

Anaphylaxis: Parts Unknown



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The remembered chef and world traveler Antony Bourdain in the television series *Parts Unknown* once said, “The more I travel, the less I know.” He took to remote destinations to discover the foods of the world. For Antony Bourdain, traveling the unbeaten paths provided for stunning discoveries, where he familiarized himself with unknown worlds and opened the mind to endless culinary possibilities. Anaphylaxis (from the Greek; against protection) was recognized and named 118 years ago by Portier and Richet¹ working on dogs sensitized to *Physalia physalis* antigens. Dogs previously exposed to *P physalis* (Portuguese man of war), when injected with a nonlethal dose, presented the strange phenomenon of lack of protective immunity and died acutely of respiratory, cardiac, and gastrointestinal complications. Despite the early recognition of anaphylaxis and its cardinal symptoms only recently have we started to appreciate its heterogeneous presentation, the triggers, and unravel its etiology and pathogenesis. The discovery of IgE in 1966 by Ishizaka et al² and in 1967 independently by Johansson and Bennich³ and the demonstration that antigen/IgE crosslinking of high-affinity IgE receptors on human basophils and mast cells produced the release of vasoactive mediators capable of inducing hypotension, bronchospasm, and diarrhea led to the initial understanding of the mechanisms of anaphylaxis.⁴ Non-IgE mechanisms have also been recognized and broaden our views of the pathogenesis of anaphylaxis.^{5,6} Paradoxically, in contrast to the original detrimental role for IgE and mast cells, a new paradigm has emerged with the recent discovery that IgE-associated type 2 immune responses can increase host resistance against hymenopteran, neurotoxins, and snake venoms.⁷ An interesting concept for anaphylaxis has arisen in animal models as a protective mechanism against external threats in the form of small peptides, which will require confirmation in human.

In this issue of the journal, we embark upon Anaphylaxis Parts Unknown to visit in depth new developments in its diagnosis, demographics, biomarkers, triggers, management with epinephrine, and its intriguing association with mast cell activation syndromes.

What is our understanding of anaphylaxis and how is it diagnosed? Lieberman et al⁸ in “Diagnostic challenges in anaphylaxis” provide the current definition and its limitations. In 2004, the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network provided the most comprehensive clinical definition for pediatric and adult use, which incorporated the presence of skin findings, exposure to a known allergen, and hypotension as major criteria. Although updated in 2013 by the World Allergy Organization and validated in retrospective reviews, these definitions have limited clinical utility because they do not address the severity, heterogeneity of the presentation, or the dynamic nature of the symptoms. More importantly, they do not address patients treated with medications before mAbs administration or chemotherapy drugs, who may present limited skin or systemic involvement. Biomarkers such as tryptase in serum, histamine and prostaglandins in urine, or skin testing are useful retrospective diagnostic tools, not available at the bedside, making point-of-care testing challenging. The authors emphasize the need for a standardized procedure for acute and retrospective diagnosis based on history, presentation, timing of reaction, cofactors, biomarkers, and investigation of triggers such as alpha-gal. New sets of procedures for patients with anaphylaxis are reviewed, which have identified populations at risk, including males without skin findings and presenting with hypotension who are at high risk for clonal mast cell disorders.

Where is anaphylaxis found around the world, and is its incidence increasing? In “Global trends in anaphylaxis epidemiology and clinical implications” by Turner et al,⁹ the authors indicate that the true global scale is unknown, because its occurrence in the community does not always lead to hospitalization, and therefore it is not documented. Data collection is limited by differences in its definition and coding issues, including selection and information bias. The authors indicate that the implementation of the *International Classification of Diseases, Eleventh Revision* classification, if adopted widely, will improve consistency of coding by adding granularity for its triggers and presentations and facilitate future evaluation of epidemiological trends across the world. There is an overall global trend for an increase in hospitalizations due to anaphylaxis in the United Kingdom, Europe, the United States, Australia, New Zealand, but not for Taiwan. Hospital presentations for anaphylaxis have also increased, mostly in the pediatric populations triggered by foods. The good news is that the fatality rate has decreased globally; however, drugs have become the most common cause of fatal anaphylaxis. Hymenoptera-induced reactions represent a small proportion of the overall causes of anaphylaxis but remain overrepresented in fatalities, underscoring the importance of severe insect allergies, which may indicate the underlying presence of systemic mastocytosis. In the European Mediterranean region, lipid transfer proteins remain

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the most common cause of food allergies and oligosaccharide galactosyl- α -(1,3)-galactose (α -gal) is a global emergent cause of anaphylaxis in tick-endemic regions across the world and the cause of cetuximab-induced anaphylaxis. mAbs and chemotherapy drugs have been increasingly identified as new triggers, with the elderly as a target population, in part related to the use of multidrug treatments. Biphasic anaphylaxis is described to occur in up to 4.6% of cases and up to 72 hours after the onset of symptoms, leading to intensive care admissions in up to 14% of cases, with initial delay in epinephrine administration as a risk factor. Tryptase, a biomarker for anaphylaxis, is found across studies to have high positive and low negative predictive values. Although epinephrine continues to be underused across the world, new data suggest that the value of steroids is limited and potentially harmful.

Each year, millions of patients are dosed with radiocontrast media to improve their diagnosis, and radiocontrast media effects are unpredictable and potentially lethal causes of anaphylaxis. In "Anaphylaxis in the radiology suite," Hsu Blatman et al¹⁰ present the opposing views from the old (Europe) and new world (United States) in regard to the approach to radiocontrast media reactions, regarding skin testing, premedications, and challenges. The mechanisms behind adverse contrast media reactions are heterogeneous and still not well understood. For acute reactions, IgE with elevated histamine and tryptase, non-IgE-mediated reactions with complement activation and bradykinin generation, and potential direct mast cell activation through MRGPRX2 receptors have been implicated. For delayed reactions, T-cell mechanisms are invoked, but no standardized biomarkers exist for the diagnosis. Current recommendations favor nonionic dyes and gadolinium, with an adverse reaction rate 4- to 10-fold less than with ionic dyes. Shellfish allergy or topical iodine allergy are not risk factors, but psychiatric disorders, food allergy, and concomitant intake of proton pump inhibitors have been identified as predisposing factors in addition to previous reactions. Skin testing and basophil activation are frequently used as diagnostic tools in Europe, but not in the United States, to assess acute reactions and establish cross-reactivity, and in patients with negative skin test results, provocation challenges are suggested. Of growing interest, there is evidence that short premedication regimes are protective and that high doses of steroids should be avoided.

Should idiopathic anaphylaxis (IA) be considered part of mast cell activation disorders? In "Idiopathic anaphylaxis: a form of mast cell activation syndrome," Giannetti et al¹¹ shed new light into the pathogenesis of IA as part of mast cell activation disorders. IA has been considered an intriguing and frustrating disease for clinicians due to the unexpected and severe nature of symptoms. As described by the authors, it represents 30% of all episodes of anaphylaxis, has no clear trigger, predominates in females and atopic patients, and is rarely seen in childhood. Its presentation as paroxysmal episodes of multiorgan involvement, including skin, respiratory, gastrointestinal, and cardiovascular symptoms, rarely leads to death and has been associated with temporally elevated mast cell mediators. Similarly, mast cell activation disorders are rare disorders associated with chronic and/or acute multiorgan symptoms due to the release and tissue actions of inflammatory mediators from activated mast cells. Current classification includes primary mast cell activation disorders with clonal expansion of mast cells due to KIT mutations,

secondary disorders associated with connective tissue and allergic conditions, and idiopathic disorders, among which IA can be considered. On the basis of authors' recommendations, patients presenting with recurrent episodes of unprovoked anaphylaxis, in particular in the presence of hypotension, should be evaluated for mast cell activation disorders. Elevated tryptase levels during episodes and at baseline can identify the newly recognized hereditary alpha tryptasemia syndrome. Evaluation of KIT mutations in peripheral blood can identify clonal mast cell disorders. Whether steroids or anti-IgE should be first-line treatments will require further studies.

Regarding anaphylaxis management, is epinephrine warranted, and how and when should it be administered? Brown et al¹² provide in their article, "Epinephrine in the management of anaphylaxis," a comprehensive and much-needed review of the efficacy, safety, costs, and barriers for its uses. Because of its broad vascular and cellular effects, it is the only recommended life-saving medication during anaphylaxis that can reverse hypotension, bronchoconstriction, and mast cell degranulation, among other beneficial actions, but its dosage and pharmacokinetics have not been thoroughly studied. Intramuscular administration in the lateral thigh is superior to all other routes and localizations, with increased and severe cardiac and neurological side effects during intravenous administration. Autoinjectable devices circumvent latency and errors in administration and are preferred; patients with recurrent anaphylaxis should carry 2 devices. The length of needles poses a challenge for infants and patients with increased body mass index. Current criteria for administration are of limited value, due to the heterogeneous nature of initial symptoms and the evolution in a short period of time. Storage conditions and expiration dates need to be specific for each device, and devices should be affordable. Although highly patient-specific, children older than 6 years are expected to recognize the symptoms of anaphylaxis and to be able to manage epinephrine delivery devices. The authors identify major barriers for epinephrine use, such as the cost of autoinjectable devices, lack of unified criteria, difficulties in recognition of symptoms, and the physical and emotional barriers regarding the use of needles.

This enlightening trip should increase our awareness of anaphylaxis and help to educate all health care providers on its diagnosis, the indications and techniques for its immediate treatment with epinephrine, and provide a powerful rationale for referral to an allergist to improve its outcomes and protect patients from future episodes. Allergists should be able to optimize its management and search for its triggers and mechanisms, including looking for mast cell activation disorders. All patients with anaphylaxis should be screened with tryptase, which can provide the clue to the recently described hereditary alpha tryptasemia syndrome. New management options should include its long-term treatment with biologicals capable of modifying IgE and mast cell responses, such as anti-IgE, anti-IL-4/13, and others.

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