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. A while back, I had a consult for food allergy. This young man had the usual list of comorbid offenders associated with eczema, still there, environmental allergies, and before you even ask, no, he didn't own a cat, and he had asthma exacerbations at least once or twice a year and a recent hospitalization in the last five years. We conducted spirometry in the clinic. His baseline FEV1 made my nurse actually double-check the calibration on our machines. But no, it really was that low. Four puffs of Ventolin, repeat, bam, 48% reversibility. We sidelined any food allergy discussion for today and talked about severe asthma. He was young and, as I like to embellish just a little bit, walking around with an 80-year-old smoker's set of lungs; he needed biologics.

Mom's eyes lit up as if saying, "Thank you." Actually, she literally did say "thank you." We've been asking for years, and the doctor just didn't feel comfortable prescribing them. So that's my story, at least a decade ago. But I'll tell you, the narrative really hasn't changed too much. Okay, let me be optimistic. We are seeing an uptick in recognition and use in select populations of biologics. Today's guest, actually, I hope, will arm allergists with the knowledge, resources, and confidence they need to manage severe asthma in their clinics. It's my pleasure to welcome Dr. Jason Lee. Dr. Lee is a global speaker, presenter, and part of multiple global research and steering committees. He's the past section advisor on asthma at the Canadian Society of Allergy and Clinical Immunology and a current member of the Biologics and Therapeutics Committee at the American College of Allergy, Asthma, and Immunology. Dr. Lee has over 150 peer-reviewed publications and abstracts and is active on TikTok with the handle @JasonK.LeeMD and on Apple Podcasts, where he discusses topics in our field. And with that, it's my pleasure to introduce Dr. Lee. Welcome to the podcast.

Dr. Jason Lee:

Hey, thanks for having me, Mariam.

Dr. Mariam Hanna:

Let's start with how you would define severe asthma, practically speaking, to your patients?

Dr. Jason Lee:

Yeah, so practically speaking, assuming that the patient is adherent and compliant with all their medications and they're using everything correctly, it is the amount of

medication required so that you could live a normal life. And what we look at are how many times do you have an exacerbation? So, a severe asthmatic would be someone who requires, on the last step or GINA five, we say all sorts of medications, maximized all their conventional therapies maximized, but still having exacerbations or requiring more, such as biologic medication to control their asthma.

Dr. Mariam Hanna:

What do you think, Dr. Lee, has changed in this space over the past 10 years in that GINA five severity of asthma?

Dr. Jason Lee:

Yeah, so it's a great question, and it's a really exciting time to be a physician who treats asthma because we have a lot of tools in our toolkit. There's that old saying, "A carpenter is only as good as his tools." We now have a lot of tools in the toolkit. So, for the GINA five asthmatics who are very difficult to control, we now have globally six different biologic therapies that are approved for the treatment of asthma. We can use the characteristics of a patient, both how they present and some of the markers inside their body, to determine what may be the best fit for this patient. And you know what, I want to point out one thing, Mariam, it was allergists who mainly started treating asthma historically, and it was allergists who started using inhaled corticosteroids. If you think back to the 1950s and '60s, how the model of asthma has changed, especially even up to the '80s, we thought it was one of hyperresponsiveness or bronchospasm, but now the model has changed into more of an inflammatory and now even more of an immune dysregulation issue. The whole evolution has really evolved. A lot of allergist immunologists are here, but there aren't that many of us in Canada. So, we're growing.

Dr. Mariam Hanna:

We're growing; we're gaining steam. Yeah. Okay. So let's flip to the other side of it, the patient side of it. How do you even approach the topic of biologics with your patients?

Dr. Jason Lee:

Usually, when I see a patient in consultation, they will have had many exacerbations and often requiring prednisone. One of the big gaps in knowledge that we have on both patients and other physicians is that of the cumulative effect of oral corticosteroids. So, oral corticosteroids do control most people's asthma exacerbations, or cortico-systemic steroids, but it has consequences for the patient that they may or may not notice

acutely, but certainly chronically as well. So, the chronic side effects, everyone knows about things like osteoporosis and vertebral fractures, but other things such as coronary artery disease, loss of lung function, premature decline in lung function, remodeling that occurs, this is often not talked about enough with patients. So, I spend a lot of time speaking to patients about how I want to get them on the most normal lung function decline curve as possible and appropriate for their age, gender, height, and weight to some degree. So we want to optimize the lung function and the best way to do that is to keep you from having exacerbations or keep you well-controlled so that you don't have more than your fair share of consequences from an infection or a complication of asthma.

Dr. Mariam Hanna:

I like how you've discussed the complications because, in pediatrics, we often spend time talking about like, "No, it will not significantly stunt the child's growth. Don't worry about that." There are bigger issues here.

Dr. Jason Lee:

Yeah, absolutely. We're finding out more and more each day about the cumulative effects of oral steroids. And so, the way I would phrase it if you were my patient is we want to try to prevent this because even one exacerbation per year is way too many. As a lifelong asthmatic myself, I've not had any exacerbation requiring oral steroids, so this is how it should be, and that's what we aim for each patient to reduce future risk and reduce future exacerbations as well as optimize function. Currently,

Dr. Mariam Hanna:

The Canadian Lung Association a while back had this target zero, zero symptoms, zero exacerbations like target perfection for all your patients, or almost all. But isn't it scary? How do you present, "I'm going to talk to you about a biologic, an injection to control your asthma." That discussion isn't easy when I start having it in my clinic. Their eyes double in size because we're talking about an injectable type medication and a biologic nonetheless. How does that go over in your office?

Dr. Jason Lee:

The term "biologic" in itself is a little scary. So, I just say we can make a drug toward anything we imagine if we make a customized antibody, and unfortunately, these antibody molecules get digested by the gut, so there's no way to get them into your

body unless we do an injection. So, I try to explain because knowledge is really power, and fear often stems from not understanding or not knowing about something. So, once the patients understand that if they take this medication orally, it's going to be broken down by stomach acid and digestive enzymes, and the only way to get this medication is through an injection, it does alleviate a lot of fear in patients. Just think about any other medications, except that it is probably safer and has fewer interactions than all your other medications. A perfect example of this is that many of these medications that we use in the biologic class for asthma have very high safety ratings, and they have pediatric indications; they're often safe in breastfeeding and pregnancy as well. There are large human registries that have already been reported that show no significant issues. So yeah, in fact, a lot of these medications will get even a higher pregnancy class rating than the inhalers, in fact. So, I try to allay all the safety fears like this because let's face it, people get scared by reading the monographs and the warning labels or whatever they hear on Facebook or social media too.

Dr. Mariam Hanna:

They read it on a Facebook group, or they had a chat with somebody about it. Right.

Dr. Jason Lee:

Yeah. I find that's a common cause now of a barrier to care.

Dr. Mariam Hanna:

It is. Okay. So, you nicely made a statement to say, once we've optimized medication and medication delivery, we will switch to this different class of medications, or we will add on this class of medications. At what point, Dr. Lee, are you satisfied that you have done all you can in optimizing other routes or other types of medications? I see people get stuck in this step for an obscene amount of time as well.

Dr. Jason Lee:

So, one of the things I do, and it literally takes one minute in my clinic, is I watch the patient take all their medications and inhalers, and you'd be surprised how many times I find little ways that they're either completely doing it wrong or that I can suggest pointers to coach them to take the medication more optimally. So, once I've done that, I see them in follow-up, and I tend to follow especially the severe asthmatics at least every three months until I get them stable. And in some cases, if they're really not doing well, it can be even every month just to make sure that they are doing well. We will often double-check everything with spirometry and or a fractional exhaled nitric oxide, so

that's FeNO, to measure both their adherence and response to therapy as well. Once we have done this, and generally, I follow the GINA guidelines in terms of the non-severe asthmatics too, so they suggest follow-up every three to six months as well. And this is where my thinking and reasoning come for the follow-up.

Dr. Mariam Hanna:

So we've decided that this patient has optimized all their medications, they still don't have good enough control, they've had enough exacerbations each year to qualify. How do you choose, this seems to be like the most common CME topic from 2020 to 2024 to date, as how do you phenotype them and how do you choose which biologic? How does that work practically in your office?

Dr. Jason Lee:

Yeah, so clinical gestalt and clinical judgment are still hard to quantify, but with experience, you sometimes get a good sense of whether our patient's symptoms are really driven by immune dysregulation or by allergies or by certain biomarkers that we can check in the patients, such as a blood eosinophil level or their overall CBC. And we have to always be mindful that these biomarkers are not a perfect or an exact science; things can fluctuate with time. So the same measurement can vary from day to day, time of day, and if they've just had an exacerbation or whatnot. So, yeah, I try to do my best at predicting which patient will do well with certain drugs, X, Y, and Z. But like I said, there is no exact way. There's a fellow by the name of Dr. Busque in France who, in his retirement, has developed an AI algorithm to try to predict based on something called a Getty score in terms of which biologic to pick. But I'm very skeptical because the biomarkers we have currently in 2024 are imprecise, but we have to make do with the best we have. And really, in my experience, in all honesty, you have to just try something. And if the patient responds, great; if they don't respond enough after about three to six months, usually the GINA guidelines recommend a minimum of four to six months, but you give it a fair try, and if it doesn't work out, it's time to kind of scratch my head again.

Dr. Mariam Hanna:

Clinical gestalt, gut instinct trumps AI is what I have heard from somebody that really appreciates

Dr. Jason Lee:

Tech so far. Yeah, yeah,

Dr. Mariam Hanna:

Fair enough. I respect that too, that we've said for severe asthmatics, typically they are coming into the clinic every three months, if not monthly, if they're really poorly controlled. What about once you start them on biologics? You've already touched on it a little bit, but how often are you bringing them back and what are you monitoring for when you're bringing them back?

Dr. Jason Lee:

I like to lay out expectations fairly clearly. When you look at most of the phase three trials, which are what's called the pivotal trials for most of the biologics, that's the big enough trial that's randomized, double-blinded, and placebo-controlled. You see a response rate starting typically around the two months to six months range. So I try to lay this out for patients: don't expect too much in the first month or two. If you do, that's great, and I'm very happy that you are a fast responder, and some patients are fast responders, but currently, if I'm following the GINA guidelines, you want to reassess at the four to six-month mark. And that's what I usually do and say at the outset because I don't want to overpromise and underdeliver. And some patients feel that they're expecting a night and day difference when it may very well be a slow gradual process of improvement as well.

Dr. Mariam Hanna:

Alright. When you're bringing them back, are you just doing a routine asthma check, or what specifically are you looking for in your patients that are on biologics?

Dr. Jason Lee:

Yeah, so I try to do my very best to keep things objective as much as possible. So this will usually involve a repeat spirometry and a repeat pheno level. And I started implementing this as of last year, 2023, especially the repeat pheno measurements because you get a very objective kind of number, and that number you can follow over time to measure the amount of global inflammation the patient may have in their airway. The lung function, such as PFT, gives me a rough proxy of which segments of the lung have flared up and how the patient may feel. Now, there doesn't always correlate as the numbers versus how patients are doing, but it's a good kind of objective measure. In some settings, we do asthma control questionnaires. It's pretty quick and gives us a

number to gauge if a patient is doing well, I'll feel that all of these things are less necessary as they obtain control. So then it becomes, after the six-month mark, more about seeing if we can maybe cut back on some of the inhaler medication or decrease some of their medications just to optimize the management and reduce side effects.

Dr. Mariam Hanna:

What adverse events worry you, and which ones do you say that's not common?

Dr. Jason Lee:
Mariam, I'm a big fan of shared decision-making. And with the monograph, of course, every patient usually reads it or will have heard some snippets of it on an online forum or whatnot. Patients are always given a brochure from each pharmaceutical company that produces each medication too. And unfortunately, when you read adverse events or side effects out of context, it's really always alarming and troubling. So one of the things that comes up a lot are patients think that it increases the risk of infection. So again, this is just my personal approach; there's no right way of doing this, I think. But what I like to do is show a slide presentation where we look at the data, the raw data from the clinical trials, and I don't have a paternalistic approach to my practice. So I like it when patients can see and follow along my reasoning with actual hard data so they know that I'm not making things up.
So I point out the baseline demographics of the placebo and the treatment arm, and I actually highlight that, hey, look, the infection rate is sometimes actually much higher in the placebo group than in the treatment group, but the way the monographs are written, any infection is reported as an adverse event, and it's the delta, the difference between placebo and treatment arms that really determines the true side effects. And when you enroll patients who have severe asthma, we always have to take into account what is the difference with placebo. So yeah, I'll show them little graphs that I've taken a snippet from, and the monograph actually has these tables too of the placebo versus the actual rate. And I find that really reassures patients as a whole. If the adverse event of this is actually higher, then it's concerning. Now, are there any side effects that concern me?

Yeah, I guess it's all relative to what concerns you. There are side effects of special interest. I think some medications are more known for, so we will spend some time talking about it, but I also will reassure them, "Hey, if this happens, we can deal with it and we can treat it too. We can certainly change the medication, stop the medication, or we can retool and redose as well." There's some dose flexibility in some of the biologics. So yeah, there are conversations to be had with the specialist on how to manage expectations from both a benefit and potential downsides. And you definitely want to lay the groundwork so that patients don't get too much of a nocebo effect as well, where they feel that they have all sorts of side effects that they've read about. But

yeah, other severe serious adverse events are something that is very drug specific, and I will discuss it with patients and I'll use the most correct accurate numbers if at all possible, usually with a slide deck or so.

Dr. Mariam Hanna:

So, you have a patient-specific slide deck where you try to share with them adverse events and specifically what we're expecting to see as results. Is that right? Yeah, that's wonderful. This is a great tip for people that if they want to use that or incorporate that as part of their practice. And speaking of the nocebo effect, you've reminded me of my med student syndrome days of developing every single symptom known to mankind according to the disease I was learning about. So yeah,

Dr. Jason Lee:

Absolutely. And the mind is very powerful. Yeah,

Dr. Mariam Hanna:

Absolutely. Okay. At what point do we decide if a patient has failed a biologic?

Dr. Jason Lee:

So if they haven't really improved one iota, or if things are getting worse, for example, their lung function or their pheno level continues to rise and the patient is continuing to not be able to sleep or experience symptoms that are limiting their life, I do consider that a failure, and I hate to use the FDA standard, but the FDA and now Health Canada are starting to use a lot for this 30% rule where an intervention has to have a minimal difference of 30% compared to the standard of care or placebo. So if a patient, and it is a rough kind of use of that, and patients can do a visual analog score, it doesn't sound very scientific, but when you ask patients do you feel 10%, 20%, 30%, 50% better, they can usually give you a number. And if they tell me they're not at least 30% better, it's kind of time to think maybe there's something else I can optimize. One thing I am mindful of, though, are sometimes patients will forget to tell you that, "Hey, I just stopped all my asthma inhalers. I was feeling good at some point." So they're only 30% better, but they've stopped all their inhalers. Well, you get the gist of it. There's a bit of nuance and trying to just tease out all the information first.

Dr. Mariam Hanna:

Fair. Fair. Okay. How often has this happened in your practice? For example, how often do you think a failure to biologics has occurred?

Dr. Jason Lee:

In real-life practice? It happens all the time. Okay. And I do always remind patients too, and I'm glad I showed them the raw data first, because if you do what's called an intention to treat analysis, where you take the whole study and anyone who dropped out is considered a failure, this is what an intention to treat analysis is. What you see is an asthma exacerbation rate, roughly about a 50% reduction across all biologic medications. So what we expect is patients to decrease their asthma exacerbations by 50%. Now, people are talking about this concept of asthma. Are you able to have a normal functioning life, which has always been the goal of any asthma treatment, or should you be able to do everything everyone else can, but can we get there with a medication add-on such as a biologic? So that's a long way of answering the question you asked. But yeah, I would say in my practice, at least what we see in clinical trials is roughly about 30 to 20% of patients will not really improve in a significant way.

Dr. Mariam Hanna:

That's an important number to keep in mind actually, as more and more physicians use biologics in their practice. Okay, can we get there? Can we modify their disease? Can we get them off biologics? Can we change their course?

Dr. Jason Lee:

It's a very interesting question you ask. So the very first biologic that we all used, called Xolair, had an interesting study with the NIH in the US looking at whether we start early enough in children in pediatrics, can we change their course of their atopic conditions so that they don't develop

Dr. Mariam Hanna:

Outcomes? Yes, I want to know this. I think about this, yes.

Dr. Jason Lee:

Yeah. And now Dupilumab is also conducting a very similar study in the same group, and as we know as immunologists, part of our allergy and immunology specialty, the immune system is much more malleable, and the polarization of the immune system. There are some studies suggesting that even at age one or infancy, you can predict

outcomes to a certain degree. But I believe that if you do start early enough, you may be able to move away to a more balanced T1 and T2 inflammatory type as opposed to a T2 skew. Now, of course, things like infections, viruses—we know COVID is one of these that can skew toward more type two. These things can change things, but I believe that, yeah, in patients we can accomplish disease modification. And for some of the biologics, we do have already discontinuation data showing that at least in a subset of patients, typically younger, but in a subset of patients, we can actually change the trajectory of that patient so that they have a more balanced immune response to certain medical conditions that they may have had.

Dr. Mariam Hanna:

We're like putting ourselves out of the job, but I don't mind. That's exciting. Alright, one last one. At what point do you take them off biologics or consider a drug holiday for them, expensive medications?

Dr. Jason Lee:
There is some data suggesting that spacing out the interval for certain medications is actually okay and accomplishes the same level of degree of control. These medications do have fairly long half-lives, and on average, as a rule of thumb, it's about 20 days or so. So we can try spacing the medication out, and patients also ask me this question all the time: how long am I going to be on this medication for? And as an optimist who really believes that things keep continuing to improve—and they have, they've exponentially improved—I say that there's going to be something better that comes up. I guarantee you, within the next five years or within my lifetime, there may be a permanent solution to a lot of medical conditions, including this. So, I don't think it's going to be forever. If a patient has accomplished excellent control and they're doing extremely well with their asthma for a good solid two years, I will consider discontinuation.

Okay. The other condition where this occurs is if I've also used the opportunity of better asthma control to control an asthmatic where I think their asthma is really driven by allergies, and I have disease-modified that with allergen immunotherapy on top. Once things have been controlled and the lung function is okay, we can safely initiate allergen immunotherapy that may have reduced the triggers that lead them to an exacerbation, and it certainly may have reduced their risk of infections. And infections are a big driver of asthma exacerbation. So I guess there's a third one too, if a patient has had great lifestyle modification as well. So I'm thinking about the patients who are sedentary, maybe eating too many Cinnabuns like myself or donuts, and if they have really started to exercise, improve their lung dynamics and function by exercising and changing their

lifestyle, then yeah, that's also another situation where I have successfully discontinued a lot of therapies. I'll give you an example. I mean, this patient has given me their permission to share, but I had a patient lose over 140 pounds while on biologic medication for asthma. His lung function improved actually by 60%, 60%. And he is very thankful that this kind of let him take control of his asthma, let him exercise, and improve his quality of life like this.

Dr. Mariam Hanna:

Wow. What a very nice story to end on.

Dr. Jason Lee:

He was very motivated. But yeah, I think I want to enable people to have the opportunity to become motivated and to change their life.

Dr. Mariam Hanna:

I like all these empowering words to end off our episode. Alright, time to wrap it up and ask today's allergist, Dr. Jason Lee, for his top three key messages to impart to patients and physicians on today's topic, severe asthma. Dr. Lee, over to you.

Dr. Jason Lee:

Number one, we're learning so much. We're in an information growth, an exponential part of informational growth. We're learning so much more and understanding in 2024, there's a very good chance that if you've had bad asthma, we can now control it with one of the newer therapeutics in our toolkit, number one. Number two is to never lose hope even if you are one of the patients who do not respond to the things that have been already tried. Because again, there are clinical trials ongoing for every different permutation of phenotype of asthma that may not be triggered or covered by the previous existing biologics. And number three, the science is always, always, always changing, especially now more rapidly than ever, which goes back to number one, please see a doctor and give your physicians and specialists a chance because they may have picked up a new toolkit that may change your life or at least result in better asthma control and it may have future repercussions for sure.

Dr. Mariam Hanna:

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

Dr. Jason Lee:

Thank you, Mariam, for having me.

Dr. Mariam Hanna:

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