Dismantling Disparities in Primary Immunodeficiency Care: Building Blocks to Equity

CMEO Podcast Transcript

Niraj Patel, MD, MS:

Hello, I'm Dr. Niraj Patel and on behalf of CME Outfitters, I would like to welcome you to today's educational event titled *Dismantling Disparities in Primary Immunodeficiency Care: Building Blocks to Equity*. This is supported by an educational grant from Takeda Pharmaceuticals. This CME activity is brought to you by CME Outfitters, a jointly accredited provider of continuing education for clinicians worldwide.

So again, I am Niraj Patel. I'm an Associate Professor in Allergy and Immunology at Duke University School of Medicine in Durham, North Carolina. I am really pleased to be joined today by a superb panel who I'll ask now to introduce themselves, starting with Dr. Azar.

Antoine Azar, MD:

I'm Antoine Azar, the Clinical Director of Allergy and Immunology at Johns Hopkins in Baltimore, and it's my pleasure to be part of this program.

Vivian Hernandez-Trujillo, MD:

I'm Vivian Hernandez-Trujillo. I'm founder of Allergy and Immunology Care Center, South Florida, and the Medical Director of the Division of Allergy and Immunology at Nicklaus Children's Hospital and Clinical Professor of Pediatrics at Herbert Wertheim School of Medicine, which is part of Florida International University in Miami, Florida.

Ilana Jacqueline:

Hi, I'm Ilana Jacqueline. I'm a patient living with primary immunodeficiency disease as well as a patient advocate and the author of the book *Surviving and Thriving with an Invisible Chronic Illness*.

Niraj Patel:

Thank you all. Let's start with our learning objectives for today. One, to identify the signs and symptoms of PI or primary immunodeficiency to decrease the diagnostic delays, especially in underserved populations. Number two, implement evidence-based treatment strategies to optimize PI management. And finally, three, educate and inform patients and clinicians about PI from the patient's perspective.

In a moment we'll start a brief overview of PI, but first, let's get our audience involved with our first audience response question. Which of the following primary immunodeficiencies are most common? Is it A) severe combined immunodeficiency, B) humoral or antibody immunodeficiency, C) phagocyte abnormalities, D) T-cell immune deficiencies, or E) I don't know.

Great. Well thanks for the participation. It looks like we had 29% select humoral antibody deficiency and looks like 7% severe combined immunodeficiency. Looks like there was a significant amount who was not sure or didn't know, and so this is, we hope to educate you on this type of issue or problem.

So, okay, let's get to primary immunodeficiency and its impact on patients. PI is also known as PID or PIDD. It's a group of genetic disorders affecting development or function of the immune system. Unfortunately, patients often present with frequent, severe and unusual infections. Now, there are a quarter of a million people estimated in the US to be diagnosed with immunodeficiency, and even worse, more than double of that are undiagnosed. And unfortunately, White individuals are two times more likely to receive diagnosis versus Black and Hispanic individuals. So, there's a disparity among different ethnicities and delayed diagnosis is very common, especially in underserved populations.

Including in the types of primary immunodeficiency disease, by far and away the most common is in this pie diagram, the blue area. You can see here, 65%, that is humoral. So, when we ask that audience response question, this is really what we were getting at. And it is important because it can give you clues on what may be going on with the patient. Also, with a diagnosis and treatment. This is a graph showing the increase in the number of genetic disorders associated with PI over a period of time. PI is also a called inborn errors of immunity. And you can see all the way at the top in 1980, there was very few known genes that were associated with primary immunodeficiency and disease. And as you go down the chart, you can see that each bar gets bigger and bigger. And finally, as recently as 2021, there are more than 450 known genetic disorders associated with PI or inborn errors of immunity.

And so, with that, I would like to present our next speaker, Dr. Vivian Hernandez-Trujillo, who's going to talk about signs and symptoms as well as disparities of primary immunodeficiency disease. And this will address our first learning objective, which is identify signs and symptoms of PI to decrease diagnostic delays, especially in underserved populations.

But before we get to that, to set the stage, we have another audience response question. So, which of the following is a social determinant of health? Is it A) ancestry and inherited genetic factors? B) any social intervention specifically tailored to an individual patient, C) neighborhood and built environment, D) targeted small scale social mediation or E) I don't know. Okay, looks like the majority actually got the correct answer. Neighborhood and built environment. Great job. So with that, Dr. Hernandez Trujillo, take it away.

Vivian Hernandez-Trujillo:

Thank you so much. It's truly a pleasure to be part of this panel, and this is something that's really near and dear to my heart. Over the last few years, especially since the pandemic started, I've had the opportunity to work and study a little bit more about disparities that exist. And I'm happy, tonight, to share with you some of the information that we know. There's a lot that we don't know, and that's why it's important that we highlight this.

First and foremost, as a pediatric immunologist, it's important to remember that we need to increase education not only amongst patients, families, but amongst physicians and the medical team in general. And there's different campaigns that have been used over the years. The Immune Deficiency Foundation has a campaign

about, and this is a simple question that I like to ask patients is, “Are you always sick? Well, it might be your immune system.”

And the following questions include, do you have infections that are recurrent, so they keep coming back? Are they unusual? Are they caused by an uncommon organism? Are they persistent? They just won't completely clear or they clear very slowly. Are they severe? So, do they require hospitalization or intravenous antibiotics? And then, is it shared by family members? Are there other family members that also have similar susceptibility to infection? There are different resources that you'll see throughout this presentation that I feel will be very helpful. And for example, you can scan this QR code and learn a little bit more information.

Another organization is the Jeffrey Modell Foundation, and they've been very successful with the warning signs. So there's 10 warning signs of primary immunodeficiency. They split it into adults and pediatrics. And I'm going to go through these for the sake of time a little bit quickly, but they're important to keep in mind.

So, things to remember, not only as a patient or as a family member, but if you're a clinician as well: Two or more new ear infections within a year in an adult, two or more new sinus infections within a year in the absence of allergy, one pneumonia per year for more than a year. Chronic diarrhea with weight loss: this is one that many people don't think about, but gastrointestinal disease can be present in our patients with immunodeficiency and inborn errors of immunity. Also, recurrent viral infections that can include colds, herpes, warts, or condylomas. Recurrent need for intravenous antibiotics to clear infections, and then recurrent deep abscesses of the skin or other internal organs, persistent thrush or fungal infections on the skin or elsewhere, infections with normally harmless bacteria. So, in most patients it may not be a problem, but in some patients it can be. Then, obviously, a family history of primary immunodeficiency disease.

When we shift gears and talk about the pediatric patients, it's four or more new ear infections within a year, two or more serious sinus infections within a year, two or more months on antibiotics with little effect, two or more pneumonias within a year, failure of an infant to gain weight or grow normally. So, as a pediatric subspecialist, I will say that this is very important. So keeping an eye on the growth parameters, both height and weight. Recurrent deep skin or organ abscesses, persistent thrush or fungal infections on the skin, the need for intravenous antibiotics to clear infections, two or more deep-seated infections, including sepsis, and then a family history again.

Then we can talk a little bit about what are the stages of testing. When we talk about how do we work up the patient with immunodeficiency or suspected immunodeficiency, the history and physical are essential. That's the most important thing. Again, reviewing the growth parameters, especially in children, but in an adult, someone who may have rapid weight loss or unexpected weight loss without a reason. A CBC with differential, and then the serum immunoglobulins, these are your first stage. So that's really the first screening stage. As we move on, there are several other stages.

So, stage two would include specific antibody response. How do you respond to vaccines, to tetanus, to diphtheria, response to pneumococcal. So, looking at what we call the pre-, before they're vaccinated, their titers, and then comparing the post for patients ages three and up. And then IgG subclass analysis.

And the next stage is really looking further at functional studies. So, looking at response to candida or tetanus, which looks at T-cell function. Lymphocyte subsets or surface markers, mononuclear lymphocyte proliferation, which again, looks at T-cell function including your mitogens and antigens. And then neutrophil oxidative burst if it's indicated. Obviously, these stages are fluid. Sometimes we can, if we're suspecting a specific type of immunodeficiency, we'll run some tests in stage one earlier or stage three earlier or stage four. It just depends on the specific type of immunodeficiency, but this is to give a general sense of the different stages.

And then in the final stage, it can include things including complement testing, CH50, C3, C4, enzyme measurements, looking at phagocyte studies. NK cytotoxicity studies: how are the NK cells able to kill. Further complement studies, including the alternative pathway, and then neoantigens to test antibody production. And then cytokine receptor studies. So these are a little more specific.

Now I'd like to shift and talk a little bit more about racial, ethnic, and socioeconomic disparities in the diagnosis of primary immunodeficiencies. The reality is that few studies have addressed the disparities that exist in our patients with primary immunodeficiency. There was a work group report by the AAAAI committee on the underserved, which highlighted some of the information we do know. We know that patients with private insurance and administrative databases have higher rates of primary immunodeficiency diagnosis. In the majority of patients with primary immunodeficiency except neutrophil disorders, white patients were more than twice as likely to be diagnosed with PI than Black or Hispanic patients. And then studies in urban settings have reported underrepresentation amongst the racial and ethnic underserved populations, which is why we need to have a better understanding and further studies in these areas. There's also other studies that have been done.

There was a study out of New York that looked at using a scoring algorithm to identify complications associated with immunodeficiency in hospitalized patients. The higher score patients were disproportionately insured by Medicaid, and 86% of the immunodeficient patients were Hispanic or Black. And that indicates that this was a group that was likely to be undiagnosed.

In patients receiving unrelated transplantation, Black patients were the least likely, only 18%, to undergo an 8 out of 8 matched unrelated donor transplantation. And we know that this is important because the closer your match, the better the outcomes. So again, an area that needs to be further studied and understood.

Now I'd like to talk a little bit about disparities and social determinants of health, because this terminology is important in understanding what are the things that really take importance and need to be looked at. So starting here, you can see the patient in the center, race and ethnicity. So, structural racism does exist. Bias and discrimination: if you have a patient that comes with recurrent infections, are we treating them the same regardless of either their race or their ethnicity. Poor access to specialty care, also, and then understudied pathophysiology are parts that fall under the race and ethnicity [category]. As far as financial resources, so healthcare related costs, inadequate access to healthcare and medical treatment, limited access to clinical trials, and then high rates of chronic risk factors. Looking at rurality and neighborhood, higher environmental pollution, we know exist in urban areas. In rural areas, there's a higher risk factor burden including higher rates of un- or underinsured patients, transportation barriers, so, it just may not be possible for them to get to either a primary care or specialist. And then low volume healthcare facilities, including limited access to healthcare. As far as health literacy, and this is something I feel really needs to be addressed, there's a limited perception of PI and related complications and limited medication adherence and healthcare utilization. When we talk about health

literacy, we also need to consider that if someone speaks a different language, then they need to have access to resources, and clinicians preferably, that can speak to them in their primary spoken or read language. And then in the social network connectedness, digital health tools, access, social integration, and then partner and caregiver support.

So what are some questions that we can ask about social determinants of health? And these are important questions that would benefit us not only as clinicians, but also as anyone caring for patients or even loved ones. So, what challenges do you have getting to appointments? If someone doesn't ask you, they may not realize that the reason that a patient isn't coming to an appointment is that they simply don't have either transportation or they need help in being reminded about the appointment. Do you have access to a pharmacy? These are simple questions that are important. Do you have access to care in your preferred language? I mentioned this a little bit earlier. Do you have insurance for visits and prescriptions? There may be a concern that they may not be able to pay for the health care that they need. Do you have safe housing? Do you have a safe place to store or refrigerate medications? We can't assume that every family has the ability to store medications in the way that they need to be. Are there family, friends and/or neighbors who can assist if you need help. This is where we can work with social workers and others to help us help those families. Are you experiencing discrimination that's negatively impacting your health? The stress that is associated with discrimination is not well understood and definitely needs to be studied because this definitely has an impact. How do you prefer to learn about things? Do they prefer to read about it? Do they prefer to hear about it? These are important. And then, can you afford and access healthy foods? Food security is a whole other topic that is important for our patients.

My last slide is talking a little bit about implicit bias. Implicit bias is an automatic reaction that we have towards other people. These are attitudes and stereotypes that can negatively impact our understanding, our actions, and decision-making. And the idea that we hold prejudices that we neither want nor believe is quite radical when it was first introduced, but the fact that people may discriminate unintentionally continues to have implications for understanding disparities in so many aspects of society. This includes healthcare, policing, education.

Harvard put together a website called Project Implicit. I've actually taken part in this. It's important to have the opportunity... and you don't have to pay for it. It's free. I think it's important, and I would encourage everyone to actually to take part because we can better understand ourselves. If you don't know that when you're given a specific scenario, you think in a certain way, you can't address it. So, Project Implicit is definitely a resource that is available and it's free of charge. Thank you so much for your attention.

Niraj Patel:

Thanks Viv. That was great. I just wanted to maybe pause here because there is a question that came up through the chat that kind of points to the diagnosis that you were talking about. I just want to ask you and then maybe if others want to chime in. The question is, when should genetic testing be ordered to look for underlying molecular defects?

Vivian Hernandez-Trujillo:

So that is a great question and I think it's really going to depend. That's a conversation. So, I didn't mention shared decision-making. That's very important when we have any patient. But I think, and I'm sure Ilana can speak to this,

it's important to understand, number one, where the family is, again, understanding the complete history. I think genetic testing is really going to depend on A) what the presentation of the patient is. Sometimes we can make a diagnosis and then do the genetic testing. Sometimes we really are not sure what's happening. And then we may have some genetic testing done earlier because now it's readily available, but it's really going to depend on patient per patient. And I would encourage everyone to have that shared decision making discussion with not only the patient and the families but with the medical team because it really, it's going to depend for some patients, it's going to happen a lot earlier than in others, but obviously it's a valuable tool that we have.

Niraj Patel:

That's great. Thank you so much. So up next is Dr. Antoine Azar, who is going to talk about treatment for PI, which will address our second learning objective: implement evidence-based treatment strategies to optimize PI management.

But before we get to that, this is our last polling question. Which of the following is a reason a patient might prefer SCIG, which is subcutaneous immunoglobulin to IVIG, which is intravenous immunoglobulin? Is it A) fewer needle sticks, B) less frequent infections, C) more contact with healthcare providers, D) self-administration without need for venous access or E) I don't know.

Great. Well, it looks like the several people chose the correct answer, self-administration without need for venous access. And I think this is an important part when it comes to management and patient preference. And like Dr. Hernandez Trujillo mentioned earlier, this is a shared decision-making. Okay, and now with that, I'll turn it over to you, Antoine.

Antoine Azar:

Thank you Dr. Patel. Pleasure to be part of this program and talk about this very, very important and relevant topic. And what I'm going to be talking about is the treatment for the PIs. And there's a variety of PIs, like Dr. Patel mentioned. They can affect the antibody function, there's combined immunodeficiencies that can affect multiple parts of the immune system, there are the innate defects, phagocytic defects, complement defects. So, there's a variety of treatments available for a variety of disorders.

Some of the top treatments that are available include immunoglobulin replacement therapy, hematopoietic stem cell transplant or bone marrow transplant is available for a number of disorders, and gene therapy is used for, again, certain limited numbers of genetic disorders. There's a variety of other treatment modalities used in patients with PI including antimicrobial prophylaxis, vaccinations, making sure that live vaccines are avoided in the majority of patients with PI, immunomodulatory therapy, interferon gamma is used, and GCSF is used.

But the highlight here that what I want to focus on is the immunoglobulin replacement therapy. As you can see, it's used for a variety of disorders of the immune system and, like Dr. Patel mentioned, antibody defects are by far, the most common disorders with primary immunodeficiency. And these are primarily treated with immunoglobulin replacement therapy. So we'll be talking about this in a little bit more detail.

There are a variety of ways to administer immunoglobulin therapy. There's IVIG or intravenous immunoglobulin, there's SubQ Ig or subcutaneous immunoglobulin, and there's a modified or a facilitated subcutaneous immunoglobulin. Let's talk about these in a little bit more detail.

IVIG is an infusion in the vein, it's indicated for both adult and pediatric patients with PI, it's infused directly into the bloodstream through the intravenous IV infusion. Typically, it's given every about three or four weeks, most commonly every four weeks. The infusion takes about two to six hours and can be done in the home setting with home infusion nurses, in the hospital setting, or an outpatient infusion center. And a lot of the side effects tend to be related to the rate of infusion, and we'll talk about these a little bit later during this section.

Subcutaneous immunoglobulin is also indicated for adults and pediatric patients with PI. Subcutaneous Ig is self-administered by the patient. It's injected under the skin. Most commonly, it's done in the abdominal area, but can be done also in the inner thighs, the buttocks, or the arms. It's very flexible in terms of dosing. It can be done often, every one or every two weeks, but some people prefer to do a little bit every day. So, there's a lot of flexibility. And an average infusion that's commonly done every one to two weeks takes about an hour or two hours to infuse. Most of the time, this is done in the home setting. That's the purpose of these subcutaneous immunoglobulins. Patients are trained on how to do the infusions, and they continue doing it themselves at home. They get the product shipped to their home, and they do the infusion themselves. In terms of the side effects, most of the side effects with SubQ Ig tends to be a local side effect where the infusion is given under the skin.

And the third form of immunoglobulin therapy is the facilitated SubQ Ig. Currently, this is indicated for adult patients with PI. It's frequently self-administered also at home, or it can be given by a nurse as well. It's also infused under the skin, exactly the same as with the regular SubQ Ig, except that it's given less often. It can be given every four weeks or every three weeks, and the infusion typically takes one to two hours. Most of the time it can be done at home, although it can be done in outpatient infusion center. What's unique about the facilitated SubQ Ig, it has hyaluronidase, which opens up the subcutaneous tissue, allowing a much larger volume of immunoglobulin to go under the skin. And this is one of the reasons that this can be done in such large volume and done once a month as opposed to every one or two weeks. On the flip side, because patients receive a higher volume of immunoglobulins, they tend to have a larger lump under the skin that may take sometimes two to three days to resolve.

So, there's a variety of options for immunoglobulin therapy and a lot of flexibility in this regard. Now, what are some of the pluses of SubQ versus IVIG? Most of you answered the question correctly in terms of the SubQ Igs, there's no need for venous access, no need to put in IVs under the skin. There's no wear off effect that is seen with IV. With IV, there's a peak and trough, but with SubQ, it's more steady state, so you don't have the very good days and very bad days that some patients experience. It’s self-administered, you don't need to depend on an infusion nurse and schedule and make an appointments and call and so on to do it yourself at home. Most patients receive no pre-medications, or much lesser pre-medication, than with IVIG. It's generally much better tolerated, and the side effects are much less than with IVIG. As we mentioned, there's a lot of flexibility in the dosing from perhaps once a week or once every two weeks, once a month. There's a lot of flexibility in the dosing that can be adjusted and tailored to the particular patient. There's some reports that it results in improved quality of life and decreased healthcare costs, given that there's no involvement of an infusion nurse to administer infusion.

Some of the positives or the advantages of IVIG, it has fewer needle sticks, so it's one IV in the vein and it's less frequent, typically every four weeks. Some patients really prefer to get an IV infusion, they prefer to get an IV and somebody to get the infusion for them. They're more comfortable with that. And there's a possibility that IVIG may have a better impact on autoimmune disease than SubQ Ig. Although a lot of data is coming as we have more experience with this, and a lot of patients with PI do have autoimmune disease as well. That's why this is relevant.

I just want to mention the pharmacokinetics of IRT. In red, here, you'll see the IVIG. When you get an IV infusion, there's a significant increase in the level of IgG in the first few hours after the infusion, and the slowly declines over time and by the fourth week, it reaches a trough level before the patient receives another infusion again. That's why some patients report feeling better initially, but then feeling the wear-off effect at the end of that infusion. The triangles in gray are the SubQ Ig. They're given under the skin and therefore there's more steady state level. So, if you check the level throughout the month, throughout the cycle, they will be more steady throughout the duration of the month. And in between is the facilitated SubQ in blue, where there's a smaller peak and a smaller trough than what you see with IVIG therapy.

How do we dose IRT? IV and facilitated SubQ range from about 400 to 600 mg/kg/month. So, these are based on the patient's weight and as we mentioned, use every three to four weeks. SubQ Ig ranges from a hundred to 150 mg/kg/week, infused every one to two weeks. Now, the doses are very flexible and really depend on the individual patient. For example, certain patients may require much higher immunoglobulin doses to remain under better control and to reduce their infections as compared to others. So, there's a lot of variability in these ranges. The most important factor in determining the dose and how to adjust the dose, going up or going down in the dose, is the clinical course. Is the patient getting a lot of infections, serious infections? Do they have bronchiectasis? Patients with bronchiectasis do require higher doses of immunoglobulins usually. And the other thing we use is the immunoglobulin or IgG levels. We check a trough level where patients on IVIG and a steady state level, that can be done any day of the month in patients with the subcutaneous Immunoglobulin. So these are the main determinants of those in PI.

As more SubQ Ig products have become available over the past several years and there's been more use of SubQ Ig and more experience with it, a lot of patients who were receiving IVIG before are now switching to SubQ Ig or would like to switch SubQ Ig and have that self-infusion done at home. An important thing to remember is that when switching from IV to SubQ, the first dose of SubQ should be given preferably within a week after the last IV, and that's important order to maintain a good steady state IgG level, otherwise it will take a long time to rebuild that steady state. So that's important when the patient are switching the dose to make sure that this is done properly. The dose of SubQ Ig is basically dividing the monthly dose of IVIG by four to obtain a weekly dose.

And now every label with SubQ Ig has an FDA-mandated note that an adjustment factor of 1.37 should be used. So if somebody's on certain dose of IVIG, you'll multiply this by 1.37. However, when they were asked, most immunologists actually do not use an adjustment factor and use the same dose when they switch from IV to SubQ. There are a variety and a large number of both IV and SubQ Ig, and there's one facilitated SubQ Ig. So there's a lot of options to treat patients with and some patients may tolerate one product better than the other. If somebody's tolerating a product well, try to maintain the same product that the patient's tolerating rather than changing these products.

What are the adverse effects of SubQ and IV? I mentioned a little bit earlier that the most common side effect with SubQ are just under the skin. These are local redness, swelling, pain, and itching where the infusions are. Systemic reactions are really very infrequent, and can include fatigue, dizziness, chills, nausea, headaches, and systemic or severe reactions are very rare, although can occur such as aseptic meningitis or anaphylaxis. With IVIG, the injection site is basically where the IV line is. There may be some mild irritation with that line. The mild to moderate systemic reactions are more common than SubQ and include flu like symptoms, headaches, migraines, fatigue, dizziness, nausea, vomiting. And severe reactions can occur, but again, these are very uncommon, including lung damage clots or thromboembolic disease, kidney problems, neutropenia, hemolysis, anaphylaxis, and aseptic meningitis.

So, what are some strategies, I'll go over this a little bit, to reduce the Ig-associated adverse effects. Before I start any patients on immunoglobulins, I go over all these questions regarding their comorbidities. Do they have risk factors or, for example, thromboembolic disease? Have they had strokes or heart disease, thrombosis? Do they have diabetes, hypertension? Are there any other drugs that are taken at the same time? Is it their first infusion where patients tend to have more reactions versus subsequent course? What are the previous adverse effects and what are the things that have been done or that we can do to reduce these side effects? And monitoring the labs are important. We typically monitor CBC or complete blood count liver and kidney tests every about six months.

With IVIG infusions, it is often easy to reduce the side effects or significantly reduce them by reducing the infusion rate, keeping infusion rate of one ml per minute for the first 30 minutes and then three ml per minute for the second 30 minutes and slowly and incrementally go up on the infusion rate. If patients still have side effects, three medications can be used. These include antihistamines, and nonsteroidal anti-inflammatory drugs, and sometimes steroids, although we don’t commonly have to use these steroids, it's not that common.

If patients do have a lot of problems with IVIG, we can offer them to switch from IV to SubQ, which is generally better tolerated. And if a patient is not tolerating a certain product, we can offer them also to switch among products, and of course reassess what kind of reactions they're having. I typically see patients soon after I start immunoglobulins, after their first or second immunoglobulin, I want to see them to exactly go over the details of their reaction and what are the things that we can change. But overall, what I would say is that most patients are able to tolerate IV or SubQ or some form of immunoglobulins without a problem. These are generally safe and very well-tolerated medications.

And I'm going to wrap up by mentioning that the treatment of PI is a, requires a multidisciplinary approach. Patients with PI not only get recurrent infections, they are also predisposed to autoimmune disease, malignancy, lymphoproliferative disease, allergic disease, inflammatory disease. So, it's not just the infections. And often, the management of patients with PI requires a number of providers, of course the primary care physician, the allergy immunology physician, but also pulmonologist or hematologist or gastroenterologist and infectious disease specialist and ENT and nutritionist. So, there's a variety of specialties involved in the treatment of patients with PI. And of course, most importantly, is the patient. And here's where I bring it back to you, Dr. Patel.

Niraj Patel:

Great, thank you very much. That was very informative, Antoine, which comes up to a question that was asked in the chat, and I think Antoine, you discussed a very beautifully, immunoglobulin. How do you choose among the wide variety of immunoglobulin products that are available?

Antoine Azar:

Yeah, great question. And I would start by saying that there's so many options right now, which is great because we are able to choose through a large variety. The first decision would be, again, like Dr. Hernandez-Trujillo mentioned, shared decision-making with the patient. Does the patient want to get IV or SubQ or facilitated SubQ, or are they interested in one or the other? That's number one conversation to have. And some patients may have strong preference for one or the other, and sometimes I may have strong preference.

If a patient has a lot of risk factors that we mentioned earlier, for example, for thromboembolic disease or they've had a lot of side effects with IV, I would pick SubQ. And then after that, once the decision is made on what delivery we are using for patients, the next thing is to look at the different products. And different products have different characteristics, like what's their sodium content or osmolarity, do they have sugar in them, what kind of preservative do they have in them? For example, if a product has sugar in it, then you want to avoid that in patients with diabetes. And we look at the details of what the products are, and we tailor it to the patient.

Niraj Patel:

Fantastic. That's a great segue because of course, just like you mentioned, it is a shared decision-making process, and so they have a lot of input, which actually brings us to our next topic, and you are in for a real treat because we are joined today by a very active patient advocate, Ilana Jacqueline, to tell us her story. So, this is going to address learning objective number three, which is to educate and inform patients and clinicians about PI from the patient's perspective. Ilana, take it away.

Ilana Jacqueline:

Hello. Thank you again for having me. And hello again. I'm Ilana Jacqueline, and I have what we in the patient community call "lucky girl syndrome", as in due to my social determinants of health, I was lucky enough to get diagnosed far sooner than many patients with PI, which might be a bit confusing to point out, as since you can see on this slide, I was not diagnosed with my disease until I was 19 years old. And in the general health sphere, this would seem extremely unlucky. However, beyond being a patient, I have also worked as a patient advocate for the last decade in the rare disease community. And if there's one thing that I've come to realize, it's that most patients do not have the resources, the finances, the connections, or the simple physical ability to endure what I had to endure to get this diagnosis.

So, my story starts like this. I was born sick, constantly dealing with infections, mostly lung, bronchitis, mucosal, sinus, strep, and viruses, and they would not improve, not without aggressive intervention and oftentimes without hospitalizations. I was fortunate in that I had a mother who was a great advocate for me, but who

endured many instances of medical gaslighting where she was told she was being overprotective and paranoid and that some children were just sickly children.

Before the age of 18, with great insurance and access to a university hospital just one hour from my home in south Florida, I would see pediatricians, pulmonologists, allergists and have many hospitalists who would look over my care and assess me as a patient, but none that would make the diagnosis and I slipped through the cracks. When I was in high school, I was becoming extremely burnt out from nonstop, untreated infections. I had mono for a year where I was only able to stay awake for a few hours each day. And I almost failed out of high school because of truancy laws. But because I had a parent who advocated for me in the exam room, I was able to advocate for myself with the school board, and I was able to get by and get an education with help that most students wouldn't know how to access, or how to ask for. And I would begin to develop allergies or simply become immune to most antibiotics from overuse.

And by the time I turned 18, I realized I was not going to be able to leave home and go away to college. So, I went to a local community college and struggled to do simple things like climb a staircase or carry my books to class because my body was so weak and so run down, and I would nap in my car between classes, and if I didn't have a car, I wouldn't have been able to get back and forth to school quickly enough to get the rest that I needed and I probably would've had to drop out.

And I was young, and I was still on my parents' insurance, and I was working part-time jobs remotely from my bed, and I had the support system to be able to continue looking for help. I started to see every specialist I could get into, every single one. And we ran so many tests and I had so many doctors who just like couldn't wrap their heads around what it was that I was experiencing. And I started to feel like I was crazy. I got to a point where I did not want to keep seeking answers, but I was also too sick to live like this. So, one day, my stepfather went to synagogue and asked his congregation to pray for me out loud. And after he did that, one of the men in his temple introduced himself as an infectious disease doctor – “lucky,” – and he told him to bring me to his office and that he would try to figure me out.

And my parents dragged me to that appointment. I mean dragged. I was so scared to have another doctor gaslight me and make me feel silly and paranoid for being so sick. But he didn't. He took my history for over an hour. He looked through all the blood tests and scans that had already been performed. He did his own exam and he said, “I think I know what's wrong with you.” And I didn't want to get my hopes up because I'd heard that before, but this time just seemed different. And not long after that, we went home and we waited for results and he called and he said, "Hey, you have this disease. You have something called hypogammaglobulin anemia, and your levels are critically low, and you need to go to the hospital right now and start IVIG." And I'd honestly never been more relieved or at peace in my life than in that moment during that phone call, knowing I wasn't crazy, knowing that all the pushing and money and quality of life lost was finally coming to an end. It was more than I could have ever hoped for.

Our insurance was contracted with the hospital he directed us to, and we were able to get into treatment the very same day. Lucky. This was all fortunate, but I did react poorly to the IVIG. And this was one of the first times it seems that that doctor had prescribed it directly, so there were no pre-meds, there were no IV fluids, and I ended up getting aseptic meningitis from it. And I wanted to quit the treatment right then and there, but they convinced me to do it one more time, and unfortunately, I had a similar response. And after that, we transferred

my care to an immunologist, and he prescribed me SubQ therapy, but he admitted he didn't have experience providing that either. So, the SubQ was much easier to manage, and I could rely on an infusion nurse to guide me, and I thought things were going well, but after two or three months, they retested my blood. And when they didn't see an enormous improvement, they canceled the treatment and they put me on prophylactic antibiotics. And I didn't know any better. I had no idea that SubQ needed longer to see a change in the system. And this was all very unfortunate, because for the next 10 years I would be on and off powerful antibiotics regularly. I would at some point develop sepsis through a central line. I would age my lungs eight years with repeated pneumonia, MRSA, sinus infections, and just countless antibiotics. I'd have a breakdown in my autonomic nervous system and develop postural orthostatic tachycardia syndrome. And all of this would only make me harder to treat.

Finally, when I was 30 years old, just before Covid hit, I decided to search out a new immunologist. I was now on my husband's health insurance. And despite being as sick as I was, I was working full-time remotely and making a decent enough living to afford my copays. And when I came into that new immunologist's office and told her my story, she was aghast. My IgG levels were just under 200. She put me back on SubQ and told me it would be at least six months before she would even look at my blood to see if things had improved. And I was really sluggish for the first few weeks before I started to feel the uptick of my energy levels. And I started to see my lack of infections. A year later, I would make the move across the country from south Florida to Vancouver, Washington, and I'd get a new immunologist who would take over my care. And she taught me a lot about my immune system. She took time to hear about my treatment and how it was impacting me. And together we realized that I did much better by adding one liter of IV fluids before my SubQ treatment. And we upped my dose from eight grams to nine grams.

In 2022, my levels had risen to 800. And when recently checked again at the end of 2023, I was at over 1200. That's the highest I had ever seen my IgG levels in my life, and I have been infection free for one year. Since my diagnosis, I've met with many patients in our community, ones who were diagnosed with a PI through the newborn screening process, others who weren't diagnosed until their late 60s. Interestingly enough, my diagnosis led to my mother being tested and being diagnosed with CVID. While waiting 19 years for a diagnosis and 30 years for a successful treatment plan is too long, I often wonder about how long it would've taken me to get help if my circumstances were different. If I didn't always have good insurance to collect that long paper trail of questionable blood work. If I hadn't been able to get admitted to good hospitals who treated my more severe infections so aggressively. And if I hadn't spoken the language to be able to communicate with my HCPs about what I was experiencing and the long pattern of symptoms over so many years. At 16, I couldn't imagine what my life would look like at 20 because I thought I'd be dead. Undiagnosed and constantly ill, I did not see a feature for myself that made any sense. And at 19, I finally had that hope, but in my twenties, I lost it again. I had a rare disease, but I hadn't found a treatment plan that worked for me and I couldn't see myself making it to 30.

When I saw my levels rise last year after continuous successful weekly doses of SubQ IG, I started to see the feature so much more clearly again. For patients without access to all that I have: insurance, copays, medication, doctors who believe me to be an accurate historian for my health, knowledge on how to advocate for myself as a patient in hospital settings, and connections with pharmaceutical companies, patient programs to help me access treatment in case of temporary gaps in my insurance coverage. I don't see how they [patients without access] would make it smoothly through this journey with PI. We have to be smart to survive this, but more importantly, we have to be lucky. In the circumstances we were brought up in, we have to have the resources to cover costly care, and we have to have the audacity to fight back when we feel our treatment isn't working well enough and

demand our quality of life. We have to be proactive and adamant about our HCPs taking our care seriously. And that is impossible to do when you're limited to specialists on Medicare. When you're unable to spend hours during the workday on the phone with the insurance company or the pharmacy or the doctor's office.

It's impossible when the disease drags on for more than 19 years, when your body breaks down, when your medical records become this hazy matrix of unknowns instead of a clear and textbook case of untreated PI. Without the help I received, thanks to my circumstances in life, my family income and later my own, my consistently good private insurance, my location, which afforded me options to choose from different providers, the lack of medical bias imposed on me as a White woman in clean clothes who spoke English, often brought in by both my parents or my husband. I don't know if I could have made it this far in my journey. I think the fact that that I am the one speaking here today on this topic is proof alone of how difficult it is for those who have been without privileges that I have access to in order to survive and thrive.

I may have gripes and frustrations about my late diagnosis, but the fact remains that I was lucky to have been diagnosed at all. And it's so important that we remember and are constantly reminded that for every patient that you see that looks like me and lives like me, there are many others who are being failed by the medical system, by the infrastructures that are supposed to lift and support them, by the government-aided programs that limit their ability to advocate for their best care.

We need to meet patients where they are, which means we need to meet providers where they are. Broaden education and testing on PI and empower patients and their caregivers to advocate for the potential of rare diseases like PIs. Because the outcome of having or not having a diagnosis ultimately impacts the likelihood of survival and the quality of life thereafter.

Niraj Patel:

Well, thank you very much, Ilana. That's a really powerful story, and I'm really glad you shared it. You obviously had a long struggle and I'm really proud of you to have made your way through that journey and come out being lucky. So, there is a question for you, Ilana, that I think kind of speaks to your journey, but also emphasizes part of the program, which is disparities. The question is, do you have patients in your following from underserved and/or marginalized populations? And if so, what have you learned from them in terms of the barriers they face?

Ilana Jacqueline:

Absolutely, I do. And one topic I talk about constantly on my social media is about medical bias and how that works. There are a lot of patients that are facing a lot of obstacles to getting the best kind of care. It's underserved communities, it's being of certain ethnicities, it's language barriers, it's money, it's insurance, it's being in rural areas. There are so many problems that patients come to me with that they're struggling with that are both situational, where there are things that they simply can't change their circumstances, and there are situations where they go into the exam room and it does not matter who they truly are or what they've done to survive their disease, but simply the fact that they are who they are, the color of their skin, or the language that they speak or the clothes that they're wearing, are faced with bias that makes doctors not believe them. And so a lot of the work that I do is kind of just situational tactics for representing yourself as best you can, knowing that

these biases exist, and knowing that you are walking into situations where you're going to face things like this, whether your healthcare providers realize that that's something that they're doing or not.

Niraj Patel:

Great, well said. So, I think we're going to go to the next slide, which is SMART goals. And these are goals that you can implement in your practice immediately. One is, conduct a careful history, physical exam, and screening evaluation, including quantitative and qualitative tests to identify patients with PI. Individualizing Ig dose and delivery to prevent infection, foster adherence, and improve quality of life. Be aware of implicit bias that can prevent equitable diagnosis and treatment of PI in patients from racial and ethnic underserved communities. As Dr. Hernandez Trujillo emphasized, assess social determinants of health to ensure every patient receives appropriately tailored and optimized care.

We're going to go and answer as many questions as we can as we're running a little bit out of time, this one goes to Dr. [Hernandez]-Trujillo. Can you tell me about when you would send a patient with PI to an immunologist or a PI specialist?

Vivian Hernandez-Trujillo:

Depending on where you live, so, we talked a little bit about that too, right? So, you may have access to an immunologist who is nearby and then the patient can get there. So, I would say I actually spend a lot of time speaking with primary care providers, whether it's pediatricians or internal medicine doctors, do as much as you feel comfortable doing and then whatever you don't feel comfortable doing, we will obviously help you. But as long as you're in a situation where you have people nearby that you can trust. I honestly feel, I have a lot of people that just call me and ask questions, and I think having a local person you can reach out to is important because when you feel like something's not right, they can guide you on either starting the workup and then sending them, or just sending them to us. But I definitely feel if you have an immunologist that is available, that is the best case scenario for everyone because it does take a multidisciplinary team, as you have heard.

Niraj Patel:

That's fantastic. And I just want to add to that awesome response that the Immune Deficiency Foundation has resources to identify an immunologist in your area. And so, if you don't know who to refer to, the Immune Deficiency Foundation can be of a great help. There were a lot of questions and really great ones, and I'm sorry we didn't get to them all, and we're really just about out of time. But I'd really like to thank our panel for an excellent and great discussion. And thank you, our audience, for joining us today.

To receive credit for today's activity, please complete the post-test and evaluation and click on the request credit tab. And don't forget to visit the Rare Disease Hub at cmeoutfitters.com for more free resources and education for healthcare professionals and patients. Thank you and goodnight.