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

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

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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

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TABLE I. Classification of target antibiotic allergy and recommended testing

ADR Type*	Immunological mechanism	Timing	Clinical	Commonly involved antibiotics	Testing†
Gell Coombs class I type B ADR	IgE mediated	Immediate or accelerated (30 min to 1 h and less commonly 6-48 h)	Pruritis/urticaria Angioedema/ laryngeal edema Bronchospasm Anaphylaxis	Beta-lactams Sulfa antimicrobials Macrolides Fluoroquinolones	RAST/ImmunoCAP IgE‡ SPT IDT Drug provocation§
Gell Coombs class II type B ADR	Cytotoxic IgG mediated	Accelerated or nonimmediate (5->72 h)	Hemolytic anemia Thrombocytopenia	Sulfa antimicrobials Rifampin Dapsone Beta-lactams Vancomycin	G6PD (for deficiency) Drug-specific antiplatelet antibodies
Gell Coombs class III type B ADR	Immune complex IgG mediated	Accelerated or nonimmediate (3->72 h)	Serum sickness	Beta-lactams Sulfa antimicrobials Minocycline	None
Gell Coombs class IV type B ADR	T-cell−mediated IVa: Macrophage IVb: Eosinophils IVc: T cells IVd: Neutrophils	Nonimmediate (24->72 h)§	Contact dermatitis, SCAR (DRESS/ DIHS/HSS/SJS/ TEN, AGEP), DILI, AIN, FDE Nonspecific (maculopapular) exanthem	Beta-lactams Sulfa antimicrobials Fluoroquinolones Tetracyclines Macrolides Antiretrovirals (abacavir, nevirapine, and other NNRTIs) Dapsone Vancomycin Antituberculous drugs Telaprevir (hepatitis C)	LTT/ELISpot/ICS‡ PT Delayed IDT Drug provocation Pre-prescription HLA screening‖
Nonallergic drug hypersensitivity reactions					
G-protein−coupled receptor-mediated mast cell activation	Mast cell degranulation via receptor MRGPRX2	Immediate or accelerated (30 m to 1 h and less commonly 6-48 h)	Pruritis/urticaria Angioedema/ laryngeal edema Bronchospasm Anaphylaxis (dose dependent)	Fluoroquinolones	No direct testing but patients may tolerate low-dose oral challenge (differentiates from IgE mediated). Also, reactions are responsive to antihistamines or slower infusion
Non-G-protein−coupled receptor mast cell activation	Unknown receptor Non−IgE-mediated mast cell degranulation	Immediate or accelerated (30 m to 1 h and less commonly 6-48 h)	Pruritis/urticaria Angioedema/ laryngeal edema Bronchospasm (dose dependent)	Vancomycin Polymyxin B Miconazole Minocycline	None

AGEP, Acute generalized exanthematous pustulosis; *AIN*, acute interstitial nephritis; *BAT*, basophil activation testing; *DIHS*, drug-induced hypersensitivity syndrome; *DILI*, drug-induced liver injury; *DRESS*, drug reaction with eosinophilia and systemic symptoms; *ELISpot*, enzyme-linked immunospot; *FDE*, fixed drug eruption; *HSS*, hypersensitivity syndrome; *LTT*, lymphocyte transformation test; *NNRTI*, non-nucleotide reverse transcriptase inhibitor.

Adapted from McNeil et al,[23] Trubiano and Phillips,[24] Gell and Coombs,[25] Pichler,[22] Rive et al,[26] and Lagace-Wiens and Rubinstein.[27]

*Type B ADRs—immunologically mediated allergies, further subclassified into classes I to IV on the basis of updated Gell and Coombs classification[22,25] and newer classification of G-protein−coupled receptor-mediated mast cell activation.[23] Type A ADRs—common and predictable drug reactions that are dose dependent and based on pharmacological properties.

†Combination *in vivo* testing recommended; SPT/IDT and oral provocation are considered criterion standard.

‡RAST/ImmunoCAP IgE screening only (specific not sensitive) and not available in all countries. The negative predictive value of RAST/ImmunoCap IgE is poor and it should not be used in isolation as the basis for rechallenge in patients with a history suggestive of an IgE-mediated reaction. LTT and ELISpot not recommended for IgE- mediated drug allergy testing but can be used for type IV−mediated reactions.

§Can occur from 1 to 2 d (in the presence of previous exposure) to 8 wk following drug. Otherwise, with first exposure, onset is usually from day 5 to 7. May be a more rapid/ severe on second exposure.[26]

||HLA associations have been described for antimicrobials; however, currently screening is only routine for abacavir with HLA-B*57:01.

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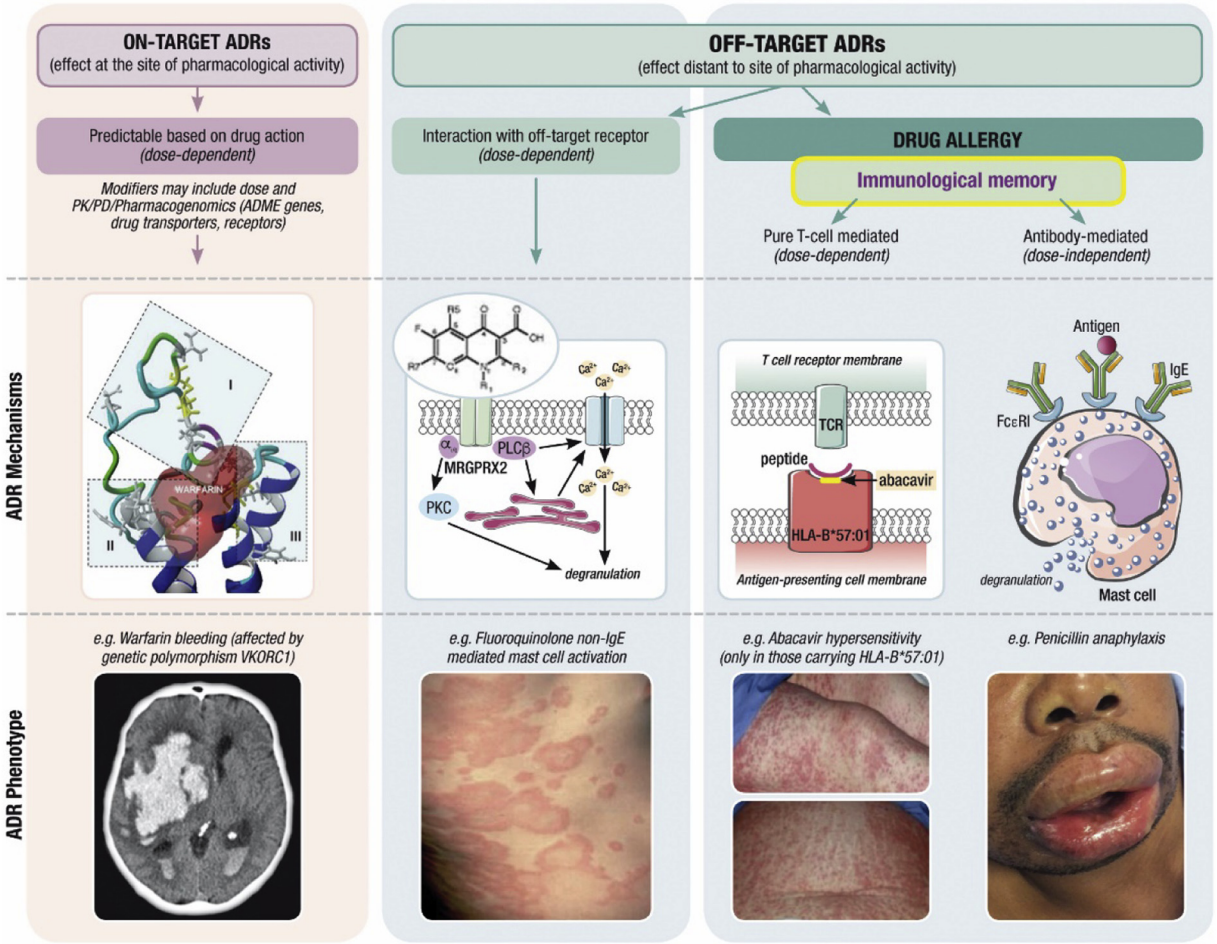

FIGURE 1. Reclassification of ADRs. *PD*, Pharmacodynamics; *PK*, pharmacokinetics. Adapted from Peter et al,[28] White et al,[29] and Phillips.[30]

symptoms (DRESS) or SJS/TEN, to date antibiotic class avoidance has been the preferred management.

Immediate (IgE) allergy skin testing. Penicillin skin prick testing (SPT) and intradermal testing (IDT) in combination with a single or graded oral challenge can successfully remove the label of penicillin allergy in more than 90% of those tested.[68,69] Often the accessibility to such testing and reagents has been the rate-limiting steps. The negative predictive value of penicillin skin testing with major (benzylpenicilloyl-poly-L-lysine) and minor (benzylpenicillin, sodium benzylpenilloic acid, benzylpenicilloic acid) determinants is reported to be 97% to 98%.[70,71] Although some centers use SPT only, the modern practice is to include IDT and oral provocation to improve sensitivity for immediate hypersensitivities.[52,72,73] There does remain a lack of consistency across skin testing practices, recently demonstrated in a survey of European allergy service providers.[52] Adverse reactions following SPT/IDT, although often feared, are infrequently reported, and are potentially the result of incorrect drug volume or concentration.[74-77] The concept of resensitization following a negative SPT/IDT and oral provocation to antibiotics, although often feared, is a rare event; hence, retesting before each treatment is not recommended.[78,79]

Despite the haptens for other penicillins and beta-lactams being relatively unknown, the parental form is commonly used for *in vivo* skin testing practices.[24,60,67,80-92] Consensus regarding administered concentrations also remains elusive.[93-95] The negative predictive value of cephalosporin SPT/IDT is also less than that seen with penicillin testing (sensitivity, 30%-86%)[46,47,80,96] and may be lost over time (68% positive at 1 year).[97] Romano et al[48] demonstrated that patients with cephalosporin allergy can frequently tolerate alterative cephalosporins with different R1 side chains.

Delayed (T-cell) allergy skin testing. Antibiotics, especially beta-lactams, sulfa antimicrobials, and glycopeptides, are common causes of severe cutaneous adverse reactions (SCARs).[98] A long-held belief is that skin testing should not be performed in patients with nonimmediate (T-cell—mediated) hypersensitivity due to the risk of reactivation and lack of reliable information. Although IDT may be associated with an increased risk of systemic events,[99,100] patch testing (PT) in SCARs is considered safe.[101-104] Guidelines suggest that IDT can be performed only after a negative PT and at least 6 weeks after skin healing.[105]

Performed with the highest nonirritating concentrations of drug, both PT and delayed IDT are highly specific and can be helpful in some cases for elucidating causes of nonimmediate hypersensitivity; the utility, however, varies between studied regions (eg, North America vs Europe).[106-109] It is important to note that the sensitivity of testing methods varies for the approach, the underlying clinical phenotype, and the implicated drug. PT sensitivity varies, highest for

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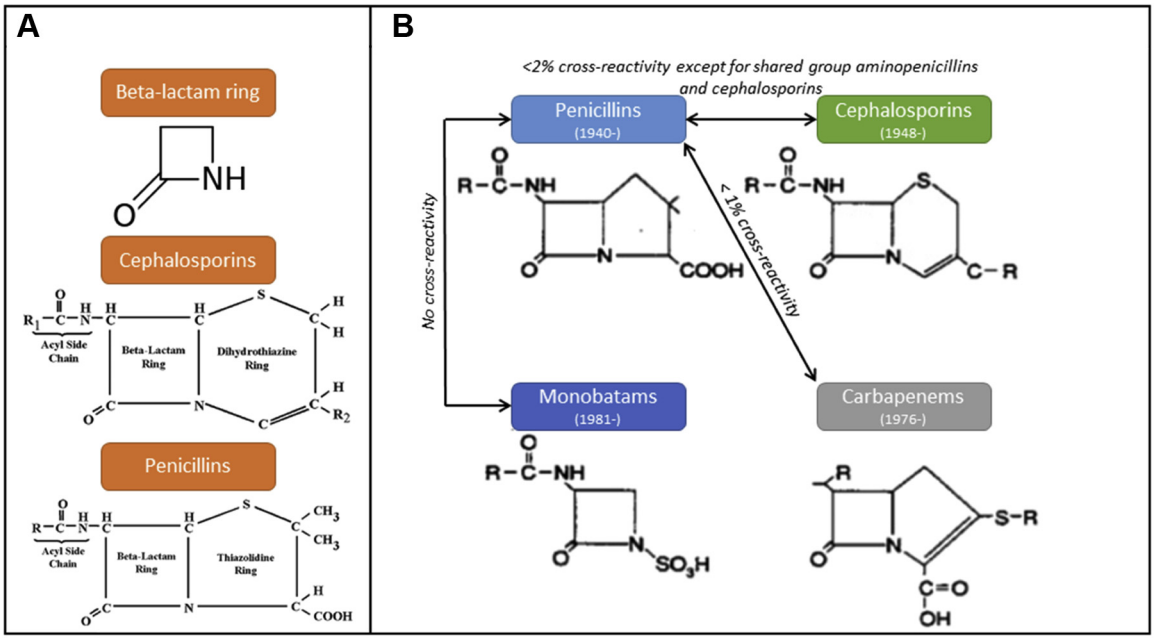

FIGURE 2. Beta-lactam structure and cross-reactivity. **A**, Basic beta-lactam structures. Beta-lactams are classified as "penicillin" if they have a beta-lactam ring fused to a thiazolidine ring. A dihydrothiazine ring in cephalosporins replaces this thiazolidine ring. Monobactams and carbapenems have an alternative adjacent ring structure, a monocyclic ring and a 5-membered ring, respectively. In patients who have a penicillin allergy, it is possible to remain sensitized to other "penicillins," including aminopenicillins (amoxicillin, ampicillin) and anti-staphylococcal penicillins (flucloxacillin, oxacillin, dicloxacillin, methicillin, piperacillin-tazobactam, ticarcillin-clavulante), via the thiazolidine ring ("penicillin ring"), rather than the beta-lactam ring. **B**, Beta-lactam structures and cross-reactivity. Isolated allergy to single penicillin (eg, amoxicillin) is also possible if a side chain is involved (eg, "R" side chain). The true rates of overall penicillin-cephalosporin cross-reactivity are dependent on the generation of cephalosporin: less than 5% with first-generation cephalosporins, 2% to 5% with second-generation cephalosporins, and less than 1% with third-generation cephalosporins.[43,44] If cross-reactivity does persist, it is most likely the result of shared "R" side chains (Figure 3).[45,46] Cross-reactivity between penicillins and cephalosporins with the same R1 side chain such as aminopenicillins and aminocephalsoporins is reported as 14% to 38%.[43,45,46] Some cephalosporins such as cefazolin do not share R1 or R2 groups with any other beta-lactam. Cross-reactivity between cephalosporins is usually based on the shared side chain structures (typically the R1 group) and not the shared cephalosporin dihydrothiazine ring (36%-48%).[46,47]

DRESS (32%-80%)[104,110] and acute generalized exanthematous pustulosis (58%-64%)[104,111] and lowest for SJS/TEN (9%-24%)[104,111] and maculopapular exanthem (10%-40%).[101,110] The sensitivity is also dependent on the implicated antibiotic, lowest with sulfa antimicrobials and fluoroquinolones and highest with abacavir, beta-lactams, and pristinamycin.[101,112,113] Along with causality assessment this type of testing is most useful when multiple drugs (antibiotics and nonantibiotics) were implicated at the same time. The importance of identification and correct labeling in patients with SCARs is highlighted by Finkelstein et al[114] who demonstrated that 42% of patients with SCARs were hospitalized with a subsequent episode of SJS or TEN. *Ex vivo* diagnostics, such as T-cell enzyme-linked immunospot[115-122] and lymphocyte transformation testing,[100,123-126] and flow assays may improve the sensitivity and specificity of current testing and provide additional insights into immunopathogenesis. In some cases of appropriately selected phenotypes (maculopapular exanthem) and implicated antibiotics (penicillin or aminopenicillin), direct oral challenge without skin testing has been safely used to exclude nonimmediate hypersensitivity.[127,128] Previous studies have previously demonstrated that childhood antibiotic-associated exanthems or nonimmediate hypersensitivities were difficult to reproduce on oral challenge.[102] The "pickup" of nonimmediate hypersensitivity has been improved when a prolonged oral challenge (5-7 days) has been used.[129]

Key points.

A. SPT/IDT combined with single-dose oral challenge is a validated testing strategy to exclude immediate IgE-mediated penicillin allergy and should be used.
B. SPT/IDT can also be applied for antibiotics outside penicillin including cephalosporins and other beta-lactams; however, skin testing to these agents has a significantly lower negative predictive value and for appropriate labeling should always be followed by single-step or multistep ingestion challenge.
C. Resensitization is rare (<1%) following routine use of oral antimicrobials and therefore retesting following negative skin testing and oral provocation is not recommended.
D. Delayed intradermal skin testing and/or PT has utility in selective phenotypes of T-cell–mediated ADRs (DRESS/acute generalized exanthematous pustulosis >> SJS/TEN) and if positive these are helpful. However, the negative predictive value of these tests still falls significantly short of 100% and clinical history remains the criterion standard. The use of delayed intradermal testing may vary on the basis of regional preferences and practices.
E. Currently *ex vivo* cellular studies (ie, enzyme-linked immunospot assay) appear promising but have not been validated in large-scale studies and they remain as research tools.

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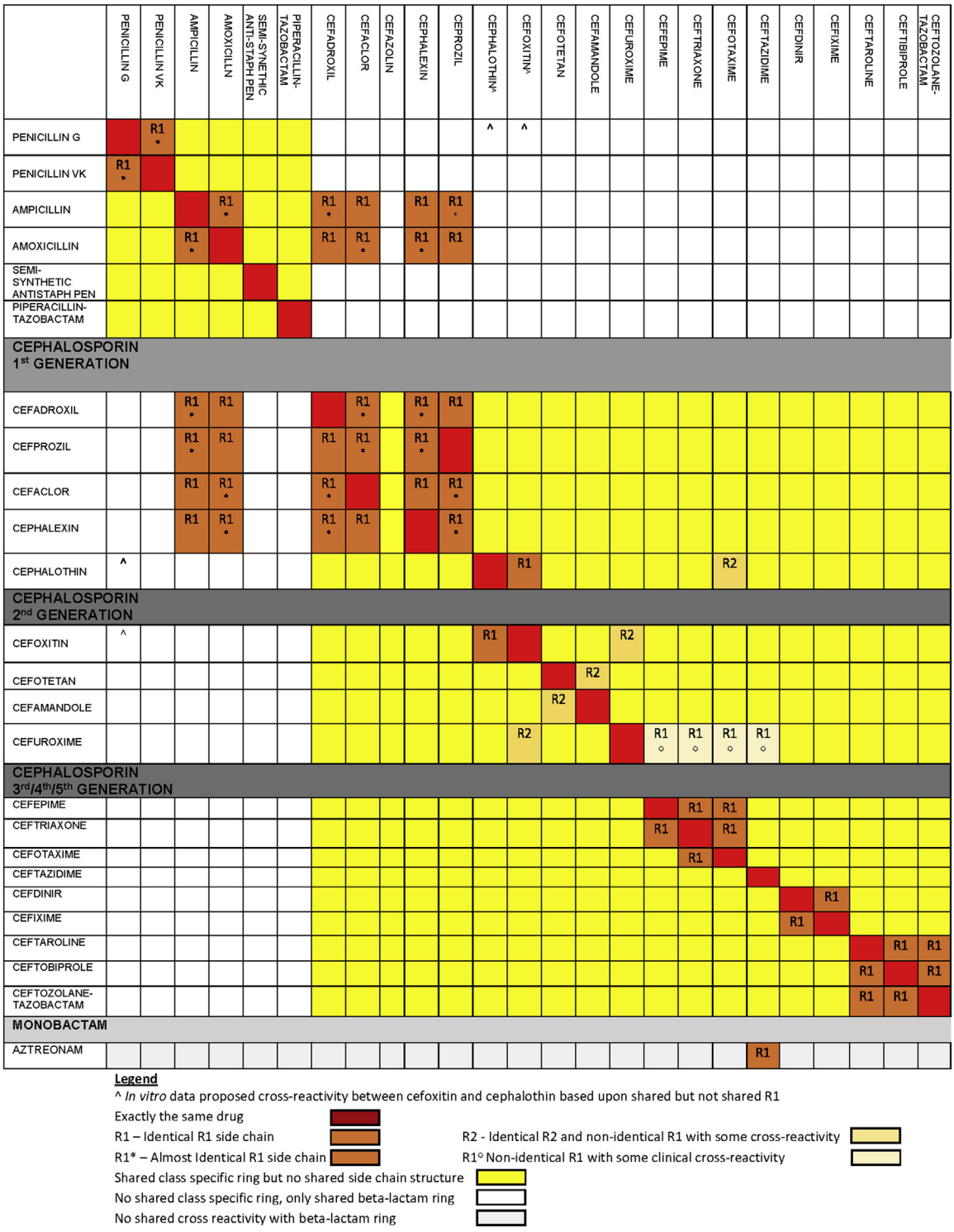

FIGURE 3. Common penicillins, aminopenicillins, and cephalosporins that share an identical or similar R_1- and R_2-group side chains. *Note*: Aminopenicillin/aminocephalosporin cross-reactivity: cefaclor, cefadroxil, and cephalexin share an identical R1 group with ampicillin; cefadroxil shares an identical R 1 group with amoxicillin.

Collaboration—New pathways and partnerships

Antibiotic allergy knowledge and the EMR. Assessments of antibiotic allergy knowledge among immunologists, allergists, general practitioners, and infectious diseases physicians have demonstrated deficiencies in drug allergy knowledge.[42,130-134] Education programs aimed at hospital providers can increase knowledge of penicillin skin testing and preparedness to investigate allergy histories.[132] Sastre et al[5] demonstrated that 40% of physicians do not verify the AAL during a

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hospital admission. Fehily et al[131] identified that only 38% of hospital doctors were aware of their patients' penicillin ADR history. "Delabeling" patients via any of these means is only half the battle, because both clinicians and patients often revert to the pretest labels postassessment.[72,135,136] Although penicillin allergy may be recorded in 8% of inpatients or more, a description in the EMR is often missing (36%).[42] Updating EMRs and ensuring correct AALs are reinforced or removed posttesting are also essential to effect change,[42] yet studies evaluating the impact of the EMRs on antibiotic allergy are missing.

Antibiotic allergy testing outside the outpatient clinic. Patient AALs often drive inappropriate antibiotic use in the operative setting.[134] Trautmann et al[137] demonstrated that allergy testing could successfully aid drug causality assessment and safe antimicrobial prescribing in subsequent anesthesia. However, the impact of such a program on reducing restricted antibiotics in the operating theater has yet to be explored. Inpatient penicillin skin testing has been used to improve appropriate antibiotic use.[138] A pilot prospective study and retrospective review of inpatient testing, predominately of patients with remote penicillin allergy, demonstrated cost savings and reduction in non−beta-lactam use with the implementation of inpatient penicillin skin testing.[139-141] In a small retrospective case series of infective endocarditis, inpatient skin testing allowed the implementation of the preferred beta-lactam therapy in 15 of 16 patients.[142] The use in acute care and intensive care settings, where the highest numbers of antibiotics are used, has not been extensively studied. The potential for a false-negative result in acutely unwell patients has limited this application to date.[143,144] The safe use of penicillin skin testing in the emergency department setting was demonstrated by Raja et al.[145] Antibiotic allergy rechallenge protocols, examined in before/after studies, can increase simple beta-lactam uptake, reduce glycopeptide usage, and improve patient outcomes.[132,146,147]

Antibiotic allergy and antimicrobial stewardship. The Infectious Diseases Society of America Antimicrobial Stewardship (AMS) Guidelines raise awareness of the need for further study of antimicrobial allergy testing and its incorporation into stewardship programs.[148] Further reports have called for the incorporation of antibiotic allergy services into antibiotic stewardship programs.[24,149,150] Small pilot studies have demonstrated that pharmacy-led referral systems, antibiotic allergy stewardship rounds, and direct oral provocation programs can safely increase simple beta-lactam use and reduce restricted antibiotic usage and hospital costs.[14,72,132,140,151-157] Recent published experiences with inpatient allergy testing, either pharmacist, allergist, or infectious diseases led, have also demonstrated improved uptake of preferred beta-lactam therapies.[139,158-160] Targeted AMS programs have demonstrated a reduction in restricted antibiotic usage, with such an intervention.[157,161,162] A limitation of these studies has been a focus on aztreonam use, without an examination of other restricted antimicrobials, such as carbapenems and fluoroquinolones. Pharmacist engagement is potentially underused, as Wall et al[163] demonstrated that a pharmacist-led allergy testing service was well received by physicians and reduced unnecessary antibiotic usage. Incorporation of decision support software into AMS regarding antibiotic choice in patients with beta-lactam allergy was shown to reduce unnecessary antipseudomonal penicillin and increased third-generation cephalosporin use.[164] Addressing the allocation of resources is an important step in the collaborative approach, determining who would most benefit from testing on the basis of antibiotic need(s), rather than simply allergy history (eg, preference for an immunocompromised patient with multiple infective complications over an otherwise well patient with multiple drug hypersensitivities). Developing targeted testing via an integrated AMS model is likely to lead to improved patient outcomes (eg, utilization of beta-lactam therapies in invasive staphylococcal infections) in addition to preventing *C difficile* and antimicrobial resistance generation.[4]

Key points.

A. Antibiotic allergy testing, if made readily available to physicians, may aid "delabeling" initiatives and improve antibiotic usage. The impact of a multidisciplinary antibiotic allergy delabeling model that engages the entire health care team and involves the expertise of allergists/immunologists, pharmacists, infectious diseases physicians, and AMS teams on long-term antibiotic prescribing, antibiotic appropriateness, and patient AALs is yet to be fully evaluated.
B. The impact of EMR systems on antibiotic allergy labeling has currently been underinvestigated.

CONCLUSIONS

The high prevalence of antibiotic allergies coupled with the potential adverse downstream effects on antibiotic appropriateness, antibiotic resistance, heightened risk of *Clostridium difficile* infection, and other adverse drug effects has brought the problem of antibiotic allergy overlabeling into the spotlight. Addressing key areas of accurate allergy labeling, diagnosis, and novel management strategies remains key to reducing the burden. Correct labeling of an ADR, as a manageable side effect due to a pharmacologically predictable effect of the drug versus a severe potentially life-threatening immunological event is likely to help allergy label phenotyping in terms of defining those who could be exposed to the drug in the future with a specific management versus those who should permanently avoid the drug. A greater understanding of side-chain cross-reactivity is likely to lead to more appropriate antibiotic selection and aid medication safety. Broadening the evidence base of antibiotic delabeling strategies that include combinations of skin testing and/or ingestion challenge and incorporation into infectious diseases programs, such as AMS, is also a potential avenue to reducing the impact of AALs on antibiotic prescribing.

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