Rostrum

The Revenge of Unintended Consequences of Anaphylaxis-Risk Overdiagnosis: How Far We Have Come and How Far We Have to Go

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Overdiagnosis of anaphylaxis risk is an underappreciated aspect of anaphylaxis prevention. Whereas the benefits of anaphylaxis-risk prevention are well known, potential harms resulting from preemptive approaches to mitigate anaphylaxis-risk are not insignificant. Still, great progress has been made in recent years to avoid the unintended consequences of anaphylaxis-risk overdiagnosis. Reflection on recent advances in the use of diagnostic testing, as well as the application of diagnostic labels, provides an important perspective to understand how far the specialty of allergy and immunology has come in improving the lives of patients and families. Examples of recent paradigm shifts in anaphylaxis-risk management include approaches to peanut allergy prevention without screening, deferral of corticosteroids to prevent biphasic anaphylaxis reactions, reevaluation of reflex use of emergency medical services for resolved community anaphylaxis, and an approach to penicillin allergy delabeling with direct oral challenge. Routine medical practices to decrease anaphylaxis risk can have lifelong impacts for patients—beyond just preventing anaphylaxis. As our understanding of these trade-offs evolves, it becomes necessary to weigh both the benefits and the harms of past management approaches. Because medicine remains a science of uncertainty and an art of probability, a critical approach to risk mitigation remains necessary to find the often-elusive balance in anaphylaxis prevention. © 2021 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2021;■:■-■)

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INTRODUCTION

Medicine is a science of uncertainty and an art of probability
—William Osler (1849-1919)

Anaphylaxis is defined as a serious allergic reaction that is usually rapid in onset and might cause death.[1-3] The lifetime prevalence of anaphylaxis in the United States has been estimated to be between 0.05% and 5.1% with the largest number of incident cases among children and adolescents.[4-6] Most episodes of anaphylaxis are immunoglobulin E (IgE)—mediated and the most common triggers are foods, medications, and stinging insects.[6,7]

Although a morbidity is associated with anaphylaxis, including the risk of a reaction at school or at preschool,[8] fatality due to anaphylaxis is exceptionally rare. The case-fatality rate of anaphylaxis has decreased over time in the United States and is estimated at 0.09 per million (95% confidence interval [95% CI] 0.07-0.11).[9] For individuals with food allergy, the incidence of fatal anaphylaxis is 1.81 per million person-years.[10] For people with known venom or food allergy, fatal anaphylaxis constitutes less than 1% of total mortality risk.[11] The annual incidence of

Abbreviations used
COVID-19- Coronavirus disease 2019
DPT- Drug provocation testing
ED- Emergency department
EMS- Emergency medical services
IgE- Immunoglobulin E
LEAP- Learning Early About Peanut

fatal anaphylaxis in an unselected population is lower than death due to fire, murder, or lightning.[11] Limitations of the literature regarding anaphylaxis fatality include high heterogeneity of studies, variation between studies in methods of data capture and anaphylaxis case definitions, and potential differences based on age, ethnicity, and cause of allergic anaphylaxis.[9-11]

Anaphylaxis treatment policies are geared toward a hypervigilance on the prevention of the highly unlikely outcome of anaphylaxis fatality. Well-intentioned practice precautions or interventions motivated by perception of anaphylaxis risk can have unintended consequences. Not infrequently, allergy labels are applied preemptively in an effort to prevent a risk owing to concern of anaphylaxis.

Overdiagnosis, often synonymous with overlabeling, represents the phenomenon of turning a healthy individual into a patient with a disease on the basis of a clinical test or examination finding when they are not likely to suffer any of the consequences of the condition associated with the label.[12,13] Although most commonly implicated in cancer screening, the phenomenon of overdiagnosis may also be common in anaphylaxis management. Examples in which overdiagnosis may occur for allergic diseases include risk-stratified food introduction in infants, screening skin testing of infants with atopic dermatitis, drug allergy labels of children with maculopapular amoxicillin rashes, screening testing in urticaria, and most recently coronavirus disease 2019 (COVID-19) vaccine deferral in patients with a history of food allergy in the United Kingdom (a practice which has been subsequently abandoned).[14-23] In each of these examples, the benefit in mitigating the risk of anaphylaxis morbidity and mortality may be outweighed by unintended harm resulting from deferral of a definitive diagnostic procedure (ie, supervised challenge to establish a clear diagnosis). There is also the possibility of overestimation of anaphylaxis risk, in particular, mortality. This may result in therapeutic decisions, such as oral corticosteroid use or reflex activation of emergency medical services, that may not be necessary and may in fact cause harm.

A 2009 clinical vignette (Figure 1) highlights that we need to be vigilant to maintain the perspective to "First do no harm (*primum non nocere*)" and that, paradoxically, when trying to avoid anaphylaxis risk, practitioners may be in fact causing harm. An updated contemporary vignette (Figure 2) highlights progress made in finding a balance to prevent anaphylaxis-risk overdiagnosis while providing safe and effective allergy care.

The goal of this Rostrum is to examine with a few specific examples the unintended consequences associated with diagnostic and management steps to prevent and treat anaphylaxis. Unintended consequences can subtly take their revenge resultant to well-intentioned efforts to improve safety, creating an all-too-often reality that "our control of the acute has indirectly promoted chronic problems."[24] Whereas prevention of anaphylaxis fatality is an important goal, it is also key to prevent overdiagnosis of anaphylaxis risk. Finding this balance is critical to delivering high-value health care to prevent real and tangible harms.

COLLATERAL DAMAGE: PREVENTING OVERDIAGNOSIS OF ANAPHYLAXIS FATALITY RISK FROM ALLERGY SCREENING

Preemptive peanut screening

After publication of the Learning Early About Peanut (LEAP) study, which demonstrated that early peanut introduction into the diets of high-risk infants reduced the relative risk of peanut allergy by 81%,[25] the National Institute of Allergy and Infectious Disease convened an expert panel that recommended that high-risk infants (with severe eczema and/or egg allergy) have preemptive peanut testing prior to peanut introduction.[26] The potential benefit of screening is prevention of a first allergic reaction to peanut at home; however, many of these reactions are nonsevere[19] and there has never been a known or reported life-threatening reaction or fatality reported on first ingestion of peanut in infancy, although underreporting of fatalities for anaphylaxis likely occurs in all age ranges.[1,27,28]

There are significant harms with preemptive screening prior to peanut introduction related to the poor specificity of first-line allergy testing.[29,30] Preemptive screening may result in unnecessary peanut avoidance and overdiagnosis of peanut allergy[19]; it may not even be feasible in large populations owing to the high prevalence of eczema and egg allergy within the infant population. HealthNuts, an Australian prospective population-based cohort study, demonstrated using their cohort that screening all infants with early-onset eczema and/or egg allergy would require testing 16% of the population, of whom 29% would require follow-up because of positive results.[31] The large numbers of infants who would require follow-up (such as oral challenges) after screening could further burden the medical system in North America, in which access to allergy evaluation has been identified as a significant barrier.[32,33] A cost-effectiveness analysis demonstrated that screening prior to peanut introduction in high-risk infants in the United States would result in 3,208 additional peanut allergy diagnoses and would cost $654,115,322.[14] A screening creep is also possible in which testing occurs to foods other than peanut or in infants who do not truly meet high-risk criteria.[34]

In addition, the true risk of a severe/fatal reaction to peanut in infancy must be taken into account. Preemptive screening does not reduce anaphylaxis mortality. Early introduction of peanut in both low- and high-risk infants has been shown to be safe, with very low rates of anaphylaxis.[27,31] In the LEAP study itself, only 2.2% (7 of 319) high-risk infants had positive oral food challenges at baseline, and none required epinephrine, although the LEAP study used a skin prick test of 4 mm as a cut-off for study entry. In the HealthNuts cohort, there were no life-threatening reactions among either low- or high-risk infants whose parents chose to introduce peanut at home in infancy nor in 150 peanut-allergic infants with hospital-based oral food challenges.[31]

Recent evidence suggests that, whereas screening for peanut allergy may not improve health care value, if screening is pursued, there may be a more optimal choice of testing with better specificity.[14,17,35,36] Keet et al[36] reported Ara h2- specific IgE levels above 0.1 kUa/L to have 94% sensitivity with 98% specificity established variably by food challenge or investigator-presumed food allergy. Although Ara h2-specific IgE specificity may be lower in the real world in different cohorts, even with

The year is 2009, and M.M. is a 5-year-old child who received screening skin testing for food allergens due to moderate to severe eczema as an infant in 2004. He was diagnosed with egg allergy due to a positive skin test, and carries a peanut allergy diagnosis for the same reason. M.M. receives annual skin testing and sIgE testing to foods. Because his peanut IgE is > 100 Ku/L, and egg white IgE is 15 Ku/L, he has not undergone a food challenge with his local allergist. His eczema has now largely resolved, and he has never eaten egg or peanut. M.M. develops wheezing during infancy, is subsequently diagnosed with asthma, and has significant medical utilization including an admission to the pediatric intensive care unit (PICU) at 24 months of age. At 3 years of age during a treatment course for pharyngitis he develops a generalized rash and receives a penicillin allergy drug label.

In April of 2009, a new influenza A H1N1 virus is detected in California and in June the World Health Organization declares a pandemic. By September the FDA announces approval of 2009 H1N1 vaccines. M.M. receives skin testing to seasonal influenza in September 2009 vaccine by prick (full strength) and 1:100 volume-to-volume dilution intradermal testing (ID). Testing is positive, so he does not receive flu vaccine. He returns in November 2009 when the H1N1 influenza vaccine is available for skin testing by prick (full strength) and 1:100 v/v ID. Testing is difficult, because he has developed a fear of procedures and needles due to repeated skin testing and sIgE testing annually. His H1N1 influenza skin testing is also positive. The allergist recommends he avoid this vaccine as well. He is given a prescription for oseltamivir to be used at the first sign of an influenza-like-illness. Still, he develops influenza and is hospitalized in the PICU in February 2010. He again returns for skin testing in the fall of 2010, but with positive skin testing influenza vaccine is again deferred. However, in 2011, with the release of the Joint Task Force on Practice Parameters guidance stating "egg allergic individuals can receive influenza vaccine without prior skin testing, with the vaccine administered in a 2-step graded challenge", M.M. receives and tolerates influenza flu vaccine. In subsequent years with evolving guidance, he receives single-dose influenza vaccine annually at his primary care provider without any additional observation, given the low risk for egg allergy associated influenza vaccine anaphylaxis.

By eight years of age M.M. has started to develop fear of accidental "deadly" food allergen exposures and insists on repeatedly checking foods for egg and peanut contamination. He is isolated at school due to the requirement he sit at a segregated table. He has been injected with epinephrine twice and seen in the emergency department for accidental exposure to peanut, although he did not have any reactions. M.M.'s needle phobia worsens and he begins counseling. There is family tension around food allergy and family finances, and M.M.'s parents divorce in 2013.

In 2014, M.M. undergoes a food challenge to egg which he tolerates. Given his success, an oral challenge to peanut is scheduled but he reacts - receiving a dose of epinephrine for urticaria and an episode of vomiting. At sixteen years of age, M.M. again reacts to a supervised peanut challenge. Shared decision-making is leveraged and he begins peanut oral immunotherapy (OIT). This therapy is associated with an improved sense of empowerment. His needle phobia improves with counseling, using cognitive behavioral therapy. At his most recent visit, the family approaches you about his penicillin allergy label…

FIGURE 1. A clinical vignette describes a compilation of author experiences over the past decades, illustrating risks of potential unintended consequences of anaphylaxis-risk overdiagnosis. *FDA,* U.S. Food and Drug Administration; *sIgE,* serum IgE.

more specific testing and a high peanut allergy prevalence, screening without supervised challenge would still result in overdiagnosis of 8% of the screened population with positive testing and would still not be cost effective.[35-37] A more specific test still does not render screening necessary, nor improve quality of life for the overdiagnosed , and may result in increasing challenge procedures and ultimately the risk of delaying food introduction. Although some infants may be at higher risk of peanut allergy, including those with moderate to severe eczema and later introduction of peanut, home peanut introduction without screening can still be chosen by families well-informed of risks, benefits, and alternatives.[38] Ultimately, any screening decision involves trade-offs and should incorporate patient values and preferences in a shared decision construct realizing that screening is not required prior to first introduction of peanut for any infant, even in infants with an elevated relative risk of peanut allergy.[39]

Intradermal testing for penicillin/amoxicillin allergy

In children with a possible immediate (IgE-mediated) reaction to amoxicillin, multiple guidelines recommend skin testing (epicutaneous followed by intradermal) followed by drug provocation testing (DPT) if skin testing is negative.[40] Testing prior to DPT is often thought to be an extra safety step that reduces the risk of a possible severe reaction to amoxicillin. However, the benefits of skin testing prior to DPT must be balanced against the risks. The positive predictive value of skin testing is poor (only ~23%),[41,42] likely resulting in significant overdiagnosis of

M.M. is born 16 years later, in 2020 instead of 2004. During infancy he has moderate to severe eczema. He is referred to a pediatric allergist, who engages the family in shared decision-making regarding food allergen introduction. The family opts to try egg and non-chokable peanut at home. He enjoys eggs and tolerates the food without issue. He develops a mild rash to peanut, so is begun on peanut oral immunotherapy at 9 months of age – which he tolerates well. He continues daily peanut oral immunotherapy. At 4 years of age, he consumes 2 tablespoons of peanut butter during a supervised challenge with his pediatric allergist, and continues to eat peanut several times per week. He attends kindergarten without a food allergy label or requirement for any special accommodation. He returns to his allergist for evaluation of an antibiotic allergy at 6 years of age, because he had developed a rash with amoxicillin when he was 3 years old. Through shared decision making he undergoes a direct oral challenge to amoxicillin and tolerates it without difficulty.

FIGURE 2. A contemporary vignette highlights the progress made in recent years and how shared decision making may be leveraged to improve patient outcomes.

amoxicillin allergy. Significant public health consequences result from overdiagnosis of amoxicillin allergy related to the subsequent use of alternative antibiotics leading to higher rates of antibiotic-resistant bacterial infections, higher risk of antibiotic adverse events, increased risk of hospitalization, and increased health care costs.[43-46] Skin testing reagents are also very costly, can be difficult to obtain, and have very short shelf life once diluted, all of which reduce feasibility of broad testing.[23]

The risks associated with testing must be balanced against the mounting evidence that DPT alone is safe and effective in ruling out amoxicillin allergy, in particular for those at lower risk.[23] A recent systematic review found approximately 95% of over 5,000 participants with a reported history of penicillin allergy tolerated oral penicillin challenge without any adverse reaction.[47] Graded DPT alone has a positive predictive value of 100.0% (95%CI: 86.3-100.0%).[48] The cost, poor feasibility, and risk of false-positive results of skin testing to penicillins must also be considered against the exceptionally low risk of anaphylaxis to penicillins, which has been described as between 0.004% and 0.015% (with a fatality rate of between 0.0002% and 0.0015%).[6,49] Besides, skin tests are painful, time consuming, labor intensive, and resource dependent.[22]

BEST INTENTIONS: CONSEQUENCES OF ANAPHYLAXIS-RISK OVERESTIMATION FROM TREATMENT AND MONITORING RECOMMENDATIONS

Corticosteroid use

Corticosteroids are often administered in anaphylaxis based on the theory that the anti-inflammatory effects will reduce the risk of a biphasic reaction. However, evidence to support this practice is lacking. A retrospective cohort study of 2,701 emergency department (ED) encounters for anaphylaxis noted no difference in rate of allergy-related ED revisits between those that were, and were not, treated with corticosteroids (5.8% vs 6.7%, respectively; adjusted odds ratio [OR] 0.91; 95% CI 0.64-1.28).[50] A systematic review and meta-analysis of 17 observational studies from 2015 examined the predictors of biphasic anaphylactic reactions and noted no significant association between the use of corticosteroids and the risk of a biphasic reaction (pooled OR 1.52, 95% CI 0.96-2.43).[51] A more recent 2017 systematic review regarding the role of corticosteroids in biphasic anaphylaxis noted that only 1 out of 22 studies analyzed supported benefit for the role of corticosteroids.[52] This systematic review also specifically commented on the pediatric population, based on the results of a retrospective review of 5,203 children hospitalized with anaphylaxis noting no association between corticosteroid administration and a 3-day revisit among discharged children (adjusted OR 1.01; 95% CI 0.50-2.05).[53]

There is increasing literature that even short-term use of corticosteroids can have significant side effects. A recent systematic review of the toxicity of short-course oral corticosteroids in the pediatric population (38 studies of 3,200 children) noted common adverse effects to include vomiting (5.4%), behavioral changes (4.7%), and sleep disturbance (4.3%) although several other more systemic side effects including hypertension, adrenal suppression, weight gain, and hyperglycemia were noted.[54] Even with short-term oral corticosteroid use, there was increased susceptibility to infection that was documented in 5 randomized controlled trials (including 3 cases of varicella zoster requiring intensive care and 1 resulting in fatality).[54] In addition, there is some paradoxically increasing evidence that prehospital management of anaphylaxis with corticosteroids may actually increase the risk of negative anaphylaxis outcomes. The Cross-Canada Anaphylaxis Registry, which included 3,498 cases of anaphylaxis (of which 80.3% were children) found that prehospital corticosteroid treatment was associated with an increased risk of intensive care unit/hospital ward admission (adjusted OR 2.84; 95% CI 1.55-6.97) when adjusted for anaphylaxis severity, treatment with epinephrine and antihistamines, sex, age and asthma.[55] However, limitations to this study include its observational design and the potential for reverse causation.

Reflex activation of emergency medical services after epinephrine use

If an epinephrine autoinjector is used for treatment of anaphylaxis, it is commonly recommended and common practice that emergency medical services (EMS) be activated, with the patient transported to the hospital for observation in the case of a biphasic reaction.[56,57] However, there are several unintended consequences of this practice, including the potential for patients to misperceive epinephrine itself as dangerous. No study to date has examined whether early EMS activation actually reduces anaphylaxis fatality.[58] Biphasic reactions are rare and early (nonpreemptive) epinephrine use may be protective against their occurrence.[59,60] Recent adult and pediatric studies have found

that patients who received intramuscular epinephrine therapy within 60 minutes of onset of anaphylaxis were at low risk for a biphasic reaction[59,60] and observational studies have demonstrated that epinephrine was underused or delayed during treatment of the initial reaction among patients who developed biphasic anaphylaxis.[60-64]

Reflex EMS activation is not cost effective. Markov modeling of immediate EMS activation versus a wait-and-see approach for peanut-induced anaphylaxis noted an incremental cost per life year saved of $142,943,447 for immediate EMS versus the wait-and-see approach and a cost per death prevented of $1,349,335,651, both of which greatly exceeded standard cost-effectiveness thresholds.[65] Immediate EMS activation was only cost-effective with modeling that included exceptionally high fatality risk combined with the majority of children requiring additional care in the ED.

The risks of requiring EMS activation as a standard part of all emergency action plans are even more apparent during the current pandemic, in which other risks become associated with EMS activation, including infection risk in the ED and opportunity cost for other diagnoses through overutilization of already overburdened medical services.[66,67] Food Allergy Research and Education has provided a modified anaphylaxis action plan for use during COVID-19 that recommends that automatic EMS activation is not required with certain provisions (including availability of a second epinephrine autoinjector and a proactive discussion with the family).[66] Paradoxically, the requirement for EMS activation may be a barrier to epinephrine autoinjector use because patients and caregivers may not want to or be unable to go to the ED, thereby creating unintentional potential harm.

Prolonged observation after COVID-19 vaccination potentially contributing to vaccine hesitancy

The approval of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines for COVID-19 represented the first hope for disease mitigation in a global pandemic that had affected 109 million individuals and caused 2.4 million deaths as of February 16, 2021.[68] The highest number of cases (27.7 million) and deaths (486,000) have been in the United States (as of mid-February 2021). Although there was no statistically significant difference in hypersensitivity-related adverse events in the randomized controlled studies of these vaccines[69-71] there have been reports of potential anaphylaxis among vaccine recipients in the United States and abroad. The U.S. Centers for Disease Control and Prevention currently recommend that anyone with any history of prior anaphylaxis (not limited to vaccines) be observed for 30 minutes instead of the standard 15 minutes postvaccination.[72] Although this recommendation aims to prevent severe reactions to the vaccine, it will have broad feasibility implications. Consider that the estimated prevalence of food allergy in U.S. adults is 10.8% (>26 million individuals) and that close to double that number (19%) believe that they have a food allergy.[73] Food allergy is a leading cause of anaphylaxis presenting to the ED in the United States each year (~30,000 cases per year).[6,74] If the monitoring period increases from 15 to 30 minutes, the risk of vaccine deferral may increase owing to (1) feasibility of observation for some patients, and (2) more importantly, perception of risk associated with vaccine, which may lead to deferral in a significant proportion of individuals. With current public health restrictions, such as the need for physical distancing in waiting rooms, this seemingly minor change (increasing the observation time) has the potential to significantly reduce the capacity of vaccination centers to immunize people as rapidly as required, compromising the feasibility of controlling the pandemic. In addition, extended observation has not been demonstrated to be cost-effective unless the risk of vaccine anaphylaxis exceeds 6%, which is highly unlikely in a population with a history of non−COVID-19 vaccine anaphylaxis.[75]

Through the end of January 2021, the U.S. Centers for Disease Control and Prevention reported 68 cases of anaphylaxis (out of over 19.4 million doses of Pfizer-BioNTech and Moderna vaccines or ~2.8 per million doses of Moderna vaccines and 5 per million doses of Pfizer-BioNTech administered) with no anaphylaxis fatalities to date.[76] The risk of anaphylaxis must weighed against the known risks of COVID-19 infection (~5% in the United States) and mortality (~1.7% of patients infected).[15,68]

DISCUSSION

Overestimation of anaphylaxis-risk is an underappreciated challenge in providing high-quality health care.[77] The examples presented here demonstrate how well-intentioned interventions can have unanticipated harms at both patient and population levels.[78] Moving forward, overdiagnosis of anaphylaxis-risk should also be considered across the spectrum of allergy care—from delivery of allergen immunotherapy and biologics,[79-82] food allergy management in schools,[83,84] food allergen immunotherapy, premedication to prevent radiocontrast media reactions,[6,85] length of clinical observation of resolved anaphylaxis to prevent unobserved biphasic allergic reactions,[6,86] prescription of epinephrine autoinjectors,[82,87-92] and even evaluation and management of chronic spontaneous urticaria.[18]

There are several key messages to mitigate the risk of mortality related to anaphylaxis that do not lead to overdiagnosis of anaphylaxis-risk. First, the best way to prevent severe anaphylaxis is to use an epinephrine autoinjector as soon as anaphylaxis is recognized.[6,60,61,93] Second, clinicians should carefully consider the distinction between actual versus perceived risk, relative compared with absolute risk, and contextualize these risks.[11,78,94,95] Now more than ever, it is critical to utilize shared decision making to both optimize patient care choices and inform policy. Finally, when we intervene in health care settings assuming our choices will improve patient safety and health care delivery, we should be aware of the trade-offs and downstream consequences of these actions that may cause more harm than avoiding these interventions in the first place.

In the 1985 movie *Back to the Future*,[96] Marty McFly asked Emmet Brown, "Wait a minute, Doc. Are you telling me you built a time machine?" As we continue to improve the care we deliver in 2021, and we share a moment to reflect on the past 2 decades of clinical practice, we can appreciate how far we have come. Whereas we may not have a flux capacitor to travel in time, it is clear the specialty of allergy continues to evolve and that whatever the future holds, contemporary approaches to engage patients in medical decisions, balance risk, and minimize overdiagnosis will allow us to provide better care tomorrow.[97-99]

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