



Dr. Stukus: Hello and welcome to "Conversations from the World of Allergy," a podcast produced by the American Academy of Allergy, Asthma & Immunology. I'm your host, Dave Stukus. I'm a board certified allergist and immunologist and serve as the social media medical editor for the Academy. Our podcast series will use different formats to interview thought leaders from the world of allergy and immunology. This podcast is not intended to provide any individual medical advice to our listeners. We do hope that our conversations provide evidence-based information. Any questions pertaining to one's own health should always be discussed with their personal physician. The Find An Allergist search engine <http://allergist.aaaai.org/find/> on the Academy website is a useful tool to locate a listing of board certified allergists in your area. Finally, use of this audio program is subject to the American Academy of Allergy, Asthma & Immunology Terms Of Use agreement which you can find at www.aaaai.org.

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Dr. Shaker: Oh Dr. Stukus, it's a pleasure to be with you today.

Dr. Stukus: So for full disclosure I'm also a member of the Joint Task Force and I've known Marcus for years and I've secretly wanted to have him on the podcast for many reasons but mostly because of his wonderful radio voice that you're all going to have the pleasure of listening to for the next 45 minutes to an hour or so. It's a thrill to have you. We're going to spend a lot of time talking about the recently updated Anaphylaxis Practice Parameters. But before we get into that, I think it would be helpful for you to discuss just overall the Joint Task Force on Practice Parameters to help our listeners better understand who this group is comprised of and what they do.

Dr. Shaker: Thanks David. It's great to be with you. My twin brother always told me I had a face made for radio so I appreciate that.

Dr. Shaker: So it's a great question and it's an interesting story. So the Joint Task Force on Practice Parameters was formed in 1989 to develop practice parameters for the diagnosis and management of allergic and immunologic diseases. The members bring an enormous breadth of knowledge and experience in the field and really a critical eye for review and analysis of the published edits. Through three generations of members the JCF has embraced the evolution of evidence-based medicine. Now members of the JCF represent the two premier allergy organizations in the United States, which are the American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma and Immunology. The JCF coordinates work of world experts in the development of parameters to provide guidance that maximize safe, effective and high value medical care. The practice guidelines produced by the JCF are an important vehicle for translating best evidence to patient care.

Dr. Stukus: So these practice parameters that get put out and there's a variety of topics and they're all available on the Joint Task Force website which is great because they're open access for anybody to read which is the whole point of it all, but are these parameters designed as the end all to be followed to the letter and if not, what's really the best way for clinicians to use the information that's provided in these documents?

Dr. Shaker: Well that's a great question. As your listeners know, the practice of medicine is always evolving and there are many aspects of patient care for which evidence may be more or less certain. Because of this parameters provide guidance with varying degrees of certainty, when appropriate, the JCF's practice parameters provide flexibility for clinicians and patients to weigh the evidence in the context of their values and preferences. Recommendations can also vary somewhat in different regions due to social and cultural differences and feasibility factors in various healthcare systems. Now the JCF produces two types of parameters, traditional and GRADE parameters. Traditional parameters provide a 30,000 foot view of a wide swath of topics and recommendations for certain conditions. These parameters still include clarification on how confident the reader can be in the evidence and contextual considerations for recommendations. Now GRADE documents are more targeted parameters that tackle specific questions the JCF is asked to answer by our parent organizations. More importantly GRADE guidelines make recommendations based on a more rigorous review and analysis of the evidence and a much broader range of considerations that affect many stakeholders besides just the published evidence.

Dr. Stukus: That's great. So it sounds like really this is an accumulation of the evidence to date surrounding a particular topic along with recommendations for clinical practice, but there are no guideline police, if people don't stick to the letter of what these documents say, there's no repercussions, but as you mentioned very astutely it's really to help provide really guidance and that's the whole point behind guidelines. And then you mentioned the GRADE methodology and that's what we're going to discuss today with the 2020 practice parameter on anaphylaxis. Can you give us a little bit of a deeper dive and I know that's a whole other conversation, but let's orient our listeners to what is GRADE and how can it be used?

Dr. Shaker: Yes. I'd like to talk a bit more about that, thanks for asking the question. You know, through the years a myriad of well meaning guideline development groups have added complexity to published recommendations and recommendations and guidelines through the use of non uniform codes, letters,

numbers, Roman numerals, mixed letters and number combinations to try to describe certainty of evidence and strength of recommendations. For example, when reviewing recommendations for oral anticoagulation, one group noted a confusing array of descriptions from various groups, these ranged from a class Roman numeral I based on level D evidence from the American Heart Association, a grade C recommendation based on Roman numeral level IV evidence by sign two and a 1C positive sign based on a recommendation from the American College of Test Physicians. Some of these go in various and conflicting orders and as a result many guidelines present a confusing alphabet soup that's hard for readers, patients, clinicians and stakeholders to really understand. To introduce clarity into these guideline systems, back in 2000 the Grade Working Group was established to create a rating system in which certainty or quality of evidence could be transparently and independently described together with strength of recommendations. Now GRADE stands for Grading of Recommendations, Assessment, Development and Evaluation and this framework has emerged as a leading approach in guideline development. It's important to note it is the most rigorous and transparent approach to guideline development because it specifically evaluates evidence certainty and separates those from making the recommendation and describing the strength of the recommendation. It is well suited to tackle specific questions as it is informed by systematic reviews, meta analyses and well characterizes your quality of evidence. Now in making and applying medical recommendations, guideline groups, practitioners and patients, you have to balance varying degrees of evidence certainty and make judgments about desirable and undesirable effects of treatment. The available evidence must also be considered in the context of individual values, preferences and resource constraints. What GRADE guidelines allow is the ability to explicitly and transparently consider and incorporate both evidence certainty as well as issues of equity, feasibility, acceptability and even cost effectiveness. Now for example in considering length of observation for anaphylaxis, severity of presentation in multiple epinephrine doses are major considerations, but the clinician would also want to consider patient access to medical care their preferences and values around risk.

Dr. Stukus: That's a great introduction and I will actually just opine here and recommend that anybody who's interested-- because when you look at the 2020 Anaphylaxis Practice Parameter Update, it's going to read very differently than the traditional practice parameters based upon exactly what you mentioned. So I would encourage listeners to either have the document pulled up while they listen to the podcast or even look at it very soon after you listen to our conversation because you'll clearly see how it's sort of laid out and how this GRADE approach can be utilized in this manner. So I appreciate the background. So let's go back to this document, why was an update for anaphylaxis necessary at this time?

Dr. Shaker: Well as you know and as your listeners are familiar, anaphylaxis is an acute life threatening systemic allergic reaction with a wide range of clinical manifestations. The lifetime prevalence of anaphylaxis has been estimated at between 1.6 and 5.1 percent. This is actually the first GRADE anaphylaxis parameter ever produced by the JCF. Prior to this parameter, the most recent JCF traditional anaphylaxis parameter was published in 2015 by Dr. Phil Lieberman and colleagues.

Dr. Stukus: Yeah, so it sounds like time for-- as the evidence evolves and then to apply this new methodology, that's great. I would direct all the listeners to the parameters themselves because there's an excellent introduction and background section that really give great information for anyone seeking to

learn more just about anaphylaxis in general. And as we talked about now, this is a unique way of approaching it and unlike the non-GRADE practice parameters, the 2020 Anaphylaxis Update really only addresses five specific questions pertaining to two topic areas. We're going to address each of these in detail through today's conversation. But before we get into that, can you just give us some insight as to how those questions were chosen and why was it decided to focus on these specific areas?

Dr. Shaker: Oh sure thing. So questions are selected in coordination with the American Academy and the American College of Allergy, Asthma and Immunology. These questions were selected because there was a critical need to inform practice in two major domains. The first, to identify risk factors for biphasic anaphylaxis and this is important to inform management preparedness and education. And the second is to understand if giving patients glucocorticoids and/or antihistamines prevents anaphylaxis. Now because anaphylaxis has a variety of causes and occurs in a variety of contexts, topic area two needed to be evaluated by the role of supplementary therapies to prevent biphasic anaphylaxis, anaphylaxis due to chemotherapy, recurrent anaphylaxis from radiocontrast media and anaphylaxis from immunotherapy and other agents.

Dr. Stukus: Okay, so really specific targeted areas. And we're about to get into that. But let's go back to, you gave us a great broad overview of anaphylaxis and you mentioned that there's different causes, but can you give our listeners just a better sense of how would anaphylaxis present clinically and some of the more common causes as well as routes of exposure that would cause that?

Dr. Shaker: Sure. Yeah, as we mentioned anaphylaxis I mean the bottom line is it's a potentially life threatening allergic reaction. It's important to recognize risk factors can include cardiovascular disease, asthma and older age, medication and stinging insects are the leading triggers in adults while foods and stinging insects are the most frequent triggers in children and adolescents. For example, food allergy impacts 8 to 11 percent of children and adults in the U.S. So how do we recognize anaphylaxis, how is it defined? Well anaphylaxis is highly likely when a patient fulfills one of three different criteria. The first is the sudden onset within minutes to hours of an illness with involvement of the skin or mucosal tissue or both with either sudden respiratory or cardiovascular symptoms or signs. The second would be sudden onset of allergic symptoms and two or more organ systems after exposure to a likely allergen or other trigger. For example involvement of skin or mucosa, respiratory, cardiovascular or GI organ systems with at least two of those organ systems impacted. And then the third criteria would be reduced blood pressure after exposure to a known allergen for that patient.

Dr. Stukus: And to put this in context for our listeners, I've heard you say a couple of times it's sudden onset, so this is a very sort of acute event. And then as far as the systems that you mentioned, what are the typical symptoms that may occur say from cutaneous or skin or mucosal surfaces or GI or things like that?

Dr. Shaker: So your patient may present with sudden hives or swelling of the lip, they might have wheezing or coughing, stridor, abdominal cramping, uterine cramping may occur and these symptoms and signs can present fairly abruptly and evolve very rapidly and as such recognition is really critical and early and appropriate treatment cannot be overstated.

Dr. Stukus: And anaphylaxis you mentioned is a clinical diagnosis based upon the symptoms and the context and things like that. What is the first line treatment of anaphylaxis regardless of the cause and have we identified any barriers that have been shown to interfere with people consistently receiving that treatment?

Dr. Shaker: So the first line treatment of anaphylaxis is epinephrine and there are no absolute contraindications to epinephrine in the treatment of anaphylaxis. Importantly delayed epinephrine increases the risks for fatal anaphylaxis and unfortunately, studies continue to suggest a disparity between diagnosis of anaphylaxis and appropriate epinephrine treatment. For example, in one study of drug-induced anaphylaxis only eight percent of patients received epinephrine. Now barriers to epinephrine continue to be failure to recognize anaphylaxis and understanding of the need for rapid epinephrine as the means of treating it. While many clinicians try to use antihistamines or glucocorticoids as a means of avoiding or deferring epinephrine, these medications are not effective as first line treatments, they don't work fast enough and they don't affect the necessary organ systems to prevent life threatening progression of symptoms. As the listeners are aware, epinephrine is a non-selective adrenergic agonist and works rapidly to increase peripheral vascular resistance through vasoconstriction, it increases cardiac output and it reverses bronchoconstriction and mucosal edema. Now it also stabilizes mast cells and basophils. Unlike epinephrine, antihistamines will not effectively treat cardiovascular and respiratory symptoms such as hypotension or bronchospasm when used acutely and monotherapy. And although glucocorticoids are frequently used as an adjunctive therapy for anaphylaxis, they should also not be administered in place of epinephrine in the treatment of acute anaphylaxis.

Dr. Stukus: Can you give us a sense of the difference in time to onset of action for say epinephrine versus like an antihistamine or glucocorticoid?

Dr. Shaker: Epinephrine works within minutes, antihistamines work within maybe 30 minutes to an hour and glucocorticoids are not going to have their effect for about four to six hours and by that time a patient's symptoms may have really progressed to a dangerous point.

Dr. Stukus: And I hear from a lot of patients, and this is something I counsel about and I know you do as well, but why do we have to give epinephrine through a needle and why do we have to give it through an intramuscular injection, what's the purpose behind that?

Dr. Shaker: Well when it comes to anaphylaxis seconds matter and the appropriate delivery of epinephrine is through the needle and into the muscle and that's where absorption's going to be the greatest. And really when I give patients epinephrine in clinic who are experiencing anaphylaxis, I continue to be impressed at how quickly their symptoms improve and how frequently they can tell me that they are suddenly feeling this relief of this sense of this really impending doom that anaphylaxis often carries with it.

Dr. Stukus: Yeah, I'm really glad you mentioned that Marcus, I had the same conversation actually just this week of it's remarkable how fast it works and how much better people with receiving it, so I'm glad that we had this conversation leading into the discussion because we need to overcome these barriers,

there's a lot of mental barriers, there's a lot of inertia for decades' worth of avoiding use for whatever reason, but it works fast, it treats all the symptoms as you mentioned, it can prevent additional symptoms from occurring and we want to recommend it as much as we possibly can.

Dr. Shaker: Your patient will thank you for the epinephrine. But it's also important to make sure that when you're giving the epinephrine especially to young children, that you're restraining them such that they don't receive an injury from the needle especially with young children, they may move suddenly and some injury can result from that. So provided the patient's properly restrained and the epinephrine if it's an auto injector is held in place for two to three seconds, those are important safety considerations.

Dr. Stukus: Yeah, absolutely, thank you. We could probably spend the next 40 minutes just saying over and over again epinephrine is the first line treatment of anaphylaxis, epinephrine is the first line...

Dr. Shaker: That's right.

Dr. Stukus: Well I'd like to skip ahead just a little bit because there's a part of the parameters that I find intriguing and these are the good practice statements that appear immediately after the summary recommendations. What are these four statements, what do they state and why are they included if not part of the formal GRADE analysis?

Dr. Shaker: Right, so a good practice statement may be used by guideline groups when there's high certainty that a recommendation will do more good than harm, but little direct evidence. So a common example cited where a good practice statement is appropriate relates to parachutes and skydivers, right? So a situation in which a good practice statement can confidently be endorsed in the absence of randomized trials or observed studies demonstrating benefit. So if you're going to jump out of a plane, you should have a parachute. Good practice statements are valuable, but they're intentionally not graded and the anaphylaxis parameter endorse several good practice statements in regards to anaphylaxis management. So the first is to administer epinephrine as first line pharmacotherapy for uniphasic and/or biphasic anaphylaxis, a point that we've made. The second is do not delay administration of epinephrine for anaphylaxis as doing so may be associated with higher morbidity and mortality. Good practice statement number three highlights that after diagnosing and treating anaphylaxis all patients should be kept under clinical observation in a setting capable of managing anaphylaxis until symptoms have fully resolved. And good practice statement number four highlights post anaphylaxis management and that all patients with anaphylaxis should receive education on anaphylaxis including avoidance of identified triggers, presenting signs and symptoms, biphasic anaphylaxis, treatment with epinephrine and the use of epinephrine autoinjectors as well as referral to a board certified allergist. Of note, there may be some circumstances where self injectable epinephrine is deferred such as resolved anaphylaxis after a known drug trigger and a high likelihood of successful avoidance, but shared decision making definitely needs to play a role in those circumstances.

Dr. Stukus: So basically it's common sense recommendations that it's unethical to perform a randomized control trial, we're not going to have half of people present with anaphylaxis and not give them the first line treatment or we're not going to educate half of the people who have anaphylaxis.

Dr. Shaker: Yeah, you know Dave, there's actually a very funny publication out there where they actually launched a trial on parachutes for people jumping out of planes and you can actually find it on PubMed and it's been published and there was nobody they were able to enroll.

Dr. Stukus: And, you know, Marcus, what is the hardest part about skydiving?

Dr. Shaker: I don't know, Dave, what is the hardest part about skydiving?

Dr. Stukus: The ground.

Dr. Shaker: Yeah, well said, well said.

Dr. Stukus: All right, let's get back to the topic at hand. Okay, so back to the parameters, topic one as you mentioned before, but we're going to rephrase so we can orient our listeners as we go through this, this is a great conversation, very dense. Topic one focuses on the identification and mitigation of risk factors for biphasic anaphylaxis. What is biphasic anaphylaxis?

Dr. Shaker: So biphasic anaphylaxis is recurrent anaphylaxis occurring 1 to 72 hours after resolution of the initial anaphylactic episode and it might actually be closer to 1 to 48, but the definition that's commonly used is 1 to 72 hours. Now estimates of biphasic anaphylaxis vary from less than 1 percent to 20 percent of patients and it's probably closer to the 1 percent figure. However the ability of antihistamines and glucocorticoids to affect this outcome is unclear. Now despite a lack of clear evidence supporting the role of antihistamines and glucocorticoids in anaphylaxis, these agents continue to be routinely used in anaphylaxis management.

Dr. Stukus: Okay. And so biphasic anaphylaxis is one trigger whether it's say a yellow jacket sting or ingestion of peanut, one trigger, anaphylaxis, all that resolves but then symptoms can come back again from that same acute trigger, is that correct?

Dr. Shaker: Without re-exposure to another trigger, exactly.

Dr. Stukus: All right, excellent. Now question one under this topic asks what risk factors should clinicians take into consideration in determining the likelihood of biphasic anaphylaxis? Can you explain what recommendation was made for that question?

Dr. Shaker: Sure. So the guideline suggests that a clinician incorporate severity of anaphylaxis presentation and/or the administration of more than one dose of epinephrine for the treatment of initial anaphylaxis as a guide to determining a patient's risk for developing biphasic anaphylaxis and the need for extended observation. Now this was a conditional recommendation with very low certainty of evidence and this means that a patient whose reaction is not very severe who gets treated early on with epinephrine and shows good clearing of the reaction is at very low risk for biphasic anaphylaxis and therefore does not need the resources and cost of an extended hospital observation or admission.

Dr. Stukus: And I think that's a point that's lost on a lot of folks, I think people stick to this mantra of if you give epi, you have to be observed for six hours or whatever it may be, so that's an important question to address. And you mentioned something really important and I want to go back and use this first recommendation as an example to discuss the ratings as well as the certainty of evidence that are included with each summary recommendation and how they should be interpreted. So can you repeat that again for question one and explain just what that means?

Dr. Shaker: Yeah, so question one has a conditional recommendation and a very low certainty of evidence and this relates to one of the really great features of GRADE is that the analysis is distilled into easy to understand recommendations, it's not an alphabet soup. In GRADE there are only two choices, a recommendation for or a recommendation against, then the recommendation is qualified as either strong or weak. Another term for weak is conditional, which is a navigational signal for shared decision making meaning a conversation is especially needed to tailor management to individual patients and circumstances. Now while strong recommendations may be adopted as policy in most situations, conditional recommendations should not and certainty of evidence definitely impacts the strength of recommendation. So evidence can be downgraded for risk and bias, imprecision, inconsistency and directness and even publication bias, evidence certainty can also be upgraded for a large magnitude of effect, a dose response gradient or situations in which all plausible confounding and bias would actually reduce the demonstrated effect. Through this process evidence certainty is clearly and simply described as very low, low, moderate or high.

Dr. Stukus: So essentially it's a description of the quality of and the body of the literature and evidence supporting that recommendation, it doesn't mean don't do it because it's weak or anything like that, it's just a matter of, "Hey, this is what's been published to date and this is how the recommendation came to pass." Is that a very basic understanding of that?

Dr. Shaker: That's very basic. And the other thing that we've noticed throughout medical specialties and guidelines is that when the literature base is subjected to really the critical eye of GRADE, we find that the certainty of evidence is not as high as we thought it was, it's very common in life, you don't know what you don't know and it's always important not to be over confident.

Dr. Stukus: If you continue to quote "Hamilton" this is going to be the best interview ever, but thank you.

Dr. Shaker: Well, you know, it's kind of that part of "Star Wars" right where Luke Skywalker actually gets one of the bad guys and he looks up at Han Solo and he says, "Hey Han, hey Han, I got one," and Han Solo looks back and says, "That's great kid, that's great. Don't get cocky."

Dr. Stukus: <laughs>

Dr. Shaker: So humility from what we know especially in patient care is always important.

Dr. Stukus: Fantastic. Okay, so topic one very important and essentially boils down to from what I'm hearing from you and I encourage everybody to go through the document thoroughly as well as people

who come in with more severe anaphylaxis or who require more intervention to help resolve anaphylaxis are at greater risk for biphasic, those who have either mild symptoms or who completely resolve with epinephrine may not require the same level of therapy or observation I should say. So let's dive into the second topic because this is where we get into some more specific questions pertaining to certain areas. The second topic in these parameters is the evaluation of the use of supplemental glucocorticoids and/or antihistamine premedication for prevention of anaphylaxis. It seems like this is an acknowledgement of how often these medications are used in place of epinephrine as you've already touched upon and discussed. What was really the impetus for evaluating the evidence surrounding this topic?

Dr. Shaker: Well through the years, practices have evolved to premedicate with antihistamine and glucocorticoids to prevent anaphylaxis. The thinking is then what could it hurt? However, there are downsides to use of these agents. Glucocorticoids and first generation antihistamine may have adverse effects particularly in certain vulnerable populations, which include sedation and confusion especially in the elderly. Side effects of these therapies may confound [ph?] recognition and assessment and treatment of anaphylaxis. In addition, medical complexity of these treatments can create obstacles to efficient healthcare delivery. So the question is do they work, because if they don't work, why are we using them?

Dr. Stukus: Yeah, that's a lot of years of doing the same thing over and over again just because it's been taught that way. So this would be very interesting to get into some of this evidence. But before we get into the specific questions, we do have some non medically trained listeners to our show especially a lot of patients out there or parents who have children who are at risk for anaphylaxis. Can you just describe what is meant by the term glucocorticoids as well as antihistamines and some of the common examples?

Dr. Shaker: Sure, sure thing. So glucocorticoids are anti-inflammatory medications commonly called steroids, these medications have no proven role in the treatment of an acute reaction as they work slowly and at the cellular level to inhibit gene expression of new signals that promote inflammation. Now histamine is an important mediator released during anaphylaxis, but unlike epinephrine antihistamines will not effectively treat cardiovascular or respiratory symptoms such as hypotension or bronchospasm when acutely used as monotherapy. While they may improve hives and provide comfort they cannot reliably treat anaphylaxis.

Dr. Stukus: Okay, great. And then we already talked about the onset of action for glucocorticoids. So essentially steroids we're talking like prednisone and dexamethasone, is that correct?

Dr. Shaker: Yes.

Dr. Stukus: Okay. And then for antihistamines, the trade names would be things like Benadryl or Zyrtec along those lines, is that correct?

Dr. Shaker: That's right Dave.

Dr. Stukus: Okay. All right, great. So let's go to question two. Question number two in the parameters asks, should antihistamines and/or glucocorticoids be used to prevent biphasic anaphylaxis? What's the summary recommendation for that question?

Dr. Shaker: So for this question the guidelines suggest against glucocorticoids or antihistamines as an intervention to prevent biphasic anaphylaxis. Again, this was a conditional recommendation with very low certainty of evidence.

Dr. Stukus: So essentially these agents have been used for decades for anybody with anaphylaxis but the evidence does not support that they'd actually prevent the biphasic anaphylaxis which you mentioned is really close to about one percent of the time, is that correct?

Dr. Shaker: Which sort of makes sense, right, if you have a patient who came in with anaphylaxis and you treated them and their symptoms had completely resolved and they already have a pretty low chance of having a biphasic reaction, putting them on three days of steroids and diphenhydramine every six hours for a few days to zonk them out isn't going to really likely give you a lot of benefit over the next few days, probably the best you can do is patient education about what to expect and make sure they have epinephrine in their pocket.

Dr. Stukus: Yeah, I'm sure that's going to be very different information from what a lot of folks listening have either been taught or have been practicing or have been told, so another important reason to update all of the evidence and practice parameters. Now question three asks should antihistamine and or glucocorticoid premedication be used to prevent index hypersensitivity infusion reactions to chemotherapy? Why is this question important and what are some common examples of how this is utilized?

Dr. Shaker: So various chemotherapy protocols incorporate the use of supplemental therapies because some chemotherapies like taxanes are associated with higher rates of anaphylaxis. And while prolongation of infusion time appears to have decreased the rate of hypersensitivity reactions, the addition of premedication with antihistamines and glucocorticoids has also become common practice in some circumstances.

Dr. Stukus: And what's the recommendation for that question?

Dr. Shaker: The guidelines suggest in favor of administering glucocorticoids and/or antihistamines to prevent anaphylaxis or infusion related reactions when indicated for specific agents in chemotherapy protocols.

Dr. Stukus: Okay. Question number four asks should antihistamine and/or glucocorticoid premedication be used to prevent recurrent hypersensitivity reactions to radiocontrast media? Can you tell us, what does this pertain to, a lot of people may not be familiar with radiocontrast media, what's the common situation where this may occur?

Dr. Shaker: Yeah, so premedication is also used in patients with prior reactions to radiocontrast media. However, it has been suggested that the most important change in decreasing a hypersensitivity reaction to contrast is the use of an alternative low osmolar non-ionic agent. Evidence supporting the use of premedication in the setting of a low osmolar non-ionic contrast agent for high risk patients is pretty poorly described and there is concern that the routine use of glucocorticoid premedication in many settings can actually cause more morbidity and complexity and delay needed procedures for many patients.

Dr. Stukus: So we're talking basically like CT scans with contrasts, that sort of thing?

Dr. Shaker: Exactly, some of which are emergent to prevent some dangerous conditions.

Dr. Stukus: Well what's the recommendation for that question?

Dr. Shaker: So the guidelines suggest against routinely administering glucocorticoids and/or antihistamines to prevent anaphylaxis in patients with prior radiocontrast hypersensitivity reactions when they are receiving re-administration of a low or iso-osmolar non-ionic radiocontrast media agent. This is again a conditional recommendation with very low certainty of evidence and, you know, the 2020 Anaphylaxis GRADE Parameter did not identify significant benefit for premedication prior to contrast administration to prevent recurrent reactions. Moreover, there is potential harm in terms of untoward effects such as hyperglycemia in diabetic patients, cost and length of stay due to potential pretreatment regimens. For this reason the risk of undesirable effects of the intervention of premedication may actually exceed the likelihood of desirable effects when we kind of think about it in a balance. In fact estimates suggest that the number needed to prevent a fatal reaction in a high risk patient, the number needed to premedicate to prevent a fatal reaction in a high risk patient would be 50,000 at a cost of 131 million dollars per death prevented. Now while the 2020 Anaphylaxis GRADE Guideline was consistent with the prior suggestion that most individuals who have had a prior hypersensitivity reaction can be effectively managed by selecting an alternative low osmolar contrast agent without premedication, I should acknowledge some controversy exists around this recommendation in the management of such patients. For example, the American College of Radiology Manual on Contrast Media suggests that while a premedication strategy may be considered in patients with prior contrast hypersensitivity if it does not adversely delay care or treatment decisions, it is not a substitute for anaphylaxis preparedness and breakthrough reactions can occur. Now utilizing a low osmolar contrast agent has been associated with a greater effect size than premedication alone, so switching to an alternative agent is probably a better bet. Now I should acknowledge that there's a diversity of clinical circumstances around contrast prophylaxis, the guideline highlighted that clinicians may consider contrast premedication in clinical circumstances associated with a high level of perceived risk of anaphylaxis or comorbidities associated with greater anaphylaxis fatality risks such as underlying cardiovascular disease, use of beta blockers, asthma, prior severe anaphylaxis, provided it's not delaying care although clear evidence to support this practice is really absent. So only low osmolar non-ionic radiocontrast agents were evaluated and the recommendation did not apply an analysis to patients receiving high osmolar contrast agents for whom prophylaxis may be appropriate in some settings.

Dr. Stukus: Okay, that's a very thorough sort of explanation behind a lot of things to unpack there. So to kind of summarize from what I'm hearing from you, it should not be a kneejerk response to treat every patient with premedication who requires radiocontrast media even if they've had prior reactions to the radiocontrast media and to focus instead on the lower osmolar reagents. And then also I love that you pointed out the important factor a lot of people don't consider is there's risk in using antihistamine and/or glucocorticoids in a lot of these patients who require these procedures, so really a thoughtful approach to this is really recommended and supported by the guidelines, that's great.

Dr. Shaker: And the other thing to realize is that in the analysis patients receiving prophylaxis were those who had a history of both mild and severe contrast reactions and the analysis was unable to stratify prophylaxis by patients who had the more severe index reaction which is why there's really a role for a conditional recommendation and some contextual discussion with patients around this recommendation.

Dr. Stukus: Okay, great. And now I'm going to put you on the spot here, so bear with me. Why did the GRADE document not evaluate use of premedication in patients who have a history of shellfish allergy.

Dr. Shaker: Oh, so you're asking whether or not patients with a history of shellfish allergy need to receive any particular precautions when they're receiving radiocontrast media. And I'm glad you brought that up because that is really a persistent myth that shellfish cross reacts with iodine and contrast media and what we know is that's not the case. Patients who have a shellfish allergy have no increased risk for a reaction to contrast, that's just a common myth within allergy practice that's always important to discuss because there's a lot of unnecessary care that patients who have a shellfish allergy can receive if they are undergoing premedication for contrast because there's no need for it.

Dr. Stukus: Thank you for clarifying that. Yeah, that's something that comes up all the time, so I just thought we should address that. Okay, as we wind down here, let's discuss the last question. Question five asks should antihistamine and/or glucocorticoid premedication be used to prevent hypersensitivity reactions to allergen immunotherapy or other agents? What clinical situations does this question really address, what are we talking about here?

Dr. Shaker: So allergists at times treat patients using a rapid or rush protocol for allergen immunotherapy, a treatment intended to retrain the immune system so it does not react severely to allergens. Such treatment is associated with a higher risk of anaphylaxis. Similarly, there are other situations in which medications are used that carry a higher rate of anaphylaxis such as the use of infliximab for patients with inflammatory bowel disease.

Dr. Stukus: Okay. And what's the recommendation for this question?

Dr. Shaker: For this question, the guideline suggests in favor of the administration of glucocorticoids and/or antihistamines as an intervention to prevent anaphylaxis in patients undergoing aeroallergen rush immunotherapy, again a conditional recommendation with a very low certainty of evidence.

Dr. Stukus: Okay. And again, I encourage all of our listeners to really go through the details within the document. Dr. Shaker, this has been an absolutely outstanding discussion and review of these very important practice parameters. And my takeaway as I listen to this conversation and listen to your explanation of things, having already read the document of course as well is the details matter when treating or preventing anaphylaxis and blanket use of commonly used approaches really isn't supported by evidence, which it's going to be a bit of a paradigm shift for a lot of hospitals and physicians and medical providers across the board. But what's your takeaway, how would you summarize the parameters?

Dr. Shaker: So very low certainty evidence exists regarding supplemental therapies to inform anaphylaxis management. While epinephrine remains the cornerstone of anaphylaxis treatment in any setting, the role of antihistamines and/or glucocorticoids has not been previously subjected to a rigorous methodological evaluation and a GRADE analysis. The 2020 Anaphylaxis GRADE Guideline suggests that while glucocorticoids and antihistamines should not be relied upon to prevent biphasic anaphylaxis there are some circumstances in which these agents may provide significant benefit in anaphylaxis prevention, specifically in some chemotherapy protocols and in rush allergen immunotherapy.

Dr. Stukus: Okay. And lastly, there's a lot to take in as we talked about, this does contradict some common practice and things like that, so if you could assist our readers, or I'm sorry, listeners, or actually readers and listeners I should say given the written document with any pearls of wisdom as to how to interpret the recommendation of these parameters and really ultimately incorporate them into clinical practice, what advice would you give?

Dr. Shaker: Well quite frequently, GRADE lays bare knowledge gaps that exist and sets a course for future investigations to better inform our routine practice. It allows the opportunity to critically evaluate assumptions that we need to reevaluate. Understanding the significance of a conditional recommendation is critical to translating evidence to guidelines to practice. GRADE teaches us that not all evidence is reliable, that quality beats quantity in evidence and that many recommendations will still be contestable. Still, with careful analysis the perfect is not the enemy of the good and conditional recommendations provide important guidance to clinicians and patients on how to navigate the implications of the evidence and expert consensus.

Dr. Stukus: Okay. Well, Dr. Shaker thank you so much for taking the time to be with us today to walk through this important document, I think this was extremely helpful. Before we say goodbye is there anything else you'd like to add?

Dr. Shaker: Well I've really enjoyed our conversation, thanks for the opportunity to chat a bit about it. I often reflect on the quadruple aim of healthcare, which aspires to achieve value-based care by improving the patient experience, improving population health, reducing cost of care and improving the provider experience. And, you know, I think these guidelines help us do that. In addition even in anaphylaxis, there is a significant role for shared decision making where the clinician provides expert guidance on medical science and the patient provides expertise in their own personal context. And we each need to treat the

patient in front of us and only together can we provide the right care at the right time every time. Again, thanks for the chance to be with you and be well and stay safe in these interesting times.

Dr. Stukus: Thanks. Well said, great summary. Thank you again, we really appreciate you taking the time to be with us Dr. Shaker. We hope you enjoyed listening to today's episode. Information about credit claiming for this and other episodes can be found at <https://education.aaaai.org/podcasts/podcasts>. Credit claiming will be available for one year from the episode's original release date. Please visit www.aaaai.org for show notes and any pertinent links from today's conversation. If you like the show, please take a moment to subscribe to our podcast through iTunes, Spotify or Google Play so you can receive new episodes in the future. Thank you all for listening.

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