

Big Datasets in Antibiotic Allergy: What's the Story?



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"Data are just summaries of thousands of stories."

— Chip & Dan Heath, Authors

Our evidence base in medicine ultimately comes from our patients' stories. A case report is the story of 1 patient with a unique presentation or outcome. A case series is a collection of stories from a small group of people with shared symptoms, diagnoses, or treatments. A controlled clinical trial tells the stories of people with a specific commonality that are meticulously recorded, compared, and systematically reported. More recently, advances in data acquisition, storage, and analysis have facilitated the summary of immense numbers of patient stories into large datasets. These datasets can, in turn, tell logical, useful, and compelling stories that we should listen to. However, we also must be aware that the stories from these large datasets may be fragmented or incomplete. It is our job to decide which storybook to heed and apply to our practice.

In this issue of the *Journal of Allergy and Clinical Immunology: In Practice*, Liang et al¹ employ the vast available data from Kaiser Permanente to tell us the story of patients with adverse reactions to penicillins, carbapenems, monobactams, and clindamycin. The authors examined data from 2009 to 2017 regarding the number of antibiotic prescriptions, length of therapy, and new reactions to these antibiotics in 6,144,442 unique individuals who had at least 1 health care visit during the study interval. New *allergies* were defined by whether an antibiotic was added to the electronic health record (EHR) allergy field within 30 days of therapy. The prevalence of allergies to the antibiotics was determined at the end of the study period. Using International Classification of Diseases, Ninth Revision (ICD-9) codes, the authors also looked at the incidence of anaphylaxis, severe cutaneous adverse reactions (SCARs), nephropathy, and *Clostridioides difficile* infection associated with the studied antibiotics. With such a large

number of patients with stories to tell, it is possible that some of the completeness of the data varies.

The strong data regarding antibiotic use, adverse reaction incidence, and antibiotic prevalence provide a useful, complete update regarding the epidemiology of adverse drug reactions to penicillins, carbapenems, and monobactams on a scale that has not been reported previously. The incidence and prevalence data spanning the inpatient and outpatient settings are also a strength of this study, because many other epidemiologic studies have been performed in one setting or the other. A smaller Kaiser Permanente study of 411,543 patients examining the incidence and prevalence of all drug allergy² was similar to the Liang et al study in that females were demonstrated to have a higher rate of antibiotic use and overall antibiotic *allergies*. This 2009 study showed an overall prevalence of penicillin allergy of 11%, compared with 9.2% in the more recent study. A different group of 29,095 subjects in outpatient community health centers in the Miami, FL area showed a similar prevalence of penicillin allergy (9.1%)³ as Liang et al. Unlike penicillin, the incidence and prevalence of allergy to carbapenems and monobactams is less well described, and the current article provides these needed data. Prior carbapenem and monobactam allergy data have generally been from smaller studies or specifically studied in the context of existing penicillin allergy.⁴ True clindamycin allergy is rare,⁵ and the clindamycin prevalence of 0.4% reported by the authors mirrors a previously reported prevalence in 3896 patients from 1999.⁵ The fact that the prevalence figures demonstrated by Liang et al agree with smaller preceding studies speaks to the completeness of the authors' reported data. Although the problems inherent to errors in EHR documentation, for example, intolerance versus allergy, have been reported,⁶ as the authors point out, it is precisely this documentation that drives antibiotic choice.

Although the epidemiologic data provided by Liang et al are undisputedly valuable, the authors also discuss that it is their hope that the information contained in their article will reassure patients and providers and assist with penicillin allergy delabeling. This analysis focuses on both incidence of penicillin allergy and prevalence, along with incidence and prevalence of alternative antibiotics to penicillin. It does not specifically focus on patients already labeled with penicillin allergy or reactions associated with reintroduction of penicillin, so it is not clear how these data would serve to drive clinical decision making or encourage further penicillin allergy delabeling. The clinical picture, including infection type, and microbial data drive antibiotic choice, rather than estimated risks of subsequent reactions.

The methodology employed to synthesize the stories of anaphylaxis, drug rash with eosinophilia and systemic symptoms (DRESS), SCARs, and nephropathy into a useful dataset calls into question the completeness of this information. The authors

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used ICD-9 codes to identify anaphylaxis, and 2 authors separately reviewed the charts to determine the appropriateness of the diagnosis. The fact that the authors manually reviewed the identified anaphylaxis cases is a strength of this analysis, but given the known under-recognition of anaphylaxis⁷ and the variation in use of billing codes among physicians, the rates of anaphylaxis are likely to be under-reported. Dhopeswarkar et al⁸ studied drug-induced anaphylaxis in 1,756,481 patients with a different approach of using the information contained in the EHR allergy field, rather than billing codes, to describe the reported prevalence. Both authors acknowledge the shortcomings of their methodologies in their discussions. However, the data regarding anaphylaxis from big datasets like this one, however incomplete, are the best we currently have given the relative rarity of anaphylaxis, and thus its low occurrence in traditional, smaller prospective trials.

It is also probable that the reported incidences of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are also smaller due to under-recognition and variation in billing codes used. The definition of DRESS employed in this study is more problematic. Most descriptions of DRESS report that a drug exposure can precede symptoms by up to 6 weeks.⁹ The authors used a cutoff of 30 days to identify cases of DRESS with ICD-9 codes, and also used the combination of an elevated eosinophil count >500 eosinophils/ μ L and alanine aminotransferase >100 U/L within 30 days of starting an antibiotic as a surrogate for DRESS. The authors likely missed some cases of DRESS presenting outside of their 30-day cutoff window. Their laboratory definition of DRESS disregards other organ involvement, and can certainly be confounded by other plausible clinical scenarios presenting with the same changes in laboratory values. The incomplete stories comprising the datasets describing anaphylaxis, SJS/TEN, and DRESS may be made whole by emerging approaches to analyzing these datasets. Banerji et al¹⁰ recently submitted their work on natural language processing (NLP), where a rule-based NLP algorithm developed by manual chart review and used with billing codes improved the positive predictive value to identify true allergic reactions to drugs. Incorporating novel

approaches such as NLP to current methodologies for dataset analysis will provide a more comprehensive summary of patient stories.

If data are summaries of thousands of stories, we need to be cognizant of which stories are effectively summarized and those that may not be yet complete. Liang et al provide a comprehensive look at the incidence and prevalence of penicillin-based antibiotic, carbapenem, monobactam, and clindamycin allergy. The data regarding anaphylaxis and SCARs may have some missing pages, but do provide updated data that can be refined as approaches to large dataset analysis improve. The stories in medicine are always unfolding. Newer datasets based on refined techniques are sequels.

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