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# Tryptase Testing: Clinical Utility and Application During COVID-19 Vaccination Reactions

Announcer:
Welcome to CME on ReachMD. This activity titled Tryptase Testing: Clinical Utility and Application During COVID-19 Vaccination Reactions features Dr. Cem Akin, Clinical Professor of Allergy and Immunology at the University of Michigan in Ann Arbor and is brought to you by the Academy for Continued Healthcare Learning and supported by an educational grant from Phadia US Inc. a part of Thermo Fisher Scientific.

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Dr. Caudle:
370 million. That's the number of COVID-19 vaccine doses that have been administered in the U.S. by the end of August. But many people remain reluctant to receive the vaccine due to a variety of reasons, and one reason may be a small risk of anaphylaxis. I'm your host, Dr. Jennifer Caudle, and joining me to share his insights on serum tryptase testing in clinical practice, and its importance in assessing anaphylaxis in response to COVID-19 vaccination, is Dr. Cem Akin. Dr. Akin, welcome to the program.

Dr. Akin:
Thanks, Dr. Caudle. Pleasure to be here.

Dr. Caudle:
Well, we're excited that you're here. This is a very important topic, so let's dive right in, Dr. Akin. What's the primary role of serum tryptase testing in clinical practice?

Dr. Akin:
Tryptase is a biomarker of mast cell burden and activation. It is a protein that is fairly specific to mast cell lineage. There are actually two varieties of tryptase that contribute to measurable serum or plasma tryptase levels. So those are called alpha and beta tryptases. Alpha tryptase is a proenzyme with no known biologic activity, and secreted outside of the mast cell as it is produced. You can think of it perhaps as an enzyme that is not useful to the cell, so the cell gets rid of it as soon as it's produced. So, alpha tryptase levels are a good surrogate marker of mast cell burden, and are increased in a disease called mastocytosis, which is a rare, clonal overproduction of mast cells. So, a normal tryptase level, median normal tryptase level is around four to five nanograms per milliliter in serum or plasma, and a tryptase level at baseline are usually found elevated, at greater than 20 nanograms per milliliter, in mastocytosis. Baseline tryptase levels can also be increased in a common condition called hereditary alpha tryptasemia. In this condition, there are multiple copies of the gene that codes for alpha tryptase, and the serum tryptase level correlates with the copy number of the gene. This condition is fairly common, and seen in about 6% of general population, and is associated with a baseline tryptase level of greater than eight nanograms per milliliter. And it is not a disease by itself, but it can increase the severity of an allergic disorder if the patient has another reason to have that allergic reaction – for example, a patient with a venom allergy, bee or wasp sting anaphylaxis – and if they have hereditary alpha tryptasemia on top of that, those patients may experience more severe allergic reactions.

Now, beta tryptase is the mature form of the tryptase, and it is enzymatically active and it is the form that is stored in mast cell granules.

And it is released into the, tissues and makes its way to the circulation after an allergic reaction. So, when we measure the tryptase after an anaphylactic reaction, we not only have the basal alpha tryptase, but now also have the contribution from the beta tryptase, released after the mast cell activation, and that is why it is a useful marker of mast cell activation and anaphylaxis. Tryptase levels are particularly increased in severe hypotensive, anaphylactic reactions and correlate with the extent of the severity and the hypotension.

Dr. Caudle:
Excellent, and thank you for that information. Now, who should receive a serum tryptase test?

Dr. Akin:
So patients with suspected mastocytosis or patients with suspected anaphylaxis are the two major patient groups that should receive serum tryptase testing. Mastocytosis usually presents with skin lesions called urticaria pigmentosa, or maculopapular hyperpigmented skin lesions, so a good skin examination is important in diagnosing these patients. But because tryptase level is also included as a minor diagnostic criterion, and usually found greater than 20 nanograms per milliliter, serum tryptase level is important in assessing these patients. These patients usually present with flushing and recurrent mast cell activation symptoms, including tachycardia, sometimes anaphylactic reaction, syncopal reactions, and abdominal cramping that are episodic. So, if, you see a patient with this constellation of symptoms, and they don't have any other good explanation for these symptoms, then consider a baseline serum tryptase level, and if it's elevated, a referral to an allergy/immunology specialist is warranted.

The second group of patients who should be tested for tryptase are patients presenting with suspected anaphylaxis or mast cell activation symptomatology. So those patients are usually seen in the outpatient setting, when they are not having any symptoms, and a baseline tryptase level should be determined in those patients. And they should be sent home with a prescription for a tryptase level, if they are to experience any anaphylactic-type symptomatology again, in the future. And that tryptase level should be drawn within four hours of the onset of the reaction, so that it could be compared to the baseline tryptase, and an assessment could be made whether there is an increase that would confirm the mast cell activation nature of the event.

Dr. Caudle:
Great. And, you know, in the case of anaphylaxis, let's take a look at the current recommendations for serum tryptase testing. How should test results then be interpreted?

Dr. Akin:
When mast cell activation occurs tryptase is released immediately, within the first minute, into the tissue, and it takes about 30 minutes to 90 minutes to reach its peak in serum. So if you check a tryptase level immediately after a reaction, you might find an increase, but it will not be at its peak. So if you check another level, let's say within about an hour after the reaction occurs, that's when you expect to see the peak level. And then, after that peak level, they start to decline, with a half-life of about two hours. So if we check the tryptase level, let's say 24 hour after the episode, they return back to baseline. So this window is important to assess the tryptase level. We usually recommend within four hours after the reaction to confirm that the tryptase level is indeed increased, because if you go beyond that window, you have the risk of having the baseline tryptase, and the tryptase testing being of no use in assessing anaphylactic symptomatology.

So interpretation of the test results relies on a formula that was calculated by a group of experts that convened in early 2010, from the U.S. and Europe. And those experts analyzed the data from bee sting reactions as well as anaphylactic reactions from mastocytosis patients, and came up with the formula to consider a minimal increase in the tryptase level after a reaction. And that formula was 20% of the baseline plus two nanograms per milliliter. For example, if applied to patients with a baseline tryptase of five, 20% of five nanograms per milliliter is one, plus two nanograms per milliliter. So if the post-event tryptase is greater than eight, than that would be considered as a proof of a mast cell activation and anaphylactic reaction.

It's also important to note that tryptase levels, after these mast cell activation events, do not distinguish between IgE- or non-IgE-mediated reactions. And they can be elevated in both of these conditions, and it is important to know this, because some of the reactions to COVID vaccines may not be IgE-mediated, and may be mediated through a mechanism called complement activation-related pseudoallergy, or CARPA, that depends on formation of IgG antigen immune complexes, and the downstream activation of the complement cascade. And in those reactions, the serum tryptase levels also increase, because the mast cell is the final effector cell that causes the anaphylactic symptomatology.

There are not too many factors that can interfere with the tryptase testing. For example, we sometimes get asked the question, would antihistamines interfere? The answer is no. Perhaps a high dose of glucocorticoids, steroid medications, if they are used for more than a few days can reduce the serum tryptase levels slightly. But most other medications and other factors won't have any influence, as it is a very stable enzyme.

Dr. Caudle:
Great. And based on your experience, how could clinicians improve their implementation of tryptase testing, and incorporate multi-disciplinary perspectives?

Dr. Akin:
So, in terms of the, primary care, setting, consider tryptase testing if the patient presents with signs and symptoms of mastocytosis, and those are maculopapular skin lesions that are hyperpigmented, episodes of unexplained flushing and lightheadedness and tachycardia, that might progress all the way to syncopal or pre-syncopal episodes. And, so those patients, if they don't have any other reason to explain those episodes, a baseline tryptase level is recommended.

Also, consider tryptase testing in people with syncopal or possible allergic reactions, but we don't know if they are truly allergic, or due to other causes, so, we usually order a baseline tryptase and again, send the patient home with a prescription for a repeat tryptase level pretty soon, within four hours after allergic reactions. So, those are some of the clinical scenarios that you might consider tryptase testing. And in the emergency departments, we have a unique situation where the patient is seen shortly after an allergic reaction, and the emergency physicians have a particularly good window of opportunity to obtain an event-related, or post-event related tryptase level. And those patients should always be referred to an allergist and immunologist, to see if there is an underlying cause of a, allergic reaction. And in those patients, where the acute level is obtained, then a baseline level should be obtained, at least 24 hours, after the onset of the episode.

Dr. Caudle:
For those of you who are just joining us, this is ReachMD. I'm your host, Dr. Jennifer Caudle, and joining me to talk about serum tryptase testing in clinical practice, and its importance in assessing anaphylaxis in response to the COVID-19 vaccine, is Dr. Cem Akin. Based on the information you've given us on serum tryptase testing, Dr. Akin, let's take a look at anaphylactic reactions to the COVID-19 vaccine.

Since the initial emergency use authorization of COVID-19 vaccines last December, what have we learned about the risk of anaphylaxis following the vaccination?

Dr. Akin:
So, in the clinical trial stage Pfizer-BioNTech vaccine encountered one case of anaphylaxis, and one hypersensitivity reaction, and with the Moderna clinical trials, there were no anaphylactic or severe hypersensitivity reactions, with a close, temporal relation to the vaccine. When we look at the real-world data after the emergency use authorization most estimates range from 2.5 to 11 per one million doses. And a meta-analysis found an incidence of 7.9 per million doses. So when we compare it to something like influenza vaccination, that number is 1.3 per million doses, so there is definitely an increase in anaphylaxis. Now in other recent prospective cohorts, from the Harvard, Mass. General, and Brigham and Women's Hospital System, showed a much-increased rate 2.47 per 10,000, or 247 per million doses administered. That's clearly much more increased than the previous number of 7.9, and we don't know what the reason for that is. I can only hypothesize, perhaps the method of defining anaphylaxis or the prospective nature of the study, or perhaps even the study population who are employees of this large health care system, with more likelihood of being exposed to COVID during their work might have an increased likelihood of having allergic reaction to the COVID vaccine itself.

Now, the potential causes, for this allergic reaction are polyethylene glycol which is found in messenger RNA vaccines or polysorbate-80, that is found in Janssen vaccine, or the messenger RNA particles itself, which can stimulate mast cells directly through toll-like receptors.

That is less likely because these messenger RNA particles are enclosed in these lipid nanoparticles, so they are not directly, visible to the mast cell. Nevertheless, we really don't know what the true nature of these allergic reactions are. We know that just having the COVID vaccine itself does not elevate the tryptase level. There are some studies done on a limited number of patients with mast cell disease, before and after vaccination, and the tryptase levels do not rise just because of receiving the vaccine. They do rise, however, if there is a anaphylactic or an allergic reaction, and that can be either due to an IgE- or an IgG-related mechanism, or a complement activation related mechanism, and in both of those circumstances, the tryptase levels are found elevated.

Dr. Caudle:
And you know, with that information in mind, how should clinicians distinguish between an allergic reaction or a vasovagal reaction from a true anaphylactic reaction to COVID-19 vaccination?

Dr. Akin:
Yeah, so that's a very good question. If we consider the vasovagal and allergic reactions, there are certain symptoms that will be similar, like hypotension or the gastrointestinal symptoms – nausea, vomiting – or the fainting sensation, or even the fainting itself – loss of

consciousness. But then there are some other symptoms, like the pulse rate or the skin findings, that will be different. Pulse is usually slow in vasovagal reactions, as opposed to an allergic or anaphylactic reaction where we see tachycardia. And skin is also a very important system to examine because in vasovagal reactions, we see patients to be diaphoretic with pale, skin, as opposed to in allergy or anaphylaxis, we see flushing and hives. So that could be very helpful in differentiating the vasovagal from allergic reactions. And of course, the tryptase level is a useful surrogate marker there. If you draw the tryptase level within four hours after the suspected reaction, you will get an increase with the anaphylactic reaction, and it will be the same no increase, with the vasovagal reaction.

And as allergists, we are also familiar with the anaphylaxis criteria, which, we can apply to the patient, so most of us diagnose anaphylaxis based on clinical grounds, and don't really, go through these criteria very strictly. But, for those of us who are not familiar, there are three different circumstances that might lead to a diagnosis of anaphylaxis. The first scenario is acute onset of an illness, within minutes to several hours, with involvement of skin, like hives or flushing, and either respiratory compromise or decreased blood pressure. So this could be a scenario, for example, in a patient who presents with a allergic reaction to the first dose of COVID vaccine.

The second scenario is, two or more of the organ system involvement after exposure to a likely allergen. So this could be a scenario, for example, if the patient had a possible allergic reaction to a first dose of a COVID vaccine or one type of a messenger RNA vaccine, and had a possible reaction to the second dose, now, with this likelihood of getting that first reaction. And in this case, we bring into the organ system involvement, the gastrointestinal tract, and we also count the gastrointestinal symptoms like nausea, vomiting, abdominal cramping in addition to skin, pulmonary, or cardiovascular symptoms. And then the final scenario is that if the patient is known to be allergic to a certain allergen like, the COVID vaccine in this case and then receives the same COVID vaccine again, and there's just hypotensive reaction without any of the other organ system involvement, that's also a confirmatory diagnostic criterion.

Dr. Caudle:
Great, that was very helpful. And based on your experience and guidelines, can you share some recommendations for patients with an anaphylactic reaction to the COVID-19 vaccine?

Dr. Akin:
Sure. I think here we can look at CDC guidance and World Allergy Organization guidance which are pretty similar. So the CDC recommends laboratory testing to be collected shortly after a severe allergic reaction following COVID-19 vaccination. And the tests that are recommended are tryptase, and what we call soluble membrane attack complex of the complement system, or soluble complement 5b-9, that is activated in the complement, activation-related state of allergy, or CARCA. So these tests are recommended by CDC, to be collected between 30-90 minutes after a reaction, if possible, and up to six hours, is the timeframe that they provide. And then these patients should also be checked for a second tryptase test, 24 hours or more after the reaction, to help with the assessment of the severity and to plug these numbers into the formula of 20% plus two. And the World Allergy Organization recommendations – again, the blood sampling with tryptase level is considered critical for accurate diagnosis of vaccine-associated anaphylaxis. And the sample should be taken within half to two hours after a reaction, and again, similar to the CDC guidelines, at least 24 hours after complete resolution of symptoms.

So, those are the clinical criteria that I also use in my practice, and I think as physicians, we have the unique responsibility to assess these patients as we evaluate them, after the reaction and take advantage of that window of opportunity to check this laboratory testing, so that they can be compared to the patient's baseline tryptase.

The World Allergy Organization also came up with a different clinical consideration on which patients can receive vaccination, and which patients should not receive vaccination, and in which patient there should be some special precautions. First, if the patient has a prior history of allergic reactions, so an, identified food or venom, or a defined group of medications, like non-steroidal anti-inflammatories, well those patients can proceed with COVID vaccination. If they have, inhalant allergies or family history of allergies, or they had a local, non-systemic reaction to the prior vaccinations, or if they're on allergen immunotherapy because of allergic rhinitis or asthma, those patients are not necessarily at high risk of having an allergic reaction as compared to general population, and most of us would like to observe those patient about 30 minutes after the vaccination, just to be on the safe side, but those histories are not contraindications for COVID-19 vaccination. If the patient has a history of immediate reactions or anaphylaxis to multiple different drug classes, then we start thinking about, could that be, a preservative or excipient allergy, like polyethylene glycol, which is also found in COVID vaccines. Or if they have a history of anaphylaxis to a vaccine, or a parental, monoclonal antibody preparation, or a history of idiopathic anaphylaxis, or a mass cell disease – so those patients, we still proceed with a COVID-19 vaccination, but with special precautions. In patients with multiple drug allergies, we recommend an allergy/immunology referral and assessment of the risk for excipient allergy to polyethylene glycol, although the recent data that emerged, really does not show a very useful, result of having allergy skin testing or IgE levels to polyethylene glycol, but there are certainly those patients who can be allergic to that excipient.

We definitely want to observe these patients for at least 30 minutes after vaccination, and most of us would feel comfortable prescribing

an antihistamine such as a second-generation nonsedating antihistamine, about one hour prior to receiving, these vaccines, although the utility of that approach has not been validated. We had a recent paper, came out in an allergy journal looking at patients with mast cell disease, and we did not find any anaphylactic reactions in those patients who received COVID vaccination, but of course, the patient numbers are limited when you are dealing with a rare disease like mastocytosis. There is a larger, NIAID trial that's evaluating people with these special, high-risk conditions, as well as patients with hereditary alpha- tryptasemia, and the data has not been analyzed and fully published yet.

Finally, vaccination is considered contraindicated if the patient had a prior allergic reaction to the vaccine in question or for an mRNA-based COVID-19 vaccine, if the patient had prior allergic reaction to another mRNA vaccine, or a prior reaction to a component of the vaccine, including polyethylene glycol. Now these patients definitely deserve a referral to an allergy/immunology specialist, and need to go through an evaluation, for these, excipient allergies. There is some data that some patients with allergic reaction to the first vaccine can safely receive the second vaccine, and the allergist/immunologist may be able to give the vaccine after skin-testing, and in so-called graded challenging doses instead of giving it in one single shot. So there are ways also to risk-assess these patients and to get help from an allergy/immunology specialist.

Dr. Caudle:
Great. And before we close, Dr. Akin, are there any key take home messages you'd like to share with our audience?

Dr. Akin:
I would like to again emphasize the fact that serum tryptase is the gold standard laboratory test in diagnosis of anaphylaxis, and serial sampling, meaning the acute sample within the first four hours, as well as a baseline sample after 24 hours after the reaction, is recommended. The formula to validate an allergic reaction is 20% of the baseline plus two nanograms per milliliter is the minimal increase. And both World Allergy Organization and CDC recommendations include serum tryptase is a critical testing for allergic reactions to COVID-19 vaccine.

Dr. Caudle:
Excellent. And with those key considerations in mind, I'd like to thank my guest, Dr. Cem Akin, for helping us better understand the role of tryptase testing in the setting of COVID-19 vaccine-associated anaphylaxis. Dr. Akin, it was great speaking with you today.

Dr. Akin:
It was a pleasure to be here. Thanks for having me.

Announcer:
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