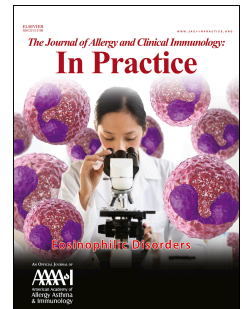


Journal Pre-proof

Positioning Drug Allergy Delabeling as a Critical Tool for Precision Medicine, Quality Improvement, and Public Health

Kimberly G. Blumenthal, MD, MSc, Elizabeth Phillips, MD



PII: S2213-2198(20)30804-7

DOI: <https://doi.org/10.1016/j.jaip.2020.07.046>

Reference: JAIP 3034

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 29 July 2020

Accepted Date: 31 July 2020

Please cite this article as: Blumenthal KG, Phillips E, Positioning Drug Allergy Delabeling as a Critical Tool for Precision Medicine, Quality Improvement, and Public Health, *The Journal of Allergy and Clinical Immunology: In Practice* (2020), doi: <https://doi.org/10.1016/j.jaip.2020.07.046>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2020 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology

Positioning Drug Allergy Delabeling as a Critical Tool for Precision Medicine, Quality Improvement, and Public Health

Kimberly G. Blumenthal, MD, MSc;^{1,2} Elizabeth Phillips, MD^{3,4}

¹Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Boston, MA, USA; ²Harvard Medical School, Boston, MA, USA; ³Institute for Immunology and Infectious Diseases, Murdoch University, Murdoch, Western Australia, Australia; ⁴Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

Corresponding Author:

Elizabeth Phillips, MD
Division of Infectious Diseases
Drug Allergy Clinic, Vanderbilt Allergy and Sinus Program,
Division of Allergy, Pulmonary & Critical Care
Vanderbilt University School of Medicine
1161 21st Avenue South
A-2200 Medical Center North
Nashville, TN 37232-2582
Phone: (615) 322-2035
Fax: (615) 343-6160
Email: elizabeth.j.phillips@vanderbilt.edu

Contents

Word count: 1,326

Figure (2)

27 References: 10

28 Videos (2)

29

30 **Abbreviations**

31 AI Allergy & Immunology

32 CTLA-4 (CD152) cluster of differentiation 152

33 DILI drug-induced liver disease

34 DRESS Drug reaction with eosinophilia and systemic symptoms

35 EBV Epstein-Barr virus

36 EHR Electronic Health Record

37 FDA Food and Drug Administration

38 HLA Human leukocyte antigen

39 HIPAA Health insurance portability and accountability act

40 HITECH Health information technology for economic and clinical health

41 ICI Immune checkpoint inhibitor

42 Ig Immunoglobulin

43 NBMA Neuromuscular blocking agent

44 NPV Negative predictive value

45 PD-1 Programmed cell death protein -1

46 PI hypothesis – pharmacological interaction

47 SJS/TEN Stevens-Johnson syndrome and toxic epidermal necrolysis

48 US United States

49

50

51

52

Disclosures: KB and EP have no disclosures relevant to the content of this paper. EJP reports grants from National Institutes of Health (P50GM115305, R01HG010863, R01AI152183, R21AI139021, U01AI154659) and from the National Health and Medical Research Council of Australia. She receives Royalties from Uptodate and consulting fees from Biocryst. She is co-director of IIID Pty Ltd that holds a patent for HLA-B*57:01 testing for abacavir hypersensitivity, and holds a patent for Detection of Human Leukocyte Antigen-A*32:01 in connection with Diagnosing Drug Reaction with Eosinophilia and Systemic Symptoms without any financial remuneration and not directly related to the submitted work. KB received funding from the American Academy of Allergy Asthma and Immunology Foundation and the Massachusetts General Hospital's Claflin Distinguished Scholars Award and Corinne A. Basler Transformative Scholar in Medicine.

Funding: Funders played no role in any aspect of this Review.

It has been over 75 years since the first use of penicillin and the first description of penicillin associated hypersensitivity reactions. In 1963, preceding the first discovery of IgE in 1966, Gell and Coombs proposed a classification of type I-IV hypersensitivity reactions (**Figure 1**). For the last several decades, what we now understand to be antibody and T-cell mediated drug hypersensitivity reactions have been viewed within this Gell and Coombs framework. However new knowledge of mechanisms and genetic predisposition continues to be paramount in shifts of how we classify and “taxonomize” drug hypersensitivity reactions. Development of validated reagents for the diagnosis of immediate penicillin allergy led Allergy and Immunology (AI) specialists to play a key and active role in identifying those with true allergy, promoting drug avoidance and introducing desensitization for safe introduction of a drugs, such as penicillin, when necessary. A significant shift from the early 1970s onwards occurred with the introduction of orally bioavailable aminopenicillins, which led to less parenteral penicillin use and fewer reports of penicillin anaphylaxis. The first recognition of delayed rash associated with ampicillin in the context of acute Epstein-Barr virus infection occurred in 1967.¹ This type of delayed rash continues to be the most common pathway towards acquiring a penicillin allergy label today. By the mid-1980s, clinical documentation began to transition to electronic health records (EHRs) and although EHRs were considered critical tools to improve patient care, EHR expansion and the United States (US) “meaningful use” of health information technology expansion from 2010 to 2017 came with unforeseen clinical documentation problems, the over-labeling of drug allergies. While it is widely recognized globally that approximately 8% of individuals carry a label of penicillin allergy in their medical record, less than 5% of these individuals will be proven allergic using validated skin testing and challenge procedures. Other drug allergy labels in the EHR have also been shown to be inaccurate and/or erroneous.

Although there have been paradigm shifts in our understanding of the mechanistic basis of drug hypersensitivity reactions over the last two decades, translation into clinical practice has substantially lagged. The AI role includes the prevention, diagnosis, and treatment of drug hypersensitivity. In the last decade, the AI role has extended from expertise in the immunological diagnosis and treatment of patients

with drug hypersensitivity to a new role as a steward to ensure that patients are not denied access to drugs to which they have a drug allergy label. Grown from data outlining the deleterious individual and public health consequences of an unverified penicillin allergy label,² the term “delabeling,” was introduced in 2013,³ and has fueled and promoted a “delabeling movement” in drug allergy (**Figure 2**). A multidisciplinary approach involving other healthcare professionals including Infectious Diseases specialists, pharmacists and generalists has also emerged as increasingly important.

This “delabeling” theme issue includes a collection of original articles, review articles, and instructional videos ([link to videos here](#)). The objective of this issue is to review how drug allergy delabeling can be enhanced by multidisciplinary approaches that utilize clinical risk stratification and diagnostic tools. Ultimately, our common goal is to promote evidence-based approaches to ensure that the drug allergy label is accurate. Doing so will avoid imprecision in diagnosis that includes drug allergy phenotype misclassification. This issue details safe and effective approaches to penicillin allergy, multiple drug allergy syndromes, chemotherapy, immune checkpoint inhibitor reactions, and delayed T-cell mediated hypersensitivity reactions.

In *Penicillin allergy delabeling: A multidisciplinary opportunity*,⁴ Staicu et al. contextualize the current practice and future directions needed to address unverified penicillin allergies. This article reviews the perspective, practice and logistics, barriers, and opportunities and innovation (inclusive of process and technology innovations) for the multidisciplinary role: AI physician, infectious disease physician, emergency medicine provider, internal medicine including hospital medicine and primary care providers, pediatricians, and pharmacists. While there are arguably additional disciplines to engage in penicillin allergy delabeling efforts, this article summarizes the most up to date evidence and approaches.

In *Tackling the patient with multiple drug “Allergies”: Multiple Drug Intolerance Syndrome*,⁵ Guyer et al. review the epidemiology and clinical features of patients with multiple drug allergy labels. They provide a methodological and diagnostic framework for the management of the patient with multiple drug allergy labels. This includes careful evaluation of history leading to appropriate classification, clinical diagnosis, and where necessary, specialized allergy testing with the realization that

the vast majority of patients will be “delabeled” of one or more reaction(s). The final steps of this evaluation includes revision of the EHR, and education and communication to the patient and all of their healthcare providers, to promote the longstanding effectiveness of multiple drug allergy delabeling.

In *Chemotherapy reactions, desensitize or de-label?*,⁶ Hong and Madrigal-Burgaleta, et al weigh empiric desensitization followed by a risk stratified de-escalation process against direct drug challenge and proceeding with desensitization only in cases where the challenge has failed and allergy has been proven. Drs. Hong, Banerji, and Castells present the case for desensitization first and argue its safety and expediency which could be protocolized for spread into community settings.⁷ Drs. Madrigal-Bergaleta and Alvarez-Cuesta present the case for drug challenge, with an initial eye towards delabeling, citing a study where up to 67% of their patients were not allergic when rechallenged.⁸ Testing during (tryptase, c-reactive protein, IL-6) and following (skin testing) the acute reaction as well as availability of AI expertise may ultimately help guide the decision making process.

In *Balancing immunotherapy efficacy and toxicity*,⁹ Johnson et al review the broad successes associated with immune checkpoint inhibitor (ICI) therapies, such as anti-PD-1/PDL-1, anti-CTLA-4 or combination ICI, in achieving durable anti-tumor responses that are balanced against an increasing number of recognized toxicities. Toxicities frequently involve single organs, and although many are thought to be autoimmune in origin, the specific risk factors, biological markers, and mechanisms of toxicity are not well understood. Furthermore, although reactions can be severe and treatment-limiting, the vast majority of ICI toxicities are mild to moderate, may not recur on redosing, and are not a contraindication to future use of ICI. Approaches to monitoring, diagnosis and management of ICI toxicities are reviewed and a case of ICI associated interstitial nephritis is used to illustrate the decision process for rechallenge and redosing with ICI in the face of toxicities.

In *Delabeling delayed drug hypersensitivity: how far can you safely go?*,¹⁰ Lehloenya et al review the challenging area of patients with delayed T-cell mediated hypersensitivity reactions. Many patients with severe delayed hypersensitivity reactions have had prolonged concurrent dosing with antibiotics and other drugs at the time they develop a severe hypersensitivity reaction. These patients require careful

work-up using the history of all potentially implicated drugs and the timeline to develop a clinical causality assessment. Additional testing such as delayed intradermal, patch testing, and or HLA typing and adjunctive in vitro/ex vivo adjunctive testing may further aid causality assessment. Ultimately, the gold standard of drug challenge followed by therapeutic trial is the only way to definitely delabel an individual of a delayed reaction, and the decision to do this must be based on the benefit and need for therapy with a specific drug(s) weighed against the risk of inducing a potentially serious reaction. A case of a patient developing Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) occurring in association with four drug anti-tuberculous therapy is used to illustrate both the clinical complexity of these cases and to demonstrate how sequential drug challenges are used to selectively remove drug labels and identify the culprit drug.

As drug development expands and diversifies, so will the spectrum of off-target adverse drug reactions including drug hypersensitivities. AI specialists need to be prepared with innovative, evidence-based approaches for drug allergy assessment and delabeling. To meet the challenge of the accumulated burden and increasing demand, pharmacists, infectious diseases specialists and generalists will need to be prepared and educated to contribute to a multidisciplinary “delabeling movement.” While we will rely on our core evaluation methods and diagnostic procedures, the patients, conditions, and circumstances of the drug allergy label impact will continue to vary. Collectively, we can improve the quality of care delivered and advance public health goals while advancing the precision of drug allergy diagnoses.

Figure 1. A Drug Allergy Timeline. This timeline outlines more than 100 years of translational research discovery and implementation related to drug hypersensitivity reactions highlighted by the early discovery of patch testing procedures for contact dermatitis, the recognition of anaphylaxis as a clinical entity and discovery of penicillin which revolutionized antibiotic use in the community. Following this upswing of drug discovery and elucidation of mechanisms and classification of drug reaction in the latter part of the 20th century there was the realization that many patients were both falsely labeled and over-labeled as having hypersensitivity reactions to both first line and necessary drugs. This drove the development of desensitization protocols and ways of introducing drug to patients who had experienced significant immediate reactions. Later strategies included risk stratification to identify patients at low risk for rechallenge in the future. Consistently in most countries <5% of patients labeled as allergic to penicillin have their allergy validated on skin testing and or drug challenge. A “delabeling movement” has ensued to improve both individual and public health, particularly targeting antibiotic delabeling to ensure that the most efficacious, safest and cost-effective antibiotics are used in the right patient at the right time.

Abbreviations: DRESS, drug reaction eosinophilia and systemic symptoms; NPV, negative predictive value; IgE, immunoglobulin E; SJS/TEN, Stevens Johnson syndrome/toxic epidermal necrolysis; DILI, drug-induced liver injury; NMBA, neuromuscular blocking agent

Figure 2. The Impact of Drug Allergy Labels.

This figure demonstrates the proposed and established relationships between drug allergy labels and important clinical and population outcomes.

References

1. Pullen H, Wright N, Murdoch JM. Hypersensitivity reactions to antibacterial drugs in infectious mononucleosis. *Lancet* 1967;2:1176-8.
2. Blumenthal KG, Lu N, Zhang Y, Li Y, Walensky RP, Choi HK. Risk of methicillin resistant *Staphylococcus aureus* and *Clostridium difficile* in patients with a documented penicillin allergy: population based matched cohort study. *BMJ* 2018;361:k2400.
3. Trubiano J, Phillips E. Antimicrobial stewardship's new weapon? A review of antibiotic allergy and pathways to 'de-labeling'. *Curr Opin Infect Dis* 2013;26:526-37.
4. Staicu ML, Vyles D, Shenoy ES, Stone CA, Banks T, Alvarex KS, et al. Penicillin allergy delabeling: a multidisciplinary opportunity. *J Allergy Clin Immunol Pract* 2020. In Press.
5. Guyer AC, Iammatteo M, Karagic M, Macy EM, Jershow E. Tackling the patient with multiple drug "allergies": multiple drug intolerance syndrome. *J Allergy Clin Immunol Pract* 2020. In Press.
6. Hong D, Madrigal-Burgaleta R, Banerji A, Castells M, Alvarez-Cuesta E. Controversies in Allergy: Chemotherapy reactions, desensitize or delabel? *J Allergy Clin Immunol Pract* 2020. In Press.
7. Levin AS, Bhattacharya G, Blumenthal K, Camargo CA, Jr., Banerji A. Platin chemotherapy hypersensitivity reactions: Expanding the scope of practice and improving care. *J Allergy Clin Immunol Pract* 2019;7:1691-5 e2.
8. Madrigal-Burgaleta R, Bernal-Rubio L, Berges-Gimeno MP, Carpio-Escalona LV, Gehlhaar P, Alvarez-Cuesta E. A Large Single-Hospital Experience Using Drug Provocation Testing and Rapid Drug Desensitization in Hypersensitivity to Antineoplastic and Biological Agents. *J Allergy Clin Immunol Pract* 2019;7:618-32.
9. Johnson D, Jakubovic BD, Sibaud VS, M.E. Balancing immunotherapy efficacy and toxicity. *J Allergy Clin Immunol Pract* 2020. In Press.

- 229 10. Lehloenya RJ, Peter JG, Copascu A, Trubiano J, Phillips EJ. Delabeling delayed drug
230 hypersensitivity: how far can you safely go? *J Allergy Clin Immunol Pract* 2020. In Press.

A DRUG ALLERGY TIMELINE: FROM DISCOVERY TO DELABELING

1800s

- 1895 » First use of patch tests in contact reactions
- 1902 » Discovery of anaphylaxis, birth of “Allergy” as a field

Journal Pre-proof

1928 » Discovery of penicillin

- 1934 » First description of phenytoin hypersensitivity (DRESS-type illness)
- 1935 » Hapten hypothesis for chemical sensitization in animal models
- 1940 » First use of penicillin
- 1944 » Delayed reactions skin test positive reactions described with penicillin
- 1945 » Discovery of cephalosporins
- 1947 » First case of drug desensitization to penicillin
 - » First description of antibiotic resistance to penicillin
- 1949 » First description of death from penicillin anaphylaxis
- 1950 » Incidence of penicillin allergy described in 6-12%
- 1960 to 1965 » Mechanisms and formation of penicillin antigens including the penicilloyl major determinant
- 1960s to 1975 » Penicillin cephalosporin cross-reactivity approximately 10%
- 1961 » First use of ampicillin
- 1963 » Gell-Coombs classification of hypersensitivity
- 1966 » Study identifies that a patients developing penicillin allergy have three times as many previous drug reactions than those who did not develop allergy
 - » Penicillin skin testing has a high NPV
- 1966 to 1967 » Discovery of IgE by two independent groups
- 1967 » First recognition of delayed rash associated with ampicillin in acute EBV infection
- 1972 » First use of amoxicillin
 - » First EHR is created
- 1976 » First description of immediate reaction to platinum chemotherapy (cisplatin)
- 1980s & 1990s » Emergence of crisis in antibiotic resistance
- 1986 » First report of successful desensitization to cisplatin
- 1989 » Recognition of multiple drug allergy as a syndrome
- 1990s to 2020 » Desensitization programs to platinum and taxane chemotherapies
- 1990s » Recognition of waning skin test responses to penicillins and cephalosporins
 - » Recognition of over-estimation of penicillin-cephalosporin cross-reactivity
- 1990s to present » Negative healthcare outcomes associated with allergy label to penicillins
- 1993 » Lack of cross-reactivity between sulfa antibiotics and non-antibiotic sulfonamides
- 1996 » HIPAA (EHR privacy standards)

2000s

- 2000s » Recognition of high burden of over-labeling of penicillin allergy
- 2000 » EHR terminology standardization
- 2002 » New models for T-cell mediated drug hypersensitivity (PI hypothesis) suggesting non-covalent interactions
 - » Association between abacavir hypersensitivity and HLA-B*57:01
- 2003 » First description of autoimmunity (toxicity) associated with CTLA-4 (immune checkpoint inhibitor) blockade in patients with metastatic melanoma
- 2004 to present » New HLA associations (SJS/TEN, DRESS and DILI)
- 2005 to 2009 » Commercial penicillin skin testing reagents unavailable
- 2008 » Guideline-based HLA-B*57:01 screening to prevent abacavir hypersensitivity
- 2009 » HITECH Act with EHR meaningful use, an effort led by the Centers for Medicare and Medicaid Services and the Office of the National Coordinator for Health IT
- 2011 » FDA approval of ipilimumab CTLA-4 inhibitor (first immune checkpoint inhibitor)
- 2012 » Altered peptide repertoire hypothesis explaining immunopathogenesis of abacavir hypersensitivity
- 2013 » First use of “delabeling” as a word
- 2014 » First PD-1 inhibitor approved for metastatic melanoma (pembrolizumab)
- 2014 to 2020 » Many epidemiological and observational studies reinforce negative effects of penicillin allergy labels:
 - increased broad-spectrum antibiotic use
 - increased antibiotic resistance
 - increased healthcare associated infections including *Clostridioides difficile* colitis and surgical site infections
 - increased healthcare resource utilization
- 2015 » Proposed mechanisms for non-IgE mediated mast cell activation (fluoroquinolone, NBMA and other drugs are small molecule ligands for MRGPRX2 receptor on human mast cells)
- 2015 to 2020 » Randomized (n=1), observational, quasi-experimental and retrospective studies underscore safety of drug challenge approaches for delabeling patients with low risk reactions to penicillins and sulfa antibiotics

PRESENT

		Impact on Patients and Health Care Systems				
		Delays in treatment	Less effective treatment	Higher healthcare utilization	Increased antibiotic resistance	Increased prescription of opioid
Drug Allergy Label	Penicillin antibiotics	✓	✓	✓	✓	
	Other antibiotics	✓	✓			
	Chemotherapeutics and biologics	✓	✓			
	Local and/or general anesthetics	✓	✓			
	Nonsteroidal anti-inflammatory drugs	✓	✓			✓
	Multiple antibiotics/drugs	✓	✓	✓	✓	