



Editorial

Anaphylaxis: watch out, it is everywhere now!



Anaphylaxis continues to be underdiagnosed, underreported, and undertreated, and this issue of the *Annals of Allergy, Asthma and Immunology* provides granularity on some of the key issues: 1) How accurate are the ICD codes that are used to make its diagnosis and what are their limitations? 2) What drugs are the usual and new etiologic suspects and by what mechanisms do they induce anaphylaxis? 3) How do new food allergens such as alpha-gal expand the understanding of reactions to monoclonal antibodies? 4) How common and severe are allergic reactions to dyes and contrast media and which tools are available for their diagnosis? and 5) Is anaphylaxis part of mast cell activation disorders?

Anaphylaxis onset is complex, with multiorgan involvement, including cutaneous, respiratory, cardiovascular, gastrointestinal, neurological, hematological, and other systemic symptoms that may mimic a patchwork of diseases.¹ Although being recognized and named over 118 years ago, no unifying definition encompasses its heterogeneous presentation. Deaths caused by anaphylaxis are difficult to account for because of the lack of solid criteria and biomarkers for diagnosis. Tryptase, the cellular protease released at the time of immunoglobulin E (IgE) and non-IgE mast cell and basophil activation, is ordered for diagnosis in fewer than 10% of cases, and epinephrine is used in fewer than 20% of cases for its acute treatment. In 1901, Paul Portier and Charles Richet observed fatal effects on dogs injected with extracts of the jellyfish *Coelentera*, which were independent of the dosage but dependent on having received a preparatory injection and a second injection more than 10 to 12 days after the first. They coined the intriguing term *ana* (against) *phylaxis* (protection), and by showing that an immune response could be pathogenic made a discovery that opened a new field of immunology.²

How accurate are the codes that are used to make the diagnosis of anaphylaxis and what are their limitations? Tuttle and Wickner³ noted that before 1993, the ICD-9-CM system did not have codes that identified anaphylaxis that was food or drug induced, anaphylaxis secondary to mast cell disorders, or idiopathic anaphylaxis. The diagnosis of anaphylaxis could be spread over multiple codes such as urticaria, angioedema, or bronchospasm. Results from a study from 2003 that considered data from 34 hospitals indicated that only 57% of food-related anaphylactic events received a diagnosis of anaphylaxis. In a more recent study of 19,836 cases of drug-induced anaphylaxis, fewer than 0.8% had a tryptase level checked, and in 2014, a study of 716 episodes of drug-induced anaphylaxis indicated that only 8% of patients received epinephrine. The authors indicate that educational programs and anaphylaxis simulation programs are suitable tools that may

mitigate anaphylaxis knowledge gaps. Systems-based improvement measures seem the most powerful approach. After an order set for implementation for anaphylaxis definitions in an emergency department were initiated, there was an 82% to 83% sensitivity and specificity of diagnosing anaphylaxis. Accordingly, the percentage of patients treated with epinephrine increased from 33% to 51%.

What drugs are the usual and new suspects and what are their pathogenic mechanisms? Chiriac and Demoly⁴ present new knowledge regarding drug-induced anaphylaxis (DIA). Of all patients seen at Partners Health Care Systems in Massachusetts, 1.1% reported DIA with a greater prevalence in whites, women, and patients with mastocytosis. Drug-induced anaphylaxis triggers included penicillins, followed by quinolones, cephalosporins, sulfonamides, and nonsteroidal anti-inflammatory drugs. As in other studies, fewer than 1% of patients had tryptase levels evaluated, and only 8% were seen by an allergist after the drug reaction. In Korean children, vaccines were recognized as the third most frequent trigger for DIA. Drugs were the second main cause of anaphylaxis in adults, being more prevalent after age 65. New proposed mechanisms for DIA include IgG-mediated pathway with FcγR engagement by immune complexes either enhancing the IgE-dependent pathway or acting autonomously. Additionally, Mas-related G-protein coupled receptor member X2 (MRGPRX2) on mast cells that bind drug may explain reactions to quinolones, opioids, and general anesthetics. New phenotypes of DIA induced by some antineoplastic drugs include cytokine release syndromes with elevated interleukin-6.

How can the discovery and recognition of new food allergens such as alpha-gal expand the understanding of reactions to monoclonal antibodies? Wilson and Platts Mills⁵ present the alpha-Gal syndrome, a new form of food allergy caused by sensitization to the oligosaccharide galactose-α-1, 3-galactose (alpha gal) with unusual clinical features and an association with cetuximab-induced anaphylaxis. Interestingly, after eating mammalian meat, sensitized patients typically present with itching and hives after 2 to 4 hours, which can progress to anaphylaxis and correlates with activation of CD63 in basophils and a significant elevation of tryptase. The delay in the response is attributed to the delay in the absorption and metabolism of dietary lipids. The emergence of the alpha gal syndrome highlights the link between tick bites and IgE induction. The authors postulate that IgE acts as a sensor for environmental “toxins” that helps to confer sensitivity, specificity, and memory to activation of the mast cell, an innate immune cell that resides in the skin and in mucosal tissues.

How common and severe are reactions to dyes and contrast media and which tools are available for their diagnosis? Schönmann and Brockow⁶ review reactions to radiocontrast agents, including iodinated contrast media (ICM), gadolinium-based

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contrast media (GBCM), and dyes for sentinel lymph node detection. With more than 70 million doses of ICM and 50 million doses of GBCM administered worldwide per year, the most common reported reactions include maculopapular exanthema and, rarely, Severe Cutaneous Adverse Reactions. Contrast dye–induced anaphylaxis is rare; it is associated with elevated tryptase and a mortality rate of less than 1 per 1 million doses of GBCM administered. Reactions to non-ionic ICM may occur in 0.7% to 3.0% of intravenous administrations, and severe reactions in 0.02% to 0.04% of cases, with a 4-fold increase for ionic monomeric ICM. Skin testing is recommended in severe IHR to help management. The choice of agent and patch test and delayed intradermal readings are recommended to evaluate the culprit for delayed reactions. Drug provocation challenges are controversial and desensitizations anecdotal.

The final question: is anaphylaxis part of mast cell activation disorders? is addressed by Alvarez-Twose and colleagues.⁷ The authors provide an updated definition and the current criteria for mast cell activation syndrome. Anaphylaxis is presented as the most severe clinical consequence of massive clonal and nonclonal mast cell activation in primary, secondary, and idiopathic mast cell activation syndrome. Of significant interest, the authors describe the hereditary alpha tryptasemia syndrome with familial inheritance of multiple alpha tryptase genes, elevated tryptase, and increase frequency of *Hymenoptera* anaphylaxis, present in 4% to 6% of the general population.⁸

Anaphylaxis is everywhere, being induced by various agents from old antibiotics to new chemotherapies and biologicals, to hidden foods allergens to contrast media and dyes and, importantly, it is part of the newly coined mast cell activation disorders. It

is on our plates to expand our understanding of the mechanisms of anaphylaxis, to recognize its symptoms, to provide prompt use of epinephrine, and to investigate its prevention, including new biologicals and small molecules. Most importantly, we need to teach the rest of the world how to protect patients from anaphylaxis and avoid deaths.

Mariana C. Castells, MD, PhD
Hypersensitivity and Desensitization Center
Mastocytosis Center, Brigham and Women's Hospital
Harvard Medical School, Boston, Massachusetts
mcastells@partners.org

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