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. Have you ever tried to teach someone something that seems like an instinct? Like pulling your hand away from something hot.

It's an instinct. It's really hard to teach. I'm often asked in clinic how a parent will be able to identify when a child is having a serious allergic reaction.

The question becomes so much more intense when the question is about an infant. It's actually a reason why some parents may delay food introductions. Some may even delay treatments given the child doesn't communicate.

There's all kinds of stats to share about the rates of anaphylaxis and signs and symptoms of allergic reactions in infants, but I often find myself explaining nonverbal communication in the clinic. Parents learn this instinctively when caring for their infant. Babies communicate long before they develop formal language.

I'm not talking about the well-meaning relatives that feel that every cry that your infant makes is a sign of hunger. What I'm talking about is that baby that cries and the parent associates it with, oh, it's actually time for this, or time for that, or, oh, don't worry about that sound. They're just navigating, or they're just playing, or nothing to be too concerned about.

I'll admit, this kind of stuff doesn't make much sense the first few weeks of life, but over time, every caregiver seems to catch on, kind of like an instinct. Then there's the inconsolable cry, an infant that just isn't acting right. We talk a lot about this when we discuss infant anaphylaxis.

It's a discussion that's increasingly common in all our clinics, for one reason or another, and it's my pleasure to really highlight this topic today with a very special guest. Allow me to introduce to you today's special guest. Dr. Anagnostou is a professor of Pediatrics in Allergy and Immunology Division at Texas Children's Hospital and Baylor College of Medicine, where she serves as Director of Allergy and Food Therapeutics and leads the Adolescent Transition Program for Allergy. She's an internationally recognized researcher and principal investigator of multiple trials in food allergy therapy, anaphylaxis, prevention, the microbiome, and shared decision-making. She chairs the American College Food Allergy Committee and serves on multiple quad-AI committees as well. Dr. Anagnostou also earned her PhD from Cambridge University with the landmark peanut oral immunotherapy research that was published in The Lancet, and whether I blame that or other reasons for how much we discuss infant anaphylaxis these days, it's my absolute pleasure to welcome Dr. Anagnostou . Thanks so much for taking the time today, and welcome to the podcast.

Dr. Katherine Anagnostou:
Thank you so much, Mariam. It's a pleasure to be here.

Dr. Mariam Hanna:
All right, so we're going to get right into it. What has really changed in our understanding of anaphylaxis, particularly when we talk about infants and toddlers in the last few years?

Dr. Katherine Anagnostou:
I think most of the conversations in this space has focused mostly on moving away from our standard usual criteria designed for diagnosing anaphylaxis and creating, or at least discussing, about different criteria for nonverbal patients, which is mostly applicable for this population you've just mentioned.

Dr. Mariam Hanna:
Okay, and before we discuss kind of what the criteria are specifically, is the incidence patterns of anaphylaxis, particularly in the younger age group, is that changing? Like, are we causing lots more infant anaphylaxis now as we introduce allergens early and start certain treatments earlier and earlier?

Dr. Katherine Anagnostou:
So that's a great question. There are some limited data suggesting a rising prevalence of anaphylaxis, especially food-induced anaphylaxis, for younger children, but this has not been linked to early food introduction. In fact, all the data that are coming from specific studies looking at early food introduction have reported that this is very safe and that anaphylaxis is rarely occurring as an outcome in this space.

So the increase that has been noted, especially for ED visits, could be because we have started seeing an increase in the allergy, the food allergy prevalence, or it could also be better coding and tracking of cases and just improved recognition overall. I think there are a lot of limitations in terms of how we collect that data. So when we're looking at it and trying to put it into the context of real life, I think we have to consider all of these things.

Dr. Mariam Hanna:
So multifactorial, but yes, the incidence is increasing. So let's talk about clinical presentation because part of increased awareness, we need to understand what it looks like and how this kind of differs in our non-verbal, as we said, or our preschoolers and infant populations.

Dr. Katherine Anagnostou:
So anaphylaxis can present differently in this population and it can also be quite confusing and difficult to diagnose, mainly because a lot of the symptoms and signs that we are looking at can also be symptoms and signs of other diseases in this age group. So, for example, thinking about urticaria, viral urticaria is also very common in this population. Thinking about vomiting, gastroesophageal reflux is also pretty common in this population.

So we can look at different body systems and find all of these sort of differences and difficulties in diagnosing anaphylaxis. I think it's important to remember that there will be certain behavioral

changes in this young population that we don't see in the older children. So, for example, they can become irritable or cranky.

They can go the other way and be more withdrawn or clingy. And all of these can be signs of anaphylaxis and they're actually part of the new suggested modified criteria for infant and toddler anaphylaxis. We also need to think of some surrogates for symptoms.

So, for example, oral itching is a very common symptom that older children can verbalize. And in this very young population, it can present differently. They feel the itching and the tingling of the oral mucosa, but they may not be able to talk about it.

So, what they would do is they will sort of thrust their tongue out of their mouth. They will start pulling on their tongue or even scratching it. They may start licking their lips.

So, these are very subtle signs that are different for how anaphylaxis presents in older populations. But they need to sort of give us an idea of what is going on with this young child that may not be normal.

Dr. Mariam Hanna:
And on the subtlety note, do you think parents will miss it? So, I have a lot that come into the office and they're worried that they'll miss when their child is having anaphylaxis or misinterpret that infant or toddler.

Dr. Katherine Anagnostou:
I guess it depends a lot on the family. Generally, the parents know their children pretty well. So, even when behavioral changes happen, a lot of the families, a lot of the caregivers are able to say, you know, this is not very common for how he or she behaves, right, in these circumstances.

So, they might get an inkling. But on the other hand, it can also be quite difficult, right? Because someone, for example, who suffers from gastroesophageal reflux and then has an episode of vomiting, you know, it can be quite difficult to differentiate.

I would say that there are a few things that can help with recognition from the caregiver's perspective. One of the most important ones is the context of the history. So, if, for example, you have just introduced a new food into the diet and within the next couple of hours, which is our usual window for IG-mediated allergic reactions related to food, you start seeing certain things, then your suspicion level should be higher.

So, history, as much important as it is within hospital, it's also important in the community, right? And I generally like to educate my families on that.

Dr. Mariam Hanna:

History trumps all. It's such a common theme in so many different conditions that we talk about on this podcast. Okay, I want to talk a little bit about stats.

How common or how reliable are these GI-dominant symptoms, the vomiting? And again, you kind of nicely mentioned we see reflux as a common comorbidity in this age group, or behavioral changes saying that the baby was fussy. How common are they to be the only criteria that we see, or how reliable are they when they're the only criteria that the patients come in with?

Dr. Katherine Anagnostou:
I generally don't think they are very reliable as standalone symptoms, and this is mostly because they're very non-specific. However, what I said before, I think still applies. You have to take everything within the context of what is happening with the child, and if there are new food introductions, or if there is suspicion that there is some sort of food trigger associated with what you're seeing in front of you, then you have to take that into account.

Generally, anaphylaxis doesn't present with a single symptom. It can, but it's not a common presentation. And a very reliable sign, I would say, is urticaria in combination with whatever else is going on.

So 90% of infants will actually develop urticaria as part of their allergic reactions, last severe anaphylaxis episode, right? So this can be a good sort of sign to combine with everything else that is going on. And again, it can be a confusing area.

We mentioned already viral urticaria, but I think with viral urticaria, you have other signs that are different. You may have, for example, fever, which does not form a part of usual anaphylaxis presentation. And that's another thing that I often educate my patients on, and the families specifically, when they say, well, if there's an infection going on, how will I know it?

Dr. Mariam Hanna:
Absolutely. And let's talk about the modified diagnostic criteria that's used in nonverbal children or in infants. How do those criteria differ, and what do they include?

Dr. Katherine Anagnostou:
A very big part of these are behavioral and mental status changes, including irritability and clingy behavior. Some infants can present with lethargy. They can look subdued, or they can be less active.

So all of these behavioral changes are incorporated as surrogate for subjective symptoms in the new and updated criteria for infants and toddlers. Also, what I mentioned before about oral pruritus and how this can be presenting differently in this age group and with different behavioral changes as well in association. Tachycardia is another one that has been highlighted as sort of an early marker of cardiovascular involvement, and that I think is really important to remember because blood pressure changes are not likely to occur, especially not in the early stages.

You have to be very, very sick and have a very severe anaphylaxis episode for your blood pressure to drop, especially in this age group. It's also very difficult to monitor. And then other signs of decreased perfusion that have been included to help with cardiovascular involvement, a sort of pallor and mottling that can present in this age group, cyanosis in very severe cases.

The other system that I think is of interest and has also been included in the updated criteria is a specific respiratory sig n. So you can observe a lot of cough and a lot of drooling. Drooling is more specific for infants and toddlers.

Tachypnea, of course, an increased work of breathing can present in both young kids and older children. You can also observe horse cry in this young population, which is different from what you would normally see in children of older ages. The GI symptoms, I think we already mentioned that vomiting is obviously part of anaphylaxis.

But things like gagging, spitting up and back arching can also be some signs that signify abdominal sort of discomfort and GI involvement as part of the anaphylactic reaction.

Dr. Mariam Hanna:
That's great. A lot of different cues and some concerning big red flags. And then, Dr. Anagnostou, as you nicely said, rash and particularly urticaria is one of the most common symptoms that we see. Now, oftentimes in our patients that have IgE-mediated food allergy, we often see some overlying or underlying eczema to these patients. And the parents are often left confused as to how to differentiate or recognize when one rash is particularly of concern versus another rash. How do you guide them through that?

Dr. Katherine Anagnostou:
I try to educate them in this way. Okay, so I generally say that with anaphylaxis, you have acute onset of symptoms. So situations like eczema are usually more slow in presenting and they're not going to develop within a couple of hours.

I talk to them about the multi-system involvement that we see in anaphylaxis so that they remember that this is a little different from say an eczema flare or say an isolated feeding intolerance or reflux episode. And I always, always talk to them about timing relative to food allergen exposure.

Dr. Mariam Hanna:
Perfect. Great tips. Those are fantastic.

Okay, now sometimes for the emergency department, we talk about obtaining a serum tryptase. Is a serum tryptase helpful in this age group if they're presenting with anaphylaxis?

Dr. Katherine Anagnostou:

I think serum tryptase has a role to play for all age groups, actually. The only problem is it has to be, the sample has to be drawn within 24 hours of the actual event. And a lot of times what happens is by the time the kids will end up in the ED, time has passed already, some time has passed already, and then they may wait a bit longer to be seen.

And people don't think about tryptase as the first thing to do if someone presents with anaphylaxis. So they usually leave it too late and then it's not usable, right, as a diagnostic marker. Again, it's not specific for anaphylaxis, so it cannot really replace a clinical judgment and the fact that, as we all know, anaphylaxis is a clinical diagnosis.

But I think it can be helpful if you can actually get it within the proper timing.

Dr. Mariam Hanna:
Okay, within the proper timing. And within the proper timing, what about administration of epinephrine for infants? Are we supposed to administer it earlier?

Is it later? Is it not needed? Let's talk about that.

Dr. Katherine Anagnostou:
So that's a great question because I have been asked all these three things separately from different people, so I like how you combine them into one question. So the way that I address this question, in whichever form it comes, is that I believe that in anaphylaxis, epinephrine should be administered as soon as people suspect that a severe reaction occurs. I don't even call it anaphylaxis a lot of times because I don't want to start thinking, is this reaction in front of me taking the boxes for anaphylaxis, right?

I think if they're worried that there is a severe reaction occurring, I just want them to use epinephrine and I want them to use it promptly regardless of the age of the person in front of them. So this is how I start. Now, I, of course, understand why people have this sort of question with regards to younger age.

So there are some arguments that you would want to give it as soon as possible for infants and toddlers if there is a delay in diagnosis. And we've already talked about some confusion around diagnosing anaphylaxis in this age group. So of course, if you suspect that there's a delay in the diagnosis, then you may want to lower the threshold.

I don't do it, but I do know people who potentially do something like this. And the other aspect of this is that as we have seen with early food introduction, we haven't really seen severe anaphylaxis in this population. And again, I have come across allergists in different countries who often don't even prescribe epinephrine for very young children that have only had a history of mild reactions.

So you can see there are different practices across the world, right? Even amongst allergies, right? Everybody here in the U.S. gets prescribed epinephrine as soon as they have a diagnosis

of food allergy, but that is not necessarily the case in other parts of the world. And in those parts of the world, there is some sort of risk stratification that occurs, and it doesn't sound like the infant toddler population is considered high risk. If anything, they are considered more low risk. I guess this is the best way I can answer a question that doesn't really have a universal answer.

Dr. Mariam Hanna:
And absolutely, I was just trying to highlight that the answer is not universal, but certain countries practice in different ways. Okay, talking about North America for a moment, with the lowest epinephrine autoinjector that we have here being a 0.15 milligram dose in little babies under 10 kilograms, what's the evidence on the safety of that epinephrine autoinjector in those infants?

Dr. Katherine Anagnostou:
The evidence says that this dose is generally safe for infants and toddlers, and especially young infants, because those generally fall below the 15 kilogram cutoff where we would want to give them the 0.15 anyway. Overall, a risk assessment that was performed by panels of experts showed that there was actually little risk posed to a kid who weighed over 15 kilos getting the 0.15 dose. Now, if the 0.1 milligram dose is available, that's great. It can be given, and we do actually prescribe it for those who can have it for all those infants that weigh between 7.5 to 15 kilos.

Dr. Mariam Hanna:
And that's wonderful. And is there ever a time where you're going to give them a needle and syringe to draw up for that infant?

Dr. Katherine Anagnostou:
That depends quite a bit on the setting. In the community setting, I think we all agree that using autoinjectors is preferable, especially because you don't really want to ask the parents to be responsible for drawing up the dose and giving it, and practically can also create difficulties. Autoinjectors are generally easier in the community setting.

In the hospital setting, I know that a lot of allergy clinics actually still use needle and syringe when there is anaphylaxis occurring. Not ours, but I do know of other places. And I think it's absolutely fine to use it within the hospital setting.

Dr. Mariam Hanna:
Absolutely. One of the other discussions that's had sometimes is the needle length discussion. I'm not sure if you've heard of this, but needle length, and it's a fixed needle length for the 0.15 strength, and the risk of striking bone, particularly in our smaller infants.

Dr. Katherine Anagnostou:
Yes, this has been a conversation. And quite a few years ago, there was a lot of conversation actually around the optimal length of the needle and also the laceration risk that may potentially

occur from the use of the epinephrine in this young age group. I think the risk is, there is a theoretical risk for sure.

I think it's a very low risk in practice. Personally, I have never seen it in my own population. And I think mitigation strategies will help avoid this risk and hopefully make it close to zero.

So when training families, it is our job to emphasize how to apply optimal pressure with whatever device they are using, and also how to position the child with their legs secured so that they can prevent these jerking movements that infants and toddlers love, which can increase the risk of laceration. I think if you train the family appropriately and you educate them, then that risk minimizes.

Dr. Mariam Hanna:
Absolutely. It's spending time on training. We spend time on training for all age groups with auto-injectors, but this is a special population to really emphasize that or highlight that.

Now, along with our changing advice, let's talk about using epinephrine and going to the emergency department afterwards, because this is an area where guidance and recommendations have shifted somewhat, particularly in the child that is showing rapid improvement after a single dose of using epinephrine with no significant prior concerning history. Can we apply these same kinds of rules to infants, or do all infants require the emergency for assessment?

Dr. Katherine Anagnostou:
I think we can apply the same rules to infants and toddlers. And you're right, our guidelines have shifted significantly since the updated parameter for anaphylaxis came out here in the United States. I think it became clear what we all knew for many years, that not everybody who suffers from anaphylaxis and responds nicely to the first dose of epinephrine actually needs the emergency department.

I don't think I would use different thresholds for the infant or toddler population, provided that the same caveats that we have for the older children still apply. I think it's okay to do the same. And the newer anaphylaxis action plans that have been created specifically for this very young population, and full disclosure, I was part of one of those, actually incorporate the same rules for the infants and toddlers that they do in terms of seeking emergency care.

Dr. Mariam Hanna:
So we discussed already giving the first dose, and potentially earlier recognition or early administration for some with epinephrine, but when to give a second dose? How do we advise caregivers around that?

Dr. Katherine Anagnostou:

Yes. So most guidelines recommend that the second dose is given within five to 10 minutes from the first dose, if there's no improvement or if there is worsening of symptoms. I have to say that 10 minutes can be a very, very long time.

In that scenario, if you're standing next to your child, who is not improving after the first dose. So I very much doubt that anybody waits longer than five minutes before administering the second dose. I usually say five minutes to my patients.

I no longer say five to 10 minutes. I say within five minutes, if you find that the symptoms are getting worse, so they're not responding, because generally with epinephrine, you will see a response pretty fast.

Dr. Mariam Hanna:
Yeah. In recess environments, five minutes feels like an incredibly long time. So that's a very practical way of advising parents.

And there's a lot of excitement around the world of epinephrine nowadays as we talk about different doses initially, but more than anything, different delivery devices in a decade, in a century of just nothing else as an alternative that's available. Can we talk about what changes you want to highlight that are coming probably in the infant population around epinephrine?

Dr. Katherine Anagnostou:
Yes. I think we're all excited about having novel routes of administration for epinephrine in all of our children, right? Any age and including the very young infants and toddlers. So in the United States, we already have intranasal epinephrine available.

And there are multiple other sort of devices that are being looked at and forms of epinephrine. I think the next one that is likely to come out if all goes well is the sublingual epinephrine. So there's a lot of excitement, especially because we are able to offer our patients choices in terms of the level of comfort that they have with using a specific form or device.

Dr. Mariam Hanna:
Fabulous. All right. Time to wrap up and ask today's allergist, Dr. Anagnostou, for her top three key messages to impart to patients and physicians on today's topic, infant anaphylaxis. Dr. Anagnostou, over to you.

Dr. Katherine Anagnostou:
I would say my first takeaway would be to administer epinephrine to anyone, regardless of age, if they show signs of a severe allergic reactions or anaphylaxis. The second key takeaway would be that not everybody who has experienced anaphylaxis needs to go to the ED. And I think I would like all providers to become more comfortable with the option of anaphylaxis being treated by their caregiver at home, provided all the caveats and safety rules that we discussed are present.

And third, I would say that using the modified criteria for recognizing anaphylaxis in infants and toddlers and also using the specific anaphylaxis action plans for this population that have mostly integrated these modified criteria will make your life as a physician much easier when you discuss this with patients and families, but will also make their lives a lot easier too, because in addition to your conversations in the clinic, they have something in writing that they can refer to and can help them recognize severe reactions when they occur.

Dr. Mariam Hanna:
Fabulous. Thank you, Dr. Agnostou, for joining us on today's episode of The Allergist.

Dr. Katherine Anagnostou:
Thank you for having me.

Dr. Mariam Hanna:
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