



Editorial

Drug allergy

Veni, vidi, vici—come, understand, and delabel, avoid, or desensitize



“Veni, vidi, vici” [I came, I saw, I conquered], said Julius Caesar in 47 BC in a letter to the Roman Senate after achieving a swift, conclusive victory against Pharnaces of Pontus in the battle of Zela in northern Turkey.¹ A modern version of the determined words of Julius Caesar can be applied to drug allergy: first, come and spend time learning about the reaction, observe the signs and symptoms, or look at the pictures sent by the patient; second, observe the phenotype, understand the endotype, and get help from the biomarkers (tryptase, skin test, challenge, genotype); and third, provide an appropriate treatment option, recommend avoidance or desensitization if possible and/or indicated, and delabel all nonallergic patients. Drug allergy is not an easy or even appealing field and yet is one of the few practiced solely by allergists. No other specialty can provide a true understanding of drug-induced reactions or recommendations that can improve patient safety or promote strategies, such as desensitization, that can save patients’ lives or improve their quality of life. No other specialty can help reduce health care costs and complications in a more profound way as when patients are delabeled of their drug allergy status.

In the 1990s, when I was an allergy fellow, drug allergy was an oddity—a topic that would occupy 10% of inpatients consultations and for which there would rarely be a morning conference. In 2018, fellows’ records indicated that 80% of all inpatient consultations were about drug reactions and that it was the most common topic discussed with attending physicians. However, drug reactions have less standardization, fewer tools for diagnosis, and few treatment options besides avoidance or desensitization.^{2,3}

Is drug allergy an old dog with new tricks or a new dog with new tricks? The discovery of penicillin by Alexander Fleming at St Mary’s Hospital in the United Kingdom in 1928 changed forever the lives of millions of women, men, and children during World War II, and its use extended to civil societies across the world starting in the early 1950s. The precipitous decline in maternal mortality rate from more than 50 per 1000 births in 1850 to fewer than 1 per 1000 births in 1950 coincided with the wide availability of penicillin.⁴ A remarkable lack of pharmacotoxicity was found for penicillin in humans, but allergic reactions surfaced shortly after its generalized use with a reported frequency of 0.7% to 10%. The first anaphylactic reaction in humans was reported in 1945.⁵ Modern statistics estimate that 300 people die annually of anaphylactic shock due to penicillin in the

United States. Drug allergy is therefore an old dog with more than 70 years of known existence. The advent and proliferation of new drugs, such as chemotherapeutic agents and, more recently, monoclonal antibodies and biologicals, have changed the landscape to the extent that the old drug-allergy dog is now a new cyberdog playing new tricks. Pathways to drug-induced anaphylaxis have widened to include non-IgE-mediated drug reactions, likely through MRGPRX2 G-coupled protein mast cell receptors, such for quinolones.^{6,7} Many other reactions to targeted therapies are not contemplated in the Gell and Coombs classification, such as infusion reactions and cytokine release/storm reactions.^{8,9} More than 100 therapeutic monoclonal antibodies are currently available for the treatment and cure of cancer and inflammatory and autoimmune diseases, and their use is rapidly expanding to cardiovascular and neurologic diseases.⁹ Adverse and allergic reactions are significant, mostly unexpected, and increasingly compromising patient safety and/or continued use.⁸ Equally important is the recent knowledge that penicillin allergy is not a lifelong occurrence for most patients and that delabeling patients of their drug allergy status reduces the morbidity and costs associated with the use of more expensive medications with increased adverse effects.¹⁰

When faced with a patient who has a label of drug allergy, allergists should ask whether the patient is truly allergic. How can a low-risk patient be safely reintroduced to the drug and be delabeled of their drug allergy status? When faced with a documented drug reaction, allergists should ask the following questions: “What are the potential mechanisms of the reaction?” “What can be recommended for its management, including the potential use of epinephrine?” “Can a patient use other drugs from the same family?” “Can the drug reaction be desensitized?”

To help standardize the approach and diagnosis of modern drug allergy and to help answer these questions, a series of articles in this month’s issue of the *Annals of Allergy, Asthma, and Immunology* are dedicated to drug allergy. Yang and Castells¹¹ provide a practical approach to rituximab hypersensitivity and management through the presentation of a clinical case and the step by step guide to successful desensitization. The case illustrates the concept that rituximab and other monoclonal antibodies can induce different reactions with complex phenotypes from IgE-mediated reactions with positive skin test results to cytokine-release syndromes, which can occur in the same patient and during different exposures and desensitization. A key concept is that desensitization protocols are tailored to each patient and drug and that premedications need to be personalized.

Hong and Sloane¹² provide an extensive overview of therapeutic monoclonal antibody hypersensitivity, which can range from classic type I (mast cell mediated, IgE and non-IgE dependent), cytokine release, or type IV T-cell-mediated reactions and their

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potential management with desensitization. Classic type I allergic reactions can be treated with rapid drug desensitization in an effective and safe manner in carefully selected patients, allowing them to continue to receive first-line therapy. In contrast, it remains uncertain whether rapid desensitization is as effective for cytokine release reactions, but such reactions seem to be limited or prevented with appropriately targeted premedications, intravenous fluids, and dose and frequency drug adjustment. Severe systemic reactions such as Stevens Johnson Syndrome (SJS), AGEP, TEN, and DRESS remain off limits for desensitization and are considered absolute contraindications because of high risk at drug re-exposure, even at low desensitization doses.

Regarding the use of penicillin, Wolfson et al¹³ provide an expanded overview of β -lactam allergy pathways, providing safe frameworks to challenges to improve antibiotic choices in acutely ill patients with penicillin allergy histories. Although no systematic reviews or meta-analysis have been performed, their conclusions indicate that β -lactam pathways are likely to improve the quality of allergy documentation, facilitate antibiotic stewardship, and save costs.

From the Pages of AllergyWatch highlights reviews¹⁴ on drug allergy, and we learn that acid-suppressive medications histamine₂ receptor antagonists and proton pump inhibitors may alter the microbiome in a dose-dependent manner, promoting the development of food allergies, anaphylaxis, allergic rhinitis, and asthma in children. We also learn about the association of anticholinergic medications and the risk for dementia. Prescribing antidepressants for conditions such as urticaria may need to be weighed against potential long-term adverse effects. We are reminded of the morbidity of penicillin allergy and the central role of the allergist on providing pathways and tools to identify nonallergic patients and on driving more equitable health care costs by not denying effective medications to patients no longer allergic.

“Veni, vidi, vici” defines our new roles as allergists facing and attempting to conquer drug allergy: come, see, and protect the patient and the health care system by delabeling, avoiding, or desensitizing.

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