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;5:1532-42)**

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 August 23, 2017.

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

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.

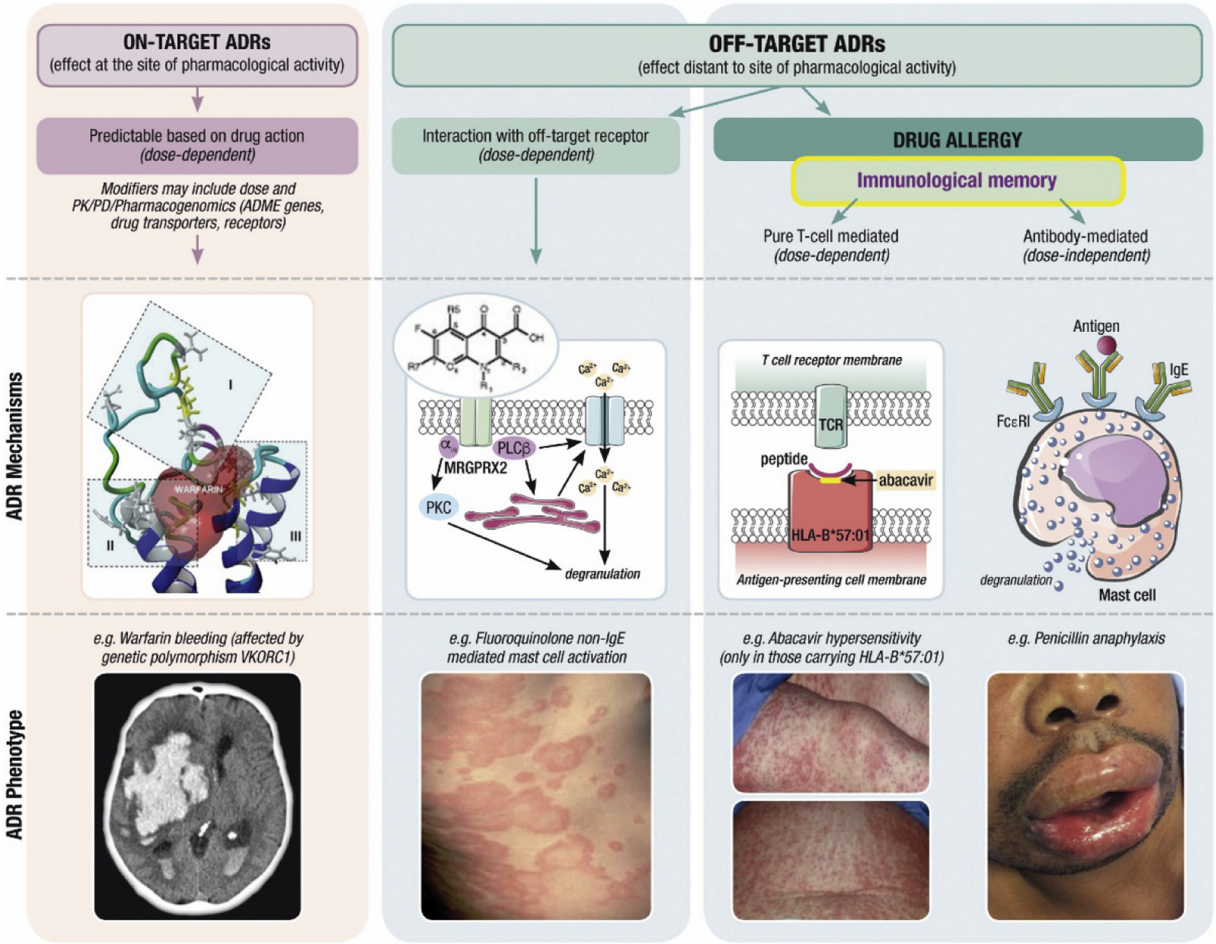

FIGURE 1. Reclassification of ADRs. *PD*, Pharmacodynamics; *PK*, pharmacokinetics. Adapted from Peter et al,[28] White et al,[29] and Phillips.[30]

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

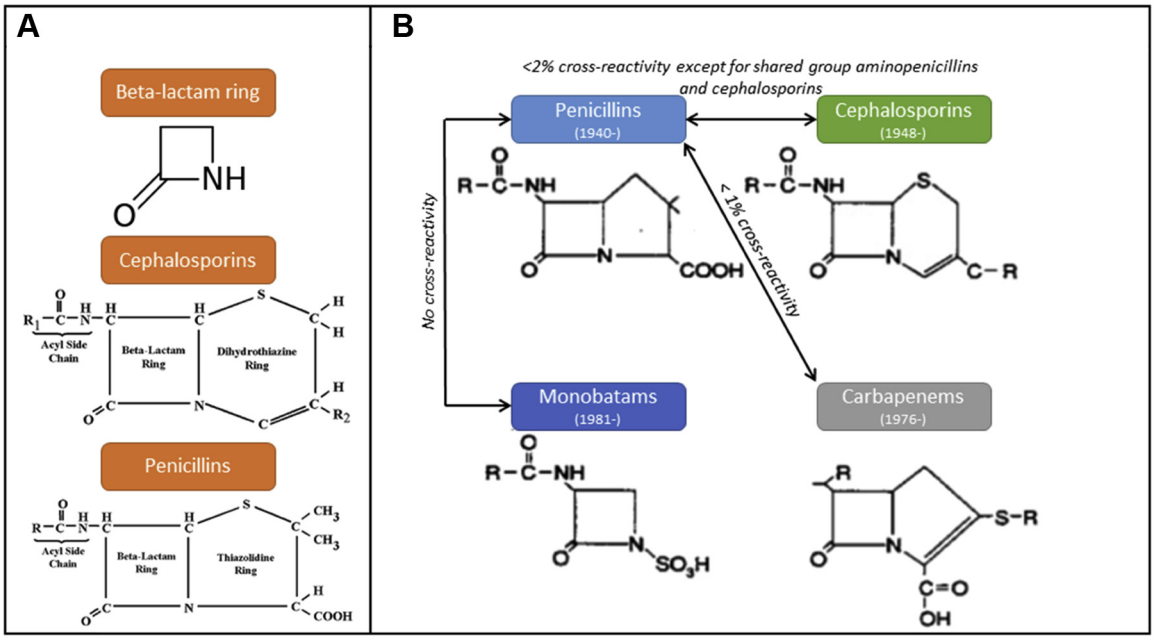

FIGURE 2. Beta-lactam structure and cross-reactivity. **A**, Basic beta-lactam structures. Beta-lactams are classified as "penicillin" if they have a beta-lactam ring fused to a thiazolidine ring. A dihydrothiazine ring in cephalosporins replaces this thiazolidine ring. Monobactams and carbapenems have 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.

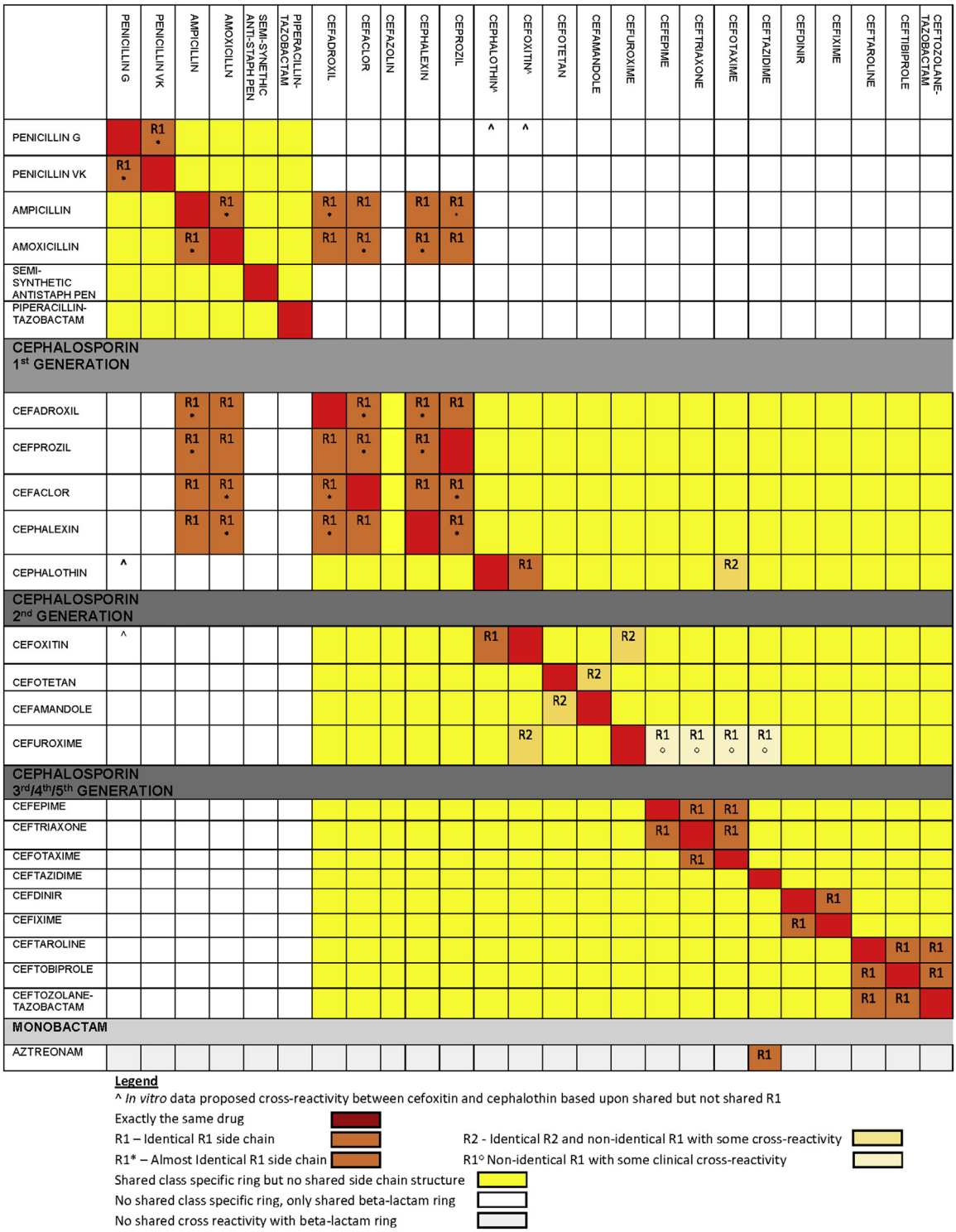

FIGURE 3. Common penicillins, aminopenicillins, and cephalosporins that share an identical or similar R_1- and R_2-group side chains. *Note*: Aminopenicillin/aminocephalosporin cross-reactivity: cefaclor, cefadroxil, and cephalexin share an identical R1 group with ampicillin; cefadroxil shares an identical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

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.

REFERENCES

1. Zhou L, Dhopeshwarkar N, Blumenthal KG, Goss F, Topaz M, Slight SP, et al. Drug allergies documented in electronic health records of a large healthcare system. Allergy 2016;71:1305-13.
2. Trubiano JA, Leung VK, Chu MY, Worth LJ, Slavin MA, Thursky KA. The impact of antimicrobial allergy labels on antimicrobial usage in cancer patients. Antimicrob Resist Infect Control 2015;4:23.
3. Charneski L, Deshpande G, Smith SW. Impact of an antimicrobial allergy label in the medical record on clinical outcomes in hospitalized patients. Pharmacotherapy 2011;31:742-7.
4. Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: a cohort study. J Allergy Clin Immunol 2014;133:790-6.
5. Sastre J, Manso L, Sanchez-Garcia S, Fernandez-Nieto M. Medical and economic impact of misdiagnosis of drug hypersensitivity in hospitalized patients. J Allergy Clin Immunol 2012;129:566-7.
6. Koliscak LP, Johnson JW, Beardsley JR, Miller DP, Williamson JC, Luther VP, et al. Optimizing empiric antibiotic therapy in patients with severe beta-lactam allergy. Antimicrob Agents Chemother 2013;57:5918-23.
7. Trubiano JA, Cairns KA, Evans JA, Ding A, Nguyen T, Dooley MJ, et al. The prevalence and impact of antimicrobial allergies and adverse drug reactions at an Australian tertiary centre. BMC Infect Dis 2015;15:572.
8. Lee CE, Zembower TR, Fotis MA, Postelnick MJ, Greenberger PA, Peterson LR, et al. The incidence of antimicrobial allergies in hospitalized

patients: implications regarding prescribing patterns and emerging bacterial resistance. Arch Intern Med 2000;160:2819-22.
9. Macy E, Poon KYT. Self-reported antibiotic allergy incidence and prevalence: age and sex effects. Am J Med 2009;122:778.e1-7.
10. Trubiano JA, Pai Mangalore R, Baey YW, Le D, Graudins LV, Charles PG, et al. Old but not forgotten: antibiotic allergies in general medicine (the AGM study). Med J Aust 2016;204:273.
11. Gonzalez C, Rubio M, Romero-Vivas J, Gonzalez M, Picazo JJ. Bacteremic pneumonia due to *Staphylococcus aureus*: a comparison of disease caused by methicillin-resistant and methicillin-susceptible organisms. Clin Infect Dis 1999;29:1171-7.
12. Turnidge JD, Kotsanas D, Munckhof W, Roberts S, Bennett CM, Nimmo GR, et al. *Staphylococcus aureus* bacteraemia: a major cause of mortality in Australia and New Zealand. Med J Aust 2009;191:368-73.
13. Thomas C, Stevenson M, Williamson DJ, Riley TV. *Clostridium difficile*-associated diarrhea: epidemiological data from Western Australia associated with a modified antibiotic policy. Clin Infect Dis 2002;35:1457-62.
14. Thornhill MH, Dayer MJ, Prendergast B, Baddour LM, Jones S, Lockhart PB. Incidence and nature of adverse reactions to antibiotics used as endocarditis prophylaxis. J Antimicrob Chemother 2015;70:2382-8.
15. van Dijk SM, Gardarsdottir H, Wassenberg MW, Oosterheert JJ, de Groot MC, Rockmann H. The high impact of penicillin allergy registration in hospitalized patients. J Allergy Clin Immunol Pract 2016;4:926-31.
16. Manzaneque A, Lopez-Cabezas C, Mensa M, Garcia-Moral A, Sanchez-Lopez J, Bartra J, et al. Potentially inappropriate prescription in patients with a history of allergy to beta-lactam antibiotics: a health care challenge. J Investig Allergol Clin Immunol 2016;26:55-6.
17. Trubiano JA, Chen C, Cheng AC, Grayson ML, Slavin MA, Thursky KA, et al. Antimicrobial allergy 'labels' drive inappropriate antimicrobial prescribing: lessons for stewardship. J Antimicrob Chemother 2016;71:1715-22.
18. Trubiano JA, Thursky KA, Stewardson AJ, Urbancic K, Worth LJ, Jackson C, et al. Impact of an integrated antibiotic allergy testing program on antimicrobial stewardship: a multicenter evaluation. Clin Infect Dis 2017;65:166-74.
19. Li M, Krishna MT, Razaq S, Pillay D. A real-time prospective evaluation of clinical pharmaco-economic impact of diagnostic label of 'penicillin allergy' in a UK teaching hospital. J Clin Pathol 2014;67:1088-92.
20. Rawlins MD, Thompson JW. Textbook of Adverse Drug Reactions. Oxford, United Kingdom: Oxford University Press; 1977.
21. Gell PG, Coombs RRA. Clinical aspects of immunology. 2nd ed. Oxford: Blackwell Scientific; 1963.
22. Pichler WJ. Drug Hypersensitivity. Basel, Switzerland: S Karger Pub; 2007:168-89.
23. McNeil BD, Pundir P, Meeker S, Han L, Undem BJ, Kulka M, et al. Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions. Nature 2015;519:237-41.
24. Trubiano J, Phillips E. Antimicrobial stewardship's new weapon? A review of antibiotic allergy and pathways to 'de-labeling'. Curr Opin Infect Dis 2013;26:526-37.
25. Gell PGH, Coombs RRA. The classification of allergic reactions underlying disease. In: Gell PGH, Coombs RRA, editors. Clinical aspects of immunology. 2nd ed. Oxford: Blackwell Scientific; 1963.
26. Rive CM, Bourke J, Phillips EJ. Testing for drug hypersensitivity syndromes. Clin Biochem Rev 2013;34:15-38.
27. Lagace-Wiens P, Rubinstein E. Adverse reactions to beta-lactam antimicrobials. Expert Opin Drug Saf 2012;11:381-99.
28. Peter JG, Lehloenya R, Dlamini S, Risma K, White KD, Konvinse KC, et al. Severe delayed cutaneous and systemic reactions to drugs: a global perspective on the science and art of current practice. J Allergy Clin Immunol Pract 2017;5:547-63.
29. White KD, Chung WH, Hung SI, Mallal S, Phillips EJ. Evolving models of the immunopathogenesis of T cell-mediated drug allergy: the role of host, pathogens, and drug response. J Allergy Clin Immunol 2015;136:219-34. quiz 235.
30. Phillips EJ. Classifying ADRs—does dose matter? Br J Clin Pharmacol 2016;81:10-2.
31. Hakkarainen KM, Hedna K, Petzold M, Hagg S. Percentage of patients with preventable adverse drug reactions and preventability of adverse drug reactions—a meta-analysis. PLoS One 2012;7:e33236.
32. Kongkaew C, Noyce PR, Ashcroft DM. Hospital admissions associated with adverse drug reactions: a systematic review of prospective observational studies. Ann Pharmacother 2008;42:1017-25.
33. Bates DW, Spell N, Cullen DJ, Burdick E, Laird N, Petersen LA, et al. The costs of adverse drug events in hospitalized patients. Adverse Drug Events Prevention Study Group. JAMA 1997;277:307-11.
34. Mallal S, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, et al. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med 2008;358:568-79.
35. Ostrov DA, Grant BJ, Pompeu YA, Sidney J, Harndahl M, Southwood S, et al. Drug hypersensitivity caused by alteration of the MHC-presented self-peptide repertoire. Proc Natl Acad Sci U S A 2012;109:9959-64.
36. Illing PT, Vivian JP, Dudek NL, Kostenko L, Chen Z, Bharadwaj M, et al. Immune self-reactivity triggered by drug-modified HLA-peptide repertoire. Nature 2012;486:554-8.
37. Pavlos R, Mallal S, Phillips E. HLA and pharmacogenetics of drug hypersensitivity. Pharmacogenomics 2012;13:1285-306.
38. Zhang FR, Liu H, Irwanto A, Fu XA, Li Y, Yu GQ, et al. HLA-B*13:01 and the dapsone hypersensitivity syndrome. N Engl J Med 2013;369:1620-8.
39. Ke CH, Chung WH, Wen YH, Huang YB, Chuang HY, Tain YL, et al. Cost-effectiveness analysis for genotyping before allopurinol treatment to prevent severe cutaneous adverse drug reactions. J Rheumatol 2017;44:835-43.
40. Phillips EJ, Sullivan JR, Knowles SR, Shear NH. Utility of patch testing in patients with hypersensitivity syndromes associated with abacavir. AIDS 2002;16:2223-5.
41. Lucas A, Lucas M, Strhyn A, Keane NM, McKinnon E, Pavlos R, et al. Abacavir-reactive memory T cells are present in drug naive individuals. PLoS One 2015;10:e0117160.
42. Moskow JM, Cook N, Champion-Lippmann C, Amofah SA, Garcia AS. Identifying opportunities in EHR to improve the quality of antibiotic allergy data. J Am Med Inform Assoc 2016;23:e108-12.
43. Novalbos A, Sastre J, Cuesta J, De Las Heras M, Lluch-Bernal M, Bombin C, et al. Lack of allergic cross-reactivity to cephalosporins among patients allergic to penicillins. Clin Exp Allergy 2001;31:438-43.
44. Anne S, Reisman RE. Risk of administering cephalosporin antibiotics to patients with histories of penicillin allergy. Ann Allergy Asthma Immunol 1995;74:167-70.
45. Miranda A, Blanca M, Vega JM, Moreno F, Carmona MJ, Garcia JJ, et al. Cross-reactivity between a penicillin and a cephalosporin with the same side chain. J Allergy Clin Immunol 1996;98:671-7.
46. Romano A, Mayorga C, Torres MJ, Artesani MC, Suau R, Sánchez F, et al. Immediate allergic reactions to cephalosporins: cross-reactivity and selective responses. J Allergy Clin Immunol 2000;106:1177-83.
47. Antunez C, Blanca-Lopez N, Torres MJ, Mayorga C, Perez-Inestrosa E, Montanez MI, et al. Immediate allergic reactions to cephalosporins: evaluation of cross-reactivity with a panel of penicillins and cephalosporins. J Allergy Clin Immunol 2006;117:404-10.
48. Romano A, Gaeta F, Valluzzi RL, Maggioletti M, Zaffiro A, Caruso C, et al. IgE-mediated hypersensitivity to cephalosporins: cross-reactivity and tolerability of alternative cephalosporins. J Allergy Clin Immunol 2015;136:685-691.e3.
49. Trubiano JA, Worth LJ, Urbancic K, Brown TM, Paterson DL, Australasian Society for Infectious Diseases Clinical Research Network, et al. Return to sender: the need to re-address patient antibiotic allergy labels in Australia and New Zealand. Intern Med J 2016;46:1311-7.
50. Trubiano JA, Beekmann SE, Worth LJ, Polgreen PM, Thursky KA, Slavin MA, et al. Improving antimicrobial stewardship by antibiotic allergy delabeling: evaluation of knowledge, attitude, and practices throughout the emerging infections network. Open Forum Infect Dis 2016;3:ofw153.
51. Prematta T, Shah S, Ishmael FT. Physician approaches to beta-lactam use in patients with penicillin hypersensitivity. Allergy Asthma Proc 2012;33:145-51.
52. Richter AG, Nasser SM, Krishna MT. A UK national survey of investigations for beta-lactam hypersensitivity — heterogeneity in practice and a need for national guidelines — on behalf of British Society for Allergy and Clinical Immunology (BSACI). Clin Exp Allergy 2013;43:941-9.
53. Herbert ME, Brewster GS, Lanctot-Herbert M. Medical myth: ten percent of patients who are allergic to penicillin will have serious reactions if exposed to cephalosporins. West J Med 2000;172:341.
54. Kelkar PS, Li JT. Cephalosporin allergy. N Engl J Med 2001;345:804-9.
55. Thoburn R, Johnson JE III, Cluff LE. Studies on the epidemiology of adverse drug reactions, IV: the relationship of cephalothin and penicillin allergy. JAMA 1966;198:345-8.
56. Girard JP. Common antigenic determinants of penicillin G, ampicillin and the cephalosporins demonstrated in men. Int Arch Allergy Appl Immunol 1968;33:428-38.

57. Dash CH. Penicillin allergy and the cephalosporins. J Antimicrob Chemother 1975;1:107-18.
58. Petz LD. Immunologic cross-reactivity between penicillins and cephalosporins: a review. J Infect Dis 1978;137:S74-9.
59. Buonomo A, Nucera E, De Pasquale T, Pecora V, Lombardo C, Sabato V, et al. Tolerability of aztreonam in patients with cell-mediated allergy to beta-lactams. Int Arch Allergy Immunol 2011;155:155-9.
60. Patriarca G, Schiavino D, Lombardo C, Altomonte G, De Cinti M, Buonomo A, et al. Tolerability of aztreonam in patients with IgE-mediated hypersensitivity to beta-lactams. Int J Immunopathol Pharmacol 2008;21:375-9.
61. Romano A, Gaeta F, Valluzzi RL, Caruso C, Rumi G, Bousquet PJ. IgE-mediated hypersensitivity to cephalosporins: cross-reactivity and tolerability of penicillins, monobactams, and carbapenems. J Allergy Clin Immunol 2010;126:994-9.
62. Saxon A, Hassner A, Swabb EA, Wheeler B, Adkinson NF Jr. Lack of cross-reactivity between aztreonam, a monobactam antibiotic, and penicillin in penicillin-allergic subjects. J Infect Dis 1984;149:16-22.
63. Romano A, Gaeta F, Arribas Poves MF, Valluzzi RL. Cross-reactivity among beta-lactams. Curr Allergy Asthma Rep 2016;16:24.
64. Buonomo A, Nucera E, Pecora V, Rizzi A, Aruanno A, Pascolini L, et al. Cross-reactivity and tolerability of cephalosporins in patients with cell-mediated allergy to penicillins. J Investig Allergol Clin Immunol 2014;24:331-7.
65. Romano A, Gaeta F, Valluzzi RL, Alonzi C, Maggioletti M, Zaffiro A, et al. Absence of cross-reactivity to carbapenems in patients with delayed hypersensitivity to penicillins. Allergy 2013;68:1618-21.
66. Romano A, Gaeta F, Valluzzi RL, Maggioletti M, Caruso C, Quaratino D. Cross-reactivity and tolerability of aztreonam and cephalosporins in subjects with a T cell-mediated hypersensitivity to penicillins. J Allergy Clin Immunol 2016;138:179-86.
67. Schiavino D, Nucera E, Lombardo C, Decinti M, Pascolini L, Altomonte G, et al. Cross-reactivity and tolerability of imipenem in patients with delayed-type, cell-mediated hypersensitivity to beta-lactams. Allergy 2009;64:1644-8.
68. Demoly P, Romano A, Botelho C, Bousquet-Rouanet L, Gaeta F, Silva R, et al. Determining the negative predictive value of provocation tests with beta-lactams. Allergy 2010;65:327-32.
69. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol 2010;105:259-73.
70. Gadde J, Spence M, Wheeler B, Adkinson NF Jr. Clinical experience with penicillin skin testing in a large inner-city STD clinic. JAMA 1993;270:2456-63.
71. Sogn DD, Evans R III, Shepherd GM, Casale TB, Condemi J, Greenberger PA, et al. Results of the National Institute of Allergy and Infectious Diseases Collaborative Clinical Trial to test the predictive value of skin testing with major and minor penicillin derivatives in hospitalized adults. Arch Intern Med 1992;152:1025-32.
72. Bourke J, Pavlos R, James I, Phillips E. Improving the effectiveness of penicillin allergy de-labeling. J Allergy Clin Immunol Pract 2015;3:365-34.e1.
73. Macy E, Romano A, Khan D. Practical management of antibiotic hypersensitivity in 2017. J Allergy Clin Immunol Pract 2017;5:577-86.
74. Weber-Mani U, Pichler WJ. Anaphylactic shock after intradermal testing with betalactam antibiotics. Allergy 2008;63:785.
75. Alonso Diaz de Durana MD, Fernandez-Rivas M, Casas ML, Esteban E, Cuevas M, Tejedor MA. Anaphylaxis during negative penicillin skin prick testing confirmed by elevated serum tryptase. Allergy 2003;58:159.
76. Valyasevi MA, Maddox DE, Li JT. Systemic reactions to allergy skin tests. Ann Allergy Asthma Immunol 1999;83:132-6.
77. Hausermann P, Bircher AJ. Immediate and delayed hypersensitivity to ceftriaxone, and anaphylaxis due to intradermal testing with other beta-lactam antibiotics, in a previously amoxicillin-sensitized patient. Contact Dermatitis 2002;47:311-2.
78. Solensky R, Earl HS, Gruchalla RS. Lack of penicillin resensitization in patients with a history of penicillin allergy after receiving repeated penicillin courses. Arch Intern Med 2002;162:822-6.
79. Bittner A, Greenberger PA. Incidence of resensitization after tolerating penicillin treatment in penicillin-allergic patients. Allergy Asthma Proc 2004;25:161-4.
80. Blanca M, Romano A, Torres MJ, Férnandez J, Mayorga C, Rodriguez J, et al. Update on the evaluation of hypersensitivity reactions to betalactams. Allergy 2009;64:183-93.
81. Atanaskovic-Markovic M, Gaeta F, Medjo B, Viola M, Nestorovic B, Romano A. Tolerability of meropenem in children with IgE-mediated hypersensitivity to penicillins. Allergy 2008;63:237-40.
82. Romano A, Viola M, Gueant-Rodriguez RM, Gaeta F, Valluzzi R, Gueant JL. Brief communication: tolerability of meropenem in patients with IgE-mediated hypersensitivity to penicillins. Ann Intern Med 2007;146:266-9.
83. Dominguez-Ortega J, Martinez-Alonso JC, Marcos-Perez MC, Kindelan C, Frades A. Allergy to cloxacillin with normal tolerance to amoxicillin and cefuroxime. Allergol Immunopathol (Madr) 2006;34:37-8.
84. Romano A, Di Fonso M, Artesani MC, Viola M, Adesi FB, Venuti A. Selective immediate hypersensitivity to ceftazidime. Allergy 2001;56:84-5.
85. Silva R, Cruz L, Botelho C, Cadinha S, Castro E, Rodrigues J, et al. Work up of patients with history of beta-lactam hypersensitivity. Allergol Immunopathol (Madr) 2009;37:193-7.
86. Blanca-Lopez N, Perez-Alzate D, Ruano F, Garcimartin M, de la Torre V, Mayorga C, et al. Selective immediate responders to amoxicillin and clavulanic acid tolerate penicillin derivative administration after confirming the diagnosis. Allergy 2015;70:1013-9.
87. Sanchez-Morillas L, Perez-Ezquerra PR, Reano-Martos M, Laguna-Martinez JJ, Sanz ML, Martinez LM. Selective allergic reactions to clavulanic acid: a report of 9 cases. J Allergy Clin Immunol 2010;126:177-9.
88. Torres MJ, Ariza A, Mayorga C, Dona I, Blanca-Lopez N, Rondon C, et al. Clavulanic acid can be the component in amoxicillin-clavulanic acid responsible for immediate hypersensitivity reactions. J Allergy Clin Immunol 2010;125:502-505.e2.
89. Moss RB, Babin S, Hsu YP, Blessing-Moore J, Lewiston NJ. Allergy to semisynthetic penicillins in cystic fibrosis. J Pediatr 1984;104:460-6.
90. Solley GO, Gleich GJ, Van Dellen RG. Penicillin allergy: clinical experience with a battery of skin-test reagents. J Allergy Clin Immunol 1982;69:238-44.
91. Mirakian R, Leech SC, Krishna MT, Richter AG, Huber PA, Farooque S, et al. Management of allergy to penicillins and other beta-lactams. Clin Exp Allergy 2015;45:300-27.
92. Rank MA, Park MA. Anaphylaxis to piperacillin-tazobactam despite a negative penicillin skin test. Allergy 2007;62:964-5.
93. Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB, et al. Skin test concentrations for systemically administered drugs — an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy 2013;68:702-12.
94. Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM, Greenberger PA, et al. International consensus on drug allergy. Allergy 2014;69:420-37.
95. Broz P, Harr T, Hecking C, Grize L, Scherer K, Jaeger KA, et al. Nonirritant intradermal skin test concentrations of ciprofloxacin, clarithromycin, and rifampicin. Allergy 2012;67:647-52.
96. Romano A, Gueant-Rodriguez RM, Viola M, Amoghly F, Gaeta F, Nicolas JP, et al. Diagnosing immediate reactions to cephalosporins. Clin Exp Allergy 2005;35:1234-42.
97. Romano A, Gaeta F, Valluzzi RL, Zaffiro A, Caruso C, Quaratino D. Natural evolution of skin-test sensitivity in patients with IgE-mediated hypersensitivity to cephalosporins. Allergy 2014;69:806-9.
98. Lin YF, Yang CH, Sindy H, Lin JY, Rosaline Hui CY, Tsai YC, et al. Severe cutaneous adverse reactions related to systemic antibiotics. Clin Infect Dis 2014;58:1377-85.
99. Barbaud A, Goncalo M, Bruynzeel D, Bircher A. European Society of Contact Dermatitis. Guidelines for performing skin tests with drugs in the investigation of cutaneous adverse drug reactions. Contact Dermatitis 2001;45:321-8.
100. Romano A, Di Fonso M, Pocobelli D, Giannarini L, Venuti A, Garcovich A. Two cases of toxic epidermal necrolysis caused by delayed hypersensitivity to beta-lactam antibiotics. J Investig Allergol Clin Immunol 1993;3:53-5.
101. Pereira N, Canelas MM, Santiago F, Brites MM, Goncalo M. Value of patch tests in clindamycin-related drug eruptions. Contact Dermatitis 2011;65:202-7.
102. Caubet JC, Kaiser L, Lemaitre B, Fellay B, Gervaix A, Eigenmann PA. The role of penicillin in benign skin rashes in childhood: a prospective study based on drug rechallenge. J Allergy Clin Immunol 2011;127:218-22.
103. Barbaud A, Trechot P, Weber-Muller F, Ulrich G, Commun N, Schmutz JL. Drug skin tests in cutaneous adverse drug reactions to pristinamycin: 29 cases with a study of cross-reactions between synergistins. Contact Dermatitis 2004;50:22-6.
104. Barbaud A, Collet E, Milpied B, Assier H, Staumont D, Avenel-Audran M, et al. A multicentre study to determine the value and safety of drug patch tests for the three main classes of severe cutaneous adverse drug reactions. Br J Dermatol 2013;168:555-62.

105. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. Allergy 2002;57:45-51.
106. Atanaskovic-Markovic M, Gaeta F, Medjo B, Gavrovic-Jankulovic M, Cirkovic Velickovic T, Tmusic V, et al. Non-immediate hypersensitivity reactions to beta-lactam antibiotics in children − our 10-year experience in allergy work-up. Pediatr Allergy Immunol 2016;27:533-8.
107. Romano A, Valluzzi RL, Caruso C, Maggioletti M, Gaeta F. Non-immediate cutaneous reactions to beta-lactams: approach to diagnosis. Curr Allergy Asthma Rep 2017;17:23.
108. Torres MJ, Romano A, Celik G, Demoly P, Khan DA, Macy E, et al. Approach to the diagnosis of drug hypersensitivity reactions: similarities and differences between Europe and North America. Clin Transl Allergy 2017;7:7.
109. Romano A, Gaeta F, Valluzzi RL, Caruso C, Alonzi C, Viola M, et al. Diagnosing nonimmediate reactions to cephalosporins. J Allergy Clin Immunol 2012;129:1166-9.
110. Barbaud A. Skin testing and patch testing in non-IgE-mediated drug allergy. Curr Allergy Asthma Rep 2014;14:442.
111. Wolkenstein P, Chosidow O, Flechet ML, Robbiola O, Paul M, Dume L, et al. Patch testing in severe cutaneous adverse drug reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis. Contact Dermatitis 1996;35:234-6.
112. Seitz CS, Brocker EB, Trautmann A. Diagnostic testing in suspected fluoroquinolone hypersensitivity. Clin Exp Allergy 2009;39:1738-45.
113. Gompels MM, Simpson N, Snow M, Spickett G, Ong E. Desensitization to co-trimoxazole (trimethoprim-sulphamethoxazole) in HIV-infected patients: is patch testing a useful predictor of reaction? J Infect 1999;38:111-5.
114. Finkelstein Y, Macdonald EM, Li P, Hutson JR, Juurlink DN. Recurrence and mortality following severe cutaneous adverse reactions. JAMA 2014;311:2231-2.
115. Cabanas R, Calderon O, Ramirez E, Fiandor A, Prior N, Caballero T, et al. Piperacillin-induced DRESS: distinguishing features observed in a clinical and allergy study of 8 patients. J Investig Allergol Clin Immunol 2014;24:425-30.
116. Rozieres A, Hennino A, Rodet K, Gutowski MC, Gunera-Saad N, Berard F, et al. Detection and quantification of drug-specific T cells in penicillin allergy. Allergy 2009;64:534-42.
117. Khalil G, El-Sabban M, Al-Ghadban S, Azzi S, Shamra S, Khalife S, et al. Cytokine expression profile of sensitized human T lymphocytes following in vitro stimulation with amoxicillin. Eur Cytokine Netw 2008;19:131-41.
118. El-Ghaiesh S, Monshi MM, Whitaker P, Jenkins R, Meng X, Farrell J, et al. Characterization of the antigen specificity of T-cell clones from piperacillin-hypersensitive patients with cystic fibrosis. J Pharmacol Exp Ther 2012;341:597-610.
119. Tanvarasethee B, Buranapraditkun S, Klaewsongkram J. The potential of using enzyme-linked immunospot to diagnose cephalosporin-induced maculopapular exanthems. Acta Derm Venereol 2013;93:66-9.
120. Jenkins RE, Yaseen FS, Monshi MM, Whitaker P, Meng X, Farrell J, et al. Beta-lactam antibiotics form distinct haptenic structures on albumin and activate drug-specific T-lymphocyte responses in multiallergic patients with cystic fibrosis. Chem Res Toxicol 2013;26:963-75.
121. Nhim C, Delluc S, Halgand F, de Chaisemartin L, Weaver RJ, Claude N, et al. Identification and frequency of circulating CD4(+) T lymphocytes specific to benzylpenicillin in healthy donors. Allergy 2013;68:899-905.
122. Bensaid B, Rozieres A, Nosbaum A, Nicolas JF, Berard F. Amikacin-induced drug reaction with eosinophilia and systemic symptoms syndrome: delayed skin test and ELISPOT assay results allow the identification of the culprit drug. J Allergy Clin Immunol 2012;130:1413-4.
123. Kim JY, Sohn KH, Song WJ, Kang HR. A case of drug reaction with eosinophilia and systemic symptoms induced by ethambutol with early features resembling Stevens-Johnson syndrome. Acta Derm Venereol 2013;93:753-4.
124. Trautmann A, Seitz CS, Stoevesandt J, Kerstan A. Aminopenicillin-associated exanthem: lymphocyte transformation testing revisited. Clin Exp Allergy 2014;44:1531-8.
125. Tagami H, Tatsuta K, Iwatski K, Yamada M. Delayed hypersensitivity in ampicillin-induced toxic epidermal necrolysis. Arch Dermatol 1983;119:910-3.
126. Romano A, Torres MJ, Di Fonso M, Leyva L, Andriolo M, Pettinato R, et al. Delayed hypersensitivity to cefazolin: report on a case involving lymphocyte transformation studies with different cephalosporins. Ann Allergy Asthma Immunol 2001;87:238-42.
127. Confino-Cohen R, Rosman Y, Meir-Shafrir K, Stauber T, Lachover-Roth I, Hershko A, et al. Oral challenge without skin testing safely excludes clinically significant delayed-onset penicillin hypersensitivity. J Allergy Clin Immunol Pract 2017;5:669-75.
128. Tucker MH, Lomas CM, Ramchandar N, Waldram JD. Amoxicillin challenge without penicillin skin testing in evaluation of penicillin allergy in a cohort of Marine recruits. J Allergy Clin Immunol Pract 2017;5:813-5.
129. Hjortlund J, Mortz CG, Skov PS, Eller E, Poulsen JM, Borch JE, et al. One-week oral challenge with penicillin in diagnosis of penicillin allergy. Acta Derm Venereol 2012;92:307-12.
130. Wall GC, Dewitt JE, Haack S, Fornoff A, Eastman DK, Koenigsfeld CF. Knowledge and attitudes of American pharmacists concerning sulfonamide allergy cross-reactivity. Pharm World Sci 2010;32:343-6.
131. Fehily SR, Stuart RL, Horne K, Korman TM, Dendle C. Who really knows their patients' penicillin adverse drug reaction status? A cross-sectional survey. Intern Med J 2015;45:113-5.
132. Blumenthal KG, Shenoy ES, Hurwitz S, Varughese CA, Hooper DC, Banerji A. Effect of a drug allergy educational program and antibiotic prescribing guideline on inpatient clinical providers' antibiotic prescribing knowledge. J Allergy Clin Immunol Pract 2014;2:407-13.
133. Sturm JM, Temprano J. A survey of physician practice and knowledge of drug allergy at a university medical center. J Allergy Clin Immunol Pract 2014;2:461-4.
134. Wang Y, Zhu R, Huang N, Li W, Yang L, Zhang S, et al. Knowledge, attitudes, and practices survey of drug allergy among healthcare practitioners in central China: a multicenter study. Asia Pac Allergy 2016;6:105-11.
135. Rimawi RH, Shah KB, Cook PP. Risk of redocumenting penicillin allergy in a cohort of patients with negative penicillin skin tests. J Hosp Med 2013;8:615-8.
136. Gerace KS, Phillips E. Penicillin allergy label persists despite negative testing. J Allergy Clin Immunol Pract 2015;3:815-6.
137. Trautmann A, Seidl C, Stoevesandt J, Seitz CS. General anaesthesia-induced anaphylaxis: impact of allergy testing on subsequent anaesthesia. Clin Exp Allergy 2016;46:125-32.
138. Macy E, Roppe LB, Schatz M. Routine penicillin skin testing in hospitalized patients with a history of penicillin allergy. Perm J 2004;8:20-4.
139. King EA, Challa S, Curtin P, Bielory L. Penicillin skin testing in hospitalized patients with beta-lactam allergies: effect on antibiotic selection and cost. Ann Allergy Asthma Immunol 2016;117:67-71.
140. Rimawi RH, Cook PP, Gooch M, Kabchi B, Ashraf MS, Rimawi BH, et al. The impact of penicillin skin testing on clinical practice and antimicrobial stewardship. J Hosp Med 2013;8:341-5.
141. Blumenthal KG, Wickner PG, Hurwitz S, Pricco N, Nee AE, Laskowski K, et al. Tackling inpatient penicillin allergies: assessing tools for antimicrobial stewardship. J Allergy Clin Immunol 2017;140:154-61.e6.
142. Ward C, Kasternow B, Haque R, Klein J. Inpatient allergy testing in patients with infective endocarditis: an un-met need? J Infect 2015;70:206-7.
143. Arroliga ME, Vazquez-Sandoval A, Dvoracek J, Arroliga AC. Penicillin skin testing is a safe method to guide beta-lactam administration in the intensive care unit. Ann Allergy Asthma Immunol 2016;116:86-7.
144. Geng B, Thakor A, Clayton E, Finkas L, Riedl MA. Factors associated with negative histamine control for penicillin allergy skin testing in the inpatient setting. Ann Allergy Asthma Immunol 2015;115:33-8.
145. Raja AS, Lindsell CJ, Bernstein JA, Codispoti CD, Moellman JJ. The use of penicillin skin testing to assess the prevalence of penicillin allergy in an emergency department setting. Ann Emerg Med 2009;54:72-7.
146. Blumenthal KG, Parker RA, Shenoy ES, Walensky RP. Improving clinical outcomes in patients with methicillin-sensitive *Staphylococcus aureus* bacteremia and reported penicillin allergy. Clin Infect Dis 2015;61:741-9.
147. Blumenthal KG, Shenoy ES, Varughese CA, Hurwitz S, Hooper DC, Banerji A. Impact of a clinical guideline for prescribing antibiotics to inpatients reporting penicillin or cephalosporin allergy. Ann Allergy Asthma Immunol 2015;115:294-300.e2.
148. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis 2016;62:e51-77.
149. Banks TA, Ressner RA, Gada SM. Antibiotic reclamation: penicillin allergy, antibiotic stewardship, and the allergist. Ann Allergy Asthma Immunol 2015;115:451-2.
150. Ressner RA, Gada SM, Banks TA. Antimicrobial stewardship and the allergist: reclaiming our antibiotic armamentarium. Clin Infect Dis 2016;62:400-1.
151. Park MA, McClimon BJ, Ferguson B, Markus PJ, Odell L, Swanson A, et al. Collaboration between allergists and pharmacists increases beta-lactam antibiotic prescriptions in patients with a history of penicillin allergy. Int Arch Allergy Immunol 2011;154:57-62.
152. Arroliga ME, Wagner W, Bobek MB, Hoffman-Hogg L, Gordon SM, Arroliga AC. A pilot study of penicillin skin testing in patients with a

history of penicillin allergy admitted to a medical ICU. Chest 2000;118:1106-8.
153. Picard M, Paradis L, Nguyen M, Begin P, Paradis J, Des Roches A. Outpatient penicillin use after negative skin testing and drug challenge in a pediatric population. Allergy Asthma Proc 2012;33:160-4.
154. Unger NR, Gauthier TP, Cheung LW. Penicillin skin testing: potential implications for antimicrobial stewardship. Pharmacotherapy 2013;33:856-67.
155. Dodek P, Phillips P. Questionable history of immediate-type hypersensitivity to penicillin in Staphylococcal endocarditis: treatment based on skin-test results versus empirical alternative treatment—a decision analysis. Clin Infect Dis 1999;29:1251-6.
156. Cook DJ, Barbara DW, Singh KE, Dearani JA. Penicillin skin testing in cardiac surgery. J Thorac Cardiovasc Surg 2014;147:1931-5.
157. Swearingen SM, White C, Weidert S, Hinds M, Narro JP, Guarascio AJ. A multidimensional antimicrobial stewardship intervention targeting aztreonam use in patients with a reported penicillin allergy. Int J Clin Pharm 2016;38:213-7.
158. Chen JR, Tarver SA, Alvarez KS, Tran T, Khan DA. A proactive approach to penicillin allergy testing in hospitalized patients. J Allergy Clin Immunol Pract 2017;5:686-93.
159. Blumenthal KG, Shenoy ES, Wolfson AR, Berkowitz DN, Carballo VA, Balekian DS, et al. Addressing inpatient beta-lactam allergies: a multihospital implementation. J Allergy Clin Immunol Pract 2017;5:616-625.e7.
160. Heil EL, Bork JT, Schmalzle SA, Kleinberg M, Kewalramani A, Gilliam BL, et al. Implementation of an infectious disease fellow-managed penicillin allergy skin testing service. Open Forum Infect Dis 2016;3:ofw155.
161. Estep PM, Ferreira JA, Dupree LH, Aldridge PJ, Jankowski CA. Impact of an antimicrobial stewardship initiative to evaluate beta-lactam allergy in patients ordered aztreonam. Am J Health Syst Pharm 2016;73:S8-13.
162. Staicu ML, Brundige ML, Ramsey A, Brown J, Yamshchikov A, Peterson DR, et al. Implementation of a penicillin allergy screening tool to optimize aztreonam use. Am J Health Syst Pharm 2016;73:298-306.
163. Wall GC, Peters L, Leaders CB, Wille JA. Pharmacist-managed service providing penicillin allergy skin tests. Am J Health Syst Pharm 2004;61:1271-5.
164. Caplinger C, Smith G, Remington R, Madaras-Kelly K. Evaluation of a computerized decision support intervention to decrease use of anti-pseudomonal carbapenems in penicillin allergic patients. Antibiotics (Basel) 2016;5.

Reproduced with permission of copyright owner. Further reproduction prohibited without permission.