Practice parameter

Drug allergy: A 2022 practice parameter update

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Abbreviations used

95% CrI:	95% Credible interval
AERD:	Aspirin exacerbated respiratory disease
AGEP:	Acute generalized exanthematous pustulosis
alpha-gal:	Galactose-α-1,3-galactose
CBS:	Consensus-based statement
dIDT:	Delayed intradermal test
DIHS:	Drug-induced hypersensitivity syndrome
DRESS:	Drug reaction with eosinophilia and systemic symptoms
FDA:	US Food and Drug Administration
FDE:	Fixed drug eruption
GRADE:	Grading of Recommendations, Assessment, Development and Evaluation
HSR:	Hypersensitivity reaction
ICIs:	Immune checkpoint inhibitors
irAEs:	Immune-related adverse events
JTFPP:	Joint Task Force on Practice Parameters
MDE:	Morbilliform drug eruption
NPV:	Negative predictive value
NSAID:	Nonsteroidal anti-inflammatory drug
OR:	Odds ratio
PD-1:	Programmed cell death protein 1
PD-L1:	Programmed death-ligand 1
PEG:	Polyethylene glycol
PPL:	Penicilloyl-polylysine
PPV:	Positive predictive value
PT:	Patch test
SCARs:	Severe cutaneous adverse reactions
SJS:	Stevens-Johnson syndrome
SPT:	Skin prick test
SSLRs:	Serum sickness-like reactions
TEN:	Toxic epidermal necrolysis
TKIs:	Tyrosine kinase inhibitors
TMP-SMX:	Trimethoprim-sulfamethoxazole

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recommendations will be appropriate or applicable to all patients and may change over time. Because this document incorporates the efforts of many participants, no single individual, including members serving on the JTFPP, is authorized to provide an official AAAAI or ACAAI interpretation of this practice parameter. Any request for information or interpretation of this practice parameter by the AAAAI or ACAAI should be directed to the executive offices of the AAAAI and the ACAAI. Practice parameters and guidelines are not designed for use by the pharmaceutical industry in drug development or promotion. The JTFPP understands that the cost of diagnostic tests and therapeutic interventions is an important concern that may appropriately influence the evaluation and treatment selected for a given patient. The JTFPP recognizes that the emphasis of our primary recommendations regarding a medication may vary, for example, depending on third-party payer issues and product patent expiration dates. However, because a given test or a therapeutic intervention's cost is so widely variable, and there is a relative paucity of pharmacoeconomic data, the JTFPP is not always able to consider cost when formulating recommendations. In extraordinary circumstances, when the cost benefit of an intervention is prohibitive as supported by pharmacoeconomic data, commentary may be provided.

TABLE OF CONTENTS

PREFACE

This practice parameter provides an updated approach to the diagnosis and management of various drug reactions. Evidence has evolved since the previous drug allergy practice parameter[1]

and currently supports the ability to risk stratify most patients based on reaction phenotype. Evaluation of suspected drug allergy focuses on preferential use of drug challenges as opposed to skin testing in many circumstances. Clarification of drug allergy history is a valuable resource that allergist-immunologists provide to patients with shared decision making regarding testing and management options central to each evaluation. These parameters will help clinicians better understand how and when to use drug challenges, including consideration for 1-, 2-, or multistep challenges. While currently, 2-step challenges are required for reimbursement in the United States, the literature supports the use of single-step challenges in certain situations, and we are optimistic that third-party payers will reimburse this procedure in the future. A proactive approach to delabeling penicillin allergy as well as use of safe antibiotic alternatives for patients with proven penicillin allergy is emphasized. Approaches to diagnosis and management of nonpenicillin drug reactions are discussed in updated sections on cephalosporins, sulfonamides, fluroquinolones, macrolides, aspirin, chemotherapeutic agents, and biologics. This comprehensive resource provides consensus-based statements (CBSs) throughout, as well as detailed background and discussion to assist implementation into clinical practice.

GLOSSARY

Allergy: For the purpose of this practice parameter, the terms "allergy" and "hypersensitivity" will be used interchangeably, and both indicate an abnormal immune response. The inclusion of both types of nomenclature reflects the variable use of these terms in the collective literature on this topic.

Delayed hypersensitivity reaction: Immunologic-mediated reaction occurring at least 6 hours after dosing, with majority occurring 1-2 weeks after drug initiation.

Delayed intradermal testing (dIDT): Intradermal injection of nonirritating drug concentration on the volar aspect of the forearm followed by evaluation for induration 24 hours after application.

Desensitization: A form of temporary induction of drug tolerance typically for IgE-mediated reactions through administration of multiple gradually increasing doses of a drug to allow for treatment. Maintaining exposure to the drug is required to continue temporary induction of tolerance. In this practice parameter, we preferentially use "induction of drug tolerance."

Direct challenge: Performing drug challenge without prior skin testing.

Drug challenge: Procedure whereby drug is administered to determine tolerance. Preferred nomenclature compared with "drug provocation tests" or "test doses," which imply intent to provoke a reaction.

Drug challenge, 1-step: One treatment dose of the drug is administered, followed by observation for objective symptoms of reaction.

Drug challenge, 2-step: One-tenth of the treatment dose of the drug is administered, followed 20-30 minutes later by 90% of the treatment dose if no symptoms occur.

Drug challenge, multiple days: Treatment dose of the drug is administered daily at home for 5-10 days.

Induction of drug tolerance: Administration of multiple gradually increasing doses of a drug to allow for treatment. Ongoing consistent exposure to the drug is required to maintain tolerance.

Infusion reactions: Unpredictable adverse reactions unrelated to known side effects from a drug. They are commonly associated with mAbs.

Latency period: Time from first exposure to a drug to the time reaction occurs.

Nocebo effect: Objective or subjective symptoms occurring after administration of a placebo dose.

Penicillin major determinant: Detects the greatest number of patients with IgE-mediated penicillin allergy through skin testing. This is penicilloyl-polylysine (PPL; Pre-Pen, ALK-Abelló, Hørsholm, Denmark).

Penicillin minor determinants: Penicillin G, penicilloate, penilloate.

Pharmacogenomics: The study of how genetic variations affect responses to medications.

Phenotype: Observable clinical characteristics associated with interactions from specific exposures.

Structurally dissimilar: Cephalosporins that have disparate R1 side chains from other cephalosporins or aminopenicillins.

Verified allergy: A patient with a verified drug allergy has confirmed their allergy via skin testing and/or challenge.

WHAT'S NEW AND WHAT'S DIFFERENT

All of the updated sections contain significant new information and recommendations compared with the previous 2010 updated drug allergy practice parameter.[1] Compared with the previous update, there is an overall de-emphasis on the use of skin testing as compared with drug challenge, particularly for the majority of patients who present with nonanaphylactic, nonsevere cutaneous drug allergy histories. In addition, more emphasis is placed on risk stratification based on reaction phenotype as well as the role for shared decision making in diagnostic testing and management. Some of the most important changes in this updated practice parameter are as follows:

- Recommendation to define a positive skin test as a wheal that is ≥3 mm than the negative control for prick/puncture or intradermal tests accompanied by a ≥5 mm flare
- Suggestion to use of 1- or 2-step drug challenges for low-risk patients
- Suggestion to use placebo challenges in patients with subjective symptoms or multiple reported drug allergies
- Suggestion to consider dIDT and/or patch tests (PTs) to identify culprit drugs for specific phenotypes of delayed drug reactions where the implicated agent is uncertain
- Recognition that most pharmacogenetic associations identified to date are currently unlikely to translate into clinical practice
- Recommendation for proactive penicillin allergy delabeling
- Recommendation against multiple-day challenges in evaluation of most cases of suspected penicillin allergy
- Recommendation against penicillin skin testing prior to direct amoxicillin challenge in low-risk pediatric patients
- Consideration for direct amoxicillin challenge in adults with low-risk penicillin allergy histories
- Recognition that patients with selective allergic reactions to piperacillin-tazobactam may be identified with skin tests to piperacillin-tazobactam and may tolerate other penicillins
- Suggestion to perform direct challenge to cephalosporins with dissimilar side chains in patients with nonanaphylactic cephalosporin allergy

- Suggestion to perform skin tests to parenteral cephalosporins with nonidentical R1 side chains (prior to challenge) in patients with anaphylactic cephalosporin allergy
- Specific guidance on administration of cephalosporins to patients with various phenotypes of penicillin allergy
- Specific guidance on administration of penicillins to patients with various phenotypes of cephalosporin allergy
- Suggestion to administer carbapenems without prior testing in patients with other beta-lactam allergies
- Recommendation that allergist-immunologists collaborate with hospitals and health care systems to implement beta-lactam allergy pathways to improve antibiotic stewardship outcomes
- Suggestion to use a 1-step trimethoprim-sulfamethoxazole (TMP-SMX) challenge rather than desensitization for low-risk patients where there is a need to delabel sulfonamide allergy
- Suggestion to use 1- or 2-step drug challenge for nonanaphylactic reactions to fluoroquinolones or macrolides without preceding skin testing
- Recommendation against aspirin challenge to confirm a diagnosis of aspirin-exacerbated respiratory disease (AERD) in cases of high diagnostic certainty based on history but that aspirin desensitization remains a therapeutic option when indicated
- Suggestion for oral aspirin challenge only in patients where there is diagnostic uncertainty of AERD
- Suggestion that COX-2 inhibitors may be used in any nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity phenotype when an NSAID is needed
- Suggestion to use oral aspirin challenge in patients with NSAID-induced urticaria/angioedema to determine tolerance to other NSAIDs
- Suggestion for 2-step aspirin challenge (not desensitization) for patients with a history of non-AERD aspirin allergy in acute need of aspirin for cardiovascular disease
- Suggestion that patients with non-IgE chemotherapy or biologic reactions be treated with slowed infusion rate, graded dose escalation, and/or premedications without desensitization
- Suggestion that for patients with immediate reactions to taxanes, the severity of the initial reaction may assist in risk stratification and management
- Suggestion that patients with non-IgE reactions to mAbs may be treated with a slowed infusion, graded dose escalation, and/or premedication without desensitization
- Recognition that excipient allergy is very rare but may be considered in patients with anaphylaxis to ≥2 structurally unrelated products that share a common excipient

EXECUTIVE SUMMARY

The primary focus of the drug allergy practice parameter historically has been to provide suggestions and recommendations for the proper diagnosis and management of the spectrum of drug hypersensitivity reactions (HSRs). Since the most recent update in 2010, which was a comprehensive review on the topic of drug allergy at the time, our understanding of several areas in the field has changed.[1] This current update is a focused update on sections that the workgroup deemed to have significant changes from (or were not addressed in) the 2010 parameter. This update is not meant to be a comprehensive overview of drug hypersensitivity reactions as was the 2010 update, but rather this parameter is a focused update that will provide important suggestions and recommendations for the management of a variety of drug HSRs.

Classification of drug allergies

The classification for drug HSRs has evolved. Allergic drug reactions can be classified based on chronology, mechanism, and clinical phenotypes. The chronology of drug allergic reactions is generally simplified into either immediate or delayed reactions. Immediate reactions are generally considered to occur within 1 hour but in some cases ≤6 hours of exposure to the drug.[2,3] Phenotypically, immediate drug reactions may present with urticaria, angioedema, bronchospasm, or in severe cases, anaphylaxis. Immediate reactions are often IgE-mediated, but IgE-independent reactions can also occur. Recently, MRGPRX2 on mast cells has been found to be responsible for non-IgE–mediated reactions to drugs such as vancomycin, neuromuscular blocking agents, and fluoroquinolones.[4] Delayed HSRs often evolve over days or, in some cases, weeks following exposure to the drug. There are numerous clinical phenotypes of delayed HSRs with the most common being benign (eg, morbilliform drug eruption) exanthems.[5] More severe delayed drug HSRs include the well-described phenotypes of drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), and Stevens-Johnson syndrome (STS)/toxic epidermal necrolysis (TEN).[6] Collectively these syndromes are referred to as severe cutaneous adverse reactions (SCARs). The immunologic mechanisms for delayed HSRs are likely related to drug-specific T cells including T_H1, T_H2, and cytotoxic T cells, depending on the phenotype.[6] Serum sickness-like reactions (SSLRs) are another phenotype of delayed drug reactions that have clinical manifestations very similar to immune complex–mediated serum sickness, but the immunopathology of SSLRs is still not entirely clear. SSLR are characterized by urticaria-like (lesions persist >24 hours) and erythema multiforme-like lesions, joint inflammation, and fever, but unlike serum sickness, nephrotoxicity and hypocomplementemia are rare. There are also a number of organ-specific delayed drug reaction phenotypes (often without cutaneous manifestations) including drug-induced cytopenias, liver injury, interstitial nephritis, and vasculitis to name a few. These primarily noncutaneous organ-specific reactions will not be addressed in this update but have been reviewed in the prior update.[1] The chronology of various drug HSRs is shown in Fig 1.

Diagnostic tests

In the United States, diagnostic tests for drug allergies are based primarily on immediate skin testing and drug challenges. Delayed drug skin testing including dIDT and PT have an evolving role in the diagnosis of certain phenotypes of delayed HSRs.[7] *In vitro* testing for drug allergy with tests such as basophil activation tests, lymphocyte transformation tests, and other testing does not have any well-validated commercial assays in the United States and will not be discussed in this parameter.

While skin testing is often performed with drug hypersensitivity evaluations, the accuracy of skin tests for most drugs is

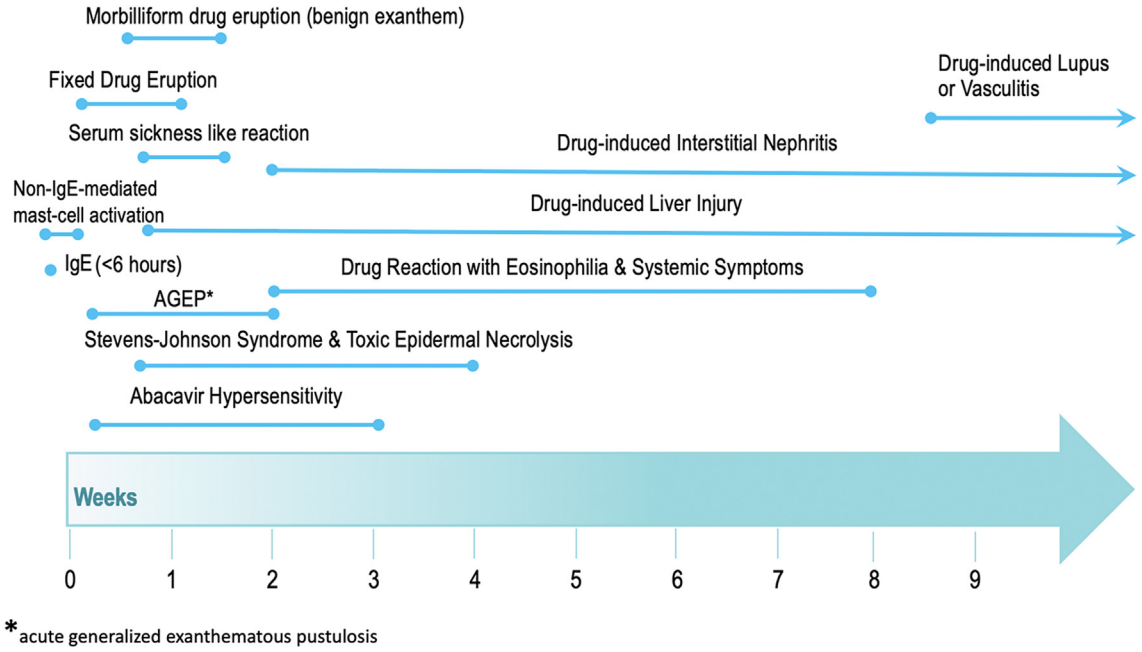

FIG 1. Time line of drug hypersensitivity reactions. The latency period is the time from first ingestion of a drug to the time a drug reaction occurs. For IgE- and non-IgE–mediated immediate reactions, these occur within hours (<6 hours) of ingestion, whereas all delayed reactions occur >6 hours. The latency period is an extremely valuable clue along with other clinical features to the clinical phenotype of the reaction with some reactions (eg, AGEP) occurring very quickly to antibiotics and other reactions; drug reaction with eosinophilia and systemic symptoms (DRESS) having a latency at minimum of 2-3 weeks; Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) appearing as early as 4 days or out to 8 weeks after initiation of medication. Because multiple drugs are frequently taken together at the time of a reaction, a time line outlining all drugs taken at the time first symptoms of a reaction occur and the evolution of the symptoms alongside the history of initiation of specific drugs should be documented and is a valuable tool to aid in drug causality for a given clinical phenotype of reaction.

unclear. Furthermore, there has not been agreement on what even constitutes a positive skin test. The workgroup now recommends that a positive prick/puncture or intradermal skin test is to be defined as a wheal that is ≥3 mm than the negative control accompanied by a ≥5 mm flare. Recently, studies have shown an optimal method for reproducible intradermal antibiotic skin testing.[8] Fluid should be drawn out first by filling the syringe with a larger volume (0.05-0.07 mL) and expelling the excess fluid and air bubbles to obtain 0.02 mL, then injecting to produce a baseline 3-5 mm bleb. While immediate skin testing is often employed in the evaluation of drug HSRs, as will be discussed later in the parameter, skin testing primarily is of most value in patients with histories of drug-induced anaphylaxis. The majority of patients who have more benign, nonanaphylactic reactions may be managed without drug skin testing.

Evidence for all testing modalities for delayed HSRs is limited and of low certainty, generally based on small case series without drug challenge; hence, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) cannot be reliably calculated. However, in certain situations such as a patient with DRESS syndrome where several causal agents are potentially implicated, delayed skin testing may be considered to help identify the potential culprit. While the accuracy of delayed drug skin testing is unclear, it appears to be safe when performed at least 6 weeks to 6 months following healing of the drug reaction.[7]

In contrast to drug skin testing, drug challenges are considered the reference standard for determining tolerance to a drug. A number of terms have been used to describe this procedure including "drug provocation tests," "graded challenges," and "test doses." The term "drug challenge" is recommended as this is in keeping with other allergic diseases (eg, food challenges, sting challenges). While "drug provocation" is commonly used in the international literature, we do not recommend this term as the intent is to show tolerance rather than to provoke a reaction. Drug challenges may be given in an incremental (graded) fashion but can also be administered as a single dose. Drug challenges can be performed for both immediate and delayed phenotypes of drug reactions. There are contraindications to drug challenges that are outlined later in this parameter. In most scenarios, drug challenges are performed when the clinical probability of a drug allergy is low. In these circumstances, drug challenges can be performed with a 1- or 2-step drug challenge. A 1-step challenge would involve administering a therapeutic dose of the drug as a single step. In contrast, a 2-step challenge would involve first administering a smaller dose, such as 10%-25% of the final dose with observation, followed by administration of the rest of the dose 20-30 minutes later. Patients with primarily subjective symptoms or those who have multiple reported drug allergies should be considered for placebo-controlled drug challenges.[9]

Most pharmacogenomic associations identified to date are currently unlikely to translate into clinical practice.[10] A few

genetic associations with serious immunologically mediated HSRs have been described.[11,12] Screening for these specific HLA associations is helpful in reducing HSRs for a few drugs and specific populations. Currently, genetic testing is not typically used for diagnostic purposes; however, this may evolve as more routine single HLA markers and other genotyping strategies become available that associate with clinical evidence for use in both screening and allergy diagnosis.

Antibiotic allergy

In recent years, many important updates regarding optimal diagnostic strategies for antibiotic allergies have been published. In this parameter, updates regarding beta-lactams including penicillins, cephalosporins, carbapenems, and monobactams will be discussed. In addition, important changes to diagnostic strategies for sulfonamides, fluoroquinolones, and macrolides will also be reviewed.

Penicillin. Since the last practice parameter update on drug allergy, several lines of evidence have pointed to the fact that a label of penicillin allergy is not benign.[13] Patients with a history of penicillin allergy are more likely to be treated with less effective, more toxic, or more expensive antibiotics, leading to increased cost, antibiotic-associated infections, longer hospital stays, and even increased mortality.[14-19] Cost and simulation model-based economic studies support that penicillin allergy assessment is a cost-saving intervention.[20,21] Therefore, a proactive effort should be made to delabel penicillin allergy whenever possible, and strong efforts should be made to educate about the benefits of delabeling to patients and clinicians.

There are multiple strategies for penicillin allergy delabeling that are primarily based on the history of the reaction and patient comorbidities. While penicillin skin testing has been the most carefully studied skin test reagent for drug allergy, we suggest penicillin skin testing primarily for patients with a history of anaphylaxis or a recent reaction suspected to be IgE-mediated (eg, immediate onset urticaria).[22] For most other patients with histories of penicillin allergy that are remote and benign, direct challenge without preceding skin testing is the preferred approach. Patient histories are not always accurate, nevertheless risk stratification by historical features alone appears to be able to safely identify patients appropriate for direct challenge. One caveat is that the majority of these studies have been conducted by allergy specialists; whether outcomes would be similar with histories and challenges performed by nonallergy specialists remains to be determined. In pediatric patients with a history of benign cutaneous reactions, we recommend direct amoxicillin challenge without preceding penicillin skin testing. In contrast, adults with histories of distant and benign cutaneous reactions can be considered for direct amoxicillin challenge (without skin testing). However for those adults who are particularly anxious or uncomfortable with the idea of a direct challenge, performing penicillin skin tests first may be considered, because confirmation of negative penicillin skin testing may be useful to alleviate these fears. For patients with histories that are inconsistent with penicillin allergy (such as headache or family history of penicillin allergy), no testing is required and the patient may be delabeled. However, in patients who are reluctant to accept the removal of a penicillin allergy after appropriate counseling, amoxicillin challenge using a single treatment dose is sufficient to rule out an allergy (and to gain acceptance of the delabeling). Multiple-day penicillin challenges are not recommended because recent studies have shown that single-day challenges detect the majority of delayed reactions.[23,24] Recently, reports of patients with selective allergic reactions to piperacillin tazobactam have been published that indicate that most patients with reactions to piperacillin tazobactam can tolerate other penicillins.[25,26] Skin testing to piperacillin tazobactam may be useful to identify this selective sensitivity where traditional penicillin skin testing or amoxicillin challenge may be negative.[25,26]

Cephalosporins. Immediate allergic reactions to cephalosporins appear largely to be related to antigenic responses to the R1 group/side chains rather than the core beta-lactam portion of the molecule or R2 group/side chains.[27] As in penicillin allergy, the history of the reaction is important in determining the diagnostic approach. For immediate reactions to cephalosporins, we suggest stratifying patients based on anaphylactic reactions versus nonanaphylactic reactions. For those patients with nonanaphylactic cephalosporin allergy, a direct challenge should be performed for a cephalosporin with dissimilar side chains to determine tolerance. In contrast, for administration of cephalosporins with similar side chains and for the less common anaphylactic reaction history, a negative cephalosporin skin test to a parenteral cephalosporin should be performed prior to challenge to determine tolerance. Urticaria fulfilling "1-1-1-1" criterion (appearance within 1 hour after the first dose and regression within 1 day and occurred within 1 year) suggests a high likelihood of having a positive skin test.[22]

Beta-lactam cross-reactivity. Since the last drug allergy practice parameter update, several studies indicate that the risk of cross-reactivity among beta-lactams is lower than previous reports suggested.[28] For management approaches, we suggest stratifying patients based on anaphylactic versus nonanaphylactic histories as well as verified versus unverified (unconfirmed) penicillin allergy. We suggest that for patients with a history of an unverified nonanaphylactic penicillin allergy, any cephalosporin can be administered routinely without testing or additional precautions. For example, patients with a history of urticaria to a penicillin can receive any cephalosporin routinely without prior testing. In contrast, for those rare patients with a history of anaphylaxis to penicillin, a non–cross-reactive cephalosporin (eg, cefazolin) can be administered routinely without prior testing.

For patients with a primary allergy to cephalosporin, we suggest a similar approach: stratifying patients based on anaphylactic versus nonanaphylactic histories, as well as verified versus unverified cephalosporin allergy. We suggest that for patients with a history of an unverified nonanaphylactic cephalosporin allergy, a penicillin can be administered without testing or additional precautions. For example, patients with a prior history of urticaria to cephalexin can receive amoxicillin without prior testing. In contrast, for those rare patients with a history of anaphylaxis to a cephalosporin, we suggest penicillin skin testing and drug challenge be performed prior to administration of penicillin therapy.

Guidance on administration of carbapenems to patients with penicillin allergy has also changed since the last drug allergy practice parameter update.[28] We now suggest that in patients with a history of penicillin or cephalosporin allergy, a carbapenem may be administered without testing or additional precautions regardless of whether the reaction was anaphylactic. In regard to monobactams such as aztreonam, both patients allergic to penicillin and

those allergic to cephalosporins may be administered aztreonam without prior testing with the exception of patients who are allergic to ceftazidime (due to aztreonam and ceftazidime sharing an identical R1 side chain). However, because aztreonam is an expensive alternative for patients allergic to penicillins, and there is increasing monobactam resistance, delabeling the penicillin allergy is recommended.[29]

Cross-reactivity between beta-lactams in patients with SCARs appears to be based on the R1 side chain but data are incomplete. Avoidance of all beta-lactams is generally recommended in patients with a SCAR that is considered highly likely to be due to a beta-lactam; however, the risk of a reaction should be weighed against the benefit of treatment of the underlying infection and the availability of alternative treatment options. For some SCARs, such as DRESS, skin testing and other adjunctive testing may help identify the culprit drug and cross-reactivity patterns, but no testing has a 100% NPV. Small case series data suggest that some patients with DRESS from penicillins may tolerate other beta-lactams.[30] Although reported cases of SCARs due to 2 different classes of beta-lactams are rare, larger studies are required to determine the safety of using alternative beta-lactams in patients with SCARs due to a specific beta-lactam.

Sulfonamides. Guidance on the approach to sulfonamide allergy has also changed significantly since the last drug allergy parameter update. As opposed to recommending induction of drug tolerance protocols for those with histories of sulfonamide allergy, we now suggest direct challenges that can be completed within 2-3 hours. For patients with a history of benign cutaneous reactions (eg, morbilliform drug eruption [MDE] or urticaria) to sulfonamide antibiotics that occurred >5 years ago, a 1-step drug challenge with TMP-SMX can be performed when there is a need to delabel a sulfonamide antibiotic allergy. For patients with reactions within the past 5 years, a 2-step challenge is now recommended. Sulfonamide delabeling can be performed for both immunocompetent and immunocompromised individuals (including patients infected with HIV) when there is a need for sulfonamide antibiotic therapy.

Fluoroquinolones. Immediate-type reactions to fluoroquinolones have been increasingly described. There is evidence for both IgE-mediated and non–IgE-mediated mechanisms, because fluoroquinolones may cause nonspecific mast cell degranulation via interaction with the surface receptor MRGPRX2.[31] Unlike IgE-mediated reactions, non–IgE-mediated reactions may occur with first exposure because prior sensitization is unnecessary. However, non–IgE-mediated reactions may not be consistently or repeatedly observed for a given drug or be observed for other drugs that interact with the MRGPRX2 receptor (such as vancomycin in patients who reacted to a fluoroquinolone). For remote (ie, >5 years ago), nonanaphylactic reactions, a 1- or 2-step graded challenge with the implicated fluoroquinolone is suggested as a method of delabeling. For more severe or recent (ie, < 5 years ago) reactions, 1- or 2-step graded challenge with a different fluoroquinolone than the one implicated in the historical reaction (because they may not cross-react) may be considered.

Macrolides. Even though macrolides are one of the more common antibiotics listed in drug allergy records, very few patients are confirmed to actually be allergic to macrolides. The utility of immediate-type skin testing using nonirritating concentrations of macrolides is uncertain.[32] Therefore, based on the low pretest probability, very low rate of anaphylaxis, and disagreement on the utility of skin testing, direct challenge appears to be the most appropriate diagnostic approach for patients with a history of nonanaphylactic reactions.

NSAID hypersensitivity

Aspirin and NSAIDs can cause a spectrum of drug HSRs, including exacerbation of underlying respiratory or cutaneous diseases (urticaria, angioedema), anaphylaxis, and, rarely, pneumonitis and meningitis.[33,34] There are 4 primary categories of NSAID reactions that can be diagnosed via history, presence of comorbid diseases, and drug challenges. These reactions include AERD, NSAID-induced urticaria and angioedema, NSAID-exacerbated cutaneous disease, and single NSAID-induced reactions. A selective COX-2 inhibitor may be used as an alternative analgesic in patients with any NSAID hypersensitivity phenotype when an NSAID is needed.

In many patients with suspected AERD, the clinical history is often sufficient to make a diagnosis and an oral aspirin challenge is not required. However, in cases of diagnostic uncertainty where patients may be avoiding aspirin or NSAIDs, an oral aspirin challenge is suggested to confirm the diagnosis of AERD. Aspirin desensitization followed by aspirin therapy can be used to control nasal polyp regrowth and allow aspirin therapy for cardioprotection or use of NSAIDs for pain relief. Several different protocols for aspirin desensitization exist.

The phenotype of NSAID-exacerbated cutaneous disease manifests as exacerbations of urticaria or angioedema in patients with chronic spontaneous urticaria. The general approach to patients with this condition is to primarily control the underlying urticaria. Patients whose urticaria is controlled on either H_1-antihistamines or omalizumab may be able to tolerate NSAID therapy.

In contrast to the aforementioned phenotypes of aspirin-/NSAID-exacerbated respiratory and cutaneous diseases, the NSAID-inducible cutaneous phenotype causes urticaria/angioedema in patients without any underlying chronic spontaneous urticaria. Patients with this phenotype may react to all COX-1 inhibitors. An aspirin challenge is suggested to identify such patients where there is uncertainty regarding tolerance to other NSAIDs.

Lastly, there are patients who react specifically to single NSAIDs or structurally related NSAIDs. There are multiple phenotypes within this group, and patients may have immediate reactions (ie, urticaria, angioedema, or anaphylaxis) or delayed reactions (ie, fixed drug eruptions, meningitis, pneumonitis, or many others). These single NSAID reactions are not related to COX-1 inhibition and are thought to be either IgE-mediated reactions in the case of immediate reactions or related to drug-specific T-cell delayed hypersensitivity.

Guidance on the approach to patients with a history of aspirin allergy in the setting of an acute coronary syndrome have changed since the last updated drug allergy parameter. Rather than using an aspirin desensitization protocol, we suggest a 2-step aspirin challenge for patients labeled with an aspirin allergy if the history does not suggest AERD. A graded challenge is preferred because it provides the patient and clinician with a true diagnosis and, if negative, simplifies any further questions about aspirin use. A challenge is simpler than a desensitization (no need for compounding the aspirin dose), faster, and will efficiently answer

the question regarding hypersensitivity while simultaneously achieving the therapeutic objective.

Cancer chemotherapeutics

Guidance on management of HSRs to cancer chemotherapeutics has been expanded significantly in this parameter. The main approaches to care after a presumed HSR to a chemotherapeutic include (1) desensitization, (2) skin testing to assist with risk stratification, (3) risk stratification without skin testing and drug challenge, or (4) avoidance of the offending agent if an equally efficacious alternative exists. If the clinical assessment is consistent with an HSR, then empiric desensitization is a reasonable and safe approach to care and can be performed even when skin testing is not possible (ie, outpatient clinic without access to chemotherapy drugs for skin testing). Candidates for drug desensitization to chemotherapeutics include those with type I HSRs (mast cell–mediated/IgE-dependent) including anaphylaxis. While 3-bag desensitization protocols have been most commonly used for intravenous medications, increasing evidence suggests similar safety and efficacy by using a 1-bag protocol, resulting in a simpler and more time-efficient desensitization; however, more data are needed, especially in patients with severe initial HSRs.[35] Patients without a convincing clinical history of an HSR do not require desensitization and typically respond well to readministration of the chemotherapeutic agent. Examples include subjective symptoms of pruritus or lip swelling without any objective skin findings during the infusion. If symptoms are mild in nature (ie, flushing or pruritus alone without hives, back pain alone) or there is heightened patient concern around readministration, then premedications, such as H_1-antihistamines, and a slowed infusion rate have been used successfully without the need for desensitization.[36]

Platins. For patients with a history of immediate allergic reactions to platinum-based chemotherapeutic agents, the severity of the initial HSR and skin testing results may assist in their risk stratification and management. Skin testing may be useful in the management of patients with platin HSRs and also identifies cases where desensitization may be unnecessary despite a clinical history that is suggestive of an HSR. However, while avoiding unnecessary desensitization by identifying patients who are truly allergic, risk-stratification protocols can create operational challenges in addition to rising costs, increased patient time, multiple office visits, and potential delays in treatment. Empiric desensitization remains a safe method to manage patients after a platin HSR.

Taxanes. Taxane HSRs are generally thought not to be related to the active drug but instead may be caused by excipients. In contrast to platinum HSR where skin testing may be of value, the role of skin testing after a taxane HSR remains unclear. We suggest that for patients with a history of immediate allergic reactions to taxanes, the severity of the initial HSR may assist in their risk stratification and management. Pretreatment with systemic corticosteroids and H_1-antihistamines can decrease the rate of reactions to taxanes from 30% to 3%.[37-39] For patients with more severe initial taxane HSRs, empiric desensitizations may be employed.

Tyrosine kinase inhibitors. Tyrosine kinase inhibitors (TKIs) have been associated with significant idiosyncratic or pharmacologic effects including cutaneous and systemic side effects (including a recent US Food and Drug Administration [FDA] black box warning for serious heart-related events, cancer, blood clots, and death).[40] The mechanism of these adverse effects is pleotropic and may relate directly to tyrosine kinase effects rather than immunologic hypersensitivity. Like other reactions associated with chemotherapeutic drugs, recognition and correct clinical phenotyping is key to risk stratification and the formulation of an appropriate management plan. This includes the decision on when to reduce the dose, stop the drug, treat with corticosteroids, challenge, or desensitize.

Immune checkpoint inhibitors

Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment. The currently available ICIs are mAbs that block specific immune checkpoints, CTLA4, programmed cell death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1), leading to increases in T-cell activation and proliferation.[41] The mechanism of action of these drugs, which reduce self-tolerance, can lead to a number of toxicities that are typically organ-specific autoimmune events and are referred to as immune-related adverse events (irAEs).[41] The most common of these are mild to moderate and include dermatitis, thyroiditis, and other endocrinopathies, hepatitis, colitis, interstitial nephritis, and pneumonitis.[42-44] Rare but potentially fatal events include myocarditis and encephalitis.[45,46] It is important for the allergist-immunologist to recognize these nonallergic events because they may be consulted for common toxicities such as rashes or organ dysfunction or they may have patients that they are following for other reasons that are under treatment with an ICI.[44] Management of irAEs requires multidisciplinary care.

Biologics

Biologic agents are newer therapeutic agents created from living cells, tissues, or organisms that include mAbs (suffix "mab") and soluble fusion receptors (suffix "cept"). Biologic agents including mAbs have the benefit of target specificity and infrequent dosing yet have potential to be immunogenic. A variety of mechanisms may result in reactions including complement activation, SSLR, and mast cell activation either via IgE-mediated or direct mast cell activation.[47] Nonimmune mechanisms such as tumor lysis and cytokine storm may also cause symptoms that overlap with immune-mediated reactions. The utility of diagnostic testing (eg, skin testing and *in vitro* testing) is limited by several factors including, but not limited to, mechanistic uncertainty, the cost of the medications, availability, lack of validation, and the unknown predictive value. Given these limitations, we suggest that skin testing for mAbs is rarely clinically indicated or performed.

For patients with nonimmediate reactions or a history of reactions inconsistent with mAb HSR, a desensitization may not be required and treatment with a slowed infusion, graded dose escalation, and/or premedications is suggested. In contrast, for patients with immediate reactions including anaphylactic reactions to mAbs, drug desensitization should be considered when the implicated drug is the preferred therapy. As in cancer chemotherapy desensitization, increasing evidence suggests similar safety and efficacy by using a 1-bag protocol resulting

in a simpler and more time-efficient desensitization, but more data are needed, especially in patients with severe initial HSRs.[35]

Rituximab. The risk of rituximab HSR is especially high during the initial infusion, as ≤77% of patients being treated for a B-cell lymphoma can develop a reaction during their first exposure.[48] Paradoxically, the risk of having a reaction to rituximab appears to decrease with subsequent infusions.[49,50] Tumor burden affects the type of infusion reaction. Other reactions encompass several different immunologic mechanisms, including cytokine release syndrome, (mast cell–mediated) HSRs, and tumor lysis syndrome. Shared decision making, in which the risks and benefits of the options are considered, is an important strategy. For milder rituximab HSRs, slowed infusion (typically 50% usual infusion rate), graded challenge, or desensitization are considered reasonable options. In more severe reactions, empiric desensitization is preferred. The utility of rituximab skin testing is unclear, especially in cases where the reaction likely is not mast cell–mediated. While drug challenges have been performed in patients with moderate-severe reactions to biologics (including rituximab) and negative skin testing, several of the patients who reacted on challenge had moderate to severe anaphylaxis.[51] All challenges were carried out in an intensive care unit setting specifically assigned for patients who underwent drug desensitization. The workgroup recommends this approach should be considered only by very specialized centers. In patients who develop SSLRs to rituximab and for whom there are no equally efficacious therapies, rechallenge can be considered after shared decision making with an assessment of risks and benefits.

Cetuximab. Most of the severe HSRs to cetuximab were associated with preexisting IgE antibodies against galactose-α-1,3-galactose, a carbohydrate attached to cetuximab.[52] Investigation of the regional variation in reaction rates led to the discovery that Lone Star tick bites were the cause of specific IgE to galactose-α-1,3-galactose (alpha-gal) in these individuals. Other mAbs are produced with the murine SP2/0 cell line used for cetuximab and are glycosylated with alpha-gal. These include infliximab, abciximab, basiliximab, canakinumab, golimumab, and ustekinumab. While the alpha-gal content is lower in these antibodies, a case of first-dose anaphylaxis to infliximab due to cross-reactive alpha-gal–specific IgE has been reported.[53] There are successful reports of desensitization to cetuximab in the literature.[54,55]

Infliximab. Similar to rituximab, the mechanisms of infliximab reactions are likely diverse, including IgE-mediated hypersensitivity, cytokine release syndrome, and SSLR.[56] HSRs to infliximab occur in ~10% of patients and are usually during the first or second exposure but can also occur with subsequent doses. Antibodies against infliximab may reduce the efficacy of treatment and increase the risk of HSRs.[57,58] Risk stratification based on the severity of the HSR can be considered in the evaluation and management of individuals that develop reactions to infliximab. Testing for alpha-gal–specific IgE should be considered in patients with first dose reactions to infliximab, given the aforementioned potential for cross-reactivity in patients with alpha-gal allergy.

Omalizumab. The risk of anaphylaxis with omalizumab is <0.1%, but interestingly 36% of reactions occurred >1 hour after administration of the drug, and 7% occurred >12 hours later.[59,60] In that study, 69% of the reactions occurred with the first 2 doses. A nonirritating omalizumab concentration for intradermal skin testing was defined at 1:100,000 volume to volume dilution, a concentration of 1.25 mcg/mL, but the predictive value has not been established in individuals with anaphylaxis to omalizumab.[61] There are reports of successful desensitization to omalizumab.[62-65] SSLRs have also been reported with omalizumab.

Excipients

An excipient is an inactive substance that is formulated alongside the active pharmaceutical ingredient of a medication. Excipients include coloring agents, preservatives, stabilizers, and fillers.[66] Excipients are more likely to contribute to intolerance than to a true allergic reaction.[67] Categories of excipients include foods and sugars such as lactose, mannitol, gelatin, and cornstarch; polymers such as polyethylene glycol (PEG) and its derivatives; dyes and coloring agents; and other ingredients such as carboxymethylcellulose.[66] The average oral formulation of a product has ~9 inactive ingredients.[66] Excipients are a very rare cause of immediate or delayed reactions associated with drugs.[68-70] Although delayed reactions are associated with some excipients (eg, propylene glycol), the most worrisome reactions are life-threatening anaphylaxis associated with excipients such as PEG and carboxymethylcellulose in injectable corticosteroids.[68,71] The optimal testing strategy for polysorbates and their cross-reactivity with PEG requires further study. Excipient allergy may be considered in patients with a history of anaphylaxis to ≥2 structurally unrelated drugs or products that share a common excipient, (eg, injectable corticosteroids; PEG-based laxatives).

METHODS AND OVERVIEW OF THE PRACTICE PARAMETER DEVELOPMENT PROCESS

This practice parameter focuses on updates to the diagnosis and management of various drug allergy reactions since the previous drug allergy practice parameters were published in 2010.[1] This update focuses on evolving evidence surrounding characterization of drug allergy reactions, phenotyping, diagnosis, management, clarification of drug allergy history, and updates to nonantibiotic drug allergy. A workgroup of experts was chaired by David Khan, MD. The workgroup determined which areas warranted an update and then performed a literature search for all relevant articles published since 2008. A search of the medical literature was performed using a variety of terms that were considered relevant for this practice parameter. Literature searches were performed on PubMed, MEDLINE, Medscape, Google Scholar, and the Cochrane Database of Systematic Reviews. The time frame for most searches was 2008-2021, but some topics required searches for an expanded time frame from 1960 to present. The searches included only English-language articles.

Although the ideal type of reference would consist of a randomized, double-blind, placebo-controlled study, the topic of this practice parameter is represented by very few such studies. Consequently, it was necessary to use observational studies, case series, basic laboratory reports, and expert review articles to develop a document that addresses most of the issues included in this practice parameter. The references cited in this practice parameter represent the best quality and most relevant evidence for the discussion and recommendations made herein.

This practice parameter contains systematically developed recommendations intended to optimize care of patients and to assist physicians and/or other health care practitioners and patients to make decisions regarding diagnosis and management of suspected drug allergy. This practice parameter was not intended to be a Grading of Recommendations, Assessment, Development and Evaluation (GRADE) document. Because GRADE documents require a comprehensive literature search, systematic review, and meta-analysis for

TABLE I. Grading the strength of recommendations

Strong Recommendation
The workgroup and JTFPP are confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects. This recommendation may be appropriate to be used as a practice standard indicator. When making a strong recommendation, the wording is "we recommend," implying that the clinician would choose to follow the recommendation in most circumstances.
The implications of a strong recommendation are the following:
● For patients—most people in your situation would want the recommended course of action and only a small proportion would not; request discussion if the intervention is not offered.
● For clinicians—most patients should receive the recommended course of action.
● For policy makers—the recommendation can be adopted as a policy in most situations.
Conditional Recommendation
The workgroup and JTFPP concluded that the desirable effects of adherence to a recommendation probably outweigh the undesirable effect but are not confident. When making a conditional recommendation, the wording is "we suggest," implying that the clinician may choose to follow the recommendation but that decisions may vary based on contextual factors.
The implications of a conditional recommendation are the following:
● For patients—most people in your situation would want the recommended course of action, but many would not.
● For clinicians—you should recognize that different choices will be appropriate for different patients and that you must help each patient to arrive at a management decision consistent with her or his values and preferences. It is likely that shared decision making will plan a major role in arriving at the management decision.
● For policy makers—policy making will require substantial debate and involvement of many stakeholders.
Consensus-based Statement
When there are either no published studies, or very limited and/or weak evidence, a consensus statement without any category of certainty of evidence was developed. The degree of agreement by all JTFPP and workgroup members is indicated, with voting details provided if there were dissenting votes.

TABLE II. Grading the certainty of evidence for each recommendation

High = Further research is very unlikely to change our confidence in the estimate of effect. The recommendation is based on high-quality evidence, for example, multiple highly rated randomized controlled trials, systematic reviews, and metanalyses.
Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. The recommendation would likely be based on somewhat limited evidence, for example, reduced number or quality of randomized controlled trials or controlled trials without randomization.
Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. The recommendation would likely be based on very weak evidence, for example, nonexperimental studies, registries, or comparative studies.
Very low = Any estimate of effect is very uncertain. The recommendation is based largely very low-quality studies and/or on expert opinion.

each question, they require substantial resources, making it cost prohibitive to attempt to conduct a GRADE analysis for all of the questions for which clinicians would like an answer. In addition, for many questions, there is very limited evidence, and the workgroup/Joint Task Force on Practice Parameters (JTFPP) must in these cases rely on expert evidence and opinion. Therefore, in this practice parameter, the recommendations are CBSs, which are based, at best, on a recent literature search of PubMed to update or add to the 2010 drug allergy document.[1] We have changed our method of grading recommendations to be more transparent, choosing words that are used in a formal GRADE document (eg, strong and conditional), to be consistent in terminology and to maintain a common thread. However, the use of these words does not imply that we are equating our recommendations to the rigor required by a GRADE document.

The strength of the CBSs is determined to be either strong or conditional as defined in Table I. The certainty of evidence for each recommendation is determined to be high, moderate, low, or very low as defined in Table II. When the JTFPP did not have adequate published evidence with which to determine the certainty of evidence, but nonetheless recognized the need to provide guidance to the clinician, the CBSs were based on the collective expert opinion and experience of the workgroup and JTFPP. Table III lists all the CBSs.

The practice parameter development process involved several stages. The workgroup began the process by developing a list of key clinical questions and topics to be addressed. The topics and questions were selected to reflect the most significant advances and changes in the field that affect clinical practice. At least 2 workgroup members were assigned to write and review each section. A literature search was completed to determine the most updated information for each CBS and discussion. The draft sections were reviewed by the workgroup chair with subsequent revision by the authors. Subsequently, all sections were reviewed and revised by the entire workgroup through several rounds of electronic and teleconference reviews. The guideline was reviewed in detail by the JTFPP and revisions, when needed, were made in conjunction with the workgroup. The external review followed as described in the ''Resolving conflict of interest'' section.

DIAGNOSTIC TESTING UPDATES

Drug challenges

Drug challenges are a diagnostic test and are considered the reference standard to determine whether a patient may safely take a medication. A number of terms have been used to describe this procedure including "drug provocation tests," "graded challenges," and "test doses." The term "drug challenge" is recommended as this is in keeping with other allergic diseases (eg, food challenges, sting challenges). While "drug provocation" is commonly used in the international literature, we do not recommend this term as the intent is to show tolerance rather than to provoke a reaction. Drug challenges may be given in an incremental (graded) fashion, but they can also be administered as a single dose.

Drug challenges are typically indicated in patients who after evaluation are deemed unlikely to be allergic to the drug. Several factors are used to determine whether a certain history is a "low-

TABLE III. List of CBSs

Section and number	CBS	Strength of recommendation	Certainty of evidence
Drug challenges			
CBS 1	We suggest that when the clinical probability of a drug allergy is low, in patients without contraindications for a drug challenge, that it be performed with a 1- or 2-step drug challenge.	Conditional	Low
CBS 2	We suggest that placebo-controlled drug challenges be considered in patients with a history of primarily subjective symptoms and/or multiple reported drug allergies.	Conditional	Low
Testing for delayed HSRs			
CBS 3	We suggest that for specific phenotypes of delayed drug HSRs where the pretest probability is high (eg, DRESS), but the implicated agent is uncertain, that dIDT and/or PT may be useful as adjunctive tests to support drug causality.	Conditional	Very low
Beta-lactams			
CBS 4	We recommend that a proactive effort should be made to delabel patients with reported penicillin allergy, if appropriate.	Strong	Moderate
CBS 5	We recommend against any testing in patients with a history inconsistent with penicillin allergy (such as headache, family history of penicillin allergy, or diarrhea), but a 1-step amoxicillin challenge may be offered to patients who are anxious or request additional reassurance to accept the removal of a penicillin allergy label.	Strong	Low
CBS 6	We suggest penicillin skin testing for patients with a history of anaphylaxis or a recent reaction suspected to be IgE-mediated.	Conditional	Low
CBS 7	We recommend against the routine use of multiple-day challenges in the evaluation of penicillin allergy.	Strong	Low
CBS 8	We recommend against penicillin skin testing prior to direct amoxicillin challenge in pediatric patients with a history of benign cutaneous reaction (such as MDE and urticaria).	Strong	Moderate
CBS 9	We suggest that direct amoxicillin challenge be considered in adults with a history of distant (ie, >5 years ago) and benign cutaneous reactions (such as MDE and urticaria).	Conditional	Low
CBS 10	We suggest that for patients with a history of nonanaphylactic cephalosporin allergy, direct challenges (without prior skin test) to cephalosporins with dissimilar side chains be performed to determine tolerance.	Conditional	Moderate
CBS 11	We suggest that for patients with a history of anaphylaxis to a cephalosporin, a negative cephalosporin skin test should be confirmed prior to administration of a parenteral cephalosporin with a nonidentical R1 side chain.	Conditional	Low
CBS 12	We suggest that for patients with a history of anaphylaxis to a penicillin, a structurally dissimilar R1 side chain cephalosporin can be administered without testing or additional precautions.	Conditional	Moderate
CBS 13	We suggest that for patients with a history of an unverified (not confirmed) nonanaphylactic penicillin allergy, a cephalosporin can be administered without testing or additional precautions.	Conditional	Moderate
CBS 14	We suggest that in patients with a history of an unverified nonanaphylactic cephalosporin allergy, a penicillin can be administered without testing or additional precautions.	Conditional	Low
CBS 15	We suggest that in patients with a history of anaphylaxis to cephalosporins, penicillin skin testing and drug challenge should be performed prior to administration of a penicillin therapy.	Conditional	Low
CBS 16	We suggest against penicillin skin testing in patients with a history of nonanaphylactic cephalosporin allergy prior to administration of a penicillin therapy.	Conditional	Low
CBS 17	We suggest that in patients with a history of penicillin or cephalosporin allergy, a carbapenem may be administered without testing or additional precautions.	Conditional	Moderate
CBS 18	We suggest that in patients with a history of penicillin or cephalosporin allergy, aztreonam may be administered without prior testing unless there is a history of ceftazidime allergy.	Conditional	Moderate
CBS 19	We recommend that allergist-immunologists collaborate with hospitals and health care systems to implement beta-lactam allergy pathways to improve antibiotic stewardship outcomes.	Strong	Moderate
Sulfonamides			
CBS 20	We suggest that for patients with a history of benign cutaneous reactions (eg, MDE, urticaria) to sulfonamide antibiotics that occurred >5 years ago, a 1-step drug challenge with TMP-SMX be performed when there is a need to delabel a sulfonamide antibiotic allergy.	Conditional	Low
Fluoroquinolones and macrolides			
CBS 21	We suggest using a 1- or 2-step drug challenge without preceding skin testing to confirm tolerance in patients with a history of nonanaphylactic reactions to fluoroquinolones or macrolides.	Conditional	Low

(Continued)

TABLE III. *(Continued)*

Section and number	CBS	Strength of recommendation	Certainty of evidence
Aspirin/NSAID hypersensitivity phenotypes			
CBS 22	We suggest a selective COX-2 inhibitor may be used as an alternative analgesic in patients with any NSAID hypersensitivity phenotype when an NSAID is needed.	Conditional	Low
AERD			
CBS 23	We recommend against an oral aspirin challenge to confirm the diagnosis of AERD in cases of high diagnostic certainty based on clinical history; however, aspirin desensitization remains a therapeutic option when indicated.	Strong	Low
CBS 24	We suggest an oral aspirin challenge to confirm the diagnosis of AERD in cases of diagnostic uncertainty.	Conditional	Moderate
CBS 25	We suggest that a challenge procedure be used to diagnose AERD when there is diagnostic uncertainty and that a desensitization protocol be used when the intention is to place a patient on a daily therapeutic aspirin dose for cardioprotection, pain relief, or to control nasal polyp regrowth.	Conditional	Moderate
Multiple NSAID-induced urticaria and angioedema			
CBS 26	For patients with NSAID-induced urticaria and angioedema, we suggest an oral aspirin challenge to identify whether the reaction is COX-1 cross-reactive.	Conditional	Low
Common NSAID hypersensitivity clinical scenarios			
CBS 27	We suggest a 2-step aspirin challenge for patients with a history of non-AERD aspirin allergy to aid in the management of cardiovascular disease events.	Conditional	Very low
Cancer chemotherapeutic hypersensitivity			
CBS 28	We suggest that in patients with immediate reactions to chemotherapeutics a drug desensitization may be performed when the implicated drug is the preferred therapy.	Conditional	Low
CBS 29	We suggest that patients with nonimmediate reactions or a history of reactions inconsistent with chemotherapeutic hypersensitivity may be treated with a slowed infusion rate, graded dose escalation, and/or premedications without desensitization.	Conditional	Low
Platins			
CBS 30	We suggest that for patients with a history of immediate allergic reactions to platinum-based chemotherapeutic agents, the severity of the initial HSR and skin testing results (if available) may assist in their risk stratification and management.	Conditional	Low
CBS 31	We suggest that for patients with a history of immediate allergic reactions to taxane-based chemotherapeutic agents, the severity of the initial HSR may assist in their risk stratification and management.	Conditional	Low
Biologic hypersensitivity			
CBS 32	We suggest that patients with nonimmediate reactions or a history of reactions inconsistent with mAb hypersensitivity may be treated with a slowed infusion, graded dose escalation, and/or premedications without desensitization.	Conditional	Low
CBS 33	We suggest that for patients with immediate reactions or a history consistent with anaphylaxis to mAbs drug desensitization should be considered when the implicated drug is the preferred therapy.	Conditional	Low
Excipients allergy			
CBS 34	We suggest the clinician recognize that excipients are a very rare cause of immediate or delayed reactions associated with drugs. Still, excipient hypersensitivity may be considered in patients with a history of anaphylaxis to ≥2 structurally unrelated drugs or products that share a common excipient (eg, injectable corticosteroids; PEG-based laxatives).	Conditional	Low

risk history" and may include how remote the index reaction was, benign cutaneous signs and symptoms only, subjective symptoms only, a high number of listed drug allergies, and drugs that infrequently cause allergic reactions. Drug challenges can be particularly helpful in determining specific drug tolerance when a reaction occurs in the setting of multiple concomitant drug exposures. Shared decision making may be used in patients with a higher pretest probability of true allergy or a history of more severe reactions when the benefit of drug therapy outweighs the risks. One exception to this is in patients being evaluated for AERD with an unclear history where confirming sensitivity to aspirin may have significant therapeutic implications (eg, aspirin

TABLE IV. Contraindications to drug challenges

Severe cutaneous adverse drug reactions
SJS/TEN
DRESS
AGEP
Drug-induced neutrophilic dermatosis
Sweet's syndrome
Drug-induced autoimmune diseases
Bullous pemphigoid
Pemphigus vulgaris
Linear IgA bullous disease
Drug induced lupus
Other cutaneous drug reactions
Generalized bullous FDE
Exfoliative dermatitis
Severe drug anaphylaxis*
Organ-specific drug reactions
Cytopenias (anemia, neutropenia, leukopenia, thrombocytopenia)
Drug induced liver injury
Nephritis
Pneumonitis
Meningitis
Pancreatitis
Drug-induced vasculitis
Leukocytoclastic vasculitis
Eosinophilic granulomatosis with polyangiitis
Angiotensin-converting enzyme inhibitor angioedema

*In the absence of reliable skin testing or when the benefit does not outweigh the risk.

desensitization/therapy). In some patients with toxic reactions to ICIs, drug rechallenge may also be considered.[44] Drug challenges are generally contraindicated in more severe non-IgE–mediated reactions such as SCARs, drug-induced liver injuries, and drug-induced cytopenias (Table IV). Rare exceptions to this may include treatment of a life-threatening illness where the benefit of treatment outweighs the risk of a severe drug reaction. A study from South Africa revealed that 50% of 46 patients who were rechallenged with antituberculosis drugs causing SCAR developed reintroduction reactions; most were mild-moderate and self-resolved, but severe reactions also occurred.[72] The same group reported on a series of 6 patients with antituberculosis therapy SCARs, who reacted on rechallenge but had resolution of symptoms and no development of SCAR after treatment with a single dose of methylprednisolone (100-200 mg) within 3 hours of onset of rechallenge symptoms.[73] While drug challenges have generally been avoided in cases of serum sickness, there are reports of some patients being able to tolerate drug challenges after SSLRs to certain drugs including rituximab, amoxicillin, and other beta-lactams.[74-76] A recent study of 75 children with SSLRs to beta-lactams (all with arthralgias/arthritis), found 93% had a negative 2-step challenge; however, 5 of 20 patients who were contacted developed benign rashes with a subsequent full treatment course.[77] Therefore, drug challenge can be considered in SSLRs through shared decision making, considering factors such as remoteness of reaction, importance of the drug, and likelihood that the reaction was drug-related.

Consensus-based Statement 1: We suggest that when the clinical probability of a drug allergy is low, in patients without contraindications for a drug challenge, that it be performed with a 1- or 2-step drug challenge.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

Numerous techniques for drug challenges have been published and the approach varies considerably between clinicians and countries, but few have undergone comparative studies.[78] A US study compared outcomes of patients with low-risk histories who underwent 1- or 2-step challenges (n = 456) with multistep challenges involving 3 or 4 steps (n = 74).[79] Most challenges were for antimicrobials (most commonly penicillin) but NSAIDs, opioids, cardiovascular drugs, and others were included. While 47% of challenges underwent skin testing before challenges (the majority for penicillins), the rest did not have prior skin tests. Reactions were generally mild-moderate and occurred at a similar low frequency between 1-2–step challenges (11%) and the 3-4–step challenges (12%). Data are lacking comparing 1-step versus 2-step challenges in regard to safety. In patients with a history of more severe reaction or higher pretest probability, 2-step challenges may be preferred. The European Network for Drug Allergy and the European Academy of Allergy and Clinical Immunology interest group on drug hypersensitivity guideline for drug provocation tests has indicated a starting dose between 1:10,000 and 1:10 of the therapeutic dose but typically involving multiple steps.[80] There is a theoretical concern that multistep challenges may potentially cause a desensitization. However, an *in vitro* animal desensitization model of mast cells sensitized to dust mite showed that inhibition of mast cell mediator release was greatest with 2-fold concentration increases compared to 10-fold increases, suggesting that 10-fold increases used in drug challenges would be unlikely to cause desensitization.[81] A retrospective study from France analyzed optimal dosing for drug challenges evaluating their 6- to 9-step protocols starting as low as 1/10,000 of the final dose.[82] Based on analysis of their reactive doses, they recommended a shorter 4-step protocol starting with 5% of the therapeutic dose. However, they also performed challenges in patients with histories of anaphylaxis and found a 10-fold increased risk for anaphylaxis (compared with patients without culprit drug anaphylaxis) during challenge, even with doses at ≤1%. For these patients, they recommended starting at 1/10,000 of the treatment dose. For most drugs, which lack accurate skin or *in vitro* diagnostic testing, it is recommended to avoid drug challenges in patients with convincing histories of anaphylaxis as drug desensitization would be a safer approach. Some centers have performed 2-3 challenges in the same day to multiple antibiotics or a combination of antibiotics and NSAIDs.[83,84] While this is usually a more efficient approach, the potential drawback to this approach is that if a delayed reaction occurs, repeat, separate drug challenges would be required. Finally, drug challenges can be used for evaluation of delayed drug reactions.[85] Suggested challenge approaches are shown in Table V for patients with histories of immediate reactions and Table VI for those with histories of delayed reactions.

While drug challenges are considered the reference standard for drug allergy evaluations, some patients may have subsequent drug reactions despite a negative challenge. In fact, compared to individuals with no history of a drug allergy, those who report ≥1drug allergy report a 2- to 3-fold higher incidence rate of new adverse reactions to most classes of medications.[86] A multicenter survey from centers in France, Italy, and Portugal contacted patients after negative drug evaluations.[87] Of 365 patients surveyed, 118 took the drug found negative on testing or another related agent and 9 (7.6%) reported a reaction (urticaria or an exanthem). Of these 9 patients, 4 accepted reevaluation and 2 were found to

TABLE V. Open drug challenge protocols for immediate reactions

	Dose*	Observation
1-step	1 tab or full PO/IV/IM/SC dose†	30-60 min
2-step	Step 1: ¼ tab PO or 1/10 IV/IM/SC dose	30-60 min
	Step 2: 1 tab or full PO/IV/IM/SC dose†	30-60 min
Criteria for positive reaction	Urticaria, angioedema, exanthem, wheezing, hypoxia, hypotension, anaphylaxis	
Criteria for possible reaction‡	Flushing, vomiting, cough, abdominal cramping, persistent pruritus without rash, fever, mouth or eye soreness	
Doubtful reactions‡	Dizziness, tachycardia, subjective lip/tongue swelling, subjective throat tightness, lump in throat, dyspnea, transient pruritus without rash, headache	

IM, Intramuscular; *IV*, intravenous; *PO*, oral; *SC*, subcutaneous.
*Comparably dosed oral solution may be used ($1/10^{th}$ or full dose).
†For patients at very low risk without significant comorbidities, may use single full-dose challenge (see sulfonamide and penicillin sections).
‡Consider placebo-controlled challenges for possible or doubtful reactions to confirm or refute allergy.

TABLE VI. Open drug challenge* protocols for nonsevere delayed reactions†‡

	Dose§	Observation
1-step**	1 tab or full PO||	60 min to 2 h
2-step	Step 1: 1/10 IV/IM/SC dose	30 min
	Step 2: full PO/IV/IM/SC dose||	60 min to 2 h
Other*	Multiple-day challenge or graded reintroduction	Outpatient procedure
Criteria for positive reaction	Fever, urticaria, facial swelling, exanthem, hypoxia, hypotension, mouth, urogenital or eye soreness, fixed or blistering eruption, target or atypical target lesions	
Criteria for possible reaction¶	Isolated joint pain, appetite change, persistent pruritus without rash	
Doubtful reactions¶	Dizziness, tachycardia, subjective lip/tongue swelling, subjective throat tightness, lump in throat, dyspnea, transient pruritus without rash, headache, transient pruritus without rash	

*Sometimes called desensitization or induction of drug tolerance, but the mechanism is unknown at this time and probably functions more like a challenge reaction when beyond a critical dose a reaction can recur. These challenges are often initiated by the patient in the outpatient setting and may not be performed under direct observation.
†Contraindicated for severe cutaneous adverse drug reactions or any situation where documented organ failure has occurred (see delayed hypersensitivity section).
‡Nonsevere delayed onset reactions may also be initiated by the patient at home with in-clinic follow-up if the visit is by telehealth or direct observation in the outpatient clinic setting is not possible.
§Comparably dosed oral solution may be used (1/10 or full dose).
||For patients who are very low risk without significant comorbidities or reactions that have occurred more distantly (>5 years), single full-dose challenge may be used (see delayed hypersensitivity section).
¶Consider placebo-controlled challenges or placebo treatment lead-in for possible or doubtful reactions to confirm or refute delayed HSR.
**For mild exanthems, single full-dose challenge may be used.

be tolerant on repeat challenge with the other 2 reacting. Including the 5 who refused re-evaluation as reactors, results yielded an NPV of 94.1% for drug challenge. A study from Turkey involving 91 children who received drugs previously challenged as negative found 11 who reported reactions.[88] Nine of the 11 cases were reevaluated with drug challenge and only 2 had positive challenges. Including the 2 reactors who refused rechallenge, data yielded an NPV of 95.6%. Thus, drug challenges have a high NPV, but similar to all tests, they are not infallible. We therefore recommend that patients be delabeled following a negative drug challenge.

The safety of drug challenges has been evaluated in many studies and is dependent on the inclusion of higher risk patients, the culprit drug, and the use of placebos. In recent US studies, the lowest rates of reactions (0.8%-4%) occurred in studies of patients at low risk when a history of subjective reactions were considered and placebos were used.[9,89] Other recent US studies have shown reaction rates to be slightly higher (9%-12%), including rare reports of anaphylaxis occurring with parenteral challenges.[79,90] Several studies from a number of countries have determined the safety of drug challenges in pediatric populations with rates of reactions ranging from 4.7% to 29.8%, with higher rates attributed to inclusion of NSAID challenges.[91-95] In a meta-analysis of 112 primary studies, which included a total of 26,595 participants with previous penicillin anaphylaxis, the pooled frequency of severe reactions to challenge was estimated at 0.06% (95% credible interval [95% CrI]: 0.01%-0.13%; I^2 = 57.9%).[96] Drug challenges are more likely to be positive in patients with NSAID reaction histories when compared to antibiotic allergies, and this topic is reviewed elsewhere in this parameter. A survey of international allergy specialists reported that most respondents indicated that challenges were very safe procedures, without any reports of need for transfer to an intensive care unit for management of a reaction and low rates of need for epinephrine.[78] Fatalities from oral drug challenge are exceedingly rare.[97]

For patients who require a specific drug that is urgently needed and more effective than alternatives, treating through a mild exanthematous reaction with H_1-antihistamines and topical corticosteroids may be a reasonable approach.[98-100] Warning signs that would indicate discontinuation of the drug may include the development of (1) target or bullous lesions, (2) pustulosis, (3) widespread dark erythema, (4) painful skin, (5) mucosal erosions, (6) elevated liver enzymes, and (7) impaired renal function. In general, the intention of a drug challenge is to rule out rather

than confirm a specific delayed reaction. In the setting of SCARs, except under extreme circumstances where treatment options are limited, and the risk from an infection exceeds the morbidity of the adverse drug reaction such as in patients with tuberculosis and HIV coinfection, rechallenge should not be attempted.[6,101] A single-dose oral challenge for SCARs may not be sufficient to rule out a delayed reaction, and the challenge may need to be extended over several days.[73]

Consensus-based Statement 2: We suggest that placebo-controlled drug challenges be considered in patients with a history of primarily subjective symptoms and/or multiple reported drug allergies.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

A drug challenge should be considered positive if it results in objective symptoms. Subjective symptoms (which may include throat tightness without visible orofacial angioedema, pruritus, lightheadedness, subjective facial swelling, dyspnea without objective findings) are common in drug challenges. Subjective symptoms have been reported more frequently in women, those with prior histories of subjective symptoms, and those with a high number of reported drug allergies.[9] Drug-associated inducible laryngeal obstruction (eg, vocal cord dysfunction) can be commonly mistaken for anaphylaxis when the presentation includes only isolated throat or chest tightness, and diagnosis may require laryngoscopy.[102-104] Because drug challenges can be anxiety provoking, objective reactions can also occur, even with placebo doses. These untoward responses to a placebo are referred to as a nocebo effect; a study from Turkey reported that 11.7% of nocebo reactions resulted in objective findings such as flushing, urticaria, cough, wheezing, tachycardia, and vomiting.[105] For these reasons, placebo-controlled drug challenges should be considered in patients who are at risk for anxiety-induced reactions (eg, patients with multiple drug allergies and prior subjective symptoms). A US study of 170 patients who underwent single-blind placebo-controlled drug challenges (the majority to amoxicillin after negative penicillin skin tests) noted 8.2% reactions to placebo with only 4% reacting to the drug.[89] In this study, placebo reactors were women who were more likely to have multiple drug allergy histories.[89] For patients who report multiple drug allergies, demonstrating a nocebo reaction can be helpful to legitimize their symptoms while demonstrating they are not due to a drug allergy. Explaining to patients that placebo-controlled challenges are a routine method used to assist clinicians in interpreting identical symptoms that may be induced by an allergic drug reaction or anxiety/fear can be helpful. Suggested challenge approaches are shown in Table VII.

TABLE VII. Single-blind placebo-controlled challenge protocols

	Dose	Observation
Immediate reaction	1. Placebo	30 min
	2. Placebo*	30 min
	3. Full-dose drug	60 min
Delayed reaction	1. Placebo†	60 min in office and return ≥3-7 d
	2. Placebo	60 min in office and return ≥3-7 d
	3. Full-dose drug	60 min in office and report tolerance/reaction in 3-7 d

Example placebo masking methods: (1) opaque capsules using inert filler (eg, microcrystalline cellulose); (2) flavored yogurt with flavored compounding syrup as masking agent.

*For patients where proving reaction to placebo is important (eg, high number of multiple drug intolerances), additional placebo steps may be used.

†For patients with suspect histories of delayed reactions, the duration of placebo dosing can vary. Patients who believe their reaction requires several days of therapy can be given placebo capsules to take at home for several days.

Testing for delayed HSRs

Delayed[106,107] reactions occur on average in 2%-5% of treatment courses for common drugs such as antibiotics and may be higher in some populations, such as those treated with multiple drugs or patients coinfected with human immunodeficiency virus, where the risk of a drug exanthem is estimated to be 100-fold that of the general population.[106,108] Although delayed immunologically mediated reactions are defined as those that occur ≥6 hours after dosing, the majority of delayed or T-cell–mediated reactions occur early in the second week after initiation of drug therapy (Fig 1).[106]

Evidence is low for all testing modalities for delayed HSRs and generally based on small case series without drug challenge; hence, the sensitivity, specificity, PPV, and NPV cannot be reliably calculated. Currently, clinical diagnosis is still considered to be the gold standard. For more complex reactions, scoring systems and phenotype standardization have been proposed, including an online scoring calculator for DRESS (available at https://redcap.vanderbilt.edu/surveys/?s=LPWDTD7TYCKN3TFM) (see Fig E1 in this article's Online Repository at www.jacionline.org) and others.[107,109,110] The time from start of dosing to development of a delayed reaction varies considerably among drugs and types of reactions and is critical to defining the clinical phenotype and the culprit drug. Examples of clinically relevant delayed hypersensitivity phenotypes compared with immediate hypersensitivity phenotypes are shown in Fig 1. This latency period combined with the clinical picture, including characteristics of the rash or systemic involvement, and histopathology (usually from a skin biopsy), are valuable clues as to the clinical phenotype. Drug causality algorithms have also been derived to aid in the identification of specific drugs or classes of drugs in relation to specific drug reactions.[111,112] An instructional video on delayed hypersensitivity testing is available (https://www.youtube.com/watch?v=-KmMF_X5g4g).

***In vivo* testing (PT and dIDT).** *Consensus-based Statement 3:* We suggest that for specific phenotypes of delayed drug HSRs where the pretest probability is high (eg, DRESS), but the implicated agent is uncertain, that dIDT and/or PT may be useful as adjunctive tests to support drug causality.

Strength of Recommendation: Conditional

Certainty of Evidence: Very Low

The method and interpretation of dIDT and PT are outlined in Table VIII[8,113] and an instructional video for these tests is available (https://www.youtube.com/watch?v=-KmMF_X5g4g). The use of dIDT (intracutaneous) and PT (epicutaneous) for drugs has been less uniformly adopted in the United States by both allergist-immunologists and dermatologists.[114] Prick testing may also be used, but unless there is a suspicion of an immediate reaction, the sensitivity for delayed reactions is low. There is an overall lack of FDA-approved reagents for testing, specialty centers that prepare and compound drugs for both dIDT and PT, and standardized methods.[8,115,116] There is also lack of information on the relevant highest nonirritating concentrations for most drugs for

TABLE VIII. Testing procedures for delayed HSRs

	Delayed intradermal	Patch testing*
Volume injected or vehicle	0.02-0.05 mL	Petrolatum, water, or alternative soluble vehicle
Drug concentration and preparation	Limited to drugs available in sterile preparation Highest nonirritating concentration	10% and 30% of trade product 1% and 10% of pure substance Highest nonirritating concentration
Performance of test†	6 weeks to 6 months after complete healing of reaction 6 months following DRESS reactions 4 weeks after discontinuation of systemic steroids (>10 mg prednisone equivalent) or other immunosuppressants	At least 6 weeks to 6 months after complete healing of reaction 6 months following DRESS reactions 4 weeks after discontinuation of systemic steroids (>10 mg prednisone equivalent) or other immunosuppressants
Criteria for delayed positivity	Any obvious induration at 24 h[8]‡	24-72 h infiltrated erythema as per international contact dermatitis guidelines[113] Patch removal at 48 h with further reading at 96 h and 7 d[113]
Site	Volar aspect of the forearm§ Non–sun-exposed if possible	Flat part of the back Upper arm is alternative Ideal areas are non–sun-exposed
Negative control	Saline	Petrolatum or vehicle
Positive control specific for delayed response	None	None

*Use of commercially available patch tape.
†For DRESS/DIHS, theoretical risk of systemic reaction with testing and recommendation for testing ≥6 months following acute reaction.
‡Delayed prick and intradermal tests may occasionally turn positive out to 96 hours.
§For convenience of documentation by the patient, the volar aspect of the forearm is used; however, for young children in particular as per immediate intradermal testing the flat surface of the back is an alternative.

both immediate and delayed reactions. Concentrations for some common drugs are listed in Table E1 in this article's Online Repository at www.jacionline.org. Unlike IgE-mediated reactions, the occurrence of a T-cell–mediated reactions is much more dependent on the dose and concentration of the drug.[115,117-119] The concentration of a drug needed to evoke a T-cell–mediated response, both as a systemic or cutaneous HSR and in research-based *in vitro/ex vivo* assays, may be significantly higher than that which causes an immediate histamine release reaction.[120-123] Evidence suggests that dIDT is more sensitive than PT for certain delayed reactions, such as MDE and DRESS/drug-induced hypersensitivity syndrome (DIHS) where data are more compelling for antibiotic allergy and anticonvulsants (Table IX).[7,113,114,124-127] However, the ability to perform dIDT is dependent on the drug being available in a sterile parenteral formulation.[7,8] dIDT may be more convenient than PT for the patient because there is no need to avoid showering, the reaction generally occurs within 24-48 hours, and the testing can be done on the arm in an area visible to the patient. For PT for drugs other than abacavir, it is essential that the drug remain in a soluble vehicle affixed to the skin and undisturbed for 48 hours. It is likely that the correct soluble vehicle for PT can considerably increase its sensitivity, but this is not known for most drugs. Petrolatum, or in some cases water for soluble drugs, is widely used for pragmatic reasons. For SCARs, the sensitivity of PT and dIDT for most drugs cannot be calculated because of a lack of sufficient data with drug challenge. However, a study reported the rate of positivity of patch testing for serious cutaneous adverse drug reactions was greatest for DRESS (64%), followed by AGEP (58%) and SJS/TEN (24%).[7] In the case of a delayed reaction occurring in the setting of multiple drugs, PT and/or dIDT may be useful for both causality and cross-reactivity patterns. The use of PT and/or dIDT for different clinical phenotypes is shown in Table IX.[7,113,114,124-127] For severe cutaneous adverse drug reactions such as SJS/TEN, the concern is not in triggering a reaction, but the lack of sensitivity of the PT. Given the imperfect negative predictive value, no patient with a negative dIDT or PT with a SCAR should be rechallenged to that specific culprit drug based on the results. In cases where one drug is PT positive and other non-cross-reactive drugs administered concurrently are PT negative, the benefit of rechallenge should be considered against the risk of reaction. For DRESS, the sensitivity of PT is >50% for many drugs; however, because of the risk of DRESS relapse, which is 12% in some studies,[128] it is prudent to avoid PT or dIDT until ≥6 months have elapsed from the acute reaction and/or the patient has been off systemic corticosteroid treatment for ≥1 month. This is due to the lower sensitivity of the PT under these circumstances and also the chance of human herpesvirus reactivation and DRESS relapse, which may cause confusion with the skin testing. The testing itself does not carry a risk of precipitating a systemic reaction and it does not lead to viral reactivation.[114]

***Ex vivo* and *in vitro* testing.** Currently there are no commercially available *ex vivo* or *in vitro* tests for delayed drug HSRs in the United States. These are studied and available in select research laboratories but have not been validated across large numbers of drugs, patients, clinical phenotypes, and centers. ELISpot (Millipore, Bedford, Mass) is an *ex vivo* assay that detects antigen-specific cytokine-producing cells (most commonly IFN-γ) in the peripheral blood in the presence of pharmacological doses of the drug or a defined metabolite of the drug, but typically in a concentration-dependent manner.[129-133] Flow cytometry and single-cell technologies that define the specific cell populations involved in the immunopathogenesis of delayed T-cell–mediated reactions are evolving.[134] The lymphocyte transformation test is another

TABLE IX. Testing options for delayed HSRs[114,124]

Reaction	Usefulness of test			Challenge procedures
	Patch tests*	Prick tests†	Intradermal	
Benign exanthem or MDE‡	Potentially useful to help with drug causality Potentially helpful with cross-reactivity	Potentially useful to help with drug causality Potentially helpful with cross-reactivity	Potentially useful to help with drug causality Potentially helpful with cross-reactivity	Caution that single-dose rechallenge will miss more remote or delayed reactions Consider slow reintroduction when therapy is indicated
Contact reaction (generalized eczema)	Useful	Potentially useful	Potentially useful	Potentially indicated after negative delayed skin test with delayed readings if indication for drug. NPV is unknown Consider slow introduction as per MDE above
Photosensitivity (photoallergic drug eruption) If the rash is photo-distributed	Useful (photopatch test is needed with application of UV-A at 5 J/cm^2 at 48 h)	Not known to be useful	Not known to be useful	Potentially indicated after negative photopatch test with delayed readings if indication for drug. NPV is unknown Consider slow introduction as per MDE above. Avoidance of light (UV-A) could prevent reaction from occurring
SDRIFE	Useful	Potentially useful	Potentially useful	Potentially indicated after negative delayed skin test with delayed readings if indication for drug. NPV is unknown Consider slow introduction as per MDE above
FDE	Potentially useful with *in situ* application in area of previous reaction Sensitivity <50%	Unknown	Unknown	At full dose when patch tests at site of previous reaction negative Caution with bullous and generalized variant NPV is unknown
AGEP	Useful (may reproduce reaction at site of application)	Limited data	Potentially useful	Challenge of suspected drug or cross-reactive drugs is contraindicated
DRESS/DIHS	Useful Advised 6 months after acute resolution and when off corticosteroids for ≥4 weeks	Described delayed positive at 24 h or >24 h but unknown utility	Delayed reading at 24 h Limited safety information available	Challenge with the highly suspected drug and cross-reactive drugs contraindicated except in extreme circumstances where benefit outweighs risk (eg, antituberculous therapy)
Abacavir hypersensitivity syndrome	Identified true immunologically mediated abacavir hypersensitivity (diagnostic sensitivity 87%)[125-127] Prevented through HLA-B*57:01 screening (100% NPV)[125]	Not known to be useful	Not known to be useful	Consider if HLA-B*57:01-negative, patch test–negative, and low clinical pretest probability Contraindicated with suggestive clinical history
SJS/TEN	Low sensitivity and NPV[7] Can be considered if there is benefit of diagnostic information obtained§	Not known to be useful	Not known to be useful	Challenge with the suspected drug is contraindicated

(Continued)

TABLE IX. *(Continued)*

Reaction	Usefulness of test			Challenge procedures
	Patch tests*	Prick tests†	Intradermal	
Drug-induced liver disease (or another single organ phenotype)	Low sensitivity if no cutaneous involvement	Low sensitivity if no cutaneous involvement	Low sensitivity if no cutaneous involvement	Challenge with the suspected drug is contraindicated
Vasculitis	No	Not known to be useful	Not known to be useful	Challenge with the suspected drug is contraindicated Look for alternative cause
Drug-induced lupus	No	Not known to be useful	Not known to be useful	No

SDRIFE, Systemic drug-related intertriginous and flexural exanthema.
*Initial read at 48 hours; reading at 96 hours and 1 week if initially negative; †read at 48 hours if 24-hour reading is negative.[113] At this time, drug patch testing is not frequently offered in the United States by either allergist-immunologists or dermatologists and is offered in select centers only.
†Prick tests, patch tests, and intradermal tests should be applied concurrently; in some higher risk reactions, patch testing may be applied first followed by intradermal testing.
‡Routine patch or delayed prick and intradermal testing is not recommended for benign exanthems to antibiotics but may be useful to help risk stratify management of other drugs (eg, antiepileptic drugs).
§For allopurinol and its metabolite oxypurinol, patch testing has had 0% sensitivity.

test commonly used in research laboratories that measures proliferation of T cells cultured in the presence of drug;[123,135-138] however, this has not been widely validated and is not available as a commercial test for drugs in the United States. As with *in vivo* approaches, *ex vivo* and *in vitro* testing cannot be used to absolutely rule out a reaction to a drug, and clinical history is still the reference standard.

Pharmacogenomics

Pharmacogenomics of drug allergy. Most pharmacogenomic associations identified to date are currently unlikely to translate into clinical practice; however, they have furthered our understanding of the immunopathogenesis of these reactions.[11,12]

Immediate and accelerated reactions. *IgE-mediated.* Currently the specific ecologic and genetic factors leading to sensitization and predisposition to specific drug-induced IgE-mediated reactions and differences across various populations in relation to epidemiology and patterns of drug use have not been well defined. The natural history of these reactions suggests that most reactions associated with common drugs such as penicillins and cephalosporins will wane with time.[139] In addition, genetic factors, if important in the immunopathogenesis are likely necessary but insufficient and subject to ecologic (eg, environmental determinants) and epigenetic modification. Most of the data in this area are with the penicillins and PEG-asparaginase. Several studies have shown an association between immediate hypersensitivity to asparaginase and immune response genes.[140-145] In the first of these a strong association was noted between HLA-DRB1*07:01 and asparaginase hypersensitivity, which correlated with the presence of PEG-asparaginase antibodies.[140] A follow-up study to this demonstrated that these antibodies were specific to PEG, suggesting that PEG, and not L-asparaginase, is the major implicated antigen.[146] A subsequent study also found a strong association with the intronic variant rs6021191 in nuclear factor of activated T cells, a transcription factor that controls T-cell activation. Independent studies showed a strong association with the haplotype HLA-DRB1*07:01-HLA-DQB1*02:02-DQA1*02:01 and immediate hypersensitivity to asparaginase.[141] In a study reproducing the HLA class II association, children with variants in *CNOT3* (rs73062673), a gene shown to regulate the transcription of HLA genes, and HLA-DQA1 were more likely to experience PEG-asparaginase hypersensitivity.[143] For beta-lactams, until recently all but one study had taken a candidate gene approach. Some of the strongest associations include variation in HLA class II antigen-presenting genes, nucleotide-binding oligomerization domain-containing protein 2 genes that may affect HLA class II expression, release of preformed mediators such as beta-galactosidase-binding lectin galectin-2, genes involved in IgE synthesis (STAT6, IL4RA, IL13) and other cytokines (IL4, IL10, IL18).[11] A recent genome-wide association study was conducted on 662 patients with a clinical history of immediate reactions to either penicillins or cephalosporins that were confirmed by skin testing. A gene in linkage equilibrium with HLA-DRB1*10:01 (odds ratio [OR]: 2.93; $P = 5.4 \times 10^{-7}$) was found to be associated with immediate hypersensitivity to penicillin.[147] This was replicated in a second cohort with meta-analysis of the 2 cohorts showing significant risk of immediate penicillin hypersensitivity associated with HLA-DRB1*10:01 (OR: 2.96, $P = 4.1 \times 10^{-9}$). Another recent genome-wide association study using biobanks from the United Kingdom, Estonia, and United States associated a label of penicillin allergy with the HLA class I allele HLA-B*55:01(OR: 1.30; $P = 2.04 \times 10^{-31}$) and this was replicated in the 23andMe research cohort (OR: 1.30; $P = 1 \times 10^{-47}$).[148]

Non-IgE–mediated mast cell activation. Several drugs in common use such as opioids, neuromuscular blocking agents, vancomycin, fluoroquinolone antibiotics, and icatibant are capable of causing non-IgE–dependent mast cell mediator release, which presents with an anaphylaxis clinical phenotype (flushing, rash, minor changes in blood pressure and heart rate, and bronchospasm) without evidence of IgE cross-linking/FcεRI signaling.[149] A hallmark of non-IgE–mediated mast cell activation associated with these drugs that is distinct from IgE-mediated reactions is that presentation varies in the same individual over time and is dependent on dose and method of administration. The mechanism by which these drugs activate mast cells is now thought to be through interaction with MRGPRX2.[4,150,151] Several loss and gain mutations have been identified that alter expression of an analogous receptor MRGPRX1 expressed on dorsal root ganglia that mediates histamine-independent pain and pruritus.[152] Although variation in *MRGPRX2* has been defined. there are currently no studies associating polymorphisms in this gene with clinical phenotypes.

TABLE X. HLA associations with delayed drug HSRs

Drug phenotype	HLA allele	HLA risk allele prevalence	NPV	PPV	NNT	Current use in clinical practice
Abacavir hypersensitivity syndrome[12,125,126]	B*57:01*	5%-8% Caucasian <1% African/Asia 2.5% African American	100% for patch test confirmed	55%	13	Routine preprescription test in developed world
Allopurinol SJS/TEN and DRESS/DIHS[154]	B*58:01*	9%-11% Han Chinese 1%-6% European ancestry African American 4% African 11%	100% (Han Chinese)*	3%	250	Consider use for risk stratification. Current use is not routine†
Carbamazepine SJS/TEN[155,156]	B*15:02*	10%-15% Han Chinese <1% Koreans, Japanese <0.1% European Ancestry	100% (Han Chinese)	3%	1000	Routine in many Southeast Asian countries
Carbamazepine DRESS/MDE[157]	A*31:01*	European (≤6%) Japanese/ South Korean (10%-15%) South Central Asia (4%) Africans (≤2%)	99.98%	<1%	>3000	Available as single allele and panel test with other markers—higher NNT to prevent 1 case for SJS/TEN
Dapsone DRESS/DIHS[158]	B*13:01	2%-20% Chinese 28% Papuans/Australian Aboriginals 0% European/African 1.5% Japanese <2% African and African American	99.8%	7.8%	84	Screening programs implemented in China and Southeast Asia where leprosy prevalent
Flucloxacillin[159]	B*57:01	5%-8% European ancestry <1% African/Asia 2.5% African American	99.99	0.14%	13,819	No

NNT, Number needed to treat.
*Single allele HLA test is available in the United States and other countries.
†The negative predictive value for HLA-B*58:01 for allopurinol SCAR is <100% for non-Southeast Asian populations.

Aspirin (and NSAID)-exacerbated respiratory disease. Genetic predictors of AERD belong to the arachidonic acid pathways and genes that encode ALOX5, leukotriene C4 synthase, thromboxane A2 receptor, prostaglandin E receptor 4, proinflammatory cytokines, tumor necrosis factor, and TGF-β. Genome wide analyses have also found HLA class II genes (HLA-DPB1) as the strongest predictor for AERD in Korean studies.[11] Predictors of NSAID-exacerbated cutaneous disease are similar to AERD and are genes in the arachidonic acid pathway ALOX5 and other genes coding the ALOX5-activating protein, arachidonate, thromboxane A synthase 1, prostaglandin D2 receptor, and CYSLTR1.[11]

Delayed reactions. Class I HLA genes have been strongly associated with severe delayed T-cell–mediated adverse drug reactions.[12] These HLA associations may help to identify patients and populations at risk for severe delayed HSRs (Table X).[12,125,126,153-159] For example, screening programs for HLA-B*57:01 (abacavir hypersensitivity) and HLA-B*15:02 (carbamazepine SJS/TEN in some Southeast Asian countries) have been successfully used to reduce adverse drug reactions.[125,156] Although many HLA and other genetic associations may not translate into screening markers of immediate use, they may help shed light on immunopathogenesis.[12] HLA-B*15:01 and HLA-DRB1*06:02 have been associated with amoxicillin-clavulanate drug-induced liver injury in multiple studies; however, the diagnostic test accuracy is too low for this to be used as a routine screening test for a commonly used antibiotic.[160]

Physiologic states such as renal failure, or genetic variation in drug metabolism, may predispose to a specific T-cell–mediated drug reactions. Small molecules and drugs have been posited to activate T cells through 3 nonmutually exclusive models that may explain a variety of clinical phenotypes.[12,153] The hapten/prohapten model postulates that the drug binds to a protein that then undergoes antigen processing to generate haptenated peptides that are presented by the major histocompatibility complex. For the pharmacological interaction and altered peptide repertoire mechanisms, a drug noncovalently interacts with immune receptors in a dose-dependent fashion. For instance, accumulation of oxypurinol (the long-acting metabolite of allopurinol), slower metabolism of phenytoin by CYP2C9*3, and various CYP2B6 polymorphisms in the case of nevirapine are all associated with an increased risk of severe cutaneous adverse drug reactions.[161-164] Although the immunopathogenesis of delayed reactions entails a complex interaction of drug and the host immune system, the exact set of mechanisms through which drugs cause tissue specific reactions or by which T cells home to the skin and other organs and recognized drug altered epitopes has not been elucidated.

A summary of recently described genetic associations with serious immunologically mediated adverse drug reactions in relation to their characteristics and those genetic associations currently recommended or used in clinical practice is shown in Table X. The safety and utility of a successful screening test means a 100% NPV, a reasonable PPV, and a disease prevalence that although may be unusual is detectable in a given population. This translates into a realistic and cost-effective number needed to test to prevent 1 case of hypersensitivity (Table X). The lack of safer therapeutic alternatives is also a key consideration. A strong association between vancomycin DRESS and HLA-A*32:01 has been described (Table X).[120] DRESS usually has a latency period of 2-6 weeks, allowing a window to order testing preemptively following initiation of therapy. Because many

patients who initiate long courses of vancomycin may be on multiple antibiotics at the time of DRESS development, HLA-A*32:01 may also be a helpful diagnostic marker. More extensive databases of HLA associations with immunologically mediated adverse drug reactions are updated on a regular basis and are available in online resources such as Allele Frequency Net Database (http://www.allelefrequencies.net/hla-adr/adr_query.asp) and Litt's Drug Eruption Database (www.drugeruptiondata.com). The Clinical Pharmacogenetic Implementation Consortium also maintains and updates evidence-based gene-drug clinical practice guidance to help facilitate translation of laboratory tests into actionable prescribing decisions.[157,165] The implications for use of pharmacogenomic biomarkers in allergy and immunology practice relative to the FDA label has also recently been reviewed.[166] Although HLA class I single-allele assays such as HLA*B57-01, B58-01, B15-02, and A31-01 are now commercially available, pharmacogenomic testing should not be part of routine diagnostic evaluation for patients with delayed HSRs.

Summary of pharmacogenomics. Current actionable genes relevant to drug hypersensitivity include HLA-B*57:01, which is part of guideline-based routine HIV practice in the developed world. The accessibility of other genetic markers and their use in clinical practice has been more variable but have included HLA-B*15:02 preprescription screening for carbamazepine in Southeast Asia. The association between specific genetic markers and an immunologically mediated adverse drug reaction marks an advancement in the understanding of the immunopathogenesis of disease and serves as a valuable clue to pursue basic mechanistic studies. This area is expected to rapidly change over time as more routine single HLA markers and other genotyping strategies become available that associate with clinical evidence for use in allergy diagnosis and screening.

ANTIBIOTIC ALLERGY UPDATES

Beta-lactams

Penicillin. *Burden of a penicillin allergy label. Consensus-based Statement 4:* We recommend that a proactive effort should be made to delabel patients with reported penicillin allergy, if appropriate.

Strength of Recommendation: Strong

Certainty of Evidence: Moderate

Approximately 10% of patients report a history of reacting to a penicillin class antibiotic. When evaluated for penicillin allergy, ≥90% of these individuals tolerate penicillins and therefore are labeled allergic unnecessarily.[167,168] Potential explanations for this discrepancy include waning of penicillin-specific IgE, the fact that some cutaneous reactions were the result of the underlying infection or an interaction between the infectious agent and the antibiotic, and mislabeling predictable nonimmunologic symptoms as allergic.

The penicillin allergy mislabel is not benign. Patients with a history of penicillin allergy are more likely to be treated with less effective, more toxic, or more expensive antibiotics such as fluoroquinolones, vancomycin, later generation cephalosporins, and clindamycin.[14,15] This prescribing practice compromises optimal medical care and increases costs.[16] In 2 large-scale case-control studies, patients with a history of penicillin allergy were more likely to develop vancomycin-resistant *Enterococcus*, *Clostridium difficile*, or methicillin-resistant *Staphylococcus aureus*, and they had longer hospital days and higher medical costs, compared with nonallergic controls.[17,18] In 2 large retrospective analyses, patients with a history of penicillin allergy were more likely to develop a surgical site infection after operations because of suboptimal perioperative antibiotic choice.[169,170] Another case-control study found that patients labeled penicillin-allergic had a 14% increased risk of death over a mean follow-up of 6 years.[19] Studies have demonstrated removal of the penicillin allergy label, such as via negative penicillin skin testing and challenge, leads to improved antibiotic selection with decreased use of broad-spectrum antibiotics.[171-175] Additionally, introduction of reaction history-based algorithms in inpatient settings (without penicillin skin testing) also improved antibiotic use.[176,177] While there are no randomized interventional studies of the utility of a penicillin allergy evaluation, outpatient penicillin allergy testing was found to significantly decrease health care use (fewer outpatient visits, fewer emergency department visits, and fewer hospital days) compared with matched controls over the subsequent 4-year period.[178] Cost and simulation model-based economic studies support that penicillin allergy assessment may be a cost-saving intervention.[20,21] Therefore, a proactive effort should be made to delabel penicillin allergy whenever possible, and strong efforts should be made to educate patients and clinicians about the benefits of delabeling. Given the many benefits of removing the penicillin allergy label, evaluations are ideally performed electively, when patients are well and not in immediate need of antibiotic treatment. However, specific patients may benefit from rapid and acute assessments, such as patients prior to surgery, transplant, or chemotherapy; those on second-line, less preferred antibiotics; or pregnant women prior to delivery.[179-181] When appropriate, delabeling of penicillin allergy is endorsed by the Centers for Disease Control and allergy/immunology and infectious disease societies.[182-184]

Delabeling patients with histories inconsistent with allergy. Consensus-based Statement 5: We recommend against any testing in patients with a history inconsistent with penicillin allergy (such as headache, family history of penicillin allergy, or diarrhea), but a 1-step amoxicillin challenge may be offered to patients who are anxious or who request additional reassurance to accept the removal of a penicillin allergy label.

Strength of Recommendation: Strong

Certainty of Evidence: Low

The immunochemistry of penicillins has been well characterized, starting in the 1960s.[1] Penicillin skin testing detects the presence or absence of penicillin-specific IgE antibodies, and it is not useful or indicated for clearly non-IgE–mediated reactions. Also, skin testing is not indicated for nonallergic adverse reactions. Therefore, in patients with reaction histories inconsistent with allergy (such as headache, isolated gastrointestinal symptoms, or family history of penicillin allergy), testing is not required. However, in patients who are reluctant to accept the removal of a penicillin allergy after appropriate counseling, amoxicillin challenge using a single treatment dose is sufficient to rule out an allergy, and these patients do not require penicillin skin testing.

Penicillin skin testing. *Consensus-based Statement 6:* We suggest penicillin skin testing for patients with a history of anaphylaxis or a recent reaction suspected to be IgE-mediated.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

Penicillin skin testing is a more reliable method for evaluating IgE-mediated penicillin allergy than *in vitro* tests (radioallergosorbent test or enzyme-linked immunoassay).[185] A systematic review

and meta-analysis found that skin testing had a sensitivity of 30.7%, specificity of 96.8%, and area under the summary receiver-operating characteristic curve of 0.686, whereas serum-specific IgE had a sensitivity of 19.3%, specificity of 97.4%, and area under the summary receiver-operating characteristic curve of 0.420.[185] However, there are few prospective data comparing skin testing and serum-specific IgE with oral challenge.

Penicillin skin testing should only be performed by personnel trained and skilled in the application and interpretation of this type of skin testing, with preparedness to treat very rare anaphylaxis. Appropriate positive (histamine) and negative (eg, saline) controls should be placed, and they should test positive and negative, respectively, for the results to be valid.[186] First, full-strength reagents are applied by the prick/puncture technique, and if these results are negative, intradermal testing should be performed. Antibiotic intradermal skin testing is most reproducible when fluid is drawn up by first filling the syringe with a larger volume (0.05-0.07 mL) and expelling the excess fluid and air bubbles to obtain 0.02 mL, then injecting to produce a baseline 3-5 mm bleb.[8] There is no uniform agreement on what constitutes a positive skin test response, and the workgroup recognizes that different criteria have been used by various researchers over the years.[167,168,187-189] While there is no perfect set of criteria, the workgroup recommends that a positive test be defined by the size of the wheal, which should be 3 mm or greater than that of the negative control for either prick/puncture or intradermal tests and be accompanied by a 5 mm or greater flare. A recent study consisting of >30,000 patients with a history of penicillin allergy reported the penicillin skin test–positive rate to be 1.0% when a positive test criterion ≥3mm compared to negative control was used and 0.5% when ≥5 mm compared to negative control was used.[189] These data clearly indicate that either criterion results in the vast majority of patients being delabeled of penicillin allergy. Penicillin skin testing, using the reagents described below and proper technique, is safe; <2% of patients who are skin test–positive experience systemic reactions and very few of these are anaphylactic in nature.[167,188,190-192]

The major determinant is commercially available as PPL (Pre-Pen) in a premixed 6×10^{-5} mol/L solution (see Table E2 in this article's Online Repository at www.jacionline.org). Of the minor determinants, penicillin G is commercially available in intravenous solution and should be used for skin testing off-label at a concentration of 10,000 units/mL. The other minor determinants (penicilloate and penilloate) are used for skin testing at 0.01 mol/L; they have never been commercially available in the United States, but a penicillin skin testing kit containing these minor determinants is under FDA review. Penicillin G left in solution ("aged penicillin") does not spontaneously degrade to form other minor determinants and should not be used as a substitute. In addition to the previously mentioned penicillin major and minor allergenic determinants, skin testing with a nonirritating concentration of the culprit penicillin should be considered (if it is available in intravenous form). For example, this would be piperacillin-tazobactam in those who reacted to piperacillin-tazobactam. The ideal skin testing concentration for these extended spectrum penicillins has not been firmly established.[25,26,193-195]

When multiple penicillin skin test reagents are used (eg, PPL, penicillin G, penicilloate, penilloate, and, in some cases, amoxicillin or ampicillin), ≥10% of patients who are skin test–positive are positive to only penicilloate or penilloate.[167,168,196-198] The clinical significance of these findings is somewhat uncertain, because very few patients who are selectively positive to penicilloate or penilloate have been challenged with penicillin. Of those who have been challenged, some have experienced anaphylaxis.[199,200] Additionally, skin test–associated anaphylaxis has been described in patients who are positive only to minor determinants.[167]

The NPV of penicillin skin testing is >95%.[167,168,171,187,198,201,202] This is true if the multiple penicillin skin test reagents are used or if only PPL and penicillin G are used. However, it is not possible to directly compare the NPV obtained when all 3 minor determinants (penicillin G, penicilloate, penilloate) are used versus when penicillin G was the only minor determinant used. In the retrospective "real life" observational reports, formal inclusion and exclusion criteria were not used and heterogenous patient populations were evaluated. Additionally, in most studies, not all patients who are skin test–negative underwent penicillin challenges. Given these limitations, it is not possible to give firm guidance regarding when to include penicilloate/penilloate in skin testing (vs only using PPL and penicillin G). Clearly there are patients who are rare severely penicillin-allergic whose skin testing is solely positive to these minor determinants. However, the frequency at which this occurs and when skin testing without all the minor determinants may fail to detect these individuals is unknown.

Selective allergy to specific penicillins. Some individuals demonstrate selective allergy to specific penicillins and tolerate others. This is most commonly described in patients who clinically react to ampicillin and/or amoxicillin, yet they tolerate other penicillins such as penicillin VK and/or penicillin G.[203-205] These individuals have positive skin test results to amoxicillin or ampicillin, but test negative to penicillin major and minor determinants, meaning their IgE-mediated reactions are assumed to be directed at the R-group side chains of aminopenicillins. In the United States, patients with selective IgE-mediated allergy to amoxicillin or ampicillin are very rare,[187,198,206-208] whereas in European studies, 25%-50% of patients have positive skin test results only to amoxicillin but not PPL, penicillin G, penicilloate, or penilloate.[209-212] Similarly, patients selectively allergic to piperacillin-tazobactam and flucloxacillin (which is not available in the United States) are increasingly being described.[25,26] Typically, these individuals have positive skin testing to piperacillin-tazobactam, but they are negative to all other penicillin skin test reagents (and tolerate other penicillins). However, patients who are piperacillin-tazobactam skin test–negative have been described to react on rechallenge.[195] Therefore, the sensitivity and specificity of skin testing with a nonirritating concentration of piperacillin-tazobactam is unknown.[26,213]

Penicillin challenges. *Consensus-based Statement 7:* We recommend against the routine use of multiple-day challenges in the evaluation of penicillin allergy.

Strength of Recommendation: Strong

Certainty of Evidence: Low

Following negative penicillin skin test results, an elective challenge with the offending penicillin that caused the historical reaction is recommended. The purpose of such a challenge is to reassure the patient, patient's parents, referring physicians, and future prescribing clinicians of the safety of using penicillins and other beta-lactam antibiotics. Surveys of patients with negative penicillin skin test results (without subsequently being challenged with penicillin) found that a large proportion were not treated with beta-lactams because of fear on the part of either the patient or the

treating physician.[214] The challenge is typically completed in 1 step, but a 2-step challenge may be considered if the reaction history is severe and/or recent.

In recent years, several European studies have suggested that a single therapeutic dose of an antibiotic may not be sufficient to exclude delayed reactions. These studies used extended challenges ranging from 3 to 10 days with delayed reactions occurring in 5%-12% of subjects.[74,215-220] In most studies, the reactions were self-reported but a few required photo documentation of the rash. Most reactions were mild and easily treated. A single study of 22 patients with a self-reported history of delayed reactions to penicillins despite negative testing, found 50% had delayed reactions (mainly urticaria) at a mean of 6 days into a 10-day course of a penicillin.[221] In contrast to these studies, reports from the United States have shown very low rates of delayed reactions (0%-1.8%) after negative penicillin skin tests and prolonged or repeated therapeutic exposures to penicillins.[202,222-224]

Two recent studies have suggested that single-day challenges can detect the majority of delayed reactions. A study in children with delayed reactions to beta-lactams suggested that delayed reactions may occur ≤7 days following a single challenge.[23] Another study used a single-day challenge of amoxicillin (n = 15) or amoxicillin clavulanate (n = 104), followed by a "washout" period of 7 days prior to a 1-week therapeutic course at home.[24] Two patients developed exanthems during the 7-day "washout" period and one was lost to follow-up. Of the 116 patients who received the at-home therapeutic dose (with no reaction during the washout period), only 1 had a mild exanthem after 7 days. The number needed to challenge using this protocol was 116 to identify 1 patient reacting to a therapeutic course. These data suggest that single-day challenges are sufficient to detect delayed reactions and that using multiple-day challenges is unnecessary. Given that the majority of these delayed reactions are quite mild and that a multiple-day challenge will unnecessarily expose a patient to additional antibiotics when not needed, multiple-day challenges are not recommended after negative single-day challenges.

Rates of resensitization. Resensitization after oral treatment with penicillins is rare in both pediatric and adult patients, including after repeated courses and is comparable with the rate of sensitization.[201,202,223,225] Hence, routine repeat penicillin skin testing is not indicated in patients with a history of penicillin allergy who have tolerated one or more courses of oral penicillin. Resensitization after high-dose parenteral treatment with penicillin was thought to be more likely;[226,227] however, recent research has contradicted previous findings.[224] Still, drug allergy is more frequent in patients with repeated and parenteral exposures. Repeat penicillin skin testing is not necessary in patients who have been delabeled for penicillin allergy, whether or not future penicillin is given orally or intravenously for initial or repeated (parenteral or oral) courses, unless subsequent reaction occurs. Consideration may be given to retesting individuals who have had prior penicillin anaphylaxis before repeating parenteral administration.

Direct penicillin challenge (without preceding skin tests). *Consensus-based Statement 8:* We recommend against penicillin skin testing prior to direct amoxicillin challenge in pediatric patients with a history of benign cutaneous reaction (such as MDE and urticaria).

Strength of Recommendation: Strong

Certainty of Evidence: Moderate

Aminopenicillins are associated with development of delayed-onset MDE in ≤7% of patients, compared to about 2% for penicillin VK.[228,229] These reactions are not related to specific IgE antibodies, and they are postulated in many cases to require the presence of a concurrent viral infection or another underlying illness.[230] One example of this phenomenon is treatment of patients with Epstein-Barr infection with amoxicillin or ampicillin, where ~30%-100% of patients develop a nonpruritic morbilliform rash.[231-234]

Because infections are prominent in the development of benign cutaneous eruptions in children treated with amoxicillin,[230] resulting in low rates of confirmed allergy, some studies have investigated rechallenging with amoxicillin without preceding penicillin skin testing.[76,217,230,235-237] The rate of reactions observed ranged from about 5% to 10% and were generally no more severe than the historical reactions. None of the studies included patients reporting respiratory symptoms, cardiovascular symptoms, anaphylaxis, and vesicular or exfoliative eruptions. Some, but not all, studies excluded patients with angioedema. Most studies were carried out in specialty allergy centers, and many of the subjects reported reactions with a first-time amoxicillin course (which makes IgE-mediated reactions highly unlikely). If a pediatric patient's past reaction consisted of a maculopapular exanthem or urticarial eruption, not accompanied by any systemic symptoms, and did not involve blistering or exfoliation of the skin or mucous membranes, then single-dose amoxicillin challenge without prior allergy testing is recommended. However, the safety of this approach has not been thoroughly examined in primary care settings. Additionally, while not required, penicillin skin testing may be performed at the discretion of the clinician, such as in patients who are concerned or anxious about direct challenge. Admittedly, skin testing may "overdiagnose" penicillin allergy in a very small minority of subjects by virtue of the PPV being <100%. However, the benefit of proceeding with testing in such individuals far outweighs not testing and hence not challenging, given that in that case, ≥90% of the patients will continue to be falsely labeled as penicillin-allergic.

Consensus-based Statement 9: We suggest that direct amoxicillin challenge be considered in adults with a history of distant (ie, >5 years ago) and benign cutaneous reactions (such as MDE and urticaria).

Strength of Recommendation: Conditional

Certainty of Evidence: Low

Adults are less likely than children to have viral eruptions masquerading as drug allergy, and they are more likely to experience severe or fatal penicillin-induced anaphylaxis. Analysis of drug-related anaphylaxis deaths in the United States (with penicillins being the most common identified culprit) showed higher rates with increasing age at 0.05 per million (age <20 years), 0.18 (20-39 years), 0.51 (40-59 years), 1.23 (60-79 years), and 1.28 (≥80 years).[238,239] There is less evidence for bypassing penicillin skin testing in adults, with reported reactions rates of ~1%-6%.[240-245] Similar to the pediatric studies, only patients fulfilling low-risk criteria were eligible for direct amoxicillin challenge. These included reactions occurring longer than 1-10 years ago, limited to the skin (but not angioedema, blistering, or exfoliative features), and without other systemic symptoms suggestive of anaphylaxis. Also, adults with distant childhood reactions where features of the reaction were unknown were eligible for direct amoxicillin

TABLE XI. Summary of predictive factor for beta-lactam allergy found in different studies

Study	Anaphylaxis	SCAR	Index reaction	Reaction onset time	Required treatment	Elapsed time since reaction	Recall of index drug	Multiple reactions
Chiriac et al[246]	+	-	+	+	?	+	?	+
Siew et al[247]	+	X	+	?	?	+	+	?
Stevenson et al[248]	+	X	X	?	?	+	?	?
Trubiano et al[244]	+	+	X	?	+	+	?	?

+, Associated.
-, Not associated.
?, Unknown/not considered.
X, Excluded.

challenge. In the only study to use a prospective, randomized, controlled trial approach, penicillin skin testing (followed by challenge if negative) was compared with direct amoxicillin challenge in patients fulfilling low-risk reaction history criteria.[243] Among those patients who underwent skin testing, 70 of 80 (87.5%) were negative and all tolerated amoxicillin challenge. Direct amoxicillin challenge was negative in 76 of 79 patients (96.2%), and in those patients with positive challenges, reactions were mild.

In 4 large studies of penicillin skin testing, statistical modeling was retrospectively applied to the clinical history, to define low-risk criteria that could guide direct amoxicillin challenge.[244,246-248] Two studies reported similar criteria: (1) reaction occurring longer than 1 year ago, absence of anaphylaxis, and unknown name of index drug;[247] and (2) benign rash (no angioedema) occurring longer than 1 year ago.[248] Another study assigned values to criteria (≤5 years since reaction–2 points, anaphylaxis/angioedema or severe cutaneous reaction–2 points, treatment required for reaction–1 point) and a score of <3 was classified as low risk.[244] The fourth study was unable to accurately predict penicillin allergy based on clinical history, without skin testing.[246] Table XI summarizes the findings in these studies.[244,246-248] Most adult studies, like the pediatric ones, were all carried out in outpatient ambulatory settings. If an adult's past reaction consisted of a distant maculopapular exanthem or urticarial eruption, not accompanied by any systemic symptoms, and did not involve blistering or exfoliation of the skin or mucous membranes, then single-dose amoxicillin challenge without prior allergy testing may be considered. However, in patients who are uncomfortable or anxious about direct oral challenge, negative skin testing may be useful to alleviate those fears.

Preventing reacquisition of a penicillin allergy label. Once a patient is delabeled, it is important to make every effort to effectively communicate the updated penicillin allergy status across all medical record platforms and clinical encounters. Therefore, instructions to remove the penicillin allergy label should be relayed to hospital systems, outpatient clinics, private physician and dental offices, and pharmacies. The patient and relevant family members should be given written documentation (such as a wallet card) indicating that they are no longer penicillin allergic and at no higher risk to develop allergic reactions to penicillins than the general population is. If patients wore medical alert bracelets, these should be modified as well. Another potential strategy is an alert in the electronic health record alerting clinicians of the lack of penicillin allergy. While this process may seem straightforward, frequently the label is not universally removed, or sometimes reappears after being removed.[249,250]

Cephalosporins. Cephalosporins are documented as an "allergy" (includes adverse drug reactions) in 0.5%-2.0% of US patients.[27,251,252] New cephalosporin adverse reactions occur in about 0.5% of exposures.[252] Large database analyses demonstrate that cephalosporins are documented as one of the most common drug culprits causing a variety of immediate and nonimmediate HSRs.[253] Cephalosporins cause diverse immunologic reaction phenotypes: IgE-mediated anaphylaxis, benign T-cell–mediated exanthems, SSLRs, and rarely SCARs.[252,254-256]

Considering cephalosporin immediate hypersensitivity, evidence suggests that allergic reactions to cephalosporins are more commonly directed at the R-group/side chains rather than the core beta-lactam portion of the molecule (Fig 2).[257-261] The strongest evidence of side chain cross-reactivity is for identical side chains sharing an R1 group (Table XII, see Fig E2 in this article's Online Repository at www.jacionline.org), although cross-reactivity is plausible and has been observed for similar side chains and R2 groups (Table XII, Fig E2).[262,263] Cephalosporin sensitization may wane over time similarly to penicillin sensitization, with a loss of skin test reactivity observed in >50% of patients after 5 years.[264] In this parameter, the term "structurally dissimilar" refers to cephalosporins that have disparate R1 side chains from other cephalosporins or aminopenicillins.

An algorithm for cephalosporin administration to a patient with a history of cephalosporin hypersensitivity is shown in Fig 3, *A*.

Consensus-based Statement 10: We suggest that for patients with a history of non-anaphylactic cephalosporin allergy, direct challenges (without prior skin test) to cephalosporins with dissimilar side chains be performed to determine tolerance.

Strength of Recommendation: Conditional

Certainty of Evidence: Moderate

Patients with a history of allergy to one cephalosporin who require treatment with another cephalosporin can receive the indicated cephalosporin by a direct drug challenge if the R1 side chains are dissimilar and the reaction was nonanaphylactic.[263] Limited clinical challenge studies have demonstrated that patients allergic to one cephalosporin are able to tolerate other cephalosporins with dissimilar R1 side chains.[263]

Consensus-based Statement 11: We suggest that for patients with a history of anaphylaxis to a cephalosporin, a negative cephalosporin skin test should be confirmed prior to administration of a parenteral cephalosporin with a nonidentical R1 side chain.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

For patients with anaphylactic histories, it is recommended that parenteral cephalosporin treatment be guided by cephalosporin skin testing with nonirritating concentrations of the agent(s) desired for therapeutic use and ideally the cephalosporin(s)

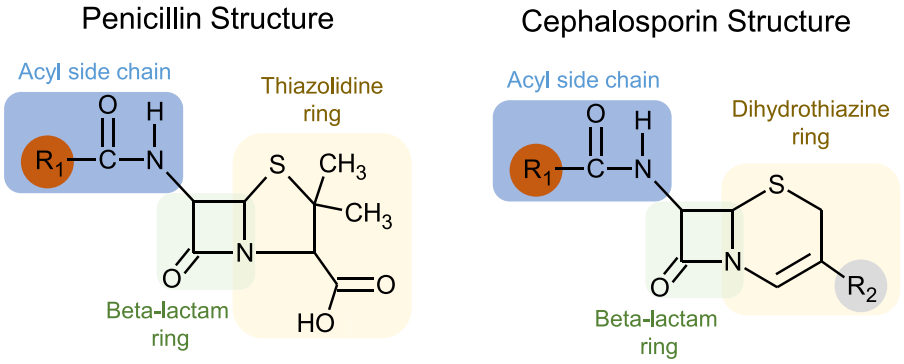

FIG 2. Penicillins and cephalosporins share common structures that are thought to be the source of cross-reactivity: (1) beta-lactam ring, shown in *green*; (2) side chain, or R group with R1 location shown in *red* and R2 location shown in *gray*. Cross-reactivity is largely based on R_1 side chains, with identical side chains in patients with IgE-mediated allergy posing the highest risk. Rarely, cross-reactivity has been demonstrated through R2 side chains and the beta-lactam ring (see Table XII).

TABLE XII. Groups of beta-lactam antibiotics that share side chains

R1—Identical side chains					
Amoxicillin	Ampicillin	Ceftriaxone Cefotaxime	Cefoxitin	*Cefamandole*	Ceftazidime
Cefadroxil	Cefaclor Cephalexin	Cefpodoxime Cefditoren Cefepime	*Cephaloridine*	*Cefonicid*	Aztreonam
Cefprozil	*Cephradine*	*Ceftizoxime*	*Cephalothin*		
Cefatrizine	*Cephaloglycin*	*Cefmenoxime*			
R2—Identical side chains					
Cephalexin	Cefotaxime	Cefuroxime	Cefotetan	Cefaclor	Ceftibuten
Cefadroxil	*Cephalothin*	Cefoxitin	*Cefamandole*	*Loracarbef*	*Ceftizoxime*
Cephradine	*Cephaloglycin*		*Cefmetazole Cefpiramide*		
	Cephapirin				

Italic indicates the drug is not available in United States or manufacturing has been discontinued.
Similar side chains may also be a source of cross-reactivity, see cross-reactivity matrix (see Fig E2).

implicated in anaphylaxis. Nonirritating concentrations of commonly used cephalosporins have been described; 2 mg/mL is often used but there is a range from 10 to 33 mg/mL (Table XIII).[27,119,265-268]

A positive cephalosporin skin test suggests drug-specific IgE antibodies, and the patient should receive a skin test–negative alternative cephalosporin or alternate antibiotic, or the patient should undergo desensitization. A negative cephalosporin skin test should be followed by a drug challenge to confirm tolerance. Although cephalosporin skin testing has unknown validity to date, and its sensitivity is reliant on testing soon after the reaction,[268-272] testing may be useful for patients with anaphylactic or convincing histories of IgE-mediated reactions, patients with multiple reported drug allergies, or those with multiple reactions to beta-lactams. Skin testing may also be useful for patients who are uncomfortable, concerned, or anxious about direct challenge. Alternative options include cephalosporin induction of drug tolerance procedure performed empirically, which may be considered for patients with a severe reaction history or if the patient is acutely ill or pregnant. Administration of a structurally similar cephalosporin may be optimally accomplished using cephalosporin skin testing results to guide administration. Cephalosporin skin testing to guide cephalosporin administration may also be advisable for recent reactions or when the patient in question is chronically ill or pregnant. If administering an oral cephalosporin or skin testing is not possible, then higher risk drug challenges or empiric induction of tolerance procedures can be performed. Oral cephalosporins are not sterile, and therefore cannot be used for intradermal skin testing, and skin testing with cephalexin, the most common oral cephalosporin used in the United States, has no clear utility.[273] Non–beta-lactam antibiotics may also be considered, but they may result in added patient morbidity, mortality, and cost of care.[16-18,169,274,275]

Consensus-based Statement 12: We suggest that for patients with a history of anaphylaxis to a penicillin, a structurally dissimilar R1 side chain cephalosporin can be administered without testing or additional precautions.

Strength of Recommendation: Conditional

Certainty of Evidence: Moderate

An algorithm for cephalosporin administration to patients with a history of penicillin hypersensitivity is shown in Fig 3, *B*. Early penicillin/cephalosporin cross-reactivity estimates were 8%, which was rounded to 10% on the cephalosporin package insert label from the FDA. This cross-reactivity estimate was falsely high, however, because of the specific cephalosporins considered and contamination of cephalosporins with penicillins before 1980.[276] Considering 417 patients across 12 clinical studies conducted after 1980, 8 (2%) had reactions to cephalosporins,[222,277-287] representing cross-reactivity ranging between 2.0% and 4.8%, rates similar to the incident rate of new drug allergies or reactions to structurally dissimilar medications in patients with prior drug allergies.[288] There is a large body of evidence that cross-reactivity is negligible even in patients with confirmed penicillin allergies.[289,290] Although cross-reactivity to the beta-lactam nucleus between penicillins and cephalosporins is very low, cross-reactivity may be higher among drugs

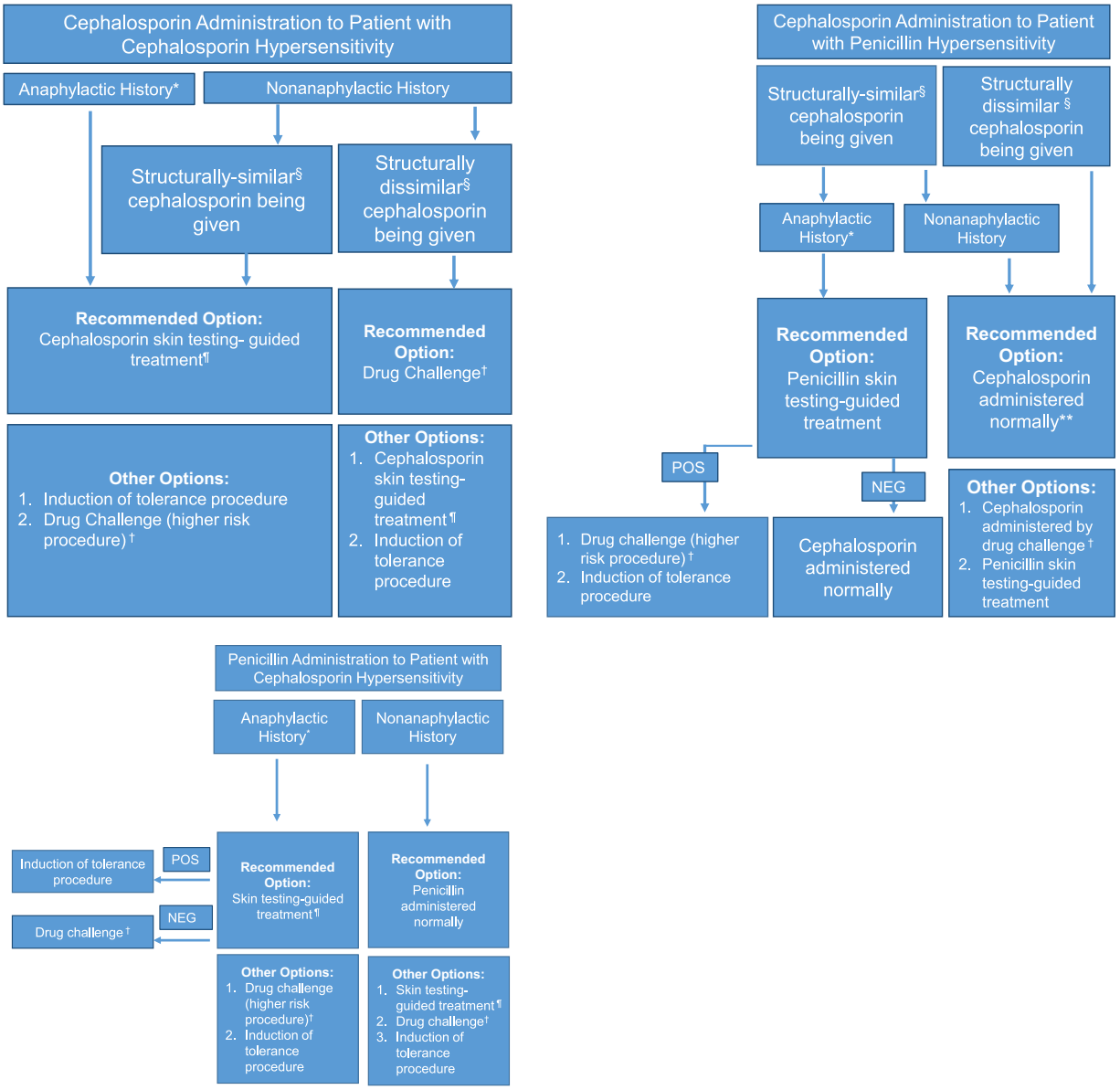

FIG 3. Recommended approach to beta-lactam administration in patients with prior beta-lactam allergies. *Anaphylaxis, angioedema, hypotension, or other severe IgE-mediated reactions. §Similarity or cross-reactivity based on R1 side chain. ¶Cephalosporin skin testing should be used for parenteral cephalosporins only. A positive (*POS*) test suggests IgE antibodies and induction of tolerance procedure should be performed or administration of an alternative cephalosporin to which the patient was skin test negative (*NEG*). A negative test should be followed by a drug challenge. †All drug challenges are 1-2 steps with the number of challenge steps should be determined based on factors including patient allergy history, patient clinical history such as comorbidities and clinical stability, and structural similarity between R1 side chains. **Penicillin allergy assessment performed in the future as the penicillin allergy label would remain. Note: The recommendations within these algorithms do not apply to patients with history of severe delayed immunologic reactions or organ-specific reactions to beta-lactams. These include reactions such as the SCARs, hemolytic anemia, drug-induced liver injury, and acute interstitial nephritis. Urticaria fulfilling "1-1-1-1" criterion (appearance within 1 hour after the first dose and regression within 1 day and occurrence within 1 year) suggests a high likelihood of having a positive skin test.[22]

that share the R1 side chain. A recent meta-analysis that considered 19 prospective and 2 retrospective studies found that the risk of cross-reactivity (based on skin testing) to cephalosporins in patients with proven penicillin (predominantly aminopenicillin) allergy varied from 16.45% (95% CI: 11.07-23.75) for aminocephalosporins (shared R1: cephalexin, cefadroxil, cefprozil, cefaclor) to 2.11% (95% CI: 0.98-4.46) for low-similarity-score cephalosporins, which include commonly used cephalosporins cefazolin, cefpodoxime, ceftriaxone, ceftazidime, and cefepime.[28] Cefazolin, notably, has a unique side chain and appears to have very low cross-reactivity with penicillins despite being a first-generation cephalosporin.[28,255,291-293] The reaction rate

TABLE XIII. Immediate hypersensitivity cephalosporin skin testing[119,265,266]

	Cefazolin*	Cefuroxime†	Cefotaxime	Ceftazidime	Ceftriaxone	Cefepime‡
Step 1: Epicutaneous (prick/puncture)	200 mg/mL	90 mg/mL	100 mg/mL	100 mg/mL	100 mg/mL	2 mg/mL
Step 2:§ Intradermal	2.0 mg/mL	1 mg/mL	1 mg/mL	1 mg/mL	1 mg/mL	2 mg/mL
Step 3: Intradermal	20 mg/mL	10 mg/mL	10 mg/mL	10 mg/mL	10 mg/mL	2 mg/mL

*Others have used 100 mg/mL for epicutaneous and 1 mg/mL and 10 mg/mL for intradermal testing.[267,268]
†Recommended 100 mg/mL for testing, but 90 mg/mL is the final concentration when the drug is resuspended.
‡For cefepime, 20 mg/mL is irritating.
§Recommended primarily for patients with history of severe and/or recurrent reactions. Penicillin skin testing may also be appropriate for patients presenting with cephalosporin allergy in some circumstances.

(when evaluated by skin testing) to cefazolin among patients with an unverified penicillin allergy is 0.7% (95% CrI: 0.1%-1.7%).[293] The reaction rate among patients with a confirmed penicillin allergy was recently determined to be just 0.8% (95% CI: 0.13%-4.1%) among 131 patients who are confirmed to be penicillin-allergic.[294] In a meta-analysis of 77 studies, a cefazolin allergy was identified in 3.0% of patients with confirmed penicillin allergy (95% CrI: 0.01%-17.0%).[293] Ceftibuten, a third-generation oral cephalosporin, also has unique side chains from any penicillin and all currently available cephalosporins that may also make cross-reaction rates exceedingly rare.[294] This CBS may require an allergy alert override in electronic health records in patients with a history of penicillin allergy who are prescribed cephalosporins, although some US health systems have been able to inactivate such alerts.[295,296] While skin testing is not recommended, it may be advisable for specific patients with multiple drug allergies because of the possibility of coexisting sensitivities.[294] For example, in a study that demonstrated lack of allergy to cefazolin and ceftibuten in 129/131 patients who were penicillin-allergic, 1 participant was skin test–positive to all reagents tested, including cefazolin, ceftibuten, carbapenems, and aztreonam, which indicates a sensitivity to an antigenic determinant of the beta-lactam ring. This single outlier patient was not challenged to determine whether these skin test findings reflect clinical cross-reactivity. Finally, it is important to note that while meta-analytic data are available, the underlying studies were observational studies that suffer from biases such as a selection bias and lack of blinding.[28,293]

Consensus-based Statement 13: We suggest that for patients with a history of an unverified (not confirmed) nonanaphylactic penicillin allergy, a cephalosporin can be administered without testing or additional precautions.

Strength of Recommendation: Conditional

Certainty of Evidence: Moderate

Given that <5% of patients with an unverified penicillin allergy are truly allergic,[297] and ~2% of those who are truly allergic will experience a reaction to a cephalosporin,[201,222,278,284] when they are given cephalosporins directly, the chance of a reaction is very low with a linked probability of ~0.1% (ie, $0.05 \times 0.02 = 0.001$). Retrospective studies of parenteral cephalosporin administration to patients with a history of penicillin allergy, without prior penicillin skin testing, have shown rare cephalosporin allergic reactions.[298,299] However, these studies suffer from selection bias as the patients at lower risk were likely those who were treated with cephalosporins instead of non–beta-lactam antibiotics.

For patients with any immediate penicillin allergy history, a non–cross-reactive cephalosporin can be administered by full dose or drug challenge (Fig 3, *B*). Performing penicillin allergy evaluation greatly simplifies all future beta-lactam administration recommendations for any patients with a penicillin allergy history and has the benefit of potentially delabeling the patients' penicillin allergy. If penicillin testing is negative, the patient can receive any cephalosporin without special precaution.

If the test is positive, there may be an increased risk of reaction with a cross-reactive cephalosporin. Challenges to cephalosporins in patients with negative penicillin skin tests in this scenario are typically well tolerated (Fig 3, *B*). An induction of tolerance procedure is also an option, particularly for patients with a severe reaction history or for patients that are acutely ill or pregnant. Non–beta-lactam antibiotics may also be considered but may result in added patient morbidity, mortality, and cost of care.[16-18,169,274,275]

From 12% to 38% of patients with penicillin allergy in Europe are proven to be selectively allergic to aminopenicillins (ie, able to tolerate penicillin but not amoxicillin/ampicillin).[300,301] The prevalence of aminopenicillin allergy in the United States appears to be rare.[189,191] Patients who are proven to be aminopenicillin-allergic should generally avoid cephalosporins with identical R1-group side chains. In patients with unverified nonanaphylactic aminopenicillin allergy, if an aminocephalosporin is recommended, a drug challenge could be performed.

Consensus-based Statement 14: We suggest that in patients with a history of an unverified nonanaphylactic cephalosporin allergy, a penicillin can be administered without testing or additional precautions.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

Consensus-based Statement 15: We suggest that in patients with a history of anaphylaxis to cephalosporins, penicillin skin testing and drug challenge should be performed prior to administration of a penicillin therapy.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

Consensus-based Statement 16: We suggest against penicillin skin testing in patients with a history of nonanaphylactic cephalosporin allergy prior to administration of a penicillin therapy.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

An algorithm for penicillin administration to patients with a history of cephalosporin hypersensitivity is shown in Fig 3, *C*. Patients with a history of an immediate-type or delayed-type (other than serious reactions such as SJS) allergic reaction to a cephalosporin who require penicillin can receive the indicated penicillin by direct challenge in most cases. In patients with an unverified nonanaphylactic cephalosporin allergy, a penicillin can be administered without any special precautions. For example, patients

with a history of urticaria to a cephalexin can receive amoxicillin without prior testing. Penicillin skin testing–guided treatment is not recommended unless the cephalosporin allergy history was anaphylaxis, angioedema, hypotension, or other severe IgE-mediated reactions. If penicillin skin testing is performed and negative, a drug challenge to the penicillin is still advised (Fig 3, *C*). The role for direct challenge to penicillin in patients with a history of anaphylaxis to cephalosporins with dissimilar R1 groups (eg, cefazolin) requires further study.

Carbapenems. *Consensus-based Statement 17:* We suggest that in patients with a history of penicillin or cephalosporin allergy, a carbapenem may be administered without testing or additional precautions.

Strength of Recommendation: Conditional

Certainty of Evidence: Moderate

The overall reported incidence of carbapenem allergy is 0.3%-3.7%.[302] Clinical cross-reactivity between carbapenems and other beta-lactams is also low.[303-308] A systematic review covering 10 studies and 12 case reports included 838 patients with proven, suspected, or possible IgE-mediated penicillin allergy, and carbapenem reactions occurred in 4.3% of patients (95% CI: 3.1%-5.9%).[309] Of the subset with positive skin tests to penicillin (n = 295), only 1 (0.3%; 95% CI: 0.06%-1.9%) had a reaction with symptoms consistent with a potentially IgE-mediated mechanism. Of the patients with possible cephalosporin reaction (n = 12), 3 (25%) reacted to the carbapenem with only 1 reaction that was potentially IgE-mediated.[309] Another systematic review and meta-analysis covering 11 observational studies including 1127 patients demonstrated a risk of cross-reactivity to any carbapenem as 0.87% (95% CI: 0.32%-2.32%).[28] A recent prospective study of 211 patients with skin test–confirmed penicillin allergy demonstrated that all tolerated carbapenems.[310] Patients with penicillin or cephalosporin allergy histories, as long as it is not a severe delayed cutaneous or organ-involved reaction, can receive carbapenems without prior testing. In certain patients or situations, such as multiple drug allergy or significant patient anxiety, a graded drug challenge might be preferred.

Monobactams (aztreonam). *Consensus-based Statement 18:* We suggest that in patients with a history of penicillin or cephalosporin allergy, aztreonam may be administered without prior testing unless there is a history of ceftazidime allergy.

Strength of Recommendation: Conditional

Certainty of Evidence: Moderate

Aztreonam is less immunogenic and rarely causes HSRs.[311-313] There is no cross-reactivity for IgE- or T-cell–mediated hypersensitivity between penicillin and aztreonam.[314-320] Likewise, no cross-reactivity has been demonstrated between cephalosporins and aztreonam, except for ceftazidime (due to shared R1 side chain of ceftazidime).[316,321,322] Patients who are penicillin- and cephalosporin-allergic (reported or confirmed-allergic) may safely receive aztreonam without prior testing, with the exception of patients who are confirmed allergic to ceftazidime. Conversely, patients who are aztreonam-allergic may be treated with all beta-lactams, except for ceftazidime, which likely has cross-reactivity with aztreonam.

Aztreonam has become a commonly used acute therapeutic drug for patients with penicillin or cephalosporin allergy histories, but it does not have activity against aerobic and anaerobic gram-positive bacteria, it is not as effective against gram-negative bacteria as other beta-lactams are (eg, cefepime, piperacillin-tazobactam), has increasing rates of resistance, and it is costly. It is thus now a common target for antibiotic stewardship efforts, especially in patients with reported penicillin allergy.[29,323-326]

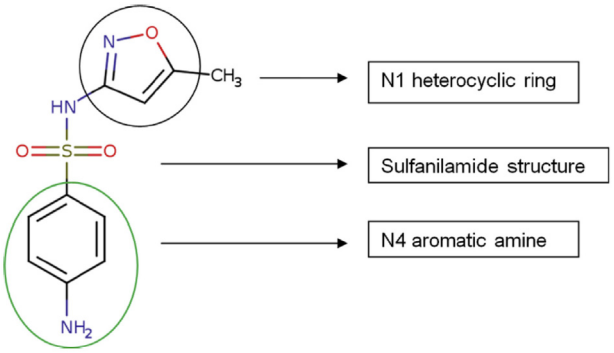

FIG 4. Structure of sulfonamide.

Drug allergy history-based beta-lactam allergy pathways. *Consensus-based Statement 19:* We recommend that allergist-immunologists collaborate with hospitals and health care systems to implement beta-lactam allergy pathways to improve antibiotic stewardship outcomes.

Strength of Recommendation: Strong

Certainty of Evidence: Moderate

Complementary to the recommendations above, integrated beta-lactam pathways can be used for patients that acutely need a beta-lactam antibiotic in the hospital setting.[327] Acute care beta-lactam allergy pathways are defined as coordinated programs that facilitate beta-lactam allergy assessments for patients in the emergency department, those who are hospitalized, and those who are perioperative as part of antibiotic stewardship.[327] Acute care beta-lactam allergy pathways have been implemented and studied; a recent nonsystematic review identified 36 articles describing acute care beta-lactam pathways.[327] Of these articles, there were interventions based solely on the allergy history (n = 8), those that used the allergy history with direct drug challenges (n = 2), penicillin skin testing (n = 15), or both (ie, comprehensive beta-lactam allergy pathways that include all allergy procedures, n = 11).[327] Comprehensive pathways have been developed and published.[177,328-332] Other effective strategies for inpatient adoption include electronic health record triage mechanisms for penicillin allergy skin testing and direct drug challenges.[333-335] An important consideration to implementing a beta-lactam allergy pathway that is not delabeling-focused is that the patients may not have their beta-lactam allergy label effectively removed. Thus, subsequent outpatient allergy/immunology evaluation requires appropriate follow-up care for these patients.

Sulfonamides

Consensus-based Statement 20: We suggest that for patients with a history of benign cutaneous reactions (eg, MDE, urticaria) to sulfonamide antibiotics that occurred >5 years ago, a 1-step drug challenge with TMP-SMX be performed when there is a need to delabel a sulfonamide antibiotic allergy.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

TABLE XIV. Drugs with no or weak evidence of cross-reactivity in patients with a history of a sulfonamide antimicrobial adverse reaction[336]

Drug class	Drug or compound	Comments
Sulfonamide non-antimicrobials		
Alpha-blocker	Tamsulosin	Cross-reactivity is unlikely between sulfonamide antimicrobials and sulfonamide non-antimicrobials
Antiarrhythmics	Ibutilide, sotalol	
Anticonvulsants	Topiramate	
Carbonic anhydrase inhibitors	Acetazolamide, methazolamide, dorzolamide, brinzolamide	
COX-2 inhibitors	Celecoxib	
Diuretics, loop	Furosemide, bumetanide	
Sulfonylureas	Glimepiride, glyburide, gliclazide	
Diuretics, thiazide	Hydrochlorothiazide, chlorthalidone, indapamide, metolazone, diazoxide	
Triptans	Sumatriptan, naratriptan	
Other		
	Sulfur Sulfate (eg, ferrous sulfate, magnesium sulfate) Sulfites (eg, sodium metabisulfite)	No sulfonamide moiety and therefore no cross-reactivity

Sulfonamides are the second most commonly reported allergy in the health record.[251] Sulfonamide antimicrobials are structurally different than nonantimicrobial sulfonamides due to the presence of an aromatic amine group at the N4 position (Fig 4).[336] Because of this, there is minimal concern for cross-reactivity between sulfonamide–nonantimicrobials in patients with histories of reactions to sulfonamide antibiotics, including the sulfone dapsone (Table XIV).[336-338] HSRs to antimicrobial sulfonamides are capable of eliciting numerous phenotypes ranging from the most common MDE to urticaria to SCAR. Immediate skin tests have been used in patients with immediate reaction histories (eg, urticaria or anaphylaxis), and limited data suggest that skin test reactivity may wane fairly rapidly within a year.[339] In contrast, delayed skin testing (IDT and PT) has poor sensitivity for MDE and fixed drug eruption (FDE).[340,341]

Due to the limitations in skin testing, particularly in patients with histories of benign exanthems, induction of drug tolerance procedures have been used where there is a need for sulfonamide antibiotic therapy. More than 20 induction of drug tolerance or multistep challenge procedures have been published, predominantly in patients with HIV in need of prophylaxis with TMP-SMX.[336] These protocols have high rates of success and may range from 6 hours to 10 days; sample protocols are included in the prior drug allergy practice parameter from 2010.[1] Whether these "desensitization" protocols truly induce drug tolerance has not been established. Three studies, all in patients with HIV who have nonanaphylactic histories, have compared full-dose challenge of TMP-SMX with an induction of drug tolerance procedure.[342-344] All 3 studies showed no difference in successfully reaching the full dose of TMP-SMX whether the dose was simply administered or given as a "desensitization." These data suggest that full-dose challenge appears equally efficacious to achieving a therapeutic dose of TMP-SMX. A small study of 8 subjects with anaphylactic reactions to TMP-SMX, including 5 with hypotension, showed the efficacy of a rapid, 5-hour desensitization protocol.[345] Induction of tolerance protocols should be relegated primarily to those with convincing histories of anaphylaxis.

Fewer data are available on challenge or induction of tolerance procedures in patients without HIV.[346-348] Multiple-step challenge or "desensitization" protocols all had high success rates from 93% to 98%. The largest study evaluated 195 patients (without HIV) who underwent a full-dose challenge (n = 173) or a 2-step challenge (n = 22).[349] The 1-step full-dose challenge group had a 95% success rate compared with 86% success in the 2-step group. Those stratified for 2-step challenges had higher risk histories including more recent reactions or anaphylactic histories, likely accounting for the lower success rate of rechallenge (Table XV). This study also showed a higher likelihood of passing the challenge with more remote histories and a vague "sulfa" allergy label. Importantly, all of these studies excluded patients with histories of SCARs. Based on these data, a 1-step full-dose challenge seems appropriate for the majority of patients with nonanaphylactic, benign cutaneous reactions that occurred >5 years ago. Criteria for patients appropriate for a 1-step or 2-step challenge are shown in Table XV.[349,350]

Fluoroquinolones and macrolides

Consensus-based Statement 21: We suggest using a 1-step or 2-step drug challenge without preceding skin testing to confirm tolerance in patients with a history of nonanaphylactic reactions to fluoroquinolones or macrolides.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

Fluoroquinolones

The most common type of allergic reaction to fluoroquinolones is a delayed onset maculopapular exanthem, which is generally benign and self-limited. These rashes occur in 2%-3% of patients treated, although the rate varies among different agents and appears to be highest for gemifloxacin.[351-353] Allergic cross-reactivity among fluoroquinolones for delayed cutaneous rashes appears to be low; only 10% of patients who developed uncomplicated MDE on gemifloxacin reacted to ciprofloxacin (which was given immediately after the gemifloxacin course).[353] PT is not useful in evaluation of delayed maculopapular exanthems.[354] When patients with history of fluoroquinolone-associated rashes

TABLE XV. Criteria for 1- or 2-step TMP-SMX oral challenge and exclusion[349,350]

Challenge type	Criteria	Dose(s)*	Follow-up
1-step challenge	Nonsevere delayed reactions without multiple features consistent with IgE-mediated reaction Nonsevere immediate (eg, isolated urticaria, maculopapular exanthem, or gastrointestinal symptoms) reaction (onset <1 h) ≥5 y ago Nonsevere accelerated reaction (onset >1 h to 36 h) ≥5 y ago Unknown, remote history	TMP-SMX 80-400 mg	2-h observation in clinic after full dose 24-h phone call after full dose
2-step challenge	Nonsevere immediate reaction (onset <1 h) within the past 5 y Nonsevere accelerated reaction (onset >1 h but <36 h) within the past 5 y Anaphylaxis† at any time point in the past; multiple (≥2) features potential compatible with IgE-mediated reaction at any time point in the past: Urticaria Angioedema Shortness of breath Hypotension Significant patient anxiety surrounding single-dose challenge	TMP-SMX 8-40 mg TMP-SMX 80-400 mg	1-h observation in clinic after first dose 2-h observation in clinic after second, full dose 24-h phone call after second, full dose
Excluded	SJS TEN DRESS AGEP Drug-induced nephritis Drug-induce hepatitis		

*Doses listed are for adults. For children, weight-based dosing can be adopted.
†For patients with convincing histories of anaphylaxis, skin testing may be considered prior to challenge.

undergo evaluation with rechallenge with the culprit agent, there is a high chance of success, because only about 5% develop recurrence.[354,355]

Immediate-type reactions to fluoroquinolones have been increasingly described. There is evidence for both IgE-mediated and non-IgE–mediated mechanisms, because fluoroquinolones may cause nonspecific mast cell degranulation via interaction with the surface receptor MRGPRX2. Unlike IgE-mediated reactions, non-IgE–mediated reactions may occur with first exposure because prior sensitization is unnecessary. Otherwise, however, the clinical presentations of these 2 types of reactions are indistinguishable. The rate of fluoroquinolone-related anaphylaxis has been reported to be 1-5 per 100,000 prescriptions and moxifloxacin is implicated most often;[356,357] this rate is comparable to cephalosporins but lower than penicillins.[356] Analogous to other antibiotic allergies such as penicillins, IgE-mediated allergy to fluoroquinolones appears to wane and resolves in many (but not all) patients.[358] Consequently, studies have shown that about 65%-75% of patients with convincing histories of immediate-type reactions to fluoroquinolones tolerate the culprit antibiotic when rechallenged.[354,355,359,360] The majority of immediate reactions to fluroquinolones are not IgE-mediated, but the extent of IgE-mediated allergic cross-reactivity among fluoroquinolones, based on limited number of case series, is ~50%.[361-367]

The urgency of fluroquinolone delabeling may be lower than that for beta-lactam delabeling, and patient preference may play some role. Skin testing with fluoroquinolones is not validated or standardized. Nonirritating concentrations are difficult or impossible to determine due to the antibiotics' propensity to cause nonspecific mast cell degranulation.[119,368] Likewise, there are no validated commercially available *in vitro* tests for IgE-mediated allergy to fluoroquinolones. Basophil activation testing has been described in the research setting.[369,370] Milder reactions, such as MDE and urticaria, that occurred longer than 5 years ago may be most amenable for a 1- or 2-step graded challenge with the implicated fluoroquinolone. For more severe or recent reactions, single-dose or 2-step graded challenge with a different fluoroquinolone than the one implicated in the historical reaction (because they may not cross-react) may be considered. Patients who are proven allergic or likely allergic and require a fluoroquinolone, with no acceptable alternative treatments, may receive the culprit fluoroquinolone via induction of drug tolerance.[371,372]

Macrolides

Allergic reactions due to macrolides are less common than those to penicillins, cephalosporins, sulfonamide antibiotics, and fluoroquinolones. The most common macrolide-related allergic reactions are delayed cutaneous reactions, and they occur in about 1% of patients.[373,374] IgE-mediated reactions are uncommon, limited to case series, and anaphylactic reactions are extremely rare. When patients with convincing histories of allergic reactions undergo formal evaluation, only about 5% are confirmed to be allergic.[32,375-378] Skin testing with macrolides is not validated or standardized because the allergenic determinants are unknown. The utility of immediate-type skin testing using nonirritating concentrations of macrolides is uncertain. Some studies have found skin testing to be useful and predictive of reactions,[377] whereas in other similarly designed studies, skin testing performance

compared with oral challenge was poor.[32] Therefore, based on the low pretest probability, very low rate of anaphylaxis, and disagreement on the utility of skin testing, direct challenge appears to be the most appropriate diagnostic approach for patients with a history of nonanaphylactic reactions. There are no commercially available *in vitro* tests for IgE-mediated allergy to macrolides.

Patients reporting purely benign cutaneous reactions (ie, MDE or urticaria) to macrolides are candidates for 1- or 2-step drug challenge. Using this approach allows 95% of patients to safely reintroduce macrolides.[32,375-378] In patients who fail the challenge or in whom challenge is not pursued and who require a macrolide without acceptable alternative treatments, the antibiotic may be administered via induction of tolerance.[379] The urgency of macrolide delabeling may be lower than that for beta-lactam delabeling, and patient preference may play some role. Given the rare nature of confirmed allergy to macrolides and lack of validated diagnostic testing, the extent of allergic cross-reactivity among macrolides is unknown.

NSAID HYPERSENSITIVITY UPDATES

Aspirin/NSAID hypersensitivity phenotypes

Aspirin and NSAIDs can cause a spectrum of allergic reactions, including exacerbation of underlying respiratory disease, urticaria, angioedema, anaphylaxis, and rarely pneumonitis and meningitis.[33,34] There are 4 primary categories of NSAID reactions that can be diagnosed via history, presence of comorbid diseases, and drug challenges. These reactions are outlined in Table XVI and include AERD, NSAID-induced urticaria and angioedema, NSAID-exacerbated cutaneous disease, and single NSAID-induced reactions. A history of nasal polyposis with subsequent acute onset respiratory symptoms after NSAID exposure suggests a diagnosis of AERD. Similarly, patients with a diagnosis of chronic spontaneous urticaria who experience a worsening of urticaria or angioedema with NSAID exposure should be diagnosed with NSAID-exacerbated cutaneous disease. These 2 phenotypes occur on COX-1 inhibition and are not IgE-mediated or drug-specific. NSAID-induced urticaria and single NSAID-induced reactions are discriminated based on cross-reactivity patterns and reaction type. Specific NSAID reactions are thought to be drug-specific reactions and are not cross-reactive with other structurally unrelated NSAIDS. Both IgE-mediated reactions causing anaphylaxis and T-cell–mediated reactions resulting in various cutaneous manifestations are examples of specific NSAID reactions. The phenotype of NSAID-induced urticaria and angioedema that cross-reacts with any other COX-1 inhibitors seems specifically to cause cutaneous symptoms, with anaphylaxis being extremely unlikely.[380-382]

Consensus-based Statement 22: We suggest a selective COX-2 inhibitor may be used as an alternative analgesic in patients with any NSAID hypersensitivity phenotype when an NSAID is needed.

Strength of Recommendation: Conditional
Certainty of Evidence: Low

Aspirin-exacerbated respiratory disease

AERD is a clinical entity characterized by aspirin- and NSAID-induced respiratory reactions in patients with chronic rhinosinusitis and asthma. The nomenclature ascribed to this type of reaction has included terms such as “aspirin sensitivity,” “aspirin intolerance,” “aspirin idiosyncrasy,” “aspirin-induced asthma,” “aspirin-intolerant asthma,” “NSAID-exacerbated respiratory disease (N-ERD) aspirin triad,” and “Widal triad” or “Samter’s triad.”[383] Although N-ERD is commonly used, this acronym may have a negative connotation, thus AERD is still preferred in the United States.

AERD is unique and does not fit precisely into the usual categories of adverse drug reactions. AERD onset is often reported following an upper respiratory infection, with onset of perennial rhinitis followed by the development of sinonasal polyposis, and progression to asthma.[384] Rhinitis is often complicated by chronic sinusitis, anosmia, and nasal polyposis. The literature on the chronology of the development of these components is mixed. Asthma and hypersensitivity to NSAIDs usually develop several years after the onset of rhinitis.[384] Upper and lower respiratory tract symptoms are frequently sudden and often severe after administration of aspirin or any NSAID that inhibits the COX-1 enzyme.

Despite avoidance of aspirin and cross-reacting drugs, these patients typically experience refractory rhinosinusitis and asthma —in some cases requiring repeated sinus surgery with frequent or chronic administration of systemic corticosteroids.[385] AERD is rare in children with asthma and becomes increasingly more common in adults with asthma. Approximately 7% of adults with asthma and one-third of patients with asthma and nasal polyposis have AERD.[386,387]

In AERD, baseline abnormalities are observed in leukotriene pathways and prostaglandin metabolism due to reduction of prostaglandin E_2 and reduction of signaling through the E prostanoid 2 receptor.[388] These biochemical changes are augmented after COX-1 inhibition by NSAIDs, leading to increased production of leukotriene mediators, manifesting as an acute clinical reaction. Long-term therapy with aspirin after desensitization leads to improvement in some of these biochemical changes and is associated with improved clinical outcomes. These molecular pathways have been reviewed extensively elsewhere and are summarized in Table XVII.[388,389]

Aspirin and NSAIDs that inhibit COX-1 can all cause reactions in patients with AERD and are considered cross-reactive (Table XVIII). Analgesics that are weak inhibitors of COX-1 (eg, nonacetylated salicylates and acetaminophen) (Table XVIII) may cause reactions in highly sensitive individuals if administered at higher doses (650-1000 mg) but are typically mild.[390,391] NSAIDs that preferentially inhibit COX-2 but also inhibit COX-1 at higher doses may result in reactions, depending on the dose given. Reactions to selective COX-2 inhibitors are extremely rare in patients with AERD and they can typically be taken safely.[392-395]

Consensus-based Statement 23: We recommend against an oral aspirin challenge to confirm the diagnosis of AERD in cases of high diagnostic certainty based on clinical history; however, aspirin desensitization remains a therapeutic option when indicated.

Strength of Recommendation: Strong
Certainty of Evidence: Low

Neither skin testing nor *in vitro* tests are useful for AERD. The diagnosis of AERD is usually established by history, with the probability of reacting to a formal challenge ranging from 80% to 100% in patients with a typical history.[387] When patients with a history suggestive of AERD (ie, asthma, rhinosinusitis, and history of a single respiratory reaction to aspirin or

TABLE XVI. Classification of common aspirin/NSAID HSRs

Phenotypes	Symptoms	COX-1–mediated	Comorbidities	Candidate for desensitization
AERD	Sneezing, congestion, bronchospasm, laryngospasm, occasionally gastrointestinal pain and flushing/urticaria	Yes	Nasal polyposis, chronic sinusitis, asthma in the vast majority	Yes
NSAID-induced urticaria and angioedema	Urticaria and angioedema	Yes	None	Can be considered
NSAID-exacerbated cutaneous disease	Urticaria and angioedema	Yes	Active chronic spontaneous urticaria	No
Single NSAID-induced reactions	Varying from mild urticaria to severe anaphylaxis	No	No	Theoretically possible, unlikely to be necessary

TABLE XVII. Immune effects of high-dose aspirin in AERD

Decreased prostaglandin E_2
Increased cysteinyl leukotrienes
Increased tryptase
Continued 5-lipoxygenase activity
Diminished prostaglandin D_2
Inhibition of STAT6
Decreased sputum IL4
Decrease in CYSLTR1

aspirin-like drug) are challenged with aspirin, ~80% will have a respiratory reaction confirming the diagnosis.[387] When there is a history of multiple reactions to structurally dissimilar NSAIDS (eg, ibuprofen and aspirin) the rate of a positive challenge increases.[387] In a study of 243 patients, all those with a history of aspirin causing a severe reaction that required hospitalization or intensive care level monitoring had positive oral aspirin challenges.[387] Thus, in most patients with histories suggestive of AERD, an aspirin challenge to exclusively confirm the diagnosis is not required or recommended. Thus, in patients with ≥2 respiratory reactions to different NSAIDS or a respiratory reaction requiring hospitalization, further diagnostic testing with aspirin challenge is unnecessary.

Consensus-based Statement 24: We suggest an oral aspirin challenge to confirm the diagnosis of AERD in cases of diagnostic uncertainty.

Strength of Recommendation: Conditional

Certainty of Evidence: Moderate

If the history is unclear or unknown (eg, no recent history of NSAID ingestion) and when a definite diagnosis is required, a controlled oral provocation challenge with aspirin should be performed (Table XIX). This may be necessary in patients who have a remote NSAID reaction history or do not take NSAIDS at all, or in whom the reaction description was atypical (cutaneous only symptoms, >3 hours from ingestion to reaction, or prolonged symptoms lasting >8-10 hours). Making an AERD diagnosis is critical for counselling patients on NSAID avoidance, provides an opportunity for aspirin desensitization, and provides more insight into the underlying polypoid disease and asthma which will likely be more recalcitrant to therapy. Twenty-four–hour urinary leukotriene E4 measurements are elevated at baseline in AERD, but a diagnostic cutoff has not yet been established. Although this could be used in conjunction with other clinical features, the gold standard diagnosis requires an observed aspirin challenge when the history is uncertain.[396]

Management of AERD–challenge and desensitization. *Consensus-based Statement 25:* We suggest that a challenge procedure be used to diagnose AERD when there is diagnostic uncertainty and that a desensitization protocol be used when the intention is to place a patient on a daily therapeutic aspirin dose for cardioprotection, pain relief, or to control nasal polyp regrowth.

Strength of Recommendation: Conditional

Level of Evidence: Moderate

Aspirin desensitization is a form of pharmacologic induction of drug tolerance. The term "desensitization" is used for historical context; however, this procedure is distinguished from any other immunologic induction of drug tolerance in that unique biochemical events occur during desensitization that can be associated with clinical benefit. Similar to other induction of drug tolerance procedures, pharmacologic induction of drug tolerance procedures induce a temporary state of tolerance to aspirin/NSAIDs that is maintained only as long as the patient continues to take aspirin. Pharmacologic induction of drug tolerance is typically performed over hours to days and generally starts with milligram amounts. The most common indication for aspirin desensitization in the United States is poorly controlled airway disease despite use of appropriate medications for patients who require long-term treatment with systemic corticosteroids to control their upper and lower respiratory disease. When the intention is to both identify whether hypersensitivity exists through a challenge and then simultaneously convert to desensitization if the patient demonstrates hypersensitivity, the term "challenge/desensitization" has been used to delineate both occurring simultaneously as part of a single procedure.[397] Although many clinicians might use the same protocol for both a challenge and a desensitization, the purpose of the challenge is to identify the HSR through objective measures such as a drop in FEV_1 >10%-15%, a drop in peak nasal inspiratory flow >25%, physical examination findings (wheezing, sneezing, rhinorrhea, conjunctival injection), and symptoms.[398-400] Any of the protocols listed in Table XX can be used as an aspirin challenge protocol in patients where diagnostic uncertainty exists for AERD and confirmation of this sensitivity is required. A patient who has objective reactivity during a desensitization procedure has simultaneously confirmed the AERD diagnosis and thus functions as a positive aspirin challenge. A challenge procedure is completed when the patient has

TABLE XVIII. COX-1 and COX-2 inhibiting medications

Drug	Route of administration
Highly selective COX-1 inhibitors	
Acetylsalicylic acid (aspirin)	Oral (OTC)
Antipyrine/benzocaine	Otic only (OTC)
Diclofenac	Oral, topical gel
Etodolac	Oral
Fenoprofen	Oral
Flurbiprofen	Oral
Ibuprofen	Oral (OTC)
Indomethacin	Oral
Ketoprofen	Oral, topical gel
Ketorolac	Oral, IM, IV, nasal
Meclofenamate	Oral
Mefenamic acid	Oral
Naproxen	Oral (OTC)
Oxaprozin	Oral
Piroxicam	Oral
Tolmetin	Oral
Weakly selective COX-1 inhibitors	
Acetaminophen	Oral (OTC)
Choline magnesium trisalicylate	Oral
Diflunisal	Oral
Salsalate	Oral
Preferentially selective COX-2 inhibitors	
Meloxicam	Oral
Nabumetone	Oral
Highly selective COX-2 inhibitors	
Celecoxib	Oral

OTC, Over the counter.

TABLE XIX. Clinical characteristics determining the need for challenge versus desensitization in patients with AERD *

Consider diagnostic aspirin challenge	Consider aspirin desensitization
Single reaction to an NSAID	Reaction to ≥2 different NSAIDs
Minor symptoms	Reaction requires hospitalization
Atypical symptoms (lightheadedness, cutaneous only, prolonged symptoms for >24 h)	Typical upper or lower airway symptoms lasting <6 h
Minor nasal polyp burden	Severe recurrent nasal polyposis

*Individual patients may exhibit some criteria from each column. The clinician will need to determine based on an aggregate assessment of these factors whether to offer a challenge or consider aspirin desensitization.

evidence of a reaction. It should be noted that there are variables that affect the outcome of the aspirin challenge. Concurrent leukotriene-modifying therapy may lead to a negative challenge in a patient with AERD.[401] Similarly, omalizumab may completely block aspirin-induced reactions.[402,403] In patients who have recently had a debulking polypectomy as many as one-third will convert to a negative challenge, thus aspirin desensitization ideally should be performed within several weeks of sinus surgery.[404,405] During desensitization, doses are repeated and advanced after the patient recovers from the reaction, and the goal is to achieve a dose of at least 325 mg aspirin daily. This dose allows use of any dose of any NSAID without concern of a reaction. If a final goal of 81 mg is desired purely for antiplatelet effect, then that can be the final dose of the desensitization, but the patient will not be desensitized to a higher dose of aspirin or another NSAID.

Precautions for aspirin desensitization in AERD should emphasize frequent monitoring of lung function and management of severe bronchospasm. Protocols vary in dose and timing of aspirin, but generally require 1-3 days to accomplish.[406-408] Newer studies outline protocols in which the intention can be to complete the desensitization in a single clinic day (Table XX).[409,410] Reaction severity and duration may still dictate the conversion to a multiday protocol (Table XIX). Desensitization involves incremental oral administration of aspirin during 1-3 days, starting at 20.25-40.5 mg and going up in steps to the full dose of 325 mg.[406,408,411] Intranasal ketorolac is used as an additional option to initiate desensitization with the intention of limiting the initial symptoms into the upper airway.[408] In cases where the days of desensitization are not consecutive, patients may continue the highest tolerated dose daily until the desensitization can be completed. Continued daily administration of at least 325 mg of aspirin once daily is required for patients to remain in a tolerant state.[412] However, higher doses are usually necessary to control nasal polyps and airway inflammation with initial doses of 650 mg twice daily being necessary for optimal effect.[413] Aspirin therapy may be associated with gastritis, epigastric pain, or gastrointestinal bleeding. Using an enteric-coated aspirin and other modes of gastrointestinal prophylaxis may be considered.[397,414] Gaps in aspirin doses >48 hours may lead to loss of tolerance and after 5 days all patients will react to aspirin and require another desensitization procedure to resume therapy.[412] This presents a problem for patients in whom a surgical procedure necessitates aspirin discontinuation. If the surgical procedure can be safely performed during a 48-hour window, aspirin can safely be restarted immediately after surgery at the previous aspirin treatment dose. Reducing the dose of aspirin to 325 mg daily for 7 days prior to surgery, holding aspirin the day prior and the day of surgery, and then restarting aspirin immediately postoperatively allows patients to retain their state of tolerance.[415] Using ibuprofen in lieu of aspirin during surgery to "bridge" the patient and have presumably less aspirin-related bleeding complications is another consideration.[416] For patients who need to be off aspirin for >48 hours, desensitization should be repeated. Decisions on the best approach for modified versus complete desensitization need to be made on an individualized basis taking into account factors including patient history, severity of symptoms during desensitization, severity of asthma, and the eliciting dose. Leukotriene-modifying agents have been found to diminish the lower respiratory asthmatic response during aspirin desensitization and, therefore, are recommended as pretreatment for patients with AERD preparing for aspirin desensitization who are not already taking one of these agents (when not otherwise contraindicated).[417,418] Inhaled corticosteroid/long-acting beta agonist inhalers serve a dual purpose of optimizing asthma control prior to desensitization but also diminishing the severity of NSAID-induced bronchospasm and, therefore, should also be considered for pretreatment.[417,419] Once patients are desensitized, universal tolerance to all COX-1–inhibiting NSAIDs (in addition to aspirin) is achieved.

Management of AERD–aspirin as therapy. Management of patients with AERD involves avoidance of aspirin and NSAIDs and aggressive medical and/or surgical treatment of underlying asthma and rhinitis or sinusitis. A pharmacologic induction of drug tolerance procedure (aspirin desensitization) is an important therapeutic option for patients with AERD. Aspirin desensitization treatment improves clinical outcomes for both upper and lower respiratory tract disease.[411,420-425] During

TABLE XX. Various commonly used aspirin desensitization protocols for AERD[406-408]

Day	Time	Aspirin (90 min)	Ketorolac/aspirin*	Aspirin (60 min)
Day 1	8:00 AM	20.25-40.5mg	1 spray	20.25-40.5 mg
	8:30 AM		2 sprays	
	9:00 AM		4 sprays	81 mg
	9:30 AM	40.5-81 mg	6 sprays	
	10:00 AM			120 mg
	10:30 AM		60 mg oral aspirin	
	11:00 AM	81-162 mg		162 mg
	12:00 PM		60 mg oral aspirin	325 mg
	12:30 PM	162-325 mg		
	2:00 PM	325 mg		
Day 2	8:00 AM		150 mg oral aspirin	
	11:00 AM		325 mg oral aspirin	

Not all protocols are necessarily appropriate for all patients. Patients with a history of gastrointestinal reactions or delay in reaction might not do as well in the faster protocols. The timing above assumes minimal or no reaction to aspirin doses. In most situations, when a reaction occurs, the protocol is paused and resumed only after the reaction has largely resolved.

Doses triggering a reaction should be repeated prior to up-dosing.

Given the above factors, many patients will require a second day to complete the desensitization even if the intention was to complete it in 1 day.

Most patients will react at a dose between 40.25 mg and 120 mg of aspirin.

*Ketorolac nasal spray—60 mg/2 mL ketorolac (2 mL + 2.75 mL preservative free saline) = 12.6 mg/mL = 1.26 mg per 100 μg spray.

long-term aspirin desensitization, urinary leukotriene E4 decreases to pre-desensitization levels; bronchial responsiveness to leukotriene E4 is greatly reduced; serum histamine and tryptase levels decrease; and leukotriene C4 and histamine in nasal secretions decrease.[411] Aspirin desensitization has been shown to be cost-effective (US$6768 per quality-adjusted life-years for AERD).[426]

Variables that might affect the NSAID-induced hypersensitivity in AERD include recent debulking polypectomy, omalizumab, and leukotriene modifiers, all of which may lead to a negative challenge in some patients.[397] With the advent of biologic therapies for nasal polyposis such as dupilumab, where benefit is observed in AERD, it remains to be seen how these may also alter the NSAID hypersensitivity in AERD.[427]

NSAID-exacerbated cutaneous disease

A second clinical presentation of aspirin and NSAID drug-allergic reactions is an exacerbation of urticaria or angioedema in patients with chronic spontaneous urticaria (Table XVI). Approximately 10%-40% of patients with chronic spontaneous urticaria develop a worsening of their condition after exposure to aspirin or NSAIDs.[428,429] The rate appears to be more frequent in patients in an active phase of their urticaria or angioedema syndrome. Most patients with a history of exacerbations induced by aspirin or NSAIDs demonstrated the presence of histamine-releasing factors assessed by autologous serum skin tests and basophil histamine release assays.[430] Isolated NSAID-induced urticaria might precede the development of chronic spontaneous urticaria.[431] All drugs that inhibit COX-1 cross-react to cause this reaction, and the arachidonic acid metabolism dysfunction described herein in the section in AERD is thought to play a pathogenic role. Selective COX-2 inhibitors are generally well tolerated in patients with chronic spontaneous urticaria, although there may be rare exceptions.[432-434]

Management of NSAID-exacerbated cutaneous disease. Aspirin or another NSAID is occasionally medically necessary in patients with NSAID-exacerbated cutaneous disease. Although desensitization has been attempted, patients with chronic urticaria or angioedema that is exacerbated by aspirin do not typically achieve tolerance via either rapid (2-5 hours) or standard (1-3 days) aspirin challenge or desensitization protocols and continue to experience flares of their cutaneous condition with exposure to aspirin or cross-reacting NSAIDs.[435,436] The general approach to patients with this condition is to primarily control the underlying urticaria. In patients with uncontrolled chronic urticaria, they are unlikely to tolerate NSAIDs at any dose, but once the urticaria is controlled, some patients tolerate single-dose NSAID challenges. Whether they may tolerate continuous daily treatment is not established.[436] Case reports suggest that when the skin disease is controlled with omalizumab, some patients may then be able to tolerate NSAIDs.[436-438]

Multiple NSAID-induced urticaria and angioedema

Consensus-based Statement 26: For patients with NSAID-induced urticaria and angioedema, we suggest an oral aspirin challenge to identify whether the reaction is COX-1 cross-reactive.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

A third type of drug hypersensitivity to aspirin or NSAIDs is urticaria or angioedema due to aspirin and any NSAID that inhibits COX-1 in individuals without a prior history or ongoing chronic urticaria (Table XVI).[33,439] These patients are usually able to tolerate COX-2 inhibitors, and their reactions are purely cutaneous without accompanying anaphylactic symptoms.[432,434,440] In a study over a 2-year period, 63% of patients became naturally tolerant to NSAIDS.[441] Patients with a history of acute urticaria to multiple NSAIDs might be at increased risk for the development of chronic urticaria, although conflicting studies exist.[431,442] It is difficult to determine the diagnosis in a patient with a history of a single NSAID reaction who now avoids all NSAIDS. An accurate diagnosis requires a challenge with several studies demonstrating the safety and utility of performing challenges with structurally dissimilar NSAIDS.[380-382] For example, if the reaction occurred with ibuprofen, an aspirin challenge will address whether this is a cross-reactive or possibly a drug-specific allergic reaction as described next.

Management of NSAID-induced urticaria and angioedema. NSAID-induced urticaria and angioedema is

generally managed by avoidance. In the setting of inflammation requiring COX-2 blocking effect, specific COX-2 inhibitors will generally be tolerated.[440,443] Given the low rate of reactions (8%-11%) that also occur to COX-2 inhibitors, the first dose could be given under observation. In contrast to the aforementioned 1- to 3-day protocols for induction of drug tolerance to aspirin (aspirin desensitization) in patients with AERD, there are limited data on more rapid (2-5 hours) protocols in patients with histories predominantly of cutaneous reactions (urticaria or angioedema) to aspirin but also include a few patients with histories of respiratory reactions.[435,439,444-446]

Concomitant high dose (2-4 times the standard daily dose of a nonsedating antihistamine) H_1-antihistamines might also be another avenue to allow occasional safe use of NSAIDS.

Single NSAID-induced urticaria, angioedema, and anaphylaxis

A fourth type of drug allergic reaction is aspirin or single NSAID-induced urticaria or angioedema or anaphylactic reaction, in which case other NSAIDs are tolerated (Table XVI).[447-450] The underlying etiology of these reactions is not fully understood. The clinical pattern of a preceding period of sensitization during which the drug is tolerated suggests an IgE-mediated mechanism, but there are limited reports of detection of specific IgE to NSAIDs. In pyrazolone derivatives, positive skin and enzyme-linked immunosorbent assay *in vitro* test results were seen in 51 of 53 patients.[451] Similarly, in 6 subjects with metamizole hypersensitivity, skin tests were positive in all patients.[452] This reaction is not due to arachidonic acid dysfunction, and any NSAID, including selective COX-2 inhibitors, may be responsible.[453,454] Although specific IgE-mediated reactions theoretically can occur to any pharmacologic agent, controversy exists regarding the presence of an anaphylactic response specific to aspirin. Aspirin reactions are typical in the cross -reactive patterns described above, but they have not been conclusively shown to exist through a structure-specific immunologic mechanism. All studies that have "desensitized" to aspirin beginning at doses designed to accommodate an IgE-mediated mechanism were done empirically based on a remote history. Specific aspirin allergy might be assumed in patients with a remote history of an aspirin reaction and recent tolerance of a separate NSAID such as ibuprofen. But this assumption should be dispelled by the lack of reports of aspirin-specific hypersensitivity. Direct challenges to aspirin in this situation are nearly always negative.[455,456]

Management of single NSAID reactors. Successful management of single NSAID reactors is contingent on determining the culprit NSAID. It would be unusual to have a patient require a specific NSAID, other than aspirin, for a medical condition. Because most NSAIDs are not available in a parenteral form, and the PPV and NPV are unknown, skin testing is generally not recommended in evaluation of these patients. Challenge to NSAIDs in a different structural class would provide options for as needed pain control (Table XXI). Direct aspirin challenges should be performed to allow future aspirin use.

Other NSAID hypersensitivity subtypes

In mastocytosis, 2%-4% of patients might exhibit hypersensitivity to aspirin or NSAIDS—through the nonspecific consequence of mast cell degranulation.[457] Separately, patients might exhibit unexpected respiratory symptoms or combined ("blended") respiratory and cutaneous reaction to aspirin or NSAIDs. These cannot be classified into 1 of the 4 reaction types described herein.[458] In addition, allergic reactions to aspirin or NSAIDs can rarely manifest as pneumonitis, eosinophilic pneumonias, or meningitis. Meningitis is much more common with ibuprofen, and although it is likely drug-specific, cross reactivity to other NSAIDs has been reported.[459] In all of the above situations, consideration should be made for the chemical structure of the culprit NSAID and that an alternative class might be tolerated in this situation, although studies in the above situations are lacking (Table XXI).

NSAIDS are also common causes of delayed drug HSRs that comprise ≤5% of all such reactions and occur >6 hours after dosing, although many will occur after days to weeks following initiation of a new NSAID.[460] Many of such reactions are thought to be T-cell–mediated. Delayed HSRs associated with NSAIDs include cutaneous phenotypes such as generalized maculopapular exanthem and urticarial drug eruption, FDE,[461] phototoxic and photoallergic rashes, contact and photocontact dermatitis, and, rarely, more severe rashes such as DRESS, SJS/TEN, and AGEP.[462] NSAIDs are also among the most common drug-induced causes of interstitial nephritis,[463] drug-induced liver injury,[464] drug-induced pneumonitis, and aseptic meningitis.[465] NSAIDs are among the most common causes of FDE and include in particular the oxicam, acetic acid, and propionic acid derivatives and acetaminophen.[461] Oxicam (eg, meloxicam, piroxicam) and acetic acid NSAIDs (eg, diclofenac) have been more highly associated with severe cutaneous adverse drug reactions; oxicam and selective COX-2 inhibitors are most commonly associated with SJS/TEN.[466] Because prodromal symptoms of SJS/TEN include fever and mucosal involvement, NSAIDs (particularly ibuprofen) and acetaminophen may be started following onset of initial symptoms; they may also be falsely implicated in some SJS/TEN and erythema multiforme cases (protopathic effect). Lesional (FDE) or general patch testing have been employed for diagnosis of cutaneous delayed reactions associated with NSAIDs with varying sensitivity. Cross-reactivities within the same chemical class although not universal (eg, lack of cross-reactivity between ibuprofen and naproxen reported for FDE) are well described, and for severe reactions, avoidance without rechallenge within that class (Tables XVIII and XXI) is recommended.[460] This is due to the potential recurrence of a severe drug hypersensitivity that cannot be well predicted with current testing approaches.

Common NSAID hypersensitivity clinical scenarios

Consensus-based Statement 27: We suggest a 2-step aspirin challenge for patients with a history of non-AERD aspirin allergy to aid in the management of cardiovascular disease events.

Strength of Recommendation: Conditional

Certainty of Evidence: Very Low

Urgent requirement for aspirin in a patient with an acute coronary syndrome. In the setting of an acute coronary syndrome, the need for the antiplatelet effect of aspirin might supersede the goal of the allergist-immunologist to first determine whether the patient has ongoing hypersensitivity. A graded aspirin challenge or aspirin desensitization are 2 options available to the allergy consultant. A graded challenge is preferred because it provides the patient and clinician with a true diagnosis and, if

TABLE XXI. NSAID classification based on chemical structure

Salicylates	Propionic acids	Nonacidic/carboxylic acid
Aspirin	Ibuprofen	Nabumetone
Salsalate	Naproxen	
Diflunisal	Ketoprofen	
	Flurbiprofen	
	Fenoprofen	
	Oxaprozin	
Enolic acids	**Acetic acids**	**Fenamic acids**
Meloxicam	Diclofenac	Meclofenamate
Piroxicam	Etodolac	Mefenamic acid
	Indomethacin	
	Ketorolac	
	Sulindac	
	Tolmetin	
Coxibs		
Celecoxib		
Parecoxib		
Etorixocib		

TABLE XXII. Graded aspirin challenge protocol for patients with cardiovascular disease[445]

Time (min)	Dose (mg)
0	1
30	5
60	10
90	20
210	40
330	100

TABLE XXIII. Rapid low-dose aspirin graded challenge for cardiovascular emergencies[456]

Time (min)	Dose (mg)
0	40.5
90	40.5*

*At this point, the goal of 81 mg of aspirin has been reached. If the patient has no symptoms after a 90-min period following the final dose, daily 81 mg aspirin can be initiated. If at a later time higher doses of aspirin are indicated, administering 325 mg with a 90-min observation can be considered for patients who do not have AERD.

the diagnosis is negative, simplifies any further questions about aspirin use.

Although aspirin desensitization has been associated with success in allowing patients who otherwise would have been denied the benefits of aspirin to receive this drug safely, it is unclear whether these protocols truly induce drug tolerance (desensitization) or are simply a multistep graded-dose challenge.[456] Most of the patients described in these reports required aspirin for acute coronary syndromes or before coronary stent placement and had a history of prior adverse reaction to aspirin. No confirmatory challenge studies could be performed to determine whether the previous reactions were causally or coincidentally associated with aspirin. For this reason, it is uncertain whether these patients were truly aspirin-sensitive. Fortunately, 2 larger studies now demonstrate the logistical feasibility and relative safety of these empiric "desensitization" strategies in the acute cardiovascular setting.[445,455] Most subjects in this same population who underwent a challenge had a negative aspirin challenge and were therefore never allergic at the time of their desensitization.[455] An example of a rapid aspirin challenge desensitization protocol is provided in Table XXII.[445] It is likely that in patients with poorly controlled NSAID-exacerbated cutaneous disease that these "desensitization" protocols might culminate in persistent urticaria. The allergy consultant will need to discuss this possibility with the cardiovascular team early on. A preferred protocol of a simple 2-step oral challenge (Table XXIII) has been reported and could be applied to any non-AERD aspirin hypersensitivity scenario.[456] This can be finished at 81 mg if that is the target dose or could be continued to 325 mg if necessary. The disadvantage of performing a "desensitization" to aspirin is that the patient retains the aspirin allergy label and the concomitant issues that might come up with future need to reintroduce aspirin after a lapse in therapy. Table XXIII provides an example protocol, but variations on this could include lower starting doses, shorter intervals between doses based on clinician preference, and patient characteristics such as unstable cardiac status or anxiety. Thus, in a patient with a remote history of an NSAID reaction and no AERD or active urticaria, a challenge is preferred. In a large series of NSAID challenges, a 2-step challenge protocol was efficient and convenient. In this group, 75% had a history of NSAID-induced urticaria or angioedema; 85% of the challenges were negative; and only 3 of 262 challenges were treated with epinephrine, none had hemodynamic instability.[467] A challenge is simpler (no need for compounding the aspirin dose), faster, and will efficiently answer the question regarding hypersensitivity while simultaneously achieving the therapeutic objective. It is understood that in some institutions, established aspirin desensitization protocols might be in place and be more convenient. Patients who are extremely unstable might also be candidates for desensitization where much lower starting doses are used. Patients with a history consistent with AERD (respiratory reactions to NSAIDs, history of nasal polyposis, and asthma) would be best served by performing a desensitization specific to AERD as outlined earlier in Table XX.

A patient requiring NSAID use for pain. In this setting, "as-needed" treatment would likely be preferred. The goals of the allergy consultant should be 2-fold. First is to make an accurate diagnosis of NSAID hypersensitivity. This is done through history and use of selected oral challenges. Proving the patient does not have NSAID hypersensitivity allows any NSAID to be used and answers the clinical question. The second goal is to find the best treatment option in a patient with verified NSAID hypersensitivity. Most frequently, a challenge with a specific COX-2 inhibitor will be tolerated and allow use of that medication. If a specific NSAID allergy is suspected, challenge with an NSAID in a different structural group should be considered (Table XXI). If regular use of an NSAID for pain control is necessary, desensitization can be considered, but as previously discussed, the effectiveness of this approach is dependent on the specific NSAID hypersensitivity phenotype. In AERD, patients may be desensitized to 325 mg daily aspirin and could take additional NSAIDs as needed for pain relief. In patients without AERD, this is also an opportunity to challenge with the culprit drug to delabel the NSAID allergy for the patient.

NSAID hypersensitivity in children

In general, the above approaches can be applied to pediatric patients with HSRs to NSAIDs, with the exception that AERD has

only rarely been reported in the pediatric population.[468,469] Only 31%-68% of children will have NSAID hypersensitivity confirmed on challenge, demonstrating the difficulty in relying on history for diagnosis. A recent report describes 526 direct provocation challenges with the culprit drug in 6 centers with a positive challenge rate of 19.6%.[470] In a subgroup of children, NSAID reaction patterns cannot be adequately explained by current mechanistic understanding.[471,472]

Clopidogrel hypersensitivity

Allergic rashes may occur in 1%-2% of patients following introduction of clopidogrel, a thienopyridine inhibitor of platelet activation that is often recommended in aspirin-intolerant patients.[473] Although the mechanisms of such reactions are unknown, successful oral induction of drug tolerance protocols have been reported.[474,475] Although induction of tolerance is successful in these situations, rechallenge or continued therapy is also reportedly successful.[473]

CANCER CHEMOTHERAPEUTIC HYPERSENSITIVITY

Infusion reactions are defined as negative or adverse reactions to specific drugs that are usually not predictable and unrelated to the known side effects from a drug. Some infusion reactions are felt to be HSRs, while others do not have an allergic component and are caused by other components of the immune system. HSRs have emerged as a significant complication for many commonly used chemotherapeutic agents.[476-479] The ability to use first-line chemotherapeutic agents in the treatment of patients with cancer is critical to good patient outcomes, but unfortunately, an increasing incidence of HSRs are limiting their use.

Immediate HSRs can range from mild cutaneous eruptions to anaphylaxis and are often mast cell–mediated. Delayed reactions typically 6-24 hours later are more likely related to T-cell–mediated mechanisms. Site-specific toxicities such as mucositis, alopecia, nail changes, or hand-foot syndrome lead to drug discontinuation and are reversible. Benign delayed exanthems can occur but often amenable to "treating through" with symptomatic management (ie, oral H_1-antihistamines). However, more worrisome reactions can include erythema multiforme or severe cutaneous adverse drug reactions such as SJS/TEN, serum sickness, DRESS, and AGEP. These types of severe T-cell–mediated delayed reactions are typically not amenable to desensitization, are associated with long-lasting memory T-cell responses, and typically indicate that the drug needs to be avoided completely. Other reactions associated with cancer chemotherapeutic agents or the underlying disease itself can include acneiform eruptions, lichenoid reactions, lichenoid bullous reactions, autoimmune bullous reactions, phototoxic and photoallergic reactions, Sweet's syndrome, and other neutrophilic dermatoses. dIDT may be useful for certain cutaneous adverse reactions (eg, SCARs) but avoided in SJS/TEN where the sensitivity is low. PT may also be useful in these severe delayed T-cell–mediated reactions (see section on Testing for delayed HSRs). The cutaneous toxicity of some chemotherapeutic agents may forbid any type of skin allergy testing.

The lack of a standardized approach to management after a presumed mast cell–mediated HSR leads to suboptimal outcomes including needless avoidance of first-line chemotherapeutic agents in patients who could tolerate rechallenge without desensitization or intentional rechallenge with a drug that may cause a recurrent and severe HSR. However, there is significant research and experience showing that an accurate clinical history and proper evaluation improves patient outcomes despite a reported HSR to chemotherapeutics. This section focuses specifically on approach to care of patients with immediate HSRs to specific chemotherapeutics that frequently prompt referral to the allergist-immunologist and cites the supporting literature on evaluation and management of these HSRs (Table XXIV).[480-488]

Consensus-based Statement 28: We suggest that in patients with immediate reactions to chemotherapeutics a drug desensitization may be performed when the implicated drug is the preferred therapy.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

The main approaches to care after a presumed HSR to a chemotherapeutic include (1) desensitization, (2) skin testing and risk stratification, or (3) risk stratification without skin testing and challenge. There are advantages and disadvantages with each approach.

While most of the desensitization protocols published in the literature initially focused on antibiotics, this principle, has since been applied successfully to other drugs including chemotherapeutic agents.[483,489,490] If the clinical assessment is consistent with an HSR, then empiric desensitization is a reasonable and safe approach to care and can be performed even when skin testing is not possible (ie, outpatient clinic without access to chemotherapy drugs for skin testing, skin toxic chemotherapeutics). Candidates for drug desensitization to chemotherapeutics include those with type I HSRs (mast cell–mediated/IgE-dependent) including anaphylaxis. Desensitization protocols allow patients to safely receive first-line chemotherapy treatments for management of life-threatening oncologic diseases to reach optimal outcomes. Drug desensitization should be performed when there is no reasonable alternative as with first-line cancer treatments. Drug desensitization protocols for chemotherapeutics can last several hours with dose doubling every 15-20 minutes and are usually performed in inpatient units or infusion centers with trained staff.

Consensus-based Statement 29: We suggest that patients with nonimmediate reactions or a history of reactions inconsistent with chemotherapeutic hypersensitivity may be treated with a slowed infusion rate, graded dose escalation, and/or premedications without desensitization.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

Patients without a convincing clinical history of an HSR do not require desensitization and typically respond well to readministration of the chemotherapeutic agent. Examples include subjective symptoms of pruritus or lip swelling without any objective skin findings during the infusion or the occurrence of redness of the skin without any itching, rash, or hives several hours after treatment is completed. In these cases, skin testing and desensitization are not indicated. If symptoms are more objective but mild in nature (ie, flushing or pruritus alone without hives, back pain alone) or there is heightened patient concern around readministration, pre-medications, such as H_1-antihistamines, and a slowed infusion rate have been used successfully without the need for desensitization.[36] For patients with a high level of anxiety around retreatment despite an unconvincing reaction

TABLE XXIV. Incidence and characteristics of chemotherapeutic HSRs[480-484]

	Overall incidence of HSR (%)	Characteristics of HSR[477]	Nonirritating ST concentrations	Cross-reactivity[485-487]
Carboplatin	1-46	Occurs within minutes or during the infusion Rare HSRs <6 cycles 27%-46% after cycle 7 (typically 2nd-line treatment)	Step 1: 10 mg/mL (skin prick) Step 2: 0.1 mg/mL (intradermal) Step 3: 1 mg/mL (intradermal) Step 4: 5 mg/mL (intradermal)*	Carboplatin cross-reactivity in patients who are oxaliplatin-allergic was 45% Oxaliplatin cross-reactivity in patients who are carboplatin-allergic was 37% Cross-reactivity to cisplatin was 0% in patients who are oxaliplatin-allergic and 7% in patients who are carboplatin-allergic
Cisplatin	5-20	Occurs within minutes or during the infusion Reactions occur most often after several cycles Increases with concomitant radiation	Step 1: 1 mg/mL (skin prick) Step 2: 0.01 mg/mL (intradermal) Step 3: 0.1 mg/mL (intradermal) Step 4: 1 mg/mL (intradermal)	
Oxaliplatin	7-24	Occurs within minutes or during the infusion Reactions occur most often after several cycles	Step 1: 5 mg/mL (skin prick) Step 2: 0.05 mg/mL (intradermal) Step 3 – 0.5 mg/ml (intradermal) Step 4 – 5 mg/ml (intradermal)	
Paclitaxel	4-10	Most reactions occur within minutes of the first or second administration Symptoms will improve quickly once infusion is stopped Rare nonimmediate reactions	Step 1: 6 mg/mL (skin prick) Step 2: 0.001 mg/mL (intradermal) Step 3: 0.01 mg/mL (intradermal) Step 4: 0.1 mg/mL (intradermal) Step 5: 1 mg/mL (intradermal)	50%-90% cross-reactivity between paclitaxel and docetaxel reported in literature†[481,486,487] Cross-reactivity rate between paclitaxel and docetaxel varies among different populations; severity of the initial HSR may influence this rate[484] Nab-paclitaxel well tolerated in paclitaxel and docetaxel allergy[481,484]
Docetaxel	5-15	Occurs within minutes or during the infusion Symptoms will improve quickly once infusion is stopped	0.4 mg/mL for both skin prick and intradermal tests	

RN training, use of hood, and precautions with chemotherapy skin testing should follow local institutional policies.
*Local skin necrosis has been reported with a full concentration of 10 mg/mL.[488]
†Unpublished clinical experience of authors (AB, EP) suggests lower risk of cross-reactivity between paclitaxel and docetaxel. Risk, benefits, and shared decision making should be considered in situations requiring use of alternate taxane in individual with taxane HSR.

history or describing a sensation of throat tightness or trouble breathing without objective findings, skin testing can be considered to provide reassurance, and subsequent slowed infusion rate may alleviate some of their treatment concerns.

Platins

HSRs occur in 8%-16% of patients with gynecologic malignancy receiving carboplatin, 5%-20% in patients receiving cisplatin, and ≤24% in patients with multiple cancer types (including gastrointestinal) receiving oxaliplatin.[476,491,492] Platinum compounds typically cause HSRs after several treatment courses,[493,494] suggesting that a period of sensitization is important and an immunologic IgE mechanism is likely. There are varying reports of cross-reactivity between platin agents, but the lowest cross-reactivity is between oxaliplatin and cisplatin.[485,495,496] With carboplatin, the incidence of HSRs increases from 1% in individuals who have received 6 or fewer carboplatin infusions to 27% in those who received ≥7, and ≤46% in patients who have received >15 infusions.[476,497] The peak incidence of carboplatin HSRs occurs with the eighth or ninth exposure, which generally corresponds to the second or third cycle of retreatment after recurrence of malignancy.[476] Pretreatment with corticosteroids and H_1-antihistamines does not prevent HSRs from occurring again and does not prevent anaphylaxis.[498]

Consensus-based Statement 30: We suggest that for patients with a history of immediate allergic reactions to platinum-based chemotherapeutic agents, the severity of the initial HSR and skin testing results (if available) may assist in their risk stratification and management.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

As discussed, desensitization can be successfully used to continue first-line treatment in cancer patients despite an immediate HSR. However, skin testing has been found to be useful in the management of patients with platin HSRs and also to identify cases where desensitization may be unnecessary despite a clinical history that is suggestive of an HSR. Skin testing to platins should be considered when it will impact patient care decisions but not delay care. Skin testing with the platin drug has been demonstrated to be helpful in confirming the diagnosis of HSR to platinum-based chemotherapeutic agents, including carboplatin, cisplatin, and oxaliplatin.[476,494,496] However, the false-negative rate of carboplatin skin testing (ie, the development of HSR with next exposure after a negative skin test) is reported to be as high as 8%-8.5% in the literature.[499,500] It has been observed that some patients with a clinical history suggestive of a platinum

agent HSR but with negative initial skin testing experienced HSRs with subsequent drug exposure even when that exposure occurred during attempted drug desensitization.[488]

When initial skin testing is negative, the time elapsed since the platin HSR occurred (<6 weeks or >6 months) should be taken into consideration and repeat skin testing has been used to identify individuals that are truly allergic.[501,502] In part, this guidance is based on the data from general anesthesia and hymenoptera venom evaluations and descriptions in the literature for platin HSRs, both of which suggesting some patients may have falsely negative skin tests for 4-6 weeks after a systemic reaction.[501,502] However, this should not delay treatment and care can proceed under the assumption of true allergy based on the clinical history until platin skin testing can be performed. Prior data have shown that skin testing may convert from negative to positive after subsequent carboplatin exposures if the time interval between initial skin testing and the HSR is >6 months.[488,502,503] One note of caution, skin testing should not be performed for chemotherapy drugs with vesicant skin reactivity such as doxorubicin.[504] Local skin necrosis has also been seen with carboplatin full concentration intradermal testing (10 mg/mL) and therefore the maximum concentration for intradermal use should be 5 mg/mL.[488]

A risk-stratification protocol using 3 serial skin tests has been shown to be safe and effective in evaluating and managing patients with carboplatin-induced HSR.[503] This protocol has been reported to safely differentiate patients who are allergic from those who are nonallergic and helps prevent unnecessary desensitizations (Fig 5).[501] However, while avoiding unnecessary desensitization by identifying patients who are truly allergic, risk-stratification protocols can create operational challenges in addition to rising costs, increased patient time, multiple office visits, and potential delays in treatment. One potential approach sought to simplify the platin skin testing/risk-stratification process while maintaining safety and efficacy by studying a modified 1-step platin intradermal skin testing protocol (using highest platin skin test concentration only) in patients with a history of platin HSR who have tolerated an initial desensitization.[505] It is important to note that empiric desensitization (without prior skin testing) remains a safe method to manage patients after an HSR, though there is limited evidence for this approach. Skin testing with chemotherapeutics is often difficult to perform due to limited access to the drugs and in many cases, institutional policies on who can handle chemotherapeutic drugs. In both academic and even more so in nonacademic centers, chemotherapeutic skin testing may not be feasible. Empiric desensitization without skin testing allows the patient to proceed with first-line therapy.

For patients with positive skin test results, various desensitization protocols have been reported.[498,506,507] The most experienced published approach has used a 12-step desensitization protocol for a variety of chemotherapeutic agents, including platinum compounds, has been reported to be successful in 413 procedures, with 94% of procedures having only a mild or no reaction and 6% had moderate to severe reactions.[506] A more recent report indicated that in 2177 cases of chemotherapy or mAbs, desensitization in 370 patients with 15 different agents, 93% of the cases had no or mild reactions and all patients were able to complete all desensitization courses and continue first-line therapy.[508] A slightly modified desensitization protocol with 13 steps using an additional step in the last/third bag where reactions were frequently occurring has also shown a high rate of success.[501] These multistep desensitization protocols are labor-intensive, leading to several recent publications showing success using a 1-bag desensitization protocol (Table XXV).[509] While these still require multiple steps, no carboplatin drug dilutions were required, significantly simplifying the burden of resources (ie, skilled pharmacist, preparation time) needed to proceed safely and shortening the time required for desensitization.

When analyzing the costs and life expectancy of patients who underwent carboplatin desensitization, it was found that overall health costs were not increased, and the life span was equal or superior to that of a cohort control group of patients with similar cancers undergoing the same treatment courses without prior infusion reaction who did not receive desensitization.[508]

There are also emerging data using drug provocation or challenge protocols based on the severity of the initial HSR as a major factor in risk stratification and subsequent delabeling of patients with a history of platin hypersensitivity.[36,51] A 2013 study evaluated 12 patients who were low risk with platin HSRs and negative platin skin testing.[510] They all underwent platin challenge and 7 of 12 tolerated the challenge and did not require desensitization. In another study, 1 of 21 patients with positive platin challenge had anaphylaxis (hives, hypoxemia, hypotension, dyspnea, and wheezing) that required epinephrine and resolved within 30 minutes.[511] The study concluded that platin challenges can reduce desensitization requirements (32% of platin challenges were negative) but still have an inherent risk. It is important to note that the risks may be different when comparing challenge protocols performed with carboplatin to other chemotherapeutic agents; however, this methodology has been safely applied to other chemotherapeutics and biologics.

Serum-specific IgE to platins is promising but remains investigational. Basophil activation test has been shown to identify patients with carboplatin and oxaliplatin allergy and to detect severe reactors and reactors during drug desensitization and may be a useful biomarker in the future.[512]

Recent data show that inherited mutations in BRCA1/BRCA2 appear to be associated with a higher risk for carboplatin HSRs.[513,514] Patients with a BRCA1/BRCA2 mutation are also at higher risk for reacting during desensitization[514] and therefore, allergist-immunologists should refer women with BRCA1/BRCA2 mutation for further counseling accordingly.

Taxanes

Consensus-based Statement 31: We suggest that for patients with a history of immediate allergic reactions to taxanes-based chemotherapeutic agents, the severity of the initial HSR may assist in their risk stratification and management.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

Taxanes are a group of chemotherapeutic agents that includes paclitaxel and docetaxel. Paclitaxel is a natural compound, originally isolated from the bark of the Pacific yew tree (*Taxus brevifolia*) and found to have anticancer properties. Taxane HSRs are generally thought not to be related to the active drug but instead may be caused by excipients. Examples include Cremophor-EL, a lipid solvent vehicle used in paclitaxel, and polysorbates, used in other chemotherapeutics such as docetaxel.[67] Within the taxane family, paclitaxel and docetaxel produce infusion reactions in 10%-50% of patients on first administration,[37] suggesting either a direct, non-IgE–mediated

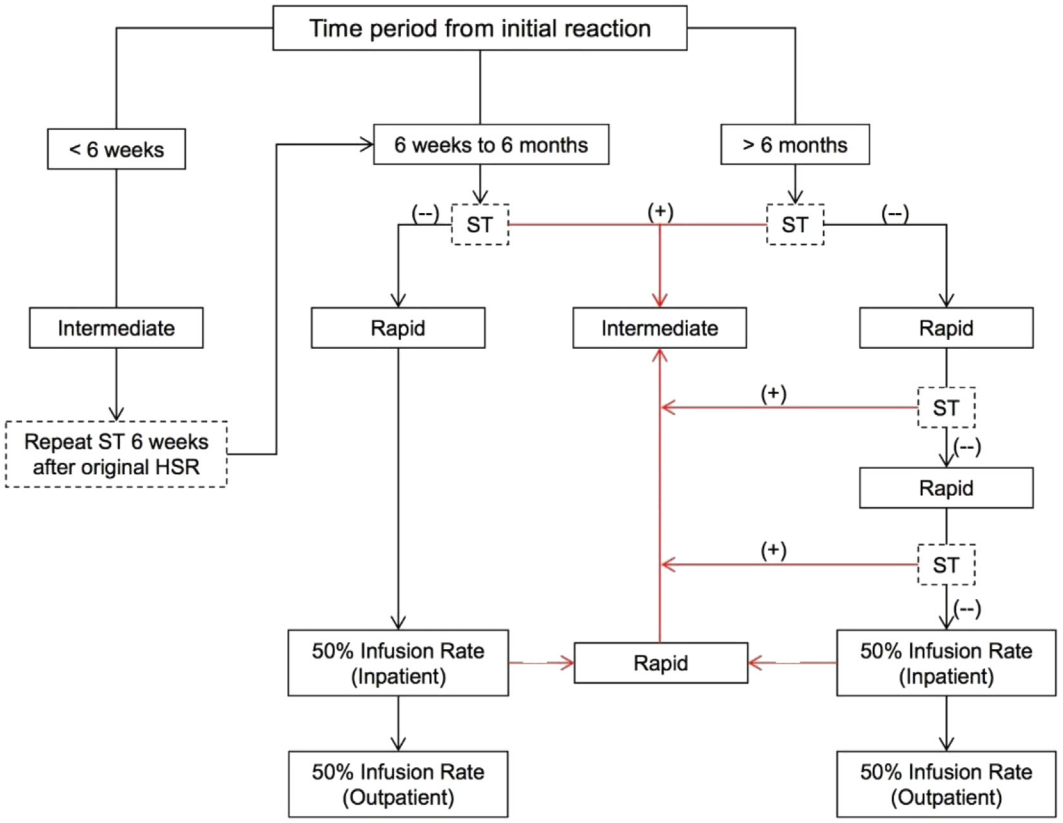

FIG 5. Sample risk stratification after a carboplatin HSR.[501] This risk-stratification algorithm follows an individual patient from the time of the initial HSR through repeat evaluations including skin test (*ST*) and subsequent treatment steps. ST is performed in between treatments (approximately every 3 weeks). "Intermediate" refers to a standard 12-step desensitization protocol; "rapid" refers to a standard 8-step desensitization protocol; and "50% infusion rate" implies slowing the initial infusion rate by 50%.

TABLE XXV. Example of a 1-bag carboplatin desensitization protocol[509]

Step	Rate (mL/h)	Time (min)	Dose (mg)	Volume (mL)	Concentration after merging with side stream (mg/mL)*
1	0.1	15	0.0135	0.025	0.005332
2	0.2	15	0.0269	0.05	0.010559
3	0.5	15	0.0673	0.125	0.025643
4	1.2	15	0.1616	0.3	0.057697
5	2.5	15	0.3366	0.625	0.107701
6	5	15	0.6731	1.25	0.179501
7	10	15	1.3463	2.5	0.269251
8	20	15	2.6925	5	0.359002
9	40	15	5.385	10	0.430802
10	60	15	8.0775	15	0.461574
11	80	15	10.7701	20	0.478669
12	150	67.7	91.1497	169.3	0.504846

Oxaliplatin 120 mg/24 mL was reconstituted with 200 mL of 5% dextrose in water and the concentration of the solution was 0.5385 mg/mL.
Dose (mg) = Rate (mL/h) × time/60 (h) × concentration (mg/mL).
*Five percent dextrose in water was infused as a side stream at a rate of 10 mL/h.

mechanism or the presence of preexisting specific IgE. Taxanes may cause mast cell and/or basophil activation through IgE-mediated mechanisms, direct action on basophils, or IgG-mediated mechanisms that cause complement activation and release of anaphylatoxins (C3a, C5a).[484] Therefore, the role of skin testing after a taxane HSR remains unclear.[484,515] If Cremophor-EL is the culprit as described in the literature,[483] then skin testing has little value while the opposite is true for IgE-mediated reactions, which appear to be much less common with taxanes. Clinically, it is not easy to differentiate IgE from non-IgE reactions based on symptoms alone with taxane HSRs, but skin testing has been described as a potential tool because a subset of patients may react via an IgE-mediated process based on prior sensitization (ie, to a cross-reactive pollen from the yew tree).[516,517] However, it is unclear that skin testing impacts clinical management and the pathophysiology of taxane hypersensitivity, which may relate more to nonspecific mast cell activation as opposed to specific IgE in most cases.

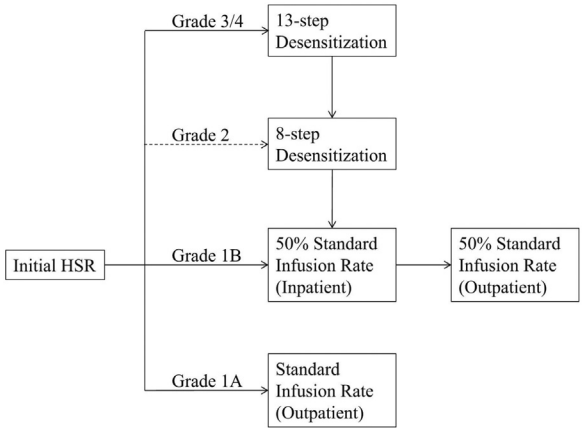

FIG 6. Sample risk stratification after paclitaxel HSR.[520] The initial grade of the HSR is used to determine optimal approach to retreatment with paclitaxel after an initial HSR. HSRs were graded according to a modified National Cancer Institute Common Terminology Criteria for Adverse Events.

Pretreatment with systemic corticosteroids and H_1-antihistamines can decrease the rate of reactions to taxanes from 30% to 3%.[37-39] However, patients who develop immediate reactions despite pretreatment can be successfully managed using a 3-bag desensitization protocol similar to platin desensitization.[506,518] Similar to other chemotherapeutics, performing the desensitization procedure is labor-intensive because pharmacists and nurses need to prepare and administer diluted solutions. To address this, a 1-bag protocol was recently shown to be noninferior to a multibag rapid desensitization protocol with 98% success and could offer a safe, effective, less labor-intensive option for paclitaxel desensitization.[519] In addition, the literature shows that the majority of patients with mild taxane reactions (ie, without respiratory symptoms or hypotension) can safely resume regular or slowed infusions without desensitization.[520,521] For example, a study developed and used a risk-stratification algorithm in 35 patients with paclitaxel HSRs (Fig 6).[520] All 5 patients with a grade 1 initial HSR tolerated retreatment without desensitization, so unnecessary desensitizations were avoided and no patients developed severe HSRs. Still, another study similarly showed safety of risk stratification based on the severity of the initial HSR in conjunction with skin testing to guide taxane reintroduction.[516] These types of algorithms can be used to aid clinicians in the management of patients who previously experienced a taxane HSR.

Another option for patients who react to paclitaxel is to switch to a noncremophor paclitaxel such as paclitaxel formulated as albumin-bound particles, which is not used routinely due to cost.

Severe delayed reactions that are often T-cell–mediated such as SJS/TEN, cutaneous vasculitis, acute interstitial pneumonitis, and subacute cutaneous lupus erythematosus have been described in case reports in association with paclitaxel, and these are not amenable to desensitization.[484,522]

Radiation recall dermatitis is a localized drug-induced inflammatory skin reaction occurring in a previously irradiated site months to years after discontinuation of ionizing radiation exposure that has been noted with certain chemotherapeutic drugs including paclitaxel.[523] The literature describes the lesions as maculopapular exanthem with erythema, edema, vesicle formation, and desquamation at the site of previous irradiation with paclitaxel treatment. Symptoms usually appear within days to weeks after exposure to the causative agent. In addition to stopping the precipitating agent, topical corticosteroids have been beneficial. Shared decision making can be used to discuss risks and benefits of using the culprit again once symptoms improve.

Asparaginase

Asparaginase is a critically important treatment for specific cancers including acute lymphoblastic leukemia and lymphoblastic lymphoma. Immediate-type reactions to asparaginase occur in 3%-45% of patients.[524]

There are 3 formulations of asparaginase that are FDA-approved for use in the United States. The first is native *Escherichia coli* asparaginase and the second is a pegylated (PEG) form of asparaginase, also derived from *E coli.* The third formulation is asparaginase, which is derived from an alternate bacterial source, *Erwinia chrysanthemi*. In patients who react to *E coli* asparaginase, substitution of either *E chrysanthemi* asparaginase or pegylated asparaginase may be better tolerated.[525] Data show that in patients who switch to asparaginase *E chrysanthemi*, after hypersensitivity to *E coli*–derived asparaginase, leukemia outcomes are similar to patients who never developed clinical hypersensitivity.[526,527] The mechanism of these reactions is unknown, but symptoms and signs consistent with mast cell mediator release, as well as anaphylaxis, have been described. Successful use of asparaginase rapid induction of drug tolerance protocols are reported.[528,529]

Patients who developed an HSR to *E coli*–derived asparaginase showed increased levels of antiasparaginase antibodies as well as decreased asparaginase activity.[524] While premedication with steroids reduces the rate of HSRs when studied across trials comparing patients premedicated with steroids and those not given steroids, it is unknown whether the development of antiasparaginase antibodies is similarly reduced. Anti–PEG asparaginase IgG has shown utility in predicting and confirming clinical reactions to pegylated asparaginase as well as in identifying patients who are most likely to experience failure with rechallenge.[146] Additionally, the presence of anti–PEG IgG antibodies may correlate to lower efficacy of other pegylated agents.[530]

Tyrosine kinase inhibitors

Tyrosine kinases are a large group of enzymes that participate in many cell functions, including cell signaling, growth, and division. The challenge with using TKIs has been their association with significant idiosyncratic or pharmacologic effects including cutaneous and systemic side effects (including a recent FDA black box warning for serious heart-related events, cancer, blood clots, and death).[40] The mechanism of these adverse effects is pleotropic and may relate directly to tyrosine kinase effects rather than immunologic hypersensitivity. In rare cases, HSRs have been described. These enzymes, which may be overactive and found at high levels in cancer cells, can be blocked using TKIs to slow the growth of the cancer cells. TKIs are broadly described as a type of targeted therapy that identifies and inhibits only specific types of tyrosine kinase in cancer cells while not affecting normal cells. Approximately 50 TKIs are currently (2021) FDA-approved in the United States, and they play a valuable role, not only in the treatment of malignancies but also in a myriad of autoimmune conditions and myeloproliferative disorders. TKIs are categorized based on the specific tyrosine kinase

TABLE XXVI. FDA-approved ICIs

Drug	Mechanism/class
Ipilimumab (Yervoy, Bristol Myers Squibb, New York, NY)	CTLA4 inhibitor
Pembrolizumab (Keytruda, Merck and Co, Rahway, NJ)	PD-1 inhibitor
Nivolumab (Opdivo, Bristol Myers Squibb)	PD-1 inhibitor
Atezolizumab (Tecentriq, Genentech, San Francisco, Calif)	PD-L1 inhibitor
Avelumab (Bavencio, Merck KGaA, Darmstadt, Germany)	PD-L1 inhibitor
Durvalumab (Imfinzi, AstraZeneca, Cambridge, United Kingdom)	PD-L1 inhibitor
Cemiplimab (Libtayo, Sanofi US, Bridgewater, NJ)	PD-1 inhibitor
Dostarlimab (Jemperli, GSK, Philadelphia, Pa)	PD-1 inhibitor

target (eg, EGFR, platelet-derived growth factor receptors, Bruton's tyrosine kinase, Janus kinase inhibitors).

Like other reactions associated with antichemotherapeutic drugs, recognition and correct clinical phenotyping is key to risk stratification and the formulation of an appropriate management plan. This includes the decision on when to reduce the dose, stop the drug, or treat with corticosteroids. Proactive approaches to care of the patient undergoing chemotherapy also start with patient education on the most important or likely adverse events that may occur and when to call their physician (ie, primary care, oncologist) so that such reactions can be recognized and managed early and effectively.

EGFR-TKI's most common adverse effect is skin toxicity, usually manifested as acneiform rash, skin fissure, xerosis, and paronychia. More than one-half of patients taking these drugs experience an acneiform eruption. It is usually mild or moderate but can be severe in a minority of cases. Because EGFRs are highly expressed in sebaceous epithelium, eruptions are generally most concentrated in seborrheic areas such as the scalp, face, neck, chest, and upper back. The periorbital region, palms, and soles are usually spared.[531] The acneiform eruption is often dose-dependent and begins within 1 week of treatment.[532] Hand-foot skin reactions, presenting with pain and blistering on the palms and soles, are reported with sorafenib, sunitinib, and other EGFR inhibitors. EGFR inhibitors have also been associated with hair changes, aphthous ulcerations of the oral and nasal mucosa, photosensitivity, and urticaria. Cases of SJS and TEN have been reported with TKIs, but the incidence is low.[533-535]

Management of cutaneous side effects includes topical and systemic corticosteroids, antibiotics (lesions can be superinfected by bacteria), topical urea, salicylic acid, and oral isotretinoin. Patients who develop pruritus may benefit from H_1-antihistamines or gamma-aminobutyric acid agonists such as gabapentin.[536,537] In some cases, the dose of TKI is reduced or the TKI is discontinued and then reintroduced at a lower dose once the cutaneous symptoms improve. Immediate discontinuation of the drug is recommended if there is any sign of a bullous or exfoliative skin rash. NSAIDs, minocycline, or doxycycline may be useful in preventing EGFR-TKI–related skin rash.[538,539]

Oral mucositis and stomatitis are also common adverse events associated with TKIs. A patient with oral mucositis may have extensive erythema or aphthous-like stomatitis.[540] Most stomatitis/mucositis cases are mild but can be very painful and make eating and drinking difficult. The frequency of diarrhea is 24%-41%.[541] Endocrine dysfunction (hyperglycemia, hypothyroidism, dyslipidemia), as well as hypertension, liver problems, ocular toxicity, peripheral edema, joint pain, and proteinuria can also occur.[542] These effects are usually mild, but severe cases can occur, significantly affecting patients' well-being, treatment compliance, and quality of life.

ADVERSE REACTIONS TO ICIs

ICIs have revolutionized cancer treatment since the first approval of the CTLA4 inhibitor ipilimumab in 2011.[41] In 2021, these include 7 drugs with indications for 17 cancer types (Table XXVI). Treatment has also diversified to include not only dual immune checkpoint inhibitor therapy that originated with CTLA4 and PD-1 inhibitor combinations in melanoma, but also combinations incorporating chemotherapy and other targeted therapies. The currently available ICI are mAbs that block specific immune checkpoints, CTLA4, PD-1, and PD-L1, leading to increases in T-cell activation and proliferation.[41] The mechanism of action of these drugs, which reduce self-tolerance, can lead to a number of toxicities that are typically organ-specific autoimmune events and referred to as irAEs.[41] The most common of these are mild to moderate and include dermatitis, thyroiditis, and other endocrinopathies; hepatitis; colitis; interstitial nephritis; and pneumonitis.[42-44] Rare but potentially fatal events include myocarditis and encephalitis.[45,46] Nonspecific adverse drug reactions such as fatigue, pruritus without rash, arthralgia, loss of appetite, and weight loss are common. Overall, some form of toxicity occurs in ~20% of those treated; however, 50% of those treated with combination therapies, such as PD-1 and CTLA4 inhibitor combined therapy, will experience an ICI-related adverse event.[43]

Infusion reactions related to ICI are typically mild and occur in ≤25% of those treated with PD-1 and PD-L1 agents in particular.[44] For avelumab these may be more pronounced and treatment with an antihistamine and acetaminophen has been recommended.[543] Allergic reactions such as anaphylaxis are extremely uncommon and consideration would need to be given for the excipients of these drugs, which contain polysorbate 80, except for avelumab, which contains polysorbate 20.[67] Exacerbation of asthma and atopic disease may occur but is uncommon.[544] Pruritus without rash is a common side effect and is postulated to have a neurologic basis.[545] Gabapentin is often effective in management.[545] It is important for the allergist-immunologist to recognize these nonallergic events because they may be consulted for common toxicities such as rashes or organ dysfunction or they may have patients that they are following for other reasons that are under treatment with an ICI.[44] Treatment of the toxicities is currently based on the common terminology criteria for adverse events.[546] For mild reactions, symptomatic and supportive treatment is recommended and therapies may be continued.[43] These could include topical corticosteroids and oral H_1-antihistamines

for rash or hormone replacement for endocrinopathies (hypothyroidism, hypophysitis, diabetes, adrenal insufficiency). In the case of more severe toxicities, the ICI should be stopped and systemic corticosteroids (0.5-2 mg/kg/day tapered over 4-6 weeks) have remained the mainstay of treatment. For those who do not improve on corticosteroids or who flare during a corticosteroid taper, a disease-specific immunomodulator directed against a specific target may be indicated. Rechallenge to the ICI is a shared decision between the patient and the provider that weighs the risk of recurrence and morbidity with rechallenge compared with the benefit of tumor response. For grade 4 reactions rechallenge is typically considered contraindicated. Several studies have now looked at the recurrence of ICI toxicities with rechallenge with the same agent or same class of agent, or deescalation from dual ICI therapy to single therapy (eg, CTLA4/PD-1 inhibitor dual therapy to PD-1 therapy).[547-551] The rates of recurrence with rechallenge with the same ICI have been ≤50% and more common with colitis, pneumonitis, and hepatitis. Deescalation of combined ICI therapy to single therapy (eg, PD-1) was associated with a more modest risk of recurrence of ≤20%. Current ICI rechallenge strategies under study include concomitant use of selective immunosuppressant therapy. Generally both the management of the toxicity and the decision for future treatment is done in conjunction with the patient's multidisciplinary care team. Recent guides to the work-up and management of ICI toxicity, including evidence and consensus-based recommendations to recognize and manage single and combination ICI irAEs, have been published by the National Comprehensive Cancer Network[552] and the Society for Immunotherapy of Cancer.[553] Identification of individual genetic factors or other biological markers that would predict which patients are at risk for irAEs has not been defined for clinical use but is under study.[554] Management of irAEs requires multidisciplinary care.

BIOLOGIC HYPERSENSITIVITY

Biologic agents are newer therapeutic agents created from living cells, tissues, or organisms that include mAbs (suffix "mab") and soluble fusion receptors (suffix "cept"). The nomenclature for mAbs is described in Table E3 in this article's Online Repository at www.jacionline.org. Structurally, these can be based on a common IgG structure but with considerable differences in the degree of the residual nonhuman component. The other main structural group are often referred to as "small molecules," and although the target is a specific immune pathway molecule or receptor, the drug size is small and generally not composed of an immunoglobulin structure. Within the mAb class, agents can be further characterized by the penultimate syllable "u" for fully humanized, "xi" for chimeric (human/foreign), and "zu" where only the complementarity determining region remains murine but the rest of the antibody is humanized (Table E3). Humanization of mAbs has decreased the immunogenicity of these agents although fully humanized antibodies carry some risk.[555] In addition to protein structures, heterogeneity can be introduced through other manufacturing processes due to glycosylation variants, carboxy or amino terminal acid additions, aggregates, and other factors. The development of biologic agents is rapidly expanding the therapeutic space with >150 agents approved for treatment of malignancy and immunologic/inflammatory conditions as well as expansion to conditions to such as migraine headaches, hypercholesterolemia, and Alzheimer's disease. All of these agents are immunogenic and potentially capable of triggering local or systemic HSRs.

Almost all biologic agents are administered via subcutaneous or intravenous injection, and they are either engineered antibodies targeted against a specific target, or mimics of human protein agonists blocking or effecting function through a specific pathway. Biologic agents have the benefit of target specificity and infrequent dosing, yet they have the potential to be immunogenic. A variety of mechanisms may result in reactions including complement activation, SSLRs, and mast cell activation either via IgE-mediated or direct mast cell activation. Nonimmune mechanisms such as tumor lysis and cytokine storm may also cause symptoms that overlap with immune-mediated reactions. The utility of diagnostic testing (eg, skin testing and *in vitro* testing) is limited by several factors including, but not limited to, mechanistic uncertainty, the cost of the medications, availability, lack of validation, and the unknown predictive value. Given these limitations, the workgroup suggests that skin testing for mAbs is rarely clinically indicated. See the "Practical Guidance for the Evaluation and Management of Drug Hypersensitivity: Specific Drugs" for more information.[556]

Consensus-based Statement 32: We suggest that patients with nonimmediate reactions or a history of reactions inconsistent with mAb hypersensitivity may be treated with a slowed infusion, graded dose escalation, and/or premedications without desensitization.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

Consensus-based Statement 33: We suggest that for patients with immediate reactions or a history consistent with anaphylaxis to mAbs, drug desensitization should be considered when the implicated drug is the preferred therapy.

Strength of Recommendation: Conditional

Certainty of Evidence: Low

There is a growing need for allergy/immunology specialists to be involved in the management of immunologic adverse events associated with use of mAbs. The mechanism of these reactions is heterogenous, which may influence management approaches. Even without knowledge of the underlying mechanism, most patients with reactions to mAbs may be managed through strategies including slowed infusion, premedication, and rapid desensitization protocols.[557] After appropriate evaluation, many patients can be managed in a way to allow continuation of the culprit agent, which often has no therapeutic equivalent. While adverse reactions and HSRs have been reported to numerous mAbs, currently only a small number of agents are suspected culprits for the majority of referrals to allergy/immunology specialists, and these will be discussed in more detail in this parameter. Details regarding management of reactions to less frequently implicated biologics are described elsewhere.[556]

Rituximab

Rituximab is a chimeric murine/human, anti-CD20 mAb approved for the treatment of several types of cancer and autoimmune diseases. However, the benefit of any mAb treatment must be balanced against its risk of causing reactions. This risk is especially high during the initial infusion, as ≤77% of patients being treated for a B-cell lymphoma can develop a reaction during their first exposure.[48] Paradoxically, the risk of having a reaction to rituximab appears to decrease with subsequent infusions.[49,50]

TABLE XXVII. Mechanisms, clinical presentation, and laboratory changes for mast cell–mediated versus cytokine release rituximab infusion reactions

Mast cell-mediated	Cytokine release	
Mechanisms		
IgE and non-IgE and involves mast cells	Innate immunologic and could involve monocytes, macrophages, T cells, and NK cells	
Clinical presentation		
Constitutional	Constitutional	Cardiovascular
Rare	Fever > 38.4°C*	Syncope
Neurologic	Rigors	Hypertension
Dizziness	Chills	Tachycardia
Cardiovascular	Malaise	Chest pain
Syncope	Weakness	Pulmonary
Hypotension†	Neurologic	Dyspnea
Pulmonary	Numbness	Tachypnea
Cough	Paresthesia	Gastrointestinal
Rhinitis	Vision disturbances	Nausea/vomiting
Nasal congestion	Tinnitus	Diarrhea
Wheezing	Unusual taste	Abdominal pain
Dyspnea	Headache	Skin
Tachypnea	Back pain	Flushing
Bronchospasm		Nonurticarial rash
Gastrointestinal		
Nausea/vomiting		
Diarrhea		
Abdominal pain		
Skin		
Flushing		
Pruritus		
Angioedema*		
Urticaria*		
Potential laboratory changes		
CBC with differential		CBC with differential
No change		↓ Cell counts
Chemistry		Chemistry‡
↑ Tryptase		↑ Cr, ESR, CRP, LDH, uric acid
		↓ K, Ca
		Cytokines
		↑ IL-6

CBC, Complete blood count; *Cr*, creatinine; *CRP*, C-reactive protein; *ESR*, erythrocyte sedimentation rate; *LDH*, lactic acid dehydrogenase; *NK*, natural killer.
*Most common symptoms.
†Systolic blood pressure drop ≥20 mm Hg.
‡These changes usually seen only for severe reactions.

Tumor burden affects the type of infusion reaction that encompass several different immunologic mechanisms, including cytokine release syndrome, HSRs (mast cell–mediated), and tumor lysis syndrome (Table XXVII). In some cases, clinical symptoms of mast cell–mediated and cytokine-release syndrome reactions may overlap, which has been termed a "mixed reaction." Cytokine release is thought to occur when rituximab interacts with CD20 on lymphocytes leading to cytokine release, whereas HSR are attributed to mast cell degranulation. Acute cell lysis akin to tumor lysis syndrome may occur, with increase in serum creatinine, potassium, calcium, phosphate, lactate dehydrogenase, and uric acid, as well as with decrease in calcium and phosphate. The severity of the cell lysis syndrome is variable, but renal failure and acute, life-threatening pulmonary edema may occur within 12-24 hours of the first infusion (Table XXVII).

Appropriate management of a reaction includes cessation of the rituximab infusion and treatment of the reaction. As a result, complete drug avoidance has been advised needlessly in some patients who would benefit from additional rituximab treatment. Other patients undergo unnecessary desensitization procedures when the reactions are not consistent with significant mast cell–mediated events. One commonly recommended approach to evaluating a patient after a rituximab HSR (mast cell–mediated) is risk stratification (Fig 7).[558,559] These algorithms, which are based on experience at a large academic institution, start by grading the reaction: grade 1 is generally cutaneous symptoms only (rash, itching, flushing); grade 2 includes urticaria, nausea, vomiting, dyspnea, or asymptomatic bronchospasm; grade 3 includes symptomatic bronchospasm, dyspnea, hypoxia, and/or wheezing; and grade 4 includes anaphylaxis. In a

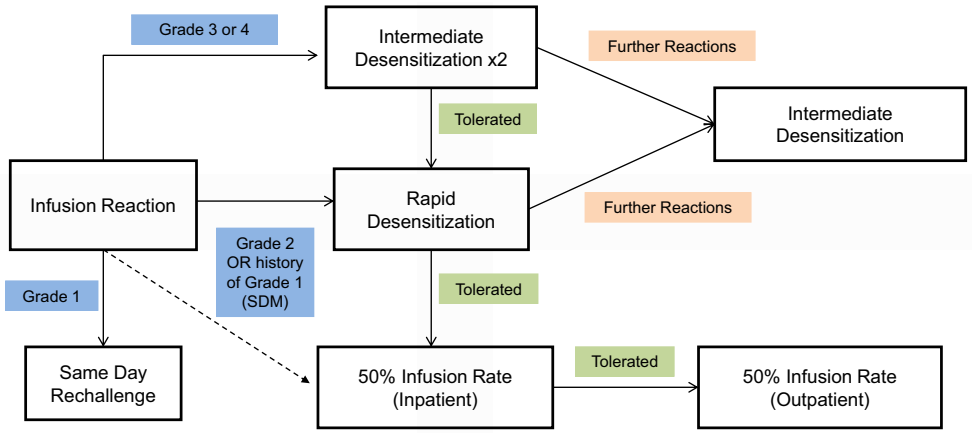

FIG 7. Rituximab risk stratification.[558] Intermediate desensitization uses a 3-bag, 12-step protocol. Rapid desensitization uses a 2-bag, 8-step desensitization protocol.[558] Clinical symptoms were classified using a modified version of the National Cancer Institute Common Terminology Criteria for Adverse Events Scale, which scores a reaction from 1 (mild reaction) to 4 (severe reaction). Grade 1A is defined by purely cutaneous symptoms (rash, itching, flushing). Grade 1B includes skin manifestations plus either back pain or hypertension. Grade 2 includes urticaria, nausea, vomiting, throat tightness, asymptomatic bronchospasm, and/or chest tightness. Grade 3 is defined by symptomatic bronchospasm, dyspnea, hypoxia, and/or wheezing. Grade 4 includes anaphylaxis or hypotension.[559] *SDM*, Shared decision making.

risk-stratification algorithm proposed by Levin et al,[558] most patients with a grade 1 reaction tolerated rechallenge. However, all 4 patients with a grade 3 reaction had a reaction during rechallenge. The outcome of same-day rechallenge after an initial grade 2 reaction was varied: most patients (26 of 31 [84%]) tolerated same-day challenge, but 5 patients had a reaction (all grade 1-2 severity). Following this algorithm, patients with a grade 1 reaction may receive same-day rechallenge once initial reaction symptoms have improved.[558] Shared decision making, in which the risks and benefits of the options are considered, is an important strategy. For grade 1 or 2 reactions, slowed infusion (typically 50% usual infusion rate), graded challenge, or desensitization are considered as reasonable options. In grade 3 or 4 reactions, an allergy specialist consultation may be a preferred option. The utility of rituximab skin testing is unclear, especially in cases where the reaction likely is not mast cell–mediated. Rituximab desensitization is safe and successful and can be completed within 1 day but should be performed under the guidance of experienced staff who can manage allergic reactions.[560] One group has described drug challenges in 60 patients with reactions to biologics (including rituximab) in patients with negative skin testing.[51] All challenges were carried out in an intensive care unit setting specifically assigned for patients undergoing drug desensitization. Forty-seven patients (78%) passed the challenge; however, of the 13 patients who reacted with the challenge, 8 had moderate-severe anaphylaxis. The workgroup recommends this approach should be considered only by very specialized centers. Separately, approach to repeat treatment after a cytokine release or tumor lysis infusion rituximab reaction may depend on tumor burden. There are case reports of mortality secondary to cytokine release syndrome in patients with a very high tumor burden supporting the notion that a decrease in tumor burden may lead to a decreased risk of reactions.[561,562] Shared decision making with a focus on risks and benefits is important when making the decision on how to proceed with treatment after an initial reaction.

SSLRs have been reported with rituximab and many other biologics. A systematic review reported on 33 cases of rituximab SSLR[75] and a French study identified 37 cases.[563]

SSLRs appear to be more common in autoimmune diseases (78%-85% of all cases) and in women and have the typical triad of arthritis, fever, and cutaneous manifestations (purpura, urticaria, erythema). In the 2 aforementioned reports, 2 of 4 and 6 of 7 rechallenges, respectively, to rituximab were well tolerated. Thus, in patients who develop SSLRs to rituximab and for whom there are no equally efficacious therapies, rechallenge can be considered after shared decision making with an assessment of risks and benefits. There are no large studies on validated premedication regimens, but both H_1-antihistamines and systemic glucocorticoids have been used.

Allergist-immunologists should be aware of the possibility for serious, nonimmediate adverse reactions to rituximab including DRESS, AGEP, SJS, TEN, myocardial infarction, arrhythmia, shock, and pulmonary toxicity. These reactions are not amenable to desensitization and drug avoidance is usually necessary.

Cetuximab

Cetuximab is a chimeric mouse–human IgG_1 mAb against the EGFR. A high prevalence of HSRs ranging from 12% to 29% has been reported in southeastern United States.[564-566] On further study, most of the severe HSRs to cetuximab were associated with preexisting IgE antibodies against alpha-gal, a carbohydrate attached to cetuximab.[52] Investigation of this regional variation in reaction rates led to the discovery that Lone Star tick bites were the cause of specific-IgE to alpha-gal in these individuals. However, cases subsequently have been reported increasingly in other parts of the United States. Alpha-gal has also been found in most mammalian or “red meat” and likely explains delayed red meat anaphylaxis.[567] Most food allergies are directed against a protein molecule, but alpha-gal is a carbohydrate, and slower absorption

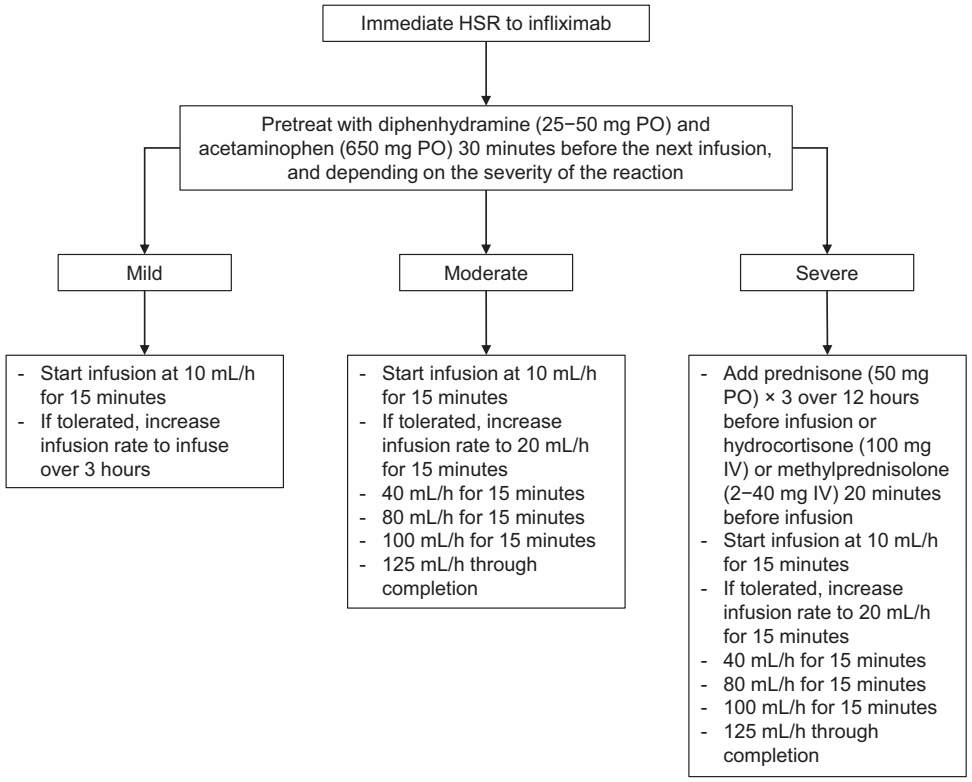

FIG 8. Protocol for desensitization to infliximab. Reproduced with permission from Broyles et al, 2020.[556] *IV,* Intravenous; *PO,* per os (by mouth).

TABLE XXVIII. Omalizumab subcutaneous desensitization (target dose 150 mg)[62]

Step	Time (min)	Concentration (mg/mL)	Volume (mL)	Dose (mg)	Cumulative dose (mg)
1	0	12.5	0.12	1.5	1
2	30	12.5	0.24	3	4.5
3	60	12.5	0.48	6	10.5
4	90	12.5	0.96	12	22.5
5	120	125	0.19	23.75	46.25
6	150	125	0.39	48.75	95
7	180	125	0.44	55	150

Vial concentration 125 mg/mL (150 mg/1.2 mL).

may explain the delayed nature of the allergic reaction to red meat. Other mAbs are produced with the murine SP2/0 cell line used for cetuximab and are glycosylated with alpha-gal. These include infliximab, abciximab, basiliximab, canakinumab, golimumab, and ustekinumab. While the alpha-gal content is lower in these antibodies, a case of first-dose anaphylaxis to infliximab due to cross-reactive alpha-gal–specific IgE has been reported.[53] There are successful reports of desensitization to cetuximab in the literature.[54,55] Use of panitumumab, another mAb specific for EGFR, after a cetuximab HSR appears to be a safe option.[568]

Infliximab

Infliximab is a mAb targeting TNF-α. After initial approval, infusion-related adverse events without a clear understanding of pathophysiology were reported. Similar to rituximab, the mechanisms are likely diverse, including IgE-mediated hypersensitivity, cytokine release syndrome, and SSLR.[56] HSRs to infliximab occur in ~10% of patients and are usually during the first or second exposure, but they can also occur with subsequent doses. Cytokine release and SSLR have been reported with symptoms 5-7 days after infusion. Interestingly, coadministration of thiopurine immunomodulators or methotrexate have been efficacious in preventing some reactions to infliximab.[56] Premedication with intravenous corticosteroids has not been shown to reduce the immunogenicity of infliximab.[569] Antibodies against infliximab may reduce the efficacy of treatment and increase the risk of HSR.[57,58] Risk stratification can be considered in the evaluation and management of individuals that develop reactions to infliximab (Fig 8).[556] This protocol is based on a small number of patients, and the effects of premedication independent of desensitization has not been studied.[570] Testing for alpha-gal–specific IgE should be considered in patients with first-dose reactions to infliximab, given the aforementioned potential for cross-reactivity in patients with alpha-gal allergy.

TABLE XXIX. Common excipients, clinical manifestations, and testing strategy

Excipient	Excipient-containing products	Clinical manifestations	Potential testing strategy
CMC[71,587-590] (also called E466, carmellose, croscarmellose, cellulose gum)	Triamcinolone acetonide (injectable)* Benzathine penicillin Barium sulfate contrast Lidocaine and other gels Eye drops Nasal corticosteroids Specific oral medication suspensions (eg, TMP-SMX) Other injectable drugs† Specific foods (eg, ice creams, frozen desserts)	Anaphylaxis Nasal congestion Conjunctival erythema Rare contact and delayed reactions	Triamcinolone acetonide (CMC and polysorbate 80) SPT (40 mg/mL) and ID (0.04, 0.4, and 4 mg/mL)* Parent drug (eg, benzathine penicillin) when indicated Oral challenge (parenteral sensitization typically shows oral tolerance eg, TMP-SMX)[587] Suggest minimal cross-reactivity with other celluloses (eg, hypromellose)[583]
Gelatin/alpha-gal[71,592-595]	Vaccines (MMR, FluMist [AstraZeneca], varicella and varicella-zoster (Zostavax, Merck and Co), yellow fever, rabies, oral typhoid) Cetuximab *Abatacept, infliximab* Crotalidae (CroFab, BTG International, Conshohocken, Pa) Intraoperative gelfoam and hemostatiscs Gelatin plasma expanders Other devices (bone replacement and collagen implants, vascular grafts, catheters)[596] Bovine/porcine tissue valve/bovine pericardium Heparins (porcine) Medications with gelatin capsules and suppositories Gabapentin oral solution	Anaphylaxis	SPT and IDT to gelatin and parent drug or vaccine (eg, gelatin prick undiluted, MMR 1:10, 1:100) sIgE ImmunoCAP[591] (Thermo Fisher Scientific, Waltham, Mass)
PEG[67,70,71,349,580,582‡]	PEG3350/4000 containing bowel preparations Methylprednisolone acetate intraarticular injection Medroxyprogesterone Ultrasound gel and contrast (Lumason, Bracco, Milan, Italy) Peg-lip (perflutren Definity echocardiogram contrast) Many oral medications PEG2000 lipid nanoparticular in mRNA COVID-19 vaccines (unknown if PEG2000 plays a role in immediate reactions) Medical devices (SpaceOAR Hydrogel system PEG15000, Boston Scientific, Marlborough, Mass)[597]	Anaphylaxis	SPT and IDT to PEG and derivatives PEG3350 for SPT (undiluted, 1:10, 1:100) Methylprednisolone acetate (PEG3350 ± PS80), sodium succinate (no PEG, control) and triamcinolone (PS80) for SPT (40 mg/mL) and IDT (0.04, 0.4, 4 mg/mL). Methylprednisolone sodium succinate as a non-PEG containing control sIgE (investigational)[68,598]
PEG derivatives[71,599]	Polysorbates (20 and 80) (vaccines and most monoclonal antibodies, triamcinolone) Polyoxyl-35 castor oil (Cremophor) (paclitaxel, cyclosporine) Poloxomers 188 and 407 PEG-alcohols Pegylated drugs§	Anaphylaxis Infusion reactions Unusual delayed or contact reactions	Optimal testing strategy is unknown but is generally recommended for those with immediate reactions When available, test for the implicated PEG derivative
Propylene glycol[600]	Topical corticosteroids, acyclovir cream, ultrasound gels, lubricants Diazepam injection	Delayed reactions (allergic contact dermatitis)	Patch testing

CMC, Carboxymethylcellulose; *ID*, intradermal; *MMR*, mumps, measles, rubella; *sIgE*, serum IgE; *SPT*, skin prick test.
*See section on CMC.
†Exenatide, Sandostatin (Novartis, Basel, Switzerland), leuprolide acetate depot, aripiprazole kit, naltrexone kit, norethidrone kit, triptorelin kit.
‡More extensive protocol of PEG (higher molecular weight, eg, PEG8000) may be considered dependent on history.
§The parent drug or protein may be implicated in the reaction.

Tocilizumab

Tocilizumab is a humanized anti-human IL-6 receptor mAb that binds to both circulating soluble IL-6 receptor and membrane-expressed IL-6 receptor. The most common reported adverse events are infections and gastrointestinal symptoms; however, there are cases of HSRs and anaphylaxis.[571,572] Rapid desensitization is a safe and successful option for patients who need tocilizumab despite an immediate HSR.[573] Delayed HSRs including leukocytoclastic vasculitis have been reported.[574] Successful induction of drug tolerance has been reported in a patient with a benign exanthem to tocilizumab and a positive delayed intradermal skin test.[575]

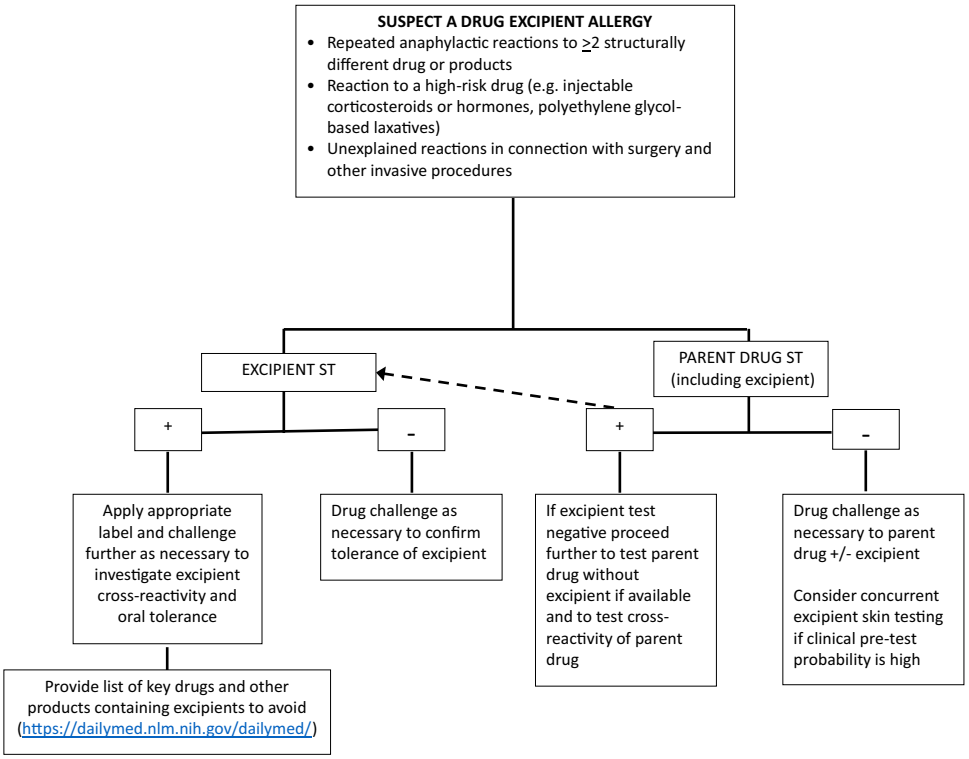

FIG 9. Approach to suspected excipient allergy.

Omalizumab

Omalizumab is an anti-IgE mAb that is currently FDA-approved for the treatment of moderate-to-severe allergic asthma, chronic idiopathic urticaria, and nasal polyposis. Review of the data shows a <0.1% risk of anaphylaxis with omalizumab, but interestingly 36% of reactions occurred >1 hour after administration of the drug, and 7% occurred >12 hours later.[59] A nonirritating omalizumab concentration for intradermal skin testing was defined at 1:100,000 volume-to-volume dilution, a concentration of 1.25 mcg/mL, but the predictive value has not been established in individuals with anaphylaxis to omalizumab.[61] There are reports of successful desensitization to omalizumab (Table XXVIII).[62-65] SSLRs have also been reported with omalizumab.[576,577]

EXCIPIENTS ALLERGY

Consensus-based Statement 34: We suggest the clinician recognize that excipients are a very rare cause of immediate or delayed reactions associated with drugs. Still, excipient hypersensitivity may be considered in patients with a history of anaphylaxis to ≥2 structurally unrelated drugs or products that share a common excipient (eg, injectable corticosteroids; PEG-based laxatives).

Strength of Recommendation: Conditional

Certainty of Evidence: Low

An "excipient" is an inactive substance that is formulated alongside the active pharmaceutical ingredient of a medication. Excipients include coloring agents, preservatives, stabilizers and fillers.[66] The main purpose of the excipient is to improve accurate dispensation of the product, facilitate drug absorption and solubility, improve stability (extend shelf-life), and enhance tolerability including appearance and taste.[578] Similar to the active pharmaceutical ingredient of a drug, excipients are more likely to contribute to intolerance than to a true allergic reaction.[67] Categories of excipients include foods and sugars such as lactose, mannitol, gelatin, and cornstarch; polymers such as PEG and its derivatives; dyes and coloring agents; and other ingredients such as carboxymethylcellulose.[66] There is a paucity of literature to support allergy to dyes as excipients of drugs. The average oral formulation of a product has ~9 inactive ingredients.[66] Excipients are a very rare cause of immediate or delayed reactions associated with drugs.[68-70] Standardized excipient testing reagents and concentrations are lacking.[67,579,580] The use of some recommended sources for excipients, such as artificial tears containing polysorbate 80, has led to frequent false positives.[581] The excipients present in specific drugs and products and their availability can vary widely across different countries.[582] In addition, the route and mechanism by which patients may become sensitized to excipients may differ. For instance, carboxymethylcellulose present in many foods has been recognized as a cause of anaphylaxis.[583] However, individuals with anaphylaxis to parenteral or high-dose oral formulations with carboxymethylcellulose, such as corticosteroids or barium sulfate preparations, appear to tolerate the low concentrations present in foods or oral medication.[71,583-585] The same is likely true for polysorbates and lower molecular weight PEG excipients.[67] Ingestion challenge is recommended to determine oral tolerance to these excipients.

Although delayed reactions are associated with some excipients (eg, propylene glycol), the most worrisome reactions are life-threatening anaphylaxis associated with excipients such as PEG and carboxymethylcellulose in injectable corticosteroids.[68,71] Although patients with PEG allergy generally tolerate mRNA vaccines that incorporate PEG, they may still have anaphylactic reaction to other drugs that have PEG.[586] Common excipients,

their associated drugs, cross-reactivity patterns and potential testing strategies are shown (Table XXIX),[67,68,70,71,349,580,582,583,587-600] and a general approach to management and testing for excipient allergies is proposed (Fig 9). As previously mentioned, the validity and diagnostic certainty for most excipient skin testing is uncertain.

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