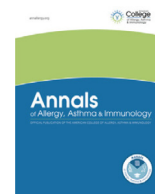




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Editorials

New role for the modern allergist in drug allergy

Assess, diagnose, and de-label



“Hi, doctor. I am here because I have a mast cell disorder.”

“Do you have a penicillin allergy?”

“Well, I am here because I Googled my symptoms and told my doctor that I may have a mast cell disorder.”

“Do you have a penicillin allergy?”

“I was not sent here for my penicillin allergy. I had it for over 40 years and my doctors told me to never take penicillins.”

Eighty percent of patients being evaluated at an allergist office or clinic have a similar story, yet they might leave the office without being evaluated, diagnosed, or de-labeled for penicillin allergy.

A study on national estimates of emergency department (ED) visits for antibiotic adverse events in adults in the United States from 2011 through 2015 published in 2018 indicated that adverse reactions to antibiotics are a common cause of ED visits by adults and represent an important safety issue and a liability for allergists evaluating these patients.¹ Female patients represented the majority (>78%) and adults 20 to 34 years old had twice the estimated rate of ED visits for oral antibiotic adverse reactions compared with those older than 65 years. Allergic reactions accounted for three-fourths of estimated ED visits for antibiotic adverse events and the 3 most frequently implicated antibiotics were oral sulfonamides (23.2%), penicillins (20.8%), and quinolones (15.7%). Nevertheless, more than 90% of patients labeled as allergic to penicillin can indeed tolerate penicillin after negative skin testing results (negative predictive value 99.3%) and an oral amoxicillin challenge.² The American Board of Internal Medicine Foundation's Choosing Wisely campaign recommended in 2014 that physicians “don't overuse non-beta lactam antibiotics in patients with a history of penicillin allergy, without an appropriate evaluation.”³

Penicillin allergy testing is safe in young children, pregnant women, ED patients, preoperative patients, and critically ill hospitalized patients.^{4,5} Patients with positive skin test reactions for whom no equally efficacious alternative antibiotic can be used are candidates for penicillin desensitization, although the procedure is rarely, if ever, recommended.⁶ Why have we not done a better job at assessing, diagnosing, and de-labeling patients? Is it because we do not believe it is important for the patient or the economy? In the past few years, we have learned that patients with penicillin allergy develop more complications when other antibiotics are chosen for their

treatment. In addition, the increased expenses can amount to a 10-fold magnitude.

It is not simply accepting a claim of penicillin allergy (eg, “My mother told me”) or addressing patients previously labeled as allergic to penicillin with symptoms compatible with hypersensitivity or allergy that should drive decisions about antibiotic selection. It requires solid tools and instruments with reliable positive and negative predictive values, multicentric studies to allow for the collection of sufficient cases of severe hypersensitivity reactions, and databases capable of retrieving outcomes, which are just emerging.

In this issue of the *Annals*, 3 important topics are presented that are aimed at helping the practicing allergist better understand, diagnose, and label or de-label patients with penicillin and other drug allergies and hypersensitivities. Jeffres et al⁷ describes 27 legal cases involving the use of β -lactams associated to an adverse outcome from 1959 to 2013. Eighteen cases involved the receipt of a penicillin-based antibiotic, and in 7 cases the defendants prevailed. Cases involving penicillin-based antibiotic prevailed or settled in 3 of 10 (30%), and plaintiffs who received a cephalosporin prevailed in 1 of 4 (25%) cases and 0 of 1 case when receiving a carbapenem. Interestingly, judges cited a lack of scientific evidence demonstrating a cephalosporin or carbapenem was contraindicated for a patient with penicillin allergy. There was limited professional liability for clinicians who prescribed cephalosporins or carbapenems to a patient with a known penicillin allergy, but Jeffres et al indicate that the vast majority of lawsuits are never published or reported, underscoring the lack of standardized criteria for the evaluation of drug hypersensitivity or allergy.

An interesting case involved a woman with a heart murmur and a history of Steven-Johnson syndrome (SJS) after taking penicillin in the 1960s who was prescribed penicillin by her dentist. When the patient told her dentist that she had a severe reaction (toxic epidermal necrolysis [TEN]) to penicillin, she was prescribed an alternative antibiotic, amoxicillin, and was hospitalized for SJS and TEN. The jury found her physician 75% guilty and awarded the patient \$125,000 in damages. Too late, too little: amoxicillin should not be prescribed to patients with SJS and TEN to β -lactams without thorough evaluation. Her compensation clearly was not enough to cover her permanent incapacity.

This is the subject of the second article by Alvarado Sasha et al.⁸ They provide an extensive and up-to-date review of the presentation, diagnosis, complications, treatments, and outcomes of severe drug hypersensitivity reactions by using published literature supplemented with the authors' clinical experience. They confirm current knowledge, such as SJS and TEN have specific genotypic associations with certain drugs, have high morbidity and mortality, and require aggressive management by a multidisciplinary team. Interestingly,

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erythema multiforme is now considered a separate category from SJS and TEN, with defined immunopathologic findings. The estimated overall incidence of SJS and TEN in the United Kingdom is similar to that in the United States, with 5.76 cases per million person-years, with a peak of 8.97 in children 7 to 9 years old and another peak of 8.75 in adults at least 80 years old, without sex differences, and a tendency toward a higher incidence in blacks and Asians. Although drug reaction with eosinophilia and systemic symptoms can present as a severe, prolonged multiorgan reaction with or without eosinophilia, with one-third of patients presenting lung involvement, the prognosis is better than for SJS and TEN. The authors conclude that much needs to be done for the accurate diagnosis and management of high-risk drug rashes, including early recognition, immediate withdrawal of the suspected drug, prompt individualized management, and patient labeling to decrease morbidity, mortality, and long-term sequelae. The lack of current reliable tests for identification of the causative agent imposes great difficulties for their diagnoses. Although treatment with a combination of immunomodulators, such as intravenous immunoglobulin, steroids, and cyclosporine, offer the best outcomes, new avenues such as the use of targeted biologicals (tumor necrosis factor- α blockers, anti-interleukin-5 for drug reaction with eosinophilia and systemic symptoms) and umbilical cord mesenchymal stem cell transplantation provide a glimpse of future treatment options yet un-validated.

Macy and Vyles⁹ answer the critical question “Who needs penicillin allergy testing?” with “Just about everyone with an unconfirmed penicillin ‘allergy.’” They describe the breakthrough approach to patients with unconfirmed penicillin allergy without the use of skin testing in selected populations. They report that the use of quinolones, macrolides, clindamycin, and vancomycin is higher in individuals with unconfirmed penicillin “allergies” and these antibiotics are associated with an increased risk of morbidity. Patients with claimed penicillin “allergy” who spend more time in the hospital, increasing overall health care costs expenditures, are exposed to significantly more antibiotics associated with *Clostridium difficile* and vancomycin-resistant enterococci infections in addition to having increased hospitalization rates and duration. In addition, many childhood illnesses, including otitis media, streptococcal pharyngitis, and community-acquired pneumonia, are optimally treated with penicillin, with the report of penicillin “allergy” leading to avoidance and poorer clinical outcomes. The lead author recently reported on antibiotic use in 100 children 1 year after being de-labeled as allergic to penicillin, with

potential annual cost savings for a pediatric ED population of \$192,223. Patients did not present with anaphylaxis or severe skin reactions, including SJS and TEN. In patients who report penicillin-associated low-risk reaction histories, a direct oral challenge currently appears to be an appropriate and safe strategy.

The message, based on these articles, is to be willing to spend the necessary time with patients to accurately assess their drug allergy clinical history, to start working on evidence-based pathways leading to penicillin allergy de-labeling, and to team up with colleagues to provide outcome data for current and new management options for uncommon and severe cases of drug allergy. For patients truly allergic to penicillin, the safest and most efficient way to be treated with first-line antibiotics is desensitization, not alternative therapies.

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References

- [1] Geller AI, Lovegrove MC, Shehab N, et al. National estimates of emergency department visits for antibiotic adverse events among adults—United States, 2011–2015. *J Gen Intern Med*. 2018;33:1060–1068.
- [2] del Real GA, Rose ME, Ramirez-Atamoros M, et al. Penicillin skin testing in patients with a history of beta-lactam allergy. *Ann Allergy Asthma Immunol*. 2007;98:355–359.
- [3] Wisely Choosing. American Academy of Allergy Asthma & Immunology Accessed May 25 <http://www.choosingwisely.org/clinician-lists/american-academy-allergy-asthma-immunology-non-beta-lactam-antibiotics-penicillin-allergy>; 2016 Accessed May 25.
- [4] Macy E, Ngor EW. Safely diagnosing clinically significant penicillin allergy using only penicilloyl-poly-lysine, penicillin, and oral amoxicillin. *J Allergy Clin Immunol Pract*. 2013;1:258–263.
- [5] Nadarajah K, Green GR, Naglak M. Clinical outcomes of penicillin skin testing. *Ann Allergy Asthma Immunol*. 2005;95:541–545.
- [6] Castells M. Desensitization for drug allergy. *Curr Opin Allergy Clin Immunol*. 2006;6:476–481.
- [7] Jeffres MN, Hall-Lipsy EA, King ST, Cleary JD. Systematic review of professional liability when prescribing β -lactams for patients with a known penicillin allergy. *Ann Allergy Asthma Immunol*. 2018;121:530–536.
- [8] Alvarado Sasha A, Muñoz-Mendoza D, Bahna Sami L. High-risk drug rashes. *Ann Allergy Asthma Immunol*. 2018;121:552–560.
- [9] Macy E, Vyles D. Who needs penicillin allergy testing? *Ann Allergy Asthma Immunol*. 2018;121:523–529.