Dr. Mariam Hanna

Hello, I'm Dr. Mariam Hanna and this is The Allergist, a show that separates myth from medicine, deciphering allergies and understanding the immune system. This is a story all about how a diagnosis got flipped and turned around, and I'd like to take a few minutes if your clinic's not packed, I'll tell you how SAD got a whole new track. We had a patient with recurrent infections every year: sinusitis, bronchitis showing up here and there.

Normal IgG check, labs looking alright, but something about the story just didn't fit quite right. We checked pneumococcal titers—that's the thing we all do—looking for polysaccharide responses coming through. But the vaccines kept changing, the serotypes got slim, and our old diagnostic framework was starting to look dim.

Then along came a practice parameter fresh off the press with recommendation 4.7 causing a little stress, because maybe SAD isn't just pneumococcus after all. Maybe protein-antigen responses deserve a closer call. Today we're talking antibodies, vaccines, and what's new: how the definition got bigger and what that means for you.

And who better to help us sort the data and the science than the Prince of SAD himself, Ben Prince from Ohio. It's my pleasure to welcome Dr. Benjamin Prince. He's an Associate Professor of Pediatrics and Associate Division Chief of Research in Allergy and Immunology at Nationwide Children's Hospital in Columbus, Ohio.

Nationally, he serves in leadership roles with both the American Academy and the American College of Allergy, Asthma, and Immunology, and is a Senior Editor of the ACAAI Review for the Allergy and Immunology Board's textbook. With a name like Ben Prince, there was absolutely no way I was passing up the opportunity to do a Fresh Prince intro. Thank you, Dr. Prince, and welcome to the podcast.

Dr. Benjamin Prince

That is the 100 percent best intro I have ever received, hands down, and I don't think anybody can ever beat it. That's amazing.

Dr. Mariam Hanna

Thank you for the opportunity. SAD doesn't get enough press, and I think today we're going to raise the bar a little bit of awareness. For listeners who don't see a ton of specific antibody deficiency in practice, one, they now have learned a cool, hip song, but let's give us a quick orientation. What is it? Who gets it, and why does it matter?

Dr. Benjamin Prince

In general, historically, we would say specific antibody deficiency applies to those folks that on first brush, when you do your initial evaluation, you get your antibodies, look at initial vaccine

responses, maybe, and things look generally normal. They might even have appropriate responses to protein vaccines, the classic one being tetanus diphtheria, for example.

But when you challenge them with polysaccharide vaccines or polysaccharide antigens that require B or T-cell independent help from your B cells—so you have your neutrophils living in the marginal zone of B cells theoretically that are helping those B cells class switch and make IgG for all those basic science nerds in the audience—and they're making a response to that antigen that's a sugar that a T-cell can't see appropriately, that would be what you'd expect.

However, in some patients, they might not make an appropriate response. They can respond to proteins and protein vaccines, but when you look at their actual response or antibody response to sugars or polysaccharides where you don't have that T-cell added help, they just don't do a great job at it.

Dr. Mariam Hanna

I'm thinking of a large group that get normal screening immunoglobulins, and then we say, "Yeah, that's it." So that's a pretty big population of recurrent sinopulmonary infections with weird encapsulated bacteria that we really should be considering. Did I catch that right?

Dr. Benjamin Prince

The big difference here between CVID and this is that you need to know vaccine responses. Your initial laboratory evaluation isn't going to really help you. You get that back—if they have low G, low A or M, maybe E, you're like, "Oh, this patient may have CVID." But in this population, that's normal. The next step is: is this maybe more of a mild deficiency of their humoral immunity? This is where we take the next dive.

You start this thought process when you're seeing the patient in front of you. In my clinic, I see a lot of patients that are referred for immune deficiency, and most of those patients don't have an immune deficiency. It's either an inaccurate diagnosis, like the classic being the asthma phenotype or maybe underlying rhinitis that hasn't been really adequately managed. You're ruling out all of those things first, and then the next dive is: are we really missing something that is innately wrong with their immune system? Not their innate immune system, but their adaptive immune system.

Dr. Mariam Hanna

Pun intended. I got it.

The workup sounds straightforward on paper, like you check immunoglobulins, challenge with Pneumovax, and see who responds. But I would like you to comment a little bit more about this 1.3 microgram per mil threshold. Is it basically expert opinion, variability in labs, or tell us what's going on there.

Dr. Benjamin Prince

First off, as you pointed out, this level of 1.3 micrograms per mL is 100% expert opinion. Not that we shouldn't take expert opinion correctly; the truth of the matter is that what is truly protective has a lot of different factors with it. It depends on the serotype itself: some serotypes you need higher levels to be protective than others. It depends on the anatomic site: you maybe need a lower antibody level to prevent bacteremia versus pneumonia, a sinus infection, or acute otitis media, as well as the age of the patient.

These are generalized to some extent to make it easy for the clinician to really weed out those patients that truly have abnormalities in their response. The other thing to point out, which is also said in the newest update to the practice parameters, is that there is a level of protection depending on how you see the antigen. If you give an unconjugated polysaccharide vaccine, that 1.3 applies. If you give a conjugated vaccine, then we're really looking for a level greater than 0.35 micrograms per mL. It's confusing, I know, but that is the dogma. The point of it is to really identify patients and show objective evidence of some abnormalities here within humoral immunity.

In addition to this level being established, when that level was established as the standard, we used enzyme-linked immunosorbent assays, or ELISA, as we call them. Now, because it takes so much longer, we use a different kind of test: multiplex fluorescent bead assays, where you can look at multiple serotypes at once. However, while there's some correlation, studies have shown that it doesn't always correlate perfectly. Even though we established this level, it was established on a different testing platform than most clinical labs currently use.

To go a step further, there have been several studies that have shown that lab-to-lab variability is a thing. You can send the same sample to two different labs and get different responses, with some studies even showing that up to 30% of patients will have protective levels on certain serotypes and not protective levels on other serotypes. There's definitely not a great correlation, even from lab to lab.

It's important that when you're sending these studies, you send them to the same lab, because that's going to really play a role in your interpretation. If you are sending to multiple different places, even though your reference range of 1.3 is the same, those other factors may play a role. Again, some of this goes into a little bit of voodoo, which goes back to: what does the patient look like in front of us? We're really trying to gather objective data of: does this patient need further intervention because they potentially have an underlying humoral immune deficiency?

Dr. Mariam Hanna

And does it vary based on age? Is there age variability as well in these levels?

Dr. Benjamin Prince

Yes, even age. I will give the new guidelines credit. If you look back historically, there were two main definitions of specific antibody deficiency: the European Society for Immunodeficiencies and the US practice parameters. They separated patients out because, as we mentioned,

individuals less than two years of age—their immune system, this is why we developed conjugated vaccines—don't respond as well to pure polysaccharide antigens.

They did try to simplify this a little bit in the newest update to the practice parameters, and they basically just say 50%. You should respond to 50% of the serotypes that you're challenged to. They leave out the age piece, which makes it a little bit easier, but it also could make things a little bit more complicated because potentially there was that patient who responded to 60%, they were older than six, they responded to 60%, they were previously abnormal, but now they may be normal. Again, you have to treat the patient in front of you. I would argue you're doing this testing if you're truly concerned that this patient might actually have an underlying humoral immune deficiency.

Dr. Mariam Hanna

A little bit of voodoo and a little bit the art of medicine, depends on how you frame it. How are we going to make this diagnosis then, if we're going to this next level because of concern?

Dr. Benjamin Prince

This is actually one of the hardest things to do in making this diagnosis because it requires records. You have to know what vaccines that patient has already seen, and half the time that patient doesn't know, or if you're a pediatrician, that parent doesn't know. It requires records, so it's not a diagnosis you're going to make on day one.

True historical specific antibody deficiency involves responses to serotypes or antigens that are pure polysaccharide, where you may not have had T-cell help. Any vaccine that you've received that includes a serotype that was conjugated cannot really be relied upon; you really have to look at those serotypes that were naive that the patient hasn't seen before. That's where it goes into comparing pre- and post-vaccination when you're evaluating that patient. The historical specific antibody deficiency evaluation involves giving an unconjugated vaccine and looking at the serotypes in that unconjugated vaccine that the patient has not been exposed to in a prior conjugated vaccine.

With the common one being Prevnar 13, there were 11 serotypes that were different or novel in Pneumovax that were not in Prevnar 13. A few years ago, prior to Prevnar 20, I would just hone in on those 11 serotypes after vaccine challenge to see how they did and what changed after challenge.

Dr. Mariam Hanna

And now that's different. Even now, that's going to affect a portion of the population that received old vaccines versus new vaccines; we have to track down which vaccines. What you were talking about or what you were alluding to is that this Prevnar 20 situation is providing a big headache.

Some provinces across Canada at this point have defunded the 23 unconjugated vaccine as of mid-2025. It might disappear, but currently, it's available through the private market. Stay tuned, that might just vanish. Walk us through diagnostically what we're actually left to work with now in this era.

Dr. Benjamin Prince

Historically, what I would say to patients is we're going to give you this vaccine, this unconjugated 23-serotype vaccine, which in the United States we call Pneumovax, and it's going to be a diagnostic and potential therapeutic intervention. Therapeutic means it may help you if you're exposed to those serotypes in the future, if you respond appropriately, because we're showing your immune system this. From a diagnostic standpoint, though, and this is the primary reason we're giving it, we want to make sure you can respond appropriately.

With the advent of Prevnar 20, the 11 serotypes that I just mentioned have dwindled down even more. There are now only four serotypes in Pneumovax (the unconjugated 23 polysaccharide pneumococcal vaccine) that are not in Prevnar 20. Serotypes 9N, 17F, and 20 are the four that are not in Prevnar 20. When you're then challenging a patient who had received Prevnar 20 and looking for their response, you're left with those four serotypes. Knowing that those serotypes may be differently immunogenic from person to person, even in a healthy adult or a healthy child, and knowing that even in a healthy adult you might not respond to all four, this adds into that murky, gray zone in making this diagnosis.

How I would think about it is actually completely unrelated: venom testing. When you're thinking about a patient in front of you that may have hypersensitivity to venom, like Hymenoptera, whom do you test? You're going to test somebody that you're going to do something for. You're going to put them on subcutaneous immunotherapy, potentially; you test that patient.

If going into it you're like, "Any intervention I have, whether that be prophylactic antibiotics or immunoglobulin replacement therapy, wouldn't really be beneficial to this patient," then don't test that patient. That's where it goes really down to what is the patient in front of you, do you think that this could be a diagnosis to consider, and what will you do with the information that you get from evaluating that patient?

Dr. Mariam Hanna

Such an excellent plug. Don't test unless you're going to do something about this information. This is great.

One of the other ones that I wanted you to clarify for us: there's mention about using Salmonella typhi in your practice. Is this something that you're regularly using or reserve for specific situations to try to prove your point so that you can start an intervention? How does this one fit in?

Dr. Benjamin Prince

Salmonella typhi, specifically the Vi vaccine—there are a few different vaccines for Salmonella typhi—is a distinct polysaccharide vaccine that's manufactured. It's an added tool, a thing that you can use specifically in patients that maybe are already on immunoglobulin replacement therapy, because in most people, at least in the United States and probably Canada, it's a neoantigen.

It could be something you could do in addition if you're really looking for more data or information, but you have to convince an insurance company to be able to pay for this vaccine. It's a great tool, but if you look at the studies, it's not a perfect correlation with the response to unconjugated pneumococcal vaccination.

Dr. Mariam Hanna

Perfect. You kind of alluded to the practice parameters, but let's go into the specific recommendation that's in there. You've already mentioned supplemental tests beyond the practice parameters. Specific antibody deficiency to protein antigens.

Dr. Benjamin Prince

It is recommendation 4.7. The big change that is probably causing the most controversy right now is recommendation 4.7, which you alluded to. It opens the door now, changing the definition of what specific antibody deficiency is. As we talked earlier in the podcast, historically it's normal immunoglobulins, normal responses to protein antigens, and abnormal responses to polysaccharide or sugar antigens.

Recommendation 4.7 says you can have a patient that has normal immunoglobulins and abnormal responses to protein antigens as well. Historically, I've seen these patients. They do happen; they are out there. Even though it causes a little bit of transient palpitations for people like myself who have been doing this for a while—thinking this is totally different and not specific antibody deficiency—those people are still out there.

I think the authors were thinking of two things when they included that parameter. Number one is that these people do exist, and if you have somebody that's clearly getting infections and has a poor response to proteins, we need to be able to treat that patient. It's giving you power to go and advocate for that patient.

Number two, I think they're hedging for what's going on right now in Canada and what's going to be happening even more so in the United States with the inability that we're going to have to assess for true polysaccharide suboptimal antibody response. This is due either to the loss of the unconjugated pneumococcal vaccine or because four years from now, there might be a Prevnar 23 or more evolving vaccinations available that are going to likely be conjugated. We know that not just for young children, but adults have a more robust, longer-lasting antibody response if you conjugate that polysaccharide antigen, because then you can help by adding that T-cell in to train that B-cell to have a memory, longer-lasting response.

Dr. Mariam Hanna

I love it. I also love the concept of a bunch of immunologists having palpitations over slight, nuanced definition changes, but this is the thing that makes immunologists so cool. So he reason that we said that we would test and do the next line of testing is really, ultimately, we are looking to intervene with some kind of management option. Walk us through the different management options that are available and how you decide or decipher between them with families.

Dr. Benjamin Prince

I have these conversations with every patient that I'm concerned about that may not have a robust response to protein antigens or polysaccharide antigens. Option number one is a watchful waiting approach. Especially if it's a younger child or a patient that has had other immunomodulatory or immunosuppressive therapies, and their infection history consists of one bad infection but they've otherwise done well, we talk about the warning signs to seek medical care.

If you have a fever of 38 degrees Celsius or greater (100.4 degrees Fahrenheit), any concerns about infections, or anything that makes us worried about an underlying infection, I want you to present to the ER where we would do a little bit more than we would for a typical child. Most of those infections are going to be viral. The purpose here is to make sure we're not missing a severe encapsulated bacterial infection that could escalate rapidly and cause significant harm. A simple blood culture, a CBC with diff, a viral screen, or maybe prophylactic antibiotics in that context could be used. Identifying if it's just RSV while they otherwise look fine would be reassuring. That's option one.

Option two is prophylactic antibiotics. The most studied are azithromycin or Bactrim, but there are many options. You could also consider an amoxicillin protocol or a Pen VK protocol. Basically, it's a prophylactic strategy where you're protecting that patient from a significant infection with an encapsulated bacterium, because that's what we're worried about. The capsule is made of sugar, and without an intact antibody system that's going to be able to form a protective antibody against that sugar, that patient is at risk for a more systemic infection with an encapsulated bacterium.

The third option is immunoglobulin replacement therapy, whether that be IVIG or subcutaneous IG. This is really reserved for the patient that has had multiple severe bacterial infections or very bad infections. If I'm having this conversation with a family, my style is to give them data and options, and if they ask me, I'll sway them one way or the other based on their infection history. But I want that family really to decide on their own.

I don't have a lot of patients on prophylactic antibiotics; most families end up choosing the watchful waiting approach. A family whose child has had one bad infection but otherwise is doing great with a couple of viral infections might just wait, questioning if they really want to give immunoglobulin replacement therapy monthly or weekly and what they're preventing. On the other side of the coin, if a patient has had three pneumonias in the past year, it makes more sense to use immunoglobulin replacement therapy to actually prevent infection. Those are the

three main options that we talk about, and it's important to have the family weigh in on how this would look like.

Dr. Mariam Hanna

And if you are doing immunoglobulin replacement, are you targeting particular troughs or what?

Dr. Benjamin Prince

That is a fantastic question. I usually say to families there's three things I think about when starting immunoglobulin replacement therapy and dosing it correctly. Number one is the weight of the patient. How big is that patient? We have standard protocols for milligrams per kilogram to start at, usually 400 to 600 milligrams per kilogram if you're talking about infection prevention, not an immunomodulatory intervention, which would aim for higher doses.

The second thing is the trough, which in this situation is not really helpful because we don't have tests that are going to differentiate between the bad antibody that this patient may be making and the good antibody that we're giving. These patients are definitely going to have higher troughs than your CVID patients that don't make good antibody at all.

The third thing, and really I would argue is the most important thing in this population, is how they are doing. Are you making an impact? If they had three pneumonias last year and this year they're doing great, then you have a great dose. If you are in that normal range and they're doing great, unless they've had significant weight gain or growth, maintaining that same goal is very reasonable. If they're still having infections that make you worried about an underlying antibody deficiency, then pushing that dose higher is definitely warranted. That's why it's important to see these patients back in your office every four to six months after starting until things stabilize.

Dr. Mariam Hanna

Fair enough. I have a sense that your diagnostic workup is going to look different in five years.

Dr. Benjamin Prince

While genetic testing is the answer for a lot of underlying inborn errors of immunity, we know that 70% of patients that have antibody deficiencies don't have an identified inborn error of immunity. We've come a long way. I think back to when I was a fellow and what we had to evaluate patients that might have an immune deficiency: we could look at antibody levels, responses to vaccines, lymphocyte subsets, and maybe look at B-cell differentiation. That was it.

Now, the functional testing available on a clinical basis in immunology is amazing. I expect the same advancements in functional testing in this realm as well, where we're not just looking at levels, but looking at the functional status of the antibodies these patients are making.

Dr. Mariam Hanna

That sounds cool. And immunologists will get palpitations all over again.

Dr. Benjamin Prince

We'll have email chains upon email chains discussing it and talking about it. It'll be fun.

Dr. Mariam Hanna

It'll be fun. All right. Time to wrap up and ask today's immunologist, Dr. Ben Prince, for his top three key messages to impart to patients and physicians on today's topic: specific antibody deficiency, protein/polysaccharide. It's okay, don't get palpitations. Dr. Prince, over to you.

Dr. Benjamin Prince

My top three takeaways:

Number one is that the clinical history is really important. You're not going to evaluate every patient in front of you for specific antibody deficiency. It's going to be those patients that are having concerning, particularly encapsulated sinopulmonary bacterial infections and other kinds of concerning infections where you think this patient might have an antibody deficiency. That patient is whom you should think about for evaluating a specific antibody deficiency.

Two is that even in the age of Prevnar 20, there still are ways that we can assess for antibody responses to polysaccharide antigens, whether that be looking at the four serotypes that we talked about that are different between Prevnar 20 and Pneumovax, using the conjugated pneumococcal vaccine, or using Salmonella typhi. There are other tools in your toolkit that you can use, and B-cell phenotyping can be helpful as well.

Three, treat the patient in front of you. The patient in front of you is whom you should think about when starting the evaluation as well as when talking about what management strategies to take. In an age where we have learned so much, it is our job to empower the patient in front of us as best as we can to make the decision that would best impact their quality of life.

I remember interviewing for med school and learning that "doctor" was Latin for "teacher." Our job is to be the teacher to our patients. If we do a good job at that, we're going to provide fantastic care, no matter if it's immunology or allergy.

Dr. Mariam Hanna

Thank you, Dr. Prince, for joining us on today's episode of The Allergist.

Dr. Benjamin Prince

Thank you, eh?

Dr. Mariam Hanna

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Sincerely, The Allergist.