Special Article

The 3 Cs of Antibiotic Allergy—Classification, Cross-Reactivity, and Collaboration

Jason A. Trubiano, MD[a,b,c], Cosby A. Stone, MD[d], M. Lindsay Grayson, MD[a,e], Karen Urbancic, BPharm[a,e,f], Monica A. Slavin, MD[b,c], Karin A. Thursky, MD[b,c,g], and Elizabeth J. Phillips, MD[d,h,i,j] *Heidelberg and Melbourne, Victoria, Australia; Murdoch, Western Australia, Australia; and Nashville, Tenn*

Antibiotic allergy labeling is highly prevalent and negatively impacts patient outcomes and antibiotic appropriateness. Reducing the prevalence and burden of antibiotic allergies requires the engagement of key stakeholders such as allergists, immunologists, pharmacists, and infectious diseases physicians. To help address this burden of antibiotic allergy overlabeling, we review 3 key antibiotic allergy domains: (1) antibiotic allergy classification, (2) antibiotic cross-reactivity, and (3) multidisciplinary collaboration. We review the available evidence and research gaps of currently used adverse drug reaction classification systems, antibiotic allergy cross-reactivity, and current and future models of antibiotic allergy care. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: *Antibiotic allergy; Antimicrobial allergy; Cross-reactivity; Prevalence; Penicillin allergy; Cephalosporin allergy*

Approximately 10% of populations engaged in medical care are labeled as penicillin allergic,[1] so that addressing antibiotic hypersensitivity and adverse drug reactions (ADRs) has emerged as a significant public health issue.[2-6] Reducing the prevalence and burden of antibiotic allergies requires the engagement of key stakeholders such as allergists, immunologists, pharmacists, and infectious diseases physicians.[3,7-9]

Antibiotic allergies are often poorly documented across electronic medical platforms[10] and associated with inferior microbiological outcomes (eg, vancomycin vs semisynthetic penicillin for invasive methicillin-sensitive *Staphylococcus aureus* infections),[11,12] adverse events (eg, ceftriaxone or clindamycin and *Clostridium difficile*),[13,14] and microbiological resistance.[4] Antibiotic allergy is also associated with increased readmissions, restricted antibiotic use, and excess mortality.[3,4,15] A better measure of the impact of patient-reported antibiotic allergy (so-called antibiotic allergy labels [AALs]) on prescribing is an assessment of antibiotic appropriateness, recent evidence demonstrating such a negative association.[16-18] Li et al[19] also demonstrated that a penicillin allergy was associated with a 1.82- to 2.58-fold increase in total antibiotic costs.

Improving the accuracy of antibiotic allergy reporting in combination with aggressive multidisciplinary "delabeling" approaches is required to reduce the impact of AALs. We assembled a group of allergist/immunologists, infectious diseases physicians, antimicrobial stewardship physicians, and pharmacists to review the 3 key antibiotic allergy domains that are central to effect change in antibiotic allergy overlabeling: (1) antibiotic allergy classification, (2) antibiotic allergy cross-reactivity, and (3) multidisciplinary allergy collaboration.

METHODS

A search of PubMed and MEDLINE was undertaken to examine the literature around antibiotic allergy classification, cross-reactivity, testing, and management (1948-2017). The search terms used were as follows: ["antibiotic allergy" OR "antibiotic hypersensitivity" OR "penicillin allergy" OR "antibiotic adverse drug reaction"] AND ["cross-reactivity" OR "side chain" OR "de-labelling" OR "pharmacists" OR "antimicrobial stewardship" OR "infectious diseases" OR "allergists" OR "classification" OR "testing"]. Only human studies in English were included. We identified 1194 articles whose content was reviewed for inclusion in this article.

[a]Department of Infectious Diseases, Austin Health, Heidelberg, Victoria, Australia
[b]Department of Infectious Diseases, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia
[c]Centre for Improving Cancer Outcomes through Enhanced Infection Services, National Health and Medical Research Council Centre of Research Excellence, The Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Victoria, Australia
[d]Division of Allergy, Pulmonary and Critical Care Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tenn
[e]Department of Medicine, University of Melbourne, Parkville, Victoria, Australia
[f]Department of Pharmacy, Austin Health, Melbourne, Victoria, Australia
[g]National Centre for Antimicrobial Stewardship, Royal Melbourne Hospital, Parkville, Victoria, Australia
[h]Institute for Immunology & Infectious Diseases, Murdoch University, Murdoch, WA, Australia
[i]Department of Medicine, Pathology, Microbiology, Immunology, Vanderbilt University Medical Center, Nashville, Tenn
[j]Department of Pharmacology, Vanderbilt University Medical School, Nashville, Tenn

J.A.T. is supported by a National Health and Medical Research Council (NHMRC) postgraduate research scholarship. E.J.P. is funded through the National Institutes of Health (NIH)/National Institute of Allergy and Infectious Diseases (grant nos. A1103348 and 1P30AI110527-01A1), NIH/National Institute of General Medical Sciences (grant no. 1P50GM115305-01), and the NHMRC of Australia.

Conflicts of interest: C. A. Stone has received research support from the National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute (grant no. T32 HL87738). K. Urbancic received research support from and was on the advisory board for Merck Sharp Dohme (Australia). M. A. Slavin has received research support from Merck and Gilead Sciences and has received lecture fees from Merck. E. J. Phillips has received research support from the National Health and Medical Research Council (NHMRC) Australia, the NIH, and ACH2 Australia; has received royalties from UpToDate; is codirector of the company that holds a patent for HLA-B*57:01 testing for abacavir HSR (hypersensitivity reaction); and has received consultancy fees from Aicuris. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication April 29, 2017; revised June 8, 2017; accepted for publication June 16, 2017.

Available online ■■

Corresponding author: Jason A. Trubiano, MD, Infectious Diseases Physician, Austin Health, Heidelberg, VIC 3084, Australia. E-mail: Jason.trubiano@austin.org.au.

2213-2198

© 2017 American Academy of Allergy, Asthma & Immunology

http://dx.doi.org/10.1016/j.jaip.2017.06.017

Classification: Antibiotic allergy and ADRs

ADRs are typically described as type A (pharmacologically predictable, dose-dependent, non−immune-mediated, and less influenced by genetic factors) and type B (pharmacologically unpredictable, non−dose-dependent, and often immune-mediated) reactions.[20] Immunologically mediated or drug hypersensitivity reactions were historically classified mechanistically by Gell and Coombs[21] (types I-IV) and later by Pichler[22] who refined type IV (T-cell−mediated) reactions (Table I).[22-27]

An improved understanding of the pathogenesis and pharmacogenomics of ADRs demands a shift in classification (Figure 1).[28-30] Many ADRs may be predicted as the result of "on-target" pharmacological effects of drugs (type A),[31-33] where "on-target" is defined as being related to the primary, intended pharmacologic mechanism of action of the drug. Individual variations in drug metabolism (ie, genetic polymorphisms in drug metabolism and transporters) occur and may be important drivers of both the enhancement of the pharmacological effect (ADR occurrence) and on-target interactions with other drugs.[30]

Contrary to previous beliefs, it is evident that some type B reactions are dose-dependent and immune-mediated through their "off-target" effects, where "off-target" is defined as being caused by mechanisms of action other than the intended primary pharmacologic mechanism of action of the drug. Because of the increasing recognition of the off-target effects of drug, these types of ADRs are increasingly being recognized as relevant to clinical practice. Dose-independent IgE- mediated immune reactions by which extremely small amounts of antigen are effectively amplified through an off-target IgE response represent the minority of ADRs. T-cell−mediated drug reactions produce long-lived immune responses that are both dose dependent and genetically mediated and an off-target mechanistic basis for this through their noncovalent interactions with immune receptors has now been defined.[34-36] HLA risk alleles have now been defined for the severest of T-cell−mediated reactions such as abacavir hypersensitivity (HLA-B*57:01) and carbamazepine Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). This has established that many of these so-called unpredictable type B reactions can now be predicted and prevented through successful screening programs both as general guideline-based practice (abacavir and HLA-B*57:01) and more targeted in particular ethnic populations, including for therapies such as carbamazepine (HLA-B*15:02).[34,37-39] Other off-target adverse reactions can present with symptoms of flushing, hives, angioedema, and rash that are typically associated with IgE-mediated reactions but are differentiated by their dose dependency and lack of immunological memory. The molecular mechanism for a group of "nonallergic drug hypersensitivity/anaphylactoid" reactions was recently explored by McNeil et al,[23] who demonstrated that basic secretagogues and cationic small molecule drugs sharing a tetrahydroisoquinolone motif (eg, fluoroquinolones) can directly bind the mas-related family of G-coupled protein receptors present exclusively on mast cells, and unlike true IgE-mediated reactions, lead to non−IgE-mediated dose-dependent mast cell activation.[23,40,41] Also, unlike true IgE-mediated reactions, these reactions can be medically managed with antihistamine pretreatment/cotreatment, or alteration of the mode of administration (slow infusion), and do not preclude use of the agent. These concepts centered on clinical phenotyping are essential to the correct reconciliation of allergies in electronic medical records (EMRs), enabling decision support for prescribing to be based on an accurate initial assessment. Improvements in the algorithms used to record allergies in the EMR and incorporating descriptive classifications are required.[42]

Key points.

A. Many antibiotic-associated ADRs are unlikely to be "true" allergies that preclude drug dosing. Furthermore, examples now exist of immunologically mediated reactions that can be predicted and prevented through genetic screening and exclusion of risk populations. Allergists, immunologists, and other clinicians need to ensure that mild "on-target" reactions (eg, side effects) and "off-target" reactions (non−IgE-mediated mast cell activation) do not lead to persisting AALs that impact antibiotic utilization.
B. An increasing understanding of the molecular mechanisms of "on-target" and "off-target" reactions, and their relevant pharmacogenomic associations and mechanisms, should be reflected in the retaxonomization of ADRs and will lead to identification of more targeted therapeutics.

Cross-reactivity and Cross-checking: The importance of side chains

Side chains. An understanding of antibiotic cross-reactivity, especially between beta-lactams, is essential (Figure 2). Cross-reactivity between penicillins and cephalosporins can in part be predicted on the presence of shared R1, and to lesser degree R2 side chains (Figure 3). Recent work by Romano et al[48] demonstrated that patients with cephalosporin allergy commonly tolerated a different cephalosporin of varied R1/R2 side chain. A recent survey of allergists, immunologists, pharmacists, and infectious diseases physicians in Australia identified significant knowledge gaps regarding antibiotic cross-reactivity and absence of skin testing diagnostics to confirm,[49] echoed in surveys from the United States and the United Kingdom.[50-52] The older literature also suggests erroneously high rates of cross-reactivity between penicillins and cephalosporins (10%-25%).[53,54] Many of the early reports of cross-reactivity of up to 18%[55-57] are likely to reflect penicillin contamination of cephalosporin manufacturing, cross-reactivity rates based on nonconsecutive case reports, and the fact that aminopenicillins and aminocephalosporins share a common R1 side chain.[58] In fact, cross-reactivity between carbapenems and penicillins or cephalosporins is as low as 1% or less and 0% with monobactams.[48,59-63] Although most of these reports of cross-reactivity are linked with immediate hypersensitivity, similar low rates of cross-reactivity have also been seen in observational studies of nonimmediate hypersensitivity, some of which have also suggested side-chain cross-reactivity.[59,64-67]

Key points.

A. In a patient with confirmed penicillin allergy (skin test positive to one of penicillin G, major penicillin determinant, or minor penicillin determinant), other penicillins should be avoided.
B. Third-generation cephalosporins can be used in patients with a history of nonimmediate or non−life-threatening allergy to penicillin.
C. Carbapenems can be used in patients with a history of immediate penicillin allergy. Because of the 1% or less rate of cross-reactivity, in cases of previous life-threatening allergy to penicillin, a risk/benefit assessment must be undertaken.
D. Monobactams can be used in patients with any history of penicillin allergy.
E. Both immediate and nonimmediate reactions appear to be commonly associated with the side-chain structures of the drugs. In the case of immediate reactions, selective delabeling strategies appear possible. In the case of severe T-cell−mediated delayed reactions such as drug reaction with eosinophilia and systemic

Download English Version:

https://daneshyari.com/en/article/8714639

Download Persian Version:

https://daneshyari.com/article/8714639

Daneshyari.com