

Potter Stewart and the definition of anaphylaxis

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Key word: Anaphylaxis

Potter Stewart was an Associate Justice of the US Supreme Court who might be best known for a snippet from his opinion in the obscenity case of *Jacobellis v Ohio* (1964). In that case he acknowledged that “hard-core pornography” was difficult to define but then added that “I know it when I see it.”

I heard that quote many times when I began clinical research on food allergy and asked my allergist/immunologist colleagues about their definitions of anaphylaxis. I complained that allergy textbooks offered definitions based on IgE levels, mast cells, and other mechanistic details that I had never seen at the bedside. Unfortunately, the experts provided very different clinical definitions, ranging from “mild anaphylaxis” (simple urticaria) to a requirement for hypotensive shock. On that broad severity spectrum, most emergency physicians were in the latter camp, with a reluctance to consider the diagnosis until there was shock. The International Classification of Diseases, ninth revision, did not help because it forced linkage of anaphylaxis with “shock” (eg, code 995.6 for “anaphylactic shock due to adverse food reaction”). In the absence of shock, our emergency department (ED) coders assigned acute allergic reactions as “allergy, unspecified” (code 995.3), regardless of the implicated allergen and number of organ systems involved. Needless to say, these issues make epidemiologic research on anaphylaxis challenging.¹

In response to this ambiguity, Dr Sunday Clark and I created a simple working definition of anaphylaxis that we applied in 2 multicenter ED-based studies: one on food-related allergic reactions² and another on stinging insect hypersensitivity.³ Our studies clearly demonstrated low use of epinephrine treatment among ED patients with multisystem allergic reactions (ie, anaphylaxis), and this finding, although disappointing, was well received by allergists/immunologists, who were eager to correct the problem. The publications were less warmly received by some in the emergency medicine community, who questioned our “soft” definition and the benefit of using epinephrine in patients who did not have shock, patients who, by their definition, did not have anaphylaxis.

To address this frustrating situation, several leaders in the allergy/immunology community began to acknowledge that the traditional mechanistic definition of anaphylaxis was not useful

for nonallergists at the bedside. Even though most allergists/immunologists knew anaphylaxis when they saw it, clinicians in other fields, such as emergency medicine, might not. Emerging evidence that most anaphylaxis is managed by emergency physicians⁴ supported calls for a simpler definition of anaphylaxis that would encourage providers to at least consider the diagnosis. After a tremendous effort by Anne Munoz-Furlong and others in the Food Allergy and Anaphylaxis Network (FAAN), the National Institute of Allergy and Infectious Disease (NIAID) and FAAN convened the First Symposium on the Definition and Management of Anaphylaxis in 2004⁵; the meeting was cochaired by Dr Hugh Sampson and me. We started the discussion with the case definition from my ED-based studies,^{2,3} and after 2 days of debate, the group created a slightly revised definition. The major challenge was getting allergists/immunologists to accept that the new definition would not capture 100% of patients with anaphylaxis (given the need for simplicity and the protean presentations of anaphylaxis) and getting emergency physicians to accept that one could have anaphylaxis without shock. The emergency physicians did not want to create a definition that worked well in the allergy/immunology clinic but that had a low positive predictive value in the ED. The example that struck home with many participants was a young woman with acute urticaria and vomiting shortly after a meal, who was correctly given a diagnosis in the ED of a long history of simple urticaria and a new case of morning sickness.

In 2005, to further advance the definition and bring aboard new partners in this multidisciplinary effort, the NIAID/FAAN convened the Second Symposium, which was chaired by Drs Hugh Sampson and Wyatt Decker.⁶ The Second Symposium yielded a sound-bite definition of anaphylaxis, “a serious allergic reaction that is rapid in onset and may cause death,” and further revisions to the criteria. To date, and despite a lack of formal validation research in any clinical setting, the NIAID/FAAN criteria have been adopted by a variety of guidelines and organizations worldwide.^{7,8}

In this issue of the *Journal*, Campbell et al⁹ retrospectively assess the diagnostic accuracy of the NIAID/FAAN criteria. Briefly, they reviewed charts of ED patients presenting with an acute allergic reaction (including anaphylaxis) to determine whether the NIAID/FAAN criteria were met. The charts were independently reviewed in a blinded fashion by 2 board-certified allergists/immunologists, and the consensus diagnosis by these experts was considered the criterion standard. The interrater agreement of the allergists/immunologists was less than perfect ($\kappa = 0.77$), which is most likely due to the limited data available in a typical ED chart. Nevertheless, of 214 patients, the investigators found that 86 (40%) met the NIAID/FAAN criteria for anaphylaxis. The allergists/immunologists made a diagnosis of anaphylaxis in 61 patients (29% of total), of whom 59 (97%) satisfied the criteria. The key test characteristics were as follows: sensitivity, 97%; specificity, 82%; positive predictive value, 69%; and negative predictive value, 98%. The authors concluded that the

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Disclosure of potential conflict of interest: C. A. Camargo, Jr, has received consultant fees from Dey and Sanofi-Aventis and has received research support from Sanofi-Aventis.

Received for publication December 22, 2011; accepted for publication January 3, 2012.

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J Allergy Clin Immunol 2012;■■■:■■■-■■■.

0091-6749/\$36.00

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doi:10.1016/j.jaci.2012.01.030

NIAID/FAAN criteria are “highly sensitive but less specific” and are “likely to be useful in the ED for diagnosis of anaphylaxis.”

I commend the investigators for undertaking this difficult validation study. I found their conclusions reasonable while also noting a slight shift from the original goals of the NIAID/FAAN criteria, which were not meant to make an actual diagnosis of anaphylaxis but rather to identify patients who were “highly likely” to have anaphylaxis. The intention was not to replace expert opinion but to encourage consideration of the diagnosis and, on further reflection, the appropriate use of epinephrine.

The negative predictive value of 98% sounds impressive, but this will not be useful to most ED clinicians because overdiagnosis of anaphylaxis is not a problem. On the contrary, ED studies consistently suggest underdiagnosis.^{2,3,10-13} As the investigators note, the true number of ED patients with anaphylaxis can only be answered by 24/7 prospective enrollment and real-time expert evaluation; accurate assays of stored biospecimens are not available. Thus although prospective research sounds attractive, it is not yet feasible for logistic, financial, and scientific reasons.

In the context of ED care today, a more valuable combination of test characteristics would be high sensitivity and very high positive predictive value. The investigators report a sensitivity of 98% but a positive predictive value of only 69%. In other words, if the NIAID/FAAN criteria identified 100 patients as being “highly likely” to have anaphylaxis, only 69 would have anaphylaxis, and 31 would not. Although I agree that use of the NIAID/FAAN criteria is likely to improve ED anaphylaxis care, which remains suboptimal, the investigators also have demonstrated that clinicians should not follow the NIAID/FAAN criteria blindly. This is true, of course, of every clinical algorithm ever created.

In summary, Campbell et al⁹ have performed a thoughtful validation study of the NIAID/FAAN criteria in a large ED. Although the criteria cannot replace expert judgment, that was never the goal, and I agree that the criteria perform well enough to justify more widespread use. Looking ahead, it will become increasingly difficult to validate the criteria as more and more clinicians use the criteria to define anaphylaxis. Accordingly, future research might focus on a related issue: patient uncertainty about when to use epinephrine autoinjectors.¹⁴ The field would take

another big step forward by creating (and validating) simple criteria that would assist patients with the epinephrine decision during an acute allergic reaction, preferably before the reaction progresses to anaphylactic shock, when the decision is obvious and the benefits are decreased.

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