Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Drug allergy labeling and delabeling in the coronavirus disease 2019 era

What is important and what do we need to know

At the time of this writing, April 7, 2020, more than 1.2 million people worldwide are infected and more than 68,000 have died because of coronavirus disease 2019 (COVID-19) induced by the novel severe acute respiratory syndrome coronavirus 2 infection, and this figure will surely multiply in the next few weeks according to Dr Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases. Severe acute respiratory syndrome coronavirus 2 uses angiotensin-converting enzyme-2 (ACE-2) (a type I transmembrane metallocarboxypeptidase) as its preferred entry receptor. The expression of ACE-2 is high in alveolar and epithelial tissues in the lungs and the gastrointestinal tract. Drugs which affect the expression of ACE-2 (such as ACE inhibitors and angiotensin receptor blockers) are being investigated as possible risk factors for the severity of coronavirus disease 2019.[1] Nonsteroidal anti-inflammatory drugs are being similarly investigated.[2] Clinical trials with azithromycin and hydroxychloroquine,[3] antiretroviral drugs,[4] and anti–interleukin-6[5] are ongoing in an attempt to improve disease outcomes before a vaccine can be available. This provides a glimpse of the complexities of this disease and reveals the importance of identifying candidate drugs for clinical trials that may save lives. It follows in importance to identify patients with allergy who are at risk, if treated, and who may need desensitization. Understanding the mechanisms of drug allergy[6] is key, given that the classification of drug hypersensitivity continues to expand.[7] Cytokine storm–like reactions with elevated interleukin-6 can be seen in patients treated with chemotherapy and monoclonal antibodies[8] and are now part of a broader definition of anaphylaxis, allowing for better management and treatment options.

The timing of this issue of the *Annals* is highly relevant given that it is dedicated to broadening our understanding of the scope of drug allergy in the general population. Various tools can be used in personalized medicine to confirm or refute specific drug allergy status through delabeling. These standardized diagnostic interventions can allow both children and adults to safely take the drug for which they had been previously labeled as allergic, thereby resulting in the removal of this label. The topics covered in this issue provide the necessary and updated knowledge for all allergists involved in labeling and delabeling procedures, aiming to broaden drug choices and treatment options for patients in this unknown world of COVID-19 pandemic and other disease states.

Our first question is: who is labeled as drug allergic in the general population and what can be done to uncover true drug allergy? A review by Macy[9] provides data on a large cohort of more than 2 million members of Kaiser Health Care, with 20% reported to have a drug allergy and more than 13% having antibiotic allergy. In this drug allergy cohort, twice as many patients are females. Age of more than 50 years and increased body mass index were found to be associated with drug allergy. The review also discusses whether drug allergy and hypersensitivity are due to increased use, given that countries with lower rates of antibiotic use have a lower prevalence of antibiotic allergy. Inappropriate use of antibiotics is still high in the setting of dental procedures. Target populations for receiving a drug allergy label include the following: (1) children with approximately 70,000 visits to the emergency department reported annually for adverse drug events with penicillins, cephalosporins, and sulfamethoxazole-trimethoprim as the most frequent medications; and (2) hospitalized patients with cancer, of whom 23% have a label of antibiotic allergy. What are the tools for the labeling or delabeling of a drug allergy? For individuals with penicillin-associated anaphylaxis, penicillin skin testing with penicilloyl-polylysine before oral amoxicillin 250 mg oral challenge (if skin test negative) is the avenue proposed by the author; however, with the lack of minor determinants, sensitization is not addressed. For patients with a history of benign cutaneous reactions, 1 single oral dose of amoxicillin is recommended.

What are the benefits and dangers of a drug allergy label? In a review by Solenki,[10] the author reviewed self-reported penicillin allergy, which accounts for at least 10% of the population, and observed that, among these individuals claiming to be allergic to penicillin, more than 90% are not truly allergic and can tolerate penicillin. These discrepancies were reviewed, which included initial mislabeling at the time of the clinical event, such as associated symptoms of viral infections, including urticaria and gastrointestinal adverse effects of antibiotics. Many drug allergies are not long-lived and the natural resolution of penicillin allergy was reviewed. The author validated current diagnostic tools for the diagnosis of penicillin, cephalosporins, and other antibiotics allergies. Multicentered clinical trials are needed to validate skin testing predictive values and to assess the value of new tools, such as specific immunoglobulin E and basophil activation test.

How to detect children with true penicillin allergy? Vyles et al[11] provide a review that describes that most allergies in pediatric patients are self-reported and often clinically inconsistent with true allergy. The rate of parent-reported adverse drug reactions ranges from 6% to 10%, and most of these so-called allergic reactions are

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attributed to beta-lactam antibiotic derivatives, anti-inflammatory drugs, and other antibiotics. Nonimmediate rashes occurring after several days of treatment are the most frequently reported symptoms. Although skin testing, followed by oral challenge, is the safest way to identify true immunoglobulin −mediated allergy in children with high-risk allergy symptoms, risk stratification and direct oral challenge of low-risk patients is becoming a standard. Of interest are 2 studies, which reported that both parents and physicians were reluctant to utilize penicillin class antibiotics after the penicillin allergy label was removed because of fear of an allergic reaction. The authors concluded that current and future efforts should focus on preventing penicillin allergy labels that can carry over into adulthood, providing education and decision support in the electronic medical record, and testing low-risk drug administration strategies in low-risk patients. Integrating penicillin allergy management into stewardship efforts with the government and third-party payer incentives should be the long-term goal for penicillin allergy delabeling at the population level.

What is the current understanding of drug hypersensitivity and allergic reactions? Jakubovic et al[12] provide a broad and updated review of the current knowledge by reviewing the classical model of drug hypersensitivity reactions and comparing this with the current and more customized classification based on phenotypes, endotypes, and biomarker profiles. This approach allows for the classification of reactions to chemotherapy drugs, monoclonal antibodies, and new small molecules. Complementing the Gell and Coombs classification drug allergy phenotypes allows for the description of classical and atypical clinical symptoms, such as cytokine storm−like manifestations in the context of drug exposure, timing, and severity. The endotypes look at the mechanisms, and also the molecular and cellular targets, whereas biomarkers are used as diagnostic tools. Biomarkers such as skin testing, tryptase, and basophil activation test provide the signature for the different endotypes. As more mechanisms of drug allergy are uncovered and new biomarkers become available, they can be incorporated into this flexible classification, guiding clinicians toward an optimal approach for patient labeling or delabeling, treatment, and management.

What is the evidence for, and how can recommendations be made for labeling and delabeling? Are there models for these recommendations? Shaker et al,[13] on behalf of the Joint Task Force for Allergy Practice Parameters (JTFPP), provided a review of the recommendations for anaphylaxis treatment. The authors introduced Grading of Recommendations Assessment, Development, and Evaluation (GRADE), a new method of evidence appraisal and translation, which has emerged as a leading approach to anaphylaxis guidelines development. GRADE creates explicit processes for evaluating the broad evidence based on a specific, structured, and answerable clinical question. Randomized controlled trials begin the evaluation process as high certainty, whereas observational studies begin as low certainty. Evidence may be downgraded depending on the following considerations: (1) the risk of bias, (2) imprecision, (3) inconsistency, (4) indirectness, and (5) publication bias. Through this methodology, evidence and certainty are clearly and simply described as “very low,” “low,” “moderate,” or “high.” The JTFPP has been producing GRADE guidelines since 2017, and the 2020 JTFPP anaphylaxis GRADE is focused on the practice of anaphylaxis prevention through identification and mitigation of risk factors for biphasic anaphylaxis and evaluation of the use of supplemental glucocorticoid and/or antihistamine premedication for immunotherapy, radiocontrast media and chemotherapy. In contrast to GRADE, Good Practice Statements include the administration of epinephrine as first-line treatment for uniphasic and/or biphasic anaphylaxis. A good practice statement may be used when there is a high certainty that a recommendation will be more beneficial than harmful, though there is little direct evidence. GRADE is prescriptive, explicit, and transparent and requires expert judgment and consensus of guideline groups as evidence is evaluated and translated into recommendations.

What is the practical approach to drug allergy labeling and delabeling? Louisias and Wickner[14] provided a review on the playground and available tools for drug allergy delabeling. The authors indicated that large-scale drug allergy delabeling is influenced by multiple factors, such as changing cultural moors, easily adapted tools to delabel, and electronic health record (EHR) crosstalk. Current functionalities of EHRs’ drug allergy sections are often at odds with providing reliable, updated, expert, safe, and affordable care. They reported that up to 35% of patients had at least 1 drug allergy listed in their EHR, and many had up to 20; nobody removed duplicates or delabel drugs with nonallergic symptoms. The authors indicated the need to uncover the integral components of drug allergy delabeling programs that can be tailored and disseminated, incentivized by insurance companies and hospitals, and standardized nationally. One study estimated penicillin allergy delabeling programs could have cost savings of $192,223 per year in tertiary care center pediatric emergency departments, thus underscoring the economic incentives of delabeling.

Allergists need to challenge every drug allergy label and to recognize drug allergy and hypersensitivity symptoms using the new framework of phenotypes and endotypes supported by biomarkers. Providing risk stratification is key to safe delabeling procedures and to help provide management options including desensitization to patients who are truly allergic. Minimizing inappropriate use, recording accurate intolerances, delabeling whenever possible, and adhering to essential elements of effective stewardship will solve the antibiotic allergy epidemic.

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