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.
Imagine recurrent sinus infections, a cough that never goes away, one round of antibiotics and then another. Pneumonia here, sinus infection there, generally feeling unwell. Patients who battle this disease know that they're acutely unwell sometimes. Then there's just this grumbling feeling, an overall feeling of illness that you can never shake. That's how a patient described it to me. They discovered on their path to recovery from advanced cancer therapy that they had actually traded it for another disease: acquired immunodeficiency. It always makes me think of this famous Spider-Man quote: "With great power comes great responsibility." The era of advanced cancer therapies includes an assortment of novel treatments targeting specific parts of the immune system, but targeting those parts has consequences. Adjusting the immune system, whether with chemotherapeutics or targeted treatments to address the cells that have evaded the immune system, is not new. It works great but may impact the immune system long-term, leading to acquired immunodeficiencies.

On today's episode, Dr. Samira Jeimy is going to explore this and dive deep into the world of acquired immunodeficiency. Dr. Jeimy is an assistant professor in the Division of Clinical Immunology and Allergy at Western University. She completed her medical training in internal medicine residency at the University of Toronto, followed by a fellowship in Clinical Immunology and Allergy at Western University. She holds a PhD in platelet immunology from McMaster University. Dr. Jeimy also holds multiple leadership roles at the Ontario Medical Association, the CSACI, and St. Joseph's Healthcare in London. She's passionate about making medical education accessible and palatable and maintains active social media profiles under many different handles. Dr. Jeimy, thank you so much for joining us today and welcome to the podcast.

Dr. Samira Jeimy:
Thank you very much. What an honour.

Dr. Mariam Hanna:
Okay, Dr. Jeimy, we're going to start right into it. Can you please define for us what an acquired immunodeficiency is?

Dr. Samira Jeimy:
Acquired immunodeficiencies are also called secondary immunodeficiencies, and they are essentially characterized by a weakening of the immune system from external factors rather than an inborn error or a genetic anomaly.

Dr. Mariam Hanna:
And do these imply a permanent or a transient state, or not necessarily in the definition itself?

Dr. Samira Jeimy:

They actually fall on a spectrum, so it's a pretty complex and challenging diagnosis to make sometimes. They include infectious diseases like HIV/AIDS, chronic diseases like diabetes and renal failure, malnutrition, and even medications, especially immunosuppressants, as you've mentioned, particularly chemotherapeutic agents and B-cell and T-cell targeted therapies.

Dr. Mariam Hanna:
Okay. What would you estimate the incidence of immunodeficiencies, be it this broad range of diseases, is overall in the general population that we see today?

Dr. Samira Jeimy:
Because the etiologies are so diverse, it's really difficult to precisely give an estimate. I will tell you that the overall estimated prevalence of primary immunodeficiency, which is now called inborn error of immunity, but I might refer to it as primary immunodeficiency just for the sake of ease. So the estimated prevalence of PID is one in 1200 individuals. Detailed epidemiologic studies are not really available for secondary immunodeficiencies yet. But the available evidence suggests that secondary causes are way more prevalent than primary causes. For example, the global burden of HIV/AIDS significantly contributes to the incidence, and we know that HIV/AIDS affects millions worldwide.

Dr. Mariam Hanna:
Okay, that makes sense. So globally then, what is the most common cause of secondary or acquired immunodeficiency?

Dr. Samira Jeimy:
Even amongst allergists and immunologists, it's controversial. Globally, acquired immunodeficiency syndrome or AIDS caused by HIV infection is the best known, and we often assume that is the most common cause because of the high prevalence and the high mortality of HIV if untreated. That's the caveat. Because of the incredible advances in HIV diagnosis and treatment, the incidence of AIDS, which is the most common suspected cause of immune deficiency worldwide, is no longer the case. It's actually malnutrition, severe malnutrition in particular, that can impact both innate and adaptive immunity. That's the most common cause. And that's actually sad because in 2024, robots are doing our chores for us, but malnutrition remains a global issue.

Dr. Mariam Hanna:
That's surprising. That's surprising. Okay, so then let's look at North America. If we're talking more about westernized cultures here, what do we see here as the most common cause of secondary immunodeficiency?

Dr. Samira Jeimy:
In Western cultures like North America, chronic conditions like kidney disease and diabetes, and our rather extensive use of immunosuppressive and immunomodulatory therapies are the leading causes. Going more granular from immunodeficiency to humoral immunodeficiency, which is also known as secondary hypogammaglobulinemia, that is essentially rooted in the

increasing use of immunosuppressive treatments, most notably the B-cell targeted therapies. We know that our colleagues in rheumatology, neurology, and hematology oncology are all using B-cell targeted therapies. To make matters more complex, there are studies that show that antibody deficits are actually seen in autoimmune and oncologic conditions even before we start treating people with immunomodulatory treatments. For this reason, many international societies from multiple specialties recommend screening for secondary hypogammaglobulinemia before initiating treatment and at the time of diagnosis of the oncologic, rheumatologic, or neurologic condition. However, observational studies show that this is not done as often as it ideally should be.

Dr. Mariam Hanna:
What would be the thought of doing it before diagnosis or before instigating treatment? Is it to know that you have to replete them as soon as you're done with treatment, or what would be the reason to do that?

Dr. Samira Jeimy:
Excellent segue. I always try to plug that primary immunodeficiencies are likely more common than we appreciate. There's a whole category of primary immunodeficiencies called primary immune regulatory disorders, which don't present in a classic way. They present with autoimmunity and a lymphoproliferative picture rather than a classic primary immunodeficiency presentation where you think of just severe or recalcitrant or unusual infection. There's a whole Venn diagram of immunodeficiency where autoimmunity and lymphoproliferative malignancies actually are sometimes part of the primary picture. You might pick up that primary immune deficiency at the time of diagnosis of the oncologic or rheumatologic condition. If a secondary immune deficiency is discovered, it's always good to wonder if this is a primary immune deficiency that we have unmasked. That's a whole category in and of itself. There are also structural causes like protein-losing enteropathies, nephropathies, and post-transplant medication. It's a really broad category of diseases.

Dr. Mariam Hanna:
Okay. Now I need you to myth-bust for me for a second. Can stress on its own lead to immunodeficiency, like just a high-stress state?

Dr. Samira Jeimy:
Have you ever noticed that after a chronic prolonged period of stress, you come down with an illness? Do you remember when you were in university and we would go home for Christmas break and all of us would be sick?

Dr. Mariam Hanna:
But isn't that because we crammed together in the same room and studied really long hours?

Dr. Samira Jeimy:
No.

Dr. Mariam Hanna:
Is this medical, or are we paranoid about this?

Dr. Samira Jeimy:
Mechanistically, it could happen. If you're familiar with the anxiety performance curve, short bursts of acute anxiety can be performance-enhancing, whereas chronic anxiety is detrimental. Similarly, it is proposed from in vitro studies and mouse models that stress is a fundamental but underappreciated survival mechanism. Short-term stress, lasting from minutes to hours, can enhance innate immunity and secondary immune responses. The mechanisms proposed and shown in vitro include enhanced trafficking, maturation, and function of dendritic cells, neutrophils, and macrophages, as well as systemic production of cytokines that promote these processes. On the other hand, long-term stress can suppress and dysregulate innate and adaptive immune responses. It alters the Th1/Th2 cytokine balance, leading to a state of low-grade chronic inflammation. The numbers, trafficking, and function of immune cells decrease. In oncology, it's been shown that chronic stress hormones like cortisol can increase susceptibility to some types of cancer by suppressing Th1 cytokines and regulatory T-cell functions. It's fascinating.

Dr. Mariam Hanna:
So I should cram, but I should not live under chronic stress conditions, if I can confirm.

Dr. Samira Jeimy:
Yeah, who should, right?

Dr. Mariam Hanna:
Who should? Okay, here's another one. Post-COVID infection, is there an acquired immunodeficiency, or do we have any knowledge about that?

Dr. Samira Jeimy:
There is a lot of chatter online. There are many postulates about COVID causing some derangement in T-cell numbers and function. Is it transient? Is it long-term? Has it actually been studied in well-controlled large numbers? I remain unconvinced. However, the mechanism for viruses inducing immune dysregulation, autoimmunity, and even malignancies is there. We have to do entire lectures on EBV, for example.

Dr. Mariam Hanna:
One of the other things that I keep hearing about is this concept of immunity debt. I hear about it in children, I hear about it in adults. People blame time away from normal, recurrent, or chronic respiratory viruses that we have seen year in, year out for a couple of years as a culprit or a cause. I understand that this is some kind of acquired immunodeficiency. Is this real? Is there any science to that?

Dr. Samira Jeimy:

I don't even know what the term "immunity debt" actually refers to. I think people attribute many different meanings to it. Some claim that because we have not had infections for a while, it weakened children's immune systems, causing them to have more severe infections. I don't believe that's real. Our immune systems don't just go dormant in the absence of infections, and it's not like I am working out the immune system with an infection, so it's getting stronger. It doesn't work like that. Our immune system is constantly in action. We coexist with a whole universe of organisms on our skin and in our gut. The immune system is constantly adapting to these exposures. I dislike when the term is used to imply that a lack of infections is weakening the immune system. Some infections can weaken the immune system, and we know that they can. Measles can cause transient, sometimes even longer-term secondary immunodeficiencies. We just spoke about HIV. So it's like the term "herd immunity." I feel like the term "immunity debt" has become fashionable but has lost all its meaning for me.

Dr. Mariam Hanna:
Yes, I use it as a red flag term when patients mention it. Okay, at what point should someone be screened for an acquired immunodeficiency or a secondary immunodeficiency? What are you looking for as flags for you to start that screening process?

Dr. Samira Jeimy:
We have excellent validated top 10 signs of immune deficiency available. One of them is from the Jeffrey Modell Foundation. Going back to what I mentioned about that Venn diagram of infection, autoimmunity, and malignancy, anytime there's something unusual in the patient's clinical history where they're having opportunistic infections or severe infections that don't respond to one, two, or three courses of antibiotics, poor response to conventional treatments, a family history of multiple autoimmune diseases, multiple malignancies, or malignancy in a young person, it's reasonable to have a baseline screen for immunodeficiency.

Dr. Mariam Hanna:
And is that kind of our best first-line screen is to screen for hypogammaglobulinemia in those kinds of patients?

Dr. Samira Jeimy:
Certainly. CBC differential, low-hanging fruits, immunoglobulin quantification are widely available and reasonable to do. Most of us in the immunology clinic also typically check for lymphocyte subsets, lymphoproliferative processes, protein-losing enteropathy with an albumin, liver and kidney disease, and imaging if indicated, like an ultrasound or a chest X-ray. My first encounter with immunodeficiency was as a senior medical resident at Toronto General Hospital. I admitted someone with Evans syndrome, which is autoimmune cytopenia of both platelets and red blood cells. This patient ended up being diagnosed with Good syndrome, which involves hypogammaglobulinemia, autoimmunity, and a thymoma. That was my introduction to immunology, and I've never looked back.

Dr. Mariam Hanna:

Yeah, this seems like a fellow quiz question. Do patients still experience delayed diagnosis? Is this an ongoing issue?

Dr. Samira Jeimy:
Yes, absolutely. Patients do experience delayed diagnosis because the symptoms can be nonspecific. People just feel a grumbling fatigue, unwell, fever, and sweats. Symptoms could be misattributed to more common and less severe things. Baseline assessment of hypogammaglobulinemia could certainly be more commonly done. A 2018 retrospective cohort study of almost 5,000 patients receiving rituximab showed that 85% of patients didn't have quantitative immunoglobulins checked before therapy. Awareness that this is a real and potentially long-term possibility for those treated with immunomodulatory medications should be more widespread. Allergists and immunologists are rare in hospitals, and education around when and how to involve us is greatly needed.

Dr. Mariam Hanna:
When should immunologists or infectious diseases be involved during the patient journey? Are we at a point where we say, "You have X chronic condition, you need a basic immunologist to look at you at least once"?

Dr. Samira Jeimy:
Some centers are already doing that. In many centers, staph or bacteremia necessitates an infectious disease consult. Similarly, a new diagnosis of a B-cell malignancy or a lymphoproliferative malignancy where you want to initiate rituximab should trigger an immunology consult. At Western, we work closely with transplant nephrologists, which has been rewarding. Patients on subcutaneous or IV immunoglobulin feel better, their energy levels improve, and it makes a great impact on their post-transplant recovery or post-chemotherapeutic regimen. I think early introduction of immunology in the patient journey is important.

Dr. Mariam Hanna:
How has the management of acquired immunodeficiency changed over time? What do you think are key changes in our specialty regarding this condition?

Dr. Samira Jeimy:
So much has changed, especially diagnostic technology. We have advanced genetic testing, functional techniques, preventative strategies like vaccinations and prophylactic antibiotics, and access to personalized medicine. Management requires shared decision-making with the patient and the multidisciplinary team. It's good to know that for many secondary immune deficiencies, there isn't one cutoff to start immunoglobulin replacement. Guidelines are available, but it comes down to collaboration between the patient, immunology, and other specialties.

Dr. Mariam Hanna:

I'm hearing collaboration and thinking about us early. Alright, time to wrap up and ask today's allergist, Dr. Samira Jeimy, for her top three key messages to impart to patients and physicians of all kinds on today's topic, acquired immunodeficiencies. Dr. Jeimy, over to you.

Dr. Samira Jeimy:
Okay. My top three takeaways are: keep a broad differential in evaluating secondary immune deficiencies, don't forget about inborn errors of immunity, and the decision about initiating immunoglobulin replacement in secondary hypogammaglobulinemia is individualized and complex, but guidelines are available. We can share some if there's a place to share them.

Dr. Mariam Hanna:
I will post them on our website if you share them. That's perfect. Thank you, Dr. Jeimy, for joining us on today's episode of The Allergist.

Dr. Samira Jeimy:
Thanks again for having me.

Dr. Mariam Hanna:
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Dr. Samira Jeimy:
Early Introduction of Immunology.

Dr. Mariam Hanna:
Thank you for listening. Sincerely, The Allergist.