blisters. But if you have the next level with mild disease, maybe you have a few more blisters or blisters in the mouth, you might need a two week course of doxycycline for flares, for example, or we might need to add a mouthwash, steroid rinse to basically clear out the mouth and get it treated more adequately. If you move up to the more moderate type of disease you might need to take prednisone which is a steroid you take by mouth and you might need to only be on it for a few weeks to get the disease to calm down but if it keeps coming back, if it doesn't seem like the steroids are keeping it away, which is very common, you might need to take a longer course of prednisone over 2 or 3 months. Then we might think about starting an additional medicine to help take the place of prednisone so that you don't have to be on it too long. With pemphigus, the first choice might be Rituximab which is an infusion, usually given two doses of 1,000 milligrams, or it might be mycophenolate which are pills. So it really depends on a lot of different situations and what your personal preference is, and what your insurance will cover. Those are the most common long-term therapies for pemphigus. But what if you have very severe pemphigus and you are not able to eat or drink and you're in the hospital because you've got so many blisters? You might get IV steroids in that situation. Then you might end up getting Rituximab while you're in the hospital, or you might need to add something like IVIg

infusions to really help get the disease controlled so that you can eat normally and not get malnutrition.

Dr. Simpson: As an example, bullous pemphigoid treatment can be a little bit different. Mild disease is kind of similar where you might use topical steroids. You might add doxycycline or do prednisone over a few weeks for this disease. Again, you might need systemic prednisone or oral prednisone if the disease is a little bit worse. In this disease we will often add dapsone in particular situations but in severe pemphigoid you might need a high dose of prednisone. Here, Rituximab has not been shown to be as helpful as in pemphigus and it is not FDA approved for this so a steroid-sparing agent that allows you to reduce your dosing of prednisone might be something different in pemphigoid versus pemphigus. We tend to use a lot of methotrexate in my clinic or mycophenolate and sometimes if the disease doesn't respond to those we might petition to the insurance company to use something like Rituximab, IVIg or some newer therapy like Dupilumab which I will talk about in just a minute.

Dr. Simpson: The final thing that I will try to answer is, are there any new therapies in the pipeline for treating pemphigus and pemphigoid? We will go through this just briefly. There are some oral B cell inhibitor, kind of like Rituximab but instead of being an infusion, it's an inhibitor of B cells that you can take by mouth to reduce the B cells production of those bad antibodies. The nice thing about these is that they are oral so you don't have to get an IV. There are two examples of them but unfortunately the first phase III trial for them was not successful. It is important to know that that drug is probably not very effective for pemphigus but might it be effective for pemphigoid, we don't know that study hasn't been done yet.

Dr. Simpson: There is a class of immunomodulator therapies. So things like IgE and interleukin are inflammation mediators that cause inflammation in the skin and cause blistering. So when the antibodies go into your skin, they recruit different immune cells. So can we knock out those recruitment factors and stop the inflammatory cells from coming into the skin? These are treatments like Omalizumab or Xolair which some patients with pemphigoid take. Or Dupilumab or Dupixent which is a newer approved treatment for atopic dermatitis or eczema. There is a trial now ongoing to see if Dupilumab might be effective for pemphigoid but we don't have the results of that trial yet.

Dr. Simpson: There are also these allergic cells called eosinophils that are involved in pemphigoid. These are factors that basically draw these allergic cells into the skin in pemphigoid and that's why they become so red, itchy a lot of the time. There are two different therapies that are out there that can block the ability of these allergic cells to come into the skin. Dupilumab as I mentioned before and another drug called Bertilimumab which has actually been given orphan drug status by the FDA for bullous pemphigoid. So there are some

bright spots on the horizon, so could these therapies basically knockout these inflammatory factors to treat these skin diseases.

Dr. Simpson: Finally, when pemphigoid antibodies deposit in the skin, they bring along a protein called complement, which allows the recruitment of inflammatory cells to come into the skin and that forms the blister. And so again, if we can use some therapies to basically block this inflammation, that can really be effective therapy for something like pemphigoid. There are two different drugs, one called the Nomacopan, which has also been given an orphan drug designation by the FDA, and then Sutimilimab. Both of these are potentially on the horizon as future therapies for pemphigoid that may be safer or more effective than some of the standard therapies that we use now.

Dr. Simpson: In summary, pemphigus and pemphigoid are rare. They're autoimmune blistering diseases, where your own immune system starts attacking your body. They're caused by autoantibodies that attack the skin or the mucosal tissue like the mouth or the eyes. They're diagnosed using a tissue biopsy and various types of antibody studies that I'll explain to you today. They're treatable with a variety of different therapies and that they're currently under investigation to try to find other more effective or less risky therapies out there that might be helpful for patients. So with that, I'd like to acknowledge my mentors, who have taught me about blistering diseases and got me excited about it. Dr. Aimee Payne, Victoria Werth, and John Stanley at Penn and Dr. Phil Fleckman at University of Washington. As well as the IPPF, which I think is an incredibly helpful organization for patients and for physicians as well. And then I've had some grant funding to sort of fuel my research. So, with that, I hope this has been informative, and I'm happy to answer any of the questions that we didn't cover during the seminar.

Becky: Thank you, Dr. Simpson. You took some really complex and difficult situations and broke them down and made them very easily, understandable and digestible for our community, so I personally really appreciate that and definitely learned some things today.

Dr. Simpson: Great, thanks.

Becky: We've had some questions come in about vaccines. We have had multiple questions about the Shingrix vaccine particularly. But can vaccines cause pemphigus or pemphigoid, or cause a flare after getting them?

Dr. Simpson: That's a really hard question to answer because, one, these diseases are rare, and a lot of these vaccines are pretty common. So the short answer is, we don't really know, and until we do know that the vaccines are definitely harmful, we generally recommend them

because, patients with pemphigus and pemphigoid are usually immunosuppressed, meaning your ability to fight off infection is going to be lower, than a typical person who's not on those types of therapy. So, we generally recommend them. But when the immune system gets revved up from a vaccine, which is the job of the vaccine, is to get you to produce helpful antibodies, we don't know. There could be a trigger that might actually flare up a disease. We don't think they're causative. It probably more unmasks the disease that may be sort of held back by the normal immune system, but maybe the vaccination sort of tips things over. But the problem is, we don't have really large datasets to prove whether that's true or not. Remember, there was a lot of controversy over whether vaccines would cause autism, and there were some initial mistakes in the literature about that. And so we're trying to be cautious before we associate things, so that we get large datasets to really prove whether that's true or not, before we sort of take those single situations and run with them. Everybody's going to have a unique body, and immune system. I can't answer that for any individual patient, but as a whole, we don't think that it necessarily causes it. Whether it causes a flare or not, is really still to be determined. That's why the IPPF is doing some surveys to get some more information from patients. Did you have a flare after you've got a vaccine for COVID for example? So, if we can accumulate more information about that, we might have a better way to answer that question more specifically. But in general, we are recommending that people get all the normal vaccines just because we can treat pemphigus and pemphigoid or even a flare of that, but if you get a severe infection with COVID, and God forbid, you get to the hospital, and don't make it, that's something we can't reverse. So we do generally recommend that people get vaccinated.

Great. Thank you, and you just mentioned COVID, how has COVID changed how pemphigus and pemphigoid are being treated?

Dr. Simpson: I think it really changed things in the beginning quite a bit. Many patients were very confused about, do I need to come off of my immunosuppressive therapies? How likely am I to get severely ill or die from COVID, and we had so little information at the beginning. Now, we have a bit more information, because there's been over two years of COVID to get information from. There are certain medications that do increase your chances of having a more severe episode of COVID. Rituximab in particular, has been called out and Mycophenolate. Some other medications might not be as high risk, like methotrexate actually seems to maybe not be quite as high risk. And then prednisone, if you get above a certain dosage of it, it can make you quite a bit higher risk. What we always try to do is to minimize the amount of immunosuppressant medicines that you are on and only keep you on as much as you need to keep your disease control, and then try to taper down that dose as much as possible. But if the choice is between having really severe pemphigus which can actually be lethal in cases versus the chance that you would get COVID, that's a very difficult decision to make sometimes. There are a lot of difficult conversations that we've had to have, and we've had to operate in a sort of lack of perfect information and try to understand with each patient, what is your risk? Are you working in a high risk area, a public facing role in your job? Do you interface with a lot of different people? Are people at your site masking and do you have a well fitting N95 you can wear it? So it really depends on your situation. Are you a person who really

stays home most of the time? Maybe, in that case, it wouldn't be quite as risky to get a more aggressive immunosuppressive therapy. So, it's really an individual decision that has to be talked about with your doctor. But if you have questions about it, it is important to bring it up because we do want to think about those types of risks when we're deciding on what type of therapy. The other question is the timing with vaccination. So if you are going to get a COVID vaccine, will it work depending on what therapy you are on. When you're on Rituximab, in particular for the first few months, you're probably not going to be able to respond to a vaccine so you might need to wait or you might need to get the vaccinations before you get your Rituximab to get those protective antibodies before you use Rituximab to get rid of the B cells. There's a lot nuance to the timing of these therapies based on vaccinations.

Becky: Great. Is there a standardized time before we start taking treatment that we should get our vaccines? It is four weeks or five weeks or months? Or is there a standardized time that's a general rule?

Dr. Simpson: Yeah, I think most people think at least a month or two after the vaccination. You want to give your immune system time to make those protective antibodies but also to make memory cells, which means that those protective B cells that know how to make those anti-COVID antibodies, that they're going to stay long term. And then they're not going to be erased by Rituximab. Rituximab doesn't get rid of your long term memory cells, like from old infections that you might have had when you were a kid. So, there is a specific timing. It's usually at least a month or two if you can wait after you get the vaccination to allow your body to make those protective antibodies and to get memory cells so that you get long term protection from that vaccine before you sort of go onto immunosuppressive therapy. But, sometimes, if a patient has really severe disease, we may not have the option of waiting. If you have such severe oral disease that you really can't keep yourself hydrated or nourished we may not have that option of waiting a couple of months. So it can get sort of tricky. It really depends on how severe the disease is and could you manage with topical therapies while you're waiting for the vaccine to work? Or is that just not an option, because your disease is too severe?

Becky: Great. Great information. Thank you. We've also got quite a few questions about how pregnancy affect the disease and the treatment and can I get pregnant? Then we've had some men write in and ask, does their treatment affect a pregnancy as well?

Dr. Simpson: Everybody has a different sort of situation, so you have to talk to your doctor about it especially if you're going to be planning a pregnancy. I think it's important to make it planned and to take measures to make sure that the timing of it is all planned. I know that doesn't always work out, but if you have the ability, it's really important that it's not a surprise. You want your doctors to know, you want to get in touch with a high risk obstetrician, so that they can help you through the process of deciding when has the lowest risk time for you to get

pregnant? How will we manage your disease during pregnancy? We wanted to be as controlled, and as planned of a thing as possible. I know that's not always possible. That really leads to the safest outcomes when planning such as would it be better to wait until your disease is under better control? Could we switch you to a safer medication? Certain medications that we use for pemphigus and pemphigoid are just not compatible with pregnancy. So if you were to get pregnant while on those medications that can cause severe birth defects, or miscarriages or other sort of trouble. It's really important to discuss those things. Certain medications are an absolute no during pregnancy, whereas others have a little bit more data from other autoimmune diseases like inflammatory bowel disease, for example, there are certain medications that are compatible with pregnancy and others that just are not. It's more of a concern with patients capable of carrying the pregnancy. So for genetics, males who are impregnating, it's not as much of an issue, but I'd still encourage you to talk to your doctor about it. Generally, we think about the person who's carrying the child, as carrying more of the risks to the ongoing therapy that that person's taking, as causing potential risks to the fetus as it's developing. So, it's really important to get in touch with someone who has familiarity with high risk pregnancy, so that they can advise you on how to manage it, how to prepare for it, and how to plan the pregnancy around the best timing. Or it may be the situation where you just have such a hard time controlling your disease that it may have to be put off. That may be where it's important to think about, are there preservation things to do for fertility. Might it be a time to preserve some eggs or sperm so that you can do this after your disease might be under control later in life to keep that option open for you later on. There are lots of other options nowadays with all kinds of technologies about surrogacy, or in vitro fertilization that can be used to help people who have more challenging situations to then allow them to carry or conceive a child, or have a surrogate. Those types of options are going to be really important to talk to your reproductive specialist about.

Becky: Great. Thank you. That's a lot of great information there. We've had some questions about surgery come in as well. Can surgery cause a flare or if I have a rotator cuff surgery but haven't had lesions on my arm, could I develop lesions in the surgical area?

Dr. Simpson: Yeah, it's possible. We think of tissue damage as potentially flaring up pemphigus or pemphigoid sometimes. I've had some patients who told me that when they got a bad sunburn, suddenly their pemphigus came out in that area of the body or if they had a thermal burn, it never really would heal properly because the pemphigus wouldn't let it heal. So we do think that that could be a risk but the important thing is that you mention it to your surgeon beforehand. Don't surprise them that you're on methotrexate. You want them to know about that. They can help to categorize how high-risk you are to have a joint replacement, for example, and should they wait until maybe your dose is a little bit lower to do the operation to reduce your risk of infection after an operation. It's really important that the person who's managing your immune medication is in contact with your surgeon so that they can come up with a plan. So again, it's not a surprise or an unplanned thing. We want to be able to really optimize the timing of the surgery and reduce your risk as much as possible. If you're in an

acute flare and things are not very well controlled, that's probably not the best time to get a surgery, of course unless it's an emergency that has to be done. But if it's a planned surgery, like a planned knee replacement or hip replacement, that's something that sometimes can be scheduled for when your disease is under control and your medications have been tapered down a bit so that it's not quite as high risk. The one thing I do want to emphasize is if you're on prednisone at any dose, it's really, really important that your surgeon knows that and you do not stop it before your surgery. Prednisone is one of those medications that cannot be stopped suddenly. You can get very, very sick if you suddenly stop prednisone. It's really important that your surgeon knows that you're on prednisone and they may actually need to temporarily increase the dose of prednisone to help you through the stress of surgery. So that's something really important to talk to your doctor about before the surgery, again so all this is planned out that way you and the doctor both know, what are the steps we need to take to make the surgery as low risk as possible.

Becky: Great. I know it's a little bit after the hour, but do you mind if I ask a few more questions? Blister care has been a common question that was submitted beforehand and during the webinar as well. People are saying that they're getting very painful blisters. Should they pop them? Should they keep them intact, and then how to care for them once they open?

Dr. Simpson: That's a tricky situation. For some patients, we kinda have a deal, that if they have sterile needles, sometimes I'm okay with them popping them once they get to a certain size because they can get really large. The problem is, what you don't want to use is some dirty pair of tweezers you've been using and then get an infection or something. You really want to be cautious with that type of thing, and I'd encourage you to talk to your doctor about it. I have some patients who are diabetics who are always using needles on their skin and they feel very comfortable lancing a blister but we've talked about the proper way to do that. What you don't want is to get an infection. The other tricky thing is, if you have a really painful blister, once it does pop, we often do tell people to sort of leave that dead skin on top as sort of a natural bandage. We don't like people peeling it off and ripping off because that can lead to more or loss of fluid. It almost serves as a natural bandage when the blisters pop. So I often tell people to just sort of leave the skin on top of it. What we don't want is the wound bed, which is the shiny moist part of it, after the blisters peeled off, we don't want that to become really dry and hard and a crusty scab. I know everybody's mom used to tell him to let it be open to the air and that would be good for a wound, my mom included, but it's actually better with those types of blisters to keep them moist. What we don't want is there to be, you can think of it sort of like a big rock in the middle of it. You're trying to cinch it close like a purse string close a wound but if you have this really hard crust in the middle, then the skin cells can't move in and sort of seal it up because that big scab is sitting here. So we generally do tell people to try to keep it moist with something like vaseline to keep it from drying out. If you get a really hard big crust it can also be really painful to remove that, to allow the skin to heal properly. So, that's something called debridement but basically you have to end up peeling that harden dead skin off, and that can be really painful. So we do encourage people to keep them moist and covered as best as you can. Mostly so that the ointment or whatever you're putting on top like steroids sometimes

doesn't evaporate as much. Also keeps it from getting pumped, if you're an active person and you're trying to exercise, oftentimes you always happen to hit that spot where you have a blister. So try to keep a bandage over it so that you don't pump it and keep the wound from healing, the more that you keep bumping it and scraping it, it's not going to really be able to fully heal. So those are a couple of things.

Becky: Great, it sounds like it's a little bit of an individual thing and communication with your provider is the ultimate key in figuring out how you should treat that.

Dr. Simpson: Yes, and different wounds heal differently on different parts of the body. A lot of doctors may want you to put steroids on top of the wounds because they think it's an inflammatory blister that needs to be calmed down so it can actually allow it to heal and some doctors are more uncomfortable with putting a steroid on a wound. So, you really have to talk to your doctor about how specifically to care for your wound. Some people end up going to wound care centers to really help them because they may not see their dermatologist that often, whereas they might be able to go weekly to a wound care center to help them. The other thing is, those types of centers are often more helpful with ordering bandage supplies and trying to get your insurance to help you pay for those because they can be quite expensive. But if you have proper documentation from a center that knows how to do that, sometimes they can be very helpful with assisting you in getting coverage for things like non-stick bandages or sterile gauzes and that kind of stuff. So it's important to talk to your doctor about that.

Becky: Okay and I wanna just follow up with one last question. You had talked before about the different lab tests in determining, for example, if you have desmoglein 1 or 3 or anything like that. Would bloodwork help determine, or is there any way to determine, if my disease is going to develop in other places or spread to other places?

Dr. Simpson: There are some situations where the blood can sort of predict that. It's not always 100%. But let's say you're somebody who has pemphigus foliaceus and you only have skin involvement, and it's pretty superficial blistering and it doesn't go very deep. Sometimes the blood tests may show only the anti desmoglein 1 antibodies, and that's typical for PF. Let's say at some point in your disease, you're checking the antibodies and suddenly now you have desmoglein 3 antibodies and you didn't have those before, it could mean that your disease is evolving a little bit and now you may be at higher risk for developing mucosal lesions or deeper blisters because now, in addition to the desmoglein 1 antibodies, you might be developing new antibodies against desmoglein 3. So sometimes it can help people to predict a little bit, but it's not always a perfect 1 to 1 correlation. So I don't want people to get too stuck on it, but it is important information that can sometimes predict whether you're only going to have skin involvement or whether your mucous membranes are involved. The other thing, in specific cases I mentioned where, in certain types of antibodies, there is sort of an association with

other diseases or cancers in rare circumstances. But normally, “garden variety” of pemphigus and pemphigoid are not necessarily associated with cancers, but there are a couple of very rare subsets that are. So those specific antibody tests can sometimes help your doctor to know, do you need to undergo some sort of screening for cancers? Everybody should be up to date for mammograms, colonoscopies and maybe a prostate exam. That's very important for all patients, but especially for patients who are going to be on immunosuppressant therapy. So, please stay up to date on all of those screening tests because you always want to have that information. If there is a malignancy then getting that taking care of much more quickly, it's going to be much better for your overall health, and for the management of your blistering disease. It's really important to stay up on those types of screenings for cancer.

Becky: Great. Thank you so much for saying that as well. I know I said the last question was the last question, but this truly is. We've had a number of requests asking if you are accepting new patients? And if so, what is the best way to get in touch with you to become one of your patients?

Dr. Simpson: The University of Washington is a little tricky because we cover a large area in the country, and some more rural areas like in Idaho and Wyoming and such. So, we do have some limited availability and because I do mostly research, I'm not in the clinic all that often. We do have a referral process but it requires that an outside doctor refer you to UW because we want to make sure that we have all of the records and biopsies and that stuff. So, it has to be done through your existing dermatologist. The other thing that people do, will be to just get an opinion from someone else and see do you agree with the therapy I'm on? So sometimes, it's like a one-time visit that people do to sort of make sure that another doctor agrees with their judgement. And that's not an insult to your current doctor. Sometimes patients will like that, and so it may not end up being a long term relationship. Some people sometimes will just get an opinion from another doctor. We do have a referral process, it has to go through our central phone system and all of that but your doctor can do a referral to the University of Washington Dermatology. So there is a process for that to make sure we have all the records and things like that that we need. I do have some occasional slots open for new patients. It's a little limited because I'm only in the clinic only on Monday afternoons because I do mostly research trying to figure out some of the biology of these diseases.

Becky: Great. Thank you. Dr. Simpson as always, thank you so much for joining us. I learned a lot today and I hope our community did too.

Dr. Simpson: Thank you! I learned a lot myself in these seminars when I have to prepare for them, going back and reviewing things. So it's always good for me to do these as well.

Becky: Great! I'd like to thank you everybody who joined us on the webinar today. And of course, a big thank you to our sponsor Sanofi Regeneron, Genentech, and argenx for helping

to make today's call possible. Before we go, I do have a few announcements. I'm excited to announce that this year's Patient Education Conference will be held virtually October 21st through the 23rd. We've invited leading bullous disease experts to present on research trends, educate on disease management, and answer some of your tough questions. The 2022 Virtual Patient Education Conference will be an exciting and educational event for any patient, caregiver, physician, researcher, or stakeholder in the field of bullous disease. Registration will be opening soon, and we hope that you'll join us for this exciting event. Do you wish there was a better understanding of our diseases by doctors and researchers? Do you wish there were more FDA-approved treatments and better treatments available? Well here's your chance to get involved and make these goals a reality - Join the IPPF Natural History Study today! The Natural History Study is a patient registry sponsored by the National Organization for Rare Disorders (NORD) and the US Food and Drug Administration (FDA). Your information is private, the IPPF Natural History Study follows strict government guidelines to assure patient information is protected. Your participation and the data will be used by the IPPF to help advance research, better understand the patient journey, find better treatments, and hopefully one day a cure. By sharing your journey and answering some questions, you directly have an effect on the future of all people affected by pemphigus and pemphigoid. So get involved today! You can find the Natural History Study by visiting www.pemphigus.iamrare.org

Do you want to become a hero in our community and continue to support the free services the IPPF provides to you, such as today's webinar, the IPPF's Peer Coaches and our find a doctor map? If so, become a Healing Hero today! Healing Heroes fund the future of the IPPF community by making sustaining, monthly gifts to support our mission of improving the quality of life for all those affected by pemphigus and pemphigoid. No amount is too small even a \$10 or \$15 monthly donation goes a long way and continues to allow us to provide for the greater good of our community. The IPPF has a number of upcoming virtual support groups across the country. If you are interested in attending a meeting, please check the IPPF's Event Page to register for a meeting. Also, we are always looking to expand our support network. If you are interested in starting a support group in your region please contact me, Becky Strong at becky@pemphigus.org. It's easier than it sounds to start a support group and you can help connect others in your area with other patients. This call recording will be sent out with the survey following this call. Thank you all for joining us.