Ask the Expert: Dr. Luke Wall

TRANSCRIPT

Emma Mertens: Alright. Thank you so much. We have some great questions lined up. I know our audience is really excited for Q and A, so looking forward to getting this started. Alright, so we're going to start off with a couple of questions about specific antibody.
This individual says hello and thank you for a great presentation. So, is specific antibody limited to children or do adults also get diagnosed with it? And I apologize, sorry if I missed this earlier in the talk.

Dr. Wall: So, that really is an excellent question. And specific antibody deficiency should be explored in adults who are having recurrent infections. Absolutely, it can be diagnosed in adulthood. Again, we have to always think could there be another underlying immune deficiency and an adult really pause and think, is there any secondary immune deficiency? Are they a For example, is there a medication but another biologic for other reasons or something else that is suppressing the immune system, but absolutely it can be diagnosed in adulthood.

Emma Mertens: Thank you so much. And building on that question, another attendee asks us. For adults who have been initially diagnosed with specific antibody deficiency and placed on IG replacement therapy, can you clarify how they know whether their disease has progressed to CVID?

Dr. Wall: Okay. So that's a very insightful question. And so there are some ways in which the antibody compartment can be monitored even while on immunoglobulin replacement, but of course it is limited. It's limited because while on replacement you cannot measure specific antibodies because you're only measuring the antibodies from the donor, right, that now are measurable in your blood. You also cannot measure the patient's intrinsic IgG level.
Because the IgG level that you measure, of course, is your IgG combined with the IgG that's been given to you. So those two measures are sort of out the window when it comes to reassessing. However, the immunologists can monitor IgA and IgM. If one or both of those becomes low, then there is suspicion for progression of the antibody deficiency. The only way to really make the diagnosis of did it really become CDID or not is really to come off of the infusions for six months and then reassess.
However, speaking personally, and every immunologist, their approach is a little bit different, if I have a patient on infusions and I'm seeing measures such as the IGA or IGM, that are becoming lower than I am not going to take that patient off of infusions because I have evidence that the antibody deficiency is becoming worse. So in that scenario, the only

reason that I would pause and reassess is, for example, if the insurance got completely completely refused to pay, and we're really forced to come off of infusions for a period of time or or for some other extraneous circumstance that the patient cannot infuse for a period of time. But I really feel that if there is evidence of progression, when I say progression, I mean, worsening, then infusions should continue. As opposed to being paused for formal reassessment. I hope that helps answer your question.

Emma Mertens: Thank you. Alright. So moving on to some more questions about CVID. This individual wants to ask a clarifying question and they would like to know, does CVID necessarily in include IgG deficiency plus IgA or IgM? Or is IgG deficiency on its own significant enough for a CVID diagnosis?

Dr. Wall: Okay. So consensus definition for CVID. In other words, the details that immunologist across the board really agree on is that it must must include low IgG, plus at least one other immunoglobulin. So plus IgA and or IgM. Okay.
So IgG plus at least one of the others as well as failure of the polysaccharide response using Pneumavax twenty three as the traditional way of measuring that. So really that is the only way to diagnose CVID. If a patient has low IgG alone, then they have hypogamoglobulinemia. That is the most appropriate diagnosis for them. That's the implications of that are very general.
And I say that because patients can have hypogam due to an intrinsic weakness of their immune system, so the immune system is just not able to make IgG. They can have hypogam due to loss of antibody. For example, if they're losing protein in the gut or in the urine, two of the most common examples, IgG is going to be the most the immunoglobulin that is lost the most. So it's going to manifest with IgG deficiency before any other antibody drops. Also, it's relatively common for hypogam or low IgG to be due to secondary immune deficiency or immune suppression.
So medications, for example, in anti epileptic drugs, any medication that is used for immune suppression, for autoimmune, or any inflammatory condition, those can often lower the IgG level. So when it is IgG alone, we as the immunologist really have to sit back and take a hard look to see is there any explanation that we can find for it? If not, then if IgG, if the low IgG is severe and the patient is getting sick significantly, then that alone can warrant immunoglobulin replacement therapy. So hypogam in isolation can warrant immunoglobulin replacement. I will say especially for pediatrics, most patients that I identify with low IgG alone most of them don't get immunoglobulin because for kids, oftentimes it's transient.
Oftentimes their symptoms are not severe. But there are patients, especially a couple of adolescents or adults that I have started on immunoglobulin replacement for IgG alone. So it really comes down to clinical decision making, how severe is the patient suffering, and

can we identify any underlying secondary immunodepiciency or reason for loss of antibodies.

Emma Mertens: Thank you so much. All right. Next question. How do you know if your antibody deficiency such as CVID is mild, moderate, or severe. Is there a criteria for these levels?
Okay.

Dr. Wall: So to my knowledge, there is not. When it comes to CVID. And I would venture to say, even if it is out there, it's probably, you know, one expert or one center saying one thing and then other experts having other opinions of how to define that because that is that is very subjective. That being said, I'm glad that you brought that point up because I really tend to look at that more through a clinical lens. Okay?
So, mild being not having any autoimmunity Patients having a good life, you know, they're not suffering drastically from infections. We've started IVIG because we've diagnosed the the CVID started IVIG and they're really doing wonderfully. They have no end organ damage, okay? Whereas severe would be in my mind. And again, this is very subjective.
It's very clinical is just the way that I see things. Your immunologist may describe things somewhat differently, but in my mind, the patients that really get my attention as far as very close follow-up aggressive treatment using the immunoglobulin to aggressively and such. Are those that have organ involvement, for example, bronchiectasis, and or interstitial lung disease, as well as other manifestations of autoimmunity. And for that small percentage of patients that really continue to struggle with infections despite immunoglobulin replacement. And so we really have to crank up the immunoglobulin dose because we really have a difficult time controlling their infections.
So to sum that up, it's very subjective. But that's sort of how I see it through my clinical lens.

Emma Mertens: Thank you. That was a great answer. And speaking of which the next is just a nice comment that I wanted to share just so you have an idea of how much our patient community appreciates your talk tonight. This individual just wanted to share the way you explained everything was so straightforward, and I really appreciate that I was able to follow along and understand through the duration of your webinar. Thank you so much.
So, thank you for that nice comment, and thank you, Dr. Wall.

Dr. Wall: Well, that's a wonderful compliment. So, thank you for sharing that.

Emma Mertens: Yes. Alright, next question. So this individual says, I know you can't speak to my specific situation. But I had a traumatic splenectomy as a young person. Do you know if there is a correlation between something like that and the development of CVID? Could it have been brought on by the splenectomy?

Dr. Wall: So I've never encountered that specific question. So I would say no, okay, as the most straightforward answer, but some of my thoughts on that. So you know, from the way that you phrased the question, I'm sure that you've done some, you know, some of your own reading and have some knowledge base along these lines. But of course, the spleen is important for vaccine response, especially that polysaccharide vaccine response. So not having a spleen can, yes, make you more likely to have a failure of that measured vaccine response.
Okay. So that part of CVID, yes. Alright. Not having the spleen certainly contributes to that. However, the spleen does not really play any direct role as far as, you know, forming the immunoglobulins, at least not to a substantial degree.
And so I really don't think that there would be any direct correlation between previous splenectomy and development of CVID. Thank

Emma Mertens: you, Dr. Wall. Alright. The next couple of questions are going to be about vaccines. So first question, since some of us do not respond to polysaccharide vaccines, are there vaccines that we should not bother getting?

Dr. Wall: So I'm trying to think which ones are predominantly polysaccharide that are commonly used. So At least one version of the meningococcal vaccine I believe is predominantly polysaccharide. Outside of that, I believe most of the other ones at least here in the United States are protein conjugated or live vaccines. Salmonella vaccine is polysaccharide vaccine and in fact that is used in some centers to measure the polysaccharide response. So, you know, all of that being said, you know, generally even if a patient does not respond well, I still encourage all of the vaccines.
However, I may also encourage in some situations additional vaccination. For example, if a patient has demonstrated that they do not respond to the pneumococcal polysaccharide vaccine, then considering the newer version of the Prevnar, the Prevnar twenty. So it's, you know, conjugated vaccine. So it has a protein component and covers for twenty serotypes now. So that could be considered for sure.
All of that being said, this would apply to patients who are not on immunoglobulin replacement, for those who are on immunoglobulin replacement. Really, you're getting the antibodies passively from the donors. So At least in our center, we generally do not immunize while on the immunoglobulin replacement. Apart from the seasonal influenza vaccine, we do recommend it, but that's really the only one.

Emma Mertens: Thank you. All right. Next vaccine question. For folks with CVID, is there a general schedule of vaccines that you would recommend?

Dr. Wall: Yeah, so I think I began to touch on that with the point that I just made. So if you have CDID or I would assume you're on immunoglobulin replacement and therefore really

only the seasonal influenza vaccine Also, now that we are that sort of, I don't know, what do you call this post COVID era, COVID era, I don't know, COVID has just become a part of our normal lives. You know, it can also be beneficial to receive the COVID a vaccine as well as a COVID boosters. But really, those are the only two. And the reason that most immunologists have do believe would still encourage those two vaccines even though we're not encouraging others.
The reason for that is that in the general donor pool, that's donating the immunoglobulin that you are receiving. We assume that most of those patients have previously been immunized for, you know, all of the other things that pneumococcus, tetanus, you know, on down the list. So you are receiving those antibodies passively. The reason that we view influenza differently and now even COVID differently is just because there is so much drift or genetic change in those viruses from one month to the next or one season to the next. And the product that you're receiving in the immunoglobulin may have been collected nine months ago or perhaps even longer.
And so the immunoglobulin that you're receiving today, at least in theory, is not going to contain good strong antibodies for the current strain of COVID that is circulating or the current strain of influenza that's circulating. Now it will have some of the antibodies against previous versions or some of the antibodies against some of the more fixed antigens, right are the antigens that don't change as much perhaps on those viruses. But as far as, you know, those neutralizing antibodies against those, the important viral proteins, the immunoglobulin you're receiving right now may be weak in that for this season's influenza and this season's COVID. And most patients even with an antibody deficiency, even on immunoglobulin, would at least have some degree of response to influenza vaccine, COVID vaccine, even though it may be a bleak response, at least gaining some t cell training or t cell memory for those vaccines. So it really would be those to while deferring really any of the other vaccines while you're on infusions.

Emma Mertens: Thank you. And last vaccine question, at least for a moment, I know that there's more coming up down the line. Will people who start receiving IG treatment therapy start to have a normal vaccine response?

Dr. Wall: Possibly. In children, we commonly use the term outgrow. And so patients may their immune system may strengthen over a period of time. Personally, I do not think that the IVIG, the immunoglobulin replacement, is really having anything to do with that. You can find experts who feel differently Yeah.
Who, you know, and you can find some very limited some very limited studies that may show or give some suggestions question that the immunoglobulin may be altering the immune system in a way that affects the vaccine response or the specific antigen response. I don't think that it really affects it in any in any clinical way. It supports you by

giving you those antibodies that you need while you're on the infusion and then time. Right? Time can be our friend.
The immune system can strengthen over the course of time, especially in children and adolescents that's why often after a couple of years. And our young patients, we made them pull them off of the infusions to reassess, see if they're strong enough. Sometimes however time goes against us and we certainly see some patients in a handful of patients in which the immune systems tends to unravel or worsen over the course of time. And that's one reason why I really emphasize that some patients such as are what seems to be not the most severe antibody deficiencies, even the THI, even when it seems that they've improved. It still warrants annual monitoring because we really never know what's going to happen to the immune system moving forward.
So bottom line, the ability to form that good vaccine response may develop. It may develop even while you're on infusions. I don't think it's related to the infusions. I think it's related to time. And the only way to assess that is to come off of the infusions receptor a couple of years and reassess.

Emma Mertens: Thank you. All right. Next question, do you have any information on how systemic inflammation is treated in CVID patients?

Dr. Wall: Sure. So there are there's a myriad of of ways to do that. A lot of it depends on where the inflammation is. I am not a rheumatologist. I do not have expertise in autoimmunity or auto inflammation.
So I oftentimes will bring in the rheumatology experts. And really let them lead the way with that. If there's a specific organ involvement, then I will bring in the expert surrounding that specific organ and then just sort of assist them with ongoing monitoring and such. Moving forward. But there are a number of ways that that could be done.
Some patients or just some immunologists may even, especially for very severe patients use rituximab, which actually wipes out the B cells with the theory that, okay, the B cells are not making good antibodies. They're not sustaining the immune system in a healthy way like we would want antibodies to do or like we would want B cells to do. And in this scenario, the B cells in fact are only making auto antibodies. And so, you know, you may use rituximab, which is an anti, you know, B cell antibody to wipe out the B cells, at least for a period of time and then just continue supporting with immunoglobulin. And then from there, there are many different medications that can be used to address that inflammation. The beautiful thing is that when we can find when there is immune dysregulation or autoimmunity, and we can identify that genetic defect, then oftentimes, we at least in the three scenarios that I described, we can treat right at the molecular defect. And generally, as greatly helpful in reducing the inflammation.

Emma Mertens: Thank you so much. All right. Next question. Do you recommend any particular centers that would be doing CVID research. This individual shares we have four people in our family with CVID and all genetic research has come back inconclusive, but they say that they have just not located the act genetic pieces that can connect the dots for us just yet?

Dr. Wall: Sure. So thanks for your question. Certainly, it's in the setting of CVID, especially if there's not severe immune dysregulation. It's not surprising to an immunologist if the testing comes back completely normal. You know, that being said, with having four individuals in your families, certainly that suggests, right, strongly, of course, suggests that there is a genetic link there that has not been found.
One thing that you could look to is to request whole exome sequencing, if that has not yet been done. And then really, I would encourage you to have a talk with your immunologist as far as who they would suggest, as far as a research center. There are a few across the U. S. I can't suggest any one particular one, but your immunologist may have an expert that they have reached out to before, that they've shared patients with before.
And so I would really recommend just having that open conversation with them and seeing if they can assist you with connecting with a a a research center in a way where your immunologist is also helping to bridge that gap as the local contact. That's the best way for that to move forward. All of that being said for anyone who's interested in research or in the field of immunology or any field for that matter, clinicaltrials dot gov is a great place to look to see if there are any open clinical trials that could involve your specific condition.

Emma Mertens: Thank you. Alright. We had a question about whole exome sequencing, but we just kind of touched on that. So we're going to move on to the last couple of questions. This individual asks in adults can sub class deficiencies be transient, transient or is IGRT typically for life?
Okay.

Dr. Wall: So Yes, I think that sub class deficiency can be transient. And if a patient is on replacement or sub class deficiency alone, especially as an adult, Yes, I would feel that, of course, the, you know, I'm not giving direct advice. This has to come through your immunologist who's looking at all the details. And if the scenario is not extremely severe, just in from a general perspective, Yes. You know, it certainly could be feasible to come off of infusions and reassess.
In my experience, one potential pitfall is that, say, for example, the defect is still there, and the patient continues to manifest infections off of immunoglobulin. If the diagnosis is not an immunologically profound one. In other words, there are not a lot of abnormal labs to go off of, for example, IgG sub class deficiency, in isolation, then sometimes it can be very

difficult to then get immunoglobulin approved again through the insurance company. So that is a potential pitfall to keep in mind. But for patients who do not have deeply ingrained or profound or antibody deficiency who have been doing well on infusions and are interested in coming off and being reassessed Generally, I do have that conversation and consider a pause from infusions for reassessment.

Emma Mertens: Thank you, Dr. Wall. All right. And this is going to be our last question. We are going to revisit something that you mentioned during your talk that I think peaked a lot of people's interest, myself included.
And we had a couple folks wondering why you mentioned that IgG's sub class deficiencies are controversial. So, you know, of course, we're not we're not getting too crazy over here, but is there anything comfortable that you'd be sharing as to why you might have said

Dr. Wall: that? Sure. So you know, there are - so a low IgG sub class alone can be detected in any - in the general population, even in people who have never had any issues with infections alone. So therefore, it really makes it hard to hang your hat on sub class deficiency as the only explanation for a susceptibility to infections. Another reason is that the normal cutoffs or or the, you know, the normal reference ranges for IgG sub classes were changed by most commercial labs, really changed substantially several years ago. So that many patients who previously flagged as having a low IgG sub class, then no longer

Emma Mertens: –

Dr. Wall: their value was now in the normal range. Okay, because that that normal reference range became much sort of stricter. Okay. And because there is overlap in the roles of the IgG sub classes. So most immunologists clinical immunologists believe that even if one sub class is low, that the other sub classes compensate enough recover enough so that the patient should not be getting sick in a substantial way.
All of that being said, I do not commonly check IgG subclasses I will check them in very limited scenarios. I will check them if the patient has absent IgA to see if there is that connection with the absence of IgA and the low IgG two sub class I haven't found that yet in ten years, but it is in the literature. And I know a lot of centers have a handful of patients with that finding. Sometimes I will also check IgG subclasses in a patient in which they At every checkup, the pattern of infection really isn't impressive to me. But yet, I've I've turned over every stone and I can't find any answers and I'm looking for where else can I go with this evaluation?
Are there any additional clues that I can find? Sometimes in that scenario, I will check IgG sub classes, but it's rare even in that scenario. And the way that I use it in my mind at that point is that I think Okay. If there's a low IgG sub class and especially if I capture that on at more than one point in time, so it is really is consistent. Might that be one small piece of

information that tells me, okay, this is some degree of laboratory evidence that tells me that your antibody compartment is not entirely intact, right, or is not entirely robust.
And the only way that that and and the way that that translates moving forward to me is to say, okay. Well, instead of me just saying, alright, let me just turn you back over to EMT or to pulmonology writer to whoever referred you to me saying, We've turned over every stone and we can't find anything with the immune system. Let me check again in six months. Right? Let me check the subclasses again, but let me also check the total immunoglobulins.
Let me also check your pneumococcal titers again in six months. Because might this be the very first sign of the development of sort of an unraveling or worsening of the immune system? In ten years, I've had only one patient with IgG sub class deficiency whom I have it on immunoglobulin replacement is the patient that I mentioned just briefly earlier and that's the one that had absent IgG2. It's the only time that I've ever seen that the patient on more than one measurement had completely undetectable IgG2 and the immunoglobulin was really life changing for her.