

hospital. The system also allows for quicker notification of key personnel. Once notification occurs, it is essential to have the capability for defibrillation readily accessible. Since delays in defibrillation have been successfully overcome with AEDs, these devices could be placed in every patient's room to enable the first responder to deliver timely defibrillation.¹¹

Although most of the factors associated with delayed defibrillation could be mitigated by more effective monitoring and response, some of the observed associations are more alarming. In the analysis by Chan et al., black race and small hospital size were correlated with a greater likelihood of delay. If such disparities in care are real, they raise concerns beyond the adaptation of monitoring technology. Nonetheless, technological advances, being blind to socioeconomic factors, should improve outcomes for all patients.

As a community of physicians, we spend a lot of time thinking about strategies to improve survival for persons who have out-of-hospital cardiac arrests. The study by Chan et al. should refocus some of our attention on improving outcomes for hospitalized patients, especially those who have in-hospital ventricular tachycardia or ventricular fibrillation. It is probably fair to say that most patients assume — unfortunately, incorrectly — that a hospital would be the best place to survive a cardiac arrest. Surely we can do better to fulfill this expectation by better using existing technology and the lessons learned from public-access defibrillation. Let's work to improve the survival of hospitalized patients with ventricular tachycardia or ventricular fibrillation directly under our care. What are we waiting for?

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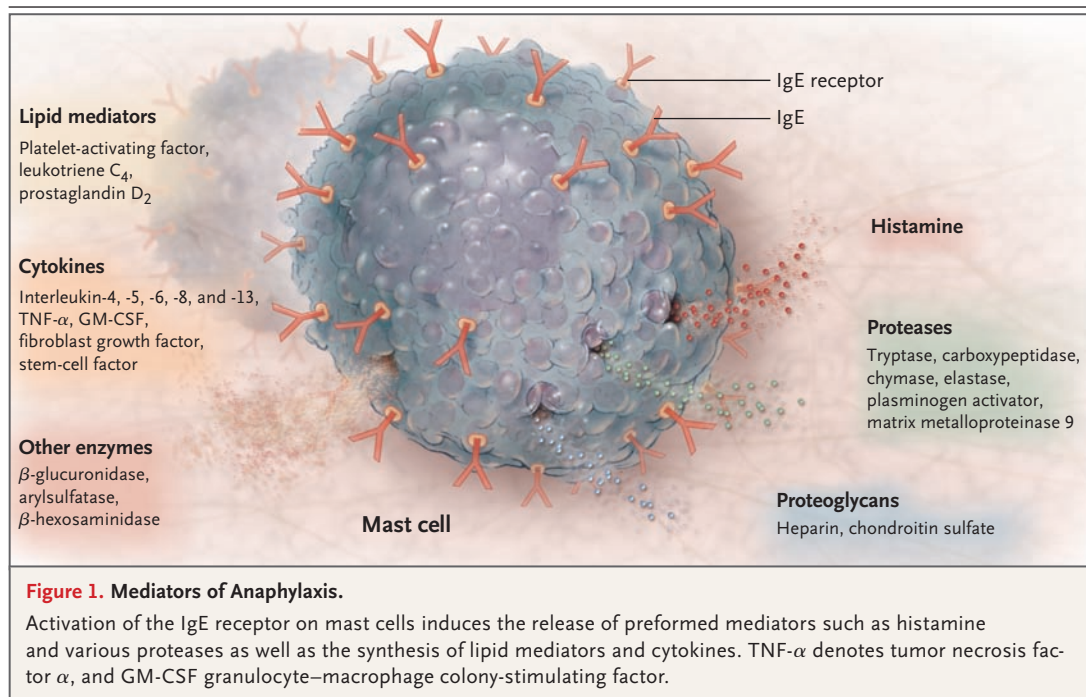
Factoring PAF in Anaphylaxis

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Anaphylaxis has been recognized for more than 100 years, but it remains a condition that is difficult to predict, diagnose, and treat. Generally defined as a serious allergic reaction that is rapid in onset and may cause death,¹ anaphylaxis and its potential to occur can be of great concern for patients and clinicians. Compounding this concern in the United States and other industrialized societies is the increasing incidence of food allergies, which are the leading cause of cases of

anaphylaxis reported in hospital emergency departments, where there are approximately 30,000 reactions and 200 deaths from anaphylaxis each year.² The alarming nature of anaphylaxis and the limitations of current care fuel a critical need for understanding the basic immunology and pathophysiology of anaphylaxis and for the development of more sophisticated strategies for its diagnosis and treatment.

Mediators of anaphylactic reactions are a focus



of current study because they can potentially be used as biomarkers in diagnosing and determining risk for reactions and are also potential targets for treatment. Common triggers for anaphylaxis include foods (primarily peanuts, tree nuts, fish, and shellfish), insect venoms, medications such as β -lactam antibiotics, and natural rubber latex. Exposure to these antigens leads to activation of the IgE receptor on mast cells or basophils, and in mast cells, activation induces the release of preformed mediators such as histamine, tryptase, and chymase, as well as synthesis of cysteinyl leukotrienes, prostaglandin D₂, platelet-activating factor (PAF), and cytokines such as tumor necrosis factor α (TNF- α) (Fig. 1).³ Measurements of plasma histamine and serum tryptase concentrations have been evaluated for their ability to confirm anaphylaxis. However, both measures are limited by their very low sensitivity. In addition, serum tryptase concentrations are seldom elevated during anaphylactic reactions to food, even after physician-supervised food challenges in which blood samples for tryptase measurement are obtained promptly at the onset of symptoms.⁴

The mediator PAF is a proinflammatory phospholipid that is secreted by mast cells, monocytes, and fixed tissue macrophages. In normal conditions, PAF can stimulate a variety of responses,

including phagocytosis, exocytosis, aggregation, proliferation, and adhesion in endothelial cells and several types of leukocytes. When secreted during a pathologic reaction, PAF can lead to bronchoconstriction, hypotension, and vascular permeability, which can result in pulmonary edema and impaired cardiac and renal function. PAF is inactivated by enzymatic cleavage through the activity of PAF acetylhydrolase. In animal models, inactivation of PAF by PAF acetylhydrolase or PAF receptor antagonists protects against anaphylaxis,⁵ and gene knockout provides protection from fatal anaphylaxis.⁶

A two-part study by Vadas and colleagues in this issue of the *Journal* provides evidence suggesting that the PAF concentration is related to the severity of anaphylaxis triggered by foods, medications, or insect stings.⁷ In the first part of the study, a prospective analysis in teenagers and adults was performed in which PAF and PAF acetylhydrolase concentrations were measured against anaphylaxis severity in 41 patients with anaphylaxis and 23 healthy volunteers. Increased PAF concentrations correlated with increased anaphylactic severity, and decreased PAF acetylhydrolase concentrations were frequently observed in patients with severe symptoms.

The second part of the study was a retrospective investigation of PAF acetylhydrolase activity

in nine children and young adults with fatal peanut anaphylaxis. PAF acetylhydrolase levels in the nine persons who died were compared with the levels in five comparison groups. The serum PAF acetylhydrolase levels in patients with fatal anaphylaxis were significantly lower than those in the control patients, suggesting that the failure of PAF acetylhydrolase to inactivate PAF may contribute to an increase in anaphylactic severity.

The results could have long-term implications in the development of biomarker assays for diagnosing the occurrence and risk of anaphylaxis. Currently, the diagnosis of anaphylaxis is based primarily on clinical history and supporting laboratory tests. Patients can have hives, itching, flushing, swelling, difficulty breathing, hypotension, or gastrointestinal symptoms. Anaphylaxis can be difficult to recognize because, although the majority of cases involve skin symptoms, not all do, especially those in patients with life-threatening symptoms,⁴ and patients can have diverse symptoms between episodes. Anaphylaxis is also difficult to recognize if it is triggered by a new agent, is a person's first episode, or occurs in an uncommunicative patient, such as an infant. Symptoms can also be resolving or masked by medications by the time patients present for treatment. Standardized risk assessment for reactions does not exist, and patients with confirmed sensitivities to certain triggers are counseled to avoid them and to treat themselves with epinephrine should an exposure occur. Sensitive and specific biomarkers of anaphylaxis and evolving anaphylaxis could be used to establish the presence of the disorder or the likelihood of its future occurrence.¹ In addition to PAF, mast-cell mediators that have been correlated with anaphylaxis and could be included in a biomarker panel include histamine, tryptase, chymase, and mast-cell carboxypeptidase A3.

Strategies for treating anaphylaxis are based on clinical experience. Epinephrine is used widely to treat acute anaphylaxis, but there are limited data on its appropriate dosing, timing, or repeated administration. H₁- and H₂-antihistamines, corticosteroids, or both are also often used in the treatment of anaphylaxis, but there are few data that define their effectiveness. Prospective, controlled trials are needed to evaluate treatment strategies,

although such trials are difficult to conduct, given the sporadic nature of onset and the potential severity of anaphylactic reactions. The effect of treatment on levels of mediators also remains to be investigated.

Food allergies, which affect more than 12 million persons in the United States,⁸ present perhaps the greatest urgency in research related to anaphylaxis. In the past 10 years, the prevalence of food allergies in the United States has doubled to more than 4% of the total population and 6% of children younger than 3 years.⁸ Since we know so little, we need both basic and clinical research related to the mechanisms, diagnosis, treatment, and prevention of food allergies and related anaphylaxis. Finding additional biomarkers of disease and developing genetic testing for the prediction of disease, its severity, and the response to treatment should be a priority. With further understanding of the mechanisms involved in anaphylaxis, we can hope that some certainty can be provided toward managing such an uncertain condition.

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