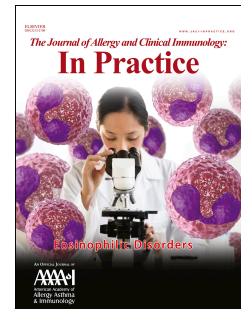


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Allison Ramsey, MD, Eric Macy, MD MS FAAAAI, Anca-Mirela Chiriac, MD, PhD,
Kimberly G. Blumenthal, MD, MSc



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Drug Allergy Labels Lost In Translation: From Patient to Charts and Backwards

Allison Ramsey, MD^a

Eric Macy MD MS FAAAAI^b

Anca-Mirela Chiriac, MD, PhD^c

Kimberly G. Blumenthal, MD, MSc^d

Affiliations:

^aRochester Regional Health, Rochester; Clinical Assistant Professor of Medicine, University of Rochester, NY

^b Kaiser Permanente Southern California, Allergy Department, San Diego, CA

^c Department of Pulmonology, Division of Allergy, Hôpital Arnaud de Villeneuve, University Hospital of Montpellier and IDESP INSERM University of Montpellier, Montpellier, France

^dHarvard Medical School, Boston, Mass; Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Boston, MA; Mongan Institute, Department of Medicine, Massachusetts General Hospital, Boston, MA

Corresponding author:

Allison Ramsey

222 Alexander Street, Suite 3000, Rochester, NY 14607

allison.ramsey@rochesterregional.org

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47

48 Abbreviations:

49 ADR: Adverse drug reaction

50 DHR: Drug hypersensitivity reaction

51 E-consult: Electronic consult

52 EHR: Electronic health record

53 FAERS: United States Food and Drug Association adverse event reporting system

54 HSR: Hypersensitivity reaction

55 MGH: Massachusetts General Hospital

56 MGB: Massachusetts General Brigham Healthcare System (formerly known as Partners
57 Healthcare)

58 NLP: Natural language processing

59 PST: Penicillin skin testing

60 SIDER: Side Effect Resource Database

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Abstract

The current method of defining, reporting, assessment, labeling, delabeling, and reconciliation of adverse drug reactions (ADRs), and specifically immunologically-mediated drug hypersensitivity reactions (HSRs), in electronic health records (EHRs) is inadequate and compromises care quality and safety. It is critical to accurately and succinctly report the signs and symptoms associated with ADRs and suspected HSRs to enable clinicians to determine the plausible reaction type and help guide appropriate future management plans. Despite the current limitations of the EHR allergy module, we must encourage improved clinical documentation and demand technological improvements. Telehealth methods have been shown to be valuable in the assessment of ADRs and HSRs, particularly in the case of penicillin allergy evaluation and delabeling. The implementation, assessment, and refining of advanced technologies, including clinical informatics and artificial intelligence, along with continued education of healthcare providers has potential to improve EHR documentation and communication, thereby advancing patient safety efforts.

Introduction

The drug allergy history is similar to the childhood “telephone game.” A phrase is whispered successively to participants. The fun of the game is that the phrase spoken at the end of the game is often hilariously different from that at the beginning. Unfortunately, in the case of the allergy history, the morphing of the original history is no laughing matter as it has patient care or possibly legal consequences. There are many scenarios where the “telephone game” of drug allergy results in patients unnecessarily avoiding needed medications. For example, patients incorrectly perceive symptoms as a hypersensitivity reaction (HSR) and symptoms are entered, without scrutiny, into the electronic health record (EHR), becoming an allergy label. Signs or symptoms from a non-drug etiology may be incorrectly attributed to a drug and entered into the EHR. With these scenarios, and others, time passes and as other healthcare team members review and edit the EHR allergy module, incremental changes occur that take the current allergy label further from the true history (Figure 1). While there is a chance to reconcile the beginning and ending phrases in the “telephone game,” no similar opportunity for drug allergy reconciliation currently exists. On the contrary, allergy labels are rarely removed, a process sometimes called delabeling. Indeed, data suggest that allergy labels accumulate over time (1), creating a never-ending telephone game. Within the context of these drug allergy labeling challenges, this article reviews the current use and accepted definitions of adverse and allergic drug reactions with a focus on technological advances and future needs to optimize allergy module documentation for improved patient care.

Throughout this manuscript, we will refer to the location in the EHR where ADRs and HSRs are entered as the allergy module or allergy list, although we recognize that many reactions documented here are not IgE-mediated or even immunologically-mediated.

Adverse and Allergic Drug Reactions: Definitions and Epidemiology

An adverse drug reaction (ADR) includes any unintended or harmful effect of a drug that occurs at usual doses (2). In recent literature, ADRs have been divided into “on target” and “off target” mechanisms (3). “On target” ADRs are predictable based on the drug’s mechanism and pharmacologic action, whereas “off target” reactions can be either non-immunologically or immunologically mediated(3). Non-immunologic ADR examples include acute tubular necrosis with aminoglycosides or tinnitus with aspirin. Immunologically-mediated, “off target,” ADRs include antibody- and T-cell-mediated reactions.

All immunologically-mediated reactions have been variably referred to in the literature as “drug allergy” (2), drug hypersensitivity reaction (DHR) (4) , and hypersensitivity reaction (HSR) (3). The use of “drug allergy” has been used to defineimmunologically-mediated reactions (4) , but may not be the preferred term given its ambiguous nature in the broader medical community outside of allergy/immunology. The international consensus on drug allergy (ICON) recommends the use of “DHR” and defines this as “the adverse effects of pharmaceutical formulations (including active drugs and excipients) that clinically resemble allergy (5) (Although pathophysiologic data continue to improve our understanding of the underlying

mechanisms of HSRs, it may not be possible to completely classify a HSR when it occurs. In such cases, the clinical history should guide risk estimation of patient re-exposure to the drug.

A drug intolerance is an undesirable effect that occurs at low or therapeutic doses of the drug that is not thought to be immune-mediated or caused by underlying abnormalities of metabolism or drug excretion (2). It is this category of ADRs that is often misinterpreted by patients and healthcare providers as HSRs, erroneously termed an “allergy,” and initiates an allergy telephone game. To improve allergy labeling and encourage appropriate allergy delabeling, it is critical to take an appropriate allergy history and, if possible, correctly categorize the reaction.

ADRs occur in 15-35% of patients (4, 6), and an ADR complicates a hospital stay in 20% of patients (7, 8). HSRs comprise 6-10% of ADRs (9). Although the intent behind placing an allergy label is patient safety, a poorly maintained allergy field results in negative clinical consequences, demonstrated most notably for unverified penicillin allergy (10-13), but also problematic for patients with unverified opioid (14), NSAID (15), and radiocontrast (16) allergy labels.

Electronic Health Record Allergy Module: The Current State

Although the EHR has potential to improve allergy labeling and delabeling, studies demonstrate that its current state is fraught with inaccuracies. A 2018 study of 1,014 patients evaluated in an academic emergency department found that 42% of adult patient records contained

discrepancies between patient self-reported allergy history and the allergy history documented in the EHR allergy module. Less than 20% of records contained reaction history details without errors of drug omission, commission (i.e., adding a drug reaction), and/or reaction type error (17). A US penicillin allergy documentation study identified that EHR accurately reflected the patient's allergy history less than 50% of the time, with inaccurate records including a different, missing, and/or incomplete reaction history (18). An Australian cross-sectional review of EHR penicillin allergy documentation found that of 5,023 documented penicillin ADRs, 95% were entered as reaction type allergy although just 68% of reaction histories were consistent with a HSR. This finding was attributed to an EHR requirement that providers choose either "allergy" or "intolerance" for any ADR prior to any patient care order entry (19). Similar documentation problems have been demonstrated with drugs beyond penicillins; one study of radiocontrast reactions demonstrated that the providers entering the reactions relied on patient self-report rather than direct observation (20). Another study examining the reasons for applying the radiocontrast allergy label in the EHR showed that the accuracy of this label was only 17%. The label most often represented unknown reactions or non-immunologic ADRs (21).

Accurate allergy documentation may be hindered by the EHR technology itself and/or by the variety of health care team members editing the EHR allergy label. There are different EHRs across healthcare systems with mixed capabilities for documentation; EHR communication across systems is variable. Although it is a best practice to enter both a coded drug and reaction, studies at the Mass General Brigham (MGB) Health System demonstrated at least 6% of allergy entries were entered in free text. Among the most problematic free text entries were radiocontrast media and drug allergies, and the majority of free text entries were entered by

medical assistants and registered nurses (22). A different study at MGB showed a breadth in provider types editing the allergy module, including nurse practitioners, physician assistants, registered nurses, pharmacists, social workers, physical therapists, nutritionists, dentists, and medical students (1). Given the diversity of healthcare providers entering ADRs and the current state of documentation, there are tremendous challenges with improving EHR allergy documentation, especially given that ADRs best practice documentation is not taught to most healthcare providers (23).

EHR transitions also contribute to inaccurate EHR drug allergy fields. An analysis of a sample of 511 drug allergy patients evaluated at Vanderbilt prior to a 2017 EHR transition to Epic (Verona, WI) found 114 specific label differences. After the EHR transition, 30 of the 114 labels (26%) had incorrect reactions or omitted safe alternatives or recommended avoidances (24). Allergy safety events were also identified during the MGH EHR transition to Epic during which patient safety events related to the allergy EHR module were 2–4 times as high 6 months post-EHR transition compared to pre-transition (25). As EHR adoption increases in line with the US's healthcare information technology Meaningful Use, the problem of inaccurate drug allergy labels is likely to increase.

Electronic Health Record Allergy Module: Optimization for the Future

Although there are no national guidelines for EHR allergy documentation, allergy and informatics experts have advocated for a “quick pick” list of the most common drugs causing ADRs (26). Current commercial EHRs display a dictionary of all allergens in alphabetical order when the user looks up an allergen for entry rather than display a “quick pick” list. The latter

would include antibiotics, opiates, non-steroidal anti-inflammatory medications, antihypertensives, radiocontrast media, antidepressants, anti-seizure medications, and corticosteroids (6, 26). Although rare, excipients known to cause HSR could also be added as an option in EHR allergy documentation. Further expert recommendations include limiting free text allergen entries to allow for clinical decision support system triggering (27), along with coded reaction entries for common (e.g., rash, hives, gastrointestinal upset) and severe (e.g., anaphylaxis, Stevens-Johnson syndrome) reactions. There should also be an option to label “suspicion of a HSR” until further evaluation, rather than a binary “present” or “absent” HSR that is the current EHR state. Allergy labels that are not useful (e.g., metoprolol allergy in someone who is on metoprolol) or particularly informative (e.g. a free text allergy entry for “purple pill”) should be removed. The minimum details needed to convey the allergy history are an allergen and a reaction (Figure 2).

Most commercial EHRs have “reaction type” options; for example, Epic EHR “reaction types” include: allergy/hypersensitivity, contraindication, intolerance, and unspecified (Figure 2). Given the importance of “reaction type” for future prescribing, improved accessibility of “reaction type” has been proposed. Blumenthal et al. envisioned “reaction type” categories: patient preference, contraindication, adverse effects, and immunologic (26). Within each type, additional information would be included, such as date of symptoms, sign/symptom detail, and formal evaluation results (e.g. testing or challenge). In the case of immunologic or intolerance reactions, clinical decision support at time of entry could immediately assist health care team members with assessment, documentation, and management. For example, immunologic reaction documentation would deploy decision support that would capture timing, organ

involvement, and rash morphology prior to displaying assessment, documentation, and management guidance.

Healthcare providers are estimated to encounter >100 allergy alerts for each 1 that may improve patient safety (28). Alert fatigue is prevalent, and almost 90% of allergy alerts are overridden (29-31). Although it is necessary to reform allergy alerts, such changes will rely on improved EHR allergy documentation. If drugs, symptoms, and reaction types were coded in the EHR allergy module, allergy alerts could be precisely targeted. For example, alerting could be silenced for intolerances such as headache or fatigue or for known previously tolerated medications (29).

Electronic Health Record Allergy Module: Recent System Advances

Despite documentation and EHR allergy module shortcomings, there has been technological progress and innovation. Wang et al. developed a “dynamic” reaction picklist where the reactions shown for each drug were based on its common and notable reactions. This model was different from current practice in which the same listed reactions are options for all drugs in alphabetical order. This innovative approach consolidated drugs based on duplicate entries and class, created a reaction set, and then used natural language processing (NLP) to reconcile free text entries with the reaction set to create a dynamic picklist. The dynamic reaction picklist significantly outperformed the usual static list that is the current practice (32). Another study utilized NLP on free text allergy descriptions from clinical emergency department notes to reconcile allergies (33). These preliminary data suggest that detailed clinical notes could be used to improve allergy labeling (33). The same investigators also harnessed 2,400,000

reactions to create a common reaction value set for ADRs (33). Although the value set included more than 1,000 distinct reactions making it impractical for direct use in an EHR allergy module, the value set can be a foundation to coordinate reactions across institutions and EHRs. Recently, a novel allergy reconciliation module was designed to consolidate duplicate information, use drug challenge results, and latex serum specific IgE blood testing for allergy module reconciliation recommendations (34).

Some institutions have also initiated comprehensive allergy EHR remediation. An MGB patient safety initiative tackled the issue of free text allergy entries by extracting free text entries from the Epic EHR and creating a list of priority allergens (22). The free text categories were either corrected via use of the EHR technology (an Epic “utility”), or remediated manually, with the latter being employed if multiple drugs were included in free text. Consequently, MGB categorized over 130,000 free text entries into coded entries (22). In order to maintain the quality of the EHR allergy records, the Epic technology continues to check and correct free text and a “tip sheet” encourages accurate allergy documentation system-wide. A manual allergy remediation was performed in a 2013 study where pharmacists clarified allergy labels through 2,174 chart reviews and patient interviews using a pre-specified protocol. This intervention improved allergy documentation completeness, defined as “useful information that could potentially enable a provider to make a clinical decision whether a drug could be re-administered to a patient” and decreased blank EHR allergy fields (35). These data support that successful EHR allergy documentation improvements will likely require both technological and manual components.

Electronic Health Record Allergy Module: Penicillin Allergy Delabeling and Relabeling

Penicillin Allergy and the EHR

Given the widespread poor quality of EHR ADR data, a large focus of allergy/immunology clinical practice includes the assessment of patients with ADRs. Because of the negative consequences of an unverified penicillin allergy label (11-13, 36), there has been an appropriate focus on this (37). There is now substantial evidence supporting penicillin ADR/HSR delabeling strategies through in-person assessments using diagnostic procedures, such as penicillin skin testing (PST) and drug challenges (38, 39). While useful to do electively for all patients, some patient groups, such as perioperative patients and obstetric patients, have demonstrated immediate clinical benefits to penicillin allergy delabeling (40, 41)

Telemedicine Visits

More recently, telemedicine has been used to triage, evaluate, and de-label drug HSRs. Staicu et al. demonstrated the feasibility of using telemedicine for PST performed by a physician assistant in 50 inpatients. This approach de-labeled penicillin allergy at a lower associated cost while reducing second line antibiotic use and maintaining patient satisfaction (42). An outpatient pediatric study employed allergy/immunology telemedicine monitoring of pediatric office-based amoxicillin challenges in 102 children with low risk penicillin allergy histories, and de-labeled 99 (97%) of them (43). In an allergy/immunology telemedicine study, Waibel et al. reported 1 of 6 total drug allergy consults did not necessitate in-person assessment (44).

The COVID-19 pandemic's natural expansion of telemedicine may have a lasting impact on ADR assessments. Indeed, a UK-based study determined that 28 of 97 patients (29%) did not need an in-person ADR evaluation (45) and the large number of allergists evaluating ADRs via telemedicine during the COVID-19 pandemic could further support the feasibility of remote ADR evaluation, with the delabeling of low-risk patients.

Electronic Consults

Electronic consultations (e-consults) have also emerged as a tool enabling ADR triage, assessment, and delabeling(46, 47). E-consults are asynchronous, consultative, provider to provider communications within a shared EHR. The goal of e-consults is to improve health care access and to potentially avoid unnecessary in-person consultations (48). The first e-consult study in the allergy/immunology field was an outpatient study from MGH; 55 of 201 e-consults for ADRs (27%) did not require an in-person allergy/immunology visit. Importantly, most e-consults took less than 10 minutes and were a point of access in a healthcare system with long in-person wait times (46). The ADR e-consults that required in-person encounters were generally those necessitating skin testing or drug challenges (46). Another study by the same investigators used the e-consult as a formal exchange between obstetrics and allergy/immunology to identify patients who should have PST during pregnancy (41). Mustafa et al. recently reported their experience with 78 e-consults performed on inpatients; the majority (86%) of which were for drug allergy, including 53 low-risk penicillin allergy patients who were de-labeled with a direct amoxicillin challenge. Similar to the MGH study, the authors

reported a short time to e-consult completion (15 minutes) (49). Providers requesting the consultations reported satisfaction with this expedited form of patient evaluation (49).

Combatting “Re-labeling”

Despite an increased awareness of the importance of delabeling penicillin allergy, it has been demonstrated that EHR allergy labels are sometimes not appropriately removed after a negative evaluation or may reappear in the EHR. A 2013 retrospective study of patients who had previously undergone PST found that of 150 de-labelled patients, 55 revisited the same hospital system, with 20/55 (36%) re-labelled with penicillin allergy without apparent reason. Risk factors for this re-labeling included age >65 years, long term care facility residence, encephalopathy, and dementia (50). A 2020 study similarly showed that 80 of 176 (45%) patients readmitted after inpatient penicillin-allergy delabeling had the label added back (51). Relabeling of the penicillin allergy appears less likely to occur in healthcare systems with a single EHR, such as Kaiser Permanente (52).

Even when outpatient penicillin allergy assessments are performed by allergists, delabeling and relabeling issues arise. In a study of 69 de-labeled outpatients at Vanderbilt, 26 (38%) did not have the penicillin allergy label appropriately removed (53). In another study of MGH allergy/immunology outpatients, penicillin allergy labels were not removed in 11 patients with the most common reason allergist error (n=9). Investigators additionally identified a 2.0% erroneously relabeling rate after label removal (54). A long term study of 639 outpatients previously tested for penicillin allergy showed that 335 (51%) still carried a penicillin allergy label, despite having tolerated a penicillin-based antibiotic (55).

Changes made to the EHR allergy list should consider approaches to help patients communicate their allergy list to their clinical providers and pharmacies. Ideally, the EHR would be accessible for all providers to review allergy list details. However, given the current limitations of commercial EHR allergy documentation and communication across systems, patient self-management tools may be needed. A free IOS app, Allergy PassportTM, can be used for patients to maintain their drug allergies and is free for download at the Apple (Cupertino, CA) app store. Another option is a “passport” or wallet type card previously endorsed by the ENDA/EAACI drug allergy working group (56). Although there are limited data to support these specific interventions, they are clinically intuitive and free to try. This patient responsibility may help with patient empowerment, as drug allergy patients appear more concerned about receiving optimal future treatment than relapse of a drug allergy (57). Multipronged delabeling strategies may be most beneficial. Parkland Hospital used a best practice alert, a pocket card, and follow up phone call from pharmacist to patient to maintain penicillin allergy delabeling after negative evaluations(58). Lastly, it would optimal if non-allergists were to avoid adding back a delabeled drug allergy until patient reevaluation by an allergy/immunology specialist.

Conclusion

The defining, reporting, assessment, labeling, delabeling, and reconciliation of adverse and allergic drug reactions can easily go awry, just like the childhood “telephone game.” The most important step with ADRs and HSRs is to accurately define the reported history and assess the most likely reaction type. Despite the current limitations of the EHR allergy module, we must encourage improved documentation and inform technological improvements. Novel methods of ADR assessments by allergy/immunology, such as the use of telemedicine or e-consults, have

338 been shown to be valuable methods for addressing drug allergy and unverified penicillin
339 allergies. Further studies might systematically evaluate methods to ensure penicillin allergy
340 delabeling and prevent erroneous re-labeling, such as the use of EHR alerts and patient
341 communication tools. Advanced technologies, including natural language processing and
342 artificial intelligence, along with continued education of non-allergists and expansion of
343 allergy/immunology assessments has notable potential to provide an improved ADR label than
344 our current “telephone game.”

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502 Figure Legends

503 Figure 1

504 **The Drug Allergy History as the “Telephone Game.”**

505 This figure demonstrates the morphing of a penicillin allergy history over time through
506 electronic and human interactions with the electronic health record. © 2021 Epic Systems
507 Corporation

508

509 Figure 2

510 **Adding and deleting allergies in the electronic allergy record.**

511 This figure demonstrates how to add and delete an amoxicillin allergy from the electronic
512 health record, shown with Epic (Verona, WI), © 2021 Epic Systems Corporation

Patient has nausea/vomiting while on amoxicillin for sinusitis. This questionable history added to EHR

Update made by healthcare provider for unclear reasons

Duplicate added at urgent care visit 9 years later

Fifteen years from initial penicillin reaction without any recent reactions or exposures, the EHR has a jumbled allergy history with conflicting entries

Journal Pre-proof				
You can use the box to the upper left to add an allergy or a contraindication for this patient.				
Allergies				
Penicillins	Unknown	Not Specified	Unknown: reaction history is not available	6/1/2005
Pt thinks she had vomiting				
Allergies				
Penicillins	Anaphylaxis	High	Allergy: immunologically mediated response	6/1/2005
Pt thinks she had vomiting				
Allergies				
Penicillins	Anaphylaxis	High	Allergy: immunologically mediated response	6/1/2005
Pt thinks she had vomiting				
Amoxicillin	Nausea And Vomiting	Not Specified	Unknown: reaction history is not available	6/25/2014
Pt was young - does not remember.				
Allergies				
Penicillins	Other (See Comments)	High	Allergy: immunologically mediated response	6/1/2005
?Hives, nausea/vomiting, "throat closing"				
Amoxicillin	Nausea And Vomiting	Not Specified	Unknown: reaction history is not available	6/25/2014
Pt was young - does not remember.				
Review Complete ☒ Mark as Reviewed ☐ Last Reviewed by Inpatient, Nurse, RN on 12/28/2020 at 9:14 AM: Review Complete (History)				

Adding an allergy: Details should include: Agent, Reaction, Reaction Type, Severity, and Date Noted. Free text comments can also be useful to indicate other clinical details, including testing results from skin tests or drug challenges.

AMOXICILLIN

Agent: AMOXICILLIN

Reactions: Hives

Severity: Medium

Noted: 12/22/2010

Reaction type: Allergy/Hyperser

Comments: When 16 years old developed hives the first day of a course of amoxicillin. Has since avoided all beta-lactams. See photo dated 12/22/2010.

Accept Cancel

Deleting an allergy: Start by adding free text comments about why you are deleting the allergy (e.g., “tolerated amoxicillin”). Next, delete the entry and select a reason for deletion. If you are deleting after an amoxicillin challenge, select “resolution of allergy,” “entry determined to be clinically insignificant,” or similar.

Category Select

Search:

- ▲ Title
- Duplicate
- Entry determined to be clinically insignificant
- Entry miscategorized as an allergy
- Erroneous Entry
- Resolution of allergy
- Wrong allergy selected
- Wrong patient selected

7 categories loaded.

Accept Cancel

Delete Allergy/Contraindication: AMOXICILLIN

Deletion reason: Resolution of allergy

Comments: Tolerated amoxicillin in allergy clinic; see note from 12/9/2020.

Accept Cancel